APPENDIX TO:

THE PERSISTENCE OF TUBERCULOSIS IN THE AGE OF DOTS:

RE-EVALUATING THE IMPACT OF CASE DETECTION

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Description of Differences from Previous Dynamic Models of TB

As stated in the manuscript text, the structure of the present model is patterned after an earlier compartmental model of TB,[1] which corroborated the initial estimate by Styblo and Bumgarner[2] that 70% case detection and 85% treatment success could reduce TB incidence by 5-10% annually. This section describes and justifies the important adaptations to that model that were made in developing the present model:

(1) Based on evidence that emerged in 1999,[3] smear-negative individuals are assumed to be infectious, although their infectivity is much less than that of smear-positive individuals.

(2) Treatment success is modeled differently. In the original model, successful treatment uniformly returns individuals to the latently-infected state. This is at odds with recent data that patients who are cured of TB have lower relapse rates than those who complete treatment without documented cure, and that patients who are cured remain at increased risk of active TB upon re-infection (e.g., because of intrinsic susceptibility).[4] Here, we conceptualize treatment success as a reduction in the bacillary burden of TB to a point that reactivation is not possible. To model the intrinsic susceptibility of these patients to active TB, we also assume that they have no protection against re-infection afforded by latent infection. Of note, achievement of this state cannot be measured; some patients who are registered as "cured" or "treatment completed" will remain at risk for reactivation, while others who are registered as "transferred" and "not evaluated" will not. Thus, we assume that recorded treatment success rates (i.e., "cure" plus "treatment completed") parallel this "actual" treatment success rate and perform wide sensitivity analysis for this parameter (between 70% and 90%, Table 1).

(3) The original model assumes that patients treated unsuccessfully remain in the “active TB” compartment and thus retain full infectiousness and heightened mortality risk. However, broader experience with DOTS has demonstrated that only 2% of all new smear-positive cases registered worldwide end in treatment failure; the most common unsuccessful outcome is default.[5] Thus, the present model assumes that patients treated unsuccessfully have a TB history as represented by defaulters within a cohort of treated patients in Cape Town, South Africa (i.e., relapse rate of 6.5 per 100 person-years),[4] assuming that patients are not infectious or at increased mortality risk until relapse occurs. At this rate of relapse, 78% of HIV-negative defaulters relapse with TB before dying of other causes. TB patients who do not receive at least one month of therapy in the present model are assumed to remain active and undiagnosed. Increasing the mortality risk of unsuccessfully-treated patients to that of patients with smear-negative TB made no material impact on our final results.

(4) The majority of patients who die on TB therapy do so in the first two months,[6] suggesting that mortality during treatment may more accurately reflect the mortality risk of underlying TB disease (i.e., failure of timely diagnosis) than true failure of treatment. Ideally, then, these patients may best be treated as individuals who crossed a “mortality threshold” before being diagnosed with TB and whose TB diagnosis is therefore inconsequential. As currently measured by the WHO, however, these patients contribute to the numerator of the case detection rate (as they are diagnosed with TB) and to the denominator of the treatment success rate (i.e., unsuccessful treatment). The original model by Dye et al does not explicitly account for such individuals. The present model assumes that a uniform 7% of all diagnosed TB cases die on therapy, representative of the WHO African region.[5] For purposes of the model, these

individuals are treated as undiagnosed; thus, patients who die on therapy during a given month are assumed to be part of the larger subset of all active TB patients who die during that month, while mortality on treatment is no higher than background. In calculating case detection rates, however, all individuals receiving a diagnosis of TB are considered to be detected. Importantly, treatment success rates apply only to survivors; thus, the base case (treatment success of 85% * 93% [100% minus the 7% of diagnosed cases who die] = 79% as measured by WHO) corresponds more closely to the current 76% success rate in the African region,[5] whereas sensitivity analysis to 2% of treated cases dying (85% * 98% = 83%) corresponds more closely to the global estimate of 84% treatment success.

(5) As described in the manuscript text, the present model explicitly incorporates both diagnostic sensitivity and a ratio of diagnostic attempts to mortality rate, rather than assuming a single parameter corresponding to the annual rate of successful diagnosis.

(6) Dye et al incorporated an explicit age structure to account for the fact that pediatric TB differs from that in adults. However, incorporating this structure requires definition of separate parameters by age, whereas the data informing most model parameters are either not collected in age-specific fashion or are limited in children. Restricting the model to adults eliminates the need to parameterize pediatric TB but (by ignoring adult-to-child transmission) reduces comparability of results to the most widely-recognized estimates of TB case detection and treatment success, which are not age-specific. Thus, we adopted the approach of assuming an explicit fraction of smear-negative TB to be extrapulmonary, as estimated by the WHO.[5] These cases – many of which occur in children (and HIV-infected patients) – are not infectious in the

present model and are detected at similar rates as smear-negative pulmonary TB. This approach accounts for the reduced infectiousness of TB in children, allows pediatric TB to appropriately contribute to estimates of TB case detection and treatment, and avoids the need to create a separate parameter set for pediatric TB.

(7) A number of parameter values in Table 1 are changed from the original model, based on data that have emerged in the past decade and our desire to model a contemporary high-burden population. Most important among these parameter changes are: (a) an increase in the duration of TB, assuming no TB treatment, from 0.5 years to 1.0 years in HIV-infected individuals, consistent with data from Wood and colleagues,[7] as well as the fact that a growing number of HIV/TB-coinfected patients are on antiretroviral therapy and thus less immunosuppressed than in 1998; (b) increase in the mean life expectancy of HIV (in the absence of TB) to 11 years, consistent with current global estimates;[8] and (c) assumption that untreated smear-positive TB in HIV-negatives carries a 50% (rather than 70%) case-fatality rate, based on modeling estimates of a historical British population by Vynnycky and Fine[9] and allowing better harmonization of parameters for smear-negative TB with the non-dynamic modeling approach currently employed by the WHO in generating its estimates of TB incidence and impact of HIV.[10]

Supplementary Table. Parameters Used in Model Equations

These parameters correspond to those in Table 1 of the manuscript text, with additional calculations as described. The subscripts *h* and *i* refer to HIV status and TB activity/smear status, as described in the following section.

Symbol	**Parameter Description**
TB Dynamics	
λ_i	Annual rate of TB transmission to a single susceptible individual from a single TB patient, according to TB activity/smear status (*i*)[a]
ip_{hi}	Proportion of incident TB that is smear-positive, by HIV status (*h*)
rp_h	Proportion of TB infections resulting in rapid progression to active TB, by HIV status (*h*)
le_h	Efficacy of latent infection in preventing re-infection, by HIV status (*h*)
er_h	Annual rate of endogenous reactivation, by HIV status (*h*)
sc	Smear conversion rate: annual rate of spontaneous conversion from smear-negative to smear-positive TB
Mortality	
m_{hi}	Annual mortality rate, by HIV status (*h*) and TB activity/smear status (*i*)[b]
c_h	Spontaneous cure rate, by HIV status (*h*) and TB activity/smear status (*i*)[c]
TB Diagnosis and Treatment	
dd	Diagnostic delay: mean time (in years) for a successful diagnostic attempt
ds_i	Diagnostic sensitivity: proportion of diagnostic attempts resulting in successful initiation of effective TB therapy, by smear status (*i*)[d]
r	Ratio of the rate of presenting for TB diagnosis to the mortality rate
tx	Proportion of TB cases successfully treated
rel	Annual relapse rate among patients treated unsuccessfully
Miscellaneous Parameters	
ts	Time step[e]
hiv	Annual incidence of new HIV infection in the population[f]

Supplementary Table. Parameters Used in Model Equations (cont.)

[a] Calculated as the number of secondary infections per smear-positive person-year, divided by an arbitrary population size (10 million in this case) and, for smear-negative disease, further multiplied by (relative infectivity of pulmonary smear-negative TB * [1 – proportion of smear-negative TB that is extrapulmonary]).

[b] Calculated as (1/mean life expectancy) for patients without active TB ($i = 0$). For patients with active TB, calculated as (1/mean duration of untreated smear-positive TB)*(proportion of untreated smear-positive patients who will die)*(relative mortality of smear-negative TB [if smear-negative]).

[c] Calculated as (1/mean duration of untreated smear-positive TB)*(1 – proportion of untreated smear-positive TB patients who will die).

[d] Calculated as (diagnostic sensitivity of the clinical algorithm)*(1 – proportion of patients who die on TB therapy), thus reflecting the concept that those who die on TB therapy are diagnosed too late in their disease course to effect proper therapy, and allowing those individuals to maintain an appropriately high mortality rate.

[e] Set at 1/100 year (3.65 days)

[f] Constant HIV incidence sufficient to generate an HIV prevalence among incident TB cases of 22% if the TB case detection rate is 61%.

Model Equations

Use of subscripts

The generic subscripts h and i are used to denote HIV status and TB smear status, respectively. When referring to a specific TB or HIV stratum, these generic subscripts are replaced by specific subscripts:

h : +, positive; –, negative

i : *1*, smear-positive TB; *2*, smear-negative active TB (including extrapulmonary)

The subscript 0 is used in the term m_{h0} to denote mortality in the absence of active TB, but 0 is otherwise not an allowed quantity of i. Thus, for example, an equation using the term A_{hi} on the left-hand side denotes four separate equations, each corresponding to one of four compartments (A_{-1}, A_{-2}, A_{+1}, and A_{+2}). By contrast, A_{+2} refers specifically to the compartment of patients with undiagnosed active, smear-negative TB.

Equation 1. Force of infection, *f*

$$f = \sum_i \left\{ \lambda_i \times \sum_h \left[PT_{hi} + A_{hi} \right] \right\}$$

where PT and A include all individuals with active TB, as described in Equations X and X below.

Equation 2. Individuals with no prior TB infection, S_h

$$\Delta S_h / ts = r_1 + r_2 - fS_h - m_{h0} S_h$$

Here, r_1 denotes new recruitment into the population (equation 2a), r_2 infection with HIV (equation 2b), fS_h infection with TB (with the force of infection f), and $m_{h0}S_h$ mortality (at rate m_{h0}).

2a. Rate of recruitment of new TB-uninfected individuals into the population:

$$r_1 = a\left[\sum_h \sum_i m_{hi} X_{hi}\right]$$

where a = 1 for S_-, and a = 0 for S_+. In this equation, X denotes any compartment of the population (e.g., S for susceptibles and L for those with latent infection). Thus, total recruitment is set equal to total mortality (giving a steady population size), with new recruits assumed to be uniformly HIV-negative.

2b. Rate of flow from S_- into S_+ as a result of HIV infection:

$$r_2 = b \times hiv \times S_-$$

where b = 1 for S_+ and b = –1 for S_-. The annual rate of HIV infection is denoted by hiv.

Equation 3. Individuals with latent TB infection, L_{hd}

$$\Delta L_h / ts = r_3 S_h + \sum_i \left[c_h \left(A_{hi} + PT_{hi}\right)\right] + r_4 - r_5 L_h - \left(er \times L_h\right) - m_{ho} L_h$$

Here, r_3S_h denotes new TB infections of susceptible individuals (equation 3a), $c_h(A_{hi} + PT_{hi})$ spontaneous cure of active TB (at rate c_h), r_4 HIV infection (equation 3b), r_5L_h re-infection with TB followed by rapid progression (equation 3c), $(er*L_h)$ endogenous reactivation of TB (at rate er), and $m_{h0}L_h$ mortality (at rate m_{h0}).

3a. Rate of flow from individuals with no prior TB infection (S_h) to those with latent infection (L_h):

$$r_3 S_h = f \times \left(1 - rp_h\right) \times S_h$$

where f gives the force of TB infection and rp_h gives the proportion of newly-infected patients that progress rapidly to active TB.

3b. Rate of flow from L_- into L_+ as a result of HIV infection:

$$r_4 = b \times hiv \times L_-$$

where $b = 1$ for L_+ and $b = -1$ for L_-. The annual rate of HIV infection is denoted by hiv.

3c. Rate of flow from L_h to active TB through TB re-infection followed by rapid progression:

$$r_5 L_h = f \times \left(1 - le_h\right) \times rp_h \times L_h$$

where f gives the force of TB infection, le_h gives the efficacy of latent TB infection in preventing re-infection, and rp_h gives the proportion of newly-infected patients that progress rapidly to active TB.

Equation 4. Individuals with undiagnosed active TB, A_{hi}

$$\Delta A_{hi} / ts = r_6 S_h + r_7 L_h + r_8 TU_h + r_9 TS_h + r_{10} + r_{11} - r_{12} A_{hi} - m_{hi} A_{hi} - c_h A_{hi}$$

Here, $r_6 S_h$ denotes new TB infections of susceptible individuals followed by rapid progression (equation 4a), $r_7 L_h$ endogenous reactivation of latent TB plus re-infection of latently-infected individuals followed by rapid progression (equation 4b), $r_8 TU_h$ relapse after unsuccessful treatment plus re-infection of unsuccessfully-treated individuals followed by rapid progression (equation 4c), $r_9 TS_h$ re-infection of successfully-treated individuals followed by rapid progression (equation 4d), r_{10} HIV infection (equation 4e), r_{11} conversion from active smear-negative to smear-positive TB (equation 4f), $r_{12} A_{hi}$ initiation of successful diagnosis for active TB (equation 4g), $m_{hi} A_{hi}$ mortality (at rate m_{hi}), and $c_h A_{hi}$ spontaneous cure (at rate c_h).

4a. Rate of flow from individuals with no prior TB infection (S_h) to A_{hi} (i.e., new TB infection followed by rapid progression):

$$r_6 S_h = f \times rp_h \times ip_{hi} \times S_h$$

where f is the force of TB infection; rp_h is the proportion of new infections progressing rapidly to active TB; and ip_{hi} is the proportion of incident TB falling into a given smear (i.e., positive or negative) stratum.

4b. Rate of flow from individuals with latent TB infection (L_h) to A_{hi} (i.e., endogenous reactivation plus re-infection and rapid progression):

$$r_7 L_h = [er_h + f \times rp_h \times (1 - le_h)] \times ip_{hi} \times L_h$$

where er_h gives the annual rate of endogenous TB reactivation, f is the force of TB infection, rp_h is the proportion of TB infections that progress rapidly to active TB, le_h gives the efficacy of latent TB infection in preventing re-infection, and ip_{hi} is the proportion of new TB falling into a given smear stratum.

4c. Rate of flow from individuals treated unsuccessfully for active TB but (TU_h) to A_{hi} (i.e., relapse plus re-infection and rapid progression):

$$r_8 TU_h = \left[rel + f \times rp_h \times (1 - le_h)\right] \times ip_{hi} \times TU_h$$

where *rel* gives the annual rate of relapse among patients treated unsuccessfully for TB, *f* is the force of TB infection, rp_h is the proportion of TB infections that progress rapidly to active TB, le_h gives the efficacy of latent TB infection in preventing re-infection, and ip_{hi} is the proportion of new TB falling into a given smear stratum. Note that, since relapse is indistinguishable from endogenous reinfection, the term "*rel*" is assumed to include all endogenous reactivation as well.

4d. Rate of flow from individuals treated successfully for TB (TS_h) to A_{hi} (i.e., re-infection followed by rapid progression):

$$r_9 TS_h = f \times rp_h \times ip_{hi} \times TS_h$$

where *f* is the force of TB infection; rp_h is the proportion of new infections progressing rapidly to active TB; and ip_{hi} is the proportion of incident TB falling into a given smear (i.e., positive or negative) stratum.

4e. Rate of flow from A_{-i} into A_{+i} as a result of HIV infection:

$$r_{10} = b \times hiv \times A_{-i}$$

where b = 1 for A_{+i} and b = –1 for A_{-i}. The annual rate of HIV infection is denoted by *hiv*.

4f. Rate of flow from A_{h2} into A_{h1} as a result of spontaneous conversion from smear-negative to smear-positive TB:

$$r_{11} = d \times sc \times A_{h2}$$

where $d = 1$ for A_{h1} and $d = -1$ for A_{h2}. The annual rate of conversion from smear-negative to smear-positive TB is denoted by sc.

4g. Rate of flow from A_{hi} to PT_{hi}, patients with active TB who have presented for diagnosis and will undergo successful diagnosis and treatment ("pre-treatment" active TB):

$$r_{12} A_{hi} = ds_i \times r \times m_{hi} \times A_{hi}$$

where ds_i is the proportion of diagnostic attempts resulting in successful initiation of TB therapy (diagnostic sensitivity), r is the ratio of diagnostic attempts made to the mortality rate, and m_{hi} is the HIV- and TB-specific mortality rate.

Equation 5. Individuals with active TB who have presented for diagnosis and will undergo successful diagnosis and treatment ("pre-treatment" active TB), PT_{hi}

$$\Delta PT_{hi} / ts = r_{12} A_{hi} + r_{13} + r_{14} - [(1/dd) \times PT_{hi}] - m_{hi} PT_{hi} - c_h PT_{hi}$$

Here, $r_{12}A_{hi}$ denotes initiation of successful diagnosis for active TB (equation 4g), r_{13} HIV infection (equation 5a), r_{14} conversion from active smear-negative to smear-positive TB (equation 5b), *dd* the time period (diagnostic delay) between initial presentation for successful TB diagnosis and the point at which that individual is rendered non-infectious, $m_{hi}PT_{hi}$ mortality (at rate m_{hi}), and c_hPT_{hi} spontaneous cure (at rate c_h).

5a. Rate of flow from PT_{-i} into PT_{+i} as a result of HIV infection:

$$r_{13} = b \times hiv \times PT_{-i}$$

where $b = 1$ for PT_{+i} and $b = -1$ for PT_{-i}. The annual rate of HIV infection is denoted by *hiv*.

5b. Rate of flow from PT_{h2} into PT_{h1} as a result of spontaneous conversion from smear-negative to smear-positive TB:

$$r_{14} = d \times sc \times PT_{h2}$$

where $d = 1$ for A_{h1} and $d = -1$ for A_{h2}. The annual rate of conversion from smear-negative to smear-positive TB is denoted by *sc*.

Equation 6. Individuals successfully treated for TB, TS_h

$$\Delta TS_h / ts = r_{16} \sum_i PT_{hi} + r_{17} - r_{18} TS_h - m_{h0} TS_h$$

Here, r_{16} represents initiation of TB therapy that will ultimately result in reduction of the TB bacillary burden to a point from which relapse will not occur (equation 6a), r_{17} denotes HIV infection (equation 6b), $r_{18}TS_h$ re-infection with TB followed by rapid progression (equation 6c), and $m_{h0}TS_h$ mortality (at rate m_{h0}).

6a. Rate of flow from PT_{hi}, patients with active TB who have presented for diagnosis and will undergo successful diagnosis and treatment ("pre-treatment" active TB) to TS_{hi} (i.e., successful treatment):

$$r_{16} \sum_i PT_{hi} = (1/dd) \times tx \times \sum_i PT_{hi}$$

where *dd* is the mean time (diagnostic delay) between initial presentation for successful TB diagnosis and the point at which the individual is rendered non-infectious, and *tx* is the treatment success rate.

6b. Rate of flow from TS_- into TS_+ as a result of HIV infection:

$$r_{16} = b \times hiv \times TS_-$$

where $b = 1$ for TS_+ and $b = -1$ for TS_-. The annual rate of HIV infection is denoted by *hiv*.

6c. Rate of flow from TS_h to active TB, A_{hi} (i.e., new TB infection followed by rapid progression):

$$r_{18} TS_h = f \times rp_h \times TS_h$$

where *f* is the force of TB infection and rp_h is the proportion of new infections progressing rapidly to active TB.

Equation 7. Individuals unsuccessfully treated for TB, TU_h

$$\Delta TU_h / ts = r_{19}\sum_i PT_{hi} + r_{20} - r_{21}TU_h - m_{h0}TU_h$$

Here, r_{19} represents initiation of TB therapy that does not ultimately result in reduction of the TB bacillary burden to a point from which relapse will not occur (equation 7a), r_{20} denotes HIV infection (equation 7b), $r_{21}TU_h$ return to the active TB state via either relapse or re-infection followed by rapid progression (equation 7c), and $m_{h0}TU_h$ mortality (at rate m_{h0}).

7a. Rate of flow from PT_{hi}, patients with active TB who have presented for diagnosis and will undergo successful diagnosis and treatment (“pre-treatment” active TB) to TU_{hi} (i.e., initiation of treatment that is ultimately unsuccessful):

$$r_{19}\sum_i PT_{hi} = (1/dd) \times (1 - tx) \times \sum_i PT_{hi}$$

where *dd* is the mean time (diagnostic delay) between initial presentation for successful TB diagnosis and the point at which the individual is rendered non-infectious, and *tx* is the treatment success rate.

7b. Rate of flow from TU_- into TU_+ as a result of HIV infection:

$$r_{20} = b \times hiv \times TU_-$$

where $b = 1$ for TU_+ and $b = -1$ for TU_-. The annual rate of HIV infection is denoted by *hiv*.

7c. Rate of flow from TU_h to active TB, A_{hi} (i.e., new TB infection followed by rapid progression):

$$r_{21}TU_h = [rel + f \times rp_h \times (1 - le_h)] \times TU_h$$

where *rel* gives the annual rate of relapse among patients treated unsuccessfully for TB, *f* is the force of TB infection, rp_h is the proportion of TB infections that progress rapidly to active TB, and le_h gives the efficacy of latent TB infection in preventing re-infection. Note that, since relapse is indistinguishable from endogenous reinfection, the term "*rel*" is assumed to include all endogenous reactivation as well.

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