

Cost-effectiveness of novel diagnostic tools for the diagnosis of tuberculosis

D. W. Dowdy,^{*†‡§} M. A. O'Brien,[¶] D. Bishai[#]

^{*} Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, [†] School of Medicine and [‡] Center for Tuberculosis Research, Johns Hopkins University, Baltimore, Maryland, [§] Department of Medicine, University of California, San Francisco, San Francisco, California, [¶] Department of Health Policy and Management and [#] Department of Population, Family and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

SUMMARY

SETTING: The potential cost-effectiveness of improved diagnostic tests for tuberculosis (TB) in resource-limited settings is unknown.

OBJECTIVE: To estimate the incremental cost-effectiveness of a hypothetical new point-of-care TB diagnostic test in South Africa, Brazil and Kenya.

DESIGN: Decision-analysis model, adding four diagnostic interventions (sputum smear microscopy, new test, smear plus new test and smear plus TB culture) to a baseline of existing infrastructure without smear.

RESULTS: Adding sputum smear was estimated to be more cost-effective (incremental cost per disability-adjusted life year [DALY] of \$86 [South Africa], \$131 [Brazil], \$38 [Kenya]) than a new TB diagnostic with 70% sensitivity, 95% specificity and price of \$20 per test (\$198

[South Africa], \$275 [Brazil], \$84 [Kenya]). However, compared to sputum smear, smear plus new test averted 46–49% more DALYs per 1000 TB suspects (321 vs. 215 [South Africa], 243 vs. 166 [Brazil], 790 vs. 531 [Kenya]), at an incremental cost of \$170 (Kenya) to \$625 (Brazil) per DALY averted. Cost-effectiveness was most sensitive to the specificity and price of the new test, the baseline TB case detection rate and the discount rate.

CONCLUSION: Novel diagnostic tests for TB are potentially highly cost-effective. Cost-effectiveness is maximized by high-specificity, low-cost tests deployed to regions with poor infrastructure.

KEY WORDS: tuberculosis; diagnostic techniques and procedures; costs and cost analysis; point-of-care systems; developing countries

TUBERCULOSIS (TB) is a leading cause of death worldwide, causing an estimated 1.6 million deaths annually.¹ Improved diagnosis could lower TB mortality by 20% or more, saving 300 000 lives per year.^{2–4} TB diagnosis worldwide currently relies on sputum smear microscopy, which identifies the most infectious cases with excellent specificity, but has an approximate sensitivity of 35% (if human immunodeficiency virus [HIV] positive) to 45% (if HIV-negative),⁵ and depends on the availability of sufficient laboratory capacity.^{6,7} Diagnosis of smear-negative TB is problematic, as chest X-rays (CXRs) and antibiotic trials, the most widely available diagnostic tools, have poor sensitivity and specificity.^{8,9} TB culture, the most sensitive technique available, is expensive, resource-intensive and takes weeks to yield positive results.^{10,11} Despite important advances in TB diagnostics,¹² a simple test with high sensitivity, rapid turnaround time and low cost remains elusive.

Development of diagnostic tests requires certain tradeoffs in design, often with economic consequences. Improvements in a test's performance can raise production costs. Improvements in sensitivity will reduce

specificity and vice versa. New TB diagnostic tests engineered to complement sputum smear may function differently from those designed for use in regions that lack the resources to conduct sputum smear. Economic research investigating these tradeoffs in developing new TB diagnostics has unfortunately been scant. To help address this knowledge gap, we analyzed the potential cost-effectiveness of adding a hypothetical new point-of-care test to the current TB diagnostic approach in three high-burden countries: South Africa, Brazil and Kenya.

METHODS

Model structure

We developed a decision-analytic model to simulate TB diagnosis in South Africa, Brazil and Kenya, three countries with a range of income levels, HIV prevalence rates, and TB diagnostic infrastructure. This model considers only adult TB suspects in whom a diagnostic workup for pulmonary TB is initiated. Patients are classified according to TB status, HIV status (positive or negative), access to antiretroviral treatment (ART)

(yes or no) and the degree of TB infectivity (for patients with active TB). Infectivity is classified as 'highly infectious' (i.e., smear-positive if specimens were submitted to an ideal laboratory, defined as one with no shortages of supplies or adequately trained staff) and 'less infectious' (smear-negative in the same situation). All three countries have adopted World Health Organization (WHO) guidelines for TB diagnosis and report TB cases to the WHO, which estimates each country's overall TB burden and case detection rate.¹

Diagnostic scenarios

The primary intervention studied is a point-of-care diagnostic test for TB, assumed to produce results in minutes with minimal infrastructure requirement (e.g., a sputum or urine dipstick). Such a test could detect either mycobacterial products (as with sputum smear) or host response elements (e.g., interferon-gamma). The sensitivity of the former may vary with patient infectivity or bacterial load, whereas the latter may not. As no such test has been developed to date, we assume that the sensitivity of a new test is independent of infectiousness, smear status or mortality risk.

The reference scenario for this analysis assumes that TB suspects in the respective countries receive the combination of tests (e.g., CXR) and clinical strategies (e.g., antibiotic trials) for TB diagnosis that is typical in each country, except that we assume no access to sputum smear microscopy, culture of *Mycobacterium tuberculosis* from clinical specimens or the hypothetical new test. We assume that the official WHO-estimated smear-negative TB case detection rates can proxy actual detection rates in this austere situation, which may correspond to regions with extremely poor laboratory access, or laboratories that lack sufficient reagents, equipment or staff. We then model the addition of the following diagnostic interventions to this reference standard. Our primary comparison is between scenarios (2) and (3):

- 1 a hypothetical new test with sensitivity ranging from 50% to 90%, specificity ranging from 90% to 100%, and price of \$1–\$20 per test;
- 2 sputum smear microscopy, with sensitivity of 86% for highly infectious TB only,¹³ specificity of 97%,³ 15% loss to follow-up,^{6,14} and price of \$2.41 per test;¹⁵
- 3 sputum smear plus new test; and
- 4 sputum smear plus TB culture, with sensitivity 73% for less infectious TB,¹⁶ no added diagnostic benefit for smear for highly infectious TB, 99% specificity,¹⁷ diagnostic delay of 8 weeks (time to negative result using Löwenstein-Jensen medium); 25% loss to follow-up (J Golub, unpublished data from Rio de Janeiro, Brazil), and a price of \$10.53 per test.¹⁵

Patients diagnosed with TB are assumed to be treated according to the local standard. Our analysis time frame was 1 year from presentation; we assume

that all incremental costs of TB treatment and all TB-related deaths occur within this year. At the end of this year, survivors are classified according to active TB status; those with active TB remain infectious for 1 more year.¹⁸

Model outcomes

The primary outcomes are the expected costs, TB infections prevented, and disability-adjusted life years (DALYs) that accrue in the target population. Calculated costs and effects are used to derive incremental cost-effectiveness ratios (ICERs), expressed as US dollars per DALY averted. Secondary outcomes include the incremental cost, incremental DALYs averted and incremental cost per secondary TB infection averted.

In the absence of reliable data on the cost to society (e.g., hospitalization and lost work) of untreated vs. treated TB, we adopted the perspective of a Ministry of Health's hypothetical 'TB Division,' consisting of the National TB Program (NTP) plus that portion of laboratory services dedicated to TB. We thus include costs of TB diagnosis and drug treatment, but not physician visits or hospitalizations. All costs in other currencies were converted to US dollars with the historical exchange rate and then inflated to 2006 US dollars using the medical care component of the United States Consumer Price Index.¹⁹ Future DALYs and secondary infections are discounted at 3% per year, with sensitivity analysis for 0% and 7% discounting. Analyses were performed using TreeAge Pro 2006 (TreeAge Software Inc, Williamstown, MA, USA).

Model parameters and sensitivity analysis

Estimated parameter values are given in Tables 1 and 2. Where possible, we adopted WHO field estimates of TB detection rates, cure rates and other parameters (e.g., TB transmission parameters). When WHO estimates were not available, literature estimates were obtained from studies performed in the countries of interest. The base-case scenario assumes a hypothetical new test with 70% sensitivity, 95% specificity, and a cost of \$20 per test.

One-way sensitivity analysis was performed on all variables with sensitivity ranges listed and three-way sensitivity analysis performed on the sensitivity, specificity and price of the new test, using the ICER for the primary study comparison as the outcome. When data from the literature were not available to suggest a high and low range, we took these values to be respectively 125% and 75% of the most likely value. Parameters with higher uncertainty were varied over a wider range.

Ethical approval was not required for this study.

RESULTS

Cost-effectiveness of alternative diagnostic scenarios

In all three countries, a new test required a sensitivity of 58–60% to avert as many DALYs as sputum smear in regions that lack existing microscopy services (Figure 1, diamonds vs. circles). As an initial diagnostic

Table 1 Global parameter estimates for model of tuberculosis diagnosis

Parameter	Base value	Sensitivity range	Reference
TB dynamics			
Probability of death for untreated TB			
Highly infectious,* HIV-positive, no ART access	0.83	0.5–0.95	5
Highly infectious,* HIV-positive, with ART access	0.76	0.5–0.95	20 [†]
Highly infectious,* HIV-negative	0.70	0.5–0.95	5
Less infectious, [‡] HIV-positive, no ART access	0.74	0.5–0.95	5
Less infectious, [‡] HIV-positive, with ART access	0.45	0.2–0.74	20 [†]
Less infectious, [‡] HIV-negative	0.2	0.15–0.25	5
Secondary TB infections per year, highly infectious	10	8–12	18
Relative infectiousness of less infectious TB	0.22	0.16–0.28	21
Fraction of new TB cases that are highly infectious			
HIV-positive	0.41 [§]	0.3–0.7	5
HIV-negative	0.53 [§]	0.3–0.7	5
Characteristics of TB diagnosis			
Sensitivity for highly infectious TB			
Sputum smear microscopy	0.86 [§]	0.64–1.0	13
New test	0.70	0.50–0.90	
Sensitivity for less infectious TB			
Sputum smear microscopy	0		
New test	0.70	0.50–0.90	
TB culture	0.73	0.55–0.91	16
Specificity for active TB			
Existing diagnostic standard	0.94	0.75–1.0	3
Sputum smear microscopy	0.97	0.9–1.0	3
New test	0.95	0.9–1.0	
TB culture	0.99	0.95–1.0	16,17
Time to TB diagnosis			
Existing diagnostic standard/sputum smear	1 week	0–4 weeks	22,23
New test	0 weeks	0–7 days	
TB culture	8 weeks	1–4 months	16
Loss to follow-up			
Sputum smear microscopy	0.15	0.11–0.19	6,14
TB culture	0.25	0.19–0.31	Unpublished
Cost and effectiveness estimates, US\$			
Unit cost			
Sputum smear	2.41	\$1–\$5	15
New test	20.00	\$1–\$40	
TB culture	10.53	\$7–\$15	15
DALY weights			
HIV-positive, no ART access	0.505	0.379–0.631	24 [¶]
HIV-positive, with ART access	0.236	0.177–0.295	24 [#]
HIV-negative, undergoing TB treatment	0.132	0.099–0.165	Assumption
HIV-negative, active TB	0.264	0.198–0.330	24
Life expectancy if TB is absent or cured, years			
HIV-positive, no ART access	1.83	1–5	25 ^{**}
HIV-positive, with ART access	7.30	1.8–13	25 ^{**}
HIV-negative	39	29–49	25 ^{††}
Discount rate	3%	0.5–7%	Assumption

* Would be smear-positive if three separate-day specimens were submitted to an ideal laboratory; result assumed to be independent of the existing diagnostic standard in such cases.

[†] Comparing TB CFRs in Brazil before and after the antiretroviral era, the CFR for HIV-positive patients after ART lies at 46.7% of the distance between the CFRs for HIV-negative patients and those for HIV-positive patients before ART.

[‡] Would be smear-negative if three separate-day specimens were submitted to an ideal laboratory; result assumed to be independent of the existing diagnostic standard in such cases.

[§] Thus, the overall sensitivity of smear is $0.41 \times 0.86 = 0.35$ in HIV-positives and $0.53 \times 0.86 = 0.45$ in HIV-negatives.⁵

[¶] Assumes that HIV-positive patients suspected of TB have similar DALYs to those with AIDS.

[#] Assumes a DALY weight of 0.136 (HIV-positive, no AIDS), plus 0.1 for the burden of ART.

^{**} Assumes that the average HIV-positive TB suspect has life expectancy equivalent to an individual who is newly diagnosed with Stage IV disease. In the absence of ART, the upper bound for sensitivity analysis is set at the median life expectancy in South Africa for patients with a CD4 count of 350.²⁶ In the presence of ART, the upper bound is set at the median life expectancy from seroconversion in the Multicenter AIDS Cohort Study in 1995–97.²⁷

^{††} Median life expectancy for a black South African aged 36 years, which is the median age at adult TB diagnosis in South Africa.¹

TB = tuberculosis; HIV = human immunodeficiency virus; ART = antiretroviral therapy; DALY = disability-adjusted life year; CFR = case-fatality rate; AIDS = acquired immune-deficiency syndrome.

Table 2 Country-specific parameter estimates for model of tuberculosis diagnosis

Parameter	Base value (range for sensitivity analyses)			Reference
	South Africa	Brazil	Kenya	
Prevalence of active TB in suspects	0.28 (0.21–0.35)	0.11 (0.08–0.14)	0.28 (0.21–0.35)	3*
Mortality rate on TB therapy				
HIV-positive	0.091 (0.068–0.114)	0.078 (0.058–0.098)	0.062 (0.046–0.078)	1
HIV-negative	0.065 (0.049–0.081)	0.056 (0.042–0.070)	0.046 (0.035–0.058)	1
Sensitivity of existing standard for diagnosing TB [†]	0.67 (0.50–0.83)	0.68 (0.51–0.86)	0.52 (0.39–0.65)	1
HIV prevalence (2005 estimate)				
All adults	0.19 (0.17–0.21)	0.005 (0.003–0.016)	0.061 (0.052–0.070)	28
Adult TB patients	0.58 (0.49–0.65)	0.14 (0.08–0.22)	0.29 (0.21–0.34)	1
Proportion of HIV patients with access to ART	0.21 (0.16–0.26)	0.83 (0.78–0.88)	0.20 (0.15–0.25)	28
Proportion of registered TB patients remaining infectious after one year	0.11 (0.08–0.14)	0.045 (0.033–0.057)	0.075 (0.055–0.095)	1,18 [‡]
Cost of treating one TB patient, US\$ [§]	\$324 (\$243–\$405)	\$516 (\$387–\$645)	\$273 (\$205–\$341)	1

* Results reflect a survey of TB laboratory facilities and thus likely overestimate TB prevalence in primary health care settings. South Africa and Kenya are modeled as representative of Africa; Brazil is modeled as representative of the lowest prevalence region studied (Western Asia).

[†] In the absence of sputum smear microscopy, TB culture, or a hypothetical new test.

[‡] Modeled as 50%¹⁸ of the combined failure, default, transfer out, and not evaluated rates.¹

[§] Cost to the National Tuberculosis Program in 2006 US dollars.

TB = tuberculosis; HIV = human immunodeficiency virus; ART = antiretroviral treatment.

strategy, sputum smear (\$38–\$131 per DALY averted) was more cost-effective than a new test with 70% sensitivity, 95% specificity and price of \$20 (\$84–\$275 per DALY averted) in all three countries (Table 3).

However, adding the new test to sputum smear microscopy was estimated to increase the yield of DALYs averted by sputum smear alone from 1.46 to 1.49 fold (e.g., from 215 to 321 in South Africa), and of

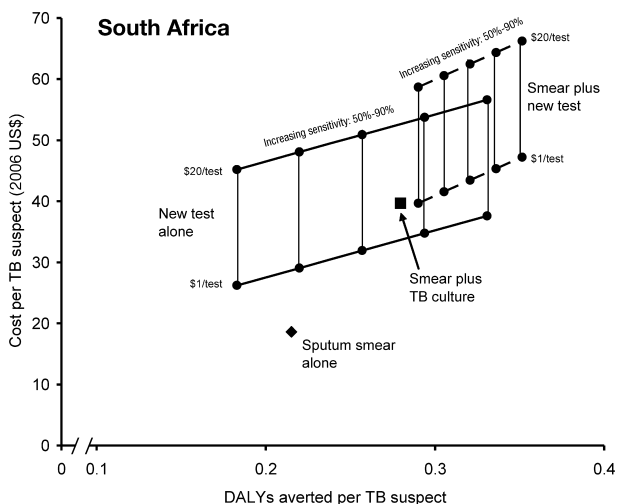


Figure 1 Cost-effectiveness of diagnostic interventions for TB in South Africa, Brazil and Kenya. The vertical axis shows costs per TB suspect relative to a baseline of no diagnosis or treatment. The horizontal axis shows DALYs averted relative to the reference scenario (no sputum smear). Options to the upper left in the diagram cost more and avert fewer DALYs than options in the lower right. Diagonal lines denote increasing sensitivity of a hypothetical new test alone (solid = new test alone; dotted = new test plus sputum smear) from 50% to 90%, while vertical lines denote increasing the unit price from \$1 to \$20. See the text and Table 1 for the estimated attributes of each test. DALY = disability-adjusted life years; TB = tuberculosis.

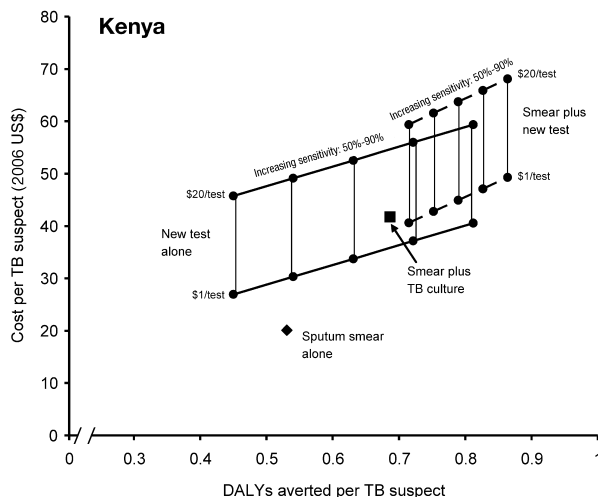
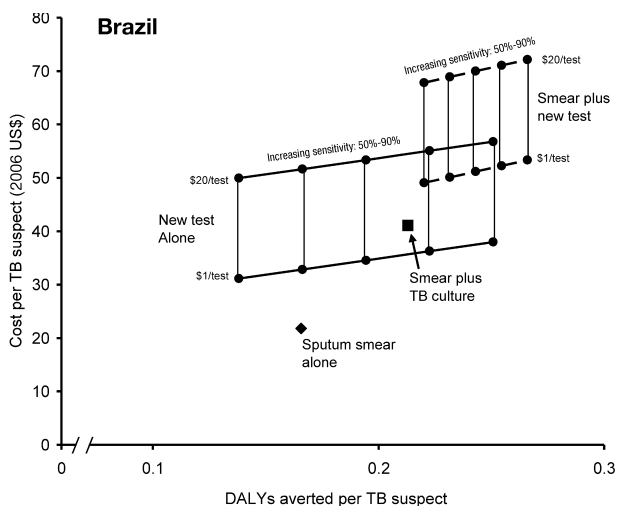


Table 3 Incremental cost-effectiveness of diagnostic tests for tuberculosis

Country and diagnostic scenario*	Relative to reference standard (no microscopy)				Relative to smear alone			
	Cost per 1000 TB suspects US\$	TB diagnoses	DALYs averted	Secondary infections averted	Cost per DALY averted US\$	Cost per infection averted US\$	Cost per DALY averted US\$	Cost per infection averted US\$
South Africa								
Sputum smear alone	18596	32	215	245	86	76	0 (reference)	0 (reference)
New test alone	50899	65	257	344	198	148		
Smear + TB culture	39648	59	280	331			327	245
Smear + new test	62441	75	321	418			415	254
Brazil								
Sputum smear alone	21768	13	166	130	131	168	0 (reference)	0 (reference)
New test alone	53552	24	194	179	275	298		
Smear + TB culture	41045	22	213	174			407	435
Smear + new test	70185	28	243	218			625	547
Kenya								
Sputum smear alone	20075	49	531	433	38	46	0 (reference)	0 (reference)
New test alone	52731	91	631	597	84	88		
Smear + TB culture	41738	86	687	584			139	144
Smear + new test	63911	109	790	727			170	149

* See text and Table 1 for the attributes of each test used to estimate cost-effectiveness. The new test is assumed to have sensitivity of 90%, specificity of 95%, and price of \$1/test for this analysis. TB = tuberculosis; DALY = disability-adjusted life year.

secondary infections averted from 1.67 to 1.71 fold (e.g., from 433 to 727 in Kenya), at an incremental cost per DALY averted of \$170 (Kenya) to \$625 (Brazil). In all but the most extreme scenarios, adding the new test to sputum smear was more costly, but also more effective, than adding TB culture (Table 3, Figure 1).

Sensitivity analysis

In all three countries, one-way sensitivity analysis showed that cost-effectiveness depended most strongly on the sensitivity, specificity and cost of the new test,

the sensitivity of the reference standard (including smear), the discount rate and TB prevalence (Figure 2). In three-way sensitivity analysis (Figure 3), cost-effectiveness ranged from \$130 per DALY averted (90% sensitivity, 100% specificity, \$1 per test) to \$693 per DALY averted (50% sensitivity, 90% specificity, \$20 per test). Corresponding ranges in Brazil and Kenya were respectively \$103–\$1296 and \$44–\$148 per DALY averted. At a price of \$1 per test, one can maximize cost-effectiveness more rapidly with an increment of one point of specificity than with one point

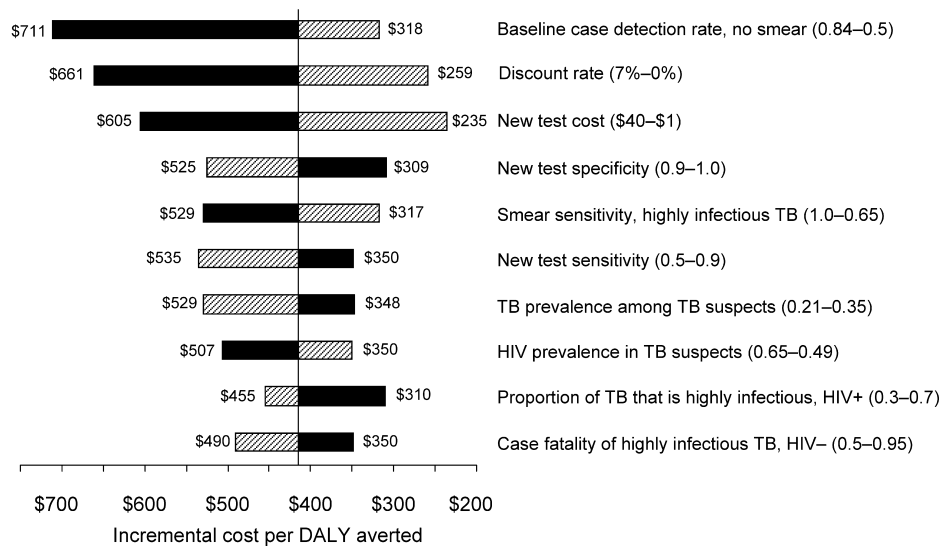


Figure 2 One-way sensitivity analysis, South Africa. All model parameters were varied over the ranges shown in Tables 1 and 2. The ten variables are shown for which such variation resulted in the greatest change in estimated incremental cost per DALY averted, comparing sputum smear plus a hypothetical new test against sputum smear alone. Black bars denote the high value of the sensitivity range, hatched bars the low value. TB = tuberculosis; HIV = human immunodeficiency virus; DALY = disability-adjusted life year.

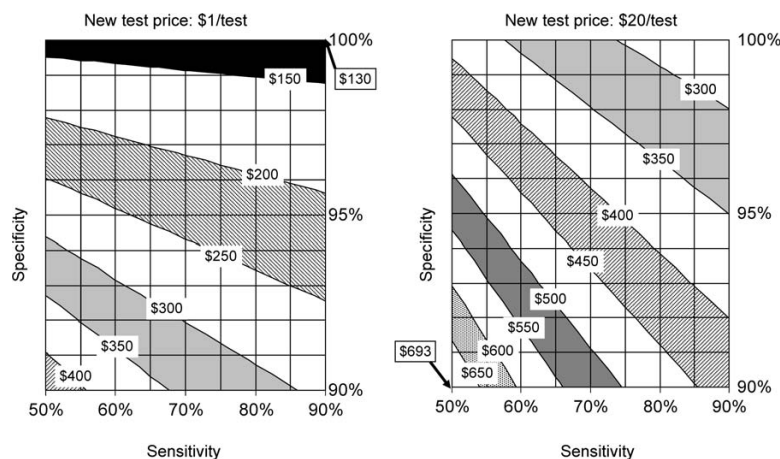


Figure 3 Three-way sensitivity analysis by sensitivity, specificity, and price in South Africa. Contour lines show iso-incremental cost-effectiveness ratio (ICER) lines in US dollars (2006) per disability-adjusted life year averted. All scenarios compare sputum smear plus a hypothetical point-of-care test with minimal infrastructure requirements or diagnostic delay against sputum smear alone.

of sensitivity. Gains in sensitivity are relatively more advantageous for a more expensive test (e.g., \$20).

Increasing sensitivity maximized the number of DALYs averted by a new test, whereas increasing specificity minimized the cost. In South Africa, increasing sensitivity from 50% to 100% increased the incremental DALYs averted from 75 to 152 and the cost per TB suspect from \$40 to \$50. By contrast, a corresponding increase in specificity reduced the cost per TB suspect from \$140 to \$33 while increasing the DALYs averted from 90 to 107.

DISCUSSION

This analysis estimates the potential cost-effectiveness of a hypothetical new point-of-care diagnostic test for TB, thus addressing the following questions:

- 1 What is the relative importance of sensitivity, specificity and price in determining the cost-effectiveness of a new TB diagnostic test?
- 2 What other considerations are important to cost-effectiveness?
- 3 Are new TB diagnostic tests potentially cost-effective?

What is the relative importance of sensitivity, specificity and price for cost-effectiveness?

The effectiveness of a new TB diagnostic depends primarily on its sensitivity, but its cost-effectiveness depends strongly on specificity and also price (Figure 2). It is therefore important to weigh the public-health aim of maximum DALYs averted (i.e., maximum sensitivity) against the economic consideration of minimum cost per DALY averted (i.e., balancing sensitivity, specificity and price). As the price of a new test drops, its cost-effectiveness becomes more dependent

on specificity, relative to sensitivity (Figure 3). Furthermore, it is particularly important to develop new tests with high sensitivity for smear-negative TB, as these are the cases most often missed in areas that rely heavily on microscopy.²⁹ For example, in South Africa, increasing new test sensitivity from 50% to 90% among the less infectious (i.e., smear-negative) vs. highly infectious (i.e., 'missed' smear-positive) TB reduced the estimated cost per DALY averted by \$137 vs. \$40, and increased the expected number of TB diagnoses made by 19 vs. 6.

What other considerations are important to cost-effectiveness?

Our sensitivity analyses suggest that the setting in which new TB diagnostics are deployed may be as important to cost-effectiveness as the test characteristics themselves. The higher cost-effectiveness ratio with lower TB prevalence suggests that new tests may be less cost-effective in primary care or out-patient settings (vs. referral microscopy centers), although their impact may be greatest in such locations. By contrast, the superior cost-effectiveness of new tests in regions without sputum smear, countries (i.e., Kenya) with weak diagnostic systems, and areas where the baseline TB case detection rate is low (Figure 2), emphasize that new TB diagnostics will be most cost-effective if implemented where existing infrastructure is poor.

Can new TB diagnostic tests be cost-effective?

In areas with poor existing infrastructure, new diagnostic tests are potentially more effective, but also more costly, than sputum smear. For example, in Kenya, implementing sputum smear in such situations would result in 49 new TB diagnoses and 531 DALYs averted per 1000 TB suspects, at a cost of \$38 per DALY averted (Table 3). A new test (70% sensitivity, 95%

specificity, \$20 per test) would cost \$84 per DALY averted, making sputum smear the preferred initial alternative. However, adding the new test to sputum smear would make 60 additional TB diagnoses and avert 259 additional DALYs, at an incremental cost of \$170 per DALY averted. Thus, while sputum smear is more cost-effective than a hypothetical new test with excellent accuracy and low price, new tests are potentially more effective than smear and could still be deployed cost-effectively to regions without the infrastructural capacity for sputum smear.

There is no universally accepted threshold for considering an intervention 'cost-effective'. The Commission for Macroeconomics and Health has proposed that interventions whose cost per DALY averted is less than the gross domestic product (GDP) per capita be defined as 'very cost-effective'.³⁰ Estimated GDP per capita is US\$13 000 for South Africa, \$8600 for Brazil and \$1200 for Kenya.³¹ Thus, by this criterion, even a 'lackluster' TB diagnostic test with 50% sensitivity, 90% specificity and cost of \$20 per test would have attractive cost-effectiveness ratios—at less than 15% of GDP per capita—of \$693 per DALY averted in South Africa (Figure 3), \$1296 in Brazil and \$148 in Kenya. The latter estimate for Kenya is lower than the world's lowest per capita gross domestic product (\$300 in the Democratic Republic of Congo).³¹ By comparison, the estimated cost-effectiveness of a new test with 70% sensitivity, 95% specificity and cost of \$20 per test (Table 3) is comparable to that of treating multidrug-resistant (MDR) TB in Peru (US\$ 248, converted to 2006 dollars).³²

Limitations

This analysis has a number of limitations. First, although the perspective of a 'national TB division' may be useful to policy makers, such divisions may not exist in reality, and our inability to incorporate the societal perspective³³ limits our ability to compare results with studies of other health-related interventions. The additional benefits to society (e.g., averted hospitalizations and clinic visits) of a new TB diagnostic are likely to exceed the additional costs (e.g., patient time to submit the clinical specimen); thus, the present analysis likely underestimates the cost-effectiveness of a new diagnostic from a societal perspective. Second, the present analysis assumes that a new test would be deployed and used uniformly, but new diagnostic tests may be used first in settings where diagnostic capacity is already strongest and the clinical presentation of TB patients missed by the existing diagnostic standard might not prompt use of the new test, even if available. To the extent that these events occur, the present analysis would overestimate the cost-effectiveness of the new test. Third, we do not include costs for the infrastructure necessary to deploy diagnostic tests. The present model may thus overestimate cost-effectiveness, although the infrastructure requirement for a point-

of-care test may be less than for more technically intensive interventions (e.g., smear, culture). Infrastructure costs are particularly relevant for the least developed countries, which were not considered here. Finally, this static model does not account for cumulative changes in TB incidence over time; a 1-year time horizon may thus underestimate long-term cost-effectiveness ratios.⁴

CONCLUSIONS

This model suggests that novel diagnostic tests have the potential to be cost-effective tools in the fight against TB. Cost-effectiveness depends most strongly on the specificity and price of the new test, as well as the discount rate, and is maximized in areas where existing diagnostic infrastructure is weakest. In conjunction with efforts to improve treatment success, further progress against TB depends on redoubling efforts to make effective TB diagnosis universally available. To produce a cost-effective tool for public health, the quest for new TB diagnostics should focus on high specificity, affordability and sensitivity for cases missed by existing diagnostic standards.

Acknowledgements

D Durack (Becton Dickinson Corporation) provided helpful insights into the model and editing for clarity. K Thompson, C Jefferson, B Pearson and S Siddiqi (BD Corporation) also played a crucial role in critiquing the model's assumptions and implications. The authors are also deeply grateful to the anonymous reviewers of the manuscript, whose comments were exceptionally well-considered. Financial support was obtained from the United States National Institutes of Health, Medical Scientist Training Program (grant 5 T32 GMO7309) and from a research grant by BD Corporation. The funding agencies had no role in the gathering or preparation of data, writing of the initial manuscript draft, or the decision to publish. An earlier draft of this manuscript has been published as part of the first author's PhD dissertation.

References

- 1 World Health Organization. Global tuberculosis control: surveillance, planning, financing. Geneva, Switzerland: WHO, 2007.
- 2 Currie C S, Williams B G, Cheng R C, Dye C. Tuberculosis epidemics driven by HIV: is prevention better than cure? *AIDS* 2003; 17: 2501–2508.
- 3 Keeler E, Perkins M D, Small P, et al. Reducing the global burden of tuberculosis: the contribution of improved diagnostics. *Nature* 2006; 444 (Suppl 1): 49–57.
- 4 Dowdy D W, Chaisson R E, Moulton L H, Dorman S E. The potential impact of enhanced diagnostic techniques for tuberculosis driven by HIV: a mathematical model. *AIDS* 2006; 20: 751–762.
- 5 Corbett E L, Watt C J, Walker N, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; 163: 1009–1021.
- 6 Squire S B, Belaye A K, Kashoti A, et al. 'Lost' smear-positive pulmonary tuberculosis cases: where are they and why did we lose them? *Int J Tuberc Lung Dis* 2005; 9: 25–31.
- 7 Hawken M P, Muhindi D W, Chakaya J M, Bhatt S M, Ng'ang'a L W, Porter J D. Under-diagnosis of smear-positive pulmonary tuberculosis in Nairobi, Kenya. *Int J Tuberc Lung Dis* 2001; 5: 360–363.

- 8 O'Brien R J, Talbot E A. The utility of an antibiotic trial for diagnosis of AFB-negative tuberculosis. *Int J Tuberc Lung Dis* 2003; 7: 198.
- 9 Harries A D, Banda H T, Boeree M J, et al. Management of pulmonary tuberculosis suspects with negative sputum smears and normal or minimally abnormal chest radiographs in resource-poor settings. *Int J Tuberc Lung Dis* 1998; 2: 999–1004.
- 10 Githui W A. Laboratory methods for diagnosis and detection of drug-resistant *Mycobacterium tuberculosis* complex with reference to developing countries: a review. *East Afr Med J* 2002; 79: 242–248.
- 11 Hudson C P, Wood R, Maartens G. Diagnosing HIV-associated tuberculosis: reducing costs and diagnostic delay. *Int J Tuberc Lung Dis* 2000; 4: 240–245.
- 12 Moore D A, Evans C A, Gilman R H, et al. Microscopic-observation drug-susceptibility assay for the diagnosis of TB. *N Engl J Med* 2006; 355: 1539–1550.
- 13 Martinez A, Balandrano S, Parissi A, et al. Evaluation of new external quality assessment guidelines involving random blinded rechecking of acid-fast bacilli smears in a pilot project setting in Mexico. *Int J Tuberc Lung Dis* 2005; 9: 301–305.
- 14 Creek T L, Lockman S, Kenyon T A, et al. Completeness and timeliness of treatment initiation after laboratory diagnosis of tuberculosis in Gaborone, Botswana. *Int J Tuberc Lung Dis* 2000; 4: 956–961.
- 15 Albert H. Economic analysis of the diagnosis of smear-negative pulmonary tuberculosis in South Africa: incorporation of a new rapid test, *FASTPlaqueTB*, into the diagnostic algorithm. *Int J Tuberc Lung Dis* 2004; 8: 240–247.
- 16 Cruciani M, Scarparo C, Malena M, Bosco O, Serpelloni G, Mengoli C. Meta-analysis of BACTEC MGIT 960 and BACTEC 460 TB, with or without solid media, for detection of mycobacteria. *J Clin Microbiol* 2004; 42: 2321–2325.
- 17 Matos E D, Santana M A, de Santana M C, et al. Nontuberculosis mycobacteria at a multiresistant tuberculosis reference center in Bahia: clinical epidemiological aspects. *Braz J Infect Dis* 2004; 8: 296–304.
- 18 Styblo K. Epidemiology of tuberculosis. The Hague, The Netherlands: Royal Netherlands Tuberculosis Association (KNCV), 1991.
- 19 United States Bureau of Labor Statistics. Consumer price index: all urban consumers. Washington DC, USA: BLS. <http://data.bls.gov/cgi-bin/surveymost?cu=accessed June 2008>.
- 20 Oliveira H B, Marin-Leon L, Cardoso J C. [Differences in mortality profile of tuberculosis patients related to tuberculosis-AIDS co-morbidity]. *Rev Saude Publica* 2004; 38: 503–510. [Spanish]
- 21 Behr M A, Warren S A, Salamon H, et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet* 1999; 353: 444–449.
- 22 Pronyk R M, Makhubele M B, Hargreaves J R, Tollman S M, Hausler H P. Assessing health seeking behaviour among tuberculosis patients in rural South Africa. *Int J Tuberc Lung Dis* 2001; 5: 619–627.
- 23 Salaniponi F M, Harries A D, Banda H T, et al. Care-seeking behaviour and diagnostic processes in patients with smear-positive pulmonary tuberculosis in Malawi. *Int J Tuberc Lung Dis* 2000; 4: 327–332.
- 24 Murray C L, Lopez A D. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Boston, MA, USA: Harvard School of Public Health, 1996.
- 25 Actuarial Society of South Africa. ASSA2003 AIDS and demographic model. Cape Town, South Africa: ASSA. <http://www.assa.org.za/aids/content.asp?id=1000000449> Accessed March 2007.
- 26 Williams B G, Korenromp E L, Gouws E, Schmid G P, Avert B, Dye C. HIV infection, antiretroviral therapy and CD4+ cell count distributions in African populations. *J Infect Dis* 2006; 194: 1450–1458.
- 27 Detels R, Munoz A, McFarlane G, et al. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. *JAMA* 1998; 280: 1497–1503.
- 28 Joint United Nations Programme on HIV/AIDS (UNAIDS). 2006 Report on the global AIDS epidemic. Geneva, Switzerland: UNAIDS, 2006.
- 29 Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. *Lancet* 2007; 369: 2042–2049.
- 30 Commission on Macroeconomics and Health. Macroeconomics and health: investing in health for economic development. Geneva, Switzerland: WHO, 2001.
- 31 Central Intelligence Agency. The world factbook. Washington DC, USA: CIA, 2007.
- 32 Suarez P G, 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: 1980–1989.
- 33 Russell L B, Gold M R, Siegel J E, Daniels N, Weinstein M C. The role of cost-effectiveness analysis in health and medicine. Panel on cost-effectiveness in health and medicine. *JAMA* 1996; 276: 1172–1177.

R É S U M É

CONTEXTE : Le rapport coût-efficacité potentiel des tests améliorés de diagnostic de la tuberculose (TB) est inconnu dans les contextes à faibles ressources.

OBJECTIF : Estimer l'augmentation du rapport coût-efficacité d'un test hypothétique nouveau de diagnostic sur les lieux de soins en Afrique du Sud, au Brésil et au Kenya.

SCHEMA : Modèle d'analyse décisionnelle additionnant à une infrastructure de base existante sans frottis quatre interventions de diagnostic (examen microscopique des frottis de crachats, nouveau test, frottis plus nouveau test, frottis plus culture TB).

RÉSULTATS : On estime que l'addition d'un frottis de crachats a un meilleur rapport coût-efficacité (coût supplémentaire par année de survie perdue ajustée pour l'invalidité [DALY] de 86 \$ en Afrique du Sud, 131 \$ au Brésil, 38 \$ au Kenya) qu'un nouveau test diagnostic TB

de sensibilité à 70%, de spécificité à 95% et d'un prix de 20 \$ par test (DALY de 198 \$ en Afrique du Sud, 275 \$ au Brésil et 84 \$ au Kenya). Toutefois, par comparaison avec le frottis de crachats, le frottis plus le nouveau test a permis d'éviter 46% à 49% de DALY supplémentaire pour 1000 suspects de TB (321 vs. 315 en Afrique du Sud, 243 vs. 166 au Brésil, 790 vs. 531 au Kenya) avec un coût supplémentaire de 170\$ au Kenya à 625 \$ au Brésil par DALY évité. Le rapport coût-efficacité dépend le plus de la spécificité, du prix du nouveau test, du taux de base de détection des cas de TB ainsi que du taux d'escompte.

CONCLUSION : Des tests novateurs de diagnostic de la TB ont potentiellement un rapport coût-efficacité élevé. Le rapport coût-efficacité est le plus élevé par des tests de haute spécificité et de faible coût utilisés dans des régions à médiocre infrastructure.

RESUMEN

MARCO DE REFERENCIA : Se desconoce el posible rendimiento del perfeccionamiento de las pruebas diagnósticas de la tuberculosis (TB) en medios con recursos limitados.

OBJETIVO : Calcular la relación entre costo y efectividad de una nueva prueba hipotética de diagnóstico inmediato (*point-of-care test*) en Sudáfrica, en Brasil y Kenya.

MÉTODO : Se aplicó un modelo de análisis de decisiones, agregando cuatro intervenciones diagnósticas (baciloscopia del esputo, nueva prueba, baciloscopia y nueva prueba y baciloscopia más cultivo) a la infraestructura inicial existente sin baciloscopia.

RESULTADOS : Se calculó que la baciloscopia del esputo como estrategia diagnóstica inicial fue más rentable (el incremento del costo por años de vida ajustados en función de la discapacidad [DALY] fue de 86 dólares en Sudáfrica, 131 dólares en Brasil, 38 dólares en Kenya)

que una nueva prueba diagnóstica con una sensibilidad del 70 % y una especificidad del 95 % y un costo por prueba de 20 dólares (198 dólares por DALY evitado en Sudáfrica, 275 en Brasil, y 84 en Kenya). Sin embargo, comparada con la baciloscopia, la estrategia de baciloscopia más la nueva prueba evitó de 46% a 49% más DALY por cada 1000 presuntos casos de TB (321 contra 215 en Sudáfrica ; 243 contra 166 en Brasil y 790 contra 531 en Kenya), con un incremento del costo desde 170 dólares en Kenya hasta 625 en Brasil por cada DALY evitado. El rendimiento fue más sensible a la especificidad y al costo de la nueva prueba, a la tasa inicial de detección de casos y a la tasa de actualización o de descuento.

CONCLUSIÓN : Las nuevas pruebas diagnósticas de la TB pueden ser altamente rentables. La relación entre el costo y la efectividad se maximiza con pruebas de alta especificidad y bajo costo introducidas en regiones con una infraestructura precaria.