ERJ Express. Published on August 4, 2011 as doi: 10.1183/09031936.00065311

The Impact and Cost-effectiveness of Strategies to Detect Drug Resistant Tuberculosis

Olivia Oxlade[1], PhD, Dennis Falzon[2], MD, MSc, and Dick Menzies[1], MD, MSc

1- Respiratory Epidemiology & Clinical Research Unit, Montreal Chest Institute, McGill University, Montreal, Canada
2- Stop TB Department, WHO, Geneva, Switzerland

D. Falzon is a staff member of the World Health Organization (WHO). The author alone is responsible for the views expressed in this publication and these views do not necessarily represent the decisions or policies of WHO.

Keywords: cost-effectiveness, drug resistance, drug susceptibility testing, modelling, tuberculosis

Corresponding Author Address:

Dr Dick Menzies
Montreal Chest Institute
Room K1.24
3650 St. Urbain St.
Montreal, PQ, CANADA, H2X 2P4
Tel: 1-514-934-1934 ext 32128 or 32129
Fax: 1-514-843-2083
Email: dick.menzies@mcgill.ca

ABSTRACT

BACKGROUND: Drug-resistant tuberculosis is a serious emerging problem in many low resource countries. TB control programs are uncertain which drug susceptibility tests (DST) to use and when to test patients. We predicted the potential cost-effectiveness of different DST strategies, in settings with varying prevalence of drug resistance.

METHODS: Using decision analysis, we assessed the cost-effectiveness of conventional and rapid DST for already diagnosed smear positive TB cases. Five different time points were considered for administering DST. Different initial drug resistance and HIV scenarios were also considered.

RESULTS: All DST scenarios in the wide range of settings considered were found to be cost-effective. The strategy of performing a rapid DST that detects any form of isoniazid (INH) and rifampicin (RIF) resistance for all patients before the initiation of treatment was predicted to be the most cost-effective strategy. In a setting with moderate drug resistance, the cost per Disability Adjusted Life Year (DALY) gained was as low as $744.

CONCLUSIONS: Our findings support the rollout of rapid drug susceptibility testing at the moment of diagnosis to detect any form of INH and RIF resistance in all countries with moderate or greater burdens of drug-resistant TB.

BACKGROUND

Drug resistant tuberculosis (TB) is emerging throughout the world, adding enormous complexity and challenges to TB control (1). Of particular concern is the emergence of multi drug resistant TB (MDR-TB), defined as resistance to at least rifampin and isoniazid (1). MDR-TB is now estimated to account for 3% of all incident new TB cases globally with 440,000 MDR-TB cases (95% CI 390,000-510,000) emerging annually(1). Other forms of drug resistant TB also occur (2), and are expected to increase the frequency of failure and relapse (3) as well as the risk of development (or amplification) of MDR-TB if treated with standard initial therapy (2HRZE/4HR) or re-treatment regimens (2SHRZE/HRZE/5HRE) (4;5).

One of the greatest challenges to adequate control drug resistant TB in many countries is the lack of adequate laboratory facilities to perform drug susceptibility testing (DST). Standard DST involve cultures on solid or liquid media and require significant resources for equipment, facilities and highly trained human resources (6). Results are available only after a delay of months. The past decade has seen the emergence of many new technologies for DST (7). Many TB control programs now plan to expand capacity for DST and treatment for drug resistant TB but are uncertain as to which DST strategy to pursue.

The primary objective of this study was to estimate the Disability Adjusted Life Years (DALYs) and costs per DALY gained with different types and timing of DST, in settings with varying prevalence of drug-resistant TB, and HIV. We also considered the impact and cost-effectiveness of these DST strategies to prevent new MDR cases and deaths.

METHODS:

Overview of Model:

Hypothetical cohorts of 1000 newly diagnosed smear positive TB cases were modelled using a population based deterministic decision tree model to receive initial treatment. Standard treatment definitions for initial and retreatment were used (8). Those who failed or relapsed received retreatment. Those who failed or relapsed after retreatment were given no further treatment. In each scenario we assumed that once DST results were available, treatment was guided by, and appropriate for, each DST result. Only when DST was not done, or the acquisition of drug resistance occurred after the DST has been performed, was it considered that patients received inappropriate regimens for the form of drug-resistant TB they had. Figure S1 in the supplemental appendix provides a simplified overview of how DST and subsequent treatment were modeled. Two different epidemiologic scenarios were considered, one with moderate and the other with high initial drug resistance. Two different HIV TB co-infection rates were considered (0% and 50%) in the moderate drug resistance scenario. Decision analysis models were developed using TreeAge software (TreeAge Professional, 2009).

Types of DST:

Rather than considering specific DST methods we modelled two broad groups based on the usual time needed to obtain DST results under field conditions. 'Rapid' means a DST providing results of rifampicin and/or isoniazid resistance within 2 weeks, currently possible using Line Probe Assay or Xpert MTB/RIF (which usually give results in a day or two), or micro colony techniques. 'Slow' means a DST providing results after 3 months, as is typical with conventional methods using solid media.

We considered two types of 'rapid' tests: 1) DST that detected only RIF resistance (Rapid RIF DST) and 2) DST that detected only INH and/or RIF resistance (Rapid INH&RIF DST). Both tests would detect any form of RIF resistance, whether found alone (RIF-alone) or in combination with INH resistance (MDR), however the Rapid INH&RIF DST could also detect INH resistance without RIF resistance - termed non-MDR INH resistance. In the base case analysis all DST were assumed to have 100% sensitivity and specificity for RIF and/or INH resistance, regardless of HIV status. In all scenarios we assumed DST was conducted in patients who were already diagnosed with TB on the basis of positive sputum smear microscopy. All DST strategies considered are summarized in Table 1.

Initial Drug resistance:

Given that the DST would only detect RIF and/or INH resistance, drug resistance was simplified into: MDR (defined as any RIF resistance, including RIF-alone resistance) and "non-MDR INH resistance" (all INH resistance including poly drug resistance). To provide results relevant to specific countries, we used the estimated prevalence of initial drug resistance in two setings: a) South Africa – considered to have "moderate drug resistance" with non-MDR INH resistance of 5.8%, and MDR of 2.1%; and b) the Russian Federation considered "high drug resistance" with 20.1% non-MDR INH resistance and 15.2% MDR (2).

Treatment:

With the no DST strategy, all cases were assumed to receive standardized initial and retreatment, regardless of underlying drug resistance. In strategies where DST detected INH resistance, non-MDR INH resistant cases were assumed to receive an effective regimen that would provide treatment outcomes equivalent to current standard therapy for drug sensitive (DS) cases. In strategies where DST detected only RIF resistance, patients with non-MDR INH resistance would not be detected. Hence they would receive the same standardized initial treatment and retreatment regimens as DS cases, but with significantly worse outcomes (4;5;9). If RIF resistance was detected, patients would receive MDR treatment with outcomes as described in two systematic reviews (10;11). It was assumed that with rapid DST, the delay before initiating appropriate therapy would be so short as to have no clinical impact. However, patients with drug resistant isolates could die or acquire further drug resistance while waiting 3 months for results of slow DST. (For additional details of treatment regimens and outcomes – see Supplemental Appendix).

Timing of Tests

The impact on study outcomes were estimated for a Rapid DST performed: 1) in all patients - prior to initial treatment; or selectively for patients who were: 2) still smear positive after 2 months of treatment, 3) still smear positive after 3 months of treatment, 4) still smear positive after 5 months of treatment (failures), or 5) failures or relapses of initial treatment (ie re-treatment cases). These different testing strategies are included in Summary Table 1.

Model Outcomes

For each test and treat strategy the following treatment outcomes were predicted: cure, failure, relapse, death, acquired drug resistance, and DALYs. We also estimated total health system costs for each test and treat strategy, cost per MDR-TB case prevented, cost per TB related death averted, and cost per DALY gained. In this study, changes in DALYs were expressed as DALYs gained rather than DALYs averted. The occurrence of, and costs or savings related to, secondary MDR-TB cases resulting from transmission were not estimated.

HIV Infection

Model outcomes were compared with HIV prevalence of 0% and 50% in the setting of moderate initial drug resistance setting. We assumed that the accuracy of each DST, and efficacy of treatment regimens would be unchanged, but mortality would be double in HIV infected even if appropriately treated, and 100% if untreated, or inappropriately treated. We used treatment outcomes in HIV infected TB cases from settings where anti-retroviral therapy was used (12) (13).

Acquired Drug resistance:

Cases with undetected non-MDR INH resistance could acquire MDR during each course of inappropriate treatment (14). Rates of acquired drug resistance for INH resistant cases undergoing standard initial or retreatment were taken from recent systematic reviews (4;5;9) (Details in Tables S4 and S5 and accompanying text in the Supplemental Appendix).

Health System Costs and DALYs:

Direct costs included the costs for DST, drugs, and health care (15). Costs for the DST were estimated from published studies (16) and unpublished reports from FIND demonstration studies. "Slow DST" were assumed to cost 20$ per test, and "rapid DST" were assumed to cost 40$ per test. Drug costs were obtained from the Global Drug Facility (www.stoptb.org/gdf/). Health system costs associated with treatment and follow-up care (from (15)) are summarized in Table 2, (more detail is provided in the Supplemental

Appendix). Future DALYs were discounted at a rate of 3%. All costs are presented in US dollars.

Sensitivity Analyses:

We simultaneously varied the prevalence of non-MDR INH resistance and MDR to determine the impact on the cost-effectiveness of different DST strategies. Key epidemiologic parameters and test characteristics were also varied for the best strategy found in the base case analysis. For some key assumptions where there was the most uncertainty these sensitivity analyses were repeated for the top three ranking DST strategies. Test sensitivity and specificity were also varied in order to investigate the impact of inaccuracies in DST. Finally, a two way sensitivity analysis was conducted in order to consider how test inaccuracy affected cost-effectiveness at different prevalence of MDR-TB.

FINDINGS

In the setting with moderate drug resistance, as shown in Table 3, the strategy of performing a Rapid INH&RIF DST in all patients pre-treatment would result in the most DALYs gained, fewest deaths and MDR cases, with the lowest incremental cost per DALY gained ($744), death averted ($34,218), and MDR case averted ($74,972). The second best strategy in terms of cost per MDR case averted would be Rapid INH&RIF DST at 2 months. The Rapid RIF DST strategy will not avert any cases of acquired drug resistance and therefore ranks last in terms of cases of MDR averted, but ranks second in deaths averted and cost per death averted. Performing the Rapid INH&RIF DST at 5 months for failures and relapses i.e for all patients requiring retreatment, would result in the second lowest cost per DALY gained, albeit with substantially less DALYs gained.

In a high drug resistance setting, performance of the Rapid INH&RIF DST in all patients at the time of diagnosis is predicted to result in the greatest number of DALYs gained, with the lowest incremental cost per DALY gained ($499), death averted ($27,771) and MDR case averted ($120,553) (Table 4). Performing the Rapid INH&RIF DST at 2 months would be the second best strategy in terms of cost per MDR averted , while the Rapid RIF DST pre-treatment would be the second best strategy in terms of deaths averted, incremental cost per death averted, and incremental cost per DALY gained ($562).

In a moderate drug resistance setting with HIV co-infection prevalence of 50%, as shown in Table 5, the cost per death averted or per DALY gained would be substantially lower, than if co-infection prevalence was 0%. This reflects the substantial and rapid mortality of HIV co-infected persons with untreated MDR-TB. Any strategy that detects these cases earlier will avert a substantial number of deaths. The strategy of Rapid INH&RIF DST for all patients pre-treatment would result in the fewest deaths, the lowest incremental cost per death averted ($18,825) and per MDR case averted ($68,598), as well as the greatest number of DALYs gained with lowest incremental cost per DALY gained ($687). The strategy of Rapid INH&RIF DST performed in those who were smear positive after 2

months treatment would be the second best strategy in terms of costs per MDR case averted, while the Rapid RIF DST pretreatment would be second best in terms of deaths averted and DALYs gained as well as costs per death averted or per DALY gained (Table 5).

Sensitivity Analysis:

As seen in Figures 1a and 1b, when the prevalence of non-MDR-INH resistance and MDR were varied simultaneously, the use of Rapid INH&RIF DST pre-treatment remained the most cost effective strategy. However, in settings with very low prevalence of drug resistance, the strategy of Rapid INH&RIF DST for all retreatment cases was predicted to be more cost effective. The cost per DALY gained for each DST strategy at low prevalence of MDR and INH resistance is shown in Table 6.

All one-way sensitivity analyses were conducted in the setting of moderate drug resistance, where Rapid INH&RIF DST pre-treatment, Rapid INH&RIF DST at 2 months and Rapid INH&RIF DST for failures and relapses had the lowest cost per DALY gained. Therefore these sensitivity analyses considered these three strategies only. When prevalence of initial MDR, initial non-MDR INH resistance and HIV co-infection were varied widely, the Rapid INH&RIF pre-treatment remained the most cost effective strategy unless the prevalence of MDR and INH resistance were very low, consistent with other analyses conducted (Supplemental Appendix Figures S2-S4). As well, Rapid INH&RIF DST pre-treatment remained the most cost effective strategy when the effectiveness of the regimen for non-MDR-INH resistant cases was reduced, unless the efficacy was below mid-range, at which point the performance of Rapid INH&RIF DST only for failures and relapses became the most cost effective strategy (Figure 2).

When the cost of the rapid DST was varied, trends were similar for all strategies (Figure S5 in Supplemental Appendix). Cost per DALY gained remained below 1000$ when test costs were increased to 100$, although when the test cost increased above that level the cost per DALY gained increased substantially. Regardless of DST strategy, the actual test accounted for less than 10% of overall costs (Table S1 in Supplemental Appendix).

As seen in Table 7a, sub-optimal sensitivity of the Rapid INH&RIF DST did not affect findings substantially. However, poor test specificity (Table 7b) had a very substantial impact – for example the cost per DALY gained was $17,244 per DALY gained with 94% test specificity with low prevalence of MDR. However, as MDR prevalence increased the impact of poor specificity became much less. The impact of changes in specificity of the Rapid INH&RIF test on cost-effectiveness was compared for the strategy that tested all patients pre-treatment strategy versus the selective testing of failures and relapses. As seen in Table 8a, with worse specificity, the strategy that tests all patients pre-treatment was less cost-effective than the strategy that tested only failures and relapses (Table 8b) at low prevalence of drug resistance, although it became a better strategy at higher drug resistance prevalence.

INTERPRETATION

In this study all rapid DST strategies were found to be cost-effective when using conventional benchmarks (17). The strategy predicted to be the most cost-effective, and have the greatest impact on preventing MDR and deaths in all settings was to perform a rapid DST that detects INH and RIF resistance, in all patients, prior to starting treatment. Use of rapid DST in all patients in settings with moderate or higher prevalence of drug-resistant TB would be highly cost-effective; this finding is of interest for low resource countries considering large-scale implementation of DST techniques.

This study is timely as WHO has endorsed several methods for rapid DST (18-20) in the last three years based on published evidence of excellent accuracy (21-24), yet there are few published studies of their cost-effectiveness. Our finding that all rapid DST are cost-effective is consistent with results of a randomized trial of different types of DST in Peru (25). Our study differed from this one however by including amplification of drug resistance, and by evaluating the timing of giving DST in additional to type of test.

Tests that detect INH resistance, in the absence of RIF resistance, identify a group at high risk of amplification to MDR TB if they receive standard initial treatment or retreatment (4;5), particularly if HIV infected (26). We found that amplification of mono-INH resistance to MDR TB, would be most effectively prevented if all patients underwent rapid testing for INH and RIF resistance prior to starting treatment. A test that detects only RIF resistance could not provide this benefit, since non-MDR INH resistance is not detected, therefore these patients may have amplified resistance to MDR since they would receive a standard regimen for drug sensitive TB. However there is no currently proven regimen for non-MDR INH-resistant TB (18;19), although there is some evidence that fluoroquinolones may replace INH in such patients (27). Our findings underscore the need for randomized trials to identify the optimal treatment of this form of drug-resistant TB.

There are several limitations of our analysis. First, in the base case we assumed perfect sensitivity and specificity of all tests, although in sensitivity analyses these test characteristics were varied (21-24). These analyses demonstrated that when DST was used prior to initiating treatment, even modest reductions in test specificity can substantially lower cost effectiveness if prevalence of drug resistance is low. Given that most of the variability of cost is determined by test specificity, the values shown in Table 7a for 98% specificity would apply for testing with Xpert MTB/RIF. Hence if rifampicin resistance is detected by the Xpert MTB/RIF in settings with low prevalence of MDR, confirmation with another DST method is recommended (27). Given the importance of test specificity on cost-effectiveness in settings with low-moderate drug resistance, the most appropriate DST will be one with very high specificity.

We also assumed a perfect health system, meaning that all cases would undergo DST at the appropriate moment, specimens would be collected promptly, received at the lab, and results would be available to clinicians without delay. In reality, these ideal conditions are not always achieved in resource limited settings. We also did not explicitly include costs related to adverse drug events as we could not find published estimates for these costs in

the literature. Despite this, our cost estimates for treatment of MDR are higher than one other published estimate (28), as we assumed higher health system costs for follow-up.

We assumed DST were performed in patients who were already diagnosed with active TB on the basis of sputum smear microscopy, meaning that DST was the second in a two step procedure of diagnosis of drug resistant TB. Future modeling could assess the use of Xpert MTB/RIF for the detection of TB as well as MDR-TB. Finally we did not model the benefits of reduced transmission once drug resistant TB is detected, and chemotherapy started. Hence this analysis could have underestimated cases of MDR averted, particularly for strategies where rapid DST is performed pre-treatment.

We conclude that the performance of a rapid DST that detects any form of INH and RIF resistance in all smear positive TB patients before beginning treatment would be most cost effective of several test and treat strategies in terms of DALYs gained, MDR prevention and deaths averted. However such testing must be followed by appropriate therapy, administered within a strong health system in order to ensure that optimal outcomes and impact are achieved.

ACKNOWLEDGEMENTS:

We are thankful to Hojoon Sohn and the Foundation for Innovative New Diagnostics (FIND) for providing DST cost estimates from FIND TB diagnostic demonstration studies. We are also thankful to the WHO expert group on Programmatic Management of MDR-TB Patients for their valuable input in this study, and to Dr Fraser Wares for input and critical review of the manuscript.

Table 1. Summary of all DST Strategies:

1. Status quo: No DST and all patients receive the same standardized treatment
2. Solid DST: DST Detecting RIF and INH and performed in all patients at the time of diagnosis. Results obtained in 3 months. Appropriate treatment delayed for 3 months.
3. Rapid RIF (pre-treatment) : DST Detecting RIF only and performed in all patients at the time of diagnosis. Results and appropriate treatment immediate
4. Rapid INH & RIF (pre-treatment): DST Detecting RIF and INH and performed in all patients at the time of diagnosis. Results and appropriate treatment immediate.
5. Rapid INH & RIF (2 months): DST as above, however test performed only if smear positive after 2 months of treatment.
6. Rapid INH & RIF (3 months): DST as above, however test performed only if smear positive after 3 months of treatment.
7. Rapid INH & RIF (5 months-fail): DST as above, however test performed only if smear positive after 5 months of treatment.
8. Rapid INH & RIF (5 months- fail+relpase): DST as above, however test performed only if smear positive after 5 months treatment (failures), or with relapse after treatment (ie. all retreatment cases have DST).

Table 2: Details of drug regimens and associated treatment and total health system costs *

Regimen	Duration of Regimen (months)	Regimen cost**	Single visit to doctor (2007 USD)	# of visits to doctor per regimen (1 per month)	Single DOT cost*** (2007 USD)	# of DOT visits per regimen	TOTAL health system cost
Initial standardized	6	2RHZE/4RH = $16.62	$22.70	6	$7.52	95	$867
Retreatment standardized	8	2RHZES/1RHZE/5RHE (includes injection costs) = $29.43	$22.70	8	$7.52	131	$1527
INH-R regimen	6	Initial regimen, without INH but with Levoquin (Lfx)† 2RLfxZE/4RLfx = $43.33	$22.70	6	$7.52	95	$894
Standardized MDR	24	6Cm/18CsLfxEthPAS (Not including injection costs) = $2,118.79	$22.70	24	$7.52	480	$7250

* Hospitalization costs excluded- ambulatory costs only.

** Drug regimen costs estimated using data from Global Drug Facility (GDF) (www.stoptb.org/gdf/)

***Data obtained from survey of health system costs conducted in Rio De Janeiro, Brazil, 2007(15). Costs were originally obtained from direct surveys conducted in Brazil, but are assumed to be appropriate for South Africa, as the GDP per capita (PPP) for the two countries were almost identical in 2007 (29)

† In the absence of a known effective regimen for mono-INH resistant cases, for the purposes of costing, we assumed use of the regular standardized initial regimen, with a Quinolone (levofloxacin) replacement for isoniazid

Table 3: Total outcomes, effectiveness indicators and Incremental Cost Effectiveness Ratios vs. no DST, by DST Strategy (Setting: moderate drug resistance (non-MDR INH resistance of 5.8% and MDR of 2.1%)- no HIV. Assumes 100% sensitivity and 100% specificity of all DST)

	DST Strategy							
	no DST	solid DST	rapid RIF	rapid INH & RIF	Rapid INH & RIF - 2 months	Rapid INH & RIF - 3 months	Rapid INH & RIF -5 mths fail only	Rapid INH & RIF - 5 mths fail and relapse
Total outcomes per 1000 new TB cases:								
Total Cost (US$)	$918,732	$1,073,370	$1,057,742	$1,053,939	$1,047,829	$1,043,442	$1,037,331	$1,038,773
Total DALYs	52,357	52,493	52,506	52,539	52,518	52,510	52,499	52,509
Total Deaths (MDR and non MDR)	43.1	41.1	40.0	39.1	40.3	40.8	42.0	42.0
Total MDR cases (MDR cure+ relapse[1]+fail + die)	24.1	23.9	24.1	22.3	23.1	23.4	24.0	23.9
Effectiveness Indicators:								
DALYs gained vs. No DST	-	136	149	182	161	153	142	152
Deaths averted vs. No DST	-	2.0	3.5	4.0	2.8	2.2	1.2	1.2
MDR cases averted vs. No DST	-	0.3	0.0	1.8	1.0	0.8	0.1	0.3
Incremental Cost-effectiveness Ratios (US$):								
Incremental cost vs. No DST	-	$154,637	$139,010	$135,207	$129,096	$124,710	$118,598	$120,041
Incremental cost per DALY gained	-	$1,135	$935	$744	$800	$816	$838	$790
Incremental cost per death averted	-	$77,153	$40,100	$34,218	$46,678	$56,120	$101,012	$98,475
Incremental cost per MDR case averted	-	$625,556	-[2]	$75,972	$127,076	$162,446	$1,021,517	$479,779

1. Relapse after cure. Number of patients who cured represent permanent cures without relapse

2. Incremental cost per MDR case averted not reported as a tiny fraction of an MDR case is averted with Rapid RIF scenario, making the cost per case averted infinitely large.

Table 4: Total outcomes, effectiveness indicator and Incremental Cost Effectiveness Ratios vs. no DST, by DST Strategy (Setting: high drug resistance (non-MDR INH resistance of 20.1% and MDR of 15.2%.), No HIV. Assumes 100% sensitivity and 100% specificity of

all DST)

	DST Strategy							
	no DST	solid DST	rapid RIF	rapid INH & RIF	Rapid INH & RIF - 2 months	Rapid INH & RIF - 3 months	Rapid INH & RIF -5 mths fail only	Rapid INH & RIF - 5 mths fail and relapse
Total outcomes per 1000 new TB cases:								
Total Cost (US$)	$1,033,658	$1,948,510	$1,790,301	$1,777,120	$1,892,790	$1,883,146	$1,867,876	$1,861,844
Total DALYs	54,263	55,496	55,609	55,752	55,605	55,536	55,398	55,416
Total Deaths (MDR and non MDR)	78.0	63.4	52.6	51.3	59.1	62.9	70.5	70.5
Total MDR cases (MDR cure+ relapse[1]+fail + die)	159.5	156.8	159.5	153.3	155.4	156.4	159.2	158.8
Effectiveness Indicators:								
DALYs gained vs. No DST	-	1233	1346	1489	1342	1273	1135	1153
Deaths averted vs. No DST	-	14.6	25.1	26.8	19.0	15.2	7.5	7.5
MDR cases averted vs. No DST	-	3.0	0.00	6.2	4.1	3.1	0.3	0.6
Incremental Cost-effectiveness Ratios (US$):								
Incremental cost vs. No DST	-	$914,852	$756,643	$743,462	$859,132	$849,487	$834,218	$828,186
Incremental cost per DALY gained	-	$742	$562	$499	$640	$667	$735	$718
Incremental cost per death averted	-	$62,569	$30,155	$27,771	$45,320	$56,023	$110,761	$109,778
Incremental cost per MDR case averted	-	$337,384	-	$120,553	$211,110	$273,640	$3,271,443	$1,286,802

Table 5: Total outcomes, effectiveness indicators and Incremental Cost Effectiveness Ratios vs. no DST, by DST Strategy (Setting: moderate drug resistance (non-MDR INH resistance of 5.8% and MDR of 2.1%)- High HIV (50% of cases co-infected with HIV.) Assumes 100% sensitivity and 100% specificity of all DST).

	DST Strategy							
	no DST	solid DST	rapid RIF	rapid INH & RIF	Rapid INH & RIF - 2 months	Rapid INH & RIF - 3 months	Rapid INH & RIF -5 mths fail only	Rapid INH & RIF - 5 mths fail and relapse
Total outcomes per 1000 new TB cases:								
Total Cost (US$)	$855,103	$1,009,250	$968,311	$965,052	$989,026	$980,317	$963,945	$965,129
Total DALYs *	51,044	51,159	51,173	51,204	51,180	51,169	51,154	51,161
Total Deaths (MDR and non MDR)	123.6	112.0	118.8	117.7	119.1	119.7	120.8	120.7
Total MDR cases (MDR cure+ relapse[1]+fail + die)	23.8	23.5	23.8	22.1	22.7	22.9	23.5	23.4
Effectiveness Indicators:								
DALYs gained vs. No DST	-	115	129	160	136	125	110	117
Deaths averted vs. No DST	-	3.6	4.8	5.8	4.6	3.9	2.8	2.9
MDR cases averted vs. No DST	-	0.2	0.0	1.6	1.1	0.8	0.2	0.3
Incremental Cost-effectiveness Ratios (US$):								
Incremental cost vs. No DST	-	$154,147	$113,208	$109,949	$133,923	$125,214	$108,842	$110,026
Incremental cost per DALY gained		$1,343	$880	$687	$987	$999	$987	$939
Incremental cost per death averted	-	$43,106	$23,692	$18,825	$30,007	$32,504	$39,135	$38,538

Incremental cost per MDR case averted	-	$715,301	-	$68,598	$127,570	$152,737	$461,196	$324,369

*DALYs are estimated for TB morbidity and mortality only, and do not account for non-TB effect of HIV.

		DST Strategy						
MDR Prevalence (%)	non-MDR INH resistance*(%)	solid DST	rapid RIF	rapid INH & RIF	Rapid INH & RIF - 2 months	Rapid INH & RIF - 3 months	Rapid INH & RIF -5 mths fail only	Rapid INH & RIF - 5 mths fail and relapse
0.5	2	$2,087	$1,797	$1,331	$957	$897	$673	$618
1	2	$1,435	$1,231	$1,045	$911	$893	$790	$741
1.5	2	$1,241	$1,043	$931	$894	$892	$841	$801
2	2	$1,148	$949	$869	$884	$891	$869	$835
3	2	$1,057	$855	$805	$875	$891	$900	$874
4	2	$1,013	$808	$772	$870	$890	$916	$896
0.5	4	$1,893	$1,797	$1,047	$801	$767	$646	$578
1	4	$1,403	$1,231	$903	$822	$815	$762	$703
1.5	4	$1,233	$1,043	$838	$831	$836	$817	$768
2	4	$1,147	$949	$801	$836	$848	$849	$807
3	4	$1,060	$855	$761	$842	$860	$884	$852
4	4	$1,016	$808	$739	$845	$867	$903	$878
0.5	6	$1,765	$1,797	$857	$697	$679	$626	$548
1	6	$1,378	$1,231	$793	$752	$753	$739	$671
1.5	6	$1,227	$1,043	$761	$779	$789	$796	$739
2	6	$1,146	$949	$742	$794	$809	$2,522	$781
3	6	$1,062	$855	$720	$812	$833	$1,837	$832

4	6	$1,019	$808	$708	$821	$846	$1,571	$861

Table 6: Cost per DALY gained – with different prevalence of initial drug resistance and different DST strategies. (Setting: Moderate drug resistance (non-MDR INH resistance of 5.8% and MDR of 2.1%), No HIV. Assumes 100% sensitivity and 100% specificity of all DST)

*For modelling purposes “non MDR INH resistance” included all single drug resistance and poly drug resistance, except RIF-alone which was grouped with MDR

Tables 7 and 8: The potential impact of inaccuracies of DST

Table 7a: Varying sensitivity of Rapid INH & RIF test pre-treatment to detect INH and RIF. (Setting: non-MDR INH resistance of 5.8% and MDR of 2.1%, No HIV)

	Varying sensitivity for INH/RIF Strategy: Rapid INH & RIF pretreatment			
	75%/88%	80%/92%	90%/96%	100%/100% (base case)
Total DALYs per 1000 new cases	52,513	52,521	52,530	52,540
Total cost per 1000 new cases	$1,043,009	$1,046,779	$1,050,359	$1,053,939
Total DALYs gained	156	163	172	182
Total incremental cost	$124,276	$128,046	$131,626	$135,207
Cost per DALY gained	$799	$785	$763	$744

Table 7b: Varying specificity of Rapid INH & RIF test pre-treatment to detect RIF. (Setting: non-MDR INH resistance of 5.8% and MDR of 2.1%, No HIV)

	Varying Specificity for RIF Strategy: Rapid INH & RIF pretreatment			
	94%	96%	98%	100% (base case)
Total DALYs per 1000 new cases	52,387	52,438	52,489	52,540
Total cost per 1000 new cases	$1,413,400	$1,293,580	$1,173,759	$1,053,939
Total DALYs gained	29	80	131	182
Total incremental cost	$494,668	$374,847	$255,027	$135,207
Cost per DALY gained	$17,244	$4,704	$1,951	$744

Table 8a. Cost per DALY gained with different specificities for detection of RIF resistance of the Rapid INH & RIF DST used in all patients pre-treatment and with varying prevalence of MDR

	Varying specificity for RIF resistance of the Rapid INH & RIF DST Strategy: Test all patients pre-treatment			
Prevalence of MDR	94%	96%	98%	100%
2%	$17,244	$4,704	$1,951	$744*
4%	$3,477	$2,128	$1,286	$711
6%	$2,138	$1,527	$1,062	$697
8%	$1,650	$1,269	$954	$690
10%	$1,397	$1,126	$890	$685

*Base case estimate

Table 8b Sensitivity analysis: Cost per DALY gained with different specificities for detection of RIF resistance of the Rapid INH & RIF DST used in failures and relapses and with varying prevalence of MDR

	Varying specificity for RIF resistance of the Rapid Rapid INH & RIF DST. Strategy: Test only failures and relapses			
Prevalence of MDR	94%	96%	98%	100%
2%	$880	$850	$820	$790*
4%	$915	$898	$880	$863
6%	$931	$918	$906	$894
8%	$939	$930	$921	$911
10%	$944	$937	$929	$922

*Base case estimate

Figure Legends:

Figure 1a Predicting the most cost-effective rapid test under different conditions of initial drug resistance (0-15% initial MDR and 0-30% initial non MDR INH resistance*)

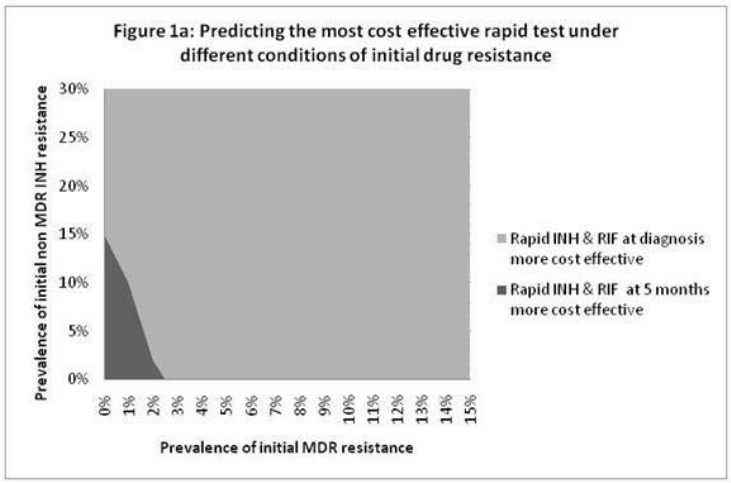


Figure 1b Predicting the most cost-effective rapid test under different conditions of initial drug resistance (0-5% initial MDR and 0-10% non MDR INH resistance*).

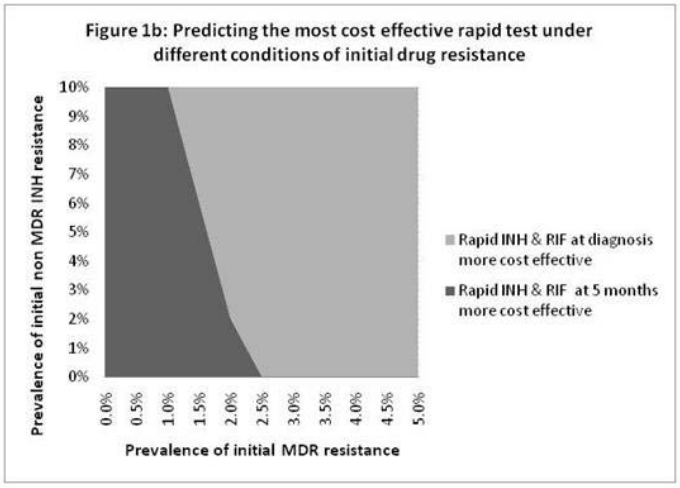
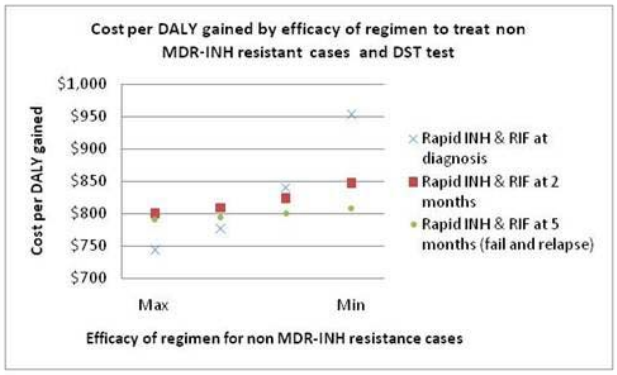


Figure 2. Sensitivity analysis- Cost per DALY gained by efficacy of regimen to treat non MDR-INH resistant cases and DST test. (Setting: Moderate drug resistance, No HIV)


Cost per DALY gained by efficacy of regimen to treat non MDR-INH resistant cases and DST test
$1,000
$950
$900
$850
$800
$750
$700
Cost per DALY gained
Max
Min
Efficacy of regimen for non MDR-INH resistance cases
Rapid INH & RIF at diagnosis
Rapid INH & RIF at 2 months
Rapid INH & RIF at 5 months (fail and relapse)

Figures:

Figure 1a Predicting the most cost-effective rapid test under widely varying conditions of initial drug resistance (0-15% initial MDR and 0-30% initial non MDR INH resistance*)

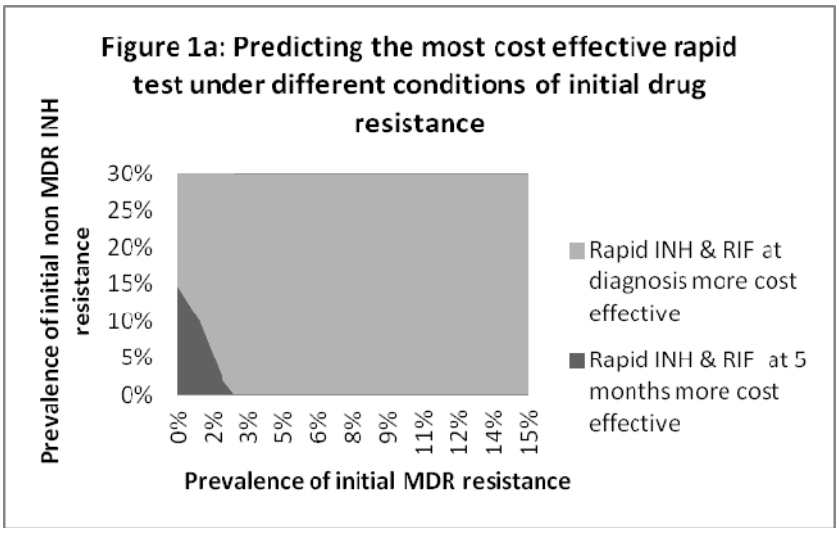
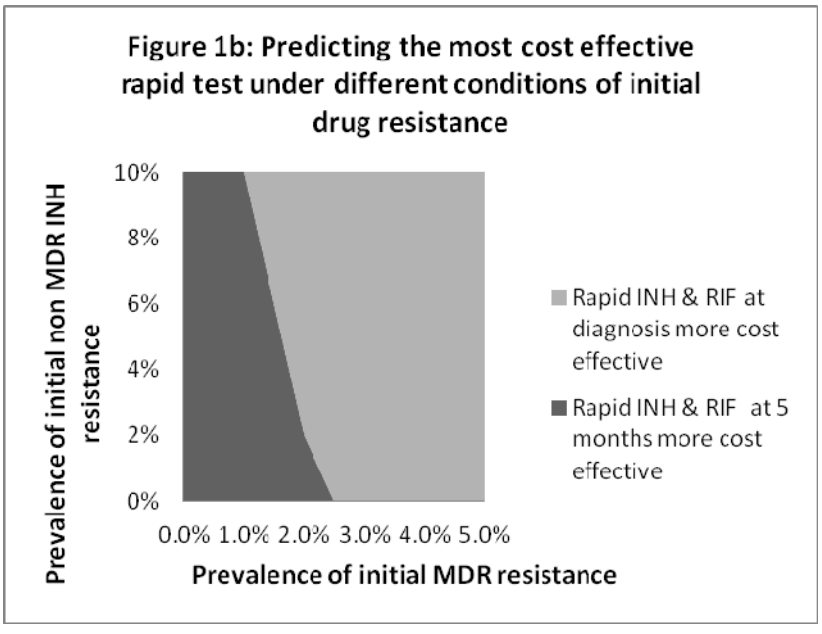
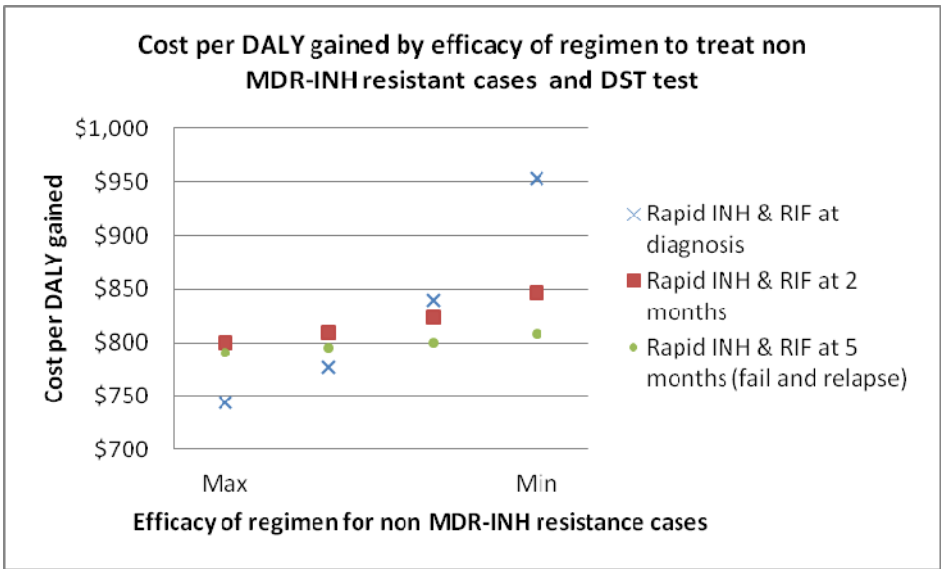


Figure 1b Predicting the most cost effective rapid test within a narrow range of prevalence of initial drug resistance (0-5% initial MDR and 0-10% non MDR INH resistance*).



*For modelling purposes "non MDR INH resistance" included all single drug resistance and poly drug resistance, except RIF-alone which was grouped with MDR

Figure 2. Sensitivity analysis- Cost per DALY gained by efficacy of regimen to treat non MDR-INH resistant cases and DST test. (Setting: Moderate drug resistance, No HIV)



Reference List

(1) World Health Organization. Multidrug and extensively drug resistant TB (M/XDR-TB): 2010 Global Report on Surveillance and Response. 2010 Mar 1.

(2) World Health Organization. Anti-tuberculosis drug resistance in the world report number 4. Geneva: http://whqlibdoc.who.int/publications/2008; 2008. Report No.: WHO/HTM/TB/2008.

(3) Mak A, Thomas A, Del GM, Zaleskis R, Mouzafarova N, Menzies D. Influence of multidrug resistance on tuberculosis treatment outcomes with standardized regimens. Am J Respir Crit Care Med 2008 August 1;178(3):306-12.

(4) Menzies D, Benedetti A, Paydar A, Martin I, Royce S, Pai M, Vernon A, Lienhardt C, Burman W. Effect of Duration and Intermittency of Rifampin on Tuberculosis Treatment Outcomes: A Systematic Review and Meta-Analysis. PLOS Med 2009;6(9):e1000146.

(5) Menzies D, Benedetti A, Paydar A, Royce S, Pai M, Burman W, Vernon A, Lienhardt C. Standardized Treatment of Active Tuberculosis in Patients with Previous Treatmnet and/or with Mono-resistance to Isoniazid: A Systematic Review and Meta-analysis. PLOS Med 2009;6(9):e1000150.

(6) 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 July;3(7):564-81.

(7) Wallis RS, Pai M, Menzies D, Doherty TM, Walzl G, Perkins MD, Zumla A. Biomarkers and diagnostics for tuberculosis: progress, needs, and translation into practice. Lancet 2010 May 29;375(9729):1920-37.

(8) International Union Against TB and Lung Disease. Management of Tuberculosis: A guide to essentials of good practice. 2010. Report No.: Sixth Edition.

(9) Lew W, Oxlade O, Pai M, Martin D, Menzies D. Initial drug resistance and tuberculosis treatment outcomes: systematic review and meta-analysis. Ann Intern Med 2008;149(2):123-34.

(10) Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, Gandhi NR, Galvani AP. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis 2009 March;9(3):153-61.

(11) Johnston JC, Shahidi NC, Sadatsafavi M, FitzGerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLOS ONE 2009;4(9):e6914.

(12) World Health Organization. Global Tuberculosis Control 2009: Epidemiology, Strategy, Financing. 2009.

(13) Gandhi NR, Shah NS, Andrews JR, Vella V, Moll AP, Scott M, Weissman D, Marra C, Lalloo UG, Friedland GH. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. Am J Respir Crit Care Med 2010 January 1;181(1):80-6.

(14) Rieder HL. Interventions for Tuberculosis Control and Elimination. 2002.

(15) Steffen R, Menzies D, Oxlade O, Pinto M, Zuleika de Castro A, Trajman A. Patients' costs and cost-effectiveness of tuberculosis in DOTS and non-DOTS facilities in Rio de Janeiro, Brazil. PLOS ONE 2010.

(16) Balabanova Y, Drobniewski F, Nikolayevskyy V, Kruuner A, Malomanova N, Simak T, Ilyina N, Zakharova S, Lebedeva N, Alexander HL, O'Brien R, Sohn H, Shakhmistova A, Fedorin I. An integrated approach to rapid diagnosis of tuberculosis and multidrug resistance using liquid culture and molecular methods in Russia. PLOS ONE 2009;4(9):e7129.

(17) World Health Organization. WHO health report 2000: Reducing risks, promoting healthy life. Geneva; 2000.

(18) World Health Organization- Expert Group Report. Modlecular Line Probe Assays for Rapid Screening of Patients at risk of Multi-drug resistant Tuberculosis (MDR-TB). 2008 May.

(19) World Health Organization. Policy statement on non-commercial and DST methods. 2010.

(20) World Health Organization, Stop TB Partnership. Roadmap for rolling out Xpert MTB-RIF for rapid diagnosis of TB and MDR-TB. 2010 Dec 6.

(21) Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, Allen J, Tahirli R, Blakemore R, Rustomjee R, Milovic A, Jones M, O'Brien SM, Persing DH, Ruesch-Gerdes S, Gotuzzo E, Rodrigues C, Alland D, Perkins MD. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 2010 September 9;363(11):1005-15.

(22) Moore DA, Evans CA, Gilman RH, Caviedes L, Coronel J, Vivar A, Sanchez E, Pinedo Y, Saravia JC, Salazar C, Oberhelman R, Hollm-Delgado MG, LaChira D, Escombe AR, Friedland JS. Microscopic-observation drug-susceptibility assay for the diagnosis of TB. N Engl J Med 2006 October 12;355(15):1539-50.

(23) Minion J, Leung E, Menzies D, Pai M. Microscopic-observation drug susceptibility and thin layer agar assays for the detection of drug resistant tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis 2010 October;10(10):688-98.

(24) Ling DI, Zwerling AA, Pai M. GenoType MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: a meta-analysis. Eur Respir J 2008 November;32(5):1165-74.

(25) Acuna-Villaorduna C, Vassall A, Henostroza G, Seas C, Guerra H, Vasquez L, Morcillo N, Saravia J, O'Brien R, Perkins MD, Cunningham J, Llanos-Zavalaga L, Gotuzzo E. Cost-effectiveness analysis of introduction of rapid, alternative methods to identify multidrug-resistant tuberculosis in middle-income countries. Clin Infect Dis 2008 August 15;47(4):487-95.

(26) Swaminathan S, Narendran G, Venkatesan P, Iliayas S, Santhanakrishnan R, Menon PA, Padmapriyadarsini C, Ramachandran R, Chinnaiyan P, Suhadev M, Sakthivel R, Narayanan PR. Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis: a randomized clinical trial. Am J Respir Crit Care Med 2010 April 1;181(7):743-51.

(27) *Rapid Implementation of the Xpert MTB/RIF diagnostic test. Technical and operational "how-to" practical considerations*. Geneva: World Health Organization; 2011.

(28) Tupasi TE, Gupta R, Quelapio MI, Orillaza RB, Mira NR, Mangubat NV, Belen V, Arnisto N, Macalintal L, Arabit M, Lagahid JY, Espinal M, Floyd K. Feasibility and cost-effectiveness of treating multidrug-resistant tuberculosis: a cohort study in the Philippines. PLOS Med 2006 September;3(9):e352.

(29) United Nations Statistics Division. United Nations Common Database. Web Database 2007;Available from: URL: http://unstats.un.org/unsd/cdb/cdb_advanced_data_extract.asp