Transmission Model

We built a deterministic, age-structured, compartmental model for the transmission of *M.tb* infection in Ethiopia, to study the impact of digital adherence technologies on TB treatment. The model was initialised to Ethiopia's estimated TB prevalence in 2010/2011 [1], and parametrised using World Health Organization Global TB reports [2] and trial data. The model's structure was informed by Ethiopia's care cascade, including compartments for undiagnosed, diagnosed and on treatment. The model included infection transmission to healthy individuals, reinfection of people already infected with TB, TB reactivation, as well as reinfection of cured individuals and relapse.

Assumptions

Due to the young age of Ethiopia's population, we considered two age groups: 0–14 years of age, and 15+.HIV and other co-infections were not considered in the model. Similarly, drug-resistance was not incorporated, as the ASCENT trial explicitly excluded drug resistance. Finally, we did not explicitly incorporate BCG vaccination in the model, however vaccination protection was considered as a rate reducing the transmission parameter in the 0–14 age stratus [3], where we calibrated to notified cases in children. This implicitly captured the impact of vaccination in the youngest population.

Model dynamics

In the model (Figure 1), individuals were assumed to be initially susceptible to TB (**S**). Following contagion (transmission rate β) they entered the early infection ($\mathbf{L_e}$) compartment where they could develop active TB at a probability p or move to the late infection ($\mathbf{L_l}$) compartment at a rate ω. In this compartment infected individuals could either reactivate to active TB with a probability v or remain there their whole life. Active TB cases were initially undiagnosed (**D**) and could be detected at a rate σ, following which they could initiate treatment (q) with ($\mathbf{D_t}$*) or without ($\mathbf{D_t}$) the intervention according to a probability g representing the intervention coverage. Individuals undergoing treatment could interrupt treatment at a rate f or f* and become lost to follow-up (**F**), where they either remained or restarted treatment at a rate $\sigma_f < \sigma$. Untreated individuals, individuals treated with the intervention and individuals treated under the standard of care, could all recover and move to compartments $\mathbf{R^n}$, **R*** and **R** at rates τ_u, τ* and τ respectively. Following this they could relapse at rates ρ^u, ρ* and ρ, respectively, and restart the cycle from **D**, or lose immunity to transmission following two years after treatment completion at rate η and move to $\mathbf{L_l}$, where they could be reinfected at rate αβ. The whole population (**N**) was therefore comprised of $\mathbf{S+L_e+L_l+D+D_t+D_t^*+R^n+R+R^*}$.

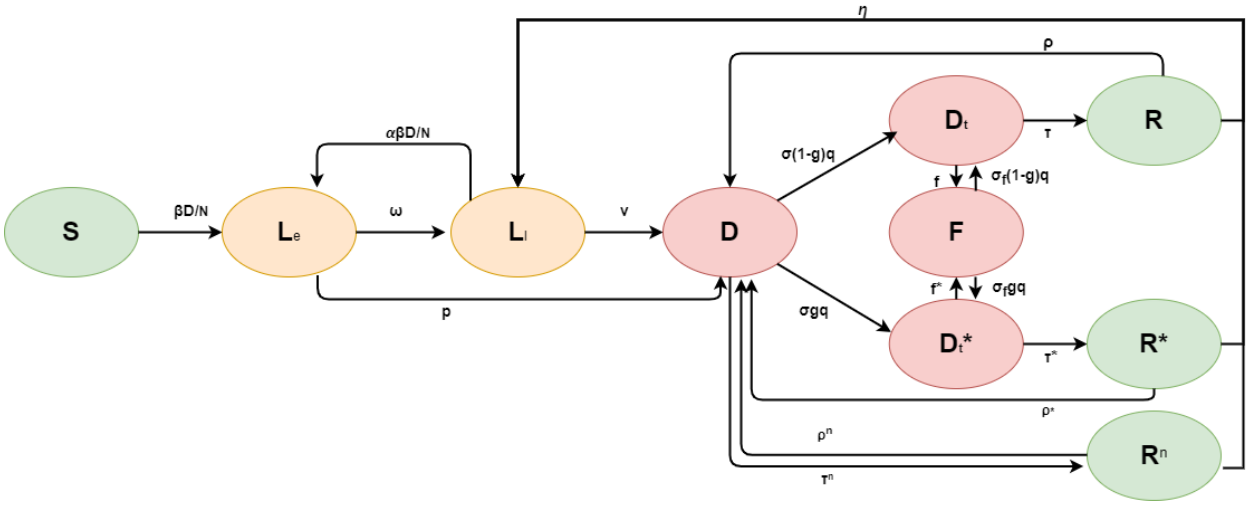

Figure 1. Model schematic.

Equations:

$$\frac{dS_i}{dt} = \pi N - \frac{\beta_i S_i (D_1 + D_2)}{N} - \mu S_i$$

$$\frac{dL_{e_i}}{dt} = \frac{\beta_i (S_i + \alpha L_{l_i})(D_1 + D_2)}{N} - (\omega + p + \mu) L_{e_i}$$

$$\frac{dL_{l_i}}{dt} = \omega L_{e_i} + \eta (R^n{}_i + R^*{}_i + R_i) - \left(\frac{\alpha \beta_i (D_1 + D_2)}{N} + v + \mu\right) L_{l_i}$$

$$\frac{dD_i}{dt} = p L_{e_i} + v L_{l_i} + \rho^n \mathrm{R}_i{}^n + \rho^* \mathrm{R}_i{}^* + \rho \mathrm{R}_i - (\sigma q + \tau^n + \mu^n) D_i$$

$$\frac{dD_t{}^*{}_i}{dt} = \sigma g q D_i + \sigma_f q F - (f^* + \tau^* + \mu^{t*}) D_t{}^*{}_i$$

$$\frac{dD_{t_i}}{dt} = \sigma (1 - g) q D_i - (f + \tau + \mu^t) D_{t_i}$$

$$\frac{dF}{dt} = f D_{t_i} + f^* D_t{}^*{}_i - (\sigma_f q + \mu^n) F$$

$$\frac{dR^n{}_i}{dt} = \tau^n D_i - \frac{\alpha \beta_i R^n{}_i (D_1 + D_2)}{N} - (\rho^n + \eta + \mu) R^n{}_i$$

$$\frac{dR^*{}_i}{dt} = \tau^* D_t{}^*{}_i - (\rho^* + \eta + \mu) R^*{}_i$$

$$\frac{dR_i}{dt} = \tau_t D_{t_i} - (\rho + \eta + \mu) R_i$$

Where i = 1,2 represents the two age groups: 0–14 years of age, and 15+ respectively. $\mathbf{D^*_t}$ represents individuals treated with the intervention according to the coverage g, while $\mathbf{D_t}$ represents individuals treated under the standard of care.

Parametrisation

Model parameters are reported in Table 1. Treatment, recovery and loss to follow-up rates were directly informed by trial data, for the intervention arms and the control (standard of care) arms.

Parameter	Meaning	Prior (year^{-1})	Source	Posterior (year^{-1})
π	average birth rate	0.0341 (0.0323–0.0359)	[4]	0.0341 (0.0323–0.0359)
μ	average mortality rate	0.0076 (0.0067–0.0086)	[4]	0.0077 (0.0067–0.0086)
β_1	transmission rate in the 0–14 age group		calibration	11.057 (8.233–14.574)
β_2	transmission rate in the 15+ age group		calibration	10.584 (8.550–11.953)
ω	progression rate from early to late infection	0.872	[5]	0.767 (0.418–0.980)
p	probability of active TB from early infection	0.0826	[5]	0.107 (0.074–0.147)
v	late infection progression rate to active TB	0.000594	[5]	0.00081 (0.00014–0.00193)
τ^n	recovery rate in untreated individuals	0.163 (0.123 – 0.247)	[6]	0.196 (0.131–0245)
τ	treatment completion in individuals under treatment (standard of care)	0.944 (0.85 – 1)	trial data	0.927 (0.856–0.996)
μ^n	death rate in untreated individuals	0.185 (0.171 – 0.236)	[6]	0.186 (0.171–0.210)

μ^t	death rate in individuals under treatment (standard of care)	disease-related death rate + μ 0.0387 (0.023 – 0.041)	trial data	0.031 (0.024–0.040)
σ	detection rate	0.57 (0.53 – 1)	[2]	0.836 (0.563–0.995)
g	intervention coverage	variable	scenario	
q	treatment initiation rate	0.94 (0.9–1)	[2]	0.953 (0.904–0.998)
σ_f	secondary detection and treatment following treatment interruption	0.222 (0.010–0.53)	[7, 8]	0.252 (0.016–0.512)
f	lost to follow-up rate (standard of care)	0.012 (0.009 – 0.029)	trial data	0.019 (0.009–0.029)
α	protection from reinfection	0.239 (0.14 – 0.30)	[9]	0.180 (0.141–0.263)
η	return to late (latent) infection	0.5	[10]	0.5
ρ^n	relapse rate following self-cure	0.02 (0.015–0.025)	[11]	0.020 (0.015–0.025)
ρ	relapse rate (standard of care)	0.01 (0.010–0.027)	[12]	0.018 (0.014–0.027)
Intervention parametrisation				
Parameter	Meaning	Label intervention (year^{-1})	Pillbox intervention (year^{-1})	Source
τ^*	treatment completion in	0.940 (0.832–1)	0.943 (0.835–1)	trial data [13]

	individuals under treatment			
μ^{t*}	death rate in individuals under treatment	0.039 (0.031–0.051)	0.031 (0.022–0.043)	trial data [13]
$f*$	lost to follow-up rate	0.006 (0.003–0.013)	0.01 (0.006–0.018)	trial data [13]
$\rho*$	relapse rate	0.019 (0.012–0.029)	0.019 (0.011–0.032)	trial data [13]

Table 1. Table of parameters. Priors are the calibration inputs while posteriors are the calibration outputs. All values were adjusted through calibration using confidence intervals sourced through literature or trial results. In the baseline scenario considered during calibration, intervention coverage was set to 0.

Initialisation

The model was initialised in 2011 using the local national prevalence survey [1] which stated that in that year Ethiopia registered 146,172 cases of TB. Among these, 139,261 were new cases; 46,132 new smear-positive (33.1%); 49,037 new smear-negative (35.2%); 44,092 new extra-pulmonary TB (31.6%). The number of new TB cases among children (0-14 years old) accounted for 10.5% of the total new cases (14,710). The authors estimated a total smear-positive prevalence of 145 (98–187) cases per 100,000 people, and a total smear-negative prevalence of 108 (72-138) cases per 100,000. Our model did not include extra-pulmonary TB, thus following these estimations we assumed smear positive to account for 48.5% of all TB cases.

To initialise the number of infections (early and late TB infection) we used estimations from [14]. The total population was assumed to be 91,818,000 based on United Nations estimations [4].

Demographics

United Nation estimations were sourced to parametrise the population's demographics [4]. Between 2011 and 2021 the Ethiopian birth rate ranged between 22 and 36.5 births per 100,000 people. Similarly, mortality ranged between 5.4 and 9 deaths per 100,000 people. This led to a steady increase of the total population, reaching approximately 120 million in 2021.

In these estimate [4] population numbers were reported by 5-years age groups, thus we used 2011 values to estimate the rate of moving between the two age strata (i.e. ageing between 14 and 15 years old) as 0.059.

Natural History

In Ragonnet et al. [6] yearly TB-specific mortality rates were estimated as 0.389 (95% credible interval [CrI], 0.335 – 0.449) and 0.025 (95% CrI, 0.017 – 0.035) for smear-positive and smear-negative TB, respectively. Using 48.5% smear-positive prevalence from Ethiopia's 2011 survey we estimated the TB natural death rate (without treatment) as 0.202 (0.171 – 0.236).

Similarly, estimates for self-recovery rates from [6] were 0.231 $year^{-1}$ (95% CrI, 0.177 – 0.288) and 0.130 $year^{-1}$ (95% CrI, 0.073 – 0.209) for smear-positive and smear-negative TB, respectively. Using 48.5% smear-positive prevalence from Ethiopia's 2011 survey we estimated the self-recovery rate as 0.179 (0.123 – 0.247).

Natural progression from early infection, to late infection and active TB was parametrised using values estimated in [5]. The impact of BCG vaccination for children was taken into account by considering a 70% vaccination coverage [15] and 71% protection against active TB disease [3] in the 0-14 age group only.

Calibration

The model was coded using R (v4.1.2) and calibration was performed through the History Matching and Emulation (hmer) package [16], which uses Bayes Linear emulation and history matching. We considered United Nations estimates of Ethiopian's population demographics [4] and calibrated to World Health Organization estimates of the incidence and mortality of pulmonary drug-sensitive TB [2]. Two transmission rates β_1 and β_2 were considered, to account for differences in contacts among the two age groups. The year of 2019 was chosen, instead of following years, as the end point for calibration, to avoid underestimating contagion due to the possible under-reporting of TB cases due to the COVID-19 pandemic. Calibration targets are shown in Table 2 and calibration results in Figure 2 (R^2 = 0.99).

Target	Year	Value (lower and upper bound)	Reference
TB incidence rate (per 100,000)	2012	1.674 (0.751 – 2.968)	Global Tuberculosis Report 2022 [2]
	2013	1.622 (0.766 – 2.782)	
	2014	1.532 (0.781 – 2.544)	
	2015	1.465 (0.952 – 2.083)	
	2016	1.391 (0.878 – 2.016)	
	2017	1.317 (0.870 – 1.860)	
	2018	1.250 (0.855 – 1.726)	
	2019	1.190 (0.833 – 1.599)	
TB mortality rate (per 100,000)	2012	0.30 (0.20 – 0.43)	Global Tuberculosis Report 2022 [2]
	2013	0.33 (0.22 – 0.46)	
	2014	0.33 (0.21 – 0.46)	
	2015	0.24 (0.16 – 0.32)	
	2016	0.23 (0.16 – 0.32)	
	2017	0.23 (0.15 – 0.32)	
	2018	0.20 (0.13 – 0.28)	
	2019	0.19 (0.12 – 0.26)	

Table 2. Calibration targets, all ages.

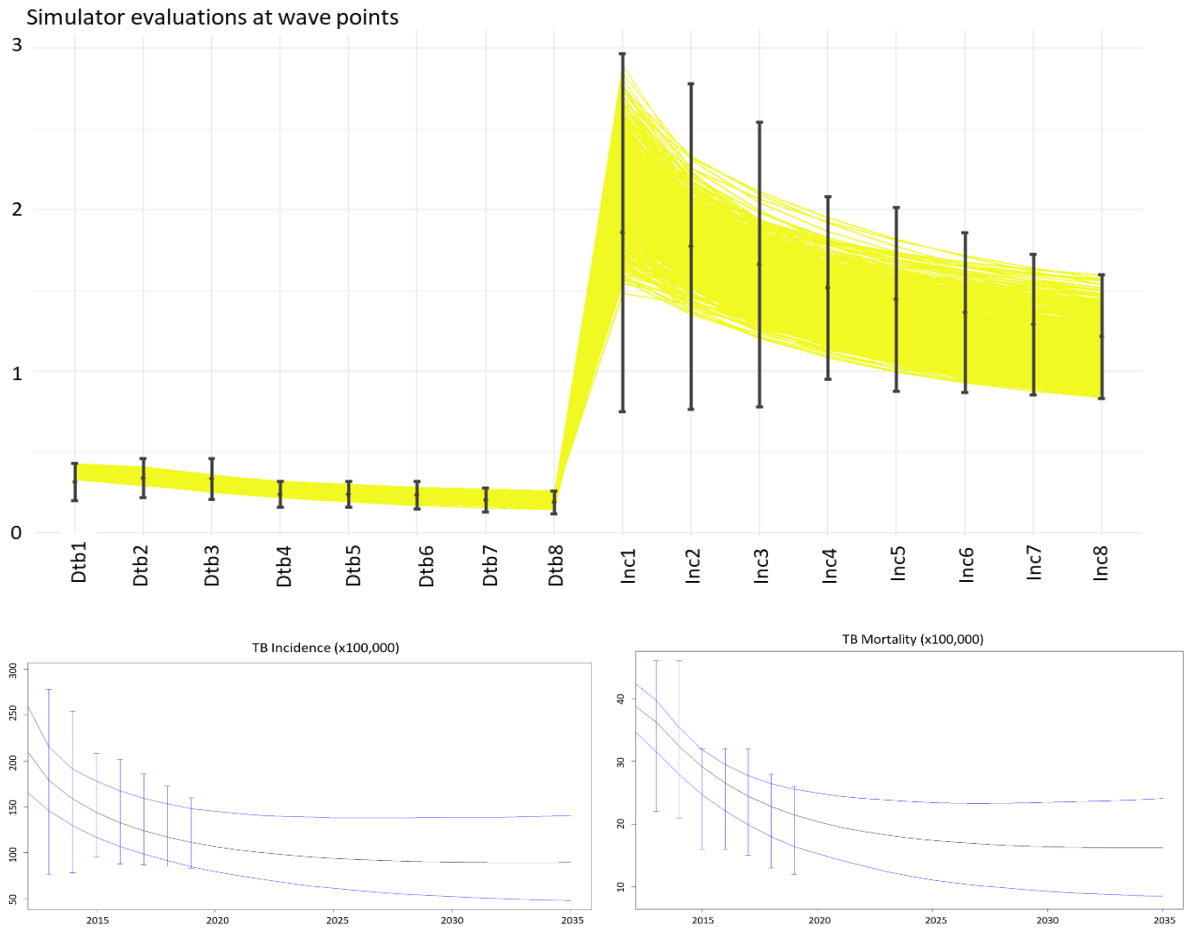

Figure 2. Calibration results (top) with modelling projections (bottom) to 2035. Incidence and death rates values x1000.

Cost-effectiveness analysis

We studied the long-term cost-effectiveness of the intervention compared to standard care. We projected outcomes of TB cases averted, TB deaths averted and LTFU cases averted until 2035. These were translated into costs and disability-adjusted life years (DALY) averted.

Costs included intervention costs from the provider perspective estimated in a post-trial scenario (see Supplementary Document S2), by considering technology costs, support costs and training costs. Additional costs estimated in [17] include: overheads such as facility-level expenditure, building space and equipment; TB treatment; staff costs including home visits; diagnostics including smear microscopy, culture test and chest x-ray; hospitalisation; patient-incurred costs such as transport and other out-of-pocket costs. Costs incurred by patients during treatment (estimated in [17]) were also accounted for, thus considering a societal perspective. These costs were summed

and then associated to modelling outcomes for each scenario in order to assess the cost-effectiveness of the interventions.

Incremental cost-effectiveness ratios (ICER) as incremental costs over DALYs averted were estimated where appropriate (that is, where both incremental costs and incremental DALYs averted were positive):

$ICER_{int} = (\sum cost_{int} - \sum cost_{SoC}) / (\sum DALY_{SoC} - \sum DALY_{int})$

where

$\sum cost_{int}$ and $\sum cost_{SoC}$ are the sum of the costs per patient associated with the intervention and standard of care (SoC) respectively, following the model's pathway.

These were calculated by first estimating (i) the total cost of fully treating one case of TB to completion, (ii) the total cost of treating one person with TB who does not complete treatment and is LTFU, (iii) the total cost of treating one person with TB who dies during treatment. Costs are considered from both a provider and a patient perspective in 2023 USD and can be found in Table 2.

Costs per patient were then multiplied by modelling results on yearly numbers of patients who completed treatment, died on treatment or were lost to follow-up, summed, and divided by the total yearly incidence of TB cases, with an annual discount rate of 3% [18] applied, to estimate yearly unit cost of single TB case. Costs are considered from both a provider and a patient perspective in 2023 USD and can be found in Table 3.

	Patient costs (sd) ($)	Provider costs (sd) ($)	Total costs (sd) ($)	Source
Standard of Care (SoC)				
Treatment completed	17.00 (12.40)	443.09 (294.50)	460.09 (294.76)	Foster et al. [17] and Supplementary Document 2
Death on treatment	10.32 (10.37)	326.62 (252.06)	336.94 (252.27)	
LTFU	15.76 (12.09)	555.94 (340.33)	571.71 (340.54)	
Pillbox intervention				
Treatment completed	12.97 (7.16)	217.52 (109.08)	230.44 (109.31)	Foster et al. [17] and Supplementary Document 2
Death on treatment	12.94 (6.99)	153.65 (92.95)	163.58 (93.44)	
LTFU	9.94 (9.59)	254.35 (98.57)	267.29 (98.81)	
Label intervention				
Treatment completed	12.81 (7.72)	194.51 (112.67)	207.323 (112.94)	Foster et al. [17] and Supplementary Document 2
Death on treatment	8.89 (9.35)	133.00 (87.69)	141.895 (88.19)	
LTFU	11.89 (6.26)	244.67 (92.19)	256.560 (92.40)	

Table 3. Patient, provider, and total costs per patient, per treatment outcome, and standard deviation.

$DALY_{int}$ and $DALY_{SoC}$ are the total number of DALYs for interventions and standard of care respectively, and were estimated according to the following formula:

$DALY = YLL + YLD*dw$

where *YLL* are the years of life lost and *YLD* are the years of life with disability and *dw* is the disability weight. YLD*dw was estimated as 0.17 per patient for the three arms (i.e. standard of care, pillbox and label) following the same method as in the health economics trial analysis [17], i.e. by considering the average time spent on treatment (including recurrence or drug-resistant

tuberculosis, ~0.51 years) multiplied by the global burden of disease (GBD) disability/utility weight for tuberculosis disease (0.33) [19]. This was then multiplied by the yearly number of people on treatment estimated by the model. YLL were estimated by multiplying the future life expectancy (39 years) for someone in Ethiopia aged 38, the average age of people treated for TB, by the yearly number of deaths estimated by the model, discounting at 3% as for costs.

The cost-effectiveness threshold (CET) range was estimated from Ochalek et al. [20]. Ochalek estimated willingness to pay thresholds for Ethiopia, and reported them as a percentage of the country's GDP in 2015. Ochalek used four different methods to estimate the threshold, obtaining four different results. We therefore considered the full range of possible thresholds from lowest to highest (27-36% of GDP) and applied these percentages to the latest Ethiopian GDP per capita ($1,027.6 in 2022), obtaining $277-370.

Additional sensitivity analysis

We performed univariate sensitivity analysis to inform the impact of patient-level adoption of DAT on the interventions' yearly costs. We considered an increased linear scale-up of costs through the following four strategies: (1) 20% DAT uptake and 80% SoC; (2) 50% DAT and 50% SoC; (3) 80% DAT and 20% SoC; and (4) 100% DAT and 0% SoC. We estimated the total cost in 2023, and compared them with the baseline scenario of 100% SoC (no DAT intervention). Results in Table 4 show that even a small uptake of either DAT intervention can save costs, from 9.93% of costs saved in the 20% pillbox intervention uptake and 80% SoC strategy, to 54.77% costs saved in the 100% label uptake strategy, when compared to standard of care alone.

	Total costs (million $) 0% DAT + 100% SoC	Total costs (million $) 20% DAT + 80% SoC	Total costs (million $) 50% DAT + 50% SoC	Total costs (million $) 80% DAT + 20% SoC	Total costs (million $) 100% uptake + 0% SoC
Pillbox intervention	0	2.80 (1.55; 3.70)	6.99 (3.88; 9.26)	11.19 (6.21; 14.82)	13.99 (7.76; 18.52)
Label intervention	0	2.51 (1.70; 3.34)	6.28 (4.25; 8.36)	10.05 (6.79; 13.37)	12.57 (8.49; 16.71)
Standard of Care (SoC)	27.79 (18.87; 36.62)	22.23 (15.10; 29.30)	13.90 (9.44; 18.31)	5.56 (3.77; 7.33)	0
Total (Pillbox + SoC)	27.79 (18.87; 36.62)	25.03 (17.84; 32.37)	20.89 (15.46; 26.42)	16.75 (12.40; 21.20)	13.99 (7.76; 18.52)
Total (Label + SoC)	27.79 (18.87; 36.62)	24.75 (17.68; 31.94)	20.18 (14.83; 25.58)	15.61 (11.53; 19.77)	12.57 (8.49; 16.71)

Table 4. Total cost (with 95%UI) of the pillbox and label interventions in 2023 for different levels of intervention uptake.

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