Mathematical modelling of the ZAMSTAR household intervention against tuberculosis: Supporting Information

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Contents

Population

Demography

The population was initialized by sampling households from a survey of the ZAMSTAR population (1). The birth and migration rates by year were based on UN ESA data (2). Data were smoothed by cubic spline interpolation. Immigrants were clones of randomly sampled individuals in the current population. Time-dependent mortality was based on 1-parameter UN model life-tables (3), using the UN ESA estimates of life-expectancy at birth for each calendar year. Because UN ESA estimates of life-expectancy at birth include HIV-related mortality, the overall trend was interpolated by hand, ignoring the HIV-related peak, and an all-age mortality hazard correction added to ensure country population growth matched the data (see Figure 1).

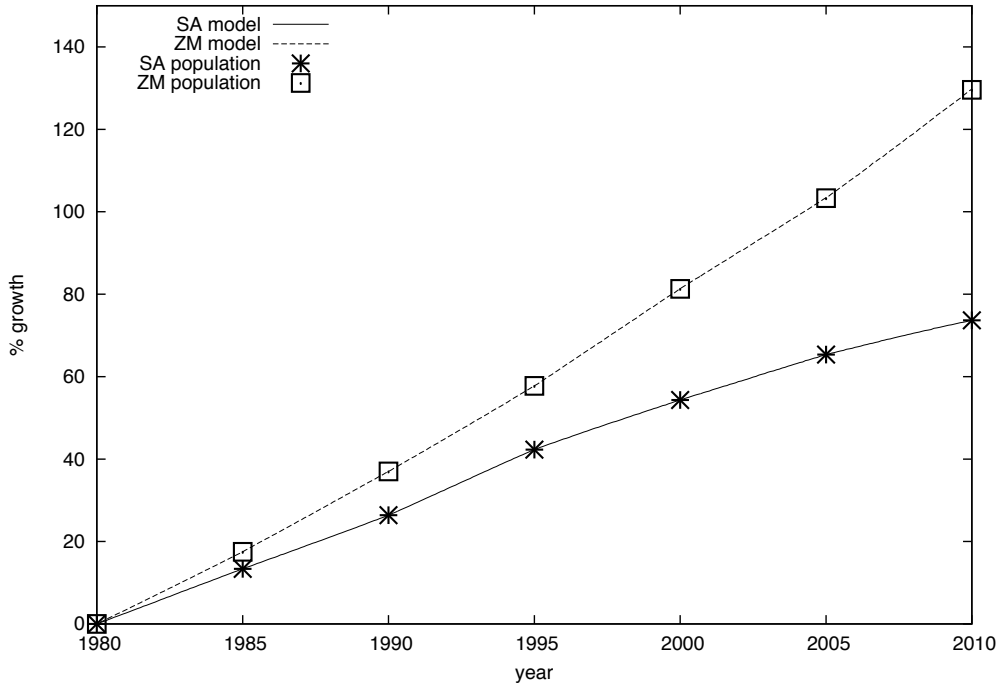

Figure 1: Population growth in the model compared with UN ESA data.

Household movement

Simulating a growing population over a period of 30 years requires construction of new households and movement between them. The rate of movement between households was based on a question in a contact survey in the ZAMSTAR communities(1). In the absence of longitudinal data on household structure, we used an algorithm for movement between households that approximately preserved the distribution of household sizes over this period.

If n_k is the proportion of households of size k, g_k, f_k and a_k are the weights for leaving, moving to, or arriving by birth or immigration in a household of size k, then the probabilistic master equation governing the evolution of n_k implies:

$$\Delta n_k = \left(a_{k-1}n_{k-1} - a_k n_k - \frac{n_k}{P}\right).\Delta P + (f_{k-1}n_{k-1} + g_{k+1}n_{k+1} - (f_k + g_k)n_k).\Delta M$$

where ΔP, ΔM and P are the number of arrivals, movements, and the number of people, respectively. Setting this to zero, and working with random movement origins (implying $g_k \propto k$) solves as:

$$f_k = (k+1)\frac{n_{k+1}}{n_k}$$

$$a_k = \frac{1}{n_k}.\left(1 - \sum_1^k n_j\right)$$

Empty houses were built as a Poisson process with rate $\Delta P.N/P$, where N is the number of households. Restricting this for realism by not allowing those aged under 18 to move still approximately preserved the distribution of household sizes (see Figure 2).

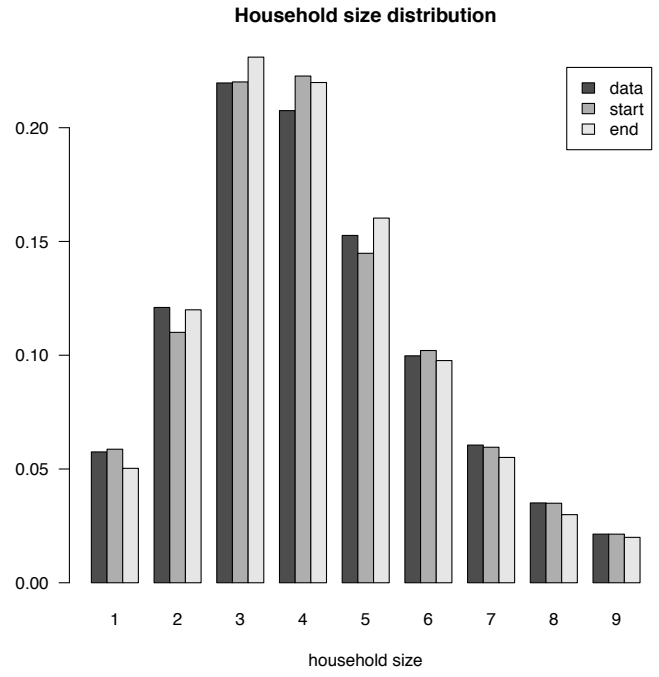

Figure 2: Household size distribution for test data comparing sampled households for 25K individuals in 1980 with that in 2010.

Models of infection natural histories & treatments

The model of natural history of TB & TB treatment

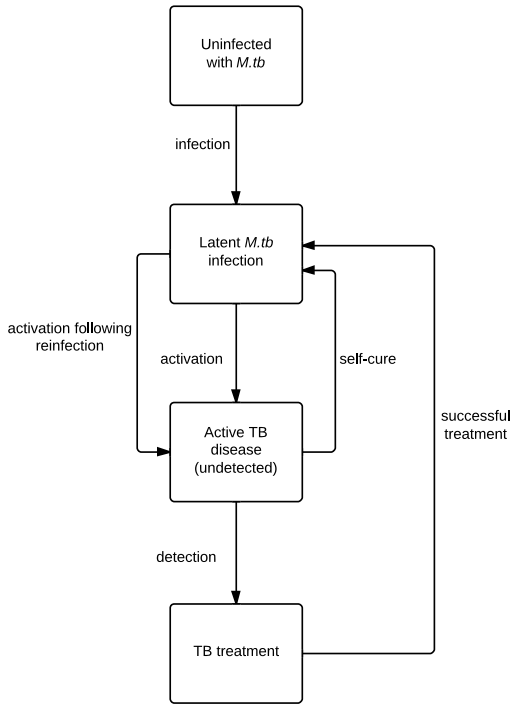

Figure 3: An overview of the natural history of TB and treatment, excluding mortality.

The TB model structure follows along the lines of the simplified representation in Figure 3: individuals are born without *M.tb* infection; can acquire an *M.tb* infection which may, or may not develop into active TB disease; and individuals may, or may not have their active TB disease detected and initiate treatment.

Upon infection with *M.tb*, individuals' time-since-infection is tracked and they are subject to a hazard of developing pulmonary TB disease per unit time. This hazard is higher in the first 2 years following (re-)infection, with an age-dependence following that used in Vynnycky and Fine (4). We also introduced a parameter that allowed this risk of fast progression to scale up and down. More than 2 years after infection, the hazard of activation assumes a lower constant value. Individuals with an *M.tb* infection have a partial protection against reinfection (4,5); however, we consider a successful re-infection is treated identically to an initial infection.

Upon activation to pulmonary TB, 65% of cases in 20 year olds were assumed smear positive among those without HIV infection, following the age pattern reported in (4); smear negative TB assumed 23% as infectious as smear positive TB (6,7). Active TB without treatment results in death (70% for smear-positive disease; 30% for smear-

negative disease) or else self-cure over a timescale of 3 years based on the review of Tiemersma *et al.* (8). These alternatives are modelled as proportional hazards with a Weibull-distributed time-to-event. The shape parameter was chosen to given a broad distribution with a non-zero mode, and the scale chosen to match the mean to the timescales reported in (8). Self-cure leaves individuals with an *M.tb* infection, and acts like a new infection in terms of activation risks.

Detection and initiation of treatment in those with active TB disease is assumed to occur with a probability taken as the WHO estimate of the case-detection rate (WHO, 2013). The timing of detection and treatment initiation occurs at a certain fraction of an individual's time-to-outcome without detection and treatment (i.e. more rapidly progressing TB disease is detected proportionately more rapidly).

Treatment lasts for 6 months, corresponding to the standard first-line TB regimen. At 6 months, treatment could either be successful (with probability reported to WHO, weighted by smear-status if disaggregated), or not. Successfully treated individuals are returned to the latent pool; a certain fraction of unsuccessfully treated individuals are assumed to die (informed by overall mortality rates on treatment (9)), with the rest remaining active TB cases.

Drug resistance was not modelled.

The model of HIV & ART

Life expectancy for those infected by HIV without ART is modelled by a Weibull distribution with parameters (k=2.3, s=13.3 years), from a weighted least-squares fit to the survival data from the CASCADE collaboration (10).

The influence of HIV on the risks of developing TB is mediated through CD4 count, which is modelled continuously for each individual. The CD4 cell count trend and incidence rate ratio for developing TB in HIV-infected individuals not receiving ART are modelled similarly to Williams *et al.* (11). Upon infection, CD4 cell count drops by 25% from an initial value of 1000 cells per microliter, followed by a linear decline to zero at death. Individuals' TB incidence rate ratio (IRR) increases exponentially with decreasing CD4 cell count with a rate 0.36 per 100 cells per microliter. This IRR applies to the hazard of an *M.tb* infection becoming active TB disease as modelled above. HIV-infected individuals are assumed not to have any protection from a prior *M.tb* infection against reinfection disease.

HIV-infected active TB cases were taken to be 45% as likely to be smear positive as HIV-uninfected TB cases (12). Untreated active TB disease in HIV-infected individuals was assumed to have 100% case-fatality, over a time-scale of 5 months (13), also modelled as a Weibull distribution. The probability of detection and treatment initiation was taken from the WHO case-detection estimate, and its timing was modelled in the same manner as for TB in HIV-uninfected individuals.

The life expectancy of an individual starting ART was modelled as in (14): for someone of age a initiating ART at CD4 count $CD4_A$ whose CD4 count immediately following seroconversion was $CD4_I$, their life-expectancy is taken as

$$\max\left(LE_0 - a, 0\right) \times \left(\frac{CD4_A}{CD4_1}\right)^{0.5}$$

where LE_0 is the individual's life-expectancy in the absence of HIV infection. In other words, life-expectancy is that without HIV infection, but discounted by a concave function of how late they start ART.

The effect of ART on TB incidence was taken to be equivalent to returning CD4 count to that following seroconversion, resulting in a population IRR of approximately 0.3 for TB in those on ART compared with HIV-infected individuals not on ART.

IPT

While on a 9 month IPT regimen, individuals' reduced risk of developing TB was modelled as a hazard ratio (HR) less than 1. For HIV-uninfected individuals, this was 0.4 [0.31-0.52] based on the review by Smieja *et al.* (15). For HIV-infected individuals not on ART, this was 0.68 [0.54-85], based on the review by Akolo *et al.* (16). For individuals on ART, the protection above that of ART was 0.63 [0.41-0.94], based on (17). Upon completion of IPT, individuals were assumed to clear their *M.tb.* infection with probability given by $(1 - HR)$ if HIV-uninfected, and with 10% probability if HIV-infected (reflecting the observations in (18)).

Epidemiology

Initial conditions

Populations were initialized in 1980 by sampling households of individuals from country-specific survey data from these communities (1). An initial TB prevalence d was used to calculate an approximate force of infection: $F = (2/3)\beta d$, and this was used to set the prevalence of *M.tb.*, L , infection under a quasi-equilibrium assumption as

$$L = \frac{F/b}{1 + F/b}$$

where b is the crude per-capita birth rate in 1980. *M.tb.* infection is apportioned weighted by age $\propto 1 - e^{-Fa}$. Individuals' time-since-infection was chosen as would result (conditional on infection) from exposure to a constant force-of-infection. The small number of individuals whose sampled activation times were smaller than their time-since-infection had their infections removed. The initial number of individuals on TB treatment was chosen in keeping with the quasi-equilibrium condition, with individuals a random proportion through their treatments.

Age-mixing and transmission

As part of ZAMSTAR, a survey of social contact patterns was carried out in these communities (1). Because interviews were only conducted with adults, knowledge of the community demography and an assumption of symmetrical contacts were used to

infer contact rates for children. The relative contact rates reported between group i and group j in Table 1 were normalized so that the next generation matrix had unit maximal eigenvalue (giving A_{ij}), and used to define the force-of-infection in group i (FOI_i) as

$$FOI_i = \beta . A_{ij} . (p_j^+ + f . p_j^-)$$

where β is the coefficient of transmission ('Styblo' coefficient), p_j^+ and p_j^+ are the prevalence of sputum smear-positive and sputum smear-negative TB in group j, and f is the relative infectiousness per unit time of an average smear-negative to smear-positive TB case.

		Age group contacted					
		0-4	5-12	13-17	18-25	26-45	>45
Age group of individual	SA 0-4	2.27	1.14	1.14	0.74	0.92	0.45
	SA 5-12	0.80	1.61	0.80	0.68	0.89	0.52
	SA 13-17	1.36	1.36	2.73	2.58	1.43	0.98
	SA 18-25	0.42	0.55	1.23	1.07	1.20	0.66
	SA 26-45	0.42	0.58	0.55	0.97	2.12	0.82
	SA >45	0.36	0.59	0.66	0.92	1.42	1.13
	ZM 0-4	3.79	1.89	1.89	0.25	0.44	0.11
	ZM 5-12	1.03	2.05	1.03	0.29	0.49	0.17
	ZM 13-17	1.64	1.64	3.28	1.89	0.75	0.31
	ZM 18-25	0.17	0.36	1.49	1.19	1.02	0.35
	ZM 26-45	0.28	0.59	0.56	0.97	2.32	0.64
	ZM >45	0.14	0.4	0.47	0.67	1.29	1.37

Table 1: Relative contact rates between age-groups used for each country.

Individuals sharing a household with a TB case were subject to an additional force-of-infection, with coefficient β_H. Household transmission of TB is though to account for a minority of transmission (e.g. (19)). We found that the rule-of-thumb $\beta_H \approx \beta/5$ led to around 20% of transmission occurring in the household, and used this to inform the range of values β_H could take.

HIV incidence

Given, our research question, we used a statistical model of HIV incidence to describe the trends through time. The history of HIV incidence was important in determining the prevalence of different levels of immune suppression present in the population at the time of the ZAMSTAR intervention. We used the same functional form as Murray and Salomon (20), i.e. a scaled gamma distribution up its peak, followed by a mixture of this and a constant:

$$i(T) = i_{peak} \times \begin{cases} \left(\frac{eT}{\beta(\alpha-1)}\right)^{\alpha-1} e^{-T/\beta} & T \leq \beta(\alpha-1) \\ \theta + (1-\theta).\left(\frac{eT}{\beta(\alpha-1)}\right)^{\alpha-1} e^{-T/\beta} & T > \beta(\alpha-1) \end{cases}$$

We parametrized this in terms of its peak value, 'peakiness' (α), the time of its peak, and the long-run incidence as a fraction of the peak (θ).

The age of HIV infection was determined by a Weibull model with shape parameter k=2.3 and scale s=25.9 years matching the gender-averaged data presented in Stover *et al.* (21).

Because HIV prevalence was observed to cluster by household, we also introduced a household incidence rate ratio that mean individuals who were cohabiting with an HIV infected individual were at increased risk of HIV infection than they otherwise would be.

ART provision

ART initiation was modelled as for the PopART model used in Eaton *et al.* (22). Individuals who were classified as in contact with health services and whose CD4 count was below the threshold of 350 cells per microliter were assumed to commence ART at a rate of 2 per year. The rate of becoming in contact with health services was modelled by a function of the form:

$$A_{max} \times \frac{[(t - t_0)/s]^k}{1 + [(t - t_0)/s]^k}$$

where t_0 was taken as 2004. The overall scale A_{max} was refitted here to match the ART prevalence in HIV-infected individuals measured by the ZAMSTAR prevalence survey (see below). Drop out from ART was taken as 5% per year. HIV-infected individuals with detected TB disease were initiated on ART after 2010.

Interventions

The interventions were modelled as summarized in Table 2. Because we were interested in bounding what could be achieved, all interventions were taken to have perfect coverage and implementation of the case-finding, IPT and HIV-testing and ART-referral components of the household intervention. These are described in detail elsewhere (23,24), but we assumed that everyone in households of newly detected TB cases was reached by the intervention: that those with HIV who were eligible for ART were initiated on therapy; that those who were eligible for IPT (children aged 5 or under, or those infected with HIV) received therapy; and that co-prevalent TB cases in the household were detected and initiated on TB treatment. In addition, we assumed that those reached in these households could have permanent changes in their care-seeking behavior for TB that improved their chances of detection and treatment, or reduced their delay to detection and treatment. These behavioral changes were modelled as a probability of detection improved by some odds ratio, and a reduced delay to detection and treatment implemented as a hazard ratio applied to the rate controlling the distribution of delays conditional on detection.

To allow for the possibility of diffusion of behavior change beyond the household, we assumed that over the period a household was engaged by the household intervention (i.e. the duration of treatment for the index case), members of this household were able to 'infect' other individuals with the same behavior changes according to an SI process. That is, individuals not already affected by behavioral change could be converted to having improved TB care-seeking behaviors at a rate proportional to the prevalence of those currently engaged with the household intervention in the population (with a proportionality constant 'beta' of 1.5 per year). We assumed that those reached indirectly were not themselves able to spread behavior change, nor were individuals reached directly by the household intervention once their household was no longer engaged directly by the intervention (i.e. after completion of TB treatment).

Intervention	Measured elements	Behaviour change	
		Change to detection:	Diffusion beyond HH:
A	case-finding/IPT/ART	None	No
B	case-finding/IPT/ART	2x faster	No
C	case-finding/IPT/ART	2x odds	No
D	case-finding/IPT/ART	10x odds & 10x faster	No
E	case-finding/IPT/ART	1.5x odds & 1.5x faster	Yes
F	case-finding/IPT/ART	1.5x odds & 1.5x faster	Yes

Table 2: A summary of the intervention scenarios considered.

Analysis

Implementation

The model comprised approximately 4,000 lines of C++, making use of the Gnu Scientific Library (25), and analyses the numerically intensive parts of the analysis were run on high performance computing clusters at the London School of Hygiene and Tropical Medicine and the University of Sheffield. Statistical analyses of data generated were performed in the R environment for statistical computing (26).

Data

8 calibration targets were chosen for each country. The only non-ZAMSTAR data used as a target was the UN HIV prevalence history, scaled to the ZAMSTAR HIV prevalence in 2010. This was used to match the historical incidence trend influencing the CD4 distribution during the trial. All other target data was from the ZAMSTAR final prevalence survey: the HIV prevalence; the ART prevalence among those living with HIV; the culture-positive TB prevalence; the prevalence of being on TB treatment; the annual risk of infection (ARI) in children aged 5 - 12; the household HIV clustering; and the household TB clustering. These data were analysed in the same way as for the trial analysis (23), but correcting for observed intervention effects to obtain an intervention-free counter factual.

Calibration

A Nelder-Mead simplex algorithm was used to pre-fit the parameters governing the overall rate of ART provision and the statistical model of HIV incidence to the ZAMSTAR-rescaled UN HIV prevalence estimates, using a sum-of-squares error term.

The weighted ensemble of runs used for results was then generated along the lines of an importance sample with flat priors. 5000 model runs were then carried out sampling the input parameters across the ranges detailed in Table 3, Table 4, Table 5, and Table 6, with a Latin hypercube design. Squared errors for each of the 8 target statistics divided by their measurement variances were again rescaled by the medians of their error distributions, so that each error statistic contributed equally to the measure of fit. Each country's error also contributed equally. This weight of each parameter sample was taken as an exponential this total error statistic with decay constant taken as the median of each target statistic's characteristic (i.e. median) error. The priors were flat over intervals of 5% for natural history parameters that were not influential for the fit, and larger ranges for those that were influential. Runs for each of the 6 intervention scenarios were performed with the same random number stream and parameter values as the base case.

Bootstrap procedure

To calculate the probability of the modelled impact exceeding the true value, 10,000 bootstrap samples were drawn weighted by fit, comparing 8 Zambian and 4 South African runs with the given intervention, against the same numbers (unpaired) without by computing the risk (or rate) ratio for the geometric mean of prevalence (or ARI) comparing the intervention with the no-intervention communities. To account for the imprecision in the impact measurements for prevalence and ARI from the trial, the trial cluster impacts on prevalence and ARI were used to parametrize a bivariate log-normal posterior for ZAMSTAR's true impacts, which had 95% credible intervals matching the trial impact confidence intervals. Because impacts on ARI and prevalence were correlated at a cluster level, this induced a correlation structure on the posterior. The log-normal posterior, $p(x|\mu,\Sigma)$, therefore had parameters

$$\mu = \begin{pmatrix}\log(0.82)\\ \log(0.45)\end{pmatrix}, \quad \Sigma = \frac{1}{6}\begin{pmatrix}0.068 & 0.058\\ 0.058 & 0.822\end{pmatrix}$$

The probability of particular model results (RR, HR) exceeding the true trial impact for each sample was calculated as $\int_{-\infty}^{RR,HR} d^2x.\ p(x|\mu,\Sigma)$. The probability that the model (conditioned on the data) predicted an impact more extreme than the true impact was computed as a weighted mean over the ensemble of parameter with weights penalizing the fit to base case data (as described above).

Sensitivity analysis

The one-way sensitivity of our results to parameter uncertainty was assessed by calculating a range by repeating this bootstrap procedure for each intervention, but

restricting each parameter in turn to values in the highest and then the lowest 10% of its uncertainty range. The resulting probabilities of the model exceeding the trial impact are shown in Figure 4 for each intervention, and with the parameters arranged in descending order of influence. The influence of each parameter was assessed as the mean over interventions of the proportional difference between the results from restricting to the top and bottom deciles. The ranges used for parameters are shown in Table 3, Table 4, Table 5, and Table 6. For most parameters, in the absence of a more rigorous description, uncertainty was represented by a uniform distribution with range equal to 10% of central value (on a logit-scale for parameters describing probabilities). See Table 2 for a description of interventions A-F.

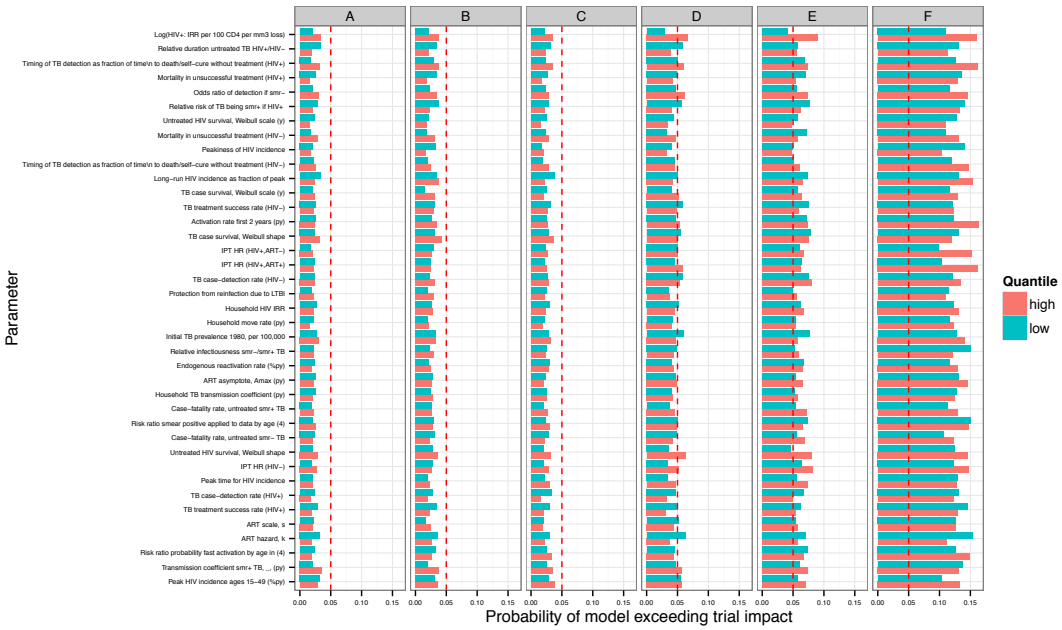

Figure 4: Sensitivity of probability model exceeding trial impact to parameter values. The bootstrap procedure was as above, but with the named parameter restricted to its top, and then bottom decile. Red dashed lines represent a probability of 0.05. See Table 2 for a description of interventions A-F.

Parameter values

Parameter	low	high	Source
TB case survival, Weibull shape	1.463	1.538	-
TB case survival, Weibull scale (y)	3.169	3.331	(8)
Case-fatality rate, untreated smr+ TB	0.683	0.718	(8)
Endogenous reactivation rate (%py)	0.020	0.600	(4)
Activation rate first 2 years (py)	0.065	0.069	(4)
Risk ratio smear positive applied to data by age (4)	0.975	1.025	-
Risk ratio probability fast activation by age in (4)	0.800	1.200	-
Case-fatality rate, untreated smr- TB	0.293	0.308	(8)
Protection from reinfection due to LTBI	0.200	0.900	-
Relative infectiousness smr-/smr+ TB	0.224	0.236	(6,7)
Odds ratio of detection if smr-	0.683	0.718	(27)
Relative duration untreated TB HIV+/HIV-	0.098	0.103	(13)
Relative risk of TB being smr+ if HIV+	0.439	0.461	(12)
Log(HIV+: IRR per 100 CD4 per mm^3 loss)	0.351	0.369	(11)

Table 3: Parameters related to the natural history of TB.

Parameter	Country	low	high	Source
Peak HIV incidence ages 15-49 (%py)	SA	2.250	2.750	fit
	ZM	1.710	2.090	fit
Peakiness of HIV incidence	SA	26.520	27.880	fit
	ZM	2.438	2.563	fit
Peak time for HIV incidence	SA	1993	1999	fit
	ZM	1987	1993	fit
Long-run HIV incidence as fraction of peak	SA	0.556	0.584	fit
	ZM	0.488	0.513	fit
Age at HIV infection, Weibull shape	Both	2.3		(21)
Age at HIV infection, Weibull scale (y)	Both	25.9		(21)
Untreated HIV survival, Weibull shape	Both	2.243	2.358	(10)
Untreated HIV survival, Weibull scale (y)	Both	12.968	13.633	(10)

Table 4: Parameters related to HIV incidence and survival.

Parameter	Country	low	high	Source
Transmission coefficient smr+ TB, β, (py)	SA	5	15	-
	ZM	5	15	-
Household TB transmission coefficient (py)	SA	0.5	5	-
	ZM	0.5	5	-
Household move rate (py)	SA	0.098	1.103	(1)
	ZM	0.098	1.103	(1)
Household HIV IRR	SA	1	10	-
	ZM	1	10	-
Initial TB prevalence 1980, per 100,000	SA	585	615	-
	ZM	390	410	-

Table 5: Parameters related to households, transmission, and the initial state.

Parameter	Country	low	high	Source
TB case-detection rate (HIV-)	SA	0.52	0.62	(28)
	ZM	0.62	0.78	(28)
TB treatment success rate (HIV-)	SA	0.740	0.778	(28)
	ZM	0.858	0.902	(28)
Mortality in unsuccessful treatment (HIV-)	SA	0.244	0.256	(9)
	ZM	0.244	0.256	(9)
Timing of TB detection as fraction of time to death/self-cure without treatment (HIV-)	SA	0.1	0.9	-
	ZM	0.1	0.9	-
TB case-detection rate (HIV+)	SA	0.52	0.62	(28)
	ZM	0.62	0.78	(28)
TB treatment success rate (HIV+)	SA	0.740	0.778	(28)
	ZM	0.858	0.902	(28)
Mortality in unsuccessful treatment (HIV+)	SA	0.878	0.923	(9)
	ZM	0.878	0.923	(9)
Timing of TB detection as fraction of time to death/self-cure without treatment (HIV+)	SA	0.1	0.9	-
	ZM	0.1	0.9	-
IPT HR (HIV-)	Both	0.31	0.52	(15)
IPT HR (HIV+,ART-)	Both	0.54	0.85	(16)
IPT HR (HIV+,ART+)	Both	0.41	0.94	(17)

Table 6: Parameters related to detection, treatment, and IPT.

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