



# Epidemiological impact of targeted interventions for people with diabetes mellitus on tuberculosis transmission in India: Modelling based predictions

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## ABSTRACT

**Introduction:** Diabetes mellitus (DM) is a leading driver of tuberculosis (TB) disease in TB-DM burdened countries. We aimed to assess the impact on TB disease of several intervention strategies targeting people with DM in India.

**Methods:** A previously validated TB-DM mathematical model was extended to include interventions targeting DM individuals. The model stratified the population by age, DM status, TB infection status and stage, TB disease form, treatment, recovery, and intervention status.

**Results:** By 2050, different TB vaccination strategies (coverage of 50 % and vaccine efficacies ranging between 50 %–60 %) reduced TB incidence and mortality rates by 4.5 %–20.8 % and 4.1 %–22.1 %, respectively, and averted 3.1 %–12.8 % of TB disease cases in the total population. Number of vaccinations needed to avert one TB case (*effectiveness*) was 14–105. Varying the coverage levels of latent TB treatment (coverage of 50 %–80 % and drug effectiveness of 90 %) reduced TB incidence and mortality rates by 7.1 %–11.3 % and 8.2 %–13.0 %, respectively, averting 4.2 %–6.7 % of TB cases, with effectiveness of 38–40. Different scenarios for dual and concurrent treatment of those with TB and DM, reduced TB incidence and mortality rates by 0.1 %–0.4 % and 1.3 %–4.8 %, respectively, averting 0.1 %–0.2 % of TB cases, with effectiveness of 28–107. Different scenarios for managing and controlling DM (regardless of TB status) reduced TB incidence and mortality rates by 4.5 %–16.5 % and 6.5 %–22.2 %, respectively, averting 2.9 %–10.8 % of TB cases, with effectiveness of 6–24.

**Conclusion:** Gains can be attained by targeting DM individuals with interventions to reduce TB burden. Most strategies were effective with < 50 intervention doses needed to avert one TB disease case, informing key updates of current treatment guidelines.

## 1. Introduction

Tuberculosis (TB) is a leading cause of mortality from infections (World Health Organization, 2017a). In 2017, 10.0 million TB disease incident cases and 1.3 million deaths were estimated globally (World Health Organization, 2018a). TB incidence and mortality rates have been declining globally, but slowly in most regions (e.g., incidence rate has decreased by 1.9 % annually) (World Health Organization, 2018a). Achieving the post-2015 End TB Strategy targets of reducing TB incidence by 90 % and mortality by 95 %, by 2035 (WHO Tuberculosis Programme, 2016), is therefore challenging and requires effective implementation of TB prevention in most affected countries.

Many TB-burdened countries are also experiencing high and rising

diabetes mellitus (DM) burden, due to population ageing, nutrition transition, and obesity (Hu, 2011; Santosa et al., 2014). People living with DM have about 2–4 times higher risk of developing TB disease (Al-Rifai et al., 2017), and experience poorer TB treatment outcomes (Huangfu et al., 2019). Globally, 425 million people are living with DM, a large proportion of them are undiagnosed, and possibly uncontrolled (hemoglobin A1c (HbA1c)  $\geq$  8.0 %), leading to an even greater risk for TB disease and poorer TB treatment outcomes (Al-Rifai et al., 2017; Critchley et al., 2018; Mahishale et al., 2017; Shewade et al., 2017). With adult DM prevalence reaching 10 %–15 % by 2045 in parts of Asia-Pacific, DM could possibly offset future declines in TB incidence and mortality (Awad et al., 2019a, b), making it impossible to achieve the TB goals. For example, 22 % of TB disease cases, and 30 % of TB-

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related deaths were estimated to be attributed to DM in India in 2017 (that is the burden of DM on TB) (Awad et al., 2019b), and by 2050, 33 % of TB disease cases and 43 % of TB-related deaths would be attributed to DM (Awad et al., 2019b).

At present, there is only one preventive (prophylactic) vaccine against TB disease, the Bacillus Calmette-Guérin (BCG) vaccine (World Health Organization, 2018a), which provides minimal protection of uncertain duration (Abu-Raddad et al., 2009), but several vaccines are being tested in clinical trials (Voss et al., 2018). Treatment of latent TB infection (LTBI) is an effective intervention against TB disease, achieved by administering isoniazid or rifampin for 3–9 months (Kwon, 2017). Novel LTBI treatments are also being developed, potentially with higher efficacy, less side effects, and simpler/shorter treatment regimens (Kwon, 2017). With the promising availability of novel TB interventions, assessments of the interventions' impact on TB transmission and disease burden is a priority, more so for the key at risk populations, such as people with DM.

Current guidance from the World Health Organization (WHO) and elsewhere recommends screening TB patients for DM and improving DM control during TB treatment (Ekeke et al., 2017; Jali et al., 2013; Lin et al., 2019a; Samal, 2016), though this is not routinely implemented in low-middle income countries (International Union Against Tuberculosis and Lung Disease and World Diabetes Foundation, 2015; Kapur et al., 2016). Beyond this guidance, there is little evidence or consensus about how other interventions among DM individuals might impact the TB epidemic (World Health Organization, 2018b). For instance, with DM being a major contributor to TB disease (Ekeke et al., 2017; Jali et al., 2013; Kapur et al., 2016; Samal, 2016), tackling the pool of DM individuals latently infected with TB may be essential to meeting the TB goals (Houben and Dodd, 2016).

We investigated the impact of intervention strategies for controlling TB among people with DM in India using a previously validated TB-DM mathematical model (Awad et al., 2019b), focusing on three main intervention areas: 1) vaccination of DM individuals with novel TB vaccines, 2) treatment of LTBI among DM individuals latently infected with TB, and 3) managing and controlling DM to alleviate the impact of DM on TB (Table 1). These modelled interventions are described in detail below.

## 2. Methods

### 2.1. Model structure

A recently-developed TB-DM age-structured deterministic model for India was extended to include targeted interventions for people with DM. Details of the original model are in previous studies (Awad et al., 2019a, b). Briefly, the dynamical model, capturing both the direct (e.g., DM increasing the risk of onset of TB disease) and indirect (e.g., onward transmission of TB from people with and without DM) effects of DM on TB (Awad et al., 2019a, b), was described by a set of differential equations stratifying the population according to age, TB infection and disease status and form, TB treatment status, TB recovery status, and DM status (Supplementary Material Text I-II). TB natural history and treatment outcomes were assumed to be influenced by ten specific effects of having concurrent DM (Awad et al., 2019a) (Supplementary Material Text I and Table S3). Accordingly, DM individuals followed a distinct TB natural history from that of non-DM individuals (Figure S1) (Awad et al., 2019a, b). The rate of DM onset in the model was assumed to be both age (Gaussian function) and time (logistic function) dependent, thus parameterized through a Gaussian-logistic function, and fitted to projections of the International Diabetes Federation for India (International Diabetes Federation, 2017) (Supplementary Material Text I, and Figure S2).

The population was further stratified by intervention status; all interventions were targeted at people with DM. Interventions were incorporated into the model through a distinct and separate TB natural

history for the proportion of individuals undergoing the intervention (Figure S1). Details of the extended model structure are in Supplementary Material Text I.

The model was coded and analyzed in MATLAB R2018b (The MathWorks and Inc. MATLAB, 2018).

### 2.2. Data sources and model fitting

The model was parametrized using empirical evidence for TB natural history, and through model fitting (Table S2 and Awad et al. (Awad et al., 2019a, b)). The parametrization of the ten DM-on-TB effects was based on either pooling evidence from different studies, or derived from specific key observational studies (Table S3 and Awad et al. (Awad et al., 2019b)). A conservative approach was opted whereby each DM-on-TB effect size was modest or set at the null value (i.e. DM has no effect on TB) if there was heterogeneity and uncertainty around the exact effect size or if evidence was not firmly established (Awad et al., 2019a, b). The model was fitted to TB incidence (Figure S3A) and mortality (Figure S3B) rates (World Health Organization, 2017b), DM prevalence (Figure S2A) (Anjana et al., 2017; International Diabetes Federation, 2017), and demographics of India (Figure S3C) (United Nations Department of Economic and Social Affairs et al., 2017). TB contact rate, case detection rate, age-specific DM onset rate, and age-specific birth and death rates were derived by model fitting. By fitting the case detection rate, the model thus implicitly aims to account for the role of both the public and private sectors in diagnosing and treating TB cases in India.

### 2.3. TB-DM interventions

For all modeled interventions, we assumed that the intervention was initiated in 2020 and scaled up at a fixed rate up to 2025. Intervention coverage attained by 2025 was maintained throughout 2026–2050.

The primary modeled outcomes of interest were the proportional reductions in TB incidence and TB mortality rates in the total population. These measures were calculated by comparing the annual TB incidence and mortality rates in the intervention scenario, with that of the baseline scenario of no intervention. The proportion of TB disease cases that are averted by the intervention (between 2020–2050) was also calculated by comparing the intervention and the baseline scenario. *Population-level effectiveness* of the TB-DM intervention was defined as the number of individuals required to undergo the intervention to avert one TB disease case (that is the “number needed to treat” (The Centre for Evidence-Based Medicine, 2019)), and was estimated by dividing the number of DM cases required to undergo the intervention, by the number of TB disease cases averted, over the chosen time horizon.

### 2.4. Intervention program scenarios

#### 2.4.1. TB vaccination

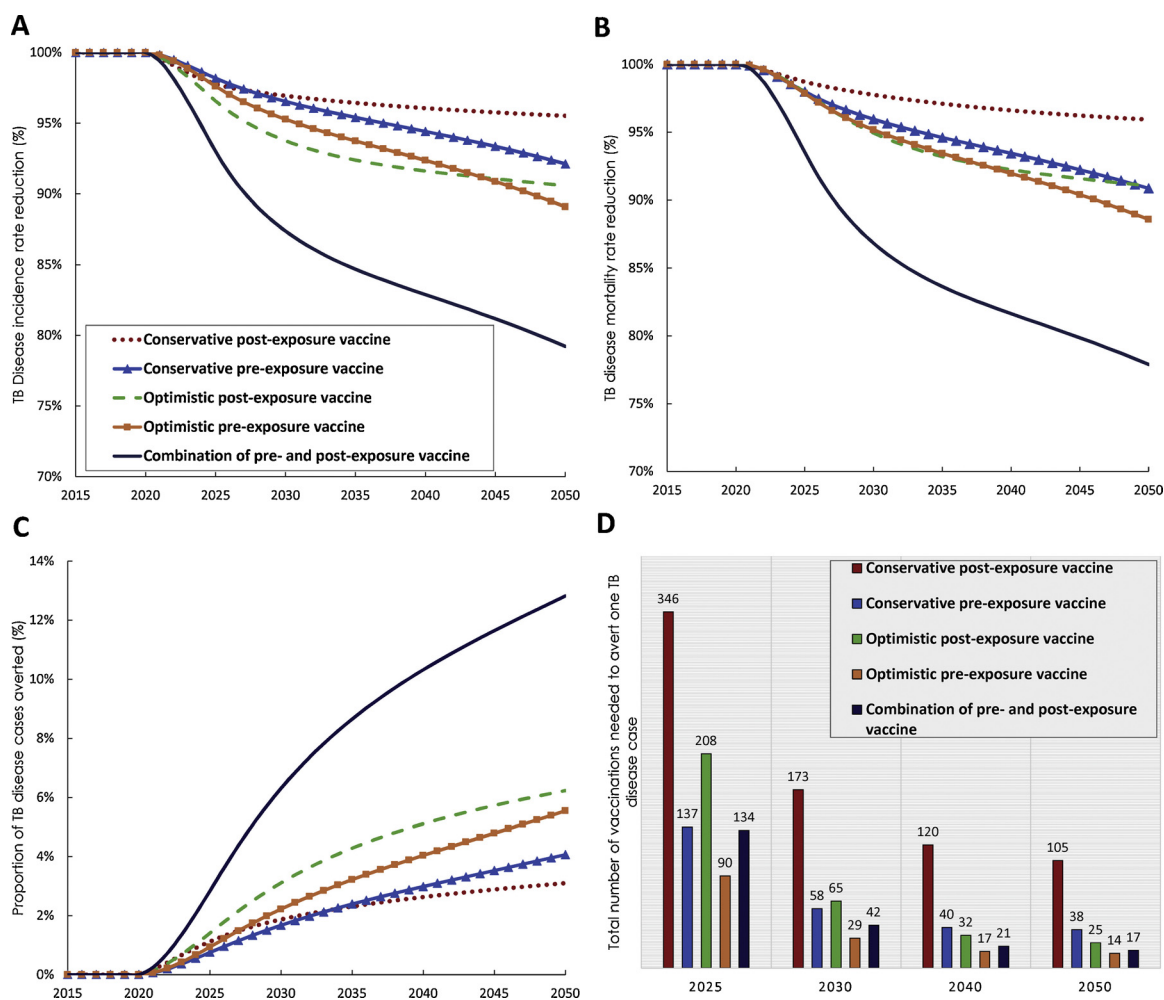
Two different types of TB vaccines were modelled: pre-exposure (prophylactic) and post-exposure vaccines, to reflect current vaccine pipeline under development (Voss et al., 2018). The pre-exposure vaccine was administered to DM individuals who are uninfected but susceptible to TB. The post-exposure vaccine was administered to DM individuals who are latently TB infected. For both vaccines, vaccine immunity was assumed to wane with time.

The “efficacy” of the vaccine was defined (per convention) as the proportional reduction in the risk of TB infection and/or disease and/or transmission among vaccinated individuals, as would be measured in randomized clinical trials. The pre-exposure vaccine was assumed to reduce the fraction of TB infected persons who were TB fast progressors, by a fraction  $VE_p$ . Both pre-exposure and post-exposure vaccines were assumed to reduce the infectiousness of those vaccinated who became infected and developed TB disease, by a fraction  $VE_i$ . Also, both vaccines were assumed to reduce the progression rate to TB disease for

**Table 1**  
Summary of research questions and modeled intervention scenarios investigated in this study.

Scenario description	Coverage	Intervention assumptions
<i>What is the impact of a TB vaccine targeting individuals with DM?</i>		
Pre-exposure TB vaccine for those unexposed to TB infection to prevent TB disease	50 %	Reduction in the fraction of those who become fast progressors to TB disease upon TB infection ( $VE_p$ ) 60 %
Optimistic pre-exposure TB vaccine for those unexposed to TB infection to prevent TB disease and transmission	50 %	60 %
Post-exposure TB vaccine for those latently infected with TB to prevent TB disease	50 %	0 %
Optimistic post-exposure TB vaccine for those latently infected with TB to prevent TB disease and transmission	50 %	0 %
Pre-exposure vaccine for those unexposed to TB, and post-exposure TB vaccine for those latently infected with TB, to prevent TB disease and transmission	50 %	60 %
<i>What is the impact of latent TB treatment targeting individuals with DM?</i>		
Latent TB treatment	50 %	90 % drug effectiveness (i.e. drug efficacy and adherence)
Optimistic latent TB treatment	80 %	90 % drug effectiveness (i.e. drug efficacy and adherence)
<i>What is the impact of managing and controlling DM in individuals with DM to reduce DM effects on TB natural history and treatment outcomes?</i>		
Reducing the effects of DM on TB treatment outcomes only for those dually and concurrently treated for both TB and DM	50 %	0-100 % <sup>#</sup> reduction in the effects of DM on TB treatment outcomes
Reducing the effects of DM on TB natural history and treatment outcomes for all DM individuals whether unexposed to TB, latently infected with TB, with TB disease, treated TB disease, or recovered TB disease	50 %	0-100 % reduction in the effects of DM on TB natural history and treatment outcomes

<sup>#</sup> Here 100 % reduction in DM-on-TB effects entails that individuals with DM have the same risk of TB infection, disease, and/or treatment outcomes as those without DM.



**Fig. 1.** Projected outcomes of the impact of tuberculosis (TB) vaccination targeting individuals with diabetes mellitus (DM). **A)** Reduction in TB disease incidence rate. **B)** Reduction in TB mortality rate. **C)** Proportion of averted TB disease incident cases. **D)** Number of vaccinations needed to avert one TB disease case (*effectiveness*) by 2025, 2030, 2040, and 2050. Vaccine coverage was scaled-up to 50 % by 2025 and then maintained at this level thereafter.

those latently infected (that is TB slow progressors), by a fraction  $VE_{PVL.S}$ . These assumptions were based on existing assumptions for the biological effects of these vaccines (Abu-Raddad et al., 2009). The modelled vaccine scenarios along with their parametrization of coverage, efficacies, and protection duration are summarized in Table 1.

In a sensitivity analysis of a *combination scenario of both post- and pre-exposure* vaccines, we assessed the impact of different vaccination coverage levels ranging from 0 %–90 %, vaccine efficacies varying (individually) from 0 %–100 %, and vaccine immunity duration from one year to lifelong.

In a second sensitivity analysis of a *combination scenario of both post- and pre-exposure* vaccines, and in context of uncertainty about the future DM prevalence trajectory over the coming decades, we assessed the impact of vaccination assuming different DM prevalence trajectories—DM prevalence was assumed to be reduced by 40 % reaching 5 % by 2050, or to remain constant at 8 % between 2020 and 2050, in addition to our baseline model of growing prevalence per the projections of the International Diabetes Federation (International Diabetes Federation, 2017) (Figure S2).

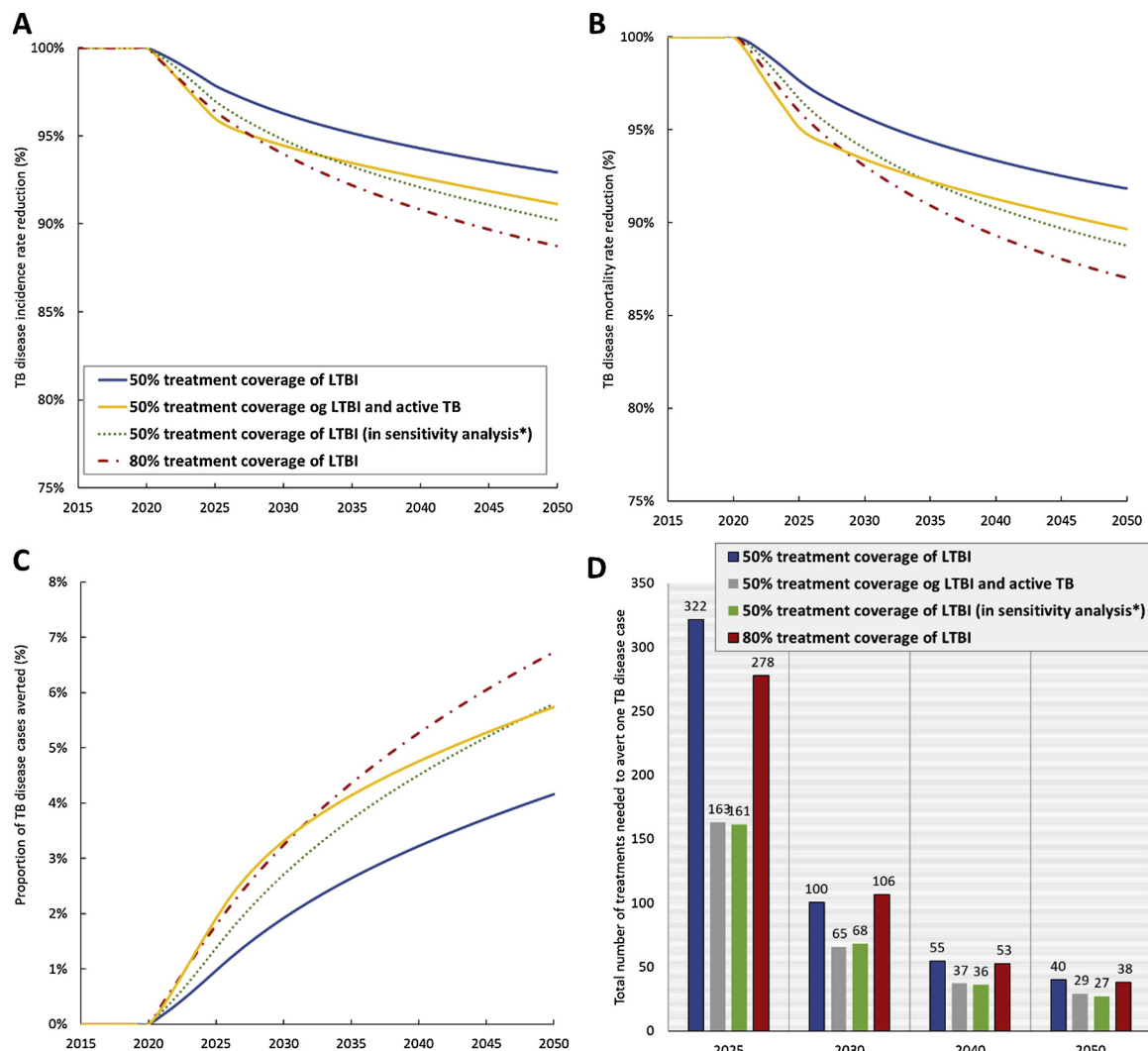
Additional sensitivity analyses were conducted to assess the sensitivity of model predictions to variations in TB epidemiological and natural history parameters (Table S2), and to variations in the effect sizes of the DM-on-TB effects (Table S3). For each individual parameter, we either used the lower and upper values from either the CI or assumed  $\pm 25$  % uncertainty around the point estimates if the uncertainty was not captured by a CI. For instance, for *Effect 1-*

*Susceptibility*, a range of 1.0–2.2 was used based on the reported 95 % CI for that effect (Martinez et al., 2017); for *Effect 2-Fast progression*, a range of 1.3–1.8 was used based on the reported 95 % CI of the pooled TB-DM association (Al-Rifai et al., 2017); and for *Effect 6-Disease infectiousness*, a range of  $\pm 25$  % around the point estimate was used (i.e. 1.1–1.8; Table S3).

#### 2.4.2. Treatment of latent TB as preventive therapy

LTBI treatment was modelled to be administered to DM individuals latently infected with TB to reach *i)* 50 % and *ii)* 80 % treatment coverage by 2025. The treatment was assumed to prevent progression to TB disease with a drug efficacy of 90 % (Table 1). Individuals successfully treated move to the recovery state, but can in principle be reinfected subsequently with TB.

At present, there are no national or international recommendations to treat DM patients with LTBI. However, if such recommendations were introduced in the future, clinical and laboratory examinations to rule out active TB disease would need to be carried out according to national policies before any decision to initiate LTBI treatment as a preventive therapy (World Health Organization, 2018c). People living with DM would thus require screening for active TB disease before any screening and treatment for LTBI. An additional analysis was therefore carried out assuming that those people with active TB disease were identified and treated first. This was done by assuming screening and treatment for TB disease and LTBI treatment would be administered at the same annual rate to individuals with DM who had either active TB



**Fig. 2.** Projected outcomes of the impact of latent tuberculosis (TB) treatment as a preventive therapy targeting individuals with diabetes mellitus (DM). **A)** Reduction in TB disease incidence rate. **B)** Reduction in TB mortality rate. **C)** Proportion of averted TB disease incident cases. **D)** Number of vaccinations needed to avert one TB disease case (*effectiveness*) by 2025, 2030, 2040, and 2050. Treatment coverage was scaled-up to the indicated level by 2025, and then maintained at this level thereafter.

disease or LTBI. Overall treatment coverage (for active TB disease or LTBI) reached 50 % for DM patients by 2025.

A sensitivity analysis was conducted to assess whether the impact of LTBI treatment could have been underestimated, by assuming that DM increases progression to TB disease not only for TB primary infection, but also for TB reactivation, given biological plausibility (Awad et al., 2019a, b) (Supplementary Material Text III). Coverage of LTBI treatment was set here at 50 % by 2025.

#### 2.4.3. Controlling DM for improved TB progression and treatment outcomes

Several modelled intervention scenarios assessed the impact on TB of managing and controlling DM (i.e. HbA1c level < 8 % (American Diabetes Association, 2017)). As supported by existing evidence (Al-Rifai et al., 2017; Critchley et al., 2018; Mahishale et al., 2017; Shewade et al., 2017), controlling DM was assumed to reduce the DM-on-TB effects relative to those with *uncontrolled* DM (Table 1).

#### 2.5. Patient and public involvement

Neither patients nor the public were involved in the study.

### 3. Results

In the no-intervention (baseline) scenario, TB disease incidence and mortality rates in India (per 100,000 population per year) were projected to decline from 190.1 and 36.9 in 2018, to 177.0 and 34.0 by 2020 (Figure S3A), and to 102.3 and 18.1 by 2050 (Figure S3B), respectively. Cumulative number of new TB cases between 2020–2050 was projected at 55.2 million.

#### 3.1. TB vaccination

Fig. 1 shows the impact of TB vaccination targeting people with DM on TB disease, while Figure S4A shows the projected TB incidence rate given the different TB vaccination strategies. By 2050, the reduction in TB incidence rate ranged from 4.5 % (post-exposure vaccine scenario) to 20.8 % (combination scenario of pre- and post-exposure vaccination; Fig. 1A and Figure S4). Here, the reduction in TB mortality rate ranged from 4.1 %–22.1 %, respectively (Fig. 1B). By 2050, 3.1 %–12.8 % of TB disease cases were averted by the scenarios, that is a total of 1.7–7.1 million cases (Fig. 1C).

By 2025, vaccination effectiveness ranged from 90 (optimistic pre-exposure vaccine scenario) to 346 (post-exposure vaccine scenario);



and by 2050, effectiveness ranged from 14 to 105 (Fig. 1D). The impact of the combination of pre- and post-exposure vaccination was larger than that of the individual pre- and post-exposure vaccinations, but the effectiveness was inferior, as more vaccinations were needed to avert one TB disease case.

The robustness of our results was assessed in a series of sensitivity analyses (Figure S5). Altering vaccine coverage from 10 %–90 %, reduced TB incidence rate by 4.0 %–34.4 % by 2050, while effectiveness stayed constant at 17. TB incidence rate was reduced by 15.6 %–23.4 %, 17.2 %–23.6 %, and 19.3 %–21.1 % as each of the vaccine efficacies of  $VE_p$ ,  $VE_i$ , and  $VE_{pVLS}$ , respectively, varied independently (and not simultaneously) from 0 %–100 %. Vaccine effectiveness ranged from 15 to 23, 15 to 20, and 17 to 18, as each of the vaccine efficacies of  $VE_p$ ,  $VE_i$ , and  $VE_{pVLS}$ , respectively, varied independently from 100 % down to 0 %. Increasing vaccine immunity from 1 year to lifelong protection, reduced TB incidence rate by 2.8 %–20.8 %, with vaccine effectiveness ranging from 17 to 157.

In further sensitivity analyses, the impact of TB vaccination on TB incidence and mortality was altered by different DM prevalence trajectories (Figure S6). In 2050, the reduction in TB incidence rate ranged between 11.6 % (declining DM prevalence scenario) and 20.8 % (growing DM prevalence as per the projections of the International Diabetes Federation (International Diabetes Federation, 2017) (Figure S6A). Meanwhile, the reduction in TB mortality rate ranged from 12.8 %–22.1 % (Figure S6B). However, vaccine effectiveness remained essentially the same regardless of the future trajectory of DM prevalence (Figure S6C).

### 3.2. Treatment of latent TB as preventive therapy

Fig. 2 shows the impact of LTBI treatment targeting people with DM, while Figure S4B shows the projected TB incidence rate of the different LTBI treatment strategies. By 2050, the reduction in TB incidence rate was 7.1 % for the 50 % and 11.3 % for the 80 % LTBI-treatment coverage scenarios, respectively (Fig. 2A and Figure S4B). Here, the reduction in TB mortality rate was 8.2 % and 13.0 %, respectively (Fig. 2B). By 2050, 4.2 %–6.7 % of TB disease cases were averted, that is a total of 2.3–3.7 million cases (Fig. 2C).

By 2025, effectiveness of LTBI treatment was 278 for the 80 % and 322 for the 50 % coverage scenarios, respectively; and by 2050, effectiveness was 38 and 40, respectively (Fig. 2D).

By reaching an overall treatment coverage of 50 % among DM individuals with active TB disease or latent TB infection, the reduction in TB incidence rate was 8.9 % (Figure 2A), the reduction in TB mortality rate was 10.7 % (Figure 2B), 5.7 % of TB disease cases were averted (Fig. 2C), and the effectiveness of treatment was 29 (Fig. 2D), all by 2050. About two percentage points of the impact on TB incidence rate were due to the screening and treatment of TB disease, while the remaining seven percentage points of the impact were due to LTBI treatment.

In the sensitivity analysis assuming that DM increases progression to TB disease also for TB reactivation, effectiveness of LTBI treatment was superior to the above scenarios—for example, by 2050, LTBI-treatment effectiveness was only 27 (Fig. 2D).

### 3.3. Managing and controlling DM for improved TB progression and treatment outcomes

Fig. 3 shows the impact of reducing the effects of DM on TB treatment outcomes by dually and concurrently treating those with TB disease and DM. By 2050, with coverage of effective DM management (i.e. reducing the effects of DM on TB) ranging from 20 % to 100%, the reduction in TB incidence rate ranged from 0.1 %–0.4 % (Fig. 3A and Figure S4B), and the reduction in TB mortality rate ranged from 1.3 %–4.8 % (Fig. 3B). By 2050, 0.1 %–0.2 % of TB disease cases were averted, that is a total of 28,803–108,893 cases (Fig. 3C).

By 2025, effectiveness of dual and concurrent TB-DM treatment ranged from 147 to 573 with coverage of DM management ranging from 100 % down to 20 %; and by 2050, effectiveness ranged from 28 to 107 (Fig. 3D).

Fig. 4 shows the impact of improved management and control of DM in people with DM regardless of their TB status and stage. By 2050, with DM-management coverage ranging from 20 % to 100%, the reduction in TB incidence rate ranged from 4.5 %–16.5 % (Fig. 4A and Figure S4B), and the reduction in TB mortality rate ranged from 6.5 %–22.2 % (Fig. 4B). By 2050, 2.9 %–10.8 % of TB disease cases were averted, that is a total of 1.6–5.9 million cases (Fig. 4C).

By 2025, effectiveness of improved DM management and control ranged from 29 to 121 with DM-management coverage ranging from 100 % down to 20 %; and by 2050, effectiveness ranged from 6 to 24 (Fig. 4D).

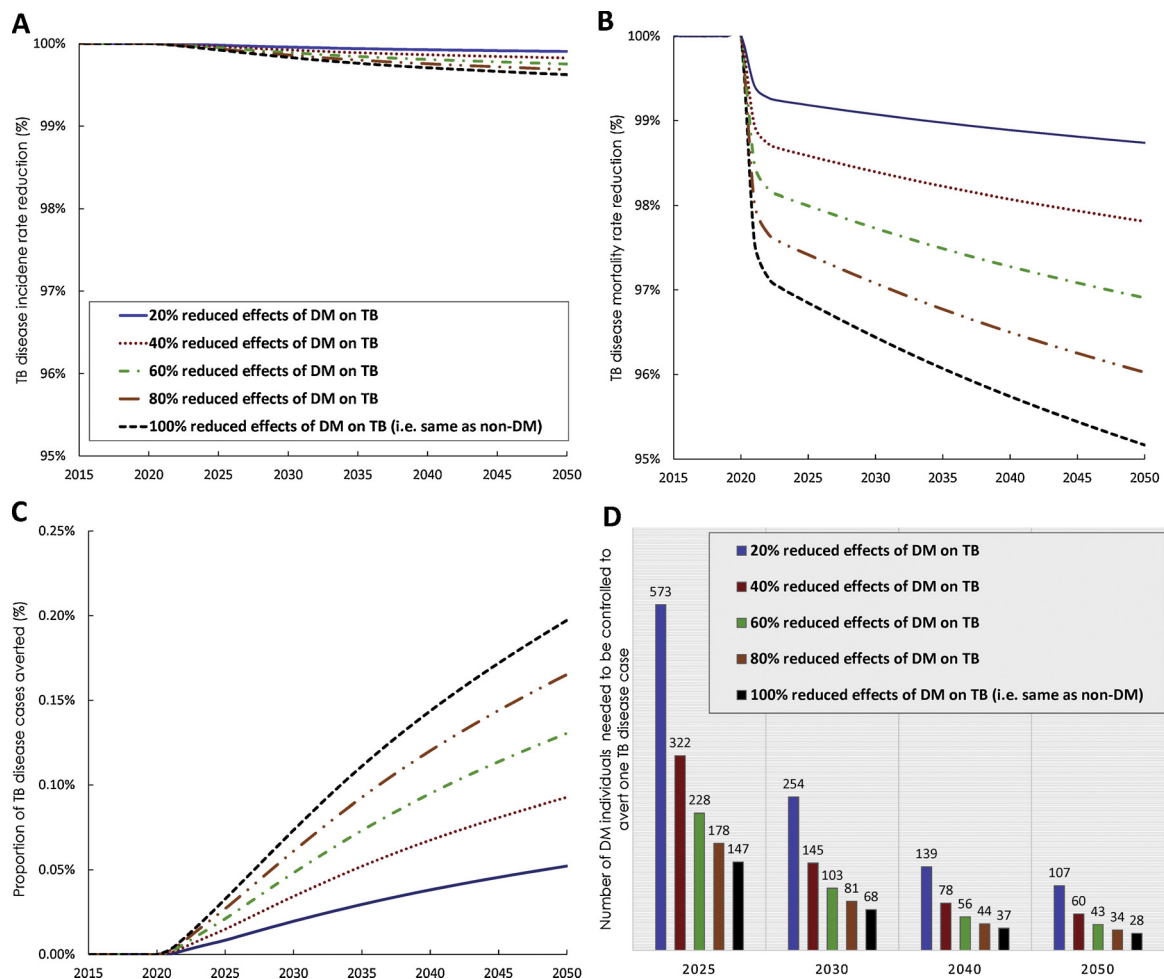
## 4. Discussion

Using an analytical approach, we quantitatively assessed the impact of interventions targeting people living with DM to reduce TB incidence and mortality in India, the country most affected by the dual TB-DM epidemic (Awad et al., 2019b). We found that substantial reductions in TB incidence and mortality could be achieved through TB vaccination, LTBI treatment, and managing and controlling DM. Administering TB vaccination to DM individuals (before being exposed to TB), or managing and controlling DM in those living with DM, was most impactful in reducing TB incidence and mortality rates by up to 22 %. LTBI treatment targeting the reservoir of DM individuals who are already TB latently infected had also important public health benefits reducing TB incidence and mortality rates by up to 13 %. While these interventions do not solely achieve the post-2015 End TB targets (Figure S4), each offers substantial reductions in TB burden making the targets more manageable.

In context of strong effects for DM on TB natural history, treatment outcomes, and epidemiology (Al-Rifai et al., 2017; Awad et al., 2019a, b; Huangfu et al., 2019), these findings highlight how interventions targeting people with DM should be at the core of the post-2015 End TB Strategy, and are integral to achieving this strategy's targets of reducing TB incidence by 90 % and mortality by 95 %, by 2035 (WHO Tuberculosis Programme, 2016). While our study was on India, this approach can be generalised to other TB-DM burdened countries, with probably similar beneficial impact.

Different vaccine scenarios, informed by current TB vaccine development (Voss et al., 2018), were found to reduce TB incidence by 5 %–21 % and mortality by 4 %–22 % (Fig. 1). In the optimistic combination vaccine scenario (of both post- and pre-exposure vaccination), about half of the burden (i.e. negative effects) of DM on TB could be mitigated (Fig. 1C). However, the public health benefits of TB vaccination were strongly dependent on the type (pre-exposure versus post-exposure vaccine), efficacy, coverage level, and importantly, duration of protection that the vaccine would entail (Figs. 1 and S2). Effectiveness of a pre-exposure vaccine was superior to that of a post-exposure vaccine—only 14 (versus 105) pre-exposure vaccinations were needed to avert one TB disease case by 2050 (Fig. 1D). Though the impact of a post-exposure vaccine was inferior, it was immediately realized, as it affected those who are already (latently) TB infected (Fig. 1). The longer the duration of vaccine protection, the better was effectiveness—131 vaccinations were needed to avert one TB disease case by 2050 for a vaccine immunity lasting five years, versus 17 for lifelong immunity (Figure S2).

LTBI treatment at high coverage of 80 % reduced TB incidence by 11 %, mortality by 13 %, and averted 7 % of TB disease cases (Fig. 2). The impact of LTBI treatment was also immediately realized (Fig. 2). However, LTBI treatment at 80 % coverage was only half as impactful as the combination vaccine scenario, since LTBI treatment affects only those latently infected, while the combination vaccine affects people



**Fig. 3.** Projected outcomes of the impact of dual and concurrent treatment of tuberculosis (TB) disease and diabetes mellitus (DM). **A)** Reduction in TB disease incidence rate. **B)** Reduction in TB mortality rate. **C)** Proportion of averted TB disease incident cases. **D)** Number of vaccinations needed to avert one TB disease case (*effectiveness*) by 2025, 2030, 2040, and 2050. Dual TB-DM treatment coverage was scaled-up to 50 % by 2025, and then maintained at this level thereafter.

before and after TB infection (Fig. 2 versus Fig. 1). Meanwhile, the impact of LTBI treatment was twice as large as that of a post-exposure vaccine (also targeting those latently infected), as LTBI treatment has higher efficacy (90 %) than that assumed for a post-exposure vaccine (50 %) (Fig. 2 versus Fig. 1).

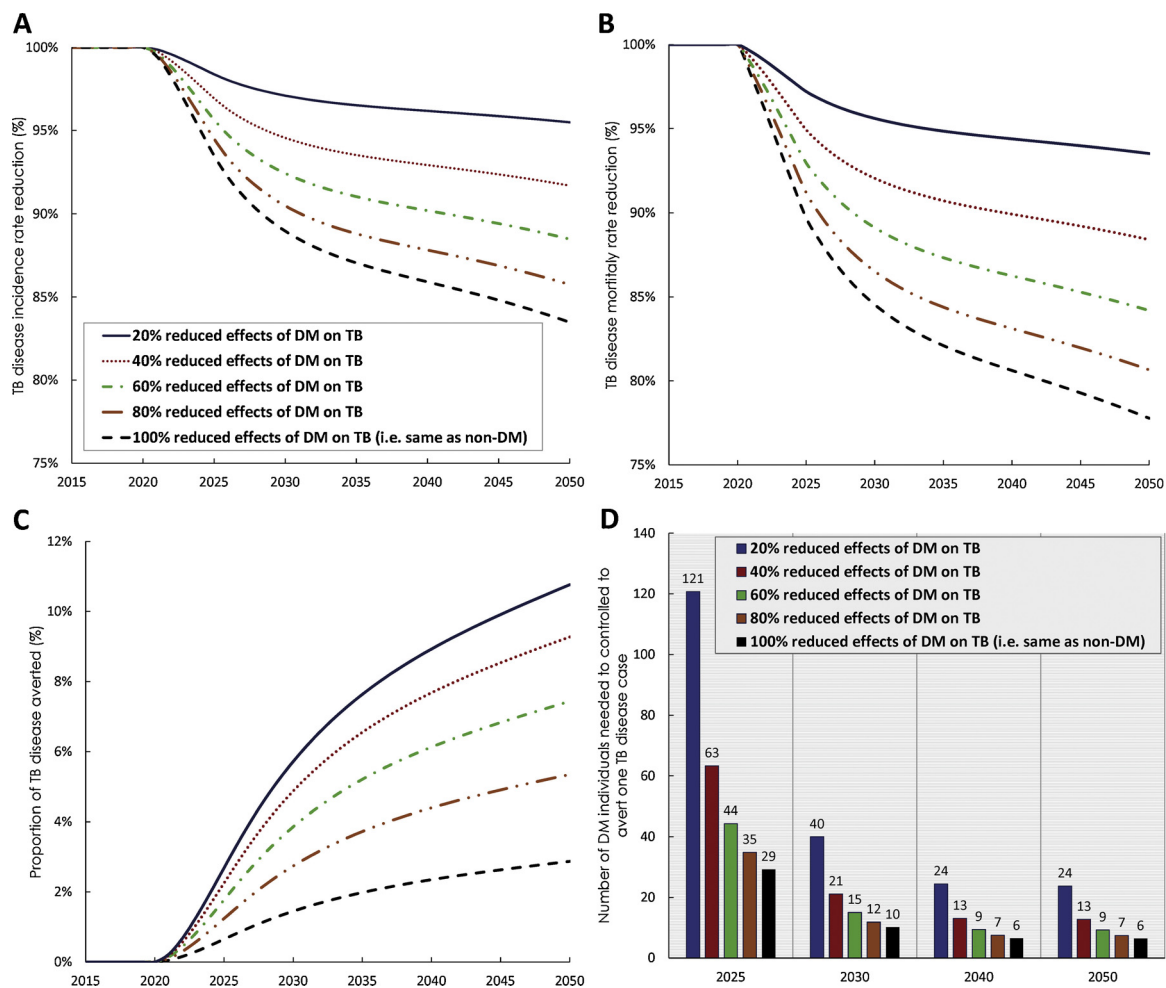
Most recent joint TB-DM management guidelines do not strongly promote screening DM patients for active TB disease (Lin et al., 2019b), mainly because several studies have identified few or no cases of active TB disease, and have also identified many practical difficulties with access to TB screening or diagnostic facilities (Kumapata et al., 2013; Mtwangambate et al., 2014; Prakash et al., 2013). However, screening for active TB disease as part of a strategy to screen and treat LTBI could be more effective, due to the substantially higher yield that would be expected. When screening and treatment for active TB disease was included in the LTBI treatment scenario (Fig. 2), the impact of the intervention was realized faster than the scenario with only LTBI treatment. Still, in this scenario the impact of such intervention was mostly arising from the treatment of the latently infected rather than the screening and treatment of active disease (Fig. 2). This is mainly due to the fact that the number of DM-active TB disease cases treated in this scenario was meagre compared to the number of DM-latently infected cases that are treated.

These findings come at a critical time as the WHO was recently unable to formulate any clear guidance about treating LTBI in people with DM (World Health Organization, 2018b). Guidelines by the United States Preventive Services Task Force do not also currently recommend

screening and treatment of LTBI in people with DM, indicating that there is not yet sufficient evidence to recommend such treatment (Bibbins-Domingo et al., 2016). Our results inform these deliberations by providing concrete quantification of the potential population-level impact of this intervention, and indicate that LTBI treatment should be integral to these guidelines, as it is an effective intervention that uses generic low-cost drugs and alleviates different negative effects of DM on TB natural history and treatment outcomes.

While dual and concurrent treatment of TB and DM has an important impact at the individual-level, the population-level impact was limited (Fig. 3). This intervention affects only a small proportion of the population, those with concurrent DM and TB disease, and is implemented well after DM has had its toll on TB natural history for a given affected person. This intervention also primarily impacts TB mortality, rather TB disease incidence (Fig. 3). Despite the limited population-level impact, the *effectiveness* is of value (Fig. 3D)—a small number of treatments is needed to avert one TB disease case (~50). These findings reinforce current guidelines that recommend screening of TB patients for DM, and improving DM control during TB treatment (Ekeke et al., 2017; Jali et al., 2013; Lin et al., 2019a; Samal, 2016). However, they also demonstrate that the excessive focus of TB-DM control on screening for and managing DM among TB patients will not have much significant population-level impact on the TB-DM epidemics.

Our results demonstrate that managing and controlling DM is potentially a powerful intervention that can reduce TB disease by up to 17



**Fig. 4.** Projected outcomes of the impact of managing and controlling diabetes mellitus (DM) in DM individuals regardless of tuberculosis (TB) status. **A)** Reduction in TB disease incidence rate. **B)** Reduction in TB mortality rate. **C)** Proportion of averted TB disease incident cases. **D)** Number of vaccinations needed to avert one TB disease case (*effectiveness*) by 2025, 2030, 2040, and 2050. DM management coverage was scaled-up to 50% by 2025, and then maintained at this level thereafter.

% and mortality by up to 22% (Fig. 4). Improved DM management has also superior *effectiveness* compared to all other studied interventions (Fig. 4D), as only about ten people with DM require better management to avert one TB disease case. The impact of improved DM management is also immediately realized, with most gains rapidly materializing in comparison to vaccination whose impact takes time to materialize (Fig. 4 versus Fig. 1). These findings demonstrate the potential population importance for TB epidemics of strengthening DM services and management in India and other countries enduring large double TB-DM burden. Improved DM management would also have multiple other positive consequences, beyond reducing TB incidence and mortality, such as reducing the risk of other DM complications and cardiovascular disease. To date though, a large proportion of DM cases in India remain undiagnosed, and probably with uncontrolled DM (International Diabetes Federation, 2017).

This study has limitations. Effect sizes of several of the DM-on-TB effects are not yet known with precision (Awad et al., 2019a, b), and this uncertainty may affect the assessed intervention impact. We assumed specific or a range of efficacies for some of the interventions, such as for the vaccines, but the exact efficacies will not be known until final development of the intervention product. Future projections of TB incidence rate are intrinsically uncertain and subject to unknown factors, such as future scale-up of other TB interventions, but this may affect the assessed impact. At present, we do not have specific interventions (e.g. TB vaccines, LTBI treatment regimens, improved diabetes management) that have been shown in randomised trials to

reduce the risk of TB disease among people living with DM. Hence, our analyses are best viewed as demonstrating the potential of such interventions rather than as precise estimates of their likely range of effects. Despite these limitations, the model has key strengths such as inclusion of several different effects through which DM can affect TB natural history and treatment outcomes, incorporation of the age-specific trends, and assessing both the direct and indirect population impacts of DM on TB. It is also possible that we may have underestimated (rather than overestimated) the impact of the interventions, as the impact of DM on TB is probably underestimated (Awad et al., 2019b).

We assumed specific input parameter values (Tables S2 and S3) and did not explore the impact on the predictions of variability in these parameters through an uncertainty analysis, since the interventions are largely hypothetical at present. However, we conducted several sensitivity analyses to explore the potential impact of many of these parameters. The sensitivity analyses demonstrated that the results were most sensitive to *Effect 6-Disease infectiousness*, *Effect 1-Susceptibility*, and *Effect 2-Fast progression* (Figure S7), given the impact of these effects on TB epidemiology (Awad et al., 2019b). Explicitly, with an effect size for *Effect 6-Disease infectiousness* ranging between 1.1–1.8, vaccine effectiveness ranged between 13.7–22.5; with an effect size for *Effect 1-Susceptibility* ranging between 1.0–2.2, vaccine effectiveness ranged between 14.3–20.8; and with an effect size for *Effect 2-Fast progression* ranging between 1.3–1.8, vaccine effectiveness ranged between 15.1–21.1 (Figure S7). Otherwise, our results were largely insensitive to variations in the rest of the explored effects (Figure S7). Our results



were also insensitive to variations in the TB epidemiological and natural history parameters (Figure S8).

In conclusion, there are major gains to be attained by targeting people with DM with interventions to reduce TB incidence and mortality. Most interventions were effective with < 50 intervention doses needed to avert one TB disease case. While none of the interventions could mitigate completely the adverse burden of DM on TB, several, such as TB vaccination and controlling and managing DM, can reduce this burden by as much as half. These findings demonstrate the urgency of continuing development of novel interventions targeting the dual TB-DM epidemic, and affirm the relevance of the concept of “know your epidemic, know your response” for tackling TB (WHO Tuberculosis Programme, 2016), as a critical and indispensable approach to addressing TB disease burden. The findings also highlight the relevance of joint TB-DM healthcare services, such as integrating better DM management and control services, which is vital to managing TB epidemics in places like India.

### Authors and contributors

SFA co-conceived and co-designed the study, programmed the model, conducted the modeling analyses, and wrote the first draft of the article. LJA and JAC obtained the funding, led the study, co-conceived and co-designed the study, and contributed to conduct of the analyses. All authors contributed to study development, analysis and interpretation of results, and writing of the article.

### Declaration of competing interest

We declare that we have no conflict of interest to disclose.

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### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.epidem.2019.100381>.

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