

1 **Introducing risk inequality metrics in tuberculosis policy**
2 **development**

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25

26 **ABSTRACT**

27 Global stakeholders including the World Health Organization rely on predictive
28 models for developing strategies and setting targets for tuberculosis care and control
29 programs. Failure to account for variation in individual risk leads to substantial biases
30 that impair data interpretation and policy decisions. Anticipated impediments to
31 estimating heterogeneity for each parameter are discouraging despite considerable
32 technical progress in recent years. Here we identify acquisition of infection as the
33 single process where heterogeneity most fundamentally impacts model outputs, due to
34 selection imposed by dynamic forces of infection. We introduce concrete metrics of
35 risk inequality, demonstrate their utility in mathematical models, and pack the
36 information into a risk inequality coefficient (RIC) which can be calculated and
37 reported by national tuberculosis programs for use in policy development and
38 modeling.

39

40 INTRODUCTION

41 Tuberculosis (TB) is a leading cause of morbidity and mortality worldwide,
42 accounting for over 10 million new cases annually¹. Although allusions are often
43 made to the disproportionate effect of TB on the poorest and socially marginalized
44 groups^{2,3}, robust metrics to quantify risk inequality in TB are lacking. Data reported
45 by the World Health Organization (WHO), which mathematical models often rely on
46 for calibrations and projections, are typically in the form of country-level averages
47 that do not describe heterogeneity within populations. In keeping with the spirit of the
48 Sustainable Development Goals agenda⁴, we postulate that mathematical models that
49 account for heterogeneity and inequality may best reflect the potential impact of TB
50 prevention and care strategies in achieving disease elimination. Further, we
51 hypothesize that disease incidence patterns in a population reflect unobserved
52 heterogeneity and may be used to inform model development and implementation.

53 Variation in individual characteristics has a generally recognized impact on the
54 dynamics of populations, and pathogen transmission is no exception⁵. In infectious
55 diseases, heterogeneities in transmission have been shown to have specific effects on
56 the basic reproduction number, R_0 , in ways which are unique to these systems⁶⁻¹⁰. In
57 TB, as in other communicable diseases, this approach motivated the proliferation of
58 efforts to collect data on contact patterns and superspreading events, to unravel
59 processes that may affect transmission indices and models. The need to account for
60 variation in disease risk, however, is not unfamiliar in epidemiology at large, where
61 so-called frailty terms are more generally included in models to improve the accuracy
62 of data analysis¹¹. The premise is that variation in the risk of acquiring a disease
63 (whether infectious or not) goes beyond what is captured by measured factors

64 (typically age, malnutrition, comorbidities, habits, social contacts, etc), and a
65 distribution of unobserved heterogeneity can be inferred from incidence trends in a
66 holistic manner. Such distributions are needed for eliminating biases in interpretation
67 and prediction^{12,13}, and can be utilized in conjunction with more common reductionist
68 approaches, which are required when there is desire to target interventions at
69 individuals with specific characteristics.

70 Individual risk of infection or disease relates to a probability of responding to a
71 stimulus and, therefore, direct measurement would require the recording of responses
72 to many exposures to obtain the frequency at which the outcome of interest occurs. In
73 TB, this is unfeasible due to the relatively low frequency of disease episodes and the
74 extremely variable time period between exposure and disease development, but may
75 be approximated by sub-dividing the population in sufficiently large groups and
76 recording occurrences in each of them. Then incidence rates can be calculated per
77 group, and ranked. Supplementary Fig. 1 illustrates the population of a hypothetical
78 country comprising low and high risk individuals distributed geographically (but
79 dividing by age or income level, for example, applied singly or in combination, could
80 also serve our statistical purposes). Forasmuch as individuals are nonuniformly
81 distributed, disease incidence will vary between groups and carry information about
82 variation in individual risks.

83 Here we adopt concepts and tools developed in economics to measure inequality in
84 wealth, such as the Lorenz curve¹⁴ and the Gini coefficient¹⁵, and modify them into
85 suitable indicators of disease risk inequality. We then calculate a risk inequality
86 coefficient for three countries – Vietnam, Brazil and Portugal, representing high to
87 low TB burdens – and derive country-specific risk distributions to inform

88 transmission models. The resulting models are applied to investigate the conditions
89 for reducing TB incidence by 90% between 2015 and 2035, one of the targets set by
90 the WHO's End TB Strategy¹⁶. The results differ significantly from those obtained by
91 a homogeneous approximation of the same models. We find that by considering
92 heterogeneity, control efforts result in a lower impact on disease burden, except in
93 special circumstances which we highlight. More generally, we elucidate how model
94 predictability relies on certain forms of heterogeneity but not others, and propose a
95 practical scheme for summarizing inequality in disease risk to be used in modeling
96 and policy development for TB and other diseases.

97 **RESULTS**

98 **Risk inequality coefficient (RIC)**

99 Fig. 1 depicts Lorenz curves¹⁴ for TB occurrences in the populations of Vietnam,
100 Brazil and Portugal structured by municipalities (level 2 administrative divisions),
101 enabling the calculation of a Gini coefficient¹⁵ that we refer to as the risk inequality
102 coefficient (RIC) (Methods). To inform mathematical models of TB transmission with
103 two risk groups^{12,17}, we discretize risk such that 4% of the population experiences
104 higher risk than the remaining 96%. This cut-off is consistent with previous
105 studies^{17,18}, although it could have been set arbitrarily as the procedure does not
106 depend on how we discretize what is conceivably a continuous risk distribution. The
107 Lorenz curves corresponding to the discretization, which are depicted by the dashed
108 lines in Fig. 1a, are then used as an approximation to the original solid curves with the
109 same RIC.

110 **RIC-compliant transmission models**

111 Inequality in TB risk among individuals was implemented in three processes which
112 were analyzed in alternation (Methods; parameters in Table 1): (i) contact rates; (ii)
113 susceptibility to infection; and (iii) progression from primary infection to active
114 disease. This study is primarily devoted to heterogeneity in contact rates, while the
115 other two modalities are included for comparative purposes. Although the models
116 differ in the precise implementation of the relative risk parameters (α_1 and α_2), in all
117 three cases these can be calculated exactly and simultaneously with the mean
118 effective contact rate (β), so as to match the country-specific incidence patterns
119 reported for the first year in the data series.

120 The procedure was applied to data from Vietnam, Brazil and Portugal (Fig. 2, for
121 heterogeneous contact rates), resulting in risk variances of 10.5 in Vietnam, 11.1 in
122 Brazil and 5.63 in Portugal. Notice that these variances are consistently higher than
123 the observed variances in TB incidence (2.3 in Vietnam, 5.1 in Brazil and 2.7 in
124 Portugal), indicating that transmission masks risk heterogeneity to some extent and
125 we need to resort to models for the inference of total variances¹¹. Model outputs were
126 then analyzed in-depth revealing a poor predictive capacity of homogeneous models
127 and leading to the identification of acquisition of infection as the single most
128 important process behind model disparities.

129 The risk distributions represented inside the various epidemiological compartments in
130 Fig. 2b, e, h, are key to understanding why model outputs diverge. Mean risks have
131 been normalized to one in all countries (i.e. the distributions in Fig. 2a, d, g have
132 mean one), but as the system runs to endemic equilibrium high-risk individuals are
133 infected predominantly. In other words, high-risk individuals are selected out of the
134 uninfected compartment when a force of infection is in operation. As a result, the

135 mean risk in the uninfected compartment decreases, decelerating the epidemic to the
136 extent that the uninfected pool sustains transmission. This effect is greater for stronger
137 forces of infection and larger risk variances, consistently with the mean risks
138 displayed inside square brackets for the various epidemiological compartments. A
139 similar process occurs for all epidemiological compartment where individuals are at
140 risk of infection (i.e. uninfected (U) and latent (L) in the case of the model adopted
141 here).

142 **Risk inequality as a compromiser of intervention impact**

143 The heterogeneous contact-rate model initiated according to 2002 incidences (Fig. 2)
144 was run forward in time with a constant decay rate in reactivation to meet an arbitrary
145 fixed target of halving the incidence in 10 years (Fig. 3b, d, f, black curves). If these
146 estimations (exact calculations in this case) and projections had been made by the
147 homogeneous model, the required control efforts would have been underestimated
148 and the target systematically missed (Methods; Supplementary Table 1), with relative
149 errors around 20-30% for Vietnam, 25-40% for Brazil and 10-20% for Portugal
150 (colored curves). This is because the force of infection decreases as the intervention
151 progresses, reducing the strength of selection described above, which in turn allows
152 for increasing mean risks in compartments at risk of infection (Fig. 3a, c, e),
153 counteracting the intended effects of the intervention. Homogeneous models
154 artificially disable this selection process, creating an illusion that control targets are
155 moving when observed from a homogeneous frame.

156 This is a general phenomenon in infectious diseases, although there may be
157 exceptional circumstances where the sign of the effect may be reversed as detailed
158 below. In any case, it is a systematic error (bias) not to be confused with uncertainty

159 in parameter estimates^{19,20}.

160 **Meeting WHO's End TB incidence targets**

161 The models were used to reproduce reported country-level trends for TB incidence in
162 Vietnam, Brazil and Portugal. Following initialization in 2002 as above, the model
163 was fitted to the incidence declines reported by WHO until 2015. In the first instance
164 we explored how much reactivation should have decreased had the observed
165 incidence declines been attributed to changing this parameter alone at a constant rate
166 (Supplementary Table 2). This was performed numerically by a binary search
167 algorithm designed to meet 2015 incidences (Fig. 4). Trajectories were then
168 prolonged until 2050 (dashed segments in the same figure) suggesting the need for
169 increased efforts to meet the End TB incidence targets (2035 targets marked by dotted
170 lines). This initial exploration was completed by the introduction of a scale-up
171 parameter (κ) to account for increased reductions in reactivation from 2020 onwards
172 and estimating the necessary scaling to meet the 2035 target in each country
173 (displayed as “ $\times \kappa$ ” in the figure). As above, the homogeneous model consistently
174 underestimates the required control efforts. In the following we refer to this as the
175 *default* expectation when comparing the outcomes of the same investigation strategy
176 applied to more realistic scenarios where incidence declines are attributed to a
177 combination of parameters.

178 When incidence declines are attributed to reductions in the probability of progressing
179 from primary infection to active disease (ϕ , with the remaining $1 - \phi$ maintaining a
180 latent infection) as well as reactivation (ω), estimating the two decay rates is not
181 possible with a simple binary search algorithm and we use a Bayesian Markov Chain
182 Monte Carlo (MCMC) approach (Methods). Fig. 5 depicts the declining annual

183 incidences and model trajectories, based on the means and 95% credible intervals of
184 the posterior distributions of decay rates in ϕ and ω (Supplementary Table 3),
185 prolonged until 2020. Also in this scenario, control measures must be intensified for
186 meeting the ambitious End TB targets. We apply the scaling factor κ uniformly to the
187 decay rates of the two parameters and estimate the required effort intensification.
188 Heterogeneous contact-rate (Fig. 5a, c, e) and homogeneous (Fig. 5b, d, f) models are
189 similarly effective at capturing the data, but require significantly different scale-up
190 efforts (Supplementary Table 4). In contrast with the case where only reactivation was
191 reduced, we now get an indication that Brazil requires less effort intensification under
192 heterogeneity (in relation to that predicted by the homogeneous model) while
193 Vietnam and Portugal comply with the default expectation. Inspection into the percent
194 reduction curves for the two parameters reveals that scale-up tends to be more
195 effective when the initial decline (pre-scale-up) is predominantly attributed to
196 reducing reactivation (homogeneous in Vietnam and Portugal; heterogeneous in
197 Brazil).

198 Under heterogeneous contact rates, the incidence declines observed in Vietnam and
199 Portugal have been predominantly attributed to reducing progression to disease from
200 recent infection (Fig. 5a, e; bottom panels show blue curve above red in pre-scale-up
201 phase). Given the assumption of identical scaling factors for both processes, the
202 reduction in ϕ (blue) reaches saturation soon after scale-up is initiated leaving most of
203 the remaining effort to ω (red) and inflating the required scaling efforts.

204 Contrastingly, in Brazil the incidence decline has been largely attributed to reducing
205 disease arising from reactivation (Fig. 5c; bottom panel shows red curve above blue
206 pre-scale-up) leaving the reduction in ϕ far from saturation and creates a scenario
207 where reducing progression maintains substantial potential to generate further impact

208 after scaling.

209 Naturally, there is no reason for scale-up factors to be the same for the two processes,
210 and this result suggest that new ways to reduce reactivation are needed in Vietnam
211 and Portugal. In relation to that, it also raises the importance of understanding what
212 may have led to the declining reactivation rates in Brazil and how might other
213 countries achieve similar goals. More detailed datasets should be interrogated in
214 search for answers, but this is potentially due to especially intense social protection
215 programs implemented over recent decades in Brazil²¹⁻²⁵, leading to improved health
216 conditions in population segments classically more at risk for TB.

217 The parameters that have been most commonly varied to explain incidence trends in
218 modeling studies are rates of successful treatment (τ) and mean effective contacts
219 (β)²⁶. For completion and comparability with other studies we conceive additional
220 scenarios where the observed declines in incidence are attributed to decays in τ and
221 ω (Supplementary Fig. 2 and Supplementary Tables 5 and 7) or β and
222 ω (Supplementary Fig. 3 and Supplementary Tables 6 and 7), and infer the respective
223 attributions as above. In both cases the scaling in control efforts required to meet End
224 TB incidence targets appears lower under heterogeneity. This seems counter-intuitive
225 at first but see the values of R_0 plotted as insets in Figs. 4, 5 and Supplementary Figs.
226 2, 3. During the scale-up phase, this transmission index is consistently below one in
227 the homogeneous implementation and above one when heterogeneity is considered.
228 Since τ and β relate to ongoing transmission, scaling changes in these parameters is
229 not effective at reducing incidence when $R_0 < 1$ and, consequently, the homogeneous
230 implementations must rely on the reduction in ω alone to meet the targets. This
231 process results in the inflation of the scale parameter κ observed under homogeneity

232 and reversion of the default expectation. The sensitivity of our conclusions to which
233 parameters are actually varying in each setting reinforces the need for more
234 discriminatory data and dedicated studies.

235 Results presented so far addressed heterogeneity in contacts rates, which implicitly
236 considers that acquisition of infection is positively correlated with transmission to
237 others^{5,8,9,10,12,18}. But irrespective of how present heterogeneity in contact rates is in
238 TB dynamics, there is a myriad of biological factors which contribute to making
239 individuals different and may affect TB incidence patterns.

240 Fig. 6 (and Supplementary Table 8) shows the results obtained by employing the
241 same procedures as in Fig. 5 but assuming that heterogeneity affects susceptibility of
242 infection given exposure, rather than the rate of contacts. The two variants are in fact
243 described by the same model, except for how the force of infection is formulated
244 (Methods). Essentially, if we write the force of infection as $\lambda = \beta(\rho_1 I_1 + \rho_2 I_2)$,
245 where the new parameters ρ_1 and ρ_2 represent the relative infectivities of individuals
246 in risk groups 1 and 2, respectively, heterogeneity in contact rates¹² is retrieved when
247 $\rho_i = \alpha_i$ and heterogeneity in susceptibility¹⁷ is obtained by imposing $\rho_i = 1$, while a
248 combination of the two would correspond to values in between.

249 The agreement between Figs. 5 and 6 supports the notion that the results are mostly
250 insensitive to whether heterogeneity affects primarily contact rates or susceptibility to
251 infection, but the case of Vietnam deserves a special note. Under the heterogeneous
252 susceptibility formulation, the contribution of reducing reactivation to the decline in
253 incidence is more evident than under heterogeneous contact rates (Fig. 6b). As a result
254 the scaling factor required to meet the 2035 incidence target is substantially reduced.
255 This is not sufficient to reverse the default conclusion that the homogeneous model

256 underestimates control efforts (as it happens again in Brazil), but it brings the
257 estimated scaling factor closer to that estimated by the homogeneous model. It
258 follows that any combination of the two forms of heterogeneity is expected to lead to
259 the same qualitative conclusions, whereas, quantitatively, the findings for Brazil and
260 Portugal are confined to narrow ranges while for Vietnam they are highly sensitive to
261 how individual predisposition to acquire infection correlates with propensity to infect
262 others. In any case, all the results presented so far imply heterogeneity in acquisition
263 of infection.

264 The results presented are in stark contrast with forms of heterogeneity that do not
265 affect acquisition of infection. Fig. 7 (and Supplementary Table 9) shows that when
266 heterogeneity is in the probability of progression from primary infection to active
267 disease, model outputs do not deviate from the homogeneous implementation. This is
268 because progression is not under the selection mechanisms described earlier in the
269 paper, as demonstrated by the mean risk among susceptible compartments remaining
270 flat at the value one (Fig. 7b) by contrast with what has been noted under
271 heterogeneous contact rates, for example (Fig. 3a, c, e). Similarly, heterogeneity in
272 rates of reactivation or treatment success should generally not lead to different model
273 outputs unless correlated with predisposition for acquiring infection. This confirms
274 our earlier premise that variation in acquisition of infection is the single most
275 important process behind the disparities between homogeneous and heterogeneous
276 models, and hence the most important to estimate.

277 In further account to sensitivity analysis we show that the original results of Fig. 5 are
278 robust to whether individuals clear the infection upon treatment or maintain a latent
279 infection (Supplementary Fig. 4 and Supplementary Table 10).

280 **Prevalence of latent TB infection**

281 Prevalence of latent TB infection (LTBI) calculated from model trajectories generated
282 by our heterogeneous models (27.0-28.9% in Vietnam, 15.2-16.1% in Brazil, and
283 16.9-18.0% in Portugal, in 2014; Supplementary Table 11) are generally consistent
284 with estimates from a recent study²⁷. This is irrespective of whether heterogeneity is
285 in contact rates or susceptibility to infection. Even though these percentages are
286 somewhat smaller than those expected under the homogeneous model, the reservoir
287 must nevertheless be contained in all three countries if incidence targets are to be met.

288 **DISCUSSION**

289 The notion that heterogeneity affects the results of population models and analyses is
290 not new^{5,28-32}, but we still face a general inability to measure it. We propose a
291 concrete way forward for infectious disease transmission models, which is based on
292 routinely collected data. Measures of statistical dispersion (such as Lorenz curves¹⁴
293 and Gini coefficients¹⁵) are commonly used in economics to represent the distribution
294 of wealth among individuals in a country and to compare inequality between
295 countries, but rarely used in epidemiology^{33,34}. Measuring disease risk of an
296 individual is less direct than measuring income, but surely this can be overcome in
297 creative ways for classes of diseases.

298 We have focused on tuberculosis, and shown how to approximate distributions of
299 individual risk from suitably structured disease notification and population data (Fig.
300 1; Supplementary Fig. 1), and how to summarize the information into a simple risk
301 inequality coefficient (RIC = 0.30 in Vietnam, RIC = 0.46 in Brazil, and RIC = 0.32
302 in Portugal), analogous to the Gini coefficients calculated by the World Bank to
303 describe inequality in the distribution of wealth (0.38 in Vietnam, 0.51 in Brazil, and

304 0.36 in Portugal). Because they are based on the use of disease estimates at the level
305 of administrative divisions within countries, there are limits to the accuracy of the
306 RIC estimates, especially due to misreporting, which may be more severe in some
307 countries than others. Other uses of the Gini coefficient, however, face the similar
308 limitations while the methodology is still used to drive policy and program decisions
309 and is improved upon as better data and formalisms become available. Importantly,
310 the availability of comparable inequality metrics in economics and health can pave
311 the way to pertinent studies between income inequality and health and provide a basis
312 for equity considerations in policy development³⁵, a major component of the
313 Sustainable Development Goals agenda⁴. In addition, we have demonstrated how to
314 input this information into tractable mathematical models and why this is essential to
315 accuracy and predictive capacity of these decision-making tools.

316 The approach followed here is in sharp contrast with those based on explicit
317 metapopulation models³⁶⁻³⁸. We use incidence data of a country stratified into its
318 administrative (geographical) divisions as a means to infer variation in disease risk
319 among individuals, rather than as a direct measure of variation between the divisions
320 themselves. To highlight this distinction we built a metapopulation model consisting
321 of two subpopulations (patches), each with its intrinsic individual variation, and
322 constrain the outputs to be consistent with patch incidences (Methods; Supplementary
323 Fig. 5), according to data from our study countries (Fig. 1). This sets a mathematical
324 problem which can be solved over a range of country-level variances in individual
325 risk (Supplementary Figs. 6 and 7), and for each variance there is an exact value of R_0
326 that makes the metapopulation model compatible with the stratified incidence data.
327 The result is a curve describing R_0 as a function of variance in individual risk which
328 is plotted in Fig. 8 together with the corresponding metrics obtained from the models

329 used in this study (circles). The common practice of implementing a metapopulation
330 without individual variation within subpopulations (lower limit of the curve), disables
331 the action of selection at the individual level and carries similar biases to those
332 present in homogeneous models (open circles). As individual variation increases, the
333 curve approaches our heterogeneous models (filled circles), supporting the notion that
334 the models proposed in this paper represent the dynamics of an average location
335 within a country (with variation captured down to the individual level), in contrast
336 with standard metapopulation models which describe an entire country structured into
337 patches (with differentiation between patches but neglecting individual variation
338 within).

339 Strikingly, the figure highlights an essential need for representing heterogeneity at the
340 finest level if transmission indices are to be estimated accurately. In placing the
341 models adopted here in the wider context of TB models with the same structure
342 whose outputs are compatible with stratified incidence data for Vietnam, Brazil and
343 Portugal, the figure also reveals one potential limitation of the approach. The range of
344 variances (and associated R_0 values) compatible with the data is wide and this is
345 arguably the greatest current attrition to reaching high levels of certainty on
346 parameters and predictions. This can be improved by combining multiple schemes for
347 stratifying country incidence data alongside the development of more sophisticated
348 methods for inferring variation in individual risk from patterns in the data.

349 In conclusion, the worldwide adoption of risk inequality metrics, such as the RIC
350 proposed here or similar, has the potential to prompt an explosion of creativity in
351 mathematical modeling, but it can also enable policymakers to assess risk inequality
352 in each country, compare the metric across countries, and monitor the impact of

353 equalization strategies and targeted interventions over time.

354 **METHODS**

355 **Lorenz curves and risk inequality coefficients**

356 Lorenz curves¹⁴ are widely used in economics to calculate indices of inequality in the
357 distribution of wealth, known as Gini coefficients¹⁵. Although rarely used in
358 epidemiology, similar metrics can be adopted to describe inequalities in disease
359 risk^{33,34}. Here we construct a Lorenz curve for each study country from TB
360 notifications and population data structured by municipalities (level 2 administrative
361 divisions). Municipalities are ordered by incidence rates (from low to high) and
362 cumulative TB notifications are plotted against cumulative population (both in
363 percentages). By construction, this results in a convex curve between (0,0) and
364 (100,100), which would be a straight line in the absence of inequality. A risk
365 inequality coefficient (RIC) can be calculated as the ratio of the area between the
366 curve and the equality line, over the area of the triangle under the equality line. This
367 gives a number between 0 and 1, which is analogous to the Gini coefficient
368 commonly used to summarize income inequality, with the exception that while
369 income can be measured at the individual level the assessment of TB risk cannot be
370 made by analyzing individuals directly, but must be approximated from group
371 measurements.

372 Supplementary Fig. 8 compares alternative Lorenz curves generated for Vietnam,
373 Brazil and Portugal to explore the effects of timespan and group size. As we must
374 comply with the administrative divisions already established in each country, level 2
375 appears to offer the best compromise between resolution (the smaller the units, the
376 closer we get to measuring individual risk) and occurrences (the larger the units, the

377 larger the numbers and the more accurate the risk discrimination³⁹). Regarding
 378 timespan, the longer the data series the better. We used 10 years (2006-2015) in
 379 Vietnam and 14 years (2002-2015) in Brazil and Portugal to generate the respective
 380 RIC values.

381 We then use the RIC to inform risk distributions for TB transmission models. The
 382 Lorenz curves utilized to obtain RIC values consist of many segments (as many as
 383 administrative divisions; 696 in Vietnam, 5127 in Brazil and 308 in Portugal). To
 384 keep our models tractable and low dimensional without compromising the overall
 385 variance in risk we construct two-segment Lorenz curves with the same RIC as the
 386 original and use this approximation to infer risk distributions for our TB models.

387 **Mathematical models**

388 We adopt a TB transmission model which is adapted from previously published
 389 studies^{12,17}, to represent risk heterogeneity in three alternative ways.

390 (i) *Heterogeneity in contact rates:*

$$391 \quad \frac{dU_i}{dt} = q_i\mu + \theta\tau I_i - \lambda_i U_i - \mu U_i \quad (1)$$

$$392 \quad \frac{dP_i}{dt} = \lambda_i(U_i + L_i) - (\delta + \mu)P_i \quad (2)$$

$$393 \quad \frac{dI_i}{dt} = \phi\delta P_i + \omega L_i - (\tau + \mu)I_i \quad (3)$$

$$394 \quad \frac{dL_i}{dt} = (1 - \phi)\delta P_i + (1 - \theta)\tau I_i - \lambda_i L_i - (\omega + \mu)L_i, \quad (4)$$

395 where subscripts $i = 1,2$ denote low and high risk groups that individuals enter at birth
 396 in proportions q_1 and q_2 , respectively. Within each group individuals are classified,
 397 according to their infection history, into uninfected (U_i), or infected in one of three

398 possible states: primary infection (P_i); latent infection (L_i); and active tuberculosis
 399 disease (I_i) which is the infectious state. The model parameters along with their
 400 typical values used herein are listed in Table 1. The force of infection upon uninfected
 401 individuals is

$$402 \quad \lambda_i = \frac{\alpha_i}{\langle \alpha \rangle} \beta (\alpha_1 I_1 + \alpha_2 I_2), \quad (5)$$

403 where α_i is a modifier of risk (contact rate in this case) of individuals in group i in
 404 relation to the population mean $\langle \alpha \rangle = q_1 \alpha_1 + q_2 \alpha_2 = 1$, and the basic reproduction
 405 number is

$$406 \quad R_0 = \frac{\langle \alpha^2 \rangle}{\langle \alpha \rangle} \left[\frac{\omega + \mu}{\mu(\tau + \omega + \mu) + \theta\tau\omega} \right] \left[\frac{\phi\delta}{\delta + \mu} + \frac{(1 - \phi)\delta\omega}{(\delta + \mu)(\omega + \mu)} \right] \beta, \quad (6)$$

407 Where $\langle \alpha^2 \rangle$ is the second moment of the risk distribution, i.e. $\langle \alpha^2 \rangle = q_1 \alpha_1^2 + q_2 \alpha_2^2$.
 408 For simplicity we have assumed individuals to mix uniformly irrespectively of risk
 409 group.

410 (ii) *Heterogeneity in susceptibility to infection:*

411 When risk heterogeneity is attributed to susceptibility to infection the model is still
 412 written as in (1)-(4), but the force of infection upon uninfected individuals becomes

$$413 \quad \lambda_i = \alpha_i \beta (I_1 + I_2), \quad (7)$$

414 where α_i is the susceptibility of individuals in group i in relation to the population
 415 mean $\langle \alpha \rangle = q_1 \alpha_1 + q_2 \alpha_2 = 1$. The basic reproduction number for this model is

$$416 \quad R_0 = \langle \alpha \rangle \left[\frac{\omega + \mu}{\mu(\tau + \omega + \mu) + \theta\tau\omega} \right] \left[\frac{\phi\delta}{\delta + \mu} + \frac{(1 - \phi)\delta\omega}{(\delta + \mu)(\omega + \mu)} \right] \beta. \quad (8)$$

417 (iii) *Heterogeneity in progression from primary infection to disease:*

418 When risk heterogeneity is attributed to factors that affect the probability of progression

419 from primary infection to active disease, the model takes the form

$$420 \quad \frac{dU_i}{dt} = q_i\mu + \theta\tau I_i - \lambda U_i - \mu U_i \quad (9)$$

$$421 \quad \frac{dP_i}{dt} = \lambda(U_i + L_i) - (\delta + \mu)P_i \quad (10)$$

$$422 \quad \frac{dI_i}{dt} = \phi_i\delta P_i + \omega L_i - (\tau + \mu)I_i \quad (11)$$

$$423 \quad \frac{dL_i}{dt} = (1 - \phi_i)\delta P_i + (1 - \theta)\tau I_i - \lambda L_i - (\omega + \mu)L_i, \quad (12)$$

424 with force of infection

$$425 \quad \lambda = \beta(I_1 + I_2), \quad (13)$$

426 and $\phi_i = \alpha_i\phi$, representing the probability of progression from primary infection to

427 disease for individuals in group i in relation to the population mean $\langle\alpha\rangle = q_1\alpha_1 +$

428 $q_2\alpha_2 = 1$. The basic reproduction number for this model is

$$429 \quad R_0 = \left[\frac{\omega + \mu}{\mu(\tau + \omega + \mu) + \theta\tau\omega} \right] \left[\frac{\langle\alpha\rangle\phi\delta}{\delta + \mu} + \frac{(1 - \langle\alpha\rangle\phi)\delta\omega}{(\delta + \mu)(\omega + \mu)} \right] \beta. \quad (14)$$

430 In all cases we use *risk* and *risk distribution* as generic terms to designate factors of

431 variation in the predisposition of individuals to acquire infection or disease, which

432 may be realized physically as rates of contacts with other individuals (*i*), or

433 biologically as susceptibility to infection given exposure (*ii*) or progression to disease

434 given infection (*iii*). We use the terminology *epidemiological compartment* to refer to

435 the composite of all compartments for the same infection status (i.e. *uninfected*

436 comprises both U_1 and U_2 , etc). We also introduce the notion of *mean risk* for each

437 epidemiological compartment to track selection (e.g. the mean risk for $U(t)$ is

438 calculated as $(U_1(t)\alpha_1 + U_2(t)\alpha_2)/(U_1(t) + U_2(t))$, etc). We adopt two risk groups

439 for concreteness, but formalisms with more groups would essentially support the

440 same phenomena. Indeed, two recent studies implemented similar selection processes
441 within populations structured into hundreds of risk groups^{40,41}.

442 The models accommodate an endemic equilibrium when $R_0 > 1$, as displayed by the
443 solution curves parameterized by β in Supplementary Figs. 9, 10 and Fig. 7a.

444 Incidence rates in each risk group are approximated from model outputs by adding the
445 positive terms in dI_i/dt and dividing by the population in that group, i.e.

446 $(\phi_{(i)}\delta P_i + \omega L_i)/q_i$ per year, and for the entire population as the weighted sum of
447 these over risk groups.

448 **Model initialization**

449 Model trajectories are initialized assuming equilibrium conditions in 2002.

450 Parameters describing the rates of birth and death of the population, the probability of
451 progression from primary infection to active disease, and the rate of successful

452 treatment, are set at the same values for the three countries: $\mu = 1/80 \text{ yr}^{-1}$; $\phi =$

453 0.05 (Ref. 42), $\tau = 2 \text{ yr}^{-1}$ (Ref. 43). The rate of reactivation is considered three

454 times higher in South East Asian than in Western populations: $\omega = 0.0013 \text{ yr}^{-1}$ in

455 Brazil and Portugal; $\omega = 0.0039 \text{ yr}^{-1}$ in Vietnam (Ref. 44). The mean effective

456 contact rate (β) was calibrated to enable model solutions to meet country-level

457 incidences estimated by the WHO for 2002 (Supplementary Figs. 9, 10 and Fig. 7a).

458 Risk group frequencies are set at $q_1 = 0.96$, and $q_2 = 0.04$, and the relative risk

459 parameters (α_1 and α_2) estimated as described below. The results are then displayed

460 in terms of the non-dimensional parameter R_0 , which is linearly related to β

461 according to (6), (8), (14).

462 The same procedure was carried out for the mean field approximations of the
463 respective models. At this point it can be confirmed that R_0 estimates are typically
464 higher under heterogeneity¹². We adopt heterogeneity in contact rates (*i*) as the default
465 model throughout the paper, and use the susceptibility (*ii*) and disease progression
466 (*iii*) variants for completion. Hence, unless specified otherwise, the results shown in
467 the paper refer to heterogeneity in contact rates.

468 **Risk distributions**

469 Given a Lorenz curve (Fig 1a), any discretization can be assumed to define how
470 concentration of risk will enter the model. We adopt a division into 96% low-risk and
471 4% high-risk groups, but the procedure is not specific to the chosen discretization. A
472 distribution of incidences is then constructed as to produce the same RIC as the
473 original curve: a segment $q_1 = 0.96$ of the population accounts for $(100 - y)\%$ of
474 the incidence, while the remaining segment $q_2 = 0.04$ accounts for the remaining $y\%$
475 (Fig 1a). The transmission model is solved as above, and the relative risk parameters
476 α_i are calculated (Fig. 2a, d, g) so as to output the country-specific incidence
477 distributions (see Fig. 2c, f, i). This was performed numerically by binary search to
478 adjust the variance in the parameters α_i such that the variance in the output incidences
479 agrees with the notification data.

480 Under any positive force of infection, the two risk groups segregate differently to
481 populate the various epidemiological compartments, as depicted in Fig. 2b, e, h,
482 resulting in mean risks that differ from one for specific compartments, and thereby
483 deviating from homogeneous approximations. Crucially, the mean risks among
484 individuals that occupy the various epidemiological compartments (square brackets in

485 the figure) respond to dynamic forces of infection causing divergence from
486 predictions made by homogenous models.

487 **Moving targets**

488 The model, with the estimated risk distributions, parameters, and initial conditions,
489 fitting the 2002 incidences (189 in Vietnam, 52 in Brazil, and 49 in Portugal, all per
490 100,000 person-years), is run forward in time with a constant decline in reactivation
491 rate as to meet an arbitrarily fixed target of halving the incidence in 10 years. As in
492 the calculation of risk variance above, also here we refer to a simple numerical
493 calculation performed by binary search. We write the reactivation rate as $\omega(t) =$
494 $\omega(0)e^{r_\omega(t-2002)}$ per year, and approximate r_ω in order to meet the desired incidence
495 target by year 2012.

496 Starting with initial reactivation rates of 0.0039 per year in Vietnam, and 0.0013 per
497 year in Brazil and Portugal, we find that meeting the target by this strategy alone,
498 would require values of r_ω as specified in the heterogeneous column of
499 Supplementary Table 1, or equivalently a decline in reactivation by $1 - e^{r_\omega}$ each
500 year. This is to say that, in 10 years, the reactivation rates would have been reduced to
501 values also shown in the respective column of Supplementary Table 1.

502 Suppose that these estimations and projections were being made by the mean field
503 approximation of the same model, and the outcomes were monitored yearly and
504 readjusted if necessary. The expectations would have been that lower absolute values
505 would be required for the decay rate parameters r_ω . Since the real population is
506 heterogeneous, however, we simulate this decline for the first year with the
507 heterogeneous model. The result is that, instead of achieving the incidences projected

508 by the homogeneous model (“target” homogeneous column in Supplementary Table
509 1), the reality would lag behind (“achieved” homogeneous column in Supplementary
510 Table 1), a result that the homogeneous model would attribute to insufficient effort
511 exerted in reducing reactivation. From the homogeneous frame, an observer would
512 have likely concluded that the decline had been lower due to some implementational
513 failure, would have re-estimated the effort to meet the target over the remaining 9
514 years, now with an intensification to compensate for the lag of the first year. This
515 process is simulated recursively for 10 years to populate Supplementary Table 1 and
516 to generate Fig. 3. The insets in Fig. 3b, d, f, depict the relative error committed each
517 year.

518 The dynamics of the mean risk of infection in the uninfected and latent compartments
519 as the described interventions proceeds are shown in Fig. 3a, c, e, to demonstrate the
520 action of selection. This is the key process leading to the deviation between the
521 homogeneous and heterogeneous models.

522 **Meeting End TB targets**

523 The model with initial conditions, parameters and distributions estimated for 2002, is
524 used to reproduce reported country-level trends for TB incidence in Vietnam, Brazil,
525 and Portugal. Incidence declines between 2002 and 2015, reported by WHO for each
526 of the three countries, are assigned to changes in pre-specified parameters (here set as
527 ϕ and ω for illustrative purposes but alternative combinations have also been used).

528 The decline is shared among the selected parameters as estimated below.

529 As incidence declines we monitor the reductions being made on each parameter,
530 namely, on the probability of progression from primary infection to active disease
531 $[1 - \phi(t)/\phi(2002)]$ and on the reactivation rate $[1 - \omega(t)/\omega(2002)]$.

532 **Parameter estimation**

533 Assuming that the incidence declines reported by WHO between 2002 and 2015 for
534 Vietnam, Brazil and Portugal, are due to reducing ϕ and ω at constant rates (r_ϕ and
535 r_ω , respectively), resulting in exponentially decaying parameters such that $\phi(t) =$
536 $\phi(2002)e^{r_\phi(t-2002)}$ and $\omega(t) = \omega(2002)e^{r_\omega(t-2002)}$, we proceed to estimate r_ϕ and
537 r_ω . We used a Bayesian Markov Chain Monte Carlo (MCMC) approach to find
538 posterior sets of these decay rates. We assume gaussian priors and base our likelihood
539 on the weighted squared error function

540
$$\chi^2 = \sum_{i=1}^n \left(\frac{B_i^d - B_i}{\sigma_i^d} \right)^2 \quad (15)$$

541 where B_i^d are the data points, B_i are the model outputs, and σ_i^d are the corresponding
542 measurement errors. This is equivalent to using the likelihood (L) such that $\chi^2 =$
543 $-2 \log(L)$, under the assumption of Gaussian noise^{45,46}. In the absence of the
544 sampling distribution for the data, the error variance is sampled as a conjugate prior
545 specified by the parameters σ_0 and n_0 of the inverse gamma distribution where σ_0 is
546 the initial error variance and n_0 is assumed to be 1 (as larger values limit the samples
547 closer to σ_0)⁴⁷. We use the MATLAB MCMC package developed by Haario *et al.*
548 (2006)⁴⁸. We initially minimize the error function and use these local minima as
549 initial values for the parameters in the MCMC run. We infer a MCMC chain of length
550 10^5 and adopt a burn in of 2×10^4 after assessing the Gelman-Rubins-Brooks
551 potential scale reduction factor (psrf) plots of the posterior distributions (see
552 Supplementary Figs. 11, 12).

553 **Comparison with metapopulation models**

554 As implied by Supplementary Fig. 1, geographical units are not conceptualized as
555 homogeneous patches but rather as harboring heterogeneity down to the individual
556 level. The transmission dynamics represented in our models is that of a country's
557 average patch (with variation in risk among individuals) rather than a metapopulation
558 consisting of multiple patches (each occupied by a homogeneous population and
559 variation in risk among patches). To highlight this essential distinction, we have
560 constructed a metapopulation model consisting of two subpopulations (A and B), each
561 characterized by a distribution in individual risk (Supplementary Fig. 5).

562 Subpopulations (or patches) in this toy model are composed of individuals drawn
563 from a common pool of high and low risk individuals (in proportions 4% and 96%,
564 respectively), and what characterizes each patch is the fraction of its individuals who
565 are high-risk (rather than introducing patch-specific effective contact rates, β_A and β_B ,
566 explicitly as commonly practiced). We assume a single β for the entire
567 metapopulation and vary the proportion of individuals in A who are high risk (q_{2A})
568 and calculate the corresponding proportion in B (q_{2B}). Basically, we have a family of
569 metapopulation models, parameterized by the proportion of high-risk individuals in
570 one of the patches, that we can completely resolve to match the incidence and RIC for
571 each of our study countries.

572 We calculate relevant measures, such as variance in individual risk at the level of the
573 entire metapopulation and R_0 . These two metrics are shown as functions of q_{2A} in
574 Supplementary Figs. 6 and 7 (for heterogeneous contact rates and heterogeneous
575 susceptibility, respectively) and one *versus* the other in Fig. 8. Open and filled circles
576 are added to Fig. 8 for comparison of the same metrics under the homogeneous and
577 heterogeneous models used in this study.

578 For simplicity we did not include transmission between subpopulations in this
579 exercise, but there is no reason to expect sudden changes in outcome when this is
580 added.

581

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588

589 **Author contributions**

590 M.G.M.G., P.B.S, and C.L. designed the study; E.L.M., R.D., and B.H.N. provided
591 data and expertise; M.G.M.G., J.F.O., A.B., D.A., and T.A.N. performed the analysis;
592 M.G.M.G. drafted the manuscript; all authors revised and approved the final version.

593

594 **Competing interests**

595 The authors declare no competing interests.

596

597 **Data availability**

598 Estimated country-level incidence obtained from the WHO's global tuberculosis
599 database (<http://www.who.int/tb/country/data/download/en/>). Municipality-level
600 notification and population data used in Figure 1 provided by National Tuberculosis
601 Programs.

602

603 **Code availability**

604 Computer programs were written in MATLAB R2015b as detailed in Methods. Maps
605 were produced with Map in Seconds (<http://www.mapinseconds.com>).

606

607 **Supplementary Information**

608 This file contains Supplementary Figures 1-12 and Supplementary Tables 1-11.

609

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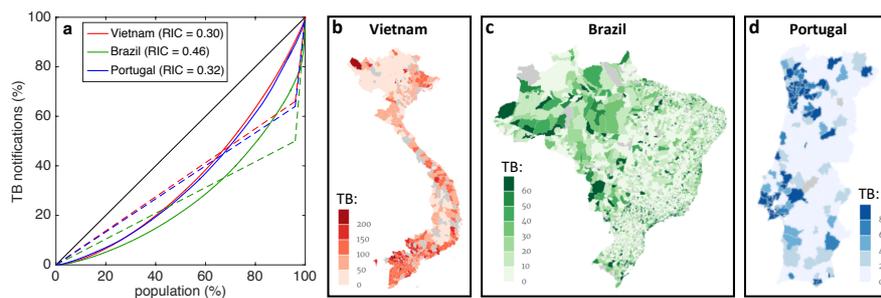
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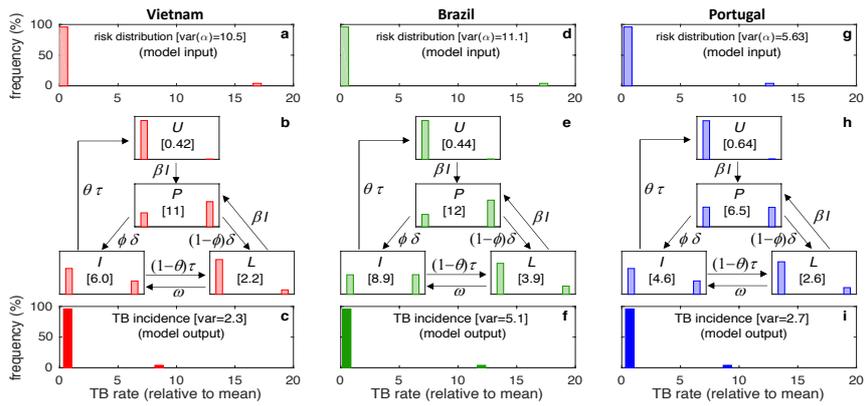
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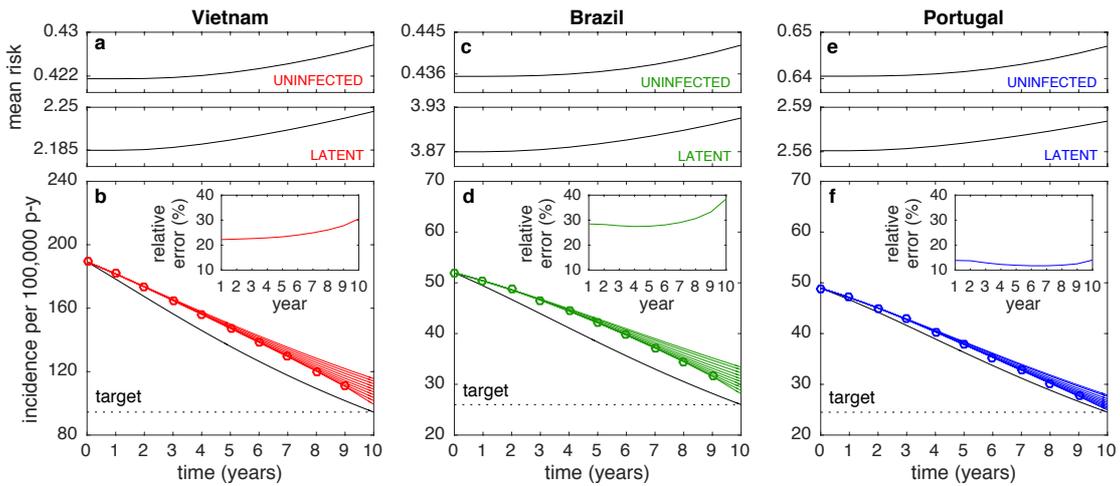
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Fig. 1: Risk inequality coefficient. **a**, Lorenz curves calculated from notification data stratified by level 2 administrative divisions (697 districts in Vietnam; 5127 municipalities in Brazil; 308 municipalities in Portugal). A risk inequality coefficient (RIC) was calculated for each country from Lorenz curves as in Methods. Country maps with administrative divisions for Vietnam (**b**), Brazil (**c**), and Portugal (**d**), colored by number of cases notified per 100,000 person-years.



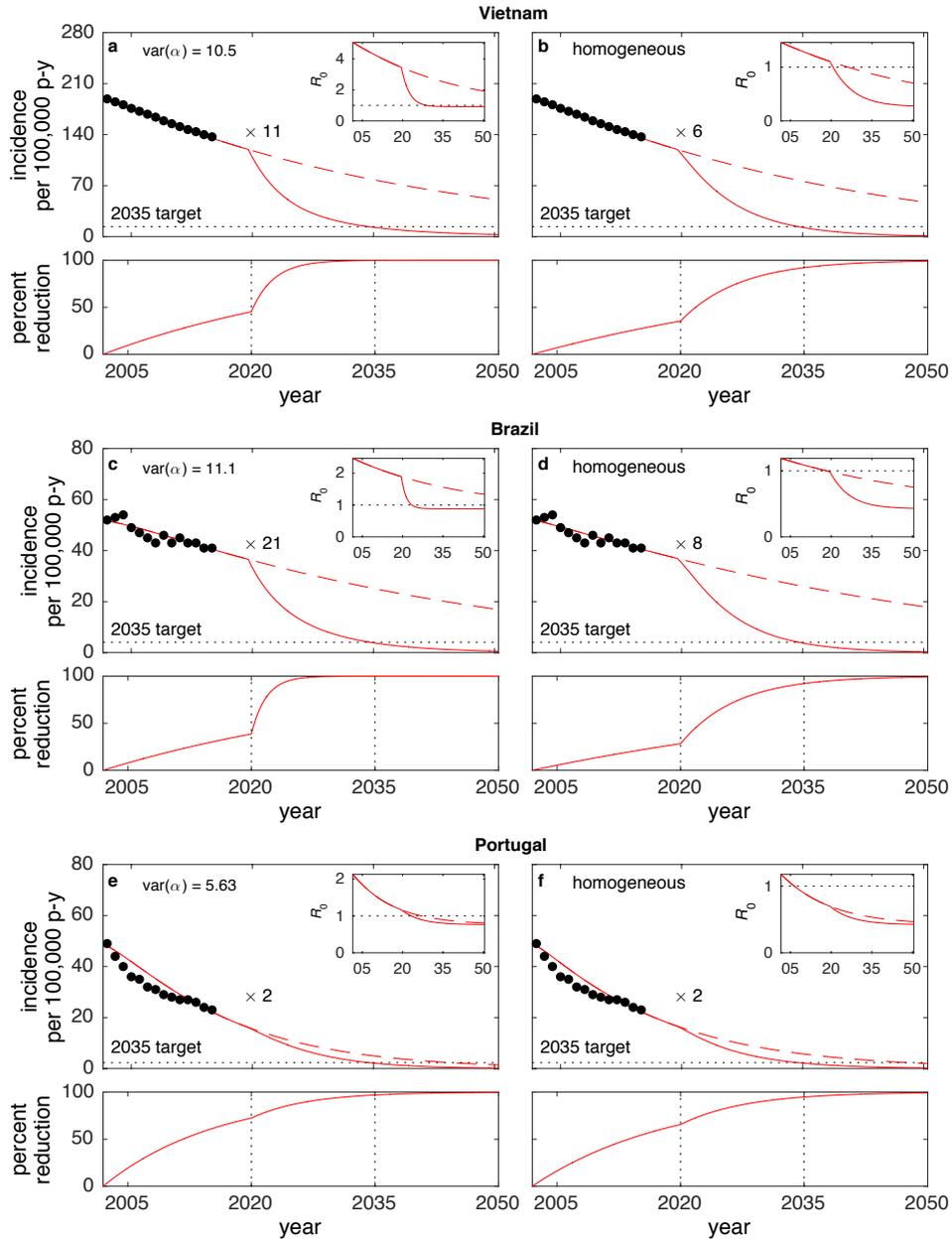
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Fig. 2: Tuberculosis transmission model with distributed contact rates. **a, d, g,** Risk (contact rate) distributions inferred by fitting a mathematical model to notification data stratified in two risk groups (96% and 4% with risk factors α_1 and α_2 , respectively) as in Methods ($\alpha_1 = 0.339$ and $\alpha_2 = 16.9$ in Vietnam [variance 10.5]; $\alpha_1 = 0.320$ and $\alpha_2 = 17.3$ in Brazil [variance 11.1]; $\alpha_1 = 0.516$ and $\alpha_2 = 12.6$ in Portugal [variance 5.63]). **b, e, h,** Risk distributions in the various epidemiological compartments segregated by the transmission dynamics. Numbers in square brackets represent the mean baseline risk $\langle \alpha \rangle$ among individuals populating each epidemiological compartment. **c, f, i,** Distribution of incidence rates calculated from stratified model outputs ($Y_1 = 0.69$ and $Y_2 = 8.5$ in Vietnam [variance 2.3]; $Y_1 = 0.52$ and $Y_2 = 12$ in Brazil [variance 5.1]; $Y_1 = 0.67$ and $Y_2 = 9.0$ in Portugal [variance 2.7]). Model parameters as in Table 1. Clearance of infection upon successful treatment: $\theta = 1$. Country-specific parameter values: $\omega = 0.0039 \text{ yr}^{-1}$ and $\beta = 3.23 \text{ yr}^{-1}$ in Vietnam; $\omega = 0.0013 \text{ yr}^{-1}$ and $\beta = 2.94 \text{ yr}^{-1}$ in Brazil; $\omega = 0.0013 \text{ yr}^{-1}$ and $\beta = 4.66 \text{ yr}^{-1}$ in Portugal. Notice that observed incidence variances $\langle (Y - 1)^2 \rangle$ indicate underlying risk variances $\langle (\alpha - 1)^2 \rangle$ which are consistently higher¹¹.



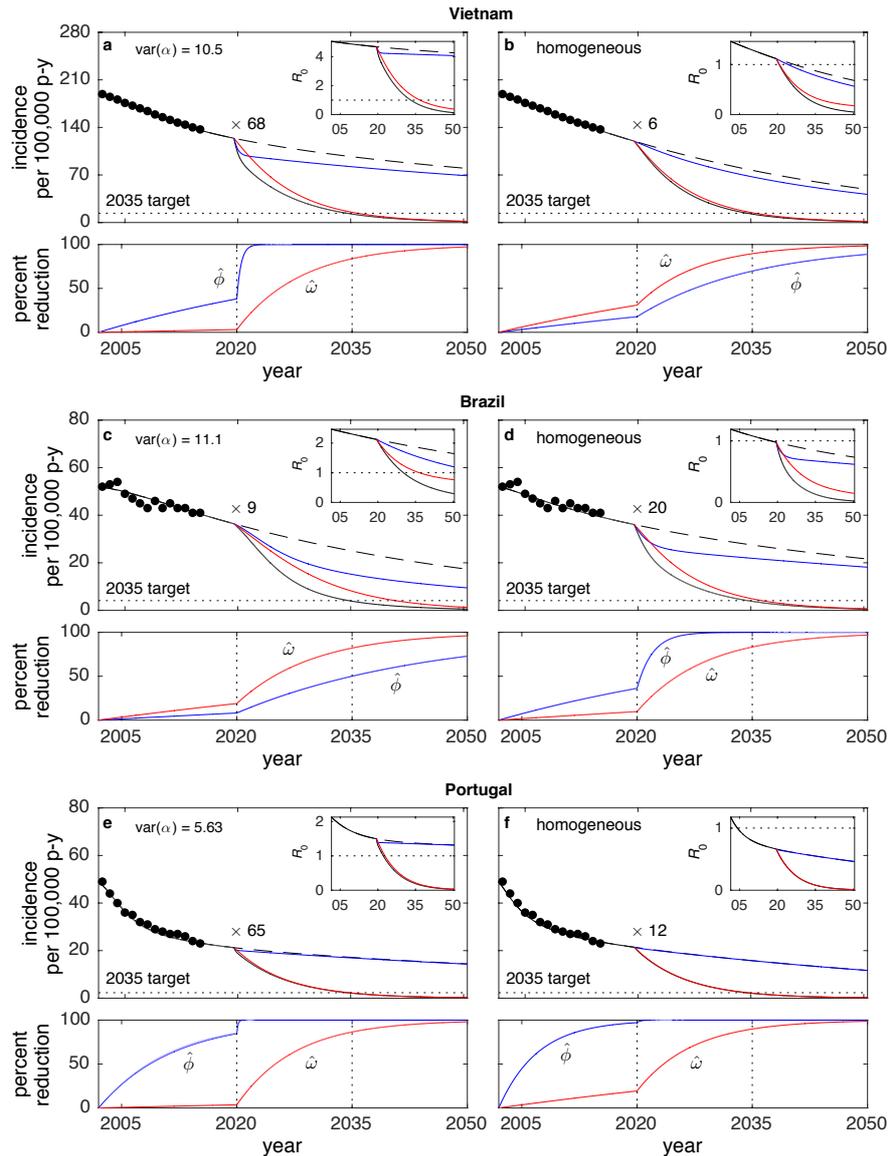
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Fig. 3: Moving targets. How (b, d, f) and why (a, c, e) fixed targets appear to be moving when observed from a homogeneous frame (Methods, and Supplementary Table 1). The model adopted in this illustration concerns heterogeneity in contact rates as governed by equations (1)-(5). Mean risks among individuals in uninfected and latent compartments are calculated as $(U_1\alpha_1 + U_2\alpha_2)/(U_1 + U_2)$ and $(L_1\alpha_1 + L_2\alpha_2)/(L_1 + L_2)$, respectively. Model parameters as in Table 1. Clearance of infection upon successful treatment: $\theta = 1$. Country-specific parameter values: $\omega = 0.0039 \text{ yr}^{-1}$, $\beta = 3.23 \text{ yr}^{-1}$ (heterogeneous) or $\beta = 10.7 \text{ yr}^{-1}$ (homogeneous) in Vietnam; $\omega = 0.0013 \text{ yr}^{-1}$, $\beta = 2.94 \text{ yr}^{-1}$ (heterogeneous) or $\beta = 17.3 \text{ yr}^{-1}$ (homogeneous) in Brazil; $\omega = 0.0013 \text{ yr}^{-1}$, $\beta = 4.66 \text{ yr}^{-1}$ (heterogeneous) or $\beta = 17.1 \text{ yr}^{-1}$ (homogeneous) in Portugal.



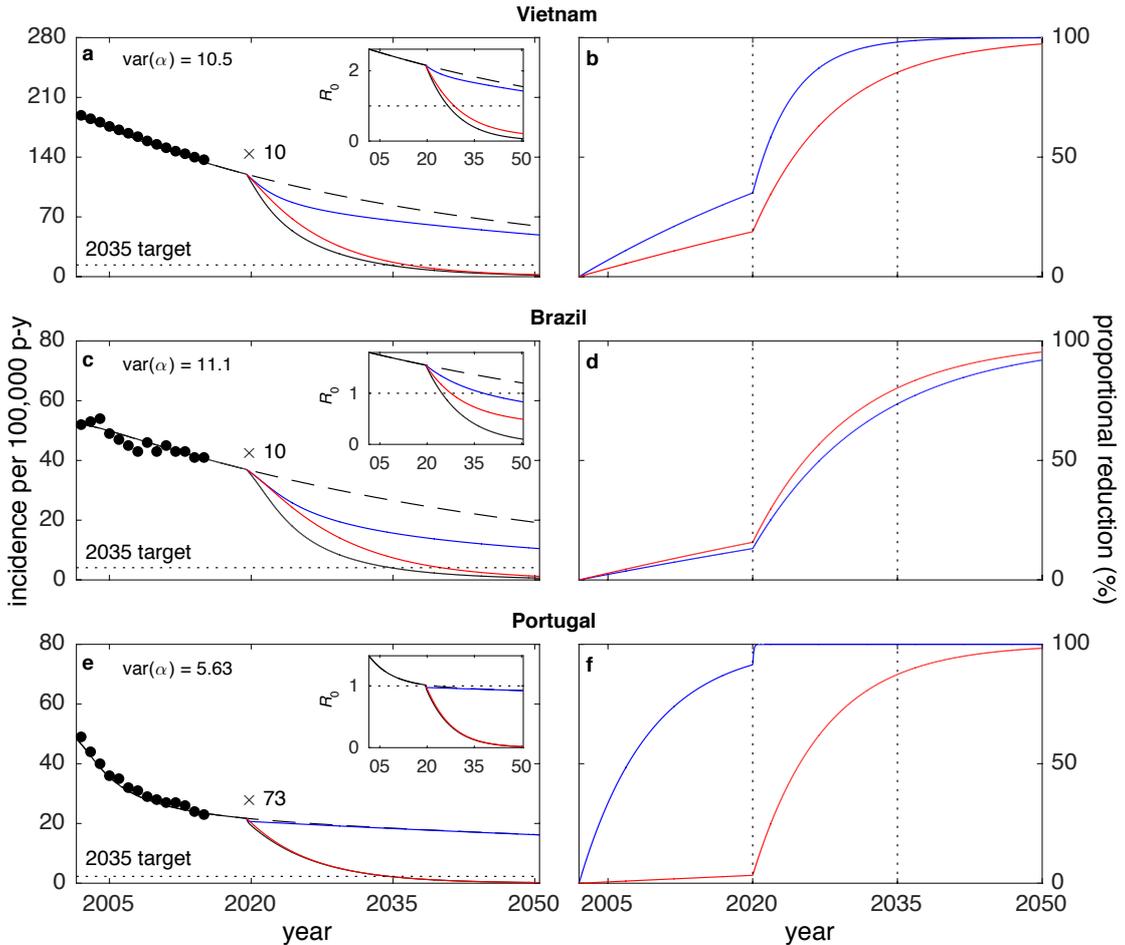
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Fig. 4: Model trajectories with heterogeneity in contact rates and gradual decline in reactivation (ω). TB incidence from 2002 to 2015 (black dots) and model solutions under heterogeneous contact rates (a, c, e); homogeneous approximation (b, d, f). Initial parameters values calculated by adjusting the mean effective contact rates (β) to fit 2002 incidence rates: $\beta = 3.23 \text{ yr}^{-1}$ (a) or $\beta = 10.7 \text{ yr}^{-1}$ (b) in Vietnam; $\beta = 2.94 \text{ yr}^{-1}$ (c) or $\beta = 17.3 \text{ yr}^{-1}$ (d) in Brazil; $\beta = 4.66 \text{ yr}^{-1}$ (e) or $\beta = 17.1 \text{ yr}^{-1}$ (f) in Portugal. Incidence declines towards 2015 attributed to reducing reactivation: $\omega(t) = \omega_0 e^{r_\omega(t-2002)}$ (where $\omega_0 = 0.0039$ in Vietnam and $\omega_0 = 0.0013$ in Brazil and Portugal), with constant rates r_ω adjusted to meet the incidences observed in 2015 (Supplementary Table 2). From 2020 onwards, the trajectories split to represent two scenarios: rates of parameter change are maintained (dashed); scale r_ω by a factor κ (represented as “ $\times \kappa$ ”) to meet WHO incidence targets for 2035 (solid). The bottom plots in each panel represent the cumulative reductions in reactivation required to meet the targets calculated as $\hat{\omega}(t) = 1 - \omega(t)/\omega(2002)$. Clearance of infection upon successful treatment: $\theta = 1$. Other parameters as in Table 1. Model described by equations (1)-(5), and R_0 given by (6).



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Fig. 5: Model trajectories with heterogeneity in contact rates and gradual declines in disease progression (ϕ) and reactivation (ω). TB incidence from 2002 to 2015 (black dots) and model solutions under heterogeneous contact rates (a, c, e); homogeneous approximation (b, d, f). Initial parameters values calculated by adjusting the mean effective contact rates (β) to fit 2002 incidence rates: $\beta = 3.23 \text{ yr}^{-1}$ (a) or $\beta = 10.7 \text{ yr}^{-1}$ (b) in Vietnam; $\beta = 2.94 \text{ yr}^{-1}$ (c) or $\beta = 17.3 \text{ yr}^{-1}$ (d) in Brazil; $\beta = 4.66 \text{ yr}^{-1}$ (e) or $\beta = 17.1 \text{ yr}^{-1}$ (f) in Portugal. Incidence declines towards 2015 attributed to reducing disease progression and reactivation: $\phi(t) = 0.05e^{r_\phi(t-2002)}$ and $\omega(t) = \omega_0 e^{r_\omega(t-2002)}$ (where $\omega_0 = 0.0039$ in Vietnam and $\omega_0 = 0.0013$ in Brazil and Portugal), with constant rates r_ϕ and r_ω estimated using MCMC (Supplementary Table 3). From 2020 onwards, the trajectories split to represent four scenarios: rates of parameter change are maintained (dashed black); scale r_ϕ and r_ω by a factor κ (represented as “ $\times \kappa$ ”) to meet WHO incidence targets for 2035 (solid black); apply the same scale up efforts to r_ϕ only (blue) or r_ω only (red). The bottom plots in each panel represent the cumulative reductions in disease progression and reactivation required to meet the targets calculated as $\hat{\phi}(t) = 1 - \phi(t)/\phi(2002)$ and $\hat{\omega}(t) = 1 - \omega(t)/\omega(2002)$, respectively. Clearance of infection upon successful treatment: $\theta = 1$. Other parameters as in Table 1. Model described by equations (1)-(5), and R_0 given by (6).



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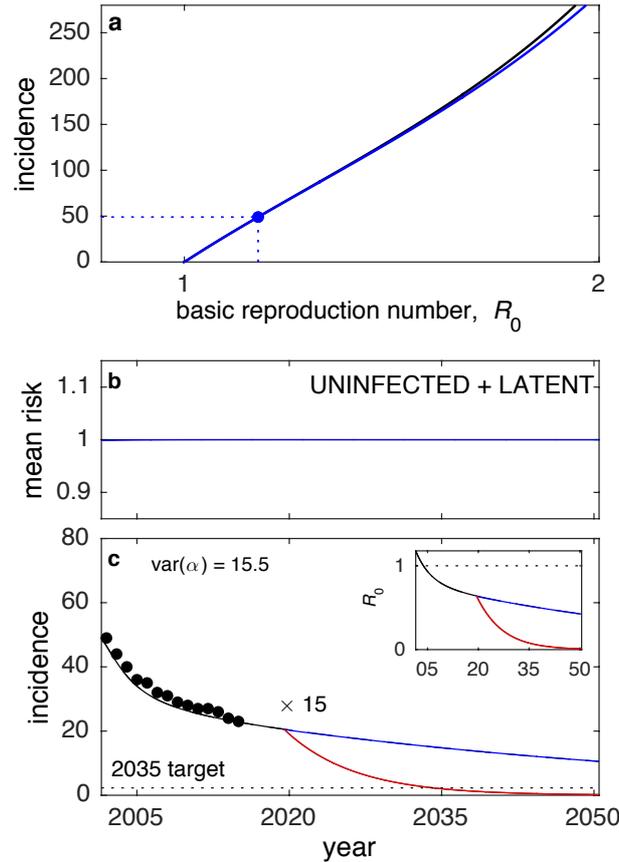
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Fig. 6: Model trajectories with heterogeneity in susceptibility to infection and gradual declines in disease progression (ϕ) and reactivation (ω). TB incidence from 2002 to 2015 (black dots) and model solutions under heterogeneous susceptibility to infection (a, c, e); cumulative reductions in disease progression and reactivation required to meet End TB incidence targets (b, d, f), calculated as $\hat{\phi}(t) = 1 - \phi(t)/\phi(2002)$ and $\hat{\omega}(t) = 1 - \omega(t)/\omega(2002)$, respectively. Initial parameter values calculated by adjusting the mean effective contact rates (β) to fit 2002 incidence rates: $\beta = 19.2 \text{ yr}^{-1}$ in Vietnam (a); $\beta = 26.1 \text{ yr}^{-1}$ in Brazil (c); $\beta = 21.6 \text{ yr}^{-1}$ in Portugal (e). Incidence declines towards 2015 attributed to reducing disease progression (ϕ) and reactivation (ω): $\phi(t) = 0.05e^{r_\phi(t-2002)}$ and $\omega(t) = \omega_0e^{r_\omega(t-2002)}$ (where $\omega_0 = 0.0039$ in Vietnam and $\omega_0 = 0.0013$ in Brazil and Portugal), with constant rates r_ϕ and r_ω estimated using MCMC (Supplementary Table 8). From 2020 onwards, the trajectories split to represent four scenarios: rates of parameter change are maintained (dashed black); scale r_ϕ and r_ω by a factor κ (represented as “ $\times \kappa$ ”) to meet WHO incidence target for 2035 (solid black); apply the same scale up efforts to r_ϕ only (blue) or r_ω only (red). Clearance of infection upon successful treatment: $\theta = 1$. Other parameters as in Table 1. Model described by equations (1)-(4) and (7), and R_0 given by (8).



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Fig. 7: Model trajectories with heterogeneity in disease progression and gradual declines

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in progression (ϕ) and reactivation (ω). TB incidence from 2002 to 2015 in Portugal (black

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dots) and model solutions under heterogeneous progression to disease (c); mean risk

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(progression fraction) among susceptible individuals

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$[(U_1(t) + L_1(t))\alpha_1 + (U_2(t) + L_2(t))\alpha_2] / (U_1(t) + L_1(t) + U_2(t) + L_2(t))$ (b); and

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endemic equilibrium parameterized by the mean effective contact rate (β) plotted in terms of

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R_0 for the heterogeneous (blue) and homogeneous (black) models (a). Initial parameter values

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calculated by adjusting β to fit 2002 incidence rates as shown in (a): $\beta = 17.1 \text{ yr}^{-1}$.

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Incidence declines towards 2015 attributed to reducing disease progression (ϕ) and

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reactivation (ω): $\phi(t) = 0.05e^{r_\phi(t-2002)}$ and $\omega(t) = \omega_0 e^{r_\omega(t-2002)}$ (where $\omega_0 = 0.0039$ in

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Vietnam and $\omega_0 = 0.0013$ in Brazil and Portugal), with constant rates r_ϕ and r_ω estimated

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using MCMC (Supplementary Table 9). From 2020 onwards, the trajectories split to represent

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four scenarios: rates of parameter change are maintained (dashed black); scale r_ϕ and r_ω by a

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factor κ (represented as “ $\times \kappa$ ”) to meet WHO incidence target for 2035 (solid black); apply

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the same scale up efforts to r_ϕ only (blue) or r_ω only (red). Clearance of infection upon

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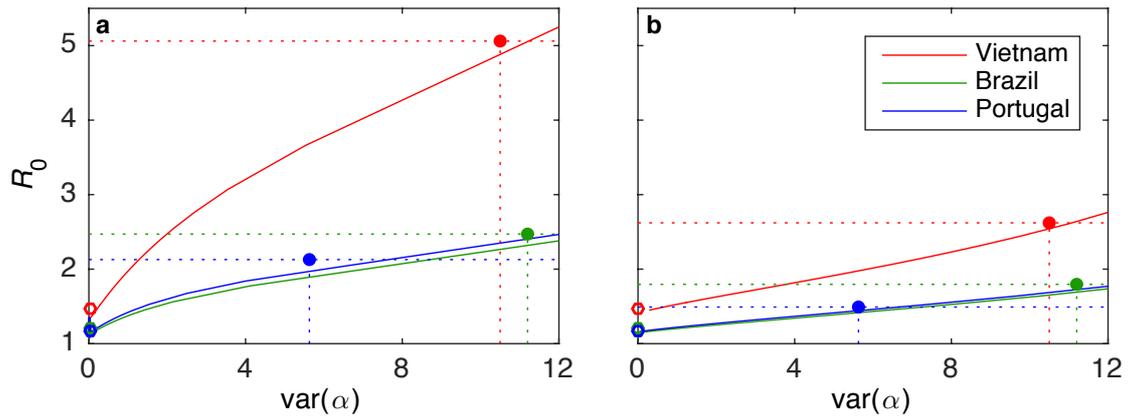
successful treatment: $\theta = 1$. Other parameters as in Table 1. Model described by equations

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(9)-(13), and R_0 given by (14).

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Fig. 8: One-parameter family of metapopulation models. (a) Heterogeneous contact rates; **(b)** heterogeneous susceptibility to infection. Each point along a solid curve represents one model that produces country incidences in agreement with RIC values calculated in Fig. 1 (procedures described in Methods). Filled circles marks variances in individual risk and R_0 obtained for each country by the procedure utilized in this study, whereas open circles indicate R_0 estimated by homogeneous approximations.

854 **Table 1:**
 855 Parameters for tuberculosis transmission model.
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Symbol	Definition	Value
β	Mean effective contact rate	estimated
μ	Death and birth rate	$1/80 \text{ yr}^{-1}$
δ	Rate of progression from primary infection	2 yr^{-1}
ϕ	Proportion progressing from primary infection to active disease	0.05
ω	Rate of reactivation of latent infection	0.0039 yr^{-1} (Vietnam); 0.0013 yr^{-1} (Brazil, Portugal)
τ	Rate of successful treatment	2 yr^{-1}
θ	Proportion clearing infection upon treatment	[0,1]
α_i	Individual risk in relation to population average	estimated
p_i	Proportion of individuals in low and high risk groups, respectively	$p_1 = 0.96; p_2 = 0.04$

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