Supporting Information

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SI Text

Parameter Estimates. This section provides a more detailed description of each parameter in Table S2, including its method of calculation. These parameters, referred to as "primary parameters" are the parameters for which the most data exist to inform parameter estimates, and the parameters on which sensitivity analyses were performed. The primary parameters and model assumptions (e.g., proportion of patients with access to culture) are directly used to calculate the values of the "secondary parameters" given in Table S4. In many cases, the primary and secondary parameters are identical. The secondary parameters are then used in the model equations, as described in *SI Appendix*.

Description of primary parameters. The population size is taken as the size of the South African population in 2004, as projected by the 2003 AIDS Demographic Model of the Actuarial Society of South Africa (ASSA) (1). Although this model projects population growth at 0.9% per year, we opt to use a static population size to fulfill equilibrium assumptions, and for ease of presentation (e.g., stable rates of TB over time). As such, we assume that new 15-year-olds are recruited to the population at a rate equal to that of the total mortality rate plus the rate of aging to 50 years old. All new 15-year-olds are assumed to be HIV-negative and either uninfected with TB or latently infected with a drug-susceptible strain (i.e., no incoming 15-year-olds with active TB, and no MDR or XDR in latently infected recruits). The proportion of 15-year-olds with latent infection assumes an annual risk of TB infection of 2% (2) over 15 years of life.

The annual mortality rates of patients without active TB are calculated from the ASSA 2003 AIDS Demographic Model (1). This model calculates mortality according to age, gender, race, province, and HIV status, which includes clinical stage, time since infection, and access to antiretrovirals (ARVs). The projected mortality is then compared with the actual recorded mortality by each characteristic. Mean mortality rates are calculated by summing the number of all projected deaths in 2005 for 15- to 49-year-olds and dividing by the projected population size. Initial estimates of annual mortality rates with untreated, active, highly infectious TB are taken as the inverse of the average assumed duration of untreated TB disease, as described in reference (3): six months in HIV-positive patients and two years in HIV-negative patients. These estimates resulted in estimated mortality rates that were much higher than World Health Organization (WHO) estimates of TB mortality in South Africa (4) and were accordingly reduced when the model was fit to those estimates (Table S2). To maintain equilibrium assumptions (and in the absence of data on future years), we assume a constant mortality rate. Thus, the model does not account for future changes such as increased access to ARVs, and if ARV access does indeed increase in future years, the model will likely overestimate HIV- and HIV/TB-associated mortality. The effect of increased ARV use on TB incidence is less clear; the ASSA model projects an increase in ARV access to 73% of all patients with AIDS by 2015, but the projected HIV prevalence remains constant (1).

The mortality ratio in highly versus less infectious TB is used to calculate the mortality rate of patients with less-infectious TB. In HIV-positives, WHO estimates that case-fatality rates in untreated smear-positive and smear-negative TB are 0.81 and 0.76, respectively; the reason for the difference in these two rates is that smear-negative patients are assumed more likely to die of other causes first (3). Thus, we assume that the mortality ratio is 1 for HIV-positive patients. In HIV-negatives, the mortality ratio is taken to be the estimated case-fatality of untreated smear-negative TB, divided by estimated case-fatality of untreated smear-positive TB, or 0.2/0.7. Regardless of HIV status, non-TB mortality is subtracted before applying the mortality ratio.

The infectivity of TB (λ) denotes the annual risk of TB transmission from a single patient with highly infectious, drug-sensitive TB to a single fully susceptible individual. The annual risk of TB infection (ARTI) can thus be calculated as λ multiplied by the number of active infectious patients, after reducing the infectivity of drug-resistant and less-infectious cases according to the corresponding parameters. Modeling studies (2) have suggested that ARTI values in a TB/HIV epidemic may reasonably vary between 1.3% and 2.7%, and the ARTI in the Western Cape has been approximated at 3.5% to 4% (5). The initial value for λ was chosen as the value that gives a stable ARTI at the midpoint of the range in reference (2). This parameter was then fit to the WHO estimated TB incidence in South Africa (4), resulting in an estimated country-wide ARTI of 2.7%.

The relative infectivity of less infectious TB is taken as the relative infectivity of smear-negative TB from reference (6). Of note, "less infectious TB" here includes all extrapulmonary disease. Thus, if a substantial proportion of extrapulmonary TB does not have a pulmonary component, and the relative infectivity of smear-negative pulmonary disease is indeed 0.22, then our model will overestimate the infectiousness of smear-negative TB. The relative infectivity of MDR-TB versus drug-sensitive strains was initially set at the approximate value that resulted in stable MDR rates over time in a prior modeling exercise (7) but was adjusted upward to fit the estimated proportion of MDR-TB among new TB cases in South Africa (4).

The proportion of TB infections progressing rapidly to active TB in HIV-negative patients is taken as the proportion of patients who develop active TB within one year of TB infection, from Vynnycky and Fine's extension, in a British population (8), of Sutherland's (9) analysis of historical TB rates in the Netherlands. Whereas Sutherland estimated an annual risk of developing pulmonary TB of 5.06% per year for five years immediately after TB infection, Vynnycky and Fine estimated a total risk of 14% over five years. We take this latter (lower) estimate and assume that all rapid TB progression occurs immediately upon infection. Of note, this estimate of 14% is greater than the classically assumed 5%, or half of a 10% lifetime risk for active TB if infected in childhood. Vynnycky and Fine (8) suggest that the risk of rapid progression is higher in adults (14%) than in children (4%). Nevertheless, to account for the possibility of overestimating this parameter, univariate sensitivity analysis was performed to a lower bound of 5%. Use of a 5% estimate for the risk of rapid progression requires an ARTI $>10\%$ to maintain TB incidence in South Africa at the level estimated by WHO.

For HIV-positive patients, no data exist to accurately inform this estimate. To arrive at an initial estimate of this parameter, we assumed an ARTI in the Western Cape of 4% per year (5), endogenous reactivation rate as described below, and 25% efficacy of latent TB infection in protecting against active TB after reinfection. Based on these assumptions (and the assumption that all TB disease is due either to endogenous reactivation or primary progression after reinfection), we calculated the rate of rapid progression required to give the mean TB incidence in HIV-positive Cape Town residents across all CD4 strata from

reference (10). After arriving at estimates of this parameter and the rate of endogenous reactivation in HIV-positive patients, the values of these parameter estimates were fit to the WHO estimated TB incidence among HIV-positive patients by fixing the ratio between these two parameters as a constant value.

The annual endogenous reactivation rate in HIV-negative patients is taken from Ferebee's 1970 review of TB chemoprophylaxis trials (11). In HIV-positive patients, this is modeled as the TB incidence rate among purified protein derivative (PPD)-positive HIV-infected Kenyan sex workers, minus the incidence rate among PPD-negative participants (12). This calculation may underestimate the endogenous reactivation rate, because it assumes all new TB disease among PPD-negative participants (some of whom may be false-negative) as due to reinfection, and no protection against reinfection afforded by latent TB infection in HIV-positives. However, the upper range for sensitivity analysis, if applied to a population of HIV-infected patients in Cape Town (10), would estimate that 93% of TB cases in HIV-positive patients are due to endogenous reactivation. As described above, this parameter was fit to the WHO estimated TB incidence, resulting in a slight downward adjustment, by assuming a fixed ratio with the rate of rapid progression.

The proportion of TB infections becoming the primary strain is modeled as equivalent to (one minus the efficacy of latent TB infection in preventing active TB after reinfection). For HIV-negative patients, this is taken as the midpoint of this value in males (37%) and females (19%) among historical patients in the Netherlands, as estimated by Sutherland *et al.* (9). Given conflicting estimates of this parameter (8) and no direct data, we conducted univariate sensitivity analysis over a range of 0–60%. For HIV-positive patients, no data exist, so we use the same assumptions as have been used in prior modeling exercises (13, 14).

The rate of conversion from less infectious to highly infectious TB is taken as the rate of conversion from smear-negative to smear-positive disease, as estimated by Ferebee (11).

The case detection rate for a single diagnostic attempt in a highly infectious case, in the absence of culture, is set at the WHO target rate of 85%. WHO estimates that the case-detection rate of new smear-positive TB in South Africa is 103%, and that total case-detection (including smear-negative TB) is 82% (4). In the model, patients who are not diagnosed with TB on the first attempt are assumed to present for an additional diagnostic attempt at a given rate, which is substantially higher than the mortality rate of TB. Thus, the great majority of TB patients will have at least two diagnostic attempts before dying of TB. Assuming a two-step Markov process with 85% case-detection at each step gives a total case-detection rate of 97.8% in smear-positive disease. Under this assumption of case-detection in smear-positives, the case detection rate in smear-negative disease (given WHO estimates of smear-positivity rates in HIV-positive and HIV-negative TB) (15) must be 66.8% to give an overall case-detection rate of 82%. Assuming the same two-step Markov process gives a case-detection rate of 42.4% per diagnostic attempt in smear-negative TB.

The sensitivity of culture is assumed to be 85% in highly infectious TB. In other words, culture offers no advantage over the existing diagnostic algorithm for highly infectious patients, other than to make DST available. The 15% of highly infectious TB cases who are not detected by the existing algorithm likely either fail to submit sputum specimens, or have specimens sent to labs that fail to appropriately recognize or report positive smears. In either of these cases, it is unlikely that the availability of culture would be of benefit. In less infectious TB, the case detection rate for culture is assumed to be 73% (sensitivity of culture for smear-negative TB) (16), among the 57.6% of patients who would not otherwise be diagnosed on the first attempt under the existing diagnostic infrastructure. Culture is assumed to have no impact on diagnosis of active TB in patients who would be diagnosed under the existing infrastructure (e.g., by chest x-ray and clinical suspicion), other than to make DST available.

The duration of infectious TB before initial presentation to the health care system is taken as the mean duration of active coughing before seeking a diagnosis in a rural South African study (17). By taking the mean (rather than the median, which is shorter), the model implicitly accounts for the small proportion of patients who delay many months before seeing a physician. The diagnostic delay from initial presentation to diagnosis (if appropriately diagnosed) is taken as the median provider delay in the same study. If a two-step Markov process (as described in the "case detection rate" paragraph) is assumed, with some patients being diagnosed only on their second diagnostic attempt, the model gives a mean provider delay of 7.6 weeks, which compares to an estimate of 6.4 weeks (rate of 15.6 per 100 person-weeks) in the cited study (17). The additional diagnostic delay associated with culture assumes a total of 6 weeks to receive a positive culture result and begin treatment for TB; the estimated time to detection for smear-negative TB is 16.5 days by Mycobacteria Growth Indicator Tube (MGIT, the recommended standard for state labs in South Africa) and 33.7 days by traditional Lowenstein-Jensen media (16). For DST, we assume that successfully treated TB patients will be seen by their physician at one month after initiating TB therapy, and that regimen changes will be made at this time based on DST results. Note that the estimates for diagnostic delay apply only to patients who will be treated; those patients who are not ultimately diagnosed and treated will remain infectious for a longer period (i.e., until being diagnosed and treated after presenting for rediagnosis, or death). Therefore, the actual period of infectiousness is shorter for HIV-positive patients (who return for rediagnosis more frequently; see below) than for HIV-negatives.

The annual rate of rediagnosis attempts was initially estimated simply as the inverse of the estimated disease duration of untreated TB (0.5 years for HIV-positive and 2 years for HIV-negative patients) (3). The estimates of rediagnosis frequency were then adjusted upward to fit the WHO estimate of TB prevalence in South Africa, thus implicitly accounting for increased disease duration before presentation and decreased disease duration after successful treatment. In the final model, the estimated duration of TB disease (prevalence/incidence) is 0.50 years in HIV-positives (reflecting the WHO estimates to which the model was fit) and 1.12 years in HIV-negatives.

The proportion of TB patients treated or lost to follow-up is based on the WHO estimate that 80% of smear-positive patients are treated in South Africa (4). For culture, we assume 10% additional loss to follow-up, consistent with the WHO-estimated 70% treatment rate in smear-negative TB patients (4).

The proportion of TB patients treated with an active regimen is based on the assumption that active regimens may fail (e.g., through default), but inactive regimens are wholly ineffective. Drug resistance emerges only through failure of active regimens (versus treatment with inactive regimens). We assume that all patients with either drug-sensitive TB or DST-confirmed MDR-TB who are diagnosed and placed on TB therapy will be treated with a regimen containing activity against that TB strain. By fitting to WHO estimates of MDR-TB incidence, the model defines multidrug resistance as *in vitro* resistance; thus, some strains labeled as MDR-TB may actually be sensitive to first-line drugs *in vivo*. The assumption that 25% of MDR-TB cases are treated with an active regimen is based on a South African study of five-year outcomes in patients with MDR-TB who were treated with first-line TB drugs before the widespread availability of second-line regimens (18). At five years, 25% of these patients were free of TB disease. (The others were either still

infected or dead.) We assume that XDR-TB is untreatable with existing drugs.

The cure rate of active therapy is estimated as the proportion of registered TB cases resulting in either cure or treatment completion in South Africa in 2005 (4).

The annual relapse rate after failing active therapy was initially assumed to be the rate of TB recurrence after default, minus the rate of confirmed reinfection, in two urban populations near Cape Town (19). This estimate was then adjusted upward to fit to the WHO estimate that 20% of incident TB cases are in previously treated individuals (4). We do not assume differential relapse rates by HIV status, based on evidence from South African gold mines that HIV-infected and uninfected individuals have similar risks of relapse after completing TB therapy (although HIV-positive patients remain at increased risk of reinfection disease) (21).

The proportion of relapses that are newly resistant was initially estimated as the proportion of pan-sensitive or single-drug resistant (SDR) strains that were found to be multidrug resistant in South African gold miners who failed TB therapy (20). This parameter was then adjusted downward to fit the WHO estimated prevalence of MDR-TB among previously treated patients in South Africa (4).

The annual incidence of HIV was taken as the UNAIDS estimated HIV incidence among 15-to-49-year-old South Africans and adjusted slightly upward to fit the UNAIDS estimated HIV prevalence in that age group in 2006.

Supporting Text 2. Narrative Description of Model Structure. Individuals enter the model on their 15th birthday, being HIV-negative and either uninfected with TB or latently infected with drug-sensitive TB. They exit the model upon dying or reaching their 50th birthday. Mortality rates depend on an individual's HIV and TB status.

All individuals at any stage of TB infection are presumed to harbor a "dominant" TB strain; this strain determines the patient's drug-susceptibility pattern upon development of active TB. Patients may develop active TB either by rapid progression after infection or endogenous reactivation of latent infection. An individual's risk of becoming infected with a specified TB strain (defined by drug resistance: not resistant, MDR, or XDR) is directly proportional to the number of active TB patients harboring the specified strain at a given time, and the relative infectivity of that strain. Upon infection, the infecting strain will become the dominant strain in 100% of previously uninfected individuals, and a smaller proportion of individuals harboring latent TB infection (i.e., latent infection provides partial protection against reinfection). Among individuals in whom the infecting strain becomes the dominant strain, a proportion will progress rapidly (i.e., instantaneously) to active TB, and the remainder will become latently infected with the new strain. Latently infected individuals remain at risk of endogenous reactivation with this same strain throughout their lifetimes. Treatment for latent TB infection with isoniazid is not incorporated into the model.

Upon development of active TB, patients are immediately assigned an infectivity level (highly or less infectious) and enter a stage of "prediagnosis," during which they are fully infectious but have no increased mortality risk. These individuals are assumed to be actively coughing in the community, but sufficiently early in their disease course that they are not at risk to die of TB. Patients exit this subpopulation at a rate defined as the inverse of the mean time of initial presentation to medical attention. At this point, they are instantaneously placed into one of three subpopulations: (*i*) those who will, if they survive, ultimately be diagnosed and treated during the present initial diagnostic attempt by traditional methods (sputum smear, chest x-ray, antibiotic trial, and clinical judgment); (*ii*) those who will, if they survive, be diagnosed and treated during the present diagnostic attempt by culture alone (i.e., would not be diagnosed by traditional methods); and (*iii*) those who will remain either undiagnosed or untreated after the present diagnostic attempt. These subpopulations remain infectious and do experience an increased mortality risk concomitant with their active TB status. The impact of expanded access to culture is modeled by increasing the size of subpopulation *ii*, with a corresponding decrease in subpopulation *iii*. If they survive, patients in subpopulations *i* and *ii* will go on to receive TB therapy, at a rate determined by the mean diagnostic delay associated with their diagnostic method (i.e., patients in subpopulation *i* will be treated more rapidly than those in subpopulation *ii*). Patients in subpopulation *iii* either die or return for rediagnosis, at which time they are immediately reassigned to one of subpopulations *i*, *ii*, or *iii*.

In this model, "TB therapy" corresponds to the initiation of a regimen with activity against a patient's TB strain, and that will ultimately last at least one month. Patients who receive either an inactive regimen (e.g., first-line therapy in patients with *in vivo* MDR-TB) or less than one month of active therapy are presumed untreated. These patients behave in the same manner as patients with active, undiagnosed TB. Active regimens are classified as either curative or noncurative (e.g., before default). Both curative and noncurative regimens immediately render the patient noninfectious and return the patient's mortality risk to that of an individual of the same HIV status, but without active TB. Curative regimens are assumed to reduce the patient's burden of tubercle bacilli to a point that relapse with the same strain cannot occur. Patients who are cured return to a fully susceptible state (i.e., no protection against reinfection); this is consistent with the increased rate of reinfection seen among HIV-negative residents of Cape Town after cure of active TB (19). Assuming that such patients do maintain 72% protection against reinfection (as assumed for HIV-negative, latently infected individuals) does not change the estimated impact of TB culture (scenario 5) on mortality or incidence of TB, MDR-TB, or XDR-TB by more than $\pm$ 1.0% in absolute terms.

Drug resistance emerges exclusively among patients who receive noncurative therapy. These patients remain at risk for relapse, which occurs at a specified annual rate. A specified proportion of relapses are assumed to occur with a "newly resistant" strain that acquired drug resistance through mutation (i.e., the relapsed strain is MDR when the original strain was not resistant, or XDR when the original strain was MDR). These newly resistant strains may then be transmitted to other susceptible patients via the airborne route. Patients receiving noncurative therapy may also experience reinfection and rapid progression (at the rates of latently infected individuals).

Drug susceptibility testing is incorporated by adding a compartment of patients with active TB whose therapy will ultimately be changed upon receipt of DST results. (Because patients with nonresistant strains will receive the same therapeutic regimen regardless of DST results, this compartment consists only of patients with MDR- or XDR-TB. Because XDR-TB is presumed untreatable, the only scenarios in which XDR-TB patients enter this compartment are those in which the infectivity of diagnosed XDR-TB patients is reduced.) These patients are labeled "DST result pending" and are assumed to receive inactive therapy (i.e., mortality risk equal to that of active TB) for a specific duration of time, after which they begin active therapy, which may in turn be curative or noncurative, as described above.

Patients who have already received at least one month of therapy (whether inactive, curative, or noncurative) are classified as previously treated and thus as retreatment cases should they experience relapse or reinfection. Previously treated patients are assumed to be biologically similar to patients who have not received prior TB therapy.

The model is run in one-year intervals with a time step of 0.01

year, beginning and ending at mid-year (e.g., the first interval spans July 2007 through June 2008). Thus, one model run consists of 100 time steps. For purposes of reporting results, TB incidence and mortality rates are measured, by compartment, at the final time step of each model run (i.e., at mid-year) and multiplied by 100 to give the annual incidence and mortality for the year in which the model run ended. The prevalence of TB for that year is taken as the point prevalence at this time step. The model was programmed in Visual Basic for Applications and run in Microsoft Excel 2003.

Description of Sensitivity Analyses. Univariate sensitivity analysis was performed on each parameter across the range specified in Table S2. All parameters were varied independently (i.e., without interparameter correlations), with three exceptions: Because an increase in additional diagnostic delay for culture would result in increased losses to follow-up, the latter parameter was simultaneously varied in the same direction when performing univariate sensitivity analysis on culture diagnostic delay (i.e., correlation of 1.0). For univariate sensitivity analysis of losses to follow-up, which could occur independently of diagnostic delay, no correlation was implemented.

Because areas with high overall case-detection rates (in the absence of culture) would also have high case-detection rates for highly infectious TB, these two parameters were combined, with correlation of 1.0, into a single univariate sensitivity analysis.

Three parameters, namely TB infectivity (λ), endogenous reactivation rate in HIV-positives (er_+), and the proportion of TB infections progressing rapidly to active TB in HIV-negatives (rp_-), cause dramatic changes in TB rates ($>10\%$ change in TB incidence in the absence of any intervention) when varied across their specified ranges. Thus, we varied λ independently (i.e., no correlations) to capture the effect of mis-specified TB incidence. However, upon variation of the other two parameters, λ was simultaneously varied to give a projected TB incidence (in the absence of intervention) similar to that at baseline (i.e., removing these two variables' impact on TB incidence).

All variables for which sensitivity analysis caused a $\pm 5\%$ change in projected TB mortality averted under scenario 5 (Table 1) were included in Fig. S1, and all variables causing a $\pm$ 10% change in projected MDR-TB incidence averted were included in Fig. S2.

Two separate multivariate sensitivity analyses were performed. In the first ("best and worst case scenario" analysis), parameters were divided into *a priori* subgroups as described in Table S5. Similar to the univariate analyses described above, case-detection rates of all TB and highly infectious TB were forced to vary in the same direction, diagnostic delay and losses to follow-up from culture were forced to vary in the same direction, and TB infectivity (λ) was forced to vary in the opposite direction as endogenous reactivation in HIV-positives and proportion of infections causing rapid progression in HIV-negatives. Results are shown in Fig. S1 (TB mortality) and Fig. S2 (MDR-TB incidence).

In the second multivariate analysis (probabilistic sensitivity analysis), we simultaneously varied each parameter across a triangular distribution defined by the parameter's sensitivity range (upper and lower bound) and final estimate (most likely value) in Table S2. As with the above analyses, correlations of 1.0 were assigned to two pairs of variables: (*i*) diagnostic delay and loss to follow-up from culture, and (*ii*) case-detection rate (in the absence of culture) for all TB and highly infectious TB. Furthermore, to prevent simulations with gross under- or overestimation of TB incidence, we constrained TB infectivity (λ) according to the simulated estimates of endogenous reactivation in HIV-positives (er_+) and rapid progression in HIV-negatives (rp_-), such that the three random numbers determining these variables' simulated values between lower bound (0) and upper bound (1) totaled no less than 1 and no more than 2.

In addition, because the model was robust ($<5\%$ change in projected TB mortality benefit from culture and DST) to variation of rapid progression in HIV-negatives at a lower bound of 0.05 in univariate analysis, we used a lower bound of 0.092 (75% of final estimate) in the probabilistic sensitivity analysis, to provide a symmetric distribution and to further avoid simulations with gross underestimates of TB incidence.

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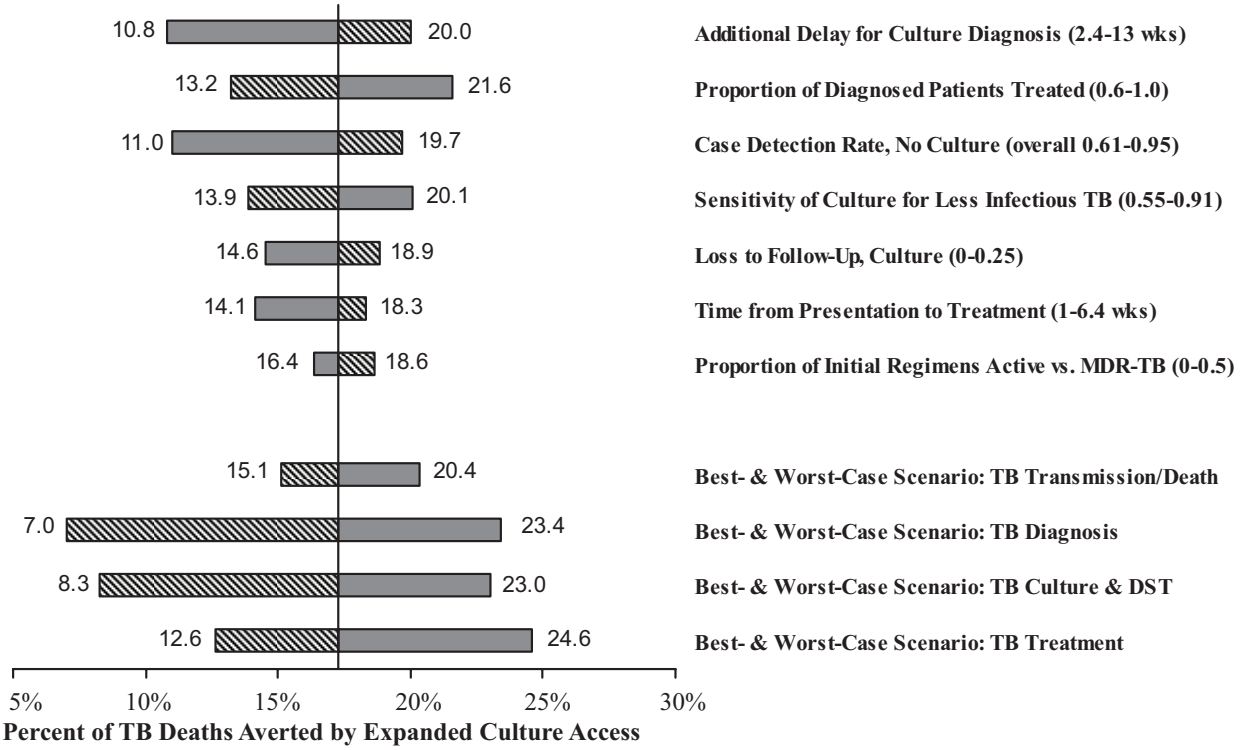

Fig. S1. Univariate and best-/worst-case sensitivity analyses: TB deaths averted. Shown are all parameters for which univariate variation (range in Table S2) caused a ±5% change in the fraction of TB deaths averted (scenario 5 in Table 1). Diagonal lines denote parameter lower bounds, and gray shading upper bounds. Multivariate best- and worst-case scenarios were created by simultaneously setting multiple parameters to their most or least favorable value (*SI Text*, *Description of Sensitivity Analyses*, and Table S5).

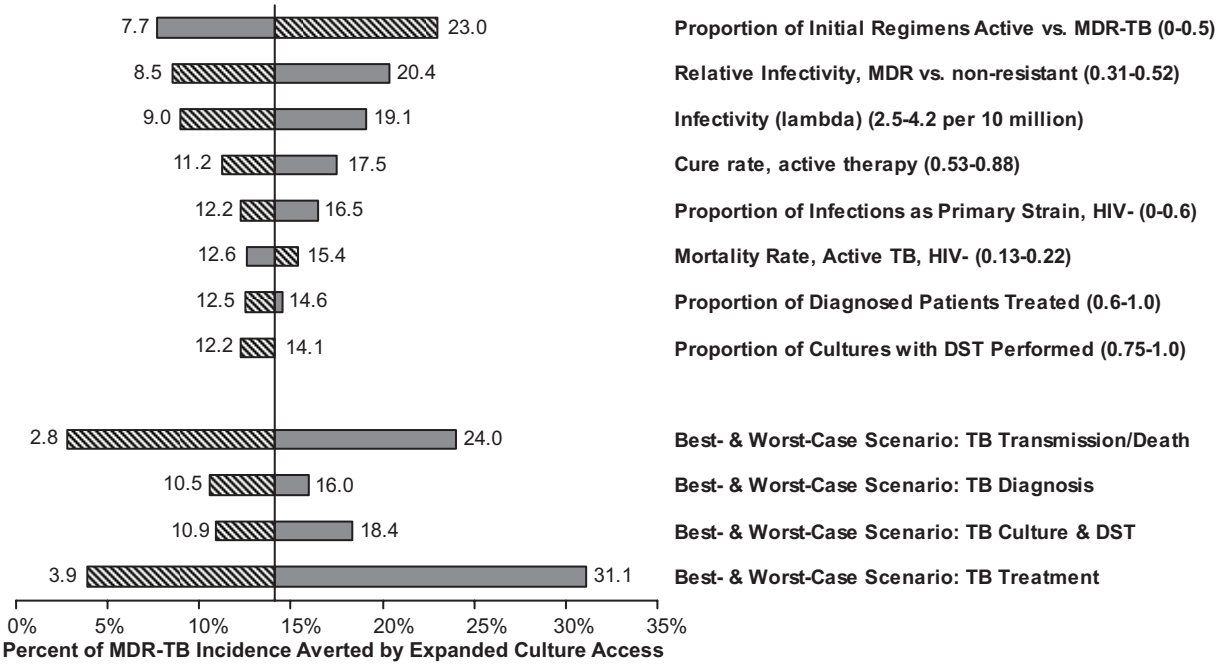

Fig. S2. Univariate and best-/worst-case sensitivity analyses: MDR-TB incidence. Shows all parameters for which univariate variation (range in Table S2) caused a ± 10% change in the fraction of incident MDR-TB cases averted (scenario 5 in Table 1). Diagonal lines denote parameter lower bounds, and gray shading upper bounds. Multivariate best- and worst-case scenarios were created by simultaneously setting multiple parameters to their most or least favorable value (*SI Text*, *Description of Sensitivity Analyses*, and Table S5). TB transmission parameters are key determinants of culture's impact on TB incidence, whereas diagnostic parameters are key determinants of impact on mortality.

Table S1. Culture utilization rates in Free State, South Africa

Year	Smear status	No. of patients (% of annual total)	No. (%) with culture performed
		New cases	
2004	Positive	9,210 (61.3%)	672 (7.3%)
	Negative	3,140 (20.9%)	231 (7.4%)
	Not available	2,668 (17.8%)	39 (1.5%)
2005	Positive	9,065 (61.9%)	294 (3.2%)
	Negative	2,966 (20.3%)	152 (5.1%)
	Not available	2,602 (17.8%)	35 (1.3%)
Total		29,651	1,423 (4.8%)
		Previously treated cases	
2004	Positive	2,564 (65.1%)	1,160 (45.2%)
	Negative	881 (22.4%)	448 (50.9%)
	Not available	491 (12.5%)	45 (9.2%)
2005	Positive	2,769 (65.2%)	922 (33.3%)
	Negative	956 (22.5%)	390 (41.0%)
	Not available	525 (12.4%)	38 (7.2%)
Total		8,186	3,003 (36.7%)

Table S2. Parameter estimates for model of TB epidemic in South Africa

Variable	Initial value	Data used for model fit*	Final value	Range for sensitivity analysis	Reference(s)
		Recruitment and mortality			
Population size (15–49 years old)	25.5×10^6		25.5×10^6	None	1
Annual mortality rate					
HIV+, no TB	0.11		0.11	0.08–0.13	1
HIV+, infectious TB	2.0	TB mortality, HIV+	0.82	0.61–1.02	2, 3
HIV−, no TB	0.006		0.006	0.004–0.007	1
HIV−, infectious TB	0.5	TB mortality, HIV−	0.17	0.13–0.22	2, 3
Mortality ratio, highly vs. less infectious TB					
HIV+	1		1	0.75–1.25	3
HIV−	0.29		0.29	0.21–0.36	3
		TB transmission and infection			
Number of secondary TB infections per highly infectious person-year	6.2	TB incidence	7.8	5.9–9.8	4
Relative infectivity					
Less infectious TB	0.22		0.22	0.16–0.28	5
MDR/XDR-TB (vs. non-resistant)	0.3	Percent of new TB cases MDR	0.39	0.29–0.48	6
Proportion of TB infections progressing rapidly to active TB†					
HIV+	0.25	TB incidence, HIV+‡	0.22	0.16–0.27	7
HIV−	0.14		0.14	0.05–0.18	8
Endogenous reactivation rate, per year†					
HIV+	0.05	TB incidence, HIV+‡	0.04	0.03–0.05	9
HIV−	0.001		0.001	$0.8–1.4 \times 10^{-3}$	10
Proportion of reinfections becoming primary strain					
HIV+	0.75		0.75	0.56–0.94	11,12
HIV−	0.28		0.28	0.0–0.6	13
Conversion rate: less- to highly infectious, per year	0.02		0.02	0.015–0.025	10
		TB diagnosis and drug sensitivity testing (DST)			
Proportion of TB cases detected, no culture†					
Highly infectious	0.98		0.98	0.87–1.0	2
All cases	0.82		0.82	0.61–0.95	2
Sensitivity of culture for less-infectious TB†	0.73		0.73	0.55–0.91	14
Duration of TB, weeks†					
Before presentation	13.9		13.9	3–26	15
Presentation to treatment	2		2	1–6.4	15
Additional delay for culture diagnosis	4		4	2.4–13	14
Treatment to receipt of DST results	4.3		4.3	1–13	
Annual rate of re-diagnosis attempts†					
HIV+	2.0	TB prevalence, HIV+	4.6	3.4–5.8	3
HIV−	0.15	TB prevalence, HIV−	0.63	0.47–0.79	3
Proportion of eligible cultures receiving DST	1.0		1.0	0.75–1.0	
		TB treatment			
Proportion of diagnosed patients being treated	0.80		0.80	0.6–1.0	2
Proportion lost to follow-up, culture	0.10		0.10	0–0.25	
Proportion of treatment regimens that are active					
Less-resistant TB	1		1	None	
MDR-TB, no DST	0.25		0.25	0–0.5	16
MDR-TB, post-DST	1		1	None	
XDR-TB	0		0	None	
Cure rate, active therapy	0.70		0.70	0.53–0.88	2
Annual relapse rate after failing active therapy	0.06	TB incidence, re-treatment/total	0.10	0.07–0.12	17
Proportion of relapses newly-resistant†	0.16	Percent of previously treated cases MDR	0.06	0.04–0.07	18

Variable	Initial value	Data used for model fit*	Final value	Range for sensitivity analysis	Reference(s)
		Miscellaneous			
Annual HIV incidence	0.03	HIV prevalence	0.03	0.02–0.04	19
Time step, years	0.01		0.01		

*Where listed, final estimates for model parameters were generated from initial estimates by iterative fitting to 2005 World Health Organization epidemiological estimates (2, 20).

†See *SI Appendix* for further details on calculation.

‡Two parameters were fit to one epidemiologic estimate by assuming a fixed ratio between parameter values.

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Table S3. Model compartments

Symbol*	Compartment description	Subcompartments†, no.
S_h	Susceptible Never infected before Maximum risk of TB infection	2
L_{hd}	Latently infected Offers partial protection against re-infection	6
PD_{hdit}	Prediagnosis Active TB prior to initial diagnostic attempt Infectious, no increased mortality risk	24
PT_{hdit}	Pretreatment Active TB that will be diagnosed and treated Infectious, increased mortality	24
PTC_{hdit}	Pretreatment if Culture Available Active TB that will only be diagnosed and treated if culture is used Infectious, increased mortality	24
U_{hdit}	Untreated, Active TB Infectious, increased mortality	24
C_h	Cured Resembles susceptible state	2
DST_{hd}	DST Result Pending Infectious‡, increased mortality	4§
F_{hd}	Partially treated/Failed TB not eradicated by therapy Not infectious, no increased mortality Increased risk of relapse Partial protection against re-infection Drug resistance may emerge	6
Q_{hi}	Quarantined XDR patients recognized by DST and isolated Not present in base-case model	4

*h refers to human immunodeficiency (HIV) status (positive or negative), d refers to drug susceptibility [nonresistant, multidrug-resistant (MDR), or XDR], i refers to infectivity (highly or less infective), and t refers to treatment status (never treated or previously treated). If a subscript is not listed for a given compartment, all individuals in that compartment are assumed to have the same status for that dimension.

†Equal to 2 (if stratified by HIV status) × 3 (if stratified by drug susceptibility) × 2 (if stratified by infectivity) × 2 (if stratified by treatment status).

‡Because of this compartment's short duration, subcompartments by infectivity were not created. Thus, infectiousness and mortality are modeled as the weighted averages of highly- and less-infectious patients.

§Stratified by two, rather than three, drug-resistance categories (MDR and XDR), resulting in four, rather than six sub-compartments. Patients with nonresistant strains do not benefit DST and thus move directly to either C or F upon receiving therapy.

Table S4. Secondary parameters used in model equations

Symbol	Parameter description
	Recruitment and mortality
Pop	Population size
r50	Annual rate of attaining 50th birthday
m_{hi}	Annual mortality rate, by HIV status (*h*)* and infectivity (*i*)†
	TB transmission and infection
λ_{di}	Annual rate of TB transmission to a single susceptible individual from a single TB patient, according to drug susceptibility (*d*)‡ and infectivity (*i*)†
rp_h	Proportion of TB infections resulting in rapid progression to active TB, by HIV status (*h*)*
$ps\text{-}_h$	Proportion of TB re-infections becoming primary strain, by HIV status (*h*)*
er_h	Annual rate of endogenous reactivation, by HIV status (*h*)*
ip_{hi}	Proportion of new TB infections in each infectivity stratum (highly or less infectious), by HIV status (*h*)*
sc	Smear conversion rate: annual rate of spontaneous conversion from less infectious to highly infectious TB
	TB diagnosis and drug sensitivity testing (DST)
cdr_i	Case-detection rate of existing infrastructure (no culture), by infectivity (*i*)†
$cdrc_i$	Case-detection rate of existing infrastructure plus culture, by infectivity (*i*)†
cx_t	Proportion of patients receiving culture, by treatment status (*t*)§
pd	Patient delay: mean time (years) from onset of infectiousness to initial diagnostic attempt
dd	Diagnostic delay: mean time (years) from initial presentation to treatment, if diagnosed by existing infrastructure
ddc	Mean diagnostic delay (years) if diagnosed only by culture
dst_t	Proportion of cultures ordered with DST, by treatment status (*t*)§
dstd	DST delay: mean time (years) from onset of TB therapy to regimen change based on DST results
redx	Annual rate of presentation for repeat diagnostic attempt (if untreated TB)
	TB treatment
tx	Proportion of diagnosed TB patients receiving at least one month of therapy
ltf	Loss to follow-up: proportion of patients who would receive treatment if diagnosed by existing infrastructure, but not if diagnosed by culture
act_d	Proportion of regimens active against TB, by drug susceptibility (*d*)‡
cr	Cure rate: proportion of patients cured if treated by an active regimen
q	Proportion of XDR patients isolated once DST result known
rel	Relapse rate among patients treated with active therapy but not cured
dr	Proportion of relapses with newly-acquired drug resistance
	Miscellaneous parameters
ts	Time step
hiv	Annual incidence of new HIV infection in the population

*Includes two strata of HIV status: +, HIV-positive; −, HIV-negative.
†Includes three strata of infectivity: *o*, no active TB; *a*, highly infectious; *l*, less infectious.
‡Includes three strata of drug resistance: *n*, not resistant; *m*, MDR; *x*, XDR.
§Includes two strata of treatment status: 0, not treated; 1, previously treated.

Table S5. Parameter values for best- and worst-case scenarios

Scenario	Parameter	TB mortality		MDR-TB incidence	
		Best case	Worst case	Best case	Worst case
TB Transmission/Death	Annual mortality rate				
	HIV+, no TB	0.13	0.08	0.13	0.08
	HIV+, infectious TB	0.61	1.02	0.61	1.02
	HIV−, no TB	0.007	0.004	0.007	0.004
	HIV−, infectious TB	0.13	0.22	0.13	0.22
	Mortality ratio, highly vs. less infectious TB				
	HIV+	1.25	0.75	0.75	1.25
	HIV−	0.36	0.21	0.21	0.36
	TB infectivity, λ	2.6×10^{-7}	4.3×10^{-7}	2.6×10^{-7}	4.3×10^{-7}
	Relative fitness				
	Less infectious TB	0.28	0.16	0.28	0.16
	MDR/XDR-TB	0.48	0.29	0.48	0.29
	Proportion of TB infections progressing rapidly to active TB				
	HIV+	0.27	0.16	0.27	0.16
	HIV−	0.18	0.05	0.18	0.05
	Annual endogenous reactivation rate				
	HIV+	0.053	0.032	0.053	0.032
	HIV−	0.0014	0.0008	0.0014	0.0008
	Proportion of TB re-infections becoming primary strain				
	HIV+	0.56	0.94	0.94	0.56
	HIV−	0.35	0.21	0.35	0.21
	Conversion rate: less- to highly infectious	0.025	0.015	0.025	0.015
	Annual HIV Incidence	0.02	0.04	0.02	0.04
TB diagnosis	Proportion of TB cases detected, no culture				
	Highly infectious	0.87	1.0	1.0	0.87
	All cases	0.61	0.95	0.95	0.61
	Duration of TB, weeks				
	Before presentation	3	26	3	26
	Presentation to treatment	1	6.4	6.4	1
	Annual rate of rediagnosis attempts				
	HIV+	3.4	5.8	3.4	5.8
	HIV−	0.79	0.47	0.47	0.79
TB culture and DST	Sensitivity of culture, less-infectious TB	0.91	0.55	0.55	0.91
	Additional delay for culture (wks)	2.4	13	13	2.4
	Time from treatment to DST result	1	13	1	13
	Proportion lost to follow-up, culture	0	0.25	0.25	0
	Proportion of cultures with DST available	1.0	0.75	1.0	0.75
TB treatment	Proportion of diagnosed patients treated	1.0	0.6	1.0	0.6
	Proportion of initial regimens active against MDR-TB	0	0.5	0	0.5
	Cure rate, active therapy	0.88	0.53	0.88	0.53
	Annual relapse rate after failing active therapy	0.12	0.07	0.07	0.12
	Proportion of relapses newly-resistant	0.07	0.04	0.04	0.07

Other Supporting Information Files

SI Appendix