Supplementary Materials:

Drivers and trajectories of resistance to new first-line drug regimens for tuberculosis.

Model Details

The 2-strain compartmental model of TB follows the transmission of a drug susceptible strain (DS-TB) and a drug resistant strain (DR-TB), with resistance defined as a reduced probability of cure upon treatment with a novel first-line regimen. We stratify individuals into 5 separate compartments: U: Uninfected; L_S: Latently infected with DS-TB; L_R: Latently infected with DR-TB; A_S: Active disease with DS-TB; and A_R: Active disease with DR-TB. Upon successful exposure to either TB strain (the rate of which is the product of the transmission parameter β and the number of individuals with active TB resulting from the strain in question, divided by the population size, i.e., a density-dependent process), individuals progress either to active TB disease or latent TB infection. The probability of "primary progression" to active TB is given by p and includes all individuals who develop active TB within five years of infection, as estimated by Vynnycky and Fine from historical data in England and Wales [29]. The strain specific forces of infection are represented by $\lambda_S = \beta\, A_S$ for DS-TB and $\lambda_R = f\,\beta\, A_R$ for DR-TB, where β is the transmission rate, and f is the relative transmission fitness of the DR-TB in comparison to DS-TB. Only the individuals with active TB are considered infectious.

Latently infected individuals can progress to active TB through endogenous reactivation, at a *per capita rate* ϕ, or by reinfection according to the process described above. Based on historical data by Sutherland et al [33] and reviewed more recently by Andrews et al [36], individuals with latent TB infection are assumed to have a degree of partial protection against successful reinfection, $1-\xi$. Successful reinfections are assumed to have similar probability p of "primary progression" to active disease, which if such event occurs, will result in active TB with the new (superinfecting) strain. Among individuals who are successfully reinfected with the opposite strain but whose reinfection event does not result in primary progression, the probability of latent TB being drug-susceptible vs. drug resistant (ie, on endogenous reactivation) is given by the relative fitness of the two strains. Mixed-strain infections (in which individuals are simultaneously infection with both strains) are therefore not explicitly allowed.

Individuals with active TB disease are assumed to be diagnosed and begin treatment after an average duration of $1/\omega$ for active, infectious disease, before accounting for competing rates of mortality (increased in the active TB state) and spontaneous cure. Upon diagnosis and initiation of treatment, the probability of a successful treatment is taken to be $1-k_s$ and $1-k_r$ for DS-TB and DR-TB, respectively. Successful treatment is modeled as a return to the latent compartment, whereas unsuccessful treatment is modeled as remaining in the infectious, active TB state. After calculating mortality rates, we maintain a stable population by matching overall birth and death rates. The following set of differential equations describe the model:

$$\begin{aligned}
\frac{\mathrm{d}U}{\mathrm{d}t} &= \mu_L\,[L_S + L_R] + \mu_A\,[A_S + A_R] - \lambda_S\,U - \lambda_R\,U \\
\frac{\mathrm{d}L_S}{\mathrm{d}t} &= (1-p)\,\lambda_S\,[U + \xi\,L_R] - (\phi + \mu_L + p\,\xi\,\lambda_S + \xi\,\lambda_R)\,L_S + \omega\,(1-k_s)\,A_S \\
\frac{\mathrm{d}L_R}{\mathrm{d}t} &= (1-p)\,\lambda_R\,[U + \xi\,L_S] - (\phi + \mu_L + p\,\xi\,\lambda_R + \xi\,\lambda_S)\,L_R + \omega\,(1-k_r)\,A_R \\
\frac{\mathrm{d}A_S}{\mathrm{d}t} &= p\,\lambda_S\,[U + \xi\,(L_S + L_R)] + \phi\,L_S - [\omega\,(1-k_s) + \mu_A]\,A_S - \epsilon\,\omega\,A_S \\
\frac{\mathrm{d}A_R}{\mathrm{d}t} &= p\,\lambda_R\,[U + \xi\,(L_S + L_R)] + \phi\,L_R - [\omega\,(1-k_r) + \mu_A]\,A_R + \epsilon\,\omega\,A_S
\end{aligned}$$

Effective Reproductive Ratio

The algebraic expression of the effective reproductive ratio, R_{EFF} [39] is as follows:

$$R_{\mathsf{EFF}} = \frac{\Psi\,[\phi + p\,(\mu_L + \xi\beta\,A_S^*)]}{[\mu_L + \xi\beta\,A_S^*]\;[\mu_A + \omega\,(1-k_r)] + \phi\,\mu_A},$$

where, $\Psi = f\,\beta\,[U^* + \xi\,L_S^*]$. Here, U^*, L_S^*, and A_S^*, are respectively, equilibrial levels of uninfected, latent TB, and active TB populations when only the drug-susceptible form of TB is circulating. In the full form, they are as follows:

$$A_S^* = \frac{-Q_B \pm \sqrt{Q_B^2 - 4Q_AQ_C}}{2Q_A}, \qquad L_S^* = \frac{[(1-p)\,(\mu_A) + \omega\,(1-k_s)]\;A_S^*}{\phi + p\,(\mu_L + \xi\,\beta\,A_s^*)}, \qquad U^* = N - A_S^* - L_S^*.$$

The coefficient of the quadratic equation corresponding to the solution of A_S^* are :

$$Q_A = p\,\xi\,\beta^2$$
$$Q_B = \beta\,\left[-N\,p\,\xi\,\beta + p\,\xi\,(\mu_A) + (1-p)\,(\mu_A+) + \omega\,(1-k_s) + \phi + \mu_L\,p\right]$$
$$Q_C = -N\,\beta\,(\phi + \mu_L\,p) + (\mu_A)\,\phi + \mu_L\,[(\mu_A) + \omega\,(1-k_s)]$$

When $\xi = 0$, ie, there are no reinfections, the effective reproductive ratio reduces to the following form:

$$R_{\mathsf{EFF}} = \frac{R_{0,R}}{R_{0,S}}$$

where, $R_{0,S}$ and $R_{0,R}$ are, respectively, the basic reproductive ratios for DS-TB and DR-TB.

$$R_{0,S} = \frac{N\,\beta\,(\phi + p\,\mu_L)}{\mu_A\,(\mu_L + \phi) + \mu_L\,\omega\,(1-k_s)}$$

$$R_{0,R} = \frac{N\,f\,\beta\,(\phi + p\,\mu_L)}{\mu_A\,(\mu_L + \phi) + \mu_L\,\omega\,(1-k_r)}$$

Derivation of Effective Reproductive Ratio

We consider the dynamics of infections with the drug-resistant TB (DR-TB) in a population that is at equilibrium with the drug-susceptible TB (DS-TB). Let the non-negative, non-trivial, drug resistance free equilibrium be DRFE $= \{U = U^*,\ L_S = L_S^*,\ A_S = A_S^*,\ L_R = 0,\ A_R = 0\}$. Note that the model itself does not lend to this equilibrium, because of the presence of acquisition driven resistance even in the absence any resistance in the population. We interpret this equilibrium, DRFE to exist in the absence of such acquisition, ie, with $\epsilon = 0$.

We follow methods described by van den Driessche & Watmough[39] to derive the expression of R_{EFF}. Let $\mathbf{X}$ be the number of individual in each of the 5 compartments of the model, $(L_R, A_R, U, L_S, A_S)^t$, ordered such that the first two are compartments where the "infected" reside. We consider the two compartments of the model, L_R and A_R, as the compartments carrying "infected" individuals, since we are only interested in the infections with the drug resistant strains. Let $\mathcal{F}_i(x)$ be the rate of inflow of new infections into compartment i, and $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$, where $\mathcal{V}_i^-(x)$ and $\mathcal{V}_i^+(x)$are respectively, rates of out-and in-flows out and in to compartment i by other means (ie, flows excluding the ones considered as new infections).

$$\mathcal{F} = \begin{pmatrix} (1-p)\, f\, \beta\, A_R\, [U + \xi\, L_S] \\ p\, f\, \beta\, A_R\, [U + \xi\, L_S] + \epsilon\, \omega\, A_S \\ 0 \\ 0 \\ 0 \end{pmatrix} \text{ and,}$$

$$\mathcal{V} = \begin{pmatrix} [\phi + \mu_L + p\,\xi\, f\, \beta\, A_R + \xi\, \beta\, A_S]\, L_R - \omega\, (1 - k_r)\, A_R \\ -[p\, f\, \beta\, A_R\, \xi + \phi]\, L_R + [\omega\, (1 - k_r) + \mu_A]\, A_R \\ -[\mu_L\, [L_S + L_R] + \mu_A\, [A_S + A_R]] + \beta\, A_S\, U + f\, \beta\, A_R\, U \\ -(1-p)\, \beta\, A_S\, [U + \xi\, L_R] + (\phi + \mu_L + p\,\xi\, \beta\, A_S + \xi\, f\, \beta\, A_R)\, L_S - \omega\, (1 - k_s)\, A_S \\ -p\, \beta\, A_S\, [U + \xi\, (L_S + L_R)] - \phi\, L_S + [\omega\, (1 - k_s) + \mu_A]\, A_S + \epsilon\, \omega\, A_S \end{pmatrix}$$

Let, $F = \left.\dfrac{\partial \mathcal{F}_i}{\partial x_j}\right|_{\text{DRFE}}$ and $V = \left.\dfrac{\partial \mathcal{V}_i}{\partial x_j}\right|_{\text{DRFE}}$ for i, j that belong to the "infected states", ie L_R and A_R.
This leads to following 2×2 matrices for F and V.

$$F = \begin{bmatrix} 0 & (1-p)\, f\, \beta\, [U + \xi\, L_S] \\ 0 & p\, f\, \beta\, [U + \xi\, L_S] \end{bmatrix}_{\text{DRFE}} \text{ and}$$

$$V = \begin{bmatrix} [\phi + \mu_L + p\,\xi\, f\, \beta\, A_R + \xi\, \beta\, A_S] & -\omega\, (1 - k_r) + p\,\xi\, f\, \beta\, L_R \\ -p\, f\, \beta\, A_R\, \xi - \phi & [\omega\, (1 - k_r) + \mu_A] - p\, f\, \beta\, \xi\, L_R \end{bmatrix}_{\text{DRFE}}$$

When evaluated at DRFE equilibrium, $\{U = U^*,\, L_S = L_S^*,\, A_S = A_S^*,\, L_R = 0,\, A_R = 0\}$,

$$F = \begin{bmatrix} 0 & (1-p)\, f\, \beta\, [U^* + \xi\, L_S^*] \\ 0 & p\, f\, \beta\, [U^* + \xi\, L_S^*] \end{bmatrix} \text{ and}$$

$$V = \begin{bmatrix} [\phi + \mu_L + \xi\, \beta\, A_S^*] & -\omega\, (1 - k_r) \\ -\phi & [\omega\, (1 - k_r) + \mu_A] \end{bmatrix}$$

The inverse of V is: $V^{-1} = \frac{1}{\det(V)} \begin{bmatrix} [\omega\, (1 - k_r) + \mu_A] & \omega\, (1 - k_r) \\ \phi & [\phi + \mu_L + \xi\, \beta\, A_S^*] \end{bmatrix}$,
where, determinant of V is $\det(V) = [\phi + \mu_L + \xi\, \beta\, A_S^*][\omega\, (1 - k_r) + \mu_A] - \phi\, \omega\, (1 - k_r)$

$$FV^{-1} = \frac{1}{\mathsf{det}(V)} \begin{bmatrix} \phi\,(1-p)\,f\,\beta\,[U^* + \xi\,L_S^*] & [\phi + \mu_L + \xi\,\beta\,A_S^*][(1-p)\,f\,\beta\,[U^* + \xi\,L_S^*]] \\ \phi\,p\,f\,\beta\,[U^* + \xi\,L_S^*] & [\phi + \mu_L + \xi\,\beta\,A_S^*][p\,f\,\beta\,[U^* + \xi\,L_S^*]] \end{bmatrix}$$

The eigenvalues of FV^{-1}, $\lambda_{1,2}$ satisfy the characteristic equation, $\mathsf{det}(FV^{-1} - \lambda\,\mathsf{I}) = 0$. In this case, the characteristic equation is:

$$\lambda^2 - \mathsf{tr}(FV^{-1})\lambda + \mathsf{det}(FV^{-1}) = 0,$$

where $\mathsf{tr}(FV^{-1})$, and $\mathsf{det}(FV^{-1})$ are, respectively, the trace and the determinant of the matrix FV^{-1}. Since, the determinant of FV^{-1}, $\mathsf{det}(FV^{-1}) = 0$, the only non-zero eigenvalue is the trace of the matrix FV^{-1}. This is also the R_{EFF} of DR-TB.

$$\lambda = \frac{\phi\,(1-p)\,f\,\beta\,[U^* + \xi\,L_S^*] + [\phi + \mu_L + \xi\,\beta\,A_S^*][p\,f\,\beta\,[U^* + \xi\,L_S^*]]}{\mathsf{det}(V)}$$

$$\lambda = \frac{f\,\beta\,\left[U^* + \xi\,L_S^*\right]\left[\phi + p\,(\mu_L + \xi\beta\,A_S^*)\right]}{\left[\mu_A + \omega\,(1-k_r)\right]\,\left[\mu_L + \xi\beta\,A_S^*\right] + \phi\,\mu_A}$$

The drug-resistance free equilibrium can be found by solving for the model without the states L_R and A_R, and taking $\epsilon = 0$.

We note that the presence of density-independent (density of A_R) acquisition of resistance, ϵ, causes the effective reproductive ratio, R_{EFF}, as derived and defined above, to differ from the invasion criterion, R_{INV}, such that when $R_{\mathsf{INV}} > 1$, the DR-TB is capable of invading a population at equilibrium with DS-TB and (given sufficient time) replacing DS-TB as the dominant population. Specifically, while R_{EFF} is independent of ϵ, R_{INV} is dependent on it, resulting in a scenario where for $\epsilon > 0$, $R_{\mathsf{INV}} > R_{\mathsf{EFF}}$, and invasion with the resistant form is possible even when $R_{\mathsf{EFF}} < 1$. Thus, $R_{\mathsf{EFF}} > 1$ is always sufficient for invasion, but is not necessary: if the acquisition rate ϵ is sufficiently high to compensate for a reduction in the effective reproduction, DR-TB can still supplant DS-TB at the population eventually.

Parameter ranges			% DR-TB at 50 years						
Parameter	Range	Incidence	Baseline	Scenario I	Scenario II	Scenario III	Recent infection dominant	Reactivation dominant	85% treatment success
β, rate of transmission	7.36 6.26-9.94	150 75-300	3.97 3.31-5.19	7.68 6.41-10.00	8.90 5.96-17.73	15.46 9.74-32.43	6.60 5.63-6.50	2.45 2.40-2.56	1.87 1.71-2.10
p, fraction of infections resulting in rapid progression	0.14 0.11-0.18	150 75-300	3.97 3.20-5.19	7.68 6.20-10.00	8.90 5.53-18.73	15.46 8.83-35.12	6.60 5.25-6.49	2.45 2.37-2.59	1.87 1.68-2.09
ω, rate of treatment	1.00 1.18-0.78	150 75-300	3.97 3.62-4.22	7.68 7.00-8.17	8.90 6.92-11.35	15.46 12.43-17.31	6.60 6.51-5.63	2.45 2.46-2.40	1.87 1.79-1.92
ϕ, endogenous rate reactivation	0.0015 0.0009-0.0027	150 75-300	3.97 3.90-4.06	7.68 7.52-7.86	8.90 9.00-8.68	15.46 16.32-14.33	6.60 NA-5.61	2.45 2.39-2.57	1.87 1.83-1.93

Table 2: One-way model sensitivity to key model parameters. The model sensitivity to each parameter is presented as the variation in 50 year projections of % DR-TB in each of the scenarios considered, when the parameter is varied such that the resulting overall TB incidence varies from 75 to 300 per 100,000 per year. The baseline scenario is described by the parameters given in Table 1. Scenarios I, II and III, respectively describe scenarios where acquisition rate is doubled from baseline, relative transmission is increased by 25% from the baseline, and treatment differential is increased by 20% from the baseline (See Fig. 3). 85% treatment success describes a scenario where treatment success of DR-TB reaches 85% (See Fig. 4). Recent-infection dominant and reactivation dominant describe scenarios where ratio of transmission and reactivation rate are altered from the baseline such that 5% and 80% of the active cases occur via reactivation, respectively (See Fig. 6). In these latter two scenarios, the parameter values commensurate to incidence levels of 75 and 300 per 100,000 per year are different and separately calculated; note that the reactivation rate cannot be taken down sufficiently low to result in an incidence of 75 per 100,000 per year without concomitant reductions in one of the other parameters above (tabulated as NA).

Additional Results

Relationship between emergence of drug resistance and pre-existing resistance levels

Here we consider a scenario where there is pre-existing drug resistance, when a new drug regimen is introduced. In a population with pre-existing drug resistance at 2% (similar to current prevalence of fluoroquinolone monoresistance), the level of resistance at 5 years were modestly higher compared to settings in which there was no pre-existing DR-TB (Figure S-1A, brown and black dashed lines). But this difference disappeared entirely by 50 years (Fig. S-1A, solid lines; Figs. S-1B,C, solid bars). These results are consistent when we consider changes with respect to relative transmission fitness f and acquisition rate ϵ.

Trends in the strength of associations between proportion of DR-TB and various model parameters.

In addition to partial (Pearson) correlation coefficients (PCC), which are presented in the main text, we also calculated partial rank correlation coefficients (PRCC), for all of the model parameters (excluding the pure demographic parameters, the population size and the background mortality rates). While the PCCs assume linearity in the correlation between parameter value and DR-TB proportion, PRCCs assume linearity in the correlation between the rankings of parameter value (which represent a uniform distribution due to Latin Hypercube Sampling) and rankings of DR-TB prevalence (which may not be uniformly distributed) across simulations.

Shown in Fig. S-2 are partial ranked correlation coefficients (PRCC) across time (in the horizontal axis), for each of the 10 model parameters presented row-wise. The values in parentheses below the parameter represent the range between which the respective parameters are varied across. Trends in these correlation coefficients are similar to PCCs shown in the main text, with the most important long-term determinants of DR-TB proportion being the relative fitness of DR-TB (f) and the differential in treatment success comparing DR-TB and DS-TB (Δk). Of note, the probability of acquired resistance (ϵ) is initially strongly associated with the proportion of DR-TB, but this correlation diminishes somewhat over time. This diminishing correlation is more pronounced in the Pearson correlation coefficients, which more directly show the relationship between the parameter value and the outcome value.

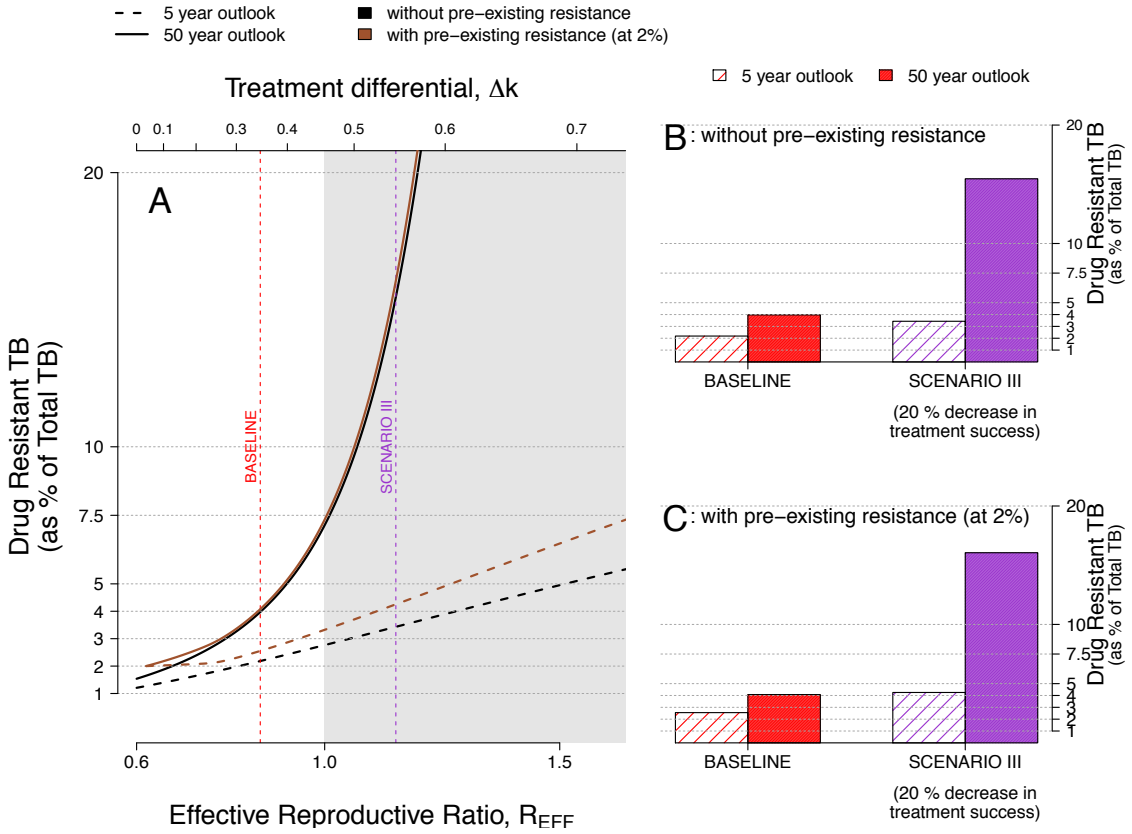

Figure S-1: Emergence of a DR-TB bacterial population that is pre-existing at the time of rolling out of a novel TB drug regimen. [A] Comparison of 5- and 50-year trajectories of proportion of DR-TB in a population (lower [black]) with no pre-existing resistance and a population (upper [purple]) with pre-existing resistance at 2% (i.e, 2% of all TB are DR-TB), similar to the prevalence of fluoroquinolone monoresistance in modern populations. Trajectories are plotted as a function of the treatment success differential, analogous to Fig. 3. To simulate pre-existing resistance of 2%, we advance the model with no pre-existing resistance until the proportion of DR-TB reaches 2%, and then project 5 and 50 year trajectories from this time point. We compare the baseline scenario with an alternative scenario (Scenario III from Fig. 3) where the treatment success probability for DR-TB is reduced by an absolute 20%. Panels B and C show projections under the baseline and scenario III assumptions for populations without (B) and with (C) pre-existing resistance. Although the 5-year trajectories have minor differences, the 50-year trajectories are nearly identical, regardless of whether resistance is pre-existing or not.

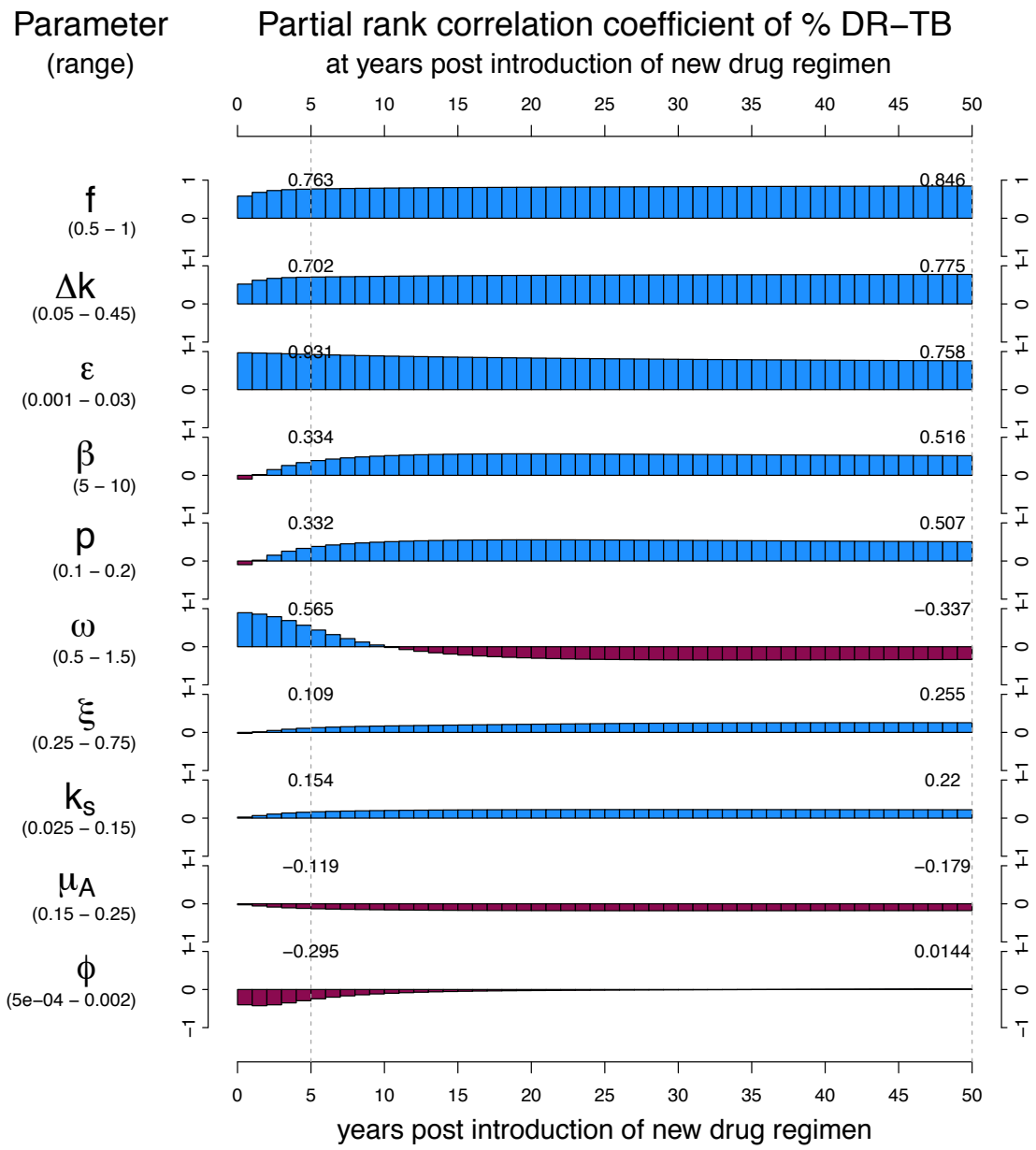

Figure S-2: Trends in partial rank correlation coefficients (PRCC) between parameters and DR-TB proportion over time. Plotted are the partial rank correlation coefficients with DR-TB proportion at each of the first 50 years after the introduction of a new drug regimen, for each of the parameters indicated on the left column. The complete description of the parameter corresponding to the symbol can be found on Table 1. Numerical values indicated on the graphs represent PRCC at years 5 and 50.

The effect of the drivers on the prevalence of DR-TB.

The outcomes in the main text were presented in terms of the proportion of DR-TB among all active TB cases. Alternatively, one may look at outcomes in terms of the raw prevalence of DR-TB. Fig. S-3 shows the projected prevalences of DR-TB at 5 and 50 years after the launch of a new drug regimen, corresponding to Fig. 3 in the main text. Fig. S-4 shows DR-TB prevalence projections, with higher levels of treatment success for DR-TB, corresponding to Fig. 4 in the main text. These figures show that outcomes in terms of the raw prevalence of DR-TB, are remarkably similar to outcomes in terms of proportion of DR-TB among active TB cases. While, in general prevalence patterns of DR-TB need not resemble patterns of proportion of DR-TB, in the scenarios we have explored, where the prevalence of TB is generally stable, the two measures of outcomes show similar patterns.

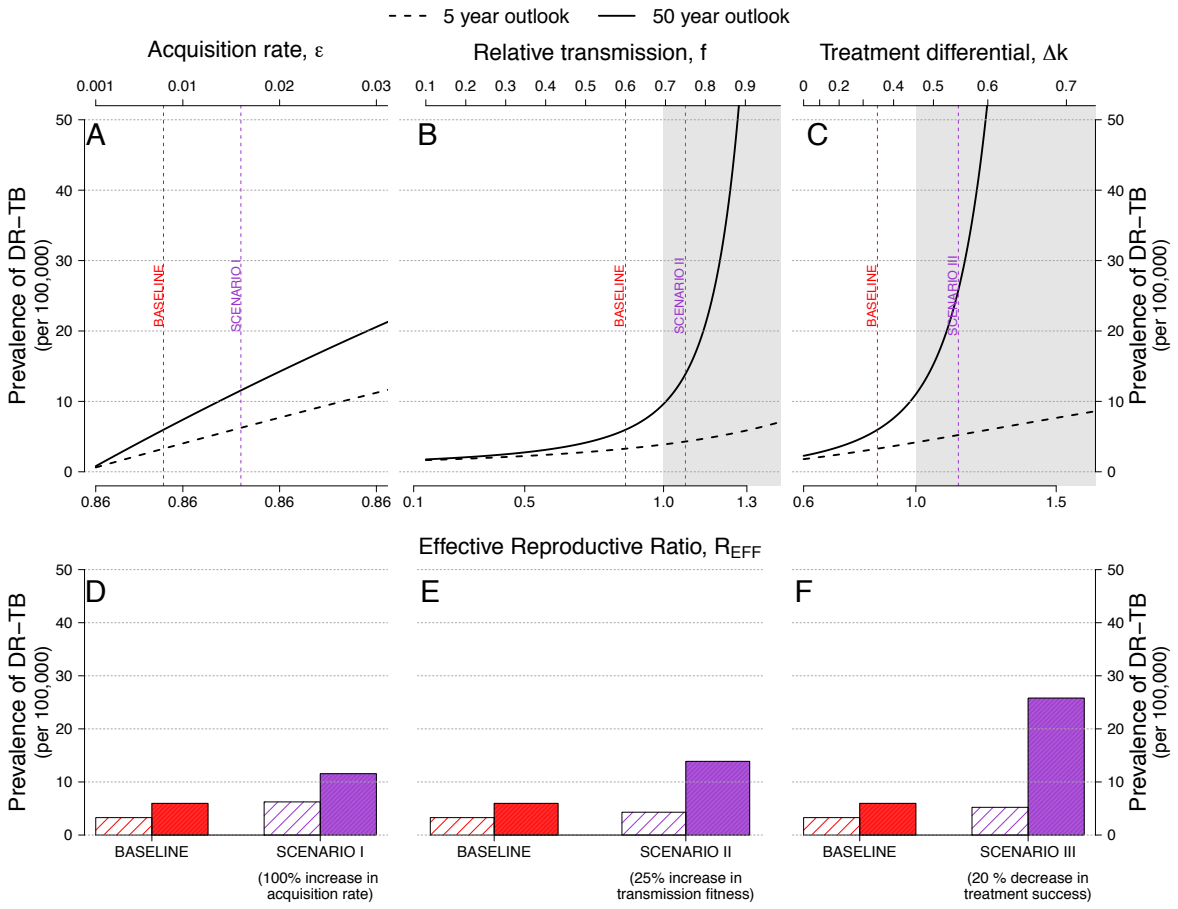

Figure S-3: Variation in 5 and 50 year projections of DR-TB prevalence as a function of the acquisition rate, relative transmission, and treatment differential. (comparable to Fig. 3 in main text). Plotted are projections of the prevalence of drug resistant TB (DR-TB) at 5 (- - -) and 50 years (——) after the introduction of a new first-line TB drug regimen. Changes from the baseline condition (dashed vertical red line) are achieved by sequentially varying [A] the probability of acquiring *de novo* resistance during treatment, ϵ; [B] the relative transmission fitness, f, of DR-TB (vs DS-TB); and [C] the absolute difference in treatment success for DR-TB vs. DS-TB, Δk. The shaded grey region indicates the parameter values which lead to an effective reproductive ratio of greater than 1. Three alternative scenarios are marked in purple: doubling the probability of *de novo* drug acquisition (Scenario I); increasing the transmission fitness of DR-TB by a relative 25% (Scenario II); and lowering the treatment success for DR-TB by an absolute 20% (Scenario III). As with proportion of DR-TB (in Fig. 3), Scenario I has a modest effect on both 5-year and 50-year projections, whereas Scenarios II and III (representing much smaller relative changes in corresponding parameter values) have little impact on 5-year projections but tremendous impact on the emergence of DR-TB at 50 years.

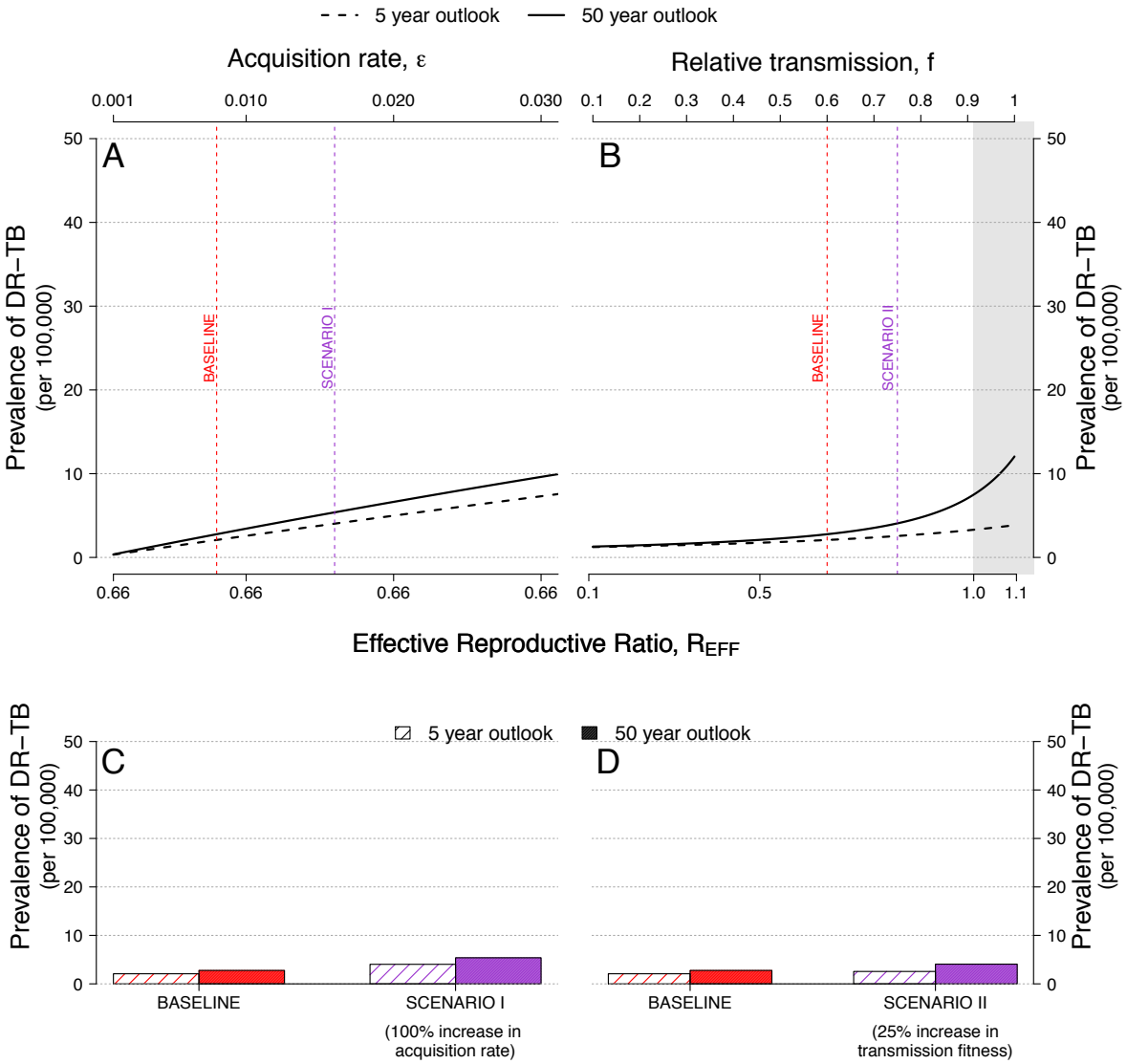

Figure S-4: 5 and 50 year projections of DR-TB prevalence with high levels of treatment success for DR-TB. (comparable to Fig 4 in ms). Plotted are projections of the prevalence of DR-TB at 5 (- - -) and 50 years (——) after the introduction of a new first-line TB drug regimen. This figure is corresponds to Fig. 3, but in the setting where the treatment success probability for DR-TB is 85% (equivalent to decreasing Δk to 0.1), representing a scenario in which DR-TB is rapidly detected with drug susceptibility testing, and then effectively treated with second-line drugs. As in Fig. 3, changes from the baseline condition (dashed vertical red line) are achieved by sequentially varying [A] the probability of acquiring *de novo* resistance during treatment, ϵ; and [B] the relative transmission fitness, f, of DR-TB (vs DS-TB). The shaded grey region indicates the parameter values which lead to an effective reproductive ratio of greater than 1. Two alternative scenarios are marked in purple. doubling the probability of *de novo* drug acquisition (Scenario I); and increasing the transmission fitness of DR-TB by a relative 25% (Scenario II). As with proportion of DR-TB (in Fig. 3), both scenarios result in low levels of DR-TB emergence even after 50 years, under the assumption of high DR-TB treatment success.