Online Supplementary Documents

Forecasting the Impact of Diabetes Mellitus on Tuberculosis Disease Incidence and Mortality in India

Susanne F. Awad,1,2 Peijue Huangfu,2 Houssein H. Ayoub,1,3,4 Fiona Pearson,2 Soha R. Dargham,1 Julia A. Critchley,2 and Laith J. Abu-Raddad,1,4,5

1Infectious Disease Epidemiology Group, Weill Cornell Medicine-Qatar, Cornell University, Qatar Foundation - Education City, Doha, Qatar

2Population Health Research Institute, St George’s, University of London, London, UK

3Department of Mathematics, Statistics, and Physics, Qatar University, Doha, Qatar

4Department of Healthcare Policy and Research, Weill Cornell Medicine, Cornell University, New York, New York, USA

5College of Health and Life Sciences, Hamad bin Khalifa University, Doha, Qatar
S1. DETAILED DESCRIPTION OF THE TB-DM MATHEMATICAL MODEL

We extended an earlier population-level deterministic mathematical model of the dynamics of tuberculosis-diabetes mellitus (TB-DM) interactions [1]. The model was described by sets of coupled nonlinear ordinary differential equations (Section S1.3) coded in MATLAB 2015a [2].

We stratified the population of India into compartments according to five-year age groups (indexed $a = 1, 2, \ldots, 20$ representing the 0—99 age cohort), DM status, and TB progression states. We described TB natural history (for those with and without DM) by the progression states of susceptible, latent TB infection, TB disease, treated TB disease, and recovered (Figure S1).

**Figure S1. A schematic diagram of the TB-DM model.** The black and red lines indicate different TB natural histories depending on DM status. The blue box/line indicates the potential TB effect on DM.
S1.1. TB transmission dynamics in absence of DM

All individuals were born \((\delta(a)\varphi(t)N_{\text{total}}; \text{here } \delta \text{ is equal one for } a = 1 \text{ and zero otherwise})\) susceptible to TB and DM \((S)\), and aged at a transition rate \(\eta\) (i.e. from one age group to the next age group). In absence of DM, all individuals were at risk of developing DM at a rate \(\beta(t, a)\) (except those 0-4 years old; \(a = 1\)), and at risk of natural mortality at a rate \(\mu(t, a)\). TB susceptible individuals were at risk of TB infection at a rate \(\lambda(t)\) (force of infection). A proportion \(p\) and \(1 - p\) of individuals move, upon TB infection, to the stage of TB latent fast progression \(L_F\) and the stage of latent slow progression \(L_S\), respectively. The proportion \(p(a)\) differed between children (<15 years old) and adults (≥15 years old). Individuals in \(L_F\) and \(L_S\) were at risk of TB disease at a rate \(\omega_{LF}\) and \(\omega_{LS}\), respectively. Individuals in \(L_S\) were also at risk of reinfection (at a rate \((1 - q)\lambda\) ), but due to prior TB exposure and acquired immunity there was a proportional reduction \((q)\) in the susceptibility to TB infection.

TB disease individuals were characterized into the three states of smear-positive pulmonary \(I^{SP}\), smear-negative pulmonary \(I^{SN}\), and extra-pulmonary disease \(I^{EP}\). The parameter \(\alpha(a)\) identified the fraction of individuals going into each of these disease states, and differed between children and adults [3]. We considered individuals with the pulmonary TB disease types \(I^{SP}\) and \(I^{SN}\) infectious, but at varying levels. Individuals in the TB disease states could leave their state by TB-related mortality at a rate \(\xi\), by spontaneous natural recovery at a rate \(\nu\) (i.e. can recover without medical treatment), or by diagnosis and effective treatment at a rate \(z\xi\). Here, \(\xi\) is TB treatment rate, and \(z\) is the proportion of new TB disease cases that successfully completed treatment (with or without) bacteriologic evidence of success (“cured” or “treatment
This proportion was derived from seven treatment outcome measures given by the World Health Organization (WHO) [4]:

\[ z = \frac{\text{"cure"} + \text{"treatment completed"}}{\text{"cure"} + \text{"treatment completed"} + \text{"death"} + \text{"treatment failure"} + \text{"default"} + \text{"transferred"} + \text{"not evaluated"}}. \]

Treated individuals were characterized according to the three TB disease types: \( T^SP \), \( T^{SN} \), and \( T^{EP} \). Individuals in the pulmonary treated states (\( T^{SP} \) and \( T^{SN} \)) were considered infectious, but at varying levels. Individuals in the treated states were assumed at risk of TB reinfection at a rate \((1-q)\lambda\), TB-related mortality at a rate \(\xi\), spontaneous recovery at a rate \(\nu\), or successful treatment completion at a rate \(\psi\).

Individuals who are successfully treated, or those who spontaneously recover, enter the recovery stage (\(R\)). Recovered TB individuals were assumed at risk of TB reinfection at a rate \((1-q)\lambda\).

The model accommodates (in principle) the risk of developing DM at a rate \(RR_{TB\rightarrow DM} \times \beta\) among individuals with current or previous TB disease (\(I^{SP}, I^{SN}, T^{SP}, T^{SN}\), and \(R\); Figure S1 blue line). Here, \(RR_{TB\rightarrow DM}\) is the relative risk (RR) of developing DM in the population with a history of TB disease compared to the general population. However, given that our estimates were generated using a conservative approach, we opted not to factor this effect in our analysis since the evidence of this effect is still inconclusive.

**S1.2. TB transmission dynamics in presence of DM**

Individuals with DM were assumed at higher risk of mortality due to DM complications at a rate \(RR_{DM}(a)\mu(t,a)\). Here, \(RR_{DM}\) is the RR of mortality in the DM population compared to the general population.
Based on review of existing evidence, DM was assumed to affect 10 different stages of TB natural history and treatment outcomes, denoted as $E_i$ to $E_{10}$ in the equations in Section S1.3.

The summary of the effects and their effect sizes is found in Table 1 of main manuscript and described in details in Section S3.1.

### S1.3. Model structure

**TB transmission dynamics for the population without DM**

**TB and DM susceptible (i.e., TB susceptible individuals without DM):**

\[
\frac{dS(a)}{dt} = \delta(a)\varphi(t)N_{\text{total}} + \eta[1-\delta(a)]S(a-1) - \left[\eta + \lambda(t) + \mu(t,a) + \beta(t,a)\right]S(a)
\]

**TB latent infection:**

\[
\frac{dL^L(a)}{dt} = \eta[1-\delta(a)]L^L(a-1) + p(a)\lambda(t)S(a) + p(a)[1-q]\lambda(t)L^L(a) + p(a)[1-q]\lambda(t)\left[R(a) + T^SP(a) + T^SN(a) + T^EP(a)\right] - \left[\eta + \omega_{pa} + \mu(t,a) + \beta(t,a)\right]L^L(a)
\]

**TB disease:**

\[
\frac{dI^S(a)}{dt} = \eta[1-\delta(a)]I^S(a-1) + \alpha^L(a)\omega_{pa}L^L(a) + \alpha^L(a)\omega_{pa}L^L(a) - \left[\eta + \xi_{pa} + \zeta_{pa} + \nu_{pa} + \mu(t,a) + RR_{\text{pa-to-ss}}\beta(t,a)\right]I^S(a)
\]
Treated TB disease:

\[
\frac{dT^{SP}(a)}{dt} = \eta \left[1 - \delta(a)\right] T^{SP}(a-1) + z\xi_{\text{trp}} I^{SP}(a) - \left[\eta + \psi_{\text{trp}} + \psi_{\text{trp}}\right] + \left(1 - q\right) \lambda(t) + \xi_{\text{trp}} + \mu(t,a) + RR_{\text{trp}-\text{dm}} \beta(t,a) \right] T^{SP}(a)
\]

\[
\frac{dT^{SN}(a)}{dt} = \eta \left[1 - \delta(a)\right] T^{SN}(a-1) + z\xi_{\text{trn}} I^{SN}(a) - \left[\eta + \psi_{\text{trn}} + \psi_{\text{trn}}\right] + \left(1 - q\right) \lambda(t) + \xi_{\text{trn}} + \mu(t,a) + RR_{\text{trn}-\text{dm}} \beta(t,a) \right] T^{SN}(a)
\]

\[
\frac{dT^{EP}(a)}{dt} = \eta \left[1 - \delta(a)\right] T^{EP}(a-1) + z\xi_{\text{trep}} I^{EP}(a) - \left[\eta + \psi_{\text{trep}} + \psi_{\text{trep}}\right] + \left(1 - q\right) \lambda(t) + \xi_{\text{trep}} + \mu(t,a) + RR_{\text{trep}-\text{dm}} \beta(t,a) \right] T^{EP}(a)
\]

Recovered:

\[
\frac{dR(a)}{dt} = \eta \left[1 - \delta(a)\right] R(a-1) + \psi_{\text{trep}} T^{SP}(a) + \psi_{\text{trep}} T^{SN}(a) + \psi_{\text{trep}} T^{EP}(a)
\]

\[
+ \left[\eta + [1 - q] \lambda(t) + \mu(t,a) + \beta(t,a)\right] R(a)
\]

TB transmission dynamics for the population with DM (aged \(\geq 5\) years)

TB susceptible with DM:

\[
\frac{dS^{\text{om}}(a)}{dt} = \eta \left[1 - \delta(a)\right] S^{\text{dm}}(a-1) + \beta(t,a) S(a) - \left[\eta + E_{\text{s}} \lambda(t) + RR_{\text{dm}}(a) \mu(t,a)\right] S^{\text{om}}(a)
\]

TB latent infection with DM:

\[
\frac{dL^{\text{tr}}(a)}{dt} = \eta \left[1 - \delta(a)\right] L^{\text{tr}}(a-1) + \beta(t,a) L^{\text{tr}}(a) + E_{\text{r}} p(a) E_{\text{r}} \lambda(t) S^{\text{om}}(a) + p(a) E_{\text{r}} \left[1 - q\right] \lambda(t) L^{\text{tr}}(a)
\]

\[
+ \left[1 - E_{\text{r}} p(a) E_{\text{r}} \lambda(t) \left[T^{\text{om}}(a) + T^{\text{om}}(a) + T^{\text{om}}(a) + R^{\text{om}}(a)\right] - \left[\eta + E_{\text{r}} \omega_{\text{r}} + RR_{\text{om}}(a) \mu(t,a)\right] L^{\text{tr}}(a)
\]

\[
\frac{dL^{\text{te}}(a)}{dt} = \eta \left[1 - \delta(a)\right] L^{\text{te}}(a-1) + \beta(t,a) L^{\text{te}}(a) + \left[1 - E_{\text{r}} p(a)\right] E_{\text{r}} \lambda(t) S^{\text{om}}(a)
\]

\[
+ \left[1 - p(a) E_{\text{r}} \left[1 - q\right] \lambda(t) \left[T^{\text{om}}(a) + T^{\text{om}}(a) + T^{\text{om}}(a) + R^{\text{om}}(a)\right] - \left[\eta + E_{\text{r}} p(a) \left[1 - q\right] \lambda(t) + E_{\text{r}} \omega_{\text{r}} + RR_{\text{om}}(a) \mu(t,a)\right] L^{\text{te}}(a)
\]

TB disease with DM:
\[
\frac{dl^{SP}_{out}(a)}{dt} = \eta [1 - \delta(a)] l^{SP}_{out}(a - 1) + RR_{TB\rightarrow DM} \beta(t,a) l^{SP}(a) + \alpha^{(LPS\rightarrow SP)_{out}}(a) E_3 \omega_{13} l^{SP}_{out}(a) + \alpha^{(LSS\rightarrow SP)_{out}}(a) E_3 \omega_{13} l^{SP}_{out}(a) \\
- \left[ \eta + E_3 \zeta_{SP} + E_3 \nu_{SP} + E_7 \xi_{SP} + RR_{DM}(a) \mu(t,a) \right] l^{SP}_{out}(a)
\]
\[
\frac{dl^{SN}_{out}(a)}{dt} = \eta [1 - \delta(a)] l^{SN}_{out}(a - 1) + RR_{TB\rightarrow DM} \beta(t,a) l^{SN}(a) + \alpha^{(LPS\rightarrow SN)_{out}}(a) E_3 \omega_{13} l^{SN}_{out}(a) + \alpha^{(LSS\rightarrow SN)_{out}}(a) E_3 \omega_{13} l^{SN}_{out}(a) \\
- \left[ \eta + E_3 \zeta_{SN} + E_3 \nu_{SN} + E_7 \xi_{SN} + RR_{DM}(a) \mu(t,a) \right] l^{SN}_{out}(a)
\]
\[
\frac{dl^{EP}_{out}(a)}{dt} = \eta [1 - \delta(a)] l^{EP}_{out}(a - 1) + RR_{TB\rightarrow DM} \beta(t,a) l^{EP}(a) + \alpha^{(LPS\rightarrow EP)_{out}}(a) E_3 \omega_{13} l^{EP}_{out}(a) + \alpha^{(LSS\rightarrow EP)_{out}}(a) E_3 \omega_{13} l^{EP}_{out}(a) \\
- \left[ \eta + E_3 \zeta_{EP} + E_3 \nu_{EP} + E_7 \xi_{EP} + RR_{DM}(a) \mu(t,a) \right] l^{EP}_{out}(a)
\]

Treated TB disease with DM:

\[
\frac{dT^{SP}_{DM}(a)}{dt} = \eta [1 - \delta(a)] T^{SP}_{DM}(a - 1) + RR_{TB\rightarrow DM} \beta(t,a) T^{SP}(a) + E_3 \zeta_{SP} l^{SP}_{out}(a) \\
- \left[ \eta + E_3 \nu_{TP} + E_7 \xi_{TP} + E_1 [1 - q] \tilde{\lambda}(t) + E_7 \xi_{TP} + RR_{DM}(a) \mu(t,a) \right] T^{SP}_{DM}(a)
\]
\[
\frac{dT^{SN}_{DM}(a)}{dt} = \eta [1 - \delta(a)] T^{SN}_{DM}(a - 1) + RR_{TB\rightarrow DM} \beta(t,a) T^{SN}(a) + E_3 \zeta_{SN} l^{SN}_{out}(a) \\
- \left[ \eta + E_3 \nu_{TS} + E_7 \xi_{TS} + E_1 [1 - q] \tilde{\lambda}(t) + E_7 \xi_{TS} + RR_{DM}(a) \mu(t,a) \right] T^{SN}_{DM}(a)
\]
\[
\frac{dT^{EP}_{DM}(a)}{dt} = \eta [1 - \delta(a)] T^{EP}_{DM}(a - 1) + RR_{TB\rightarrow DM} \beta(t,a) T^{EP}(a) + E_3 \zeta_{EP} l^{EP}_{out}(a) \\
- \left[ \eta + E_3 \nu_{TE} + E_7 \xi_{TE} + E_1 [1 - q] \tilde{\lambda}(t) + E_7 \xi_{TE} + RR_{DM}(a) \mu(t,a) \right] T^{EP}_{DM}(a)
\]

TB recovered with DM:

\[
\frac{dR^{DM}(a)}{dt} = \eta R^{DM}(a - 1) + RR_{TB\rightarrow DM} \beta(t,a) R(a) + E_9 \left[ \nu_{TP} T^{SP}_{DM}(a) + \nu_{TS} T^{SN}_{DM}(a) + \nu_{TE} T^{EP}_{DM}(a) \right] \\
+ E_9 [ \nu_{SP} l^{SP}_{out}(a) + \nu_{SN} l^{SN}_{out}(a) + \nu_{EP} l^{EP}_{out}(a) + \nu_{TP} T^{SP}_{DM}(a) + \nu_{TS} T^{SN}_{DM}(a) + \nu_{TE} T^{EP}_{DM}(a) ] \\
- \left[ \eta + E_1 [1 - q] \tilde{\lambda}(t) + RR_{DM}(a) \mu(t,a) \right] R^{DM}(a)
\]

Here, the parameter \( \alpha \) for the population with DM was determined according to:

\[
\begin{align*}
\alpha^{(LPS\rightarrow SP)_{out}}(a) &= \alpha^{(LSS\rightarrow SP)_{out}}(a) = E_5^{SP}(a) \alpha^{LPS_{out}}(a), \\
\alpha^{(LPS\rightarrow SN)_{out}}(a) &= \alpha^{(LSS\rightarrow SN)_{out}}(a) = E_5^{SN}(a) \alpha^{LPS_{out}}(a), \\
\alpha^{(LPS\rightarrow EP)_{out}}(a) &= \alpha^{(LSS\rightarrow EP)_{out}}(a) = \alpha^{LPS_{out}}(a)
\end{align*}
\]
while,

$$E_{SP}^S(a) = \kappa \frac{\alpha^{(L_{FoS}SP)}(a) + \alpha^{(L_{FoS}SN)}(a)}{[\kappa \alpha^{(L_{FoS}SP)}(a) + \kappa' \alpha^{(L_{FoS}SN)}(a)]}, \quad (S2)$$

$$E_{SN}^S(a) = \kappa' \frac{\alpha^{(L_{FoS}SP)}(a) + \alpha^{(L_{FoS}SN)}(a)}{[\kappa \alpha^{(L_{FoS}SP)}(a) + \kappa' \alpha^{(L_{FoS}SN)}(a)]},$$

and

$$\kappa = \frac{P_{DM}^{SP}}{P_{NDM}^{SP}}, \quad (S3)$$

$$\kappa' = \frac{1 - P_{DM}^{SP}}{1 - P_{NDM}^{SP}}.$$

Here, $P_{DM}^{SP}$ and $P_{NDM}^{SP}$ are the proportions of smear-positive pulmonary TB cases in the DM and non-DM groups, respectively. These proportions were obtained from observational studies discussed in Section S3.1.

**S1.4. Demographic parameters**

Total number of individuals in the population, $N_{total}$, was given by:

$$N_{total} = \sum_{a=1}^{20} \left( S(a) + I^{L}_{F}(a) + I^{S}_{F}(a) + I^{SP}(a) + I^{SN}(a) + I^{EP}(a) + T^{SN}(a) + T^{EP}(a) + T^{DM}(a) + S^{DM}(a) + L^{Fou}(a) + I^{SP}_{ou}(a) + I^{SN}_{ou}(a) + I^{EP}_{ou}(a) + T^{SP}_{ou}(a) + T^{SN}_{ou}(a) + T^{EP}_{ou}(a) + R^{DM}(a) \right)$$

The population growth rate ($\varphi(t)$) and the natural mortality rate ($\mu(t,a)$) were described by the following functions, providing a robust fit of population growth and age structure in India:

$$\varphi(t) = a_0 e^{\left(\frac{t-t_0}{b_0}\right)^2}$$

and
Here the parameters \( a_0, a_1, a_2, l_0, t_1, b_0, b_1 \), and \( b_2 \) were obtained by fitting the model to India’s demographic data from the database of the Population Division of the United Nations Department of Economic and Social Affairs [5].

**S1.5. TB force of infection and temporal evolution of TB contact rate**

Assuming that the mixing between individuals in the population was random, the TB force of infection (\( \lambda \)) was determined by the probability of transmission per respiratory contact (\( u \)), the respiratory contact rate within a population (\( \varepsilon \)), the effect of DM on TB infectiousness (\( E_6 \)), and the relative infectiousness of individuals with each type of TB disease (whether untreated or treated) compared to the infectiousness of individuals with smear-positive pulmonary TB (\( h \)):

\[
\lambda(t) = \frac{u\varepsilon(t) \sum_{a=1}^{20} \left( h_{sp} I_{sp}(t,a) + h_{sn} I_{sn}(t,a) + h_{e_p} I_{e_p}(t,a) + h_{tsp} T_{tsp}(t,a) + h_{tsn} T_{tsn}(t,a) + h_{tep} T_{tep}(t,a) \right)}{N_{\text{total}}(t,a)}
\]

\[
+ \frac{E_6 u\varepsilon(t) \sum_{a=1}^{20} \left( h_{spu} I_{spu}(t,a) + h_{snu} I_{snu}(t,a) + h_{epu} I_{epu}(t,a) + h_{tspu} T_{tspu}(t,a) + h_{tspu} T_{tspu}(t,a) + h_{tepu} T_{tepu}(t,a) \right)}{N_{\text{total}}(t,a)}
\]

Given the evidence for declining TB incidence in India, a temporal change in \( \varepsilon \) was incorporated in the model. The temporal variation was characterized through a Wood-Saxon function [6,7]. This function is mathematically designed to describe and characterize transitions. It parameterizes a transition in terms of its scale or strength, smoothness or abruptness, duration, and the turning year [6,7]. Using the Wood-Saxon parameterization, \( \varepsilon(t) \) was given by:
\[ \varepsilon(t) = \varepsilon_0 \left( 1 + \frac{Z}{1 + \exp \left( \frac{t - \xi_{\text{Turning}}}{\xi_{\text{Duration}}} \right)} \right). \]

Here, \( \varepsilon_0 \) is the asymptotic value that describes the contact rate well after the transition, \( Z \) is the level of change in \( \varepsilon(t) \) during the transition from \( \varepsilon_0 (1 + Z) \) before the transition to \( \varepsilon_0 \) after the transition, \( \xi_{\text{Duration}} \) describes the transition duration parameter, and \( \xi_{\text{Turning}} \) is the turning point year at which the contact rate crosses half way towards its asymptotic value of \( \varepsilon_0 \). The parameters \( \varepsilon_0, Z, \xi_{\text{Duration}}, \) and \( \xi_{\text{Turning}} \) were obtained by fitting the model to available empirical data on TB-incidence and mortality from the WHO’s Global Health Observatory data repository [8].

**S1.6. TB treatment rate and temporal evolution of TB case detection rate**

Treatment rate in the model depended on TB disease type and was determined using the case detection rates (\( C_{\text{Det}SP}, C_{\text{Det}SN}, \) and \( C_{\text{Det}EP} \)), TB-related mortality rates (\( \nu_{SP}, \nu_{SN}, \nu_{EP} \)), and spontaneous recovery rates (\( \zeta_{SP}, \zeta_{SN}, \zeta_{EP} \)):

\[
\begin{align*}
\zeta_{SP} &= C_{\text{Det}SP} (\nu_{SP} + \zeta_{SP}) / (1 - C_{\text{Det}SP}) \\
\zeta_{SN} &= C_{\text{Det}SN} (\nu_{SN} + \zeta_{SN}) / (1 - C_{\text{Det}SN}) \\
\zeta_{EP} &= C_{\text{Det}EP} (\nu_{EP} + \zeta_{EP}) / (1 - C_{\text{Det}EP}).
\end{align*}
\]

Given the evidence for increasing TB case detection in India [9], temporal changes in TB case detection rates were incorporated in the model. Moreover, given the likelihood of underreporting of treatment among TB cases, TB case detection rate for India was derived by fitting the model to TB incidence rate and mortality rate. The temporal variation was parametrized through a logistic function:
\[ C_{\text{denX}}(t) = \frac{p_1}{1 + e^{-p_2(t-p_3)}} \].

Here, the parameters \( p_1 \), \( p_2 \), and \( p_3 \) were obtained by fitting the model to available empirical data on TB-incidence and mortality rates from the WHO’s Global Health Observatory data repository [8].

**S1.7. DM incidence rate**

Given the evidence for increasing DM incidence and prevalence in India [10], the DM incidence rate in the TB-DM model was assumed to be time and age dependent, and was parameterized through a combined Gaussian-logistic function:

\[ \beta(t,a) = \frac{c_1 e^{\frac{(t-t_1)}{d_1}}}{1 + e^{-d_2(a-c_2)}}. \]

Here, \( c_1 \), \( c_2 \), \( t_1 \), \( d_1 \), and \( d_2 \) are fitting parameters obtained by fitting the TB-DM model to the time series of DM prevalence in India as provided through the International Diabetes Federation [10]. The shape of the age-distribution of DM prevalence was based on the national Indian Council of Medical Research-India Diabetes study [11].
S2. DATA SOURCES

The TB-DM interaction model was parameterized using empirical epidemiological and natural history data from multiple sources.

S.2.1. TB epidemiological and natural history data

The model’s parameter values for TB natural history in absence of DM, along with their references, are listed in Table S1.

<table>
<thead>
<tr>
<th>Table S1. Model assumptions in terms of parameter values.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symbol</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>$p$</td>
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<tr>
<td>$\alpha$</td>
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<td></td>
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<tr>
<td>$q$</td>
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<tr>
<td>$\omega_{LF}$</td>
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<tr>
<td>$\omega_{LS}$</td>
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<td>$\xi$</td>
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<td>$u$</td>
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<td>-----</td>
</tr>
<tr>
<td>$h$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$RR_{DM}^{Age-group}$</th>
<th>Relative risk of mortality in people with DM (per age group) compared to the general population</th>
<th>$RR_{DM}^{0-4} = 1.00$</th>
<th>$RR_{DM}^{15-29} = 4.83$</th>
<th>Calculated based on [19,20]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$RR_{DM}^{5-14} = 2.67$</td>
<td>$RR_{DM}^{30-39} = 4.46$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$RR_{DM}^{40-49} = 2.67$</td>
<td>$RR_{DM}^{50-59} = 2.19$</td>
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<td></td>
<td>$RR_{DM}^{60-69} = 1.85$</td>
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<td></td>
<td></td>
<td>$RR_{DM}^{70-79+} = 1.59$</td>
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<td></td>
</tr>
</tbody>
</table>

**Country specific variables**

<table>
<thead>
<tr>
<th>$N$</th>
<th>Total population</th>
<th>For each year per the database of the Population Division of the United Nations Department of Economic and Social Affairs</th>
<th>[5]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\varphi$</td>
<td>Birth rate</td>
<td>Gaussian function</td>
<td>Fitting parameters</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Natural mortality rate</td>
<td>Combination of logistic and Gaussian functions</td>
<td>Fitting parameters</td>
</tr>
<tr>
<td>$C$</td>
<td>Case detection rate per TB disease category</td>
<td>Logistic function</td>
<td>Fitting parameters</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>Respiratory contact rate (per year)</td>
<td>Wood Saxon (logistic function)</td>
<td>Fitting parameters</td>
</tr>
<tr>
<td>$\beta$</td>
<td>DM incidence rate (per year)</td>
<td>Combination of logistic and Gaussian functions</td>
<td>Fitting parameters</td>
</tr>
</tbody>
</table>

*The three clinical categories are smear-positive pulmonary (SP), smear-negative pulmonary (SN), and extra-pulmonary (EP) tuberculosis. X is latent slow (LS) or latent fast (LF).

**S2.2. Parametrization of DM-on-TB effects**

We incorporated seven out of ten potential DM effects on TB’s natural history and treatment outcomes. These are, along with their parameter values, summarized in Table 1 of main text. A brief justification and summary of the evidence for each parameter can be found below. Further details can be found in reference [1].

*Effect 1-Susceptibility: DM increases susceptibility to TB infection*
Supported by existing evidence [21,22], and based on a recent population-based cross sectional study using the 2011-12 National Health and Nutrition Examination Survey (NHANES) data [23], a 1.5 (95% confidence interval (CI): 1.0-2.2) increased risk of TB infection for individuals with DM, compared to individuals without DM, was incorporated in the model.

**Effect 2-Fast progression:** DM increases the proportion of TB infections entering latent-fast state as opposed to latent-slow state

A recent meta-analysis of all available study designs (N=44) and four prospective cohort studies found that DM was associated with a 2.00-fold (95% CI: 1.78-2.24) and a 3.59-fold (95% CI: 2.25–5.73) increased risk of TB disease, respectively.[24] However, it is not possible to determine from these studies whether DM increases i) the proportion of TB infections entering latent-fast state as opposed to latent-slow state (**Effect 2-Fast progression**), or ii) reactivation of latent slow TB cases (**Effect 3-Reactivation**), or iii) reinfection of latent slow TB cases (**Effect 4-Reinfection**), or iv) a combination of the three effects.

Given that these potential effects could be acting simultaneously, and their individual effects cannot be disentangled from each other [1], we included in the model only one of these effects (**Effect 2-Fast progression**). The exact effect size for **Effect 2-Fast progression** was estimated by fitting the model outcome to the more conservative pooled association of 2.00 (based on all studies) [24]. The model was also fitted to the pooled hazard ratio of 3.59 (based only on the prospective cohort studies) [24] in a sensitivity analysis. No effect sizes were assumed for **Effect 3-Reactivation** and **Effect 4-Reinfection**, as the impacts of these on TB natural history is presumably implicitly captured by **Effect 2-Fast progression**.

Only two studies estimated the age-specific relative risks (RRs) of the effect of DM on TB disease, and these demonstrated a decrease in the RR with age [25,26]. Among DM individuals,
the RR of TB disease was estimated at 7.79 among those aged 20–29, 9.98 among those aged 30–39, 4.72 among those aged 40–49, 2.30 among those aged 50–59, and 1.76 among those aged 60+ [25]. The age-specific RRs of the effect of DM on TB disease [25] were incorporated in the model (as opposed to the overall effect regardless of age), but only in sensitivity analysis. When this was done, the age effects reported in reference [25] were scaled down to reach the two-fold overall RR of the effect of DM on TB disease in the total population (as determined in the meta-analysis based on all studies [24]).

**Effect 5-Smear positivity:** DM increases the proportion of new pulmonary TB disease cases going to smear-positive as opposed to smear-negative

Based on current evidence [27,28], the proportion of individuals with extra-pulmonary TB as opposed to pulmonary (PTB) in the model was assumed not to differ based on DM status. However, studies have demonstrated that individuals with concurrent PTB and DM were more likely to be sputum acid-fast bacilli (AFB) smear-positive (i.e. have SP-PTB) as opposed to smear-negative (SN-PTB) [29-44]. Based on this evidence, the fraction of individuals who develop SP-PTB as opposed to SN-PTB was assumed to differ by DM status. These fractions were estimated using the pooled mean proportions (out of all PTB cases) by DM status, with the pooling done using a DerSimonian-Laird random-effects model [45] (Figure S2).
Figure S2. Forest plots presenting the outcomes of the pooled mean proportion of smear-positive pulmonary tuberculosis in different populations (A) without diabetes mellitus and (B) with concurrent diabetes mellitus.

(A) Forest plots presenting the outcomes of the pooled mean proportion of smear-positive pulmonary tuberculosis in different populations (A) without diabetes mellitus and (B) with concurrent diabetes mellitus.

Accordingly using Equations S1-S3 in Section S1.3, for adults upon progressing to TB disease from both $L^S$ and $L^F$, 63.1% of those with DM will develop SP-PTB compared to 50.0% of those without DM; 26.9% of those with DM will develop SN-PTB compared to 40.0% of those without DM. For children, upon progressing to TB disease from both $L^S$ and $L^F$, 16.8% of those
with DM will develop SP-PTB compared to 10.0% of those without DM; 58.2% of those with DM will be develop SN-PTB compared to 65.0% of those without DM. The proportions without DM (for adults and children) were based on earlier work [3].

**Effect 6-Disease infectiousness:** DM increases the infectiousness of PTB (SP-PTB and SN-PTB) for untreated and treated TB disease cases

DM was found to be an independent risk factor associated with increased *M. tuberculosis* bacterial load (based on AFB sputum smear examination) [18,28,29,31,46-48]. Based on this evidence, this effect was incorporated in the model by increasing TB infectiousness among those with concurrent PTB and DM. First, TB infectiousness was assumed to be linearly proportional to *M. tuberculosis* bacterial load. Second, the ratio of TB bacterial load between concurrent TB and DM and TB with no DM individuals was assumed to be equal to the ratio of infectiousness between concurrent TB and DM and TB with no DM individuals. We used available studies to estimate a weighted average of the ratio of bacterial load between concurrent TB and DM and TB with no DM. Accordingly, infectiousness of TB among those with DM was assumed to increase by 1.46-fold compared to those without DM.

**Effect 7-TB mortality:** DM increases the hazard of TB-related mortality for TB disease cases

Evidence supports an association between DM and TB-related mortality [27,31,49-53]. A recent systematic review and meta-analysis estimated a pooled mean crude odds ratio (OR) of 2.11 (95% CI: 1.76–2.51) across 48 studies, and an adjusted pooled mean OR of 4.95 (95% CI: 2.69–9.10) across four studies that appropriately adjusted for confounders [53]. Based on this evidence, an effect size of 2.11 was incorporated in the TB-DM model as part of our conservative approach for estimating the impact of DM on TB, and an effect size of 4.95 was incorporated as part of a sensitivity analysis. We assumed that, among those who have TB...
disease, DM affected (relatively) TB mortality rate similarly for those treated and untreated for TB. The OR of 2.11 was converted to a hazard ratio (HR) using the following equation for *Effect 7-TB mortality* for untreated TB-DM cases:

\[ E^X_7 = \frac{\text{OR}(E^X_8 \zeta_X + E^X_9 \nu_X)}{\zeta_X + \nu_X}. \]

Here, \( X \) is \( SP, SN, \) or \( EP \), while \( E^X_8 \) and \( E^X_9 \) are the effects of DM on TB cure and recovery, respectively (see below). The OR was also converted to a HR using the following equation for *Effect 7-TB mortality* for treated TB-DM cases:

\[ E^X_7 = \frac{\text{OR}[E^X_9 (\nu_X + \psi_X) + E^X_{10} (1-q) \lambda]}{\nu_X + \psi_X + (1-q) \lambda}. \]

Here, \( X \) is \( TSP, TSN, \) or \( TEP \), while \( E^X_{10} \) is the effect of DM on TB reinfection after recovery (see below).

**Effect 8-Treatment failure**: DM reduces the proportion of successful treatment

Several studies reported on “cure” and “treatment completed” as well as the other treatment outcome measures to calculate the proportion of successful treatment with and without DM [42,47,54-67]. Pooling the RR across these studies using a DerSimonian-Laird random-effects model [45], the RR for treatment success was 0.96 (95% CI: 0.93–1.00; Figure S3). Because the RR was not statistically significant, this effect was not included in the TB-DM model—the RR for *Effect 8-Treatment failure* was assumed to equal 1.
Figure S3. Forest plot presenting the outcome of the pooled mean crude relative risk of tuberculosis treatment success with or with no DM in different populations.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>DM TB cured</th>
<th>TB not cured</th>
<th>non-DM TB cured</th>
<th>TB not cured</th>
<th>Relative Risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrosetti, 1999</td>
<td>22</td>
<td>10</td>
<td>601</td>
<td>135</td>
<td>0.84 [0.67, 1.07]</td>
</tr>
<tr>
<td>Ambrosetti, 1999</td>
<td>36</td>
<td>14</td>
<td>656</td>
<td>117</td>
<td>0.85 [0.71, 1.01]</td>
</tr>
<tr>
<td>Ambrosetti, 1999</td>
<td>33</td>
<td>7</td>
<td>519</td>
<td>148</td>
<td>1.06 [0.91, 1.23]</td>
</tr>
<tr>
<td>Centis, 2000</td>
<td>26</td>
<td>18</td>
<td>693</td>
<td>366</td>
<td>0.97 [0.76, 1.23]</td>
</tr>
<tr>
<td>Centis, 2002</td>
<td>28</td>
<td>12</td>
<td>649</td>
<td>203</td>
<td>0.92 [0.76, 1.13]</td>
</tr>
<tr>
<td>Mbouassa, 2003</td>
<td>17</td>
<td>23</td>
<td>77</td>
<td>15</td>
<td>0.61 [0.35, 0.74]</td>
</tr>
<tr>
<td>Singla, 2006</td>
<td>130</td>
<td>7</td>
<td>367</td>
<td>16</td>
<td>0.99 [0.95, 1.03]</td>
</tr>
<tr>
<td>Talar, 2009</td>
<td>70</td>
<td>3</td>
<td>72</td>
<td>6</td>
<td>1.04 [0.96, 1.13]</td>
</tr>
<tr>
<td>Sangar, 2012</td>
<td>19</td>
<td>4</td>
<td>213</td>
<td>46</td>
<td>1.00 [0.83, 1.22]</td>
</tr>
<tr>
<td>Jiménez-Corona, 2013</td>
<td>308</td>
<td>55</td>
<td>711</td>
<td>136</td>
<td>1.01 [0.96, 1.07]</td>
</tr>
<tr>
<td>Sulaiman, 2013</td>
<td>258</td>
<td>84</td>
<td>717</td>
<td>197</td>
<td>0.86 [0.70, 1.03]</td>
</tr>
<tr>
<td>K.V.N., 2013</td>
<td>554</td>
<td>113</td>
<td>1639</td>
<td>287</td>
<td>0.96 [0.92, 1.00]</td>
</tr>
<tr>
<td>Reis-Santos, 2013</td>
<td>411</td>
<td>262</td>
<td>12926</td>
<td>4221</td>
<td>0.83 [0.79, 0.88]</td>
</tr>
<tr>
<td>Viswanathan, 2014</td>
<td>80</td>
<td>9</td>
<td>115</td>
<td>5</td>
<td>0.94 [0.87, 1.02]</td>
</tr>
<tr>
<td>Ali, 2014</td>
<td>47</td>
<td>6</td>
<td>272</td>
<td>60</td>
<td>1.08 [0.97, 1.21]</td>
</tr>
<tr>
<td>Viswanathan, 2014</td>
<td>91</td>
<td>5</td>
<td>142</td>
<td>7</td>
<td>0.99 [0.94, 1.05]</td>
</tr>
<tr>
<td>Cavanaugh, 2015</td>
<td>93</td>
<td>8</td>
<td>162</td>
<td>12</td>
<td>0.99 [0.92, 1.06]</td>
</tr>
</tbody>
</table>

**Effect 9-Recovery:** DM reduces the rate of TB recovery (prolonging the recovery time) for those who recover naturally or due to treatment.

Three studies reported on and compared the number of days it takes to convert from smear positive to smear negative among treated concurrent TB-DM cases and TB-non-DM cases [18,33,61]. The average ratio of the inverse duration (with DM compared to no DM) was pooled across studies by weighting by sample size. The pooled inverse duration ratio was 0.82 implying that DM reduces TB recovery rates (Ψ and ν) by 18%.

**Effect 10-Cured reinfection:** DM increases susceptibility to TB reinfection among those treated or recovered from TB disease.

TB reinfection was defined as a subsequent episode of TB disease in a TB patient treated successfully for at least 6 months (i.e. smear or sputum culture was negative at the end of the
treatment period), but developed subsequently active TB. If this new TB episode is due to the same strain as the previous TB episode, this is considered TB relapse, otherwise it is considered TB “recurrence”. Due to the variable definitions for reinfection, recurrence, and relapse in the literature, we opted to define broadly relapse + recurrence as simply “reinfection”.

A recent meta-analysis reported that the risk of TB reinfection is higher (RR of 1.80 95% CI: 1.40-2.30) among those with DM compared to those without DM [53]. This effect size was accordingly incorporated in the TB-DM model.
S3. POPULATION ATTRIBUTABLE FRACTION

The epidemiologic implications of the TB-DM interactions in India were assessed using two (incidence and mortality) “true” population attributable fraction (PAF) measures, representing the proportions of all TB disease incidence or mortality that could be prevented if there was no interaction between TB and DM. They were defined as:

\[
P_{\text{true}}^{\text{TBM}} = \frac{D_{\text{TBM}} - D_{\text{Counter-factual}}}{D_{\text{TBM}}},
\]

Here, \( D \) indicates the epidemiological measure of incidence or mortality. \( D_{\text{TBM}} \) is the measure in a scenario where there is a biological synergy between TB and DM, while \( D_{\text{Counter-factual}} \) is the measure in a counter-factual scenario where the biological synergy between TB and DM is absent.
ADDITIONAL FIGURES

Figure S4. India demographics. (A) Estimated population size between 1980-2050, compared to the projections by the Population Division of the United Nations (UN) Department of Economic and Social Affairs [5]. (B) Estimated population size by age group between 1980-2050, compared to the UN projections.
Figure S5. Model projections for the proportion of tuberculosis (TB) disease (A) incident and (B) mortality cases attributed to diabetes mellitus in India at 10 different TB disease incidence rate trajectories. The change in TB incidence rate at 2050, relative to the baseline model scenario, was assumed to range between -50% to +50%.

(A) Proportion of TB disease incident cases attributed to diabetes mellitus by 2050 (%)

(B) Proportion of TB-related deaths attributed to diabetes mellitus by 2050 (%)

Relative TB incidence rate to baseline model projection at 2050
Figure S6. Model predictions for the proportion of tuberculosis (TB) disease incident (solid black line) and mortality (dashes blue line) cases attributed to diabetes mellitus (DM) in India between 1990 and 2050, assuming age-dependency in the proportion of individuals developing latent slow versus latent fast TB infection.
Figure S7. Model predictions for the proportion of tuberculosis (TB) (A) disease incident and (B) mortality cases attributed to diabetes mellitus (DM) in India by 2050, assuming different risk levels of the susceptibility to TB reinfection among individuals: i) latently infected with TB, ii) who successfully completed TB treatment, and iii) both latently infected with TB or who successfully completed TB treatment.

(A) 65% reduction in susceptibility to reinfection (baseline assumption)
- No change in susceptibility to reinfection
- 35% increase in susceptibility to reinfection

(B) 65% reduction in susceptibility to reinfection (baseline assumption)
- No change in susceptibility to reinfection
- 35% increase in susceptibility to reinfection
Figure S8. Uncertainty intervals for the proportion of tuberculosis (TB) disease (A) incident and (B) mortality cases attributed to diabetes mellitus in India between 1990 and 2050. The solid red lines represent the mean, while the dashed lines bracket the 95% uncertainty interval.
Figure S9. Sensitivity analyses to assess the sensitivity of the proportion of tuberculosis (TB) disease (A) incident and (B) mortality cases attributed to diabetes mellitus in 2050, to variations in the key parameters in the model. Blue bars are based on the lower bound of parameter values (lower bound of the 95% confidence interval; CI) and red bars are based on the upper bound of parameter values (upper bound of the 95% CI; Table 1).

(A) Proportion of TB disease incident cases attributed to diabetes mellitus (%)

- Effect 6-Disease infectiousness*
- Effect 2-Fast progression
- Effect 1-Susceptibility
- Effect 7-TB mortality
- Effect 9-Recovery*
- Effect 10-Cured reactivation
- Effect 5-Smear positivity

(B) Proportion of TB-related deaths attributed to diabetes mellitus (%)

- Effect 2-Fast progression
- Effect 6-Disease infectiousness*
- Effect 1-Susceptibility
- Effect 9-Recovery*
- Effect 7-TB mortality
- Effect 10-Cured reactivation
- Effect 5-Smear positivity

* A range (±20%) was used for the parameter’s lower and upper bounds
REFERENCES


