WORKING
PAPER

A Technical Supplement: Reducing the Global Burden of Tuberculosis

The Contribution of Improved Diagnostics

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HEALTH

Preface:

This working paper contains technical material supporting the article by Keeler et al. "Reducing the global burden of tuberculosis: the contribution of improved diagnostics," Nature S1 49-57 2006. It should be read in conjunction with that article. It includes additional discussion referred to in the published article as well as supplementary analyses and tables, in particular, some preliminary analyses of tests for Multi-Drug Resistant Tuberculosis (MDR TB) that were not included in the published paper. Although this technical supplement in its current form has not been formally peer-reviewed, an earlier version of this paper, which also contained material that appears in the corresponding Nature paper, was reviewed by two outside experts and was revised in response to their comments. The work was funded by the Bill and Melinda Gates Foundation to support the Global Health Diagnostics Forum.

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The additional text and tables are organized by section of the paper.

Introduction

Other Current diagnostic tests

In addition to the tests discussed in the paper, there are:

Drug susceptibility testing for MDR-TB is discussed in Appendix C.

The tuberculin skin test can detect latent tuberculosis in immuno-competent patients. However, because so many people in developing countries harbor latent TB (estimates of up to 2 billion) and so few progress to active tuberculosis, this knowledge is not useful in controlling the spread of disease.

Methods

Other diagnosis indications thought to have less promise

Here we give other indications and the reasons we did not consider them.

Prognostic indicator for latent infection (i.e. asymptomatic adults) in HIV- adults

Successful treatment for people with latent TB who will develop active TB would dramatically reduce the incidence of active TB. Such a test would allow stratification for preventive therapy, because treatment is prolonged and onerous and only a relatively small proportion of individuals with latent disease progress to active infection. This would permit targeted preventive therapy to stress the importance of continuing on a prescribed regimen (e.g., INH) in the absence of active disease. We know some risk factors: HIV+, malnutrition, smoking, air quality, living with person with active TB. Unfortunately, we do not know what might be an additional independent prognostic indicator for active TB that would have a high enough positive predictive value (PPV) and would be sufficiently common for screening to be cost-effective. (The efficacy would also depend on how the probability of completing treatment depends on the probability that the person would develop TB.)

Prognostic indicator for latent infection (i.e. asymptomatic adults) in HIV+ adults

Currently, HIV+ status is the best predictor of development of active TB in patients with latent TB. It was argued that this group does not need to be tested, but should simply be treated with (one course of) Isoniazid.

A test for determining when treated patients are free of disease. A test here would permit therapy to be discontinued sooner for many patients. While patients now receive a prescribed course of therapy, many are likely treated longer than they need to be because no test currently exists that indicates when treatment can safely be stopped. The potential resource savings from this test seemed less important than a proper assignment of treatment to patients in the first place.

Screening or active case-finding for pulmonary TB could shorten the infective period and improve treatment outcomes, but the major benefit would be in detecting cases that otherwise would not be treated. (Murray, (in Borghoff)). Because most cases eventually do present, we agreed with current WHO recommendations that the highest priority is passive case finding.

Tests for children and for extra-pulmonary TB was considered to be of lower value, because of the low transmission from such cases.

Other modeling assumptions for adults presenting with persistent cough

In each of the 4 regions, the estimated number of smear diagnostic work-ups for suspected TB is smaller than the incidence of suspects. We assume each TB suspect gets at most one full work-up through the year. With a fixed number of work-ups, multiple work-ups for some patients increase the number of TB suspects not getting any work-ups. However, if previous false negatives have the same probabilities of the second test results as untested TB suspects, the assumption of at most one full work-ups is conservative. If instead, some people got several tests and some get none, not so many people with TB get discovered. So this assumption makes detection a little better in status quo world and also in new world. Because estimates of % getting sputum test come from estimates on DOTS treatment, we put people who have failed say a trial of antibiotics, and subsequently get sputum test onto the sputum branch – classified by the best test they get in the episode. So, the modeled episode is assumed to be the last chance for diagnosis and false negatives of the episode are considered untreated for the consequences in mortality and transmission.

With highly sensitive new tests, there are few true cases who are called negative. As a result, follow-up of those cases can be counter productive, and the model calculates results with and without follow-up, picking the better option.

Further notes on Model Parameters and parameters for all regions.

The parameters for the model are given in Table 1 of the paper for South East Asia HIV- and Africa HIV+ patents. In Table 1 here and in Appendix A1 and A2 of this report, we give the parameters for all regions analyzed. They are discussed briefly below along with the assumptions needed to transform estimates from the literature to fit our model. Details of the calculations and additional references are given in Appendix A.

We multiplied the ss+ cases by the % adult ss+ cases and the ss- cases by the % adult ss- cases regional proportion to get the adult cases. For the adult ss- cases, we calculated pulmonary adult ss- from estimates of the % EP in the region (Who 2005, p22) assuming the probability of EP in ss- patients is half as high in adult HIV- as in children or in adult HIV+ in that region. We assume false positives in the WHO treatment estimates are negligible.

The recommended sputum microscopy procedure uses 3 samples and loss to follow-up includes those who fail to come back to give all their samples, or to obtain the microscopy results. (Squire, 2005). The x-ray branches on the tree assume a trial of antibiotics is usually given following a suspicious x-ray as recommended in WHO treatment guidelines 2003 so we use the more sensitive point on the ROC curve (Van Cleef 2003; Harries 1997), relying on the trial of antibiotics to improve specificity. Studies on symptomatic relief of active TB by antibiotics show that 40% get relief. (O'Brien 2003). In a trial of antibiotics, patients will be asked to return if there is no relief but some will not so we need to assume a loss to follow-up as with microscopy. Putting the symptomatic relief and return rates together we can calculate the sensitivity of x-ray + a possible trial of antibiotics = 76% (suspicious x-ray) x [25% immediate treatment + 75%(trial of antibiotics) x 60% (no relief) x 85% (return) = 48%, and the specificity is calculated similarly.

DALYs per fatality are calculated from regional averages data in the Global Burden of Disease report. Averted Transmission is calculated as a simple multiplier assuming the TB epidemic is in steady state. (Details are given in Appendix A) The DALYs saved also represent only the index cases, not averted future cases, and are proportional to lives

saved within each region. They and the cases averted from interrupted transmission are roughly proportional to adjusted lives saved so that results on adjusted lives saved suffices to show where the opportunities for better tests lie. Transmission estimates were not reported in the published paper, but are given here in Table 3.

Results

Model Validation back-up

To validate the model, we compared our status quo mortality and proportion treated results with the related WHO estimates. Our calculated numbers of deaths of adults with pulmonary TB by region, assuming the status quo, varied from 70% of the total WHO-estimated deaths (which include the overlapping categories of children and extrapulmonary TB) in the eastern Mediterranean region to 81% in Africa. If we add in the children and extra pulmonary cases, mortality estimates are close except in west Asia, where they are sill low. The calculated status quo detection rates were 66% for adult ss+ cases (with ~51% starting with SSM and the other 15% being diagnosed by other methods) and 45% for adult pulmonary ss– cases. These detection estimates seem a little high – this may be due to the assumption of at most one work-up per suspect. Multiple work-ups for some imply that more people are not getting any, which would lead to lower detection. These rates make the modelled status quo slightly better than the current WHO detection estimates, which reduces the estimated gains of new tests. However the assumption is maintained in both the status quo and new world branches of the tree, so changes in detection may not be greatly affected by the assumption. (See Table 2 for the calculations underlying these numbers).

Output by Region:

In the paper, we only presented world totals. The regional output of the main TB model is given in Table 3. This also gives additional detail on how the increase in lives saved is achieved by breaking out changes in adjusted lives into changes in true positive smear-positives, true positive smear-negatives and true negatives with new tests. It also includes estimated incremental transmission based on the multipliers for untreated smear positive and smear negative TB, discussed in Appendix A.

Discussion

Other Limitations of the modeling approach:

- We calculated the annual impact of the hypothetical new diagnostic on outcomes, and did not try to project gains up to some future data such as 2020.
- We did not consider the financial cost of diagnosis or treatment explicitly.
- The model is static: Changes in DALYs and Transmission were estimated using a simple multiplier of changes in correct treatments.
- We did not consider other behavioral changes that might follow from the availability of better diagnosis.
- Data are lacking on several key parameters.
- The unit of analysis is the WHO region, so that adjustments in diagnostic protocols for unusual local circumstances are not modeled.

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Table 1: Parameters for Cast Detection of Active (pulmonary) TB in all Patients:

	Base Case Clinical Values					
	HIV - PULMONARY TB CASES				**HIV+ Cases**	
	Africa	**Eastern Medit.**	**South Asia**	**Western Asia**	**Africa HIV+**	**South Asia HIV+**
Natural History						
Population (millions)	**687***	**518**	**1615***	**1732**		
Incidence cases of ss+ TB (1000s)	**820**	**281**	**1344**	**863**	**192**	**26**
Incidence cases of ss- TB (1000s)	**1003**	**344**	**1642**	**1055**	**357**	**49**
Adult cases/all cases In ss+	**0.8**	**0.72**	**0.72**	**0.62**		
Adult cases/all cases in ss-	**0.6**	**0.55**	**0.64**	**0.59**		
Incidence adult SS+ (1000s)	**618**	**202**	**960**	**533**	**192**	**26**
Pulmonary ss-/all ss-	**0.62**	**0.56**	**0.78**	**0.84**	**0.62**	**0.78**
Pulmonary ss-/all ss- in Adult	**0.77**	**0.7**	**0.84**	**0.89**	**0.54**	**0.68**
Incidence adult pulm SS- (1000s)	**355**	**130**	**869**	**550**	**195**	**33**
Prob (active TB in suspects)	**0.28**	**0.17**	**0.17**	**0.11**	**0.28**	**1.25**
"Adult pulmonary TB suspects"	**3,487**	**1,988**	**10,756**	**9,434**	**1,387**	**47**
Status Quo Diagnosis						
Total Number of sputum diagnostic work-ups (1000s)	**3071**	**888**	**6551**	**6284**		
% of adult pulm TB by HIV status	**0.72**	**0.99**	**0.97**	**0.99**	**0.28**	**0.03**
Number workups by HIV status	2197	875	6346	6227	874	28
Proportion of "TB suspects" who at some point are tested with AFB Microscopy	**0.63**	**0.44**	**0.59**	**0.66**	**0.63**	**0.59**
Proportion of TB suspects who only get X-ray or trial of ABx	**0.35**	**0.41**	**0.34**	**0.31**	**0.35**	**0.34**
Proportion of adults with pulm TB symptoms who are not tested for TB.	**0.02**	**0.15**	**0.07**	**0.03**	**0.02**	**0.07**
Microscopy loss to follow-up	**0.15**	**0.1**	**0.1**	**0.1**	**0.15**	**0.1**
trial of antibiotics loss to follow-up	**0.15**	**0.1**	**0.1**	**0.1**	**0.15**	**0.1**
Proportion of those who return for negative smear result who are then X-	**0.3**	**0.6**	**0.9**	**0.6**	**0.3**	**0.9**

rayed						
Proportion of those with non-sputum work-up who are X-rayed	**0.3**	**0.6**	**0.9**	**0.6**	**0.3**	**0.9**
proportion of those with x-ray but no subsequent trial of Antibiotics	**0.075**	**0.15**	**0.225**	**0.15**	**0.075**	**0.225**
Sensitivity of field microscopy for "ss+"	**0.85****					
Sensitivity of microscopy for ss-	**0**					
Specificity of microscopy	**0.97**					
Sensitivity of x-ray for active TB	**0.76**					
Specificity of x-ray for active TB	**0.68**					
Symptom relief with antibiotic if Active TB	**0.4**					
symptom relief with antibiotics if no TB	**0.85**					
Sensitivity of x-ray + Trial of Antibiotics	**0.48**					
Specificity of x-ray + trial of antibiotics	**0.94**					
Outcomes						
cf Rate **for Dots SSC treated ss+ TB**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**
cfRate **for Dots SSC treated ss- TB**	**0.05**	**0.05**	**0.05**	**0.05**	**0.1**	**0.1**
cf Rate **for noDots SSC treated ss+ TB**	**0.3**	**0.3**	**0.3**	0.2	**0.38**	**0.38**
cfRate **for no dotsSSC treated ss- TB**	**0.15**	**0.15**	**0.15**	0.1	**0.5**	**0.5**
Mortality Rate **for untreated ss+ TB**	**0.7**	**0.7**	**0.7**	**0.7**	**0.83**	**0.83**
Mortality Rate **for untreated ss- TB**	**0.2**	**0.2**	**0.2**	**0.2**	**0.74**	**0.74**
cost of a treatment in mortality terms	**0.05**					
*DALYS **lost per adult TB mortality***	**23**	**19**	**16**	**12**	23	16
Transmission multiplier for untreated ss+ TB	**6.6**	**6.6**	**6.6**	**6.6**	**2**	**2**
Transmission multiplier for untreated ss- TB	**1.45**	**1.45**	**1.45**	**1.45**	**0.44**	**0.44**
Discount rate	**0.03**					

*** if HIV+ columns are empty, estimates are for all patients, not just HIV-.**

**** When only one column is filled, parameter applies to all regions.**

Table 2: Validating status quo model outputs against WHO 2003 estimates of mortality and % detected

Model Data

	Deaths	Suspects Correctly Treated	Trans-mission	TP_SS+	TP_SS-	TN	Adult ss+	Adult pulm ss-	detect ss+	detect ss-
Africa	259	2,778	1,530	415	158	2,206	618	355	67%	44%
West-Asia	230	7,938	1,358	379	256	7,303	533	550	71%	47%
Easter-Medit	101	1,647	633	117	54	1,476	202	130	58%	41%
South-Asia	455	8,925	2,679	636	380	7,910	960	869	66%	44%
Africa-HIV+	177	1,093	540	129	87	878	192	195	67%	44%
South-Asia-HIV+	28	287	80	17	14	255	26	33	66%	44%

Other data

	2003 WHO TB mortality	Model estimates (000s)	**Model % of world estimate**	Children's TB Deaths in 1990	GBD % Total TB deaths in 1990	% children deaths in 1990	Extra Pulmonary TB
Africa	538	436	**81%**	65	386	17%	19%
West-Asia	327	230	**70%**	9	278	3%	9%
Easter-Medit	144	101	**70%**	13	169	8%	20%
South-Asia	617	483	**78%**	42	752	6%	12%

Comments: We used data from the Global Burden of disease study (reference 2) to estimate % of TB deaths by children. Extra-pulmonary TB mortality comes from Global Health 2005 WHO report estimates of percent of notifications that are EP by region. Children and EP overlap. Detection rates seem slightly high, but reasonable.

Table 3: Results by WHO Region

World Totals

Test	sens.SS+	sens.SS-	specificity	1 - loss to follow-up	Individual Lives	Adjusted Lives	Averted Transmission	TP_SS+	TP_SS-	True Neg.
Advanced Infrastructure (20% access)										
1	1	1	1	1	104	118	-890	92	235	589
TB clinics and Hospitals (44-66% access)										
2	0.85	0	0.97	0.85	0	0	0	0	0	0
3	1	0	0.97	0.85	-33	46	278	49	-426	1206
4	0.85	0	0.97	1	117	95	-1128	165	75	-217
5	0.85	0.85	0.97	0.85	15	60	147	-103	363	1145
6	0.85	0.85	0.97	1	169	195	-1290	87	547	1121
7	1	1	1	0.85	137	200	-1017	49	521	1801
8	1	1	1	1	318	359	-2708	280	717	1801
No infrastructure (100% access)										
9	0.85	0	0.97	0.85	98	133	-1324	288	-336	646
10	0.85	0	0.97	1	258	263	-3459	602	-200	497
12	0.85	0.85	0.97	1	383	392	-4469	521	908	1587
13	1	1	1	0.85	337	407	-4029	459	865	2708
14	1	1	1	1	591	625	-6820	838	1183	2708

Notes:
All outcomes are given in thousands
Individual lives represent mortality of index cases
Adjusted lives include a .05 penalty for each treatment
Cases averted from interrupted transmission based on untreated ss+.ss- multipliers
Differences from paper: test 1 has 20% access, test 7,13 has 15% LTFU
TP_SS+, TP_SS-, True Neg. represents differences in these categories from status quo

Africa HIV-

Test	sens.SS+	sens.SS-	specificity	1 - loss to follow-up	Individual Lives	Adjusted Lives	Averted Trans-mission	DALYs	TP_SS+	TP_SS-	T Neg.
Advanced Infrastructure (20% access)											
1	1	1	1	1	22	22	-219	564	26	41	64
TB clinics and Hospitals (44-66% access)											
2	0.85	0	0.97	0.85	0	0	0	0	0	0	0
3	1	0	0.97	0.85	15	14	-153	321	25	0	0
4	0.85	0	0.97	1	35	30	-358	687	54	17	-35
5	0.85	0.85	0.97	0.85	12	8	-110	183	0	81	0
6	0.85	0.85	0.97	1	49	39	-487	893	54	112	-35
7	1	1	1	0.85	29	33	-283	256	25	95	200
8	1	1	1	1	69	69	-691	1580	83	128	200
No infrastructure (100% access)											
9	0.85	0	0.97	0.85	20	24	-267	550	57	-62	84
10	0.85	0	0.97	1	76	64	-991	1466	156	17	-60
12	0.85	0.85	0.97	1	93	74	-1201	1695	156	170	-60
13	1	1	1	0.85	66	69	-883	1580	111	144	308
14	1	1	1	1	121	116	-1530	2656	203	197	308

Notes:
All outcomes are given in thousands
Individual lives represent mortality of index cases
Adjusted lives include a .05 penalty for each treatment
Cases averted from interrupted transmission based on untreated ss+.ss- multipliers
Differences from paper: test 1 has 20% access, test 7,13 has 15% LTFU
TP_SS+, TP_SS-, True Neg. represents differences in these categories from status quo

Eastern Mediterranean

Test	sens.SS+	sens.SS-	specificity	1 - loss to follow-up	Individual Lives	Adjusted Lives	Averted Trans-mission	TP_SS+	TP_SS-	True Neg.
Advanced Infrastructure (20% access)										
1	1	1	1	1	6	7	-61	7	14	44
TB clinics and Hospitals (44-66% access)										
2	0.85	0	0.97	0.85	0	0	0	0	0	0
3	1	0	0.97	0.85	-3	2	28	1	-26	78
4	0.85	0	0.97	1	5	4	-55	8	3	-11
5	0.85	0.85	0.97	0.85	0	0	0	0	0	0
6	0.85	0.85	0.97	1	4	7	-39	1	22	75
7	1	1	1	0.85	4	8	-39	1	22	97
8	1	1	1	1	13	16	-133	15	31	97
No infrastructure (100% access)										
9	0.85	0	0.97	0.85	14	17	-205	39	-27	59
10	0.85	0	0.97	1	29	24	-427	68	3	-36
12	0.85	0.85	0.97	1	27	28	-418	55	57	130
13	1	1	1	0.85	27	31	-418	55	57	179
14	1	1	1	1	44	45	-633	85	76	179

Notes:
All outcomes are given in thousands
Individual lives represent mortality of index cases
Adjusted lives include a .05 penalty for each treatment
Cases averted from interrupted transmission based on untreated ss+.ss- multipliers
Differences from paper: test 1 has 20% access, test 7,13 has 15% LTFU
TP_SS+, TP_SS-, True Neg. represents differences in these categories from status quo

Southeast Asia

Test	sens.SS+	sens.SS-	specificity	1 - loss to follow-up	Individual Lives	Adjusted Lives	Averted Trans-mission	TP_SS+	TP_SS-	True Neg.
Advanced Infrastructure (20% access)										
1	1	1	1	1	34	39	-329	32	95	227
TB clinics and Hospitals (44-66% access)										
2	0.85	0	0.97	0.85	0	0	0	0	0	0
3	1	0	0.97	0.85	-29	9	255	10	-232	535
4	0.85	0	0.97	1	35	28	-360	52	26	-74
5	0.85	0.85	0.97	0.85	-17	6	198	-62	139	535
6	0.85	0.85	0.97	1	36	51	-339	10	204	511
7	1	1	1	0.85	36	59	-339	10	204	669
8	1	1	1	1	99	114	-971	95	281	669
No infrastructure (100% access)										
9	0.85	0	0.97	0.85	41	55	-545	121	-148	255
10	0.85	0	0.97	1	113	91	-1571	248	26	-174
12	0.85	0.85	0.97	1	112	123	-1608	180	359	750
13	1	1	1	0.85	112	136	-1608	180	359	1017
14	1	1	1	1	201	211	-2679	324	489	1017

Notes:
All outcomes are given in thousands
Individual lives represent mortality of index cases
Adjusted lives include a .05 penalty for each treatment
Cases averted from interrupted transmission based on untreated ss+.ss- multipliers
Differences from paper: test 1 has 20% access, test 7,13 has 15% LTFU
TP_SS+, TP_SS-, True Neg. represents differences in these categories from status quo

West Asia and Pacific

Test	sens.SS+	sens. SS-	specif icity	1 - loss to follo w-up	Individual Lives	Adjusted Lives	Averted Trans- mission	TP_SS+	TP_SS-	True Neg.
Advanced Infrastructure (20% access)										
1	1	1	1	1	19	27	-190	18	59	222
TB clinics and Hospitals (44-66% access)										
2	0.85	0	0.97	0.85	0	0	0	0	0	0
3	1	0	0.97	0.85	-22	16	196	5	-168	593
4	0.85	0	0.97	1	22	16	-228	33	19	-81
5	0.85	0.85	0.97	0.85	-10	17	116	-39	94	593
6	0.85	0.85	0.97	1	24	45	-225	5	140	568
7	1	1	1	0.85	24	54	-225	5	140	733
8	1	1	1	1	64	88	-627	58	195	733
No infrastructure (100% access)										
9	0.85	0	0.97	0.85	14	28	-165	46	-88	242
10	0.85	0	0.97	1	4	53	-113	74	-256	797
12	0.85	0.85	0.97	1	66	92	-750	74	212	797
13	1	1	1	0.85	66	104	-750	74	212	1048
14	1	1	1	1	122	152	-1358	154	294	1048

Notes:
All outcomes are given in thousands
Individual lives represent mortality of index cases
Adjusted lives include a .05 penalty for each treatment
Cases averted from interrupted transmission based on untreated ss+.ss- multipliers
Differences from paper: test 1 has 20% access, test 7,13 has 15% LTFU
TP_SS+, TP_SS-, True Neg. represents differences in these categories from status quo

Africa HIV+

Test	sens.SS+	sens.SS-	specificity	1 - loss to follow-up	Individual Lives	Adjusted Lives	Averted Trans-mission	TP_SS+	TP_SS-	True Neg.
Advanced Infrastructure (20% access)										
1	1	1	1	1	20	20	-81	8	22	25
TB clinics and Hospitals (44-66% access)										
2	0.85	0	0.97	0.85	0	0	0	0	0	0
3	1	0	0.97	0.85	6	5	-48	8	0	0
4	0.85	0	0.97	1	18	16	-117	17	9	-14
5	0.85	0.85	0.97	0.85	28	26	-60	0	44	0
6	0.85	0.85	0.97	1	51	47	-188	17	61	-14
7	1	1	1	0.85	39	40	-119	8	52	80
8	1	1	1	1	64	63	-256	26	71	80
No infrastructure (100% access)										
9	0.85	0	0.97	0.85	9	8	-129	22	-5	-2
10	0.85	0	0.97	1	32	28	-314	49	9	-24
12	0.85	0.85	0.97	1	74	65	-429	49	94	-24
13	1	1	1	0.85	57	58	-321	34	79	123
14	1	1	1	1	90	87	-540	63	108	123

Notes:
All outcomes are given in thousands
Individual lives represent mortality of index cases
Adjusted lives include a .05 penalty for each treatment
Cases averted from interrupted transmission based on untreated ss+.ss- multipliers
Differences from paper: test 1 has 20% access, test 7,13 has 15% LTFU
TP_SS+, TP_SS-, True Neg. represents differences in these categories from status quo

Southeast Asia HIV+

Test	sens.SS+	sens.SS-	specificity	1 - loss to follow-up	Individual Lives	Adjusted Lives	Averted Trans-mission	TP_SS+	TP_SS-	True Neg.
Advanced Infrastructure (20% access)										
1	1	1	1	1	3	3	-10	1	4	7
TB clinics and Hospitals (44-66% access)										
2	0.85	0	0.97	0.85	0	0	0	0	0	0
3	1	0	0.97	0.85	0	0	0	0	0	0
4	0.85	0	0.97	1	2	1	-10	1	1	-2
5	0.85	0.85	0.97	0.85	2	3	3	-2	5	17
6	0.85	0.85	0.97	1	5	6	-12	0	8	16
7	1	1	1	0.85	5	6	-12	0	8	22
8	1	1	1	1	9	9	-30	3	11	22
No infrastructure (100% access)										
9	0.85	0	0.97	0.85	0	1	-13	3	-6	8
10	0.85	0	0.97	1	4	3	-43	7	1	-6
12	0.85	0.85	0.97	1	11	10	-63	7	16	-6
13	1	1	1	0.85	9	9	-49	5	14	33
14	1	1	1	1	13	14	-80	9	19	33

Notes:
All outcomes are given in thousands
Individual lives represent mortality of index cases
Adjusted lives include a .05 penalty for each treatment
Cases averted from interrupted ransmission based on untreated ss+.ss- multipliers
Differences from paper: test 1 has 20% access, test 7,13 has 15% LTFU
TP_SS+, TP_SS-, True Neg. represents differences in these categories from status quo

Appendix A: Detailed parameter calculations

These contain detailed instructions for how to get from data to the parameters in the tables. Below, we will refer to three spreadsheets:
The 2003 worksheet (Rows 217-222, the regional totals) in the 2005 WHO report estimates workbook: link to Just2003.xls…
Jcunningham (version 2).xls EP calcs.xls has our own calculations used in deriving some parameters.
The tables at the end show the references used for the parameters for status quo behavior and test performance.

Rows 7-9: come directly from 2003 spreadsheet estimates (column G ,ej,ek). We assume false positives in the WHO treatment statistics are negligible.

Rows 10-11: The % adult for both ss+ and ss- come from 2003 columns K and L. We multiplied the ss+ cases by the % adult ss+ cases and the ss- cases by the % adult ss- cases regional proportion to get the adult cases.

Row 12: All the HIV+ are assumed adult, so the adult HIV- ss+ cases are calculated to make row 10 correct (= row9*row 10 - (1-row 10)* HIV+)

Row 13: I calculated the % Pulmonary of the total ss- TB in each region using the estimates from WHO 2005 report p 22 and put them in Epcalcs.xls. For the adult ss- cases, we calculated pulmonary adult ss- from estimates of the % EP in the region (Who 2005, p22) assuming the probability of EP in ss- patients is half as high in adult HIV- as in children or in adult HIV+ in that region. We assume false positives in the WHO treatment estimates are negligible.

Row 15: For the adult ss- cases, we calculated pulmonary adult ss- from estimates on the % EP in the region (Who 2005 report, p22) assuming the probability of EP in ss- patients is half as

high in adult HIV- as in children or in adult HIV+ in that region. Again we need to make row 11 correct overall, but all HIV+ are assumed adult. See spreadsheet EPcalcs for formulae.

Prop (sputum test| TB suspect): (Row 22)

Only TB suspects get into the tree – those with persistent cough, maybe with some other clinical findings. They are the people who would be given a sputum test if one were available. We have estimates from WHO on p(DOTS treatment | ss+) (2003, Column O) , where the definition of DOTS includes getting a sputum test prior to treatment. So p(DOTS & sputum) = p(DOTS). To get p(sputum) we must add p(sputum & non-DOTS) and p(sputum & untreated). We assume 10% of those who start with a sputum test are non-DOTS treated. Some of the ss+ given a sputum test would not end up being treated, either because they don't return for test results or the test is a false negative and they are not recaptured in follow-up testing. From other estimates in the literature, this loss to treatment is about 15% (the number of false negatives after return for sputum results is small). So,

p (sputum) = p(DOTS) + (10% +15%) p(sputum).

We condition the above formula on ss+ to get p(sputum|ss+) = p(DOTS|ss+) / (1-.25).
Finally, we assume the proportion of TB suspects who are tested with AFB microscopy, p(sputum test| TB suspect) = p(sputum test| ss+) = p(DOTS|ss+) / (1-.25).

(Row 24) Again, we assume the % not given any tests is the same for ss+ and other suspects. We assume 25% of those ss+ started with non-sputum diagnosis are not treated.
Now, patients are untreated ss+ TB if they have ss+ TB and either don't get test or if they are False Negatives on the test branches. So, the ss+ that are tested but not treated are subtracted from those untreated, (2003, Column Q) to get p(not tested). So p (not tested|)= p(untreated|) – p(loss to treatment) p(sputum test) - p(loss to treatment)*p(non sputum test). Fortunately, this estimate was never less than zero in any region.
(Row 23) Finally the % non-sputum tested = 1- p(sputum test) – p(untested).

(Row 19-21) We have estimates of the number N of diagnostic AFB microscopy workups given in each region in the Global Survey of TB Lab Services by Cunningham Winfrey Perkins (GS),2004.

Following Cunningham et al. 2004, we assume diagnostic smears = 75% of total smears and divide the number of estimated diagnostic smears per ss+ incident case by 2.5 smears per workup to get the number of patients getting diagnostic workups = P = Total smears/3.333. (Row 19). We calculate the % adult pulmonary TB that is HIV- (Row 20) from rows 12 and 15. We assume the workups are split according to those percentages. (Row 21).

(Row 17 and 16) The number of TB suspects and p(active TB | suspect).
If 60% of suspects get a workup, then N/60% suspects enter the tree. We can then divide the incidence of Active TB by the number of suspects to get prob (active TB in suspects). It is inversely related to the prevalence of TB around the world, perhaps because non-TB causes of TB symptoms are more evenly distributed. The probabilities are similar to the responses in the Respiratory Symptoms Survey, except in Nigeria, where the sample appears to have come entirely from DOTS clinics.

These calculations result in about 2/3 as many active pulmonary suspects as given in the Cunningham data. One possible explanation is that there is heterogeneity in her active suspects plus some correlation between who gets a smear and who has TB, so the sample entering the tree is more likely to have TB than the suspects in her reported data. I.e. there might be some judgment about who gets a sputum test If so p(TB| sputum test) is probably higher than p(TB| persistent cough + arrives at clinic.) Another explanation is that we have grouped people by the most stringent test in the episode, so that people who come in with TB symptoms, get an initial trial of antibiotics and come back for a sputum or x-ray are counted twice in her data, but only once in our model. In the tree, we only consider people who would have been given a sputum test if one were available). For example, in the African region, there are 3,071,000 sputum diagnostic workups, and 72% of adult pulmonary TB is HIV-, so we assume 72%x 3.071 million= 2.197 million are diagnostic work-ups for HIV- suspects. We assume 63% of these start with AFB microscopy (because .48 of ss+ are DOTS treated, and we assume that 25% of those starting with sputum end up non-dots treated or untreated, so .48/(1-.25) = .63, leading to 2197/.63 = 3,487,000 adult pulmonary HIV- suspects. Of the incident active cases 17% are

untreated (Global 2005), including 15% that can be calculated to be false negatives leaving 2% (of ss+) who are given no test. This leaves 35% for non-sputum diagnosis, the other possibility.

(Row 25,26) The recommended sputum microscopy procedure uses 3 samples and loss to follow-up includes those who fail to come back to give all their samples, or to obtain the microscopy results (15% in Squire, 2005). We assume this same percentage holds for those not obtaining relief from a trial of antibiotics.

Rows 27-29. We use the Cunningham regional data on number of x-rays given to TB suspects to guide subjective estimates of the proportion of those who do not get a sputum test who are x-rayed. The proportion of those going immediately from a positive x-ray to treatment varies depending on background prevalence and severity but is estimated to be small. The recent WHO guidelines recommend a trial of antibiotics before initiating Category I TB therapy.

(Row 30) estimate is based on two EQA studies and expert opinion. Row 32 is based on many studies.

(Row 33,34) The x-ray branches on the tree assume that a trial of antibiotics will often be given as recommended in WHO treatment guidelines 2003, so we pick the more sensitive point on the ROC curve (Van Cleef 2003; Harries 1997), relying on the trial of antibiotics to improve specificity.

Row 35,36 Studies on symptomatic relief of active TB by antibiotics show that 40% get relief, and 60% do not (papers in O'Brien 2003), as do 85% of those suspects without TB (Wilkinson, Bah,Somi). In a trial of antibiotics, patients will be asked to return if there is no relief but some will not so we need to assume a loss to follow-up as with microscopy. Putting the symptomatic relief and return rates together we can calculate the sensitivity of x-ray + a possible trial of antibiotics = 76% (suspicious x-ray) x [25% immediate treatment + 75%(trial of antibiotics) x 60% (no relief) x 85% (return) = 48%, and the 94% specificity is calculated similarly.

Access to new diagnostic tests:

For our advanced infrastructure category we used estimates of the % access to urban hospitals. Using the methods discussed in Girosi reference 20 of paper these were estimated to be 16% in Africa, 19% in Asia. For the TB clinics and hospital category we assumed the proportion with access would be the same as those currently going (row 22 of the table).

Outcomes:

Case fatality rates come from WHO estimates. (Rows 40-45) The treatment for those starting with the sputum test is assumed to be DOTS SCC, and treatment for the others is assumed to be non-DOTS. Because of our emphasis on diagnosis this assumption is maintained in the new world.

(Row 48,49) The estimate of additional transmission due to a case of untreated TB relies on TB being roughly in steady state in each region. TB epidemics are very slow (Blower, 1995) and the number of incident TB cases has not changed much by region in recent years, as population growth offsets slowly declining rates (Global 2005). So, each smear-positive case leads to another smear-positive case on average in each cycle of transmission. However, if the number of new smear-positive cases from an untreated case is 4 times that for treated cases (Borgdorff,MW Floyd K and Broekmans,JF). Interventions to reduce tuberculosis mortality and transmission in low and middle-income countries (Bulletin of the WHO 2002; 80:217-227), and 40% of cases are untreated, we can solve to show an untreated case infects 1.36 additional cases compared to a treated case. For a cycle of 4.5 years (DCP2, Dye and Floyd, 2005), and an annual discount rate of 3%, the cycle discount factor is $1/ (1.03^{4.5}) = 0.875$. Assuming the 1.36 additional cases receive average treatment, each will lead to another case each cycle. For an assumed horizon of 2030, there are 6 cycles, and so each initial untreated case will lead to an additional $(1- .875^{7})/(1- .875) \times 1.36 = 6.6$ discounted cases. Smear-negative cases are 22% as infectious. (Behr MA, Warren SA Salamon H, et al. Transmission of Mycobacterium Tuberculosis from patients smear-negative for acid-fast bacilli Lancet 1999 353 444-449.)

The overall costs of treatment (Row 46) (primarily opportunity costs). The bounds on the costs of treatment C compared to the benefits of treatment of a smear-positive case VSP, can be obtained by comparing sputum testing + treatment with the two alternatives of treating no-one and treating everyone. Let VSP be the value of treating a smear-positive. From the case fatality rates, estimating that two thirds of ss+ cases get DOTS SSC, and one third gets non-DOTS treatment, the mortality gain from treatment for smear-positive is $0.7 – 2/3 (.1) - 1/3 (.3) = .53$, and for smear-negative, where about 50% gets DOTS SSC it is $.2 – 1/2(.05) – 1/2 (.15) = .10$. So, $0.10/ .53 = .19$ and we assume the value of treating a smear-negative = .19 VSP[1]. Let p = the probability of TB among suspects. Assume 60% of adult pulmonary cases are smear-positive.

[1] Alternately, based on transmission, the value of treating a smear-negative = .22 VSP.

With our parameters, testing sputum and treating those with a positive test leads to .85 x .6 x p + .03 (1-p) C treatment costs per suspect with health gains of .51p VSP. Treating no one has 0 costs and 0 gains, and treating everyone has costs C and gains (.6 VSP + .4 x .19 VSP) p = .676p VSP per suspect. Now if testing is better than doing nothing, even when p = .05, we can solve to get .0255 VSP > 0.0546 C or C<.467 VSP. And if testing is better than treating everyone, even if p =.3, then .153 VSP – (.153 + .021) C > .3 (0.676) VSP - C, which implies .845 C> .0498 VSP, or C> .059 VSP.

This leads to .059 VSP < C < .47 VSP. In case fatality terms, VSP = .53 deaths, so this means .031 deaths < C < .25 deaths. In addition, we surveyed a convenience sample of experts on the disutility of over-treatment compared to under-treatment, with the median answer being that over-treatment was just as bad as under-treatment. If we set the costs of treatment = to the net average gains (mortality gains - the cost of treatment) from treating smear-negative patients, the answer .10/2 = .05 is within the bounds of the comparative exercise. Ultimately, we used C = .05, but this important number will be varied in sensitivity analysis. We did not include the impact of delay from slower tests on outcomes: each week of delay leads to about .2 discounted transmissions overall and a .004 additional chance of death. Jane Cunningham notes if the number of infections goes down over time as uninfected family and friends are used up, then early treatment might have a bigger impact than I assumed (See Girosi ref 20 of paper).

(Row 51): Our results represent one year totals, so the discount rate is used only to calculate ultimate changes in transmission, as done above. The standard for developed economies is 3% (Gold et al.), but due to capital market imperfections, but personal discount rates and possibly social discount rates would be higher in Africa.

(Row 47) (DALYs gained per TB mortality) Based on tables from www.DCP2.org we divided adult YLL discounted at 3% by Region in 2001 for TB/ adult deaths from TB in 2001. There should also be some morbidity benefit from treatment, so using WHO estimates that DOTS treatment shortens duration by a year, the Murray and Lopez GBD disability weight of about .27 for TB, and the estimate that 60% of treatment is DOTS treatment, we get a benefit of .16 per treatment. Perfect treatment in our model leads to 591,000 fewer deaths, and 1,993,000 more correct treatments so disability benefit per death = 1993 x .16/591 = .54 disability years. These were added to YLL/death, but this is a minor adjustment for YLL per death, which worldwide is 22. In an early CE article, the Murray group used a value of 22 DALYS gained per death for

high HIV Sub Saharan Africa (Murray, 1991). We assume HAART is available for treated HIV+ patients, and so have the same DALYs gained for them.

Table A1. Case Detection of Active (pulmonary, symptomatic) TB in HIV-Patients:
Base Case Clinical Values by Region

	Africa	Eastern Medit.	South Asia	Western Asia	Reference:	References and additional comments	
Natural History							
Population (millions)	**687**	**518**	**1615**	**1732**	WHO 2005		
Incidence cases of HIV- ss+ TB (1000s)	**820**	**281**	**1344**	**863**	WHO 2005		
Incidence cases of HIV- ss- TB (1000s)	**1003**	**344**	**1642**	**1055**	WHO 2005		
Adult cases/all cases In ss+	**0.8**	**0.72**	**0.72**	**0.62**	WHO2005	includes HIV+	
Adult cases/all cases in ss-	**0.6**	**0.55**	**0.64**	**0.59**	WHO 2005	includes HIV+	
Incidence adult SS+ HIV- (1000s)	**6.18**	**202**	**960**	**533**	calculated so row10 works for all HIV		
Pulmonary ss-/all ss-	**0.62**	**0.56**	**0.78**	**0.84**	WHO 2005 p22		
Pulmonary ss-/all ss- in Adult HIV-	**0.77**	**0.7**	**0.84**	**0.89**	calculated assuming EP twicd as common in kids, Adult HIV+	assumes prob(EP|ss-) is half as high in adults HIV - as in children Chauhan 2004	
Incidence adult pulm SS- HIV- (1000s)	**355**	**130**	**869**	**550**	Calculated so row 11 works for all HIV		
Prob (active TB in suspects)	**0.28**	**0.17**	**0.17**	**0.11**	calculated from # of workups	RSS WHO 2004 has similar but smaller numbers for ss+	p(ss+) =19% in tanzania, Ipuge,1996; 43% in SA Wilkinson 2000

"Adult pulmonary TB suspects" HIV-	**3,487**	**1,988**	**10,756**	**9,434**	Calculated as row 21/ row 22		
Status Quo Diagnosis							
Total Number of sputum diagnostic work-ups (1000s)	**3071**	**888**	**6551**	**6284**	Cunningham Data	includes HIV+	
% adult pulm TB that is HIV-	**0.72**	**0.99**	**0.97**	**0.99**	calculated	denominator includes row 12 + row 15 from HIV+ = 387,5,59, 10	
Number workups for HIV-	2197	875	6346	6227	row 19 x row 20	assumes # work-ups per patient same for hiv+ and hiv-	
Proportion of "TB suspects" who at some point are tested with AFB Microscopy	**0.63**	**0.44**	**0.59**	**0.66**	Calculated from % cases treated DOTS, WHO 2005	higher than % treated Dots because microscopy not always successful.	assume ss+ sputum ends with non treated 15% , and 10% shift to non-DOTS treatment.
Proportion of TB suspects who are non-sputum diagnosed X-ray or trial of ABx	**0.35**	**0.41**	**0.34**	**0.31**	100% - row21 - row 23		
Proportion of adults with pulm TB symptoms who are not tested for TB.	**0.02**	**0.15**	**0.07**	**0.03**	Calculated from % untreated WHO 2005	smaller than % untreated because some getting tests ultimately are not treated.	Assumed 25% of ss+ non-sputum end up non-treated
Microscopy loss to follow-up	**0.15**	**0.1**	**0.1**	**0.1**	Two studies	15% in Malawi Squire 2005, 14% Malawi Nyirenda	15% Botswana Creek , 5% bangladesh Van Deun

						1998	opinon	
trial of antibiotics loss to follow-up	**0.15**	**0.1**	**0.1**	**0.1**	assumed same as microscopy LTFU			
Proportion of those who return for negative smear result who are then X-rayed	**0.3**	**0.6**	**0.9**	**0.6**	Cunningham data on x-rays, calculation			
Proportion of those with non-sputum work-up who are X-rayed	**0.3**	**0.6**	**0.9**	**0.6**	Cunningham data on x-rays			
proportion of those with x-ray but no subsequent trial of Antibiotics	**0.075**	**0.2**	**0.225**	**0.15**	expert opinion, rest get trail of antibiotics	this is 25% of those getting x-ray		
Sensitivity of field microscopy for "ss+"	**0.85***				here "ss+" means would be detected by a good lab	.86 martinez 2005 mexico EQA program	Hawken nairobi 2001 26% of "ss-" were ss+ --> .15 of ss+ missed	If we pick up 50- 60% of TB as ss+, can't be missing many
Sensitivity of microscopy for ss-	**0**					Mundy Malawi 2002 had 98% concordance on good slides.		
Specificity of microscopy	**0.97**					Many studies		
Sensitivity of x-ray for active TB	**0.76**				one point on ROC curve	Harries 1997 in Toman Malawi 71%	Van Cleef 2003 76% in Nairobi, or 49%	nagpaul 88% 1970 national Indian lab
Specificity of x-ray for active TB	**0.68**				one point on ROC curve	Harries 1997 in Toman Malawi 72%	Van Cleef 2003 67% in Nairobi,or 90%	Bruchfeld Ethiopia 67%,nagpaul 96%
No Symptomatic relief w antibiotic if Active TB	**0.6**					Bah, Somi 8,9% of ss- improvers	oyewo 44% improve, Salanoponi	wilkinson2000 SA 40%,willkinson

						had TB	2000 29% of big Malawi study	1997 50%,
specificity of trial of antibiotics	**0.85**					Wilkinson 90%	too high number would not jibe with Bah, Somi results	
Sensitivity of x-ray + Trial of Antibiotics	**0.48**				**calculated 33,35**	assume each step is independent		
Specificity of x-ray + trial of antibiotics	**0.94**				**Calculated 34 36**			
Outcomes								
cf Rate **for Dots SSC treated ss+ TB**	**0.1**				**WHO 2005**	includes incomplete treatment		
cfRate **for dotsSSC treated ss- TB**	**0.05**				**WHO 2005**			
cf Rate **for noDots SSC treated ss+ TB**	**0.3**	**0.3**	**0.3**	0.2	**WHO 2005**	according to text, this higher because of delay and dots always gives rifampicin		
cfRate **for no dotsSSC treated ss- TB**	**0.15**	**0.2**	**0.15**	0.1	**WHO 2005**	we can get it right on average by using these numbers on the non-sputum test branch.		
Mortality Rate **for untreated ss+ TB**	**0.7**				**WHO 2005**			
Mortality Rate **for untreated ss- TB**	**0.2**				**WHO 2005**			

cost of a treatment in mortality terms	**0.05**				**Calculated in light of row 52**	Marginal net value of treatment calculated as average value of ss-treatment/2.
DALYS ***lost per TB mortality***	24	20	22	20	Murray Lopez GBD	
Transmission multiplier for untreated ss+ TB					**Calculated from disc. rate**	assumes transmission =1 per cycle, 4.5 year cycleup to 2050, so 10 cycles
Transmission multiplier for untreated ss- TB					**22% of row 46**	
Discount rate	**0.03**				**standard**	maybe should be higher in poorer countries

* *When the other three columns are blank, same value assumed for all regions.*

Table A2. Case Detection of Active (pulmonary, symptomatic) TB in HIV+Patients: Base Case Clinical Values*

	Africa	South Asia	Reference:	References and additional comments
Natural History				
Population (millions)	**687**	**1615**	WHO 2005	
Incidence cases of HIV+ ss+ TB (1000s)	**192**	**26**	WHO 2005	93% of cases are in these two regions
Incidence cases of HIV+ ss- TB (1000s)	**357**	**49**	WHO 2005	
% cases adult in ss+	**100**	**100**	WHO data assumption	HIV+ data in worksheet restricted to adults
% cases adult in ss-	**100**	**100**	WHO data assumption	
Incidence cases of HIV+ ss+ TB (1000s)	**192**	**26**	row 8	
Pulmonary ss-/all ss-	**0.62**	**0.78**	WHO 2005 p22	
Pulmonary ss-/all ss- in HIV+	**0.54**	**0.68**	Calculated	assumes EP is twice as likely in HIV+ as HIV- adults
Incidence cases of pulm HIV+ ss- TB (1000s)	**195**	**33**	row9*row12	note ss- bigger than ss+ in contrast to HIv- case, but …
Prob (active TB in suspects)	**0.28**	**0.17**	calculated from # of workups	RSS WHO 2004 has similar but smaller numbers for ss+
"Adult pulmonary TB suspects" HIV+	**1,387**	**347**	Calculated as row 18/ row 19	
Status Quo Diagnosis				
Number of sputum diagnostic work-ups (1000s)	**3071**	**6551**	Cunningham Data	
% adult pulm TB that is HIV+	**0.28**	**0.03**	WHO data	denominator includes row 12 + row 15 from HIV- = 973, 1829
Number workups for HIV+	874	205	row 19 x row 20	assumes # work-ups per patient same for hiv+ and hiv- suspects

...Apers had 54% TBss+ in sample 86% HIV + Zimbabwe 2004

43% in SA Wilkinson 2000

Proportion of "TB suspects" who at some point are tested with AFB Microscopy	**0.63**	**0.59**	Calculated from % cases treated DOTS, WHO 2005	higher than % treated Dots because microscopy not always successful.	assumed same as HIV-breakdown
Proportion of TB suspects who are non-sputum diagnosed X-ray or trial of ABx	**0.35**	**0.35**	100% - row21 - row 23		
Proportion of adults with pulm TB symptoms who are not tested for TB.	**0.02**	**0.07**	Calculated from % untreated WHO 2005	smaller than % untreated because some getting tests ultimately are not treated.	
Microscopy loss to follow-up	**0.15**	**0.1**	Two studies	15% in Malawi Squire 2005 14% Malawi Nyirenda 1998	15% Botswana Creek , 5% bangladesh Van Deun opinon
Proportion of those who return for negative smear result who are then X-rayed	**0.3**	**0.9**	Cunningham data on x-rays, calculation		
trial of antibiotics loss to follow-up	**0.15**	**0.1**	assumed same as microscopy LTFU		
Proportion of those with non-sputum work-up who are X-rayed	**0.3**	**0.9**	Cunningham data on x-rays		
proportion of those with x-ray but no subsequent trial of Antibiotics	**0.075**	**0.225**	expert opinion, rest get trail of antibiotics	subtracted from 27 and 28	
Sensitivity of field microscopy for "ss+"	**0.85**		here "ss+" means would be detected by a good lab	Apers, 66% ss+ in HIV +, 73% in just 38 HIV-patients Zimbabwe2003	Crampin 2001 Malawi 66% HIV+ and 89% HIV- were ss+
Sensitivity of microscopy for ss-	**0**			Bruchfeld 2002 Ethiopia says all kinds of diagnostic performace degraded in HIV+	
Specificity of microscopy for ss-	**0.97**			However, most of the refs parameters for test performance coming from SS Africa ...	do not differentiate by HIV status -- and come from countries where 30-80% of cases of HIV+
Sensitivity of x-ray for active TB	**0.76**		one point on ROC curve		
Specificity of x-ray for active TB	**0.68**		one point on ROC curve		
No Symptomatic relief w antibiotic if Active TB	**0.6**				

specificity of trial of antibiotics	**0.85**		
Sensitivity of x-ray + Trial of Antibiotics	**0.45**		**calculated 31,33**
Specificity of x-ray + trial of antibiotics	**0.95**		**Calculated 32 34**
Outcomes			
CFRate **for DOTS SSC treated ss+ TB**	**0.1**		**WHO 2005**
CFRate **for DOTS SSC treated ss- TB**	**0.1**		**WHO 2005**
CFRate **for noDOTS SSC treated ss+ TB**	**0.38**		**WHO 2005**
CFRate **for noDOTS SSC treated ss- TB**	**0.5**		**WHO 2005**
Mortality Rate **for untreated ss+ TB**	**0.83**		**WHO 2005**
Mortality Rate **for untreated ss- TB**	**0.74**		**WHO 2005**
cost of a treatment in mortality terms	**0.05**		**Calculated**
*16. DALYS **lost per TB mortality***	23	16	
Transmission multiplier for untreated ss+ TB	**2**		**Calculated from disc. rate**
Transmission multiplier for untreated ss- TB	**0.44**		**22% of row 46**
Discount rate	**0.03**		**standard**

marginal deaths due to TB -- HIV+ die of a lot of other diseases.

Marginal net value of treatment calculated as average value of HIV- ss- treatment/2.

assumes ARV therapy available

these numbers = HIV- rates/3.1 to make HIV + transmission = 1/4 that HIV-.

assumes transmission =1 per cycle, 4.5 year cycle to 2050

maybe should be higher in poorer countries

opportunity cost does not depend on current patient

they were not divided by 4 because some of difference due to more ss- in HIV+.

duration of untreated TB = .5 for HIV+, 2 for Hiv-

False positive disutility ratio compared to False Negative	**2**		**Median of survey .5 to 1**	Survey showed disutility to overtreatment, but not as much for HIV+, and some interest in prevention of TB in HIV+ Godfrey Faussett	FP did badly in HIV+ (because MD missed something else?) Crampin

APPENDIX B: PRELIMINARY ANALYSIS FOR MDR TB

B.1. INTRODUCTION

The WHO Stop TB Department estimated that there were 321,000-689,000 new multi-drug resistant tuberculosis (MDR TB) cases in 2003 (WHO, 2006) Historically, MDR TB was widely believed to be an effect of poor patient compliance with standard TB therapies. The solution to controlling the MDR TB epidemic was to improve patient compliance with first line therapies and strengthen DOTS programs. Because of the initially low incidence of MDR TB and the prohibitively high cost of second line therapies, many countries offered few or no options for patients suspected of or known to have MDR TB. Recently, MDR TB has received more attention and there is a greater impetus to diagnose MDR TB, secure second line therapies and treat MDR TB patients. MDR TB is now widely recognized to derive from several national TB program shortcomings: inadequate treatment regimens, limited drug supply, poor drug quality and limited patient compliance. (WHO,2006) Recent WHO guidelines offer a systematic approach to addressing the increasing incidence of MDR TB. (WHO,2006)

Drug Susceptibility Testing (DST) is the primary means for diagnosing MDR TB. DST can be performed directly on the sputum sample or, more commonly, it can be performed indirectly on a culture specimen. Following culture, DST requires additional time and laboratory sophistication. Direct DST is more difficult, requires greater laboratory sophistication, and has lower sensitivity than indirect DST methods. (WHO, 2006) To perform indirect DST technicians must first culture the sputum sample. Where culture is accessible, it can take up to six weeks and it is prone to error. WHO recommends taking several sputum samples to address this problem, performing DST on the sample cultured best (WHO, 2006). While the accuracy of DST can vary with the particular drug tested, it is most accurate for the drugs associated with MDR: Isoniazid and Rifampicin. WHO strongly recommends DST testing as a pre-requisite for MDR TB control programs arguing that empiric therapy with second-line drugs is dangerous in the long run (WHO, 2006). Empiric use of second-line drugs for first-line drug failures is accepted, but mainly during transition as countries build their laboratory and testing infrastructure.

Empiric therapy with second-line drugs is, in the long run, dangerous and is therefore not an acceptable long term method for distributing second line drugs.

Presently there are several DST methods for detecting MDR TB. The most commonly used are the proportion, absolute concentration, and resistance ratio methods done on solid media. DST on solid media can take an additional 2-4 weeks after culture. Sensitivity and specificity are relatively consistent across these three methods. Where culture and DST are performed, they are relatively sensitive and specific. Proficiency testing and training are increasingly common and usually result in sensitivity and specificity above 90%. (Abigail Wright, unpublished data).

Culture and Drug Susceptibility Testing (DST) tend to occur at the regional or national laboratory level. Some countries have only one laboratory capable of performing DST. In the former Soviet bloc countries, nearly everyone has access to culture and DST. In India and China, access to DST is considerably more limited (Cunningham, 2004). The public healthcare network does not even offer culture; only those who can afford to pay for culture and DST have access to these tests if recommended by their care providers.

In the context of lengthy and difficult culture and DST, a rapid test for detecting MDR TB could improve access in several regions, identify MDR TB patients more quickly and lead to reductions in mortality and transmission. (WHO, 2006) The TB Working Group of the Bill and Melinda Gates Foundation Global Diagnostics Forum considered several intervention points for improved MDR TB diagnostics.

The diagnostic situation picked for study was a test for suspected MDR TB. Such a test would be beneficial in all *new cases* in high-burden areas (e.g., Eastern Europe) and in *treatment failures* irrespective of location. Although the proportion of MDR TB cases is relatively low, the catastrophic consequences of a major MDR TB epidemic imply that MDR TB carries more weight for TB control than the absolute number of cases might

suggest. Also, Category IV[2] treatment is very expensive and onerous, so that most developing countries would want to avoid any unnecessary treatments. Currently the DST tests for MDR TB have to follow culture and are therefore hampered by both the speed with which culture can occur and limitations on where testing can be properly performed.

The group discussed the value of a diagnostic test for MDR TB in areas of high MDR TB prevalence. Two scenarios were thought to be of value: testing all new cases in areas with high MDR TB prevalence and testing those who failed initial treatment with first line drugs in all locations. In both scenarios we would assume that all patients entering the model were suspected of having TB and would receive some form of treatment irrespective of the availability of DST. The new diagnostic would focus on determining whether or not the patient had MDR TB and should therefore receive second line drugs. The new diagnostic would be provided only to those patients who are currently treated. We assume a positive test result will be followed by appropriate treatment for MDR TB in all cases.

The group selected the diagnostic scenario of highest yield for MDR TB, testing confirmed TB cases that have been previously treated for TB in Eastern Europe and Asia.[3] Due to resource constraints and the delay of current diagnosis, in many settings DST testing is limited to patients thought to have a high probability of have drug resistant TB. At the country and regional levels, those most at risk for drug resistant TB are confirmed TB cases that have been previously treated for TB. Because we model at the regional level, we limit our model to those individuals with the greatest risk of MDR TB—patients previously treated for TB. We go on to discuss the implications of testing people earlier in the course of disease.

[2] Category IV treatment refers to second-line drugs and treatment regimens used to treat MDR TB and should not include Isoniazid and Rifampicin (WHO, 2006)
[3] Previously treated cases are defined as patients receiving one or more months of continuous treatment for TB sometime in the past. (WHO,2006)

Better diagnostic technology offers the potential to improve management of patients with active tuberculosis in many ways by lowering the overall cost of testing, and increasing the speed, sensitivity and specificity of diagnosis. In particular, drug susceptibility testing for Isoniazid and Rifampicin resistance to detect MDR TB that does not depend on culture or is less technically demanding could reduce transmission of MDR TB and improve index case outcomes.

B,2, THE MODELING APPROACH FOR MDR TB

The general modeling approached used by Keeler et al (2006) to model the impact of improved TB diagnostics is here applied to MDR TB. We developed a static decision analytic model using decision trees. We characterize the status quo in current diagnosis and treatment of MDR TB and then model the introduction of an improved diagnostic for MDR TB. The diagnostic is chosen over the status quo when it produces improvements in health outcomes.

MDR TB TREE DESCRIPTION

The tree begins with a previously treated (i.e. one who reports one or more months of previous TB treatment) confirmed TB case. The ultimate treatment decision is whether to use first- or second-line drugs. Initially, there are two options: test with culture and DST or try a Category II regimen—an extended course of first-line drugs. The alternative treatment is a Category IV regimen—a course of second-line drugs where particular drugs selection is based on local resistance patterns. We assume Category IV regimens will always exclude Isoniazid and Rifampicin.

Figure B.1 depicts our standardized model of the status quo in MDR TB diagnosis and treatment. A certain percentage of the population has access to culture and DST. We assume that patients are initiated on Category II treatment while awaiting DST results. For those who test positive, because culture and DST are a lengthy process, some patients will default from treatment before they receive test results. We assume that the probability of defaulting is independent of underlying disease status. Those who default are assigned outcomes associated with untreated MDR-TB or untreated drug susceptible

(DS) TB, depending on the underlying disease status of the patient. This is noted at "do nothing" in Figure B.1. We assume culture and DST results will take approximately two months and that two months of treatment with Category II drugs will not clear DS TB or MDR TB. Those who test positive and do not default will be swapped to Category IV regimens. We do not consider individualized treatments; but, rather, assume that standardized treatment regimens are derived from local drug-resistance surveillance (DRS) data. For those with MDR-TB, we assume this is appropriate treatment and assign outcomes accordingly. For those with DS TB mistakenly treated with a Category IV regimen we assign outcomes associated with Category IV treatment.

Those who test negative will remain on a Category II regimen. We consider this appropriate treatment for those who have DS TB and assign outcomes for DOTS treated TB from the TB tree. For those who have MDR-TB we track their response to re-treatment: failed, defaulted/transferred, died, cured/successful treatment. Note that the coding of outcomes for MDR TB patients explicitly considers the possibility of default and we assume that the cumulative case fatality rate for DS TB patients appropriately treated also includes the possibility of default. From Espinal et al (2000) we know that the death rate for DS TB patients while receiving re-treatment averaged 3% across six sites with failure and default rates of 7% and 15%, respectively.

Patients who remain on Category II treatment and then fail are subsequently treated with a Category IV regimen. The mortality outcomes for this group are the same as those initially treated with Category IV drugs. Those who default or transfer out are listed as not completing treatment and are counted as untreated (Suarez, 2002). We define successful treatment to mean zero mortality.

When DST is not available, we assume previously treated patients are given a trial of Category II drugs. The possible outcomes for this group mimic those described above for MDR TB patients who test negative with DST, but the probability the patient is MDR is different than that following a negative test result.

When we introduce a new diagnostic, patients either do or do not have access to the new test. **Figure B.2.** outlines the introduction of a new MDR TB diagnostic. We assume those currently given DST are the first to have access to the test. The new diagnostic is modeled similarly to DST. Patients either test positive or negative and we have allowed for the fact that patients may default from Category II treatment while awaiting test results if the new diagnostic is not "rapid" (i.e., results can be returned during the same patient encounter). Those who test positive and do not default are swapped to a Category IV regimen and those who test negative remain on Category II drugs with outcomes assigned accordingly. The new test can improve care relative to the status quo in three areas: increased access over DST, improved test characteristics in terms of sensitivity and specificity for detecting Isoniazid and Rifampicin resistance, and reductions in the delay for test results associated with culture dependent DST.

ADDITIONAL ASSUMPTIONS

We assume that all regions have the ability to appropriately diagnose TB. Based on this assumption, we do not see patients in the tree who do not have TB. These patients would not change the mortality or transmission estimates we generate in the model as we are only calculating mortality and transmission conditional on TB or MDR TB. These patients *would* contribute to calculations of wasted treatments. We assume that all patients have access to appropriate treatment monitoring (smear).

We assume a homogenous re-treatment patient population. We group all re-treatment cases into one category and do not distinguish whether they were previously treated with first- or second-line drugs. In reality, patients who received longer courses of initial treatment or have received second-line drugs in the past may have worse outcomes than those who received only one or two months of treatment. We do not differentiate individuals based on treatment histories.

We assume that all previously treated patients have an equal probability of receiving DST. This does not account for the fact that some patients may be prioritized based on personal treatment histories or contact tracing. Further, we do not separate out special

populations such as children, pregnant women, HIV positive, elderly, or drug-dependent patients when estimating the effects of testing and treatment.

We assume that no one is given Category IV treatment without a DST result or before failing a trial regimen of Category II drugs. This is in line with WHO recommendations (WHO, 2006).[4] We assume that all previously treated patients have an equal probability of receiving DST. This does not account for the fact that some patients may be prioritized based on personal treatment histories or contact tracing. For all patients given Category IV treatment regimens, we do not consider individualized treatments; but, rather, assume that standardized treatment regimens are derived from local drug-resistance surveillance (DRS) data.

We only consider resistance to Isoniazid and Rifampicin. A new diagnostic will simply indicate whether or not a person has MDR TB—resistance to both Isoniazid and Rifampicin. We do not assume that the new diagnostic will differentiate between Isoniazid and Rifampicin resistance in reporting to allow for detection of mono-resistance.

To isolate the impact of a new diagnostic under optimal treatment conditions, we assume that all patients can access the appropriate treatment. Specifically, all patients can access DOTS and appropriate Category IV drugs for local resistance patterns through a program such as DOTS-Plus. Implicit in this strategy is the assumption that all settings can access appropriate DRS data. We assume that patients are given standardized treatment regimens consisting of 5-6 Category IV drugs. This is because we are evaluating the benefit of a binary test for MDR TB. We do not assume that all patients will have access to drug resistance testing for all first and second line drugs within the country. This would be necessary to implement individualized treatment regimens.

[4] Despite these recommendations some patients are empirically treated with Category IV drugs. This problem is particularly acute in former Soviet Union countries where up to 50 percent of previously treated patients may be initiated on Category IV regimens while awaiting DST results. Despite these occurrences, we chose to model the recommended treatment protocols.

B.3. MDR TB Model Parameters

Table B.1. outlines the input parameters used in the MDR TB model for three regions: Eastern Europe, Western Pacific and Southeast Asia. Calculations for particular parameters are noted in the calculation column of table B.1 when appropriate. Further discussion of particular parameters follows.

Percent receiving DST:

We calculate the percent of patients receiving DST in the status quo as the number of DSTs given within a given region divided by the total number of previously treated cases within that country. We use data on the number of DSTs given by region (Cunningham et al., 2004). These data do not isolate DSTs given to previously treated and new cases. Neither do the data separate out DSTs given for DRS. Thus, our calculation assumes that very few new cases receive DST, very few are done for DRS and that patients do not receive multiple tests.

Weekly default rate:

We assume the default rate is independent of underlying disease status. There is scant data to inform this parameter, particularly by underlying disease status. It is not clear whether MDR TB or DS TB patients are more likely to default from treatment with Category II drugs while awaiting DST results. MDR TB patients may be more likely to default as they are receiving ineffective treatment and will continue to feel ill. Conversely, it may be that BD TB patients are more likely to default because they are receiving appropriate treatment and beginning to feel better.

We base our estimate of a weekly default rate on the 3 month cumulative default rate reported in Suarez et al. (2002). We use the reported 2 percent 3 month default rate reported for all cases and assume a linear model to compute a weekly default rate of 0.25%.

Outcome Parameters

We track two primary outcomes: mortality—both due to MDR TB and DS TB—and transmission of MDR TB. Because we have a static model of MDR TB testing and treatment, we track transmission through static multipliers depending on the numbers of weeks a patient transmits.

Mortality:

We do not explicitly track ss+/ss- in the MDR TB model. Instead, we assume an initial distribution of smear positive patients among previously treated cases of 60%. We use this proportion to calculate case fatalities for DS TB as a weighted average of ss+ and ss- case fatalities from the coughers TB model presented in Keeler et al. (2006). We do not take HIV status into consideration.

Due to scarce data, we rely on expert opinion to determine MDR TB case fatality rates. We assume the case fatality rate for DS TB patients treated with a Category II regimen is equal to that for TB patients treated with DOTS. Based on expert consultations we assume DS TB patients mistakenly treated with second line drugs will fare worse that those treated with first-line drugs, but better than TB patients treated with non-DOTS therapy, because Category IV regimens will not contain Isoniazid and Rifampicin. We assume that the case fatality of DS TB patients treated with a Category IV regimen is higher than the ss+/- weighted case fatality of DOTS treated TB, but lower than the ss+/- weighted case fatality for non-DOTS treated TB, where the case fatalities are those calculated in the cougher's model in Keeler et al. (2006). We set the case fatality equal to the midpoint—16%--of this range [8%,24%].

Transmission multipliers:

We track transmission of MDR TB as this highlights a prime driver of the increased attention given to treating patients for MDR TB. Category IV drugs are far more expensive and difficult to manage than standard DOTS treatment. The value of treating MDR TB patients is, in part, in quelling the epidemic and averting further MDR TB cases, along with the future costs associated with treating those cases.

There is thought that the MDR TB epidemic is expanding; in some areas the first stage transmission coefficient may be greater than one (Coker, 2004). However, there is no consensus on the overall state of the epidemic and so we assume a steady-state transmission of MDR TB in calculating the weekly transmission rate for a single case of untreated MDR TB. We assume no fitness cost to MDR TB. We assume patients are infectious for two years (Borgdorff, 2002) and that a single transmission cycle is 4.5 years (Murray, 1991; Dye and Floyd, 2005). We assume patients are infectious for an average of six months before entering the model. Some MDR TB patients will be cured by Category II treatments (Espinal, 2000). We only consider transmission by MDR TB patients on Category II who eventually die, fail, default, or transfer off treatment. In the status quo, MDR TB patients fall into five transmission categories :

- Those initiated on Category II and who would be cured by Category II treatment (transmit 0 weeks)
- Those testing positive with DST and for whom Category II treatment would not have been successful (transmit 14 weeks awaiting results and assuming no transmission once patient initiated on Category IV treatment)
- Those given a trial of Category II treatment who die while on treatment (transmit an average of 16 weeks assuming deaths uniformly distributed throughout treatment period of eight months)
- Those who fail a trial of Category II treatment and are given a Category IV regimen (transmit 32 weeks assuming an eight months treatment period and no transmission following initiation of Category IV treatment)
- Those who default or transfer off Category II treatment (transmit 78 weeks)

Using the status quo decision tree we calculate the number of people in each category. With the assumption that each case will generate one new MDR TB case each transmission cycle we solve for the weekly transmission rate of 0.0186. The weekly transmission rate times the weeks a patient will transmit gives the number of new cases generated in a single transmission cycle by a patient in each of the above five categories. Assuming a transmission cycle of 4.5 years and using a three percent discount rate give a cycle discount factor of 0.875. Out to the year 2030 we have 6 transmission cycles. So,

each current MDR TB case will generate *a**4.4096 new MDR TB cases out to the year 2030, where *a* is the number of new MDR TB cases generated in a single cycle for the appropriate transmission category.

B.4. MDR TB RESULTS

Table B.2 shows the impact of hypothetical new diagnostics for MDR TB for all three regions modeled. **Tables B.3.-B.5.** give the regional breakdowns of these results. We first consider new diagnostics accessible to those currently receiving DST—status quo access. Second, we consider access to a new diagnostic requiring moderate, minimal and no infrastructure as defined in Olmsted et al. (2006). We modeled a rapid test to reflect the recent FIND and Biotec (UK) announcement of a drug susceptibility test capable of producing results within two days.

Table B.2. is split into sections by access categories defined by the infrastructure requirements of the new diagnostic: requirements equivalent to current culture followed by DST, moderate infrastructure, minimal infrastructure and no infrastructure. For the regions we consider, most people can physically access technologies requiring minimal to moderate infrastructure. Refer to Olmsted et al (2006) for more information on how we assess the percent of a given population with access to diagnostics requiring moderate, minimal or no infrastructure.

Within each infrastructure section, the rows represent hypothetical new tests described by three characteristics: sensitivity, specificity and weeks until results are available to the patient (which could be reduced by a faster test). The last four columns represent outcomes relative to the status quo, so for example, a new diagnostic requiring moderate infrastructure that is rapid and with sensitivity and specificity both equal to 90 percent will save 4,533 lives. Reducing infrastructure requirements of the same test to minimal infrastructure requirements will save 8,605 lives. Lives saved refers only to the index cases. MDR TB cases averted refers to cumulative transmission out to the year 2030. Wasted Category IV treatment is a measure of over-treatment and tracks DS TB patients mistakenly initiated on a Category IV regimen. Because Category IV drugs are much

more expensive than standard TB treatment it is important that these medications go to patients truly ill with MDR TB. Furthermore, inappropriate and excessive use of Category IV treatments has the potential to lead to increased resistance to second line therapies. The percent of total TB deaths averted refers to the percent of total annual TB deaths prevented by the new diagnostic. Because previously treated cases are only a small fraction of the total number of annual TB cases, this percentage will always be small.

Much of the mortality reduction could come from increasing access.. The first test shown—a slow test that is perfect and accessible to all who currently receive DST—saves only 1,542 lives. Compare these gains to increasing access to current DST—a 95% specific, 95% sensitive test with a 14 week delay and no infrastructure requirements--which saves 9,370 lives. This same test prevents 68,299 MDR TB cases out to the year 2030 and increases unnecessary Category IV treatments by 18,292. This and other imperfect but more accessible tests would increase unnecessary treatments with second line drugs.

The final column gives the lives saved as a percent of total annual TB deaths. So a perfect rapid test available to the entire population would save 17,464 lives each year (last row), 1% of the 1,750,000 total TB lives lost annually. Many have commented that if we did a better job of initial treatment, MDR would be an even smaller concern.

The largest gains in reducing mortality are from improvements in access. Improvements in DST test accuracy have a smaller yield because the test is already quite accurate. Alternatively, the largest gains in reducing *transmission* are from shortening the delay for test results. At all levels of access, for any test sensitivity and specificity combination, we only see notable changes in future MDR TB cases by reducing the delay from 14 weeks to a few days.

Reduced delay or increased access, in principle, might be done with current methods for DST. Investing in systems to track and follow-up people once they enter the system to

reduce defaulters would reduce the harm associated with delays in accessing test results. Improved infrastructure in Asia would increase the number of people with access to culture and DST. However, it might be more efficient to develop faster and less demanding tests that would not require those investments.

Our model depends heavily on four parameters that are not well documented in the scientific literature: Use of DST by previously treated patients, field sensitivity and specificity of DST, and the mortality rate of DS TB patients treated with second line drugs. In the next few years, as experience with MDR testing and treatment in the DOTS- plus programs becomes available, modelers should be able to improve these estimates.

B.5. MDR TB Sensitivity Analyses

The tornado diagram in **Figure B.3** highlights the percent change in lives saved for a one percent change in each input parameter listed for Southeast Asia. This one-way sensitivity analysis is presented for the scenario in which the new diagnostic is 97 percent sensitive, 97 percent specific, takes 14 weeks to produce results and requires minimal infrastructure. **Figure B.4** shows a two-way sensitivity analysis for a new rapid diagnostic that requires minimal infrastructure. These lines show the tradeoffs between sensitivity and specificity performance for a test that is widely available and convenient. Tables B.2 and B.3.-B.5 also present the results of a Monte-Carlo simulation in which we vary each input parameter within the ranges reported in Table B.1. These standard deviations are indicative of the uncertainty underlying each of the parameters used in the model. Standard deviations are reported in parentheses beneath the point estimates for health outcomes associated with each row. Given the standard deviations, it will be uncertain whether very minor improvements in the test specifications will lead to noticeable improvements.

Figure B.1. Decision tree for status quo management of previously treated TB (MDR TB suspects)

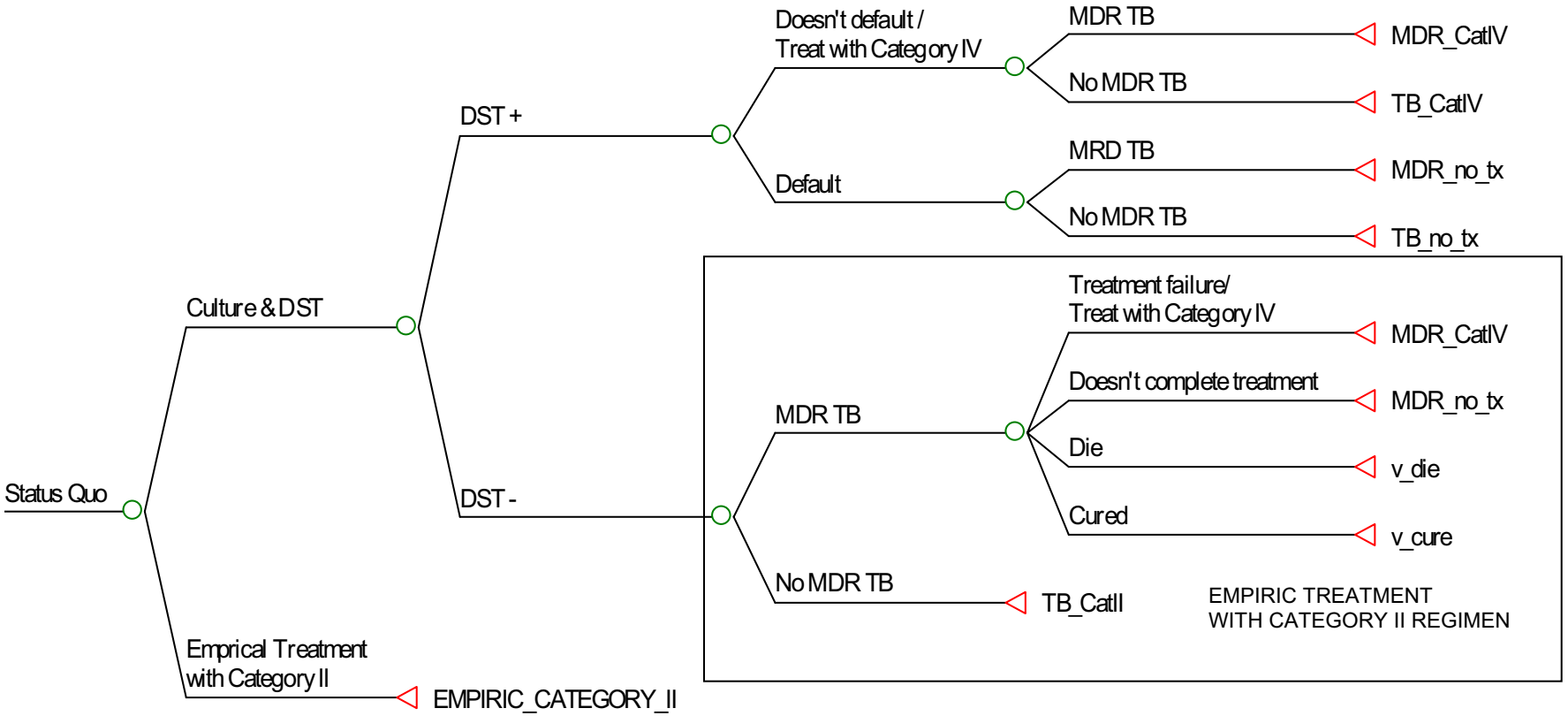


Figure B.2. Introduction of a New Diagnostic for MDR TB

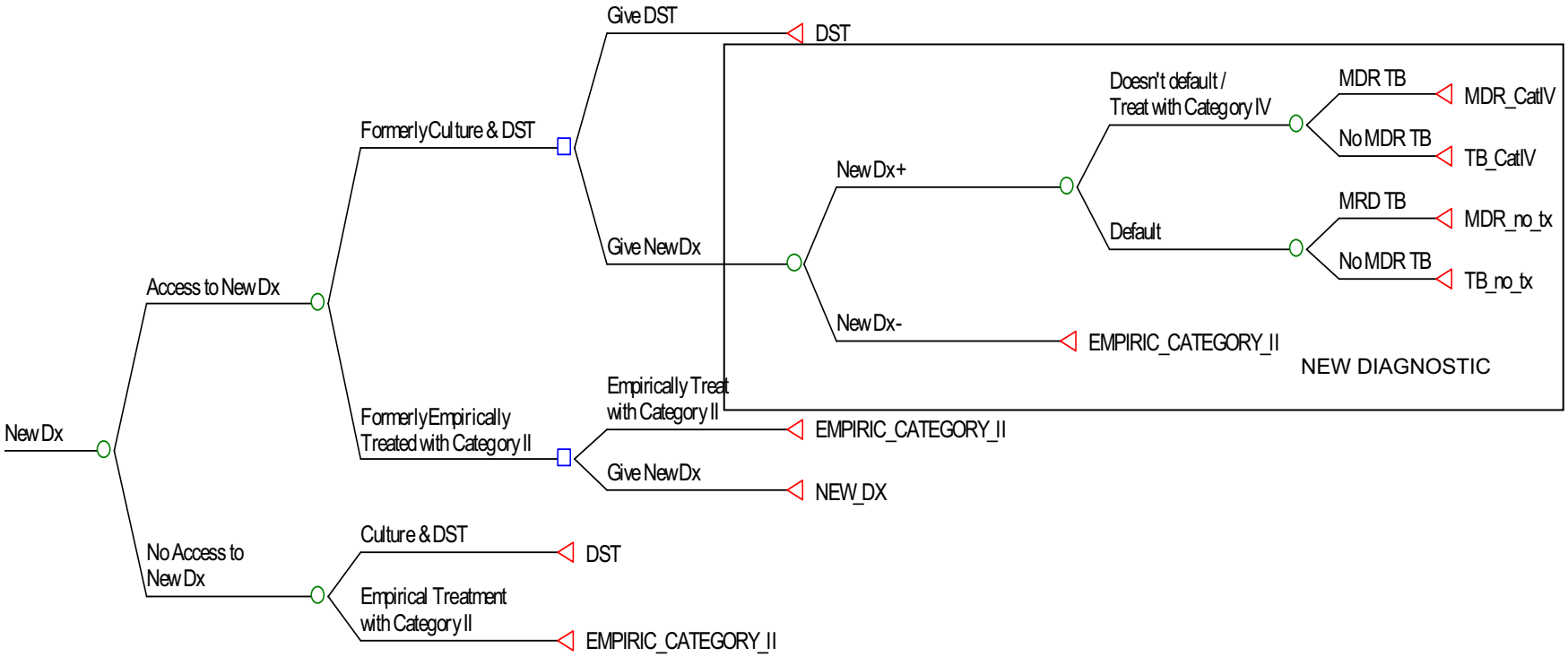
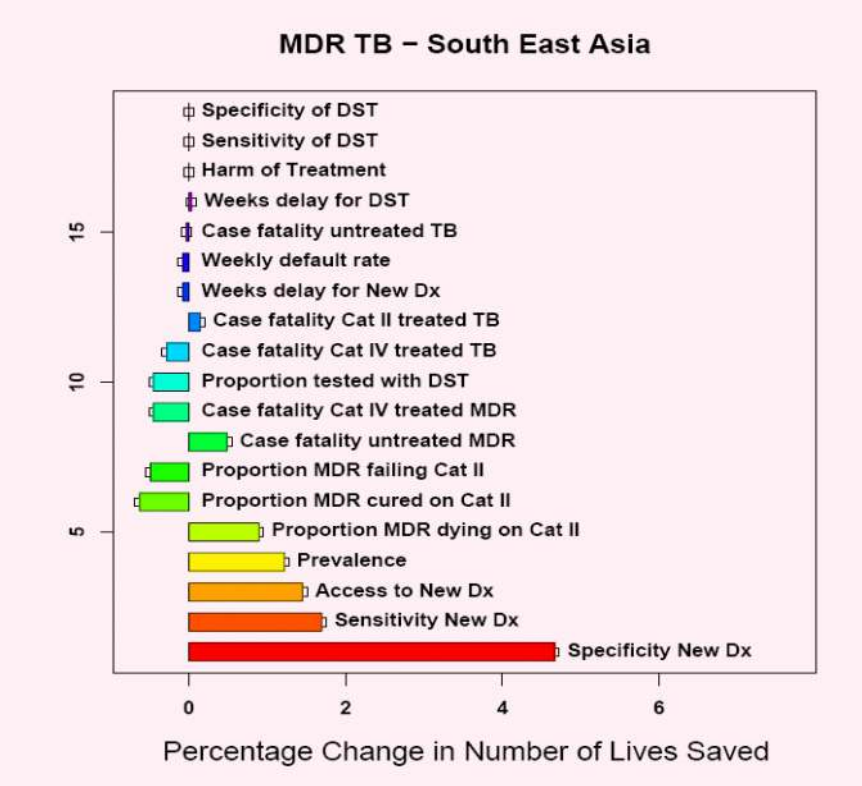
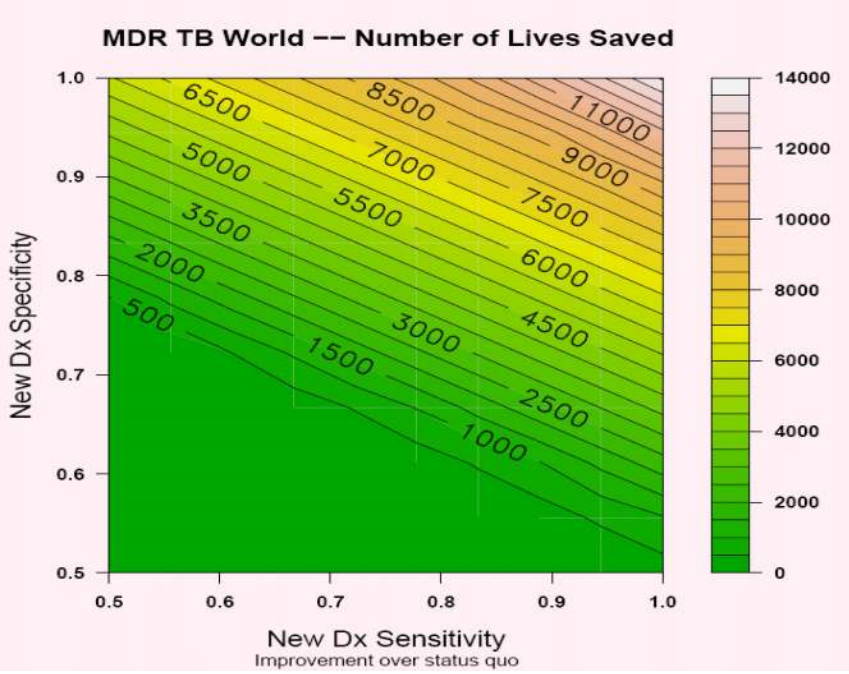


Figure B.3. Tornado diagram for Southeast Asia for a new diagnostic requiring minimal infrastructure with a 14 week delay.



This figure outlines the percentage change for an equivalent percent change in each of the input parameters. The base scenario is a new diagnostic requiring minimal infrastructure that is 97 percent sensitive, 97 percent specific and has a 14 week delay to produce results. Consider the proportion of MDR patients dying on Cat II treatment (5th line up from the bottom). This says that a 10 percent increase in that parameter means results in the proposed test saving 10 percent more lives. The test characteristics for DST are not important for this scenario because the proposed diagnostic beats DST on both sensitivity and specificity.

Figure B.4. Two-way sensitivity analysis of new diagnostic sensitivity versus specificity for a rapid test requiring minimal infrastructure.



This figure shows the trade-off between sensitivity and specificity of a new diagnostic that is rapid and requires only minimal infrastructure. For instance, a new diagnostic that is 80 percent sensitive and 80 percent specific will save 4,500 lives. Increasing sensitivity to 90 percent saves an additional 1,500 lives. Alternatively, increase specificity to 90 percent, and keeping sensitivity at 80 percent, saves an additional 2000 lives. This is due, in part, to the morality cost of mistreating a patient with H/R susceptible TB. When specificity is low more H/R susceptible patients are mistakenly given Category IV drugs. By the slope of the above lines we see that this cost of low specificity is slightly higher than the cost of low sensitivity—delaying treatment with Category IV drugs for MDR TB patients an additional 8 months or so. The true cost of low sensitivity may not be realized in examining lives saved, but, rather, is most apparent in examining changes in future cases of MDR TB.

Table B.1. Input Parameters for MDR TB Model

Parameter Name	Parameter Value*			Calculation	Source/Comment
Region	**Eastern Europe**	**South-East Asia**	**Western Pacific**		
Epidemiological Data					
Population of Interest = Previously treated TB cases	75,000	332,000	362,000		Zignol et al. Presentation at the CDC Late Breaker session, UNION Conference 2005
Prevalence of MDR TB amongst previously treated TB patients	39% [32%,45%]	23% [15%,30%]	26% [20%,33%]		Zignol et al. Presentation at the CDC Late Breaker session, UNION Conference 2005
Weekly default rate on Category II treatment	0.25% [0.05%,0.5%]			(3% cumulative default rate)/(12 weeks) = 0.25%	This assumes that the default rate is independent of underlying disease status. This assumes a linear default model. 3% is the 3 month default rate for patients undergoing re-treatment with second line drugs (Suarez et al.,2002)
Access (by region)					
Percent of TB patients currently given culture + DST	95% [80%,100%]	27% [15%,35%]	29% [20%,40%]	number of DSTs given/number of previously treated cases	Cunningham data, for Eastern Europe use Russian Federation
Percent of previously treated TB patients given Category II drugs	5%	73%	71%		Assume all previously treated cases not given DST are given a trial of category II drugs

Status Quo Test Characteristics					
Sensitivity of DST for I & R resistance	95% [80%,100%]				Abigail Wright, unpublished data *expert opinion*
Specificity of DST for I & R resistance	95% [80%,100%]				Abigail Wright, unpublished data *expert opinion*
Time delay for DST results (in weeks)	14 [12,24]				This will be used to compute additional transmission due to delay in treatment. 3-4 month delay reported in Espinal et al (2000)
Responses to Category II regiment -- MDR TB patients					
Failed	34% [8%,50%]				Espinal et al. (2000) JAMA
Not completed	26%			Taken to be defaulters and transfers = 1 - failures - deaths - cures	Espinal et al. (2000) JAMA.
Die	11% [2%,18%]				Espinal et al. (2000) JAMA
Cure	29% [14%,25%]			Taken to be "treatment success"	Espinal et al. (2000) JAMA
New Diagnostic Characteristics					
Sensitivity	*varied*				
Specificity	*varied*				
Time delay for results (weeks)	*varied [0,16]*				Consider discrete scenarios of 0 and 16 (fast and slow tests)
Time delay for New Diagnostic results (in weeks)	*varied*				
Outcomes					

Case fatality					
Case fatality for MDR patients treated with Category IV drugs	7% [5%,10%]				Leimane et al. (2005) Lancet
Case fatality for MDR patients treated with Category II drugs who transfer or default	21% [18,35%]				*expert opinion*,, assume partial Category II treatment for defaulters and transfers equivalent to no treatment
Case fatality for DS TB patients treated with Category IV drugs	16% [8%,24%]			midpoint of case fatality of DOTS treated DS TB and non-DOTS treated DS TB	Assume DS TB equivalent to standard TB. Assume that, because Cat IV regimens lack H and R, they are not as successful at clearing TB.
Case fatality for DS TB patients treated with Category II drugs	8% [5%,10%]			(% ss+)*(cf DOTs treated ss+ TB) + (1-%ss+)*(cf DOTs treated ss- TB)	weighted average of ss+/- TB parameter for treated TB
Case fatality for DS TB defaulting or transferring off Category II	54% [30%,60%]			(% ss+)*(cf untreated ss+ TB) + (1-%ss+)*(cf untreated ss- TB)	weighted average of ss+/- TB parameter for untreated TB. Applied to defaulters as well.
MDR TB Transmission to year 2030 (including all generations)					
Weekly transmission rate	0.0186 [0.012, 0.022]				Calculated, see text
Weeks transmitting for MDR patients destined to be cured by Cat II	0				assumption
Weeks transmitting for MDR TB patients destined to fail/default/transfer off Category II who test positive with DST	14				Espinal et al., 2000

Weeks transmitting for MDR TB patients given a trial of Category II drugs who then die	16			Assume deaths uniformly distributed across an 8 month Category II treatment regimen	Espinal et al., 2000
Weeks transmitting for MDR TB patients failing a trial of Category II drugs	32				Espinal et al., 2000
Weeks transmitting for those who default or transfer off of Category II regimen	78				Borgdorff, 2002; assumes a 6 month lag before patients enter the model
Harm of Treatment					
The "harm" of treatment: How many Category IV treatments of non-MDR TB will you accept to treat one more case of MDR TB properly?	1				From mortality data above, giving category IV drugs to non-MDR TB is just as dangerous as giving category II drugs to MDR TB. As C decreases, the number of false positives we will accept increases. A false positive rate of 1 corresponds to a C of approximately 0. Use a range of C = [0,0.02]

*** Parameters listed in only the first column are constant across all regions. Ranges are given below the parameter where applicable.**

Table B.2. The attributable benefit of a new diagnostic for MDR-TB --All Regions (SD*)*

Test	Sensitivity	Specificity	Delay for results (weeks)	Total Lives Saved*	MDR-TB Cases Averted	Wasted Category IV Treatments Averted	Percent of Potential Total TB Lives Lost Saved†
Status Quo: *Culture and DST*	95%	95%	14	0	0	0	0.00%
New Diagnostic with Status Quo Access‡							
Slow Test							
Perfect Test	100%	100%	14	1,542	-4,052	9,176	0.09%
				(669)	*(11,634)*	*(2,873)*	
Rapid Test							
Performance of DST	95%	95%	0	1,570	143,682	-333	0.09%
				(832)	*(30,656)*	*(3,831)*	
Perfect Test	100%	100%	0	2,778	153,926	9,176	0.16%
				(603)	*(24,559)*	*(3,805)*	
New Diagnostic requiring Moderate Infrastructure§							
Slow Test							
Performance of DST	95%	95%	14	3,837	27,809	-7,572	0.22%
				(1,206)	*(17,358)*	*(3,293)*	
Perfect Test	100%	100%	14	6,593	18,853	9,072	0.38%
				(1,906)	*(25,446)*	*(4,379)*	
Rapid Test							
Moderate Test	90%	90%	0	4,533	255,452	-25,423	0.26%
				(950)	*(48,254)*	*(3,920)*	
Performance of DST	95%	95%	0	6,655	272,407	-8,176	0.38%
				(1,447)	*(44,380)*	*(4,648)*	
Perfect Test	100%	100%	0	8,777	289,361	9,072	0.50%
				(1,094)	*(29,357)*	*(4,967)*	
New Diagnostic requiring Minimal Infrastructure§							
Slow Test							
Performance of DST	95%	95%	14	7,581	55,027	-14,911	0.43%
				(2,317)	*(44,890)*	*(5,903)*	
Perfect Test	100%	100%	14	11,551	41,397	9,176	0.66%
				(1,822)	*(46,122)*	*(4,161)*	
Rapid Test							
Moderate Test	90%	90%	0	8,605	378,433	-40,744	0.49%
				(2,194)	*(63,677)*	*(3,846)*	
Performance of DST	95%	95%	0	11,646	402,288	-15,784	0.67%
				(2,682)	*(59,264)*	*(3,412)*	
Perfect Test	100%	100%	0	14,687	426,142	9,176	0.84%
				(3,164)	*(68,831)*	*(4,471)*	
New Diagnostic with No Infrastructure Requirements§							

Slow Test								
	Performance of DST	95%	95%	14	9,370	68,299	-18,292	0.54%
					(2,760)	*(40,118)*	*(2,708)*	
	Perfect Test	100%	100%	14	13,894	52,585	9,176	0.79%
					(3,315)	*(53,163)*	*(3,799)*	
Rapid Test								
	Moderate Test	90%	90%	0	10,543	435,551	-47,751	0.60%
					(2,821)	*(67,845)*	*(4,694)*	
	Performance of DST	95%	95%	0	14,003	462,579	-19,288	0.80%
					(3,062)	*(47,345)*	*(3,856)*	
	Perfect Test	100%	100%	0	17,463	489,606	9,176	1.00%
					(2,693)	*(75,518)*	*(3,901)*	

***** Refers to the index case only
† The denominator used in this column is the total number of annual reported TB deaths: 1.75 million in 2003. The absolute best we ever achieve with respect to mortality is slightly under 1 percent of the total mortality burden, highlighting the relative importance of MDR TB diagnostics to other improvements in TB diagnostics
‡ Status Quo access for each region is defined as the percent of the population in the given region who currently receives DST: 95% for Eastern Europe, 27% for South-east Asia, and 29% for the Western Pacific Region. **Table B.1** provides further information on the source and ranges for current access to DST.
§ For information on calculations of the percent of the population with access to minimal and no infrastructure requirements refer to Olmsted et al. (2006)
SD, standard errors

Table B.3. The attributable benefit of a new diagnostic for MDR-TB in **Eastern Europe** (*SD)*

Test	Sensitivity	Specificity	Delay for results (weeks)	Total Lives Saved*	MDR-TB Cases Averted	Wasted Category IV Treatments Averted	Percent of Potential Total TB Lives Lost Saved†
Status Quo: *Culture and DST*	95%	95%	14	0	0	0	0.00%
New Diagnostic with Status Quo Access‡							
Slow Test							
Perfect Test	100%	100%	14	389	464	2,097	0.02%
				(204)	*(4,800)*	*(1,814)*	
Rapid Test							
Performance of DST	95%	95%	0	385	46,810	-76	0.02%
				(376)	*(16,907)*	*(1,741)*	
Perfect Test	100%	100%	0	723	50,570	2,097	0.04%
				(210)	*(10,271)*	*(1,676)*	
New Diagnostic requiring Moderate Infrastructure§							
Slow Test							
Performance of DST	95%	95%	14	0	0	0	0.00%
				(235)	*(6,411)*	*(1,214)*	
Perfect Test	100%	100%	14	370	441	1,993	0.02%
				(174)	*(4,626)*	*(1,182)*	
Rapid Test							
Moderate Test	90%	90%	0	44	40,920	-2,138	0.00%
				(136)	*(23,617)*	*(1,373)*	
Performance of DST	95%	95%	0	366	44,494	-72	0.02%
				(450)	*(22,244)*	*(2,106)*	
Perfect Test	100%	100%	0	687	48,068	1,993	0.04%
				(173)	*(9,128)*	*(1,038)*	
New Diagnostic requiring Minimal Infrastructure§							
Slow Test							
Performance of DST	95%	95%	14	16	156	-13	0.00%
				(97)	*(4,941)*	*(988)*	
Perfect Test	100%	100%	14	408	622	2,097	0.02%
				(187)	*(5,669)*	*(976)*	
Rapid Test							
Moderate Test	90%	90%	0	63	43,477	-2,277	0.00%
				(226)	*(22,866)*	*(945)*	
Performance of DST	95%	95%	0	403	47,261	-90	0.02%
				(361)	*(16,207)*	*(1,919)*	
Perfect Test	100%	100%	0	744	51,045	2,097	0.04%
				(329)	*(11,500)*	*(2,027)*	
New Diagnostic with No Infrastructure Requirements§							

Slow Test								
	Performance of DST	95%	95%	14	135	1,297	-110	0.01%
					(191)	*(8,867)*	*(1,080)*	
	Perfect Test	100%	100%	14	545	1,785	2,097	0.03%
					(246)	*(5,683)*	*(1,497)*	
Rapid Test								
	Moderate Test	90%	90%	0	184	46,612	-2,478	0.01%
					(184)	*(25,430)*	*(1,350)*	
	Performance of DST	95%	95%	0	540	50,570	-190	0.03%
					(213)	*(8,829)*	*(882)*	
	Perfect Test	100%	100%	0	896	54,528	2,097	0.05%
					(288)	*(11,533)*	*(1,917)*	

***** Refers to the index case only
† The denominator used in this column is the total number of annual reported TB deaths: 1.75 million in 2003. The absolute best we ever achieve with respect to mortality is slightly under 1 percent of the total mortality burden, highlighting the relative importance of MDR TB diagnostics to other improvements in TB diagnostics
‡ Status Quo access for each region is defined as the percent of the population in the given region who currently receives DST: 95% for Eastern Europe, 27% for South-east Asia, and 29% for the Western Pacific Region. **Table B.1** provides further information on the source and ranges for current access to DST.
§ For information on calculations of the percent of the population with access to minimal and no infrastructure requirements refer to Olmsted et al. (2006)
SD, standard errors

Table B.4 The attributable benefit of a new diagnostic for MDR-TB **Southeast Asia** (*SD)*

Test	Sensitivity	Specificity	Delay for results (weeks)	Total Lives Saved*	MDR-TB Cases Averted	Wasted Category IV Treatments Averted	Percent of Potential Total TB Lives Lost Saved†
Status Quo: *Culture and DST*	95%	95%	14	0	0	0	0.00%
New Diagnostic with Status Quo Access‡							
Slow Test							
Perfect Test	100%	100%	14	539	-2,471	3,330	0.03%
				(458)	*(9,149)*	*(1,107)*	
Rapid Test							
Performance of DST	95%	95%	0	556	42,921	-121	0.03%
				(398)	*(20,332)*	*(1,652)*	
Perfect Test	100%	100%	0	954	45,711	3,330	0.05%
				(424)	*(12,318)*	*(1,224)*	
New Diagnostic requiring Moderate Infrastructure§							
Slow Test							
Performance of DST	95%	95%	14	1,707	11,583	-3,824	0.10%
				(815)	*(13,033)*	*(2,027)*	
Perfect Test	100%	100%	14	2,865	6,274	3,330	0.16%
				(1,260)	*(14,096)*	*(959)*	
Rapid Test							
Moderate Test	90%	90%	0	2,046	97,790	-11,497	0.12%
				(732)	*(23,675)*	*(2,691)*	
Performance of DST	95%	95%	0	2,902	103,783	-4,083	0.17%
				(807)	*(33,194)*	*(3,261)*	
Perfect Test	100%	100%	0	3,757	109,776	3,330	0.21%
				(695)	*(20,371)*	*(3,185)*	
New Diagnostic requiring Minimal Infrastructure§							
Slow Test							
Performance of DST	95%	95%	14	1,707	11,583	-3,824	0.10%
				(815)	*(13,033)*	*(2,027)*	
Perfect Test	100%	100%	14	2,865	6,274	3,330	0.16%
				(1,260)	*(14,096)*	*(959)*	
Rapid Test							
Moderate Test	90%	90%	0	2,046	97,790	-11,497	0.12%
				(732)	*(23,675)*	*(2,691)*	
Performance of DST	95%	95%	0	2,902	103,783	-4,083	0.17%
				(807)	*(33,194)*	*(3,261)*	
Perfect Test	100%	100%	0	3,757	109,776	3,330	0.21%
				(695)	*(20,371)*	*(3,185)*	

New Diagnostic with No Infrastructure Requirements§								
Slow Test								
	Performance of DST	95%	95%	14	4,019	27,276	-9,004	0.23%
					(2,097)	*(33,019)*	*(1,451)*	
	Perfect Test	100%	100%	14	6,017	18,123	3,330	0.34%
					(2,494)	*(38,428)*	*(2,480)*	
Rapid Test								
	Moderate Test	90%	90%	0	4,605	175,909	-22,234	0.26%
					(1,559)	*(41,696)*	*(2,657)*	
	Performance of DST	95%	95%	0	6,079	186,242	-9,452	0.35%
					(2,483)	*(33,316)*	*(2,585)*	
	Perfect Test	100%	100%	0	7,554	196,575	3,330	0.43%
					(1,938)	*(60,246)*	*(2,786)*	

***** Refers to the index case only

† The denominator used in this column is the total number of annual reported TB deaths: 1.75 million in 2003. The absolute best we ever achieve with respect to mortality is slightly under 1 percent of the total mortality burden, highlighting the relative importance of MDR TB diagnostics to other improvements in TB diagnostics

‡ Status Quo access for each region is defined as the percent of the population in the given region who currently receives DST: 95% for Eastern Europe, 27% for South-east Asia, and 29% for the Western Pacific Region. **Table B.1** provides further information on the source and ranges for current access to DST.

§ For information on calculations of the percent of the population with access to minimal and no infrastructure requirements refer to Olmsted et al. (2006)

SD, standard errors

Table B.5. The attributable benefit of a new diagnostic for MDR-TB in the **Western Pacific Region** (SD*)*

	Test	Sensitivity	Specificity	Delay for results (weeks)	Total Lives Saved*	MDR-TB Cases Averted	Wasted Category IV Treatments Averted	Percent of Potential Total TB Lives Lost Saved†
Status Quo: *Culture and DST*		95%	95%	14	0	0	0	0.00%
New Diagnostic with Status Quo Access‡								
Slow Test								
	Perfect Test	100%	100%	14	614	-2,044	3,748	0.04%
					(443)	*(5,349)*	*(1,933)*	
Rapid Test								
	Performance of DST	95%	95%	0	629	53,952	-136	0.04%
					(626)	*(15,511)*	*(2,985)*	
	Perfect Test	100%	100%	0	1,101	57,645	3,748	0.06%
					(373)	*(18,599)*	*(3,190)*	
New Diagnostic requiring Moderate Infrastructure§								
Slow Test								
	Performance of DST	95%	95%	14	2,131	16,226	-3,748	0.12%
					(857)	*(9,506)*	*(2,293)*	
	Perfect Test	100%	100%	14	3,358	12,138	3,748	0.19%
					(1,419)	*(20,674)*	*(4,106)*	
Rapid Test								
	Moderate Test	90%	90%	0	2,443	116,743	-11,789	0.14%
					(591)	*(34,788)*	*(2,499)*	
	Performance of DST	95%	95%	0	3,388	124,130	-4,020	0.19%
					(1,113)	*(19,311)*	*(2,557)*	
	Perfect Test	100%	100%	0	4,333	131,517	3,748	0.25%
					(827)	*(19,067)*	*(3,667)*	
New Diagnostic requiring Minimal Infrastructure§								
Slow Test								
	Performance of DST	95%	95%	14	2,131	16,226	-3,748	0.12%
					(857)	*(9,506)*	*(2,293)*	
	Perfect Test	100%	100%	14	3,358	12,138	3,748	0.19%
					(1,419)	*(20,674)*	*(4,106)*	
Rapid Test								
	Moderate Test	90%	90%	0	2,443	116,743	-11,789	0.14%
					(591)	*(34,788)*	*(2,499)*	
	Performance of DST	95%	95%	0	3,388	124,130	-4,020	0.19%
					(1,113)	*(19,311)*	*(2,557)*	
	Perfect Test	100%	100%	0	4,333	131,517	3,748	0.25%
					(827)	*(19,067)*	*(3,667)*	
New Diagnostic with No Infrastructure Requirements§								

Slow Test								
	Performance of DST	95%	95%	14	5,216	39,726	-9,177	0.30%
					(1,784)	*(20,990)*	*(2,015)*	
	Perfect Test	100%	100%	14	7,333	32,677	3,748	0.42%
					(2,170)	*(36,294)*	*(2,458)*	
Rapid Test								
	Moderate Test	90%	90%	0	5,755	213,030	-23,040	0.33%
					(2,344)	*(47,093)*	*(3,627)*	
	Performance of DST	95%	95%	0	7,384	225,767	-9,646	0.42%
					(1,778)	*(32,460)*	*(2,723)*	
	Perfect Test	100%	100%	0	9,013	238,503	3,748	0.52%
					(1,847)	*(44,050)*	*(1,943)*	

***** Refers to the index case only
† The denominator used in this column is the total number of annual reported TB deaths: 1.75 million in 2003. The absolute best we ever achieve with respect to mortality is slightly under 1 percent of the total mortality burden, highlighting the relative importance of MDR TB diagnostics to other improvements in TB diagnostics
‡ Status Quo access for each region is defined as the percent of the population in the given region who currently receives DST: 95% for Eastern Europe, 27% for South-east Asia, and 29% for the Western Pacific Region. **Table B.1** provides further information on the source and ranges for current access to DST.
§ For information on calculations of the percent of the population with access to minimal and no infrastructure requirements refer to Olmsted et al. (2006)
SD, standard errors