Technical Description of Menzies, PopART and Goals Models

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1. Model 1, Menzies

Technical Description of the Menzies Model

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1.1 Introduction

This model is an extension of a TB-HIV model developed to analyze the implications of introducing new TB diagnostics in southern Africa [1]. Here we recapitulate the key elements of the original model and describe extensions made to this model to accommodate the different ART expansion scenarios considered by the HIV modelling consortium.

1.2 Model overview and structure

This model is a dynamic compartmental model of TB and HIV in the adult population. The model is divided into multiple compartments, with the population distributed across these compartments to describe TB and HIV natural history and treatment status at a point in time. The model simulates transitions between compartments deterministically, and recalculates the population distribution across states in discrete monthly time steps. The model was parameterized to South African epidemiology and service provision data [2], and calibrated using a Bayesian calibration approach [3, 4].

1.3 Model structure related to HIV

HIV compartments capture important features of HIV transmission, progression, and treatment status. Individuals may be HIV-negative, they may be in one of three categories reflecting untreated HIV infection with a specified CD4 cell count (>350 cells per μL, 200-350 cells per μL, and <200 cells per μL), or they may be receiving antiretroviral therapy (ART) in one of three categories distinguished by the CD4 count at treatment initiation. Individuals in the HIV negative compartment are exposed to HIV infection at a rate determined by exogenous HIV incidence estimates. Once infected, individuals transition to the CD4>350 compartment, and then transition to progressively lower CD4 count categories until they reach the CD4<200 compartment. HIV-positive individuals are initiated on ART based on extant ART eligibility guidelines at a rate determined to match observed scale-up of the national ART program. Reductions in HIV incidence that result from ART expansion are captured through the change in distribution of individuals across ART / non-ART compartments, and the reduced infectiousness [5] of those in ART compartments.

HIV co-infection can alter the rate of progression of TB disease, with HIV-infected individuals having a higher probability of primary progressive TB upon initial infection [6], a higher rate of breakdown from latent infection to active TB [7], a lower probability of smear-positivity amongst those with active TB [8], lower probability of self-cure, and higher mortality rates [9].

1.4 Model structure related to TB

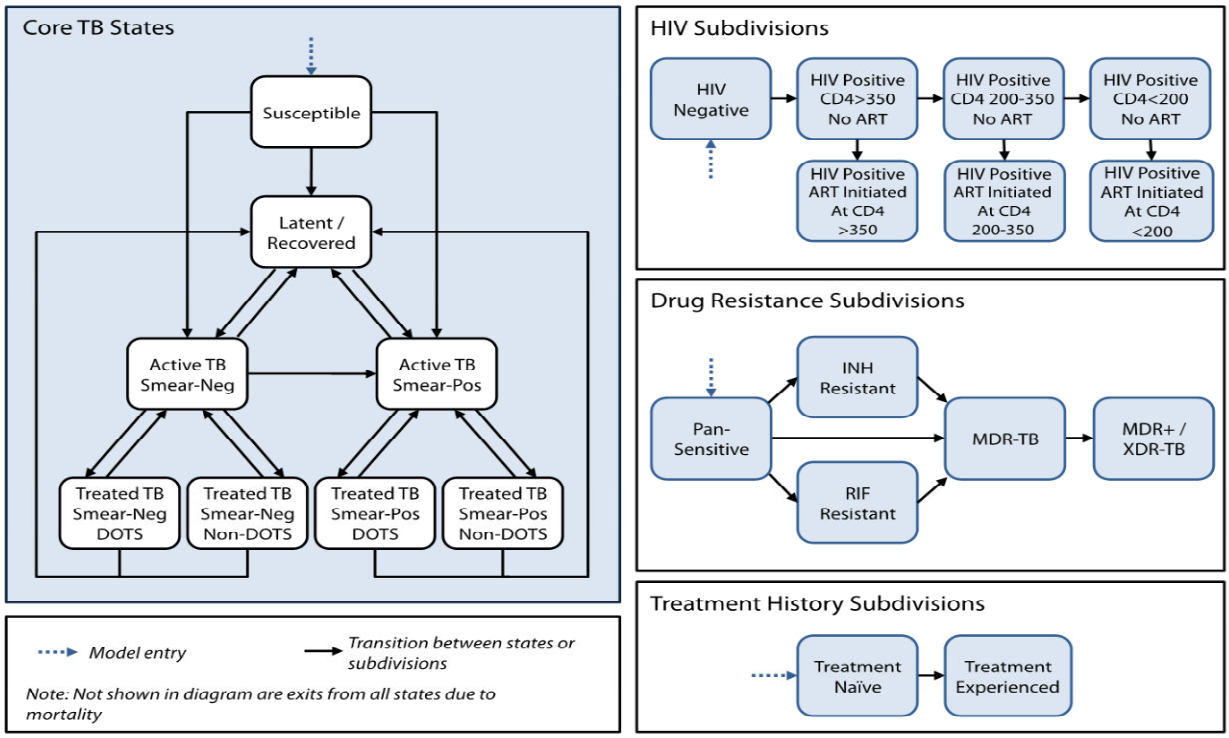
The core TB compartments capture important features of TB transmission, natural history, and treatment. Eight states are included. Individuals who have never been infected reside in the susceptible state. Those who are infected but do not have active TB are in the latent infection/recovered state. Active TB is categorized as smear-negative or smear-positive. Smear-negative or smear-positive active cases may be treated either through the national TB control program (DOTS), or through providers outside of the national program (non-DOTS).

Five subdivisions were created in this core model to account for differences in drug resistance among circulating TB strains, including: (1) pan-sensitive TB, (2) isoniazid (INH) mono-resistant TB, (3) rifampicin (RIF) mono-resistant TB, (4) resistance to both isoniazid and rifampicin (MDR-TB), and (5) resistance to isoniazid and rifampicin plus one or more second-line drugs (MDR+/XDR-TB). A final model subdivision distinguishes TB treatment-naïve from TB treatment-experienced individuals, as this has implications for TB diagnosis and treatment regimen.

1.5 Summary of model structure

At any point in time, all individuals in the model are categorized by the combination of their TB and HIV status, which yields a total of $8 \times 70 = 560$ unique compartments in the model. Some of these 560 compartments are null, in instances where the crossing of specific categories is meaningless; for example, susceptible individuals are defined by having never been infected, which means that they cannot be characterized in terms of a TB strain with a specific drug resistance profile.

Figure S1: Menzies model compartments and transitions



1.6 Model for expanded access to HIV-care

In order to model the ART expansion scenarios considered by the HIV modelling consortium, we extended the original model with a more detailed representation of the availability of HIV care to different individuals, which then informs the full model by providing appropriate rates of initiating treatment for HIV-positive individuals according to their specific CD4 category.

The sub-model contains a total of 11 states. Similarly to the HIV subdivisions in the full model, individuals may be HIV-negative, they may be in one of three categories reflecting untreated HIV infection with a specified CD4 cell count (>350 cells per μL, 200-350 cells per μL, and <200 cells per μL), or they may be receiving antiretroviral therapy (ART) in one of three categories distinguished by the CD4 count at ART initiation. However, the cohort of HIV positive individuals not receiving ART are further classified as in-care (receiving regular monitoring of health status and ART eligibility) or out-of-care.

The sub-model for expanded access to HIV-care was used to determine the rate at which HIV infected individuals not yet on treatment would transition onto ART, by CD4 stratum. It was assumed that all individuals would need to test positive and be initiated onto regular CD4 monitoring before transitioning onto ART. Consequently, improvements in ART access required greater rates of HIV testing and linkage to care to enroll untreated individuals on pre-ART care services. Expansions in ART eligibility involved allowing those already enrolled in pre-ART care to transition onto ART under the expanded eligibility criteria.

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2. Model 2, PopART

Technical Description of the PopART Model

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2.1 Model structure related to HIV

To generate outputs relevant to TB for the "PopART" contribution, an individual-based model designed to aid interpretation of the ZAMSTAR study [1] was superimposed on the "Fraser" model in [2] . The population was changed to represent only those aged over 15 years with an age-independent hazard of death. The background death and birth rates, and hazards of linking to care and initiating ART were all treated the same way as in the HIV model. Distributions of life-expectancy for HIV-infected individuals, both on and off ART were matched to those implicit in the HIV model. The per-capita HIV incidence time-series for each scenario from the HIV model was applied as hazard of infection to individuals in the TB model. CD4 status of HIV-infected individuals not on ART was assumed to decrement by 25% from 1000 cells/mm^3 upon infection, followed by a linear decline to zero at death, as in [3].

2.2 Model structure related to TB

Pulmonary TB was modelled, with 65% of cases being smear positive [4]; smear negative TB assumed 23% as infectious as smear positive TB [5,6]. HIV-infected TB cases were taken to be 45% as likely to be smear positive as HIV-uninfected TB cases [7]. TB transmission was modelled with random mixing, with smear positive TB cases having an effective contact rate of 12.6/year (fitted). In the absence of treatment, HIV-uninfected TB disease was assumed to result in death in 55% of cases over a time-scale of 2.25 years [8], with the remainder of individuals self-curing. Untreated HIV-infected TB disease was assumed to have 100% case-fatality, over a time-scale of 5 months [9]. Following infection or reinfection, the risk of progressing to TB disease in an HIV-uninfected individual was 14% during the first 2 years [4], and thereafter could occur at a rate of 0.3%/year (fitted). The rates of developing TB disease following reinfection were modelled as with an initial *M.tb.* infection, except that for HIV-uninfected individuals, a latent *M.tb.* infection conferred a protection of 68% from progression to disease following a particular reinfection event (fitted). For those infected with HIV, all rates of progression from to TB disease if infected by *M.tb.* were multiplied by an IRR that increased exponentially with decrement in CD4 cell count ($5.3 \,.\, 10^{-3}$/mm^3 fitted, resulting in an IRR of approximately 23 for TB among HIV-infected individuals in 2000). 72% of incident TB cases were assumed to begin treatment [10]. Detection and TB treatment initiation were taken to occur after a fraction 60% of an individual's TB disease duration had passed (fitted). TB treatment was then assumed to last for 6 months with individuals immediately becoming uninfectious upon initiation [11]. At the end of treatment, 70% of patients were taken to have a successful outcome [10], with 5% dying and the remainder put at higher risk of recurrence analogous to a recent infection (resulting in approximately 18% of incident TB having been previously treated in 2010). Drug resistance was not modelled. 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.

2.3 Model Calibration

Fitted parameters were determined via an adaptive importance-sampling scheme. Beginning with a Latin-hypercube sample from the priors, 10 generations comprising 2000 particles had outputs evaluated and compared against the Stop TB time-series estimates of TB incidence, prevalence, and HIV-TB incidence. Particles with a sum-squared-error statistic in the lowest 2.5-percentile were accepted and a proposal distribution for the next step matched against the collection of weighted particles generated up to this step. Priors were uniform except for the protection from previous infection parameter, which was beta (1.5,1.5). Outputs for different scenarios considered were the rescaled means of 1000 runs, each using a population initialized with 25000 individuals in 1980.

2.4 Model for expanded access to HIV-care

The ART expansion scenarios considered by the HIV modelling consortium were modeled in a spirit similar to that of the Menzies model. HIV positive individuals (on or off ART) were classified as in-care (receiving regular monitoring of health status and ART eligibility, and hence rapidly initiating ART upon eligibility) or out-of-care. HIV negative individuals were split in two mirroring categories, corresponding to individuals who get tested on a regular basis ("in-care") and individuals who rarely get tested, typically only if they have severe symptoms ("out-of-care"). To reflect the ramp-up of ART over the last decade, the rate of getting in-care was parameterized as an increasing function of time, which was calibrated to match historical ART coverage data. Improvements in ART access were modeled as a boost in the rate of getting in-care. Expansions in ART eligibility were modeled by allowing individuals in-care to transition onto ART under the expanded eligibility criteria.

2.5 References

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3. Model 3, Goals-TB

Technical Description of the Goals-TB Model

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3.1 Introduction

This document outlines the Spectrum TB model (also called Goals-TB) for the estimation of key TB indicators at country level, with an emphasis on indicators relevant to HIV-TB, and with the aim of estimating the potential impact of HIV interventions on the burden of HIV-TB [1].
An immediate application of the model is the estimation of the number of incident TB cases by CD4 category (these data are produced by the Spectrum HIV model [2]). Most countries follow 2010 ART guidelines which recommend that HIV+ cases with active TB must initiate treatment regardless of CD4 count. Many of them want to expand ART eligibility to higher CD4 thresholds. The Goals-TB model can be used to estimate resource requirements above those that will result from current ART guidelines. Another important use is to estimate HIV+ TB mortality and the impact of ART expansion.

3.2 Model structure related to HIV

HIV incidence was generated using the Goals contains a transmission model that calculates the number of new HIV infections among 15–49 year-old adults over time as a result of sexual and injecting drug transmission. Individuals enter the Goals model at age 15. They are assumed not to be sexually active until they reach the median age at first sex for a particular country. Individuals are then allocated to one of five risk categories distinguished on the basis of the number of annual sexual partners of members of these groups. The risk categories are: stable couples (men and women reporting a single partner in the last year), multiple partners (men and women who report more than one partner in the last year), female sex workers and clients (FSW), men who have sex with men (MSM), and injecting drug users (IDU). Each risk category is further characterized by number of sex acts per year, condom use and levels of other sexually transmitted infections (STI). The Goals model also has an impact matrix that summarizes the impact literature to describe changes in behavior by risk group as a result of exposure to behavior change interventions.

The Goals model uses a CD4+ T-cell (CD4) count structure to progress individuals who are HIV positive. The CD4 model has seven CD4 compartments, selected in order to inform CD4-based ART eligibility criteria issued by WHO (e.g. ART eligibility at CD4 < 350 cells/uL) and the availability of data to inform mortality patterns in these CD4 categories: CD4 < 50 cells/uL, 50-99, 100-199, 200-249, 250-349, 350-499 and > 500 cells/uL. Many HIV-related parameters vary as a function of CD4 count: progression to lower CD4 counts, HIV-related mortality, probability of initiating ART, and infectiousness.

3.3 Model structure related to TB

The model is essentially a TB incidence model, which is fit to incidence data from the WHO Stop TB database and disaggregated according to CD4 category. To this end, a regression method is devised to estimate relative risk (RR) for TB incidence according to the CD4 categories used by Spectrum for national HIV projections. Spectrum data are based on the national projections prepared towards the UNAIDS Report on the Global AIDS Epidemic 2012.

Estimating TB indicators with cubic splines

A flexible and relatively simple way of modeling TB incidence (or any time-dependent function) is to represent it as k time-dependent m'th order cubic-spline functions [p.152,3]:

$$I(x) = \Sigma_{i=1 \text{ to } k} \beta_i Bm_i(x)$$

where β_i is the i'th spline coefficient and $Bm_i(x)$ represents the evaluation of the i-th basis function at time(year) x. The order of each basis function is m and we use cubic splines, i.e. m=3. Equation 4 simply states that any time-dependent function, such as incidence, can be represented as a linear combination of cubic-spline basis functions.

The values of the cubic-spline coefficients β are determined by an optimization routine which minimizes the least squares error between incidence data (Iobs) and the estimated incidence curve I(x):

$$\Sigma_{x=1990:2010} |I(x) - Iobs(x)|^2 + \lambda \beta T S \beta$$

Here $|I - Iobs|^2$ is the sum of squared errors in estimated incidence and S is a difference penalty matrix applied directly to the parameters β to control the level of variation between adjacent coefficients of the cubic-spline, and thus control (through a choice of λ) the smoothness of the time-dependent case incidence curve. Another important purpose of the use of the smoothness penalty matrix S is to regularize (by creating smoothness dependencies between adjacent parameters) the ill-conditioned inverse problem (more unknown parameters than the data can resolve) that would tend to over fit the data when left ill-conditioned.

Cubic-Splines and confidence intervals

The WHO Stop TB database lists a lower and an upper bound for most indicators. A confidence interval is found from these bounds by drawing samples from a beta distribution, with shape parameters estimated from the given bounds. Specifically, its shape parameters are estimated by means of the 'method of moments' using the given point estimate as mean, and the difference between the given bounds divided by 4 as standard deviation. There is in fact a different beta distribution representing uncertainty at each year of available data.

The cubic-spline method is then used to fit an indicator to a set of bootstrapped data, producing a sample of projected cubic-spline curves that are practically equivalent to a set that would be obtained from fitting the model to the same number of repeated measurements (or assessments) of the given indicator.

Projecting HIV-TB incidence by CD4 category

The disaggregation of TB incidence by CD4 category is based on the idea that increase in the relative risk for TB incidence is a function of CD4 decline. Williams et al captured this idea in a model for the relationship between the RR for TB and CD4 decline [4]. They suggested a 42% (+-17% for 95% confidence interval) increase in RR for TB for each unit of 100uL CD4 decline. The Spectrum-TN model's disaggregation method is based on the Williams et al model. The model first estimates HIV- TB incidence and then calculates the risk of TB infection F=I- / P-, where I- is HIV- TB incidence and P- the number of HIV- individuals susceptible to TB.

An assumption is made that risk TB infection for HIV+ cases with CD4 count > 500 uL is proportional to F (we assume it is higher by a factor of 3). For each 100uL CD4 decline in the remaining categories (350-499, 250-349, 200-249, 100-199, 50-99 CD4 cells/uL, and CD4 count less than 50 cells uL), the risk of TB infection is represented as:

$$F(c<500) = F(c>500)\cdot p(1)\cdot p(2)dc,$$

where p(1) is a parameter that is used to recognize that HIV+ cases with high CD4 counts could be at higher risk of TB infection relative to HIV-, and p(2) controls the exponential increase in RR with CD4 decline. dc is the number of 100uL CD4 decline associated with the midpoint of each CD4 category relative to 500: dc= (3.0, 4.4, 8.6, 12.9, 19.2, 28.6, 37.3) for the six CD4 categories. A reduction in RR is applied for those being on ART for more than one year. We assume hazard ratios of 0.16, 0.35 and 0.43 for those on ART with CD4 count < 200, 200-350 and > 350 [5].

Projecting TB mortality

The following case fatality ratios are applied to different TB categories in order to estimates TB-associated mortality from TB projected incidence. The estimates were obtained in collaboration with the TB Modeling and Analysis Consortium (TBMAC). The estimates are from the following sources [6-8], and are subject to revision – the current estimates in the Spectrum-TB model may be slightly different to these estimates.

Table S1: Goals-TB casefatality ratios

	Non-Notified	Notified
HIV-	0.45	0.07
HIV+ not receiving ART	0.85	0.25
HIV+ receiving ART for less than one year	0.75	0.15
HIV+ receiving ART for more than one year	0.6	0.08

3.4 Model for expanded access to HIV-care

The Goals model disaggregates the HIV infected population by CD4 count categories and treatment status. In fitting the historical epidemic curves, country program data on the number of persons on ART treatment are used to determine the distribution by CD4 count category (for eligible CD4 counts) for the number newly starting ART each year. This distribution is estimated as the average of equal allocation into each CD4 category and allocation weighted according to mortality in each CD4 category, resulting in a pattern that matches data from southern African treatment sites.

To determine the number of persons starting treatment in the newly eligible CD4 category (350-500 cell/ μL) we need to determine the proportion of persons in these categories that are available to start treatment, i.e., tested and aware of their infection. As CD4 count eligibility prior to 2013 was CD4 <350 cells /μL, we use the proportion of persons on treatment in category 250-350 cells/μL in 2011 as an estimate of the proportion tested and available for starting treatment. This same proportion is applied for CD4 category 350-500 cell/ μL.

3.5 References

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4. Rate ratios of developing active TB, and of TB-associated mortality

Table S2: Rate ratios of developing active TB, and of TB-associated mortality, as a function of HIV status, CD4 count, and receipt of ART, relative to rates for HIV negative cases*.

	HIV Positive, CD4>350, No ART	HIV Positive, CD4<350, No ART	HIV Positive, On ART (CD4 <350 at initiation)	All HIV Positive
Rate ratio for developing active TB				
Menzies	2.7	22.2	7.7	7.0
PopART	13.4	21.3	4.3	10.9
Goals	3.5	16.6	5.7	7.4
Rate ratio for TB-related mortality				
Menzies	---	---	11.4	11.2
PopART	---	---	10.8	23.9
Goals	---	---	8.3	16.3

* Values are based on 2014 estimates in the 'status quo' scenario where it is assumed that current patterns of ART access continue. Relative rates for TB-related mortality are not disaggregated by CD4 count. 'All HIV Positive' represents the average for all individuals with HIV.

5. Model calibration to TB indicators

Figure S2: Menzies model estimates compared to calibration data

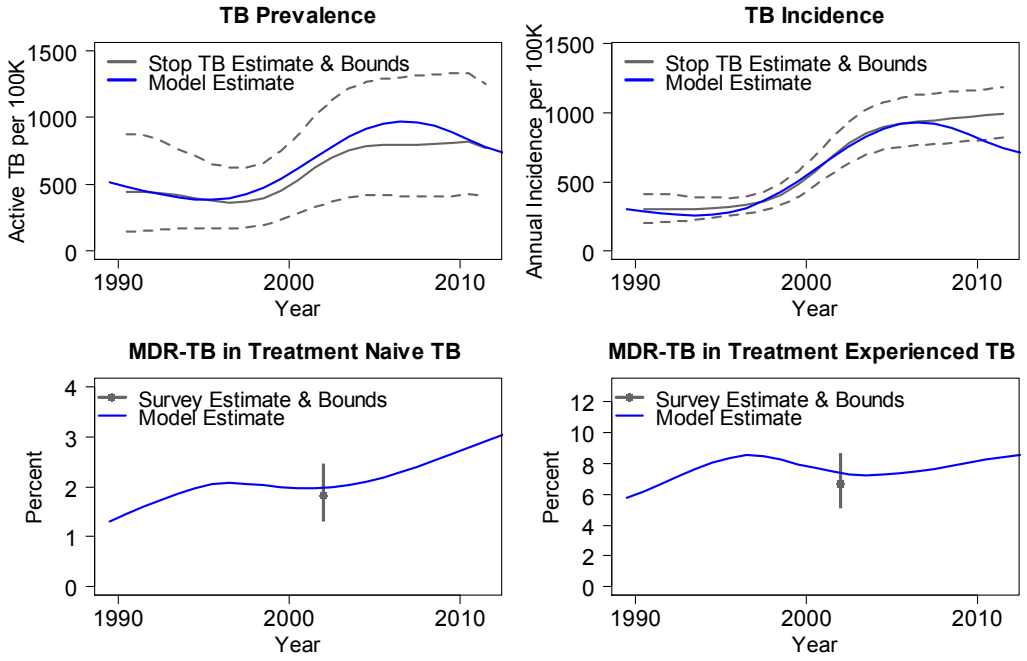

Figure S3: PopART model estimates compared to calibration data

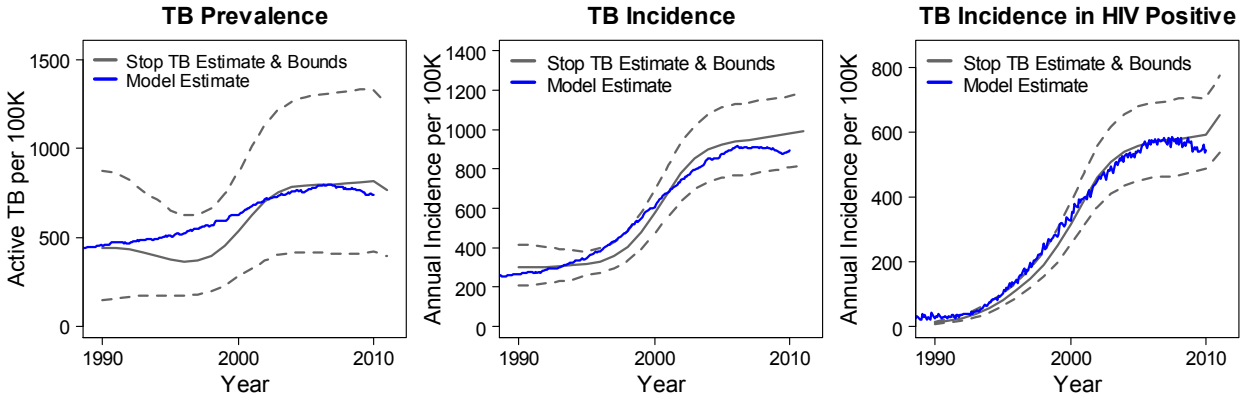

Figure S4: Goals-TB model estimates compared to calibration data