Competition and diversity determine vaccine impact on antibiotic resistance evolution

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One sentence summary: Competition and diversity are key to antibiotic resistance evolution and determine whether vaccines will prevent or increase resistant infections.

Bacterial vaccines can protect recipients from contracting potentially antibiotic-resistant infections. But by altering the selective balance between sensitive and resistant strains, vaccines may also help suppress—or spread—antibiotic resistance among unvaccinated individuals. Predicting the outcome requires knowing the drivers of resistance evolution. Using mathematical modelling, we identify competition and diversity as key mediators of resistance evolution. Specifically, we show that the frequency of penicillin resistance in *Streptococcus pneumoniae* (pneumococcus) across 27 European countries can be explained by between-host diversity in antibiotic use, heritable diversity in pneumococcal carriage duration, or within-host competition. We use our calibrated model to predict the impact of universal pneumococcal vaccination upon the prevalence of carriage, incidence of disease, and frequency of resistance for *S. pneumoniae*. The relative strength and directionality of competition between resistant and sensitive pneumococcal strains determines whether vaccination promotes, inhibits, or has little effect on the evolution of antibiotic resistance. Finally, we find that differences in overall bacterial transmission and carriage alter predictions, suggesting that evidence-based policies for managing resistance with vaccines must be tailored to both pathogen and setting.

In an age of widespread antibiotic resistance, there is growing interest in using vaccines to prevent bacterial infections that would otherwise call for treatment with antibiotics (*1–4*). This interest arises for two main reasons: first, vaccines are effective against both antibiotic-resistant and antibiotic-sensitive bacteria; and second, successful prophylaxis removes the need for a course of antibiotic therapy that might promote more resistance (*2–5*). Over the past two decades, the use of pneumococcal conjugate vaccines (PCVs) has seemingly borne out these advantages. Administering PCVs to young children has substantially reduced disease caused by *S. pneumoniae* (*5–8*)—a common asymptomatic coloniser of the nasopharynx which can cause pneumonia, meningitis and other infections when invasive—and has decreased demand for antibiotic therapy, largely by reducing cases of otitis media (*5*, *9*). But because PCV formulations target only a fraction of the ~100 known pneumococcal serotypes, the niche vacated by PCV-targeted serotypes has been filled by non-vaccine serotypes, and overall pneumococcal carriage has rebounded to pre-vaccine levels (*10*, *11*). Concomitantly, the incidence of infections

attributed to non-vaccine serotypes (*12*) and the proportion of non-vaccine-type infections exhibiting antibiotic resistance (*5*, *13*) have risen in many settings. Concern over serotype replacement—along with the high cost of PCV manufacturing—has spurred the development of "universal" whole-cell or protein-based pneumococcal vaccines protecting against all serotypes, some of which are now in early-stage clinical trials (*14*).

However, it is unclear how universal vaccination may itself impact upon the evolution of antibiotic resistance in *S. pneumoniae*, which is a concern given that vaccination is unlikely to eliminate pneumococcal disease (*15*). Mathematical models can be used to generate predictions from nonlinear transmission dynamics (*16*, *17*), but existing models focus on serotype-specific vaccines and, even then, disagree over the expected impact of vaccination on resistance evolution (*18–24*). Comparing and interpreting the results of these models is hampered by the fact that none starts from a position of recapitulating large-scale empirical patterns of antibiotic resistance. The main challenge in replicating these patterns lies in identifying the mechanisms that maintain long-term coexistence between sensitive and resistant pneumococcal strains across a wide range of antibiotic treatment rates, like those seen across Europe and the United States (*25*, *26*). Robust predictions of the long-term impact of vaccination on resistant pneumococcal disease require a mechanistic understanding of these patterns.

Results

Competition and diversity maintain stability in resistance evolution. A model must be able to explain the current burden of an infectious disease before it can be used to robustly predict the impact of interventions for managing that disease. Across Europe, the frequency of antibiotic resistance among isolates from pneumococcal infections shows two salient features for models to recapitulate (Supplementary Fig. 1). One is spatial: the frequency of penicillin non-susceptibility varies between countries, and is higher in countries where more penicillin is consumed (*27*). The other is temporal: although in individual countries resistance fluctuates from year to year, the overall frequency across Europe of penicillin non-susceptibility in pneumococcal isolates has remained steady at roughly 12% since consolidated records began in 2005 (*28*). These

observations contradict simple models of resistance evolution, which predict that intermediate frequencies of resistance cannot be stably maintained in the long term: that is, either sensitive strains will competitively exclude resistant strains, or resistant strains will competitively exclude sensitive strains, unless there is some mechanism maintaining coexistence between them (*25*, *29*).

By conducting a literature search, we identify nine such mechanisms (*25*, *26*, *30–41*) that fall into two broad classes. In one class, coexistence is maintained by environmental or genetic diversity that prevents resistant and sensitive strains from completely overlapping in competition. In the other class, competition between resistant and sensitive strains is itself the stabilising factor that maintains coexistence, because resistant and sensitive strains exhibit alternative competitive phenotypes that afford strains a competitive advantage when rare, thus promoting negative frequency-dependent selection for resistance. Thus, diversity and competition are two key forces maintaining stability in resistance evolution. Of the nine identified mechanisms, we find that four are biologically plausible for maintaining coexistence in *S. pneumoniae* (Table 1).

Four models of resistance evolution. To compare these four mechanisms, we embed each in a shared model framework of person-to-person transmission of nasopharyngeal pneumococcal carriage. This framework tracks the country-specific frequency of resistance in pneumococci circulating among children under five years old, the age group that drives the majority of pneumococcal transmission and disease (*42*, *43*). We assume that each individual makes effective contact with another random individual at rate β, thereby potentially acquiring a strain (either sensitive or resistant) carried by the contacted person. With probability c, resistant strains fail to transmit, where c represents the transmission cost of resistance (*44*, *45*). A carrier naturally clears all strains at rate u, and is exposed to antibiotic therapy at a country-specific rate τ, which clears the host of sensitive strains only. We assume this treatment rate is independent of carriage status (*46*) and we do not explicitly track disease progression in hosts.

Under the "Treatment diversity" and "Pathogen diversity" models, coexistence is maintained because diversity among hosts or among pathogens prevents resistant and

118 sensitive strains from fully overlapping in competition. In the "Treatment diversity"
119 model (Fig. 1a), heterogeneity in the consumption of antibiotics between host
120 subpopulations within a country maintains coexistence (*25*, *34*, *35*). These
121 subpopulations could correspond to geographical regions, socioeconomic strata, host
122 age and risk classes, or a combination of these. Provided that transmission between
123 high-consumption (resistance-promoting) and low-consumption (resistance-inhibiting)
124 subpopulations is not too frequent, an intermediate frequency of resistance can be
125 maintained across the whole population. The key parameters governing coexistence in
126 this model are κ, the variability in antibiotic consumption between subpopulations, and
127 g, the relative rate at which within-country contact is made within subpopulations
128 rather than between them.
129
130 In the "Pathogen diversity" model (Fig. 1b), pneumococci are divided into subtypes ("D-
131 types"(*38*)) that vary in their mean duration of natural carriage. All else equal, the D-
132 type with the longest carriage duration would be expected to competitively exclude all
133 other strains; the model assumes that diversifying selection acting on the D-type locus
134 keeps all subtypes in circulation. What D-types correspond to is not explicitly specified
135 by this model, but one candidate is serotype variation. For example, if antigenic
136 diversity is promoted by host acquired immunity to capsular serotypes, and serotypes
137 tend to differ in their intrinsic ability to evade clearance by the immune system, then
138 intermediate resistance can be maintained because selection for resistance tends to be
139 greater in strains that have a longer duration of carriage (*38*). Long-lasting serotypes
140 will tend to evolve resistance, while shorter-lived serotypes will tend not to—a pattern
141 observed in *S. pneumoniae* (*38*) and reproduced by this model (Supplementary Fig. 2).
142 The parameters governing coexistence in this model are a, the strength of diversifying
143 selection on the D-type locus, and δ, the variability between subtypes in clearance rate.
144
145 Under the "Treatment competition" and "Growth competition" models, coexistence is
146 maintained because of competition between sensitive and resistant strains. In these
147 models, hosts can be co-colonised by multiple strains, but which strain a co-colonised
148 host transmits to other potential hosts is determined by within-host competition
149 between strains (*26*). The "Treatment competition" model (Fig. 1c) assumes that
150 antibiotic therapy mediates within-host competition, such that when a co-colonised

151 host takes antibiotics (*i.e.*, at rate τ), the sensitive strains are cleared and only the
152 resistant strains are transmitted to other hosts. The "Growth competition" model (Fig.
153 1d) has both treatment-mediated and growth-mediated competition: while in the
154 presence of antibiotics, resistant strains still outcompete co-colonising sensitive strains,
155 in the absence of antibiotics, sensitive strains gradually outcompete co-colonising
156 resistant strains at rate b. We assume that there is no transmission cost of resistance in
157 this latter model (*i.e.*, $c = 0$); instead, the within-host growth advantage b of sensitive
158 strains accounts for the cost of resistance. In these competition models, resistant strains
159 have an advantage in antibiotic-mediated competition, while sensitive strains have an
160 advantage in growth-mediated competition. These alternative forms of within-host
161 competition can both promote coexistence because rare strains can more consistently
162 exploit a competitive advantage over common strains, thus creating negative frequency-
163 dependent selection for resistance (*26*). The key parameter governing coexistence in
164 these two models is k, the relative rate of co-colonisation compared to primary
165 colonisation.
166
167 In all four models, we assume that contact between individuals is assortative by
168 country, such that with probability f, contact is with a random person from the same
169 country, and with probability $1 - f$, contact is with a random person from any country.
170 We implement these models using systems of ordinary differential equations. All four
171 models (*25*, *26*, *38*) are structurally neutral (*25*, *29*), meaning that any coexistence
172 exhibited by the models is accounted for by the specified biological mechanism rather
173 than by any bias in the logical structure of the model that generates coexistence "for
174 free". Additionally, while the within-host competition models capture co-colonisation
175 using a simplified subset of only 2 "mixed-carriage" states (S_R and R_S, Fig. 1a&b), we
176 have previously shown (*26*) that this is equivalent to a more complex individual-based
177 model with an arbitrary number of mixed-carriage states.
178
179 **All four models reproduce observed patterns of resistance.** The European Centre
180 for Disease Prevention and Control (ECDC) monitors antibiotic consumption and
181 resistance evolution across European countries (*13*, *28*). These data capture a natural
182 experiment in resistance evolution: for each monitored drug and pathogen, each
183 country reports a different rate of antibiotic consumption in the community and

184 exhibits a different frequency of resistance among invasive bacterial isolates. By fitting
185 models to this multi-country data set, we can potentially rule out models that cannot
186 reproduce the large-scale patterns that are observed. We use Bayesian inference to fit
187 the model-predicted equilibrium frequency of resistance to the reported frequency of
188 penicillin non-susceptibility in *S. pneumoniae* across 27 European countries, assuming a
189 50% carriage prevalence (*11*, *42*) and a carriage duration of 47 days (*47*, *48*) in children
190 under five years old. We begin by assuming that countries only differ by their reported
191 treatment rate—where we define a treatment course as equivalent to $z = 5$ defined daily
192 doses of penicillin—with other model parameters shared across countries.
193
194 Strikingly, each model fits equally well to the empirical relationship between resistance
195 and antibiotic use (all model WAICs are similar; Fig. 2a) and recovers plausible
196 posterior parameter distributions (Fig. 2b). That is, the empirical data do not
197 distinguish between the four alternative mechanisms of resistance evolution we have
198 identified. Later, we relax the assumption that only the treatment rate varies between
199 countries, allowing us to capture additional between-country variation in resistance not
200 explained by population-wide penicillin consumption.
201
202 **Competition and diversity determine the impact of vaccination on resistant**
203 **disease.** To determine the impact of universal vaccination on pneumococcal disease, we
204 consider three outcomes. The first is the impact of the vaccine upon the prevalence of
205 pneumococcal carriage. The second is the vaccine impact upon the frequency of
206 penicillin resistance among circulating pneumococcal strains remaining after
207 vaccination. The third is the impact of the vaccine upon the prevalence of resistant
208 pneumococcal carriage—*i.e.*, the prevalence of carriage multiplied by the frequency of
209 penicillin resistance. Since all four models are equally capable of recapitulating
210 observed patterns of penicillin resistance in *S. pneumoniae*, our aim is to determine
211 whether the mechanism of resistance evolution—competition or diversity—matters
212 when forecasting the impact of interventions for managing resistance.
213
214 We consider two alternative vaccines: an "acquisition-blocking" vaccine, which prevents
215 carriage from being established with probability ε_a, and a "clearance-accelerating"
216 vaccine, which shortens the duration of carriage by a fraction ε_c. Both vaccines reduce

217 pneumococcal transmission through alternative modes of host immunity that might be
218 elicited by a whole-cell or protein-based universal pneumococcal vaccine. Analogously
219 to naturally-acquired serotype-independent pneumococcal immunity (*49*), the
220 protective effect of whole-cell vaccines manifests as accelerated clearance (*50*); it is
221 unclear whether protein-based vaccines would block pneumococcal acquisition, like
222 PCVs, or accelerate clearance (*51*). We refer to ε_a or ε_c as the vaccine efficacy, and for
223 simplicity, we assume that all children under five years old have vaccine protection, as
224 would be established by an infant vaccination programme rolled out across Europe. In
225 order to compare these vaccines with an alternative intervention of antibiotic
226 stewardship, we also evaluate the impact of reducing the rate of penicillin prescribing
227 by a fraction ε_s.
228
229 We find that both vaccines have a similar impact upon carriage prevalence, regardless
230 of whether competition or diversity maintains stability in resistance evolution (Fig. 3a).
231 Specifically, as the vaccine efficacy ε_a or ε_c increases, carriage decreases, with the
232 elimination of pneumococcal carriage occurring at a vaccine efficacy between 50 and
233 60%. Reducing antibiotic prescribing moderately increases pneumococcal carriage,
234 such that carriage prevalence increases to approximately 54% across all countries
235 when penicillin prescribing is eliminated completely.
236
237 However, the mechanism of resistance evolution has a substantial impact upon whether
238 vaccines increase or decrease the frequency of resistance in *S. pneumoniae* in the long
239 term (Fig. 3b). In the "Treatment diversity" and "Pathogen diversity" models, the
240 acquisition-blocking vaccine has relatively little impact upon the frequency of
241 resistance, because administering a universal pneumococcal vaccine to all individuals
242 does not substantially alter the distribution of antibiotic use or of heritable variation in
243 clearance rates. By contrast, in the within-host competition models, vaccination has a
244 substantial impact upon resistance evolution because by reducing pneumococcal
245 circulation, vaccines decrease the rate at which strains encounter each other within
246 hosts, and hence strongly decrease competition between pneumococcal strains.
247 Specifically, the acquisition-blocking vaccine selects strongly against resistance in the
248 "Treatment competition" model: since antibiotic-mediated within-host competition
249 benefits the resistant strain in this model, the vaccine works against this competitive

250 advantage and therefore inhibits resistance. Conversely, in the "Growth competition"
251 model, growth-mediated competition benefits the sensitive strain, and so by reducing
252 competition, vaccination tends to promote resistance. These results expand upon our
253 previous finding that the rate of co-colonisation modulates resistance evolution through
254 its impact upon within-host competition (*26*).
255
256 The clearance-accelerating vaccine exhibits similarly divergent impacts across
257 mechanisms of resistance evolution. However, compared with the acquisition-blocking
258 vaccine, it also has an additional resistance-inhibiting effect across all models, because a
259 shorter duration of carriage—whether natural or vaccine-induced—selects against
260 resistance (*38*). This suggests that vaccines that accelerate natural clearance have a
261 particular potential for managing resistant infections.
262
263 Reducing the rate of penicillin prescribing selects against resistance, as expected,
264 exhibiting a similar impact across all four models.
265
266 The impact on resistant carriage (Fig. 3c), which combines changes in the prevalence of
267 carriage and changes in the frequency of resistance, can be treated as a proxy for the
268 incidence of resistant infections. Overall, under the "Growth competition" model,
269 vaccination at intermediate efficacy is expected to increase the rate of resistant carriage,
270 and hence the number of cases of resistant disease. In other models, vaccination always
271 reduces resistant carriage, particularly under the "Treatment competition" model. A
272 summary of the strongest vaccine impacts is shown in Fig. 3d.
273
274 **Evidence to inform policy and vaccine trials.** For vaccines to be considered an
275 efficient means of controlling resistant infections, they must compare favourably to
276 existing interventions, such as reducing inappropriate antibiotic use (*52*). The UK
277 government has recently announced an initiative to reduce antibiotic consumption by
278 15% by the year 2020 (*52*). Our models predict that a 15% reduction in primary-care
279 penicillin consumption would reduce carriage of penicillin-non-susceptible
280 pneumococci from 6% to 3%. The vaccine efficacy required to yield the same effect
281 varies considerably depending upon the mechanism of resistance evolution (Fig 4a); for
282 example, the required vaccine efficacy is lowest under the "Treatment competition"

283 model (ε_a = 11%; ε_c = 7%), and highest under the "Growth competition" model (ε_a =
284 52%; ε_c = 50%). A full comparison of vaccine and stewardship interventions would
285 require accounting for the economic cost of vaccines versus antibiotics, the wider range
286 of resistant pathogens that would be targeted by restrictions on antibiotic use, and any
287 potential increase in pathogen circulation that might be brought about by inadvertent
288 decreases in appropriate antibiotic use.
289
290 In randomized controlled trials of pneumococcal conjugate vaccines, resistance-related
291 endpoints have routinely been evaluated over a follow-up period of between 6 months
292 and 3.5 years after vaccination (*53*, *54*). If vaccine-induced changes in resistance
293 evolution unfold over a considerably longer timescale, similarly-designed trials may not
294 appropriately capture vaccine impact on resistance. Indeed, we find that it can take 5–
295 10 years for the full effects of resistance evolution to be seen (Fig. 4b), and that short-
296 term drops in resistance can be reversed—or even give way to increased resistance—in
297 the long term. Moreover, a trial in which vaccination is not offered to a substantial
298 fraction of the population would not capture the full impact of reduced pneumococcal
299 circulation, which is what drives competition-mediated changes in resistance in our
300 models. Finally, our analysis assumes that vaccines are administered to all recipients
301 simultaneously. In a real-world setting where vaccination would be rolled out gradually,
302 the full effect of vaccination could take even longer to observe.
303
304 The impact of vaccination at a national level varies depending upon the treatment rate
305 in a given country. Focusing on the specific outcome of childhood pneumococcal
306 pneumonia cases, we find that while interventions have a consistent impact from
307 country to country on the total pneumonia case rate, the impact on resistant pneumonia
308 cases is greatest in those countries where antibiotic use, and hence resistance, is highest
309 (Fig. 4c). We focus on resistant carriage, but the realised health benefits of any
310 intervention targeting both resistant and sensitive strains will depend upon the relative
311 health burdens of susceptible versus non-susceptible *S. pneumoniae* infections, which is
312 an area of ongoing research (*55*).
313
314 **Vaccination in a high-burden setting.** High prevalences of carriage, disease, and
315 resistance are often observed in low-income settings, and this may substantially alter

316 predictions of vaccine impact. As an illustrative example, a 90% pneumococcal carriage
317 rate, with 81% of isolates resistant to penicillin, has been observed among children
318 under five years old in western Kenya (*56*). This may be partly attributable to a longer
319 average duration of carriage in this setting, as a 71-day mean duration of natural
320 pneumococcal carriage has been measured in Kilifi, eastern Kenya (*57*).
321
322 To model a similar high-burden setting, we adjust model parameters estimated from
323 European data: increasing the mean natural carriage duration, transmission rate, and
324 treatment rate to match observed data, and ignoring mixing with any other countries (f
325 = 1), while keeping other parameters the same. We find that a comparatively greater
326 vaccine efficacy is needed to reduce the prevalence of resistant carriage in a high-
327 burden, high-resistance setting (Fig. 5). This is particularly true under the "Growth
328 competition" model, because in this model resistant carriage only declines as total
329 pneumococcal carriage declines, and it is particularly difficult to reduce overall carriage
330 in a high-transmission setting. Simultaneously, vaccination may have a comparatively
331 greater impact in high-burden settings because of a comparatively higher incidence of
332 disease: for example, Kenya is estimated to have an 8.8-fold higher incidence of severe
333 pneumococcal pneumonia than the average in Europe (*58*).
334
335 **Accounting for additional between-country variation does not substantially alter**
336 **predictions.** Our focus thus far has been on the impact of the four identified
337 mechanisms *per se* upon resistance evolution, and accordingly we have focused on
338 reproducing the positive association between treatment rate and resistance frequency
339 rather than attempting to capture the additional variability in resistance frequency
340 between countries not accounted for by the reported treatment rate alone (Fig. 2a). This
341 additional variability may partially stem from differences in national testing and
342 reporting practices, or between-country differences in the distribution of pneumococcal
343 serotypes among invasive isolates (*59*). However, another possibility is that this
344 additional variability in resistance results from systematic differences in pathogen
345 biology or host behaviour across countries which can be captured by our modelling
346 framework.
347

348 To help identify which model parameters could account for this variability, we relax the
349 assumption that only the treatment rate varies across countries, and perform Bayesian
350 maximum *a posteriori* fitting, assuming one additional parameter (c, b, β, u, f, z, g, κ, a, δ,
351 or k) is free to vary between countries while other parameters are held constant. We
352 find that additional variation in resistance between countries can be explained by
353 variation in certain other parameters, depending upon which model is used (Fig. 6a–b).
354 Importantly, among those parameters for which additional variation between countries
355 can explain the variation in resistance (Fig. 6c), predictions for the overall impact of
356 vaccination remain similar with the major differences still attributable to the underlying
357 mechanism of resistance evolution (Fig. 6d; Supplementary Figs. 3–14). Models that
358 could make more accurate country-specific predictions would need to account for the
359 effects of demographic structure, differences in carriage prevalence and disease rates
360 between settings, and variable vaccine protection among individuals.
361
362 **Discussion**
363
364 We have identified four mechanisms of resistance evolution that are capable of
365 recapitulating the observed relationship between penicillin consumption and penicillin
366 non-susceptibility in *S. pneumoniae* across Europe. These mechanisms are not mutually
367 exclusive, but the relative importance of each is predicted to have a substantial impact
368 upon predictions for resistance evolution under vaccination. In particular, the
369 "directionality" of within-host competition—that is, whether, on average, within-host
370 competition tends to benefit resistant or sensitive strains—strongly determines
371 whether vaccination selects for a decrease or an increase in antibiotic resistance in the
372 long term. This directionality may vary between pathogens, but is also sensitive to the
373 antibiotic treatment rate, and so may also vary between settings. Although we have
374 focused on competition between sensitive and resistant strains of *S. pneumoniae* only,
375 competition between serotypes (*24*) and with other bacteria colonizing the
376 nasopharynx will also impact upon resistance evolution, and determining the
377 importance of these other sources of within-host competition is crucial.
378
379 A key result of our models is that the mode of vaccine protection—whether acquisition-
380 blocking or clearance-accelerating—has an appreciable impact upon resistance

381 evolution. Whole-cell and purified-protein pneumococcal vaccines may induce
382 antibody-mediated humoral immunity, CD4+ T helper-17 cell-mediated immunity, or
383 both, with the type of immunity mediating pneumococcal acquisition, carriage, and
384 disease in ways that are still not fully understood (*49–51*). By modelling both modes of
385 vaccine action, we have highlighted that clearance-accelerating vaccines have increased
386 potential for preventing the spread of resistance, because in shortening the duration of
387 asymptomatic carriage they limit the fitness advantage of resistant pathogens under
388 selection pressure from antibiotic use.
389
390 The prevalence of penicillin non-susceptibility in *S. pneumoniae* has remained largely
391 stable in Europe between 2005–2017, a period which saw the incorporation of PCV into
392 the routine immunization schedules of most European countries (*60*). However,
393 because serotype replacement has largely negated any vaccine impact on the
394 prevalence of nasopharyngeal pneumococcal carriage (*10*, *11*), it is not clear that we
395 should expect to see any effects of competition-mediated resistance evolution following
396 a serotype-specific vaccine such as PCV—particularly given the complexity of detecting
397 vaccine-attributable changes in resistance in a population-level associational study that
398 would be confounded both by serotype replacement and by other changes in resistance
399 evolution that might be expected to occur at a national level over the course of multiple
400 years.
401
402 Under the "Treatment diversity" and "Pathogen diversity" models, we have argued that
403 universal pneumococcal vaccination will have little impact upon the long-term
404 evolution of antibiotic resistance because it does not change the sources of diversity
405 that modulate resistance evolution. Nonetheless, it is possible to target vaccines such
406 that this diversity is harnessed to manage resistance: high-resistance serotypes could
407 be targeted with a serotype-specific vaccine, or high-treatment subpopulations could be
408 targeted for vaccination in order to more effectively manage resistance. Indeed,
409 vaccination does have an additional inhibiting effect upon resistance in our models
410 because of the latter effect. This inhibition occurs because the vaccine has a relatively
411 greater impact upon transmission in populations where the prevalence of carriage is
412 already low, which in our models occur in countries or subpopulations with more
413 antibiotic consumption. Since these populations drive resistance more strongly, the

414 vaccine's comparatively greater impact in these populations tends to moderately inhibit
415 resistance overall. We note that while previous work (*38*) has suggested that resistance
416 evolution under a "Pathogen diversity" model results in a "stepped" resistance pattern
417 in which D-types are either fully sensitive or fully resistant at equilibrium, we find that
418 small amounts of mixing between populations can smooth out this pattern and allow
419 intermediate rates of resistance within subtypes (Supplementary Fig. 2). Finally, while
420 we have framed "Treatment competition" and "Growth competition" as two distinct
421 alternatives, they can instead be viewed as endpoints on a continuum, with possible
422 models of resistance evolution for which both $c > 0$ and $b > 0$ lying between them. The
423 impact of vaccination on resistance in such a model would depend upon the relative
424 importance of treatment-mediated and growth-mediated competition.
425
426 This analysis has necessarily made simplifying assumptions. We have focused on
427 prevalence (the fraction of individuals who are carriers) rather than incidence (the rate
428 of new carriage episodes) of nasopharyngeal carriage in presenting our findings. There
429 is evidence that pneumococcal disease progression is more likely to occur shortly after
430 nasopharyngeal acquisition (*61*), suggesting that incidence may be more relevant than
431 prevalence for predicting disease outcomes. Of particular note, recent modelling work
432 has suggested that clearance-accelerating vaccines can increase rates of pneumococcal
433 acquisition, if extended carriage is protective against new acquisition (*62*). However, it
434 is not obvious how to compare rates of carriage acquisition across the models examined
435 in this paper, particularly because co-colonisation is explicitly tracked—and fitted to
436 data—in some but not all models. More work is required to clarify the links between
437 acquisition, carriage, and disease across competing models of pneumococcal
438 transmission. Additionally, we have assumed that antibiotic treatment rates among
439 pneumococcal carriers remains constant after the introduction of a vaccine, even
440 though treatment rates dropped in many settings following PCV introduction (*5*, *9*).
441 However, for a universal pneumococcal vaccine that reduces antibiotic treatment rates
442 because it reduces carriage and thereby prevents antibiotic-treatable disease, any
443 reduction in treatment will only occur among individuals who, because of vaccine
444 protection, are not pneumococcal carriers, all else being equal. It might then be
445 expected that treatment rates in carriers would remain equally high among those
446 individuals for whom vaccine protection has failed.

447

448 Our work helps resolve the question: What explains the persistent coexistence between
449 resistant and sensitive strains of *S. pneumoniae*? (*25*) by demonstrating that multiple
450 mechanisms are capable of explaining trends of resistance across European countries.
451 Since there is empirical support for within-host competition between sensitive and
452 resistant pathogen strains (*63–66*), heritable differences in the propensity for resistance
453 within species (*38*), and within-country heterogeneity in antibiotic consumption rates
454 (*67–69*), all of these mechanisms likely contribute to this pattern. Our results
455 contextualize previous mathematical studies which have variously suggested that
456 serotype-specific vaccination may increase (*24*), decrease (*22*) or have no impact upon
457 (*18*) the frequency of resistance in *S. pneumoniae*. While the potential for vaccination to
458 promote resistance because of competition between sensitive and resistant strains has
459 been described previously (*24*), we have shown that vaccination can either promote or
460 inhibit resistance depending upon the directionality of within-host competition. While
461 vaccines targeting highly-resistant serotypes can decrease resistance (*22*), we have
462 shown that a serotype-independent vaccine promoting accelerated natural clearance
463 can decrease resistance across all circulating subtypes. And where single-population
464 models have found no long-term impact of vaccination on resistance frequency (*18*), we
465 have shown that in multi-population models, vaccination can inhibit resistance if it has
466 a larger impact in subpopulations that consume more antibiotics. The direction and
467 magnitude of this effect would depend upon variation in vaccine uptake, vaccine
468 efficacy, and pathogen transmission among subpopulations, and we have not
469 systematically explored this variation here.
470

471 A highly efficacious serotype-independent pneumococcal vaccine can indeed reduce the
472 overall burden of antibiotic-resistant pneumococcal infections. However, the long-term
473 effect upon resistance of a vaccine with intermediate efficacy is less certain, as vaccine
474 impact depends crucially upon the mechanisms that drive resistance evolution. Thus,
475 empirical investigation of pathogen competitive dynamics—and the impact of setting-
476 specific factors on these dynamics—is needed to make accurate predictions of vaccine
477 impact on resistant infections.
478

479 **Methods**

Study design. This study comprises four parts: a literature search used to identify plausible mechanisms through which coexistence can be maintained between sensitive and resistant pneumococcal strains across a range of antibiotic treatment rates; a mathematical modelling study embedding these mechanisms of resistance evolution in four models of pneumococcal transmission; a Bayesian statistical analysis to fit these models to empirically observed frequencies of penicillin non-susceptibility and community penicillin consumption across 27 European countries for the year 2007; and a vaccine impact analysis using these fitted models to forecast the impact of a universal pneumococcal vaccine. We use data from 2007 because changes in pneumococcal resistance reporting standards for some countries after this year hamper the between-country comparability of data (*70*). Our objectives were to identify the mechanisms potentially responsible for maintaining coexistence between resistant and sensitive pneumococci in Europe, and to determine whether the impact of vaccination on the evolution of resistance depends upon which mechanism is assumed to operate.

Mechanisms driving resistance. We searched PubMed using the terms: (AMR OR ABR OR ((antimicrobial OR antibiotic) AND resist*)) AND ((model OR modelling OR modeling) AND (dynamic* OR transmi* OR mathematical)) AND (coexist* OR intermediate). This yielded 93 papers (Supplementary Table 1). We included all papers containing a dynamic host-to-host pathogen transmission model analysing both sensitive and resistant strains with stable coexistence as an outcome of the model. From the 11 studies meeting these criteria, we identified nine unique mechanisms, two of which correspond to alternative parameterisations of a within-host competition model. We ruled out four mechanisms because of implausibility or because previous work shows that the mechanism does not bring about substantial coexistence, leaving four mechanisms (Table 1).

Model framework. We analyse the evolution of antibiotic resistance by tracking the transmission of resistant and sensitive bacterial strains among hosts in a set of M countries indexed by $m \in \{1,2,\dots,M\}$ using systems of ordinary differential equations.

In a simple model, hosts can either be non-carriers (X), carriers of the sensitive strain (S), or carriers of the resistant strain (R). Omitting country-specific subscripts m for concision, model dynamics within a country are captured by

$$\begin{aligned} \mathrm{d}S/\mathrm{d}t &= \lambda_S X - (u + \tau)S \\ \mathrm{d}R/\mathrm{d}t &= (1 - c)\lambda_R X - uR \\ X &= 1 - S - R\,, \end{aligned} \qquad (1)$$

where λ_S is the force of infection of the sensitive strain, λ_R is the force of infection of the resistant strain, c is the transmission cost of resistance, u is the rate of natural clearance, and τ is the treatment rate. In this model, in a given country, the total carriage of the sensitive strain is S and the total carriage of the resistant strain is R. Force of infection terms are defined below.

The "Treatment diversity" model extends the simple model (eq. 1) by structuring each country into multiple subpopulations that exhibit different rates of antibiotic treatment and make contact with each other at unequal rates (*25*, *34*, *35*, *71*). In each country, we model N equally-sized representative subpopulations indexed by $i \in \{1,2,\ldots,N\}$, where we assume $N = 10$. Dynamics within a country are

$$\begin{aligned} \mathrm{d}S_i/\mathrm{d}t &= \lambda_{S,i} X - (u + \tau_i)S \\ \mathrm{d}R_i/\mathrm{d}t &= (1 - c)\lambda_{R,i} X - uR \\ X_i &= 1 - S_i - R_i \end{aligned} \qquad (2)$$

where we assume that treatment rates of subpopulations within a country approximately follow a gamma distribution with shape parameter κ and mean treatment rate τ. Accordingly, the rate of antibiotic consumption in subpopulation i is $\tau_i = \int_{Q_\Gamma\left(\frac{i-1}{N}|\kappa\right)}^{Q_\Gamma\left(\frac{i}{N}|\kappa\right)} t\, P_\Gamma(t|\kappa)\, dt$, where $Q_\Gamma(q|\kappa)$ is the quantile q of the gamma distribution with shape κ and $P_\Gamma(t|\kappa)$ is the probability density at t of the same gamma distribution.

The "Pathogen diversity" model extends the simple model (eq. 1) by structuring the pathogen population into D different "D-types" (we assume $D = 25$), each with a

different natural clearance rate, where each type is kept circulating by diversifying selection acting on D-type (*38*). Dynamics within a country are

$$\mathrm{d}S_d/\mathrm{d}t = q_d\lambda_{S,d}X - (u_d + \tau)S_d$$
$$\mathrm{d}R_d/\mathrm{d}t = q_d(1 - c)\lambda_{R,d}X - u_dR_d$$
$$X = 1 - \Sigma_d\,(S_d + R_d) \qquad (3)$$

where $q_d = (1 - \frac{S_d+R_d}{\sum_{j=1}^{D}(S_j+R_j)} + \frac{1}{D})^a$ is the strength of diversifying selection for D-type $d \in \{1,2,\ldots,D\}$ and $u_d = u\left(1 + \delta\left(2\frac{d-1}{D-1} - 1\right)\right)$ is the clearance rate for D-type d, where model parameter a is the power of diversifying selection and model parameter δ is the range of clearance rates (*38*). In a given country, the total carriage of the type-d sensitive strain is S_d and the total carriage of the type-d resistant strain is R_d.

Finally, the within-host competition models (*26*) allow hosts to carry a mix of both strains. Hosts can carry the sensitive strain with a small complement of the resistant strain (S_R) or the resistant strain with a small complement of the sensitive strain (R_S). Dynamics within a country are

$$\mathrm{d}S/\mathrm{d}t = \lambda_SX - (u + \tau)S - k(1 - c)\lambda_RS + b_0S_R$$
$$\mathrm{d}S_R/\mathrm{d}t = k(1 - c)\lambda_RS - (u + \tau)S_R + bR_S - b_0S_R$$
$$\mathrm{d}R_S/\mathrm{d}t = k\lambda_SR - (u + \tau)R_S - bR_S$$
$$\mathrm{d}R/\mathrm{d}t = (1 - c)\lambda_RX - uR - k\lambda_SR + \tau(S_R + R_S)$$
$$X = 1 - S - R - S_R - R_S\,, \qquad (4)$$

where k is the rate of co-colonisation relative to primary colonisation, b is the within-host growth benefit of sensitivity (i.e. the rate of the $R_S \rightarrow S_R$ transition), and $b_0 = 4b$ is the rate of the $S_R \rightarrow S$ transition as a function of this growth benefit. In a given country, the total carriage of the sensitive strain is $S + S_R$ and the total carriage of the resistant strain is $R + R_S$. "Treatment competition" assumes the cost of resistance is incurred by reduced transmission potential ($b = 0$ and $c > 0$), while "Growth competition" assumes that the cost of resistance is incurred through decreased within-host growth ($b > 0$ and $c = 0$).

576

577 In equations 1, 3 and 4, the force of infection of a particular strain A in country m is $\lambda_{\mathrm{A}} =$
578 $\beta\left(f A_{\mathrm{tot}|m} + (1-f)\sum_{\ell=1}^{M} h_\ell A_{\mathrm{tot}|\ell}\right)$, where β is the transmission rate, f is the between-
579 country assortativity, h_ℓ is the relative population size of country m (such that $\sum_\ell h_\ell =$
580 1), and $A_{\mathrm{tot}|\ell}$ is the total carriage of strain A in country ℓ. The probability with which
581 individuals contact an individual from another country, 1 – f, captures those contacts
582 made with individuals from another country in either one's home country or a foreign
583 country. In equation 2, the force of infection of a particular strain A in subpopulation i of
584 country m is $\lambda_{\mathrm{A},i} = \beta\left(f\left(g A_{\mathrm{tot}|m,i} + (1-g)\sum_{j=1}^{N}\frac{1}{N}A_{\mathrm{tot}|m,j}\right) + (1-\right.$
585 $\left.f)\sum_{\ell=1}^{M}\sum_{j=1}^{N}\frac{h_\ell}{N}A_{\mathrm{tot}|\ell,j}\right)$, where g is the within-country assortativity and $A_{\mathrm{tot}|\ell,j}$ is the
586 total carriage of strain A in subpopulation j of country ℓ.
587

588 *Data and model fitting.* We extracted community penicillin consumption and penicillin
589 non-susceptibility in *S. pneumoniae* invasive isolates from databases made available by
590 the ECDC (*13*, *28*). We assume that community penicillin consumption drives penicillin
591 resistance, that antibiotic consumption is independent of whether an individual is
592 colonised by pneumococcus, and that resistance among invasive bacterial isolates is
593 representative of resistance among circulating strains more broadly. Countries report
594 community penicillin consumption in defined daily doses (DDD) per thousand
595 individuals per day. To transform this bulk consumption rate into the rate at which
596 individuals undertake a course of antibiotic therapy, we analysed prescribing data from
597 eight European countries, estimating that, on average, 5 DDD in the population at large
598 correspond to one treatment course for a child under 5 years of age. This conversion
599 rate varies between countries (Supplementary Table 4), but since the data are
600 incomplete (8 of 27 countries) we have not explicitly accounted for this variability in
601 our main model fitting results.
602

603 Our model framework tracks carriage of *S. pneumoniae* among children aged 0–5 years,
604 the age group driving both transmission and disease. In European countries, we assume
605 that the prevalence of pneumococcal carriage in under-5s is 50% (*11*, *42*) and the
606 average duration of carriage is 47 days (*47*, *48*). We calculate the average incidence of *S.*
607 *pneumoniae*-caused severe pneumonia requiring hospitalisation as 610 per million

children under 5 per year (*58*) across the European countries in our data set. See Supplementary Tables 3, 5, and 6 for details of calculations relating to pneumococcal carriage duration and disease incidence.

We use Bayesian inference via differential evolution Markov chain Monte Carlo (*72*) to identify model parameters that are consistent with empirical data. Country m has antibiotic treatment rate τ_m and reports r_m of n_m isolates are resistant. Over all M countries, these data are denoted $\tau = (\tau_1, \tau_2, \dots, \tau_M)$, $r = (r_1, r_2, \dots, r_M)$, and $n = (n_1, n_2, \dots, n_M)$, respectively. The probability of a given set of model parameters θ is then

$$P(\theta|\tau, r, n) \propto P(\tau, r, n|\theta)P(\theta),$$

where $P(\theta)$ is the prior probability of parameters θ and

$$P(\tau, r, n|\theta) = C\big(Y = Y(\tau|\theta)\big) \prod_{m=1}^{M} R\big(r = r_m, n = n_m, \rho = \rho(\tau_m|\theta)\big)^{N_m/\bar{N}}$$

is the likelihood of data τ, r, n given model parameters θ. Above, $Y(\theta)$ is the average model-predicted prevalence of carriage across all countries and $\rho(\tau_m|\theta)$ is the model-predicted resistance prevalence for country m. $C(Y)$ is the credibility of prevalence of carriage Y and $R(r,n,\rho)$ is the credibility of r out of n isolates being resistant when the model-predicted resistance prevalence is ρ. For $C(Y)$, we use a normal distribution with mean 0.5 and standard deviation 0.002. For $R(r,n,\rho)$, we use $R(r, n, \rho) = \int_0^1 T\big(x|\mu = \rho, \sigma = \sigma(\theta)\big)\binom{n}{r}x^r(1-x)^{n-r}\,dx$, a binomial distribution where the probability of success is modelled as a [0,1]-truncated normal distribution centred on ρ and with standard deviation σ. The parameter σ captures the unexplained between-country variation in resistance frequency. Here, $T(x|\mu, \sigma) = \frac{\varphi(x|\mu,\sigma)}{\big(\Phi(1|\mu,\sigma) - \Phi(0|\mu,\sigma)\big)}$, where $\varphi(\mu, \sigma) = \frac{1}{\sqrt{2\pi\sigma^2}} exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right)$ is the untruncated normal PDF and $\Phi(\mu, \sigma) = \frac{1}{2}(1 + erf\left(\frac{x-\mu}{\sigma\sqrt{2}}\right))$ is the untruncated normal cumulative distribution function. Finally, N_m is the population size of country m and $\bar{N}$ is the average population size across all countries; the exponent $N_m/\bar{N}$ allows us to weight the importance of each country by its

population size, which allows a closer fit with the overall resistance prevalence across all countries.

We adopt $c \sim \text{Beta}(\alpha = 1.5, \beta = 8.5)$, $b \sim \text{Gamma}(\kappa = 2, \theta = 0.5)$, $\beta \sim \text{Gamma}(\kappa = 5, \theta = 0.35)$, $g \sim \text{Beta}(\alpha = 10, \beta = 1.5)$, $\kappa \sim \text{Gamma}(\kappa = 4, \theta = 2)$, $a \sim \text{Gamma}(\kappa = 2, \theta = 5)$, $\delta \sim \text{Beta}(\alpha = 20, \beta = 25)$, and $k \sim \text{Normal}(\mu = 1, \sigma = 0.5)$ as weakly informative prior distributions for model fitting. We set the unexplained between-country variation in resistance prevalence σ to 0.06 across all models based on a preliminary round of model fitting with σ as a free parameter, and set the between-country assortativity *f* to 0.985 (*i.e.*, 1.5% of contacts occur with individuals from a different country) based on rates of travel within the EU. See Supplementary Table 7 for MCMC diagnostics.

To match model predictions to a high-burden setting, we increase the duration of carriage to 71.4 days; increase the transmission rate by a factor of 3.49 (Treatment diversity), 3.62 (Pathogen diversity), 3.61 (Treatment competition), or 3.20 (Growth competition), so that carriage prevalence reaches 90.0%; and increase the antibiotic consumption rate to 1.670, 1.458, 1.138, or 5.887 courses per person per year, respectively, so that resistance prevalence reaches 81.4%.

Interventions. Interventions have the following impact on model parameters: for the acquisition-blocking vaccine, the transmission rate becomes $\beta' = (1-\varepsilon_a)\,\beta$; for the clearance-accelerating vaccine, the clearance rate becomes $u' = u/(1-\varepsilon_c)$; and under antibiotic stewardship, the average treatment rate in each country m becomes $\tau_m' = \tau_m (1-\varepsilon_s)$.

Capturing additional between-country variation in resistance frequency. We begin by finding the maximum *a posteriori* model fits according to the likelihood and prior distributions for each of the four models of resistance evolution. This identifies the following parameter values for each model. "Treatment diversity": β = 1.41, *c* = 0.124, *g* = 0.976, and κ = 2.22. "Pathogen diversity": β = 1.33, *c* = 0.191, *a* = 10.8, and δ = 0.608. "Treatment competition": β = 1.42, *c* = 0.191, and *k* = 1.64. "Growth competition": β = 1.39, *b* = 0.195, and *k* = 1.61. Then, we perform maximum *a posteriori* model fits for each

potentially-varying parameter under each model, allowing the varying parameter to take on a different value for each country and fixing other parameters at their maximum *a posteriori* values as determined in the previous step, or at specific assumed values for $u = 0.65$, $f = 0.985$, and $z = 5$. For the second step, we use a modified likelihood function

$$P(\tau, r, n|\theta) = C\big(Y = Y(\tau|\theta)\big) \prod_{m=1}^{M} \phi\left(\mu = \frac{r_m + 1}{n_m + 2}, \sigma = 0.001 \middle| x = \rho(\tau_m|\theta)\right)^{N_m/\bar{N}},$$

where $\phi(\mu, \sigma|x)$ is the normal probability density function. This modified likelihood function ensures that the model-predicted resistance frequency for each country is matched as closely as possible to the maximum-likelihood resistance prevalence $\frac{r_m+1}{n_m+2}$ (*i.e.*, assuming a uniform prior on resistance frequency) for each country m, so that model fits are comparable across different varying parameters. We use the Nelder-Mead algorithm to maximize the posterior probability in both steps.

Supplementary Figs. 3–6 show maximum *a posteriori* fits when allowing an additional parameter to vary freely between countries, along with the parameter values identified by model fitting. Supplementary Figs. 7–10 show the impact of vaccination, focusing on those parameters for which model fitting was able to capture the observed variability in resistance frequency between countries (*i.e.*, those parameters plotted to the left of the dashed line in Fig. 6b of the main text). Supplementary Figs. 11–14 show the impact of vaccination for the remaining parameters.

691 **List of Supplementary Materials**

692

693 **Supplementary Table 1.** Literature review.

694 **Supplementary Table 2.** Summary of model parameters.

695 **Supplementary Table 3.** Carriage duration.

696 **Supplementary Table 4.** Penicillin consumption.

697 **Supplementary Table 5.** Pneumococcal morbidity.

698 **Supplementary Table 6.** Carriage duration (Kilifi).

699 **Supplementary Table 7.** MCMC diagnostics.

700 **Supplementary Fig. 1.** Patterns of penicillin non-susceptibility across European
701 countries, 2005–2017.

702 **Supplementary Fig. 2.** Carriage and resistance of D-types in "Pathogen variability"
703 model.

704 **Supplementary Fig. 3.** Varying-parameter fits for "Treatment diversity" model.

705 **Supplementary Fig. 4.** Varying-parameter fits for "Pathogen diversity" model.

706 **Supplementary Fig. 5.** Varying-parameter fits for "Treatment competition" model.

707 **Supplementary Fig. 6.** Varying-parameter fits for "Growth competition" model.

708 **Supplementary Fig. 7.** Vaccine impact for "Treatment diversity" model, varying
709 parameters c and z.

710 **Supplementary Fig. 8.** Vaccine impact for "Pathogen diversity" model, varying
711 parameters c, δ, and z.

712 **Supplementary Fig. 9.** Vaccine impact for "Treatment competition" model, varying
713 parameters β, c, u, k, and z.

714 **Supplementary Fig. 10.** Vaccine impact for "Growth competition" model, varying
715 parameters b and z.

716 **Supplementary Fig. 11.** Vaccine impact for "Treatment diversity" model, varying other
717 parameters.

718 **Supplementary Fig. 12.** Vaccine impact for "Pathogen diversity" model, varying other
719 parameters.

720 **Supplementary Fig. 13.** Vaccine impact for "Treatment competition" model, varying
721 other parameters.

722 **Supplementary Fig. 14.** Vaccine impact for "Growth competition" model, varying other
723 parameters.

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986 **Table 1. Mechanisms for maintaining coexistence**

	Mechanism	Mode of action	Plausible mechanism for coexistence in *S. pneumoniae*?	Consistent with empirical patterns?
DIVERSITY	**Treatment diversity**	Assortatively-mixing subpopulations differ in treatment rates (*25*, *34–37*)	✓ Yes	✓ Yes
DIVERSITY	**Pathogen diversity**	Subtypes maintained by diversifying selection differ in propensity for resistance (*38*)	✓ Yes	✓ Yes
DIVERSITY	**Treated class**	Individuals currently in treatment maintain resistant strains (*25*, *34*, *39*, *40*)	✗ No: Only supports a small amount of coexistence (*25*)	■ N/A
DIVERSITY	**Within-host niches**	Sensitive and resistant strains exploit separate niches within the host (*30*, *41*)	✗ No: Resistant and sensitive strains are known to occupy the same niches (*29*)	■ N/A
DIVERSITY	**Mutation pressure**	Mutation-selection balance maintains intermediate resistance frequency (*30*, *31*, *37*)	✗ No: De novo acquisition of resistance in *S. pneumoniae* is not frequent enough (*25*)	■ N/A
DIVERSITY	**Prescription feedback**	Doctors reduce prescribing of a drug as resistance to it increases (*37*, *39*)	✗ No: Does not explain how coexistence is maintained over a range of treatment rates	■ N/A
COMPETITION	**Within-host competition: Treatment competition**	Within-host competition creates frequency-dependent selection for resistance (*25*, *26*, *32*, *33*, *40*)	✓ Yes	✓ Yes
COMPETITION	**Within-host competition: Growth competition**	"	✓ Yes	✓ Yes
COMPETITION	**Superinfection**	Superinfection creates frequency-dependent selection for resistance (*30*)	✗ No: Requires resistant strain to transmit better than sensitive strain in absence of antibiotics	■ N/A

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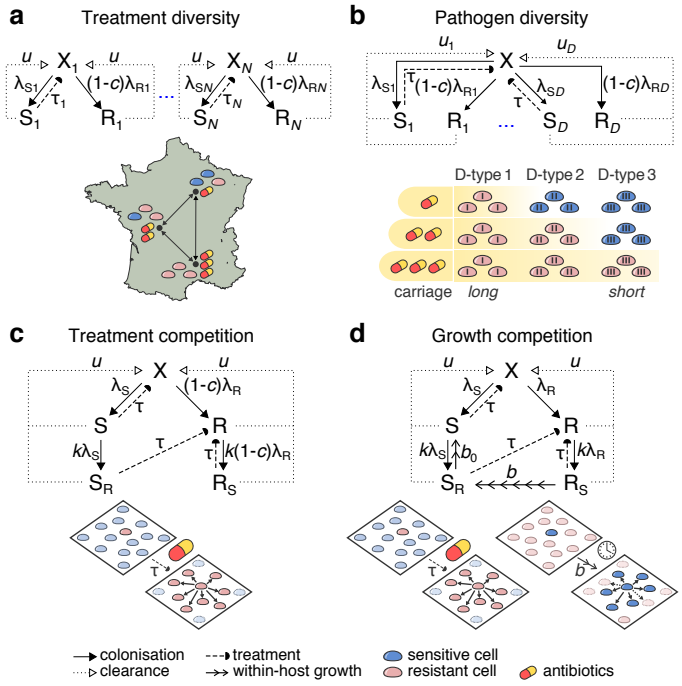


Fig. 1. Four models of resistance evolution. X hosts are uncolonised, S hosts are colonised with the sensitive strain and R hosts are colonised with the resistant strain. λ_S and λ_R are the force of infection of the sensitive and resistant strain, respectively; c is the transmission cost of resistance; u is the natural clearance rate; and τ is the rate of antibiotic treatment. **(a)** "Treatment diversity": each country is split into subpopulations varying in treatment rate τ_i. Assortative mixing between subpopulations maintains coexistence. **(b)** "Pathogen diversity": the pathogen comes in multiple subtypes maintained by diversifying selection, each with its own clearance rate u_d. Subtypes with a longer carriage duration experience stronger selection for resistance than those with a shorter carriage duration, which maintains circulation of both sensitive and resistant strains overall. **(c)** "Treatment competition": singly-colonised hosts can acquire a small amount of another strain at relative rate k (host states S_R and R_S). Population-level coexistence is maintained by treatment-mediated within-host competition between co-colonising strains. **(d)** "Growth competition": as in (c), but the transmission cost of resistance is removed and sensitive strains now outgrow resistant strains within co-colonised hosts at rate b. Coexistence is maintained by both treatment-mediated and growth-mediated within-host competition.

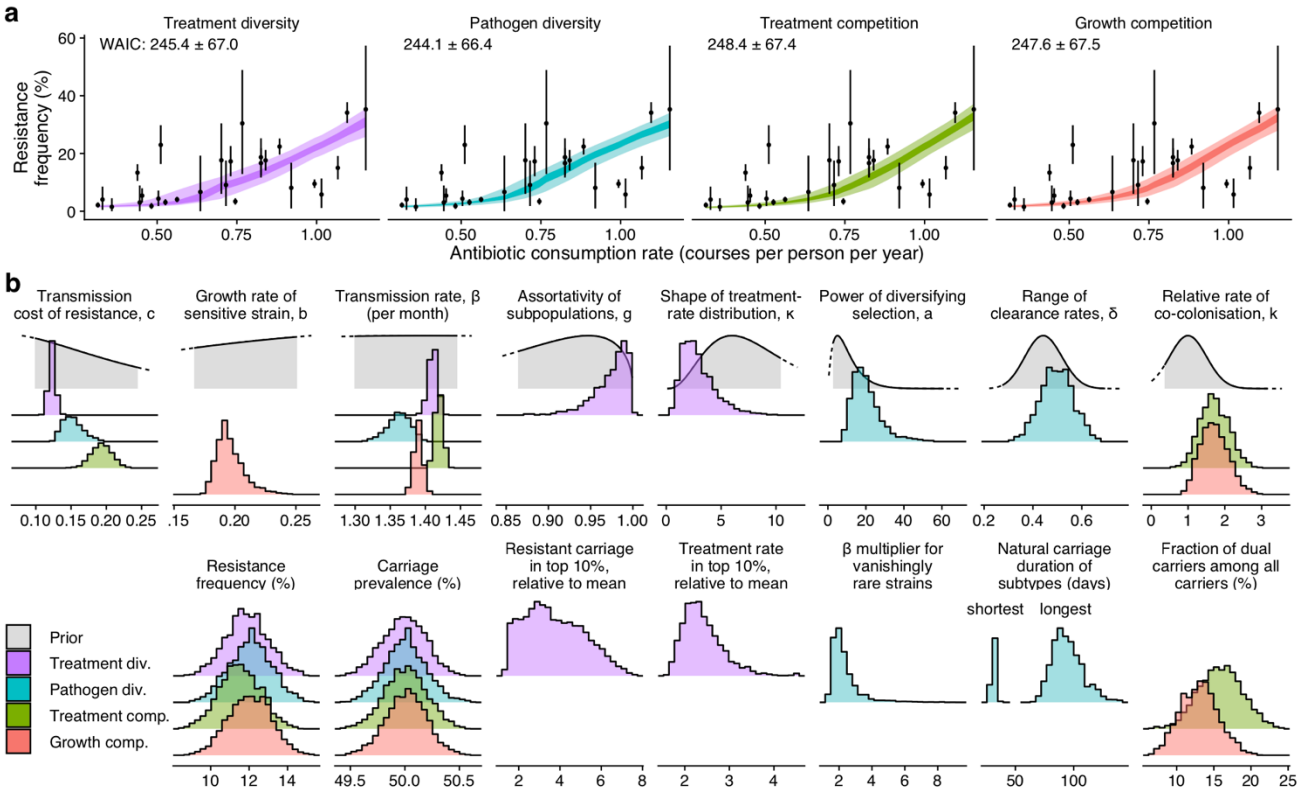


Fig 2. Four models reproduce patterns of resistance in *S. pneumoniae* in Europe. **(a)** Model fits with associated WAIC (± standard error). Vertical lines show the 95% highest density intervals (HDIs) for the reported proportion of invasive *S. pneumoniae* isolates that are resistant to penicillin plotted against the penicillin consumption rate in under-5s. Ribbons show the 50% and 95% HDIs for resistance prevalence from each fitted model. **(b)** The top row shows estimated posterior distributions for the free parameters in each model; the bottom row shows model outputs associated with these parameters to aid interpretation.

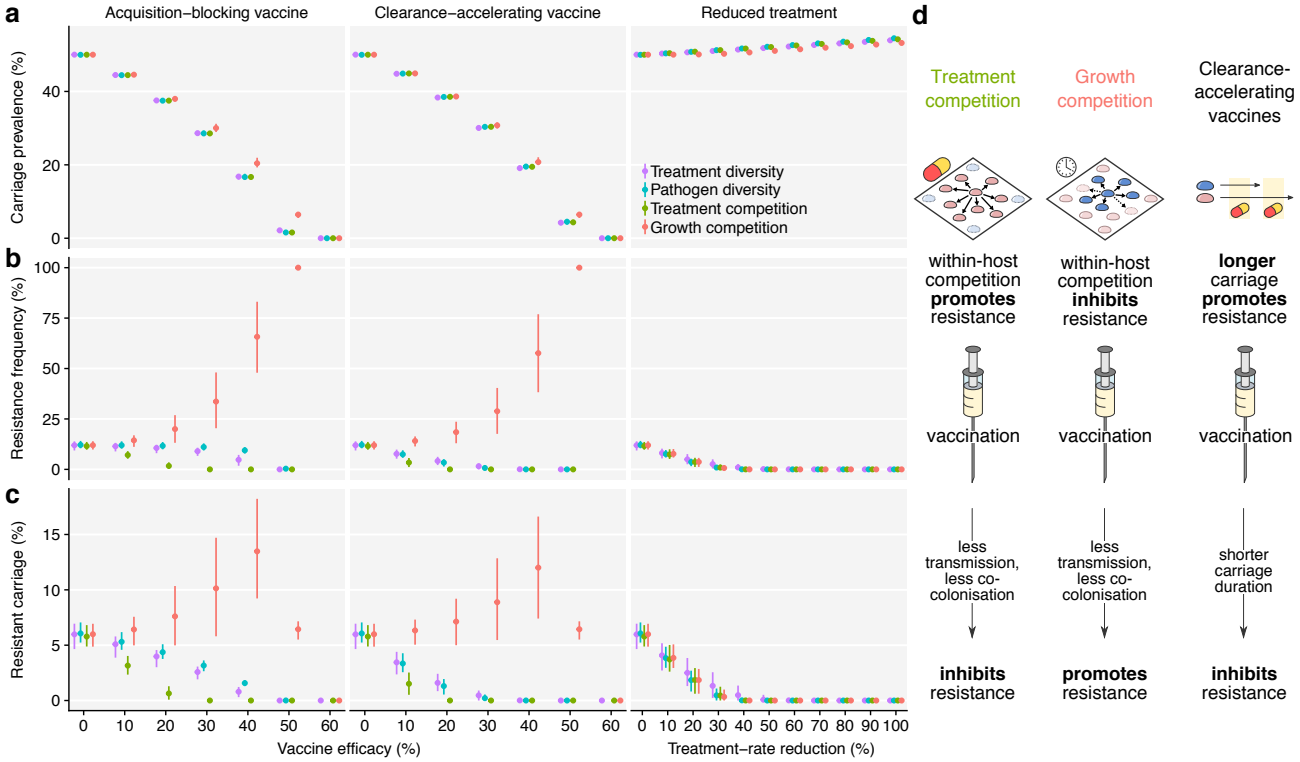


Fig. 3. Impact of interventions. Impact of vaccine and treatment interventions on **(a)** carriage prevalence, **(b)** resistance frequency, and **(c)** resistant carriage (mean and 95% HDI). **(d)** Illustration of the strongest forces selecting for greater or lesser resistance across models.

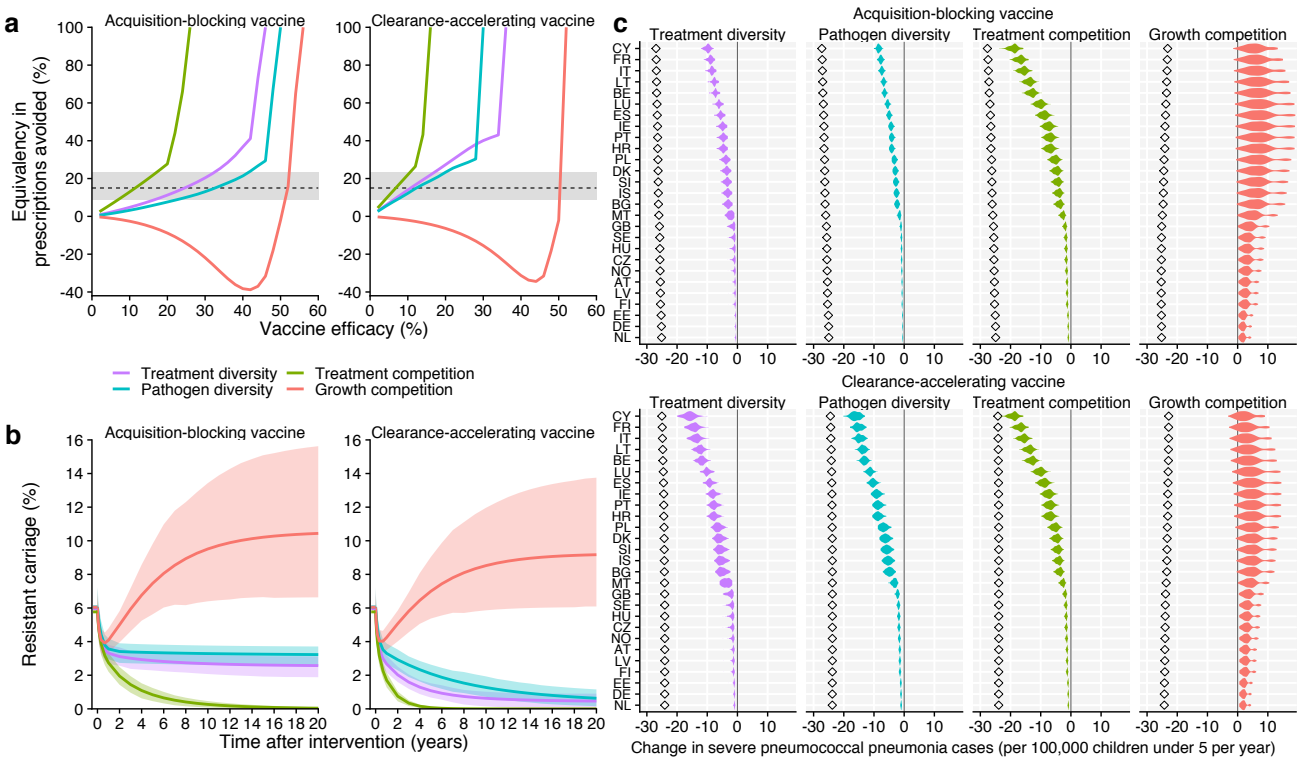


Fig. 4. Policy considerations. (a) Median equivalent reduction in prescribing across four models of resistance evolution, in terms of vaccine efficacy at reducing the prevalence of resistant pneumococcal carriage. This demonstrates the vaccine efficacy required to achieve a similar decrease in resistant carriage to a given reduction in antibiotic prescription rates. The impact on overall pneumococcal carriage is not considered here. The shaded bar shows an 8.8–23.1% reduction in prescriptions, an estimate of the percentage of prescriptions which are clinically inappropriate in the UK (*73*). The dashed line shows a 15% reduction in prescriptions, which has recently been announced as a target by the UK government (*52*). **(b)** The full impact of vaccination, illustrated here with 30% vaccine efficacy, can take 5–20 years to play out (mean and 95% HDI). **(c)** Per-country impact of vaccination at 30% efficacy. Countries reporting to ECDC are ordered from lowest (NL) to highest (CY) reported rate of penicillin consumption. Diamonds show the estimated change in all pneumococcal pneumonia cases, while filled distributions show the change in resistant cases.

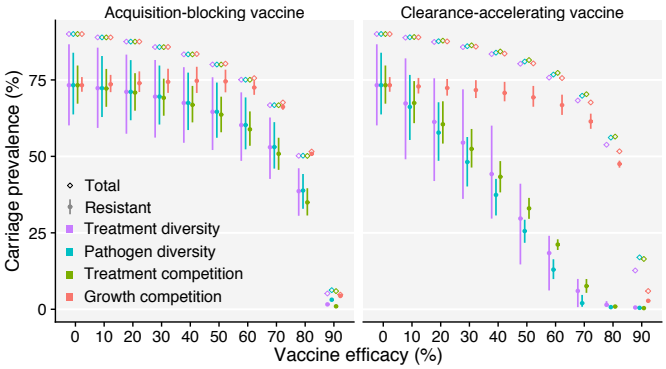


Fig. 5. Vaccine impact in a high-burden setting. Adjusting fitted models to be consistent with a high-burden setting yields different predictions for vaccine impact, highlighting both increased challenges and greater opportunities for resistance management via vaccination.

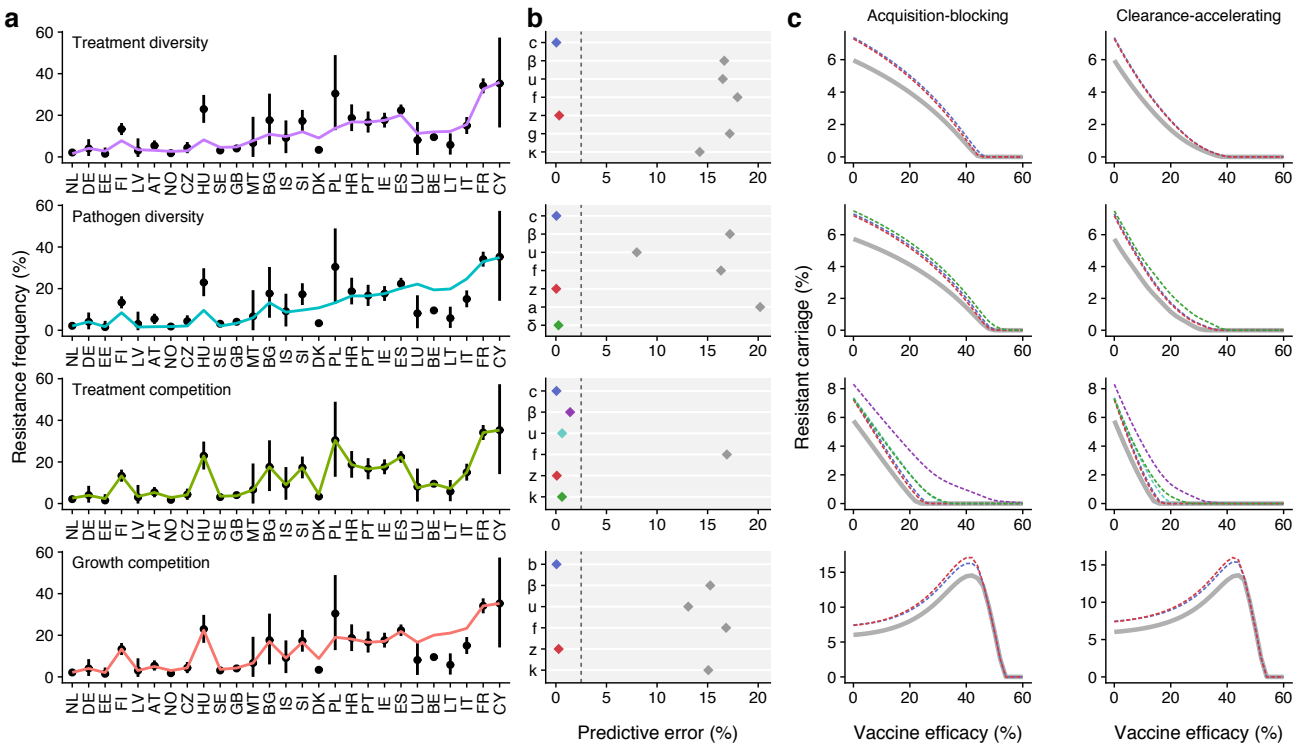


Fig 6. Explaining additional between-country variation in resistance frequency. Allowing model parameters to vary across countries captures additional between-country variation in resistance frequency not captured by variation in the treatment rate. For example, **(a)** allowing the transmission rate β to vary across countries can explain the variation in some but not all models. **(b)** Depending upon which parameter is allowed to vary, models differ in how well they explain all additional between-country variation, with a clear separation (dashed line) between flexible and inflexible models. **(c)** Model-specific predictions for the impact of vaccination among those parameters that do fully capture the observed variation remain similar. Solid grey lines show "base" model; dashed lines correspond with colours in panel b.

1057 Supplementary Materials for

1058

1059 **Competition and diversity determine vaccine impact**

1060 **on antibiotic resistance evolution**

1061

1062 Nicholas G. Davies, Stefan Flasche, Mark Jit, Katherine E. Atkins

1063 **Supplementary Tables 1–7**

1064

1065 These tables can be found in an Excel spreadsheet accompanying the article.

1066

1067 *Literature review* — Details of the literature review used to identify mechanisms for
1068 maintaining coexistence between sensitive and resistant bacterial strains.

1069

1070 *Summary of model parameters* — Table describing model parameters and assumed
1071 values or prior distributions for model fitting.

1072

1073 *Carriage duration* — Calculation of mean pneumococcal carriage duration for children
1074 under 5 years old in European settings.

1075

1076 *Penicillin consumption* — Calculation of the mean number of defined daily doses of
1077 penicillin corresponding to a single treatment course for children under 5 years old in
1078 European countries.

1079

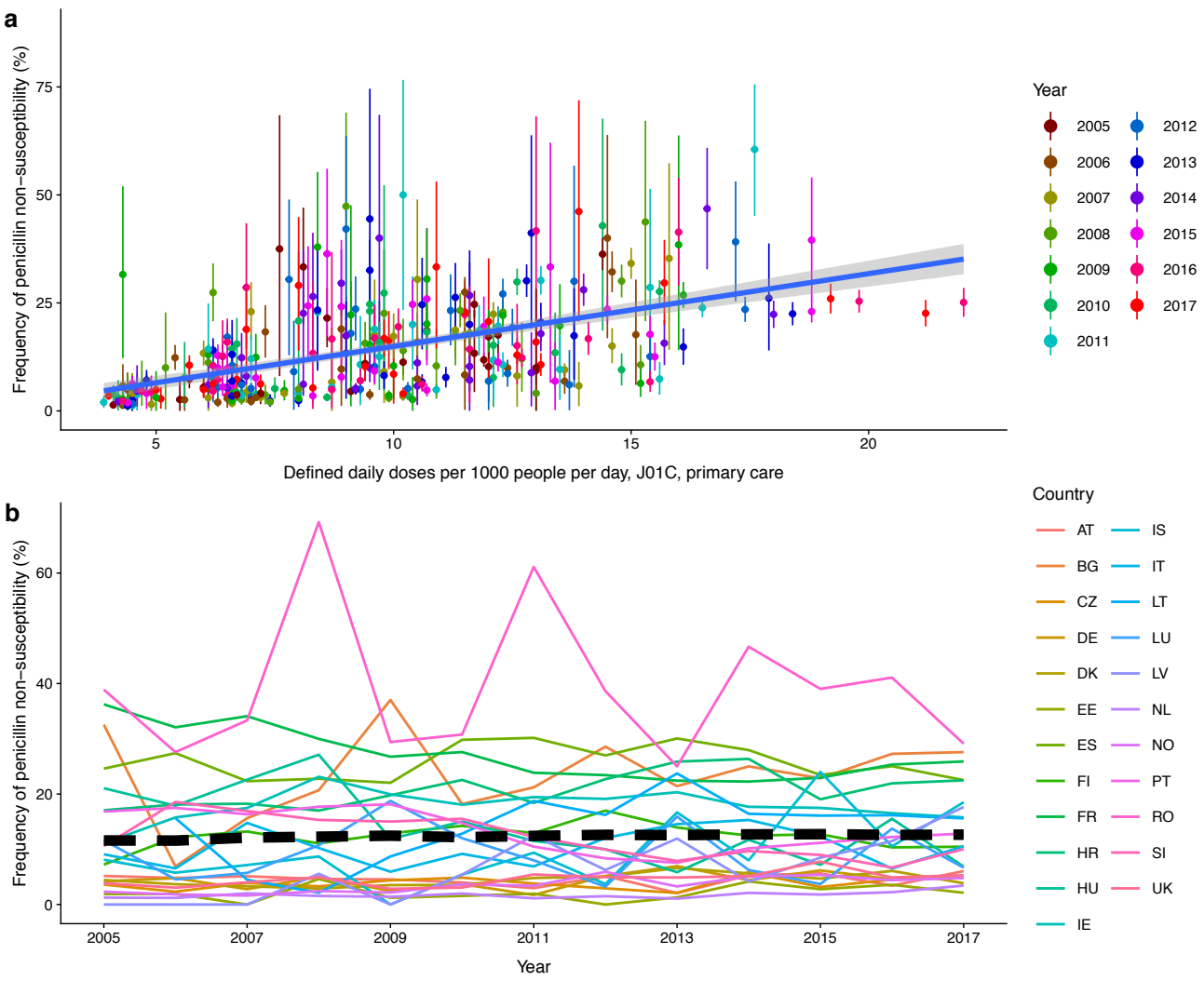
1080 *Pneumococcal morbidity* — Calculation of the annual number of pneumococcal
1081 pneumonia cases in children under 5 in Europe and Kenya.

1082

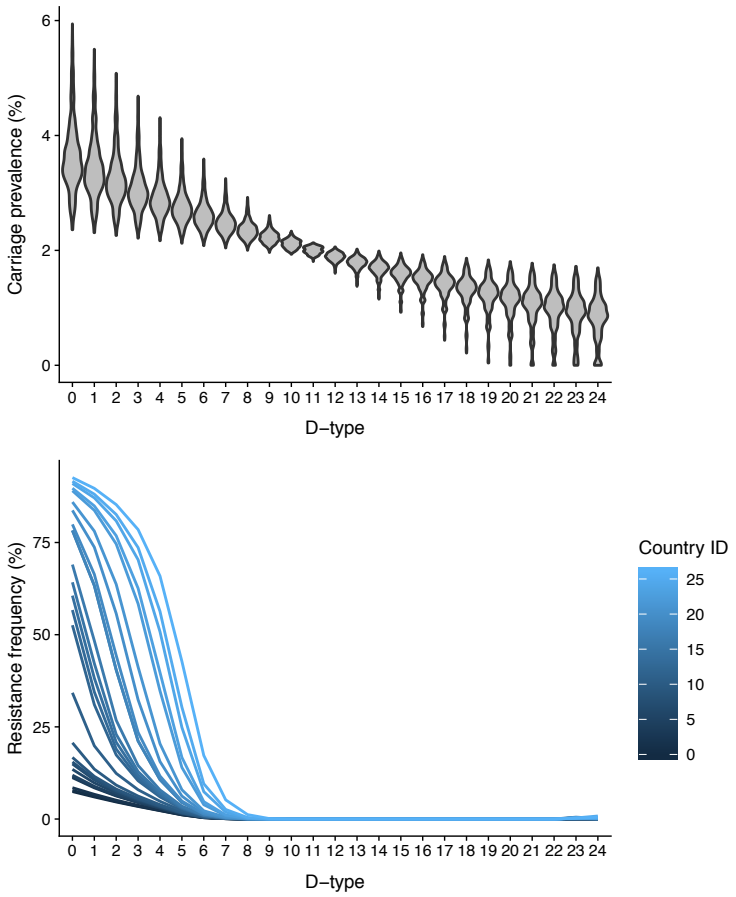
1083 *Carriage duration (Kilifi)* — Calculation of mean pneumococcal carriage duration for
1084 children under 5 years old in Kilifi, Kenya.

1085

1086 *MCMC diagnostics* — Widely Applicable Information Criteria (WAIC), Leave-One-Out
1087 Information Criteria (LOOIC), effective posterior sample size and Gelman-Rubin
1088 diagnostics for Bayesian inference model fitting using Markov chain Monte Carlo.

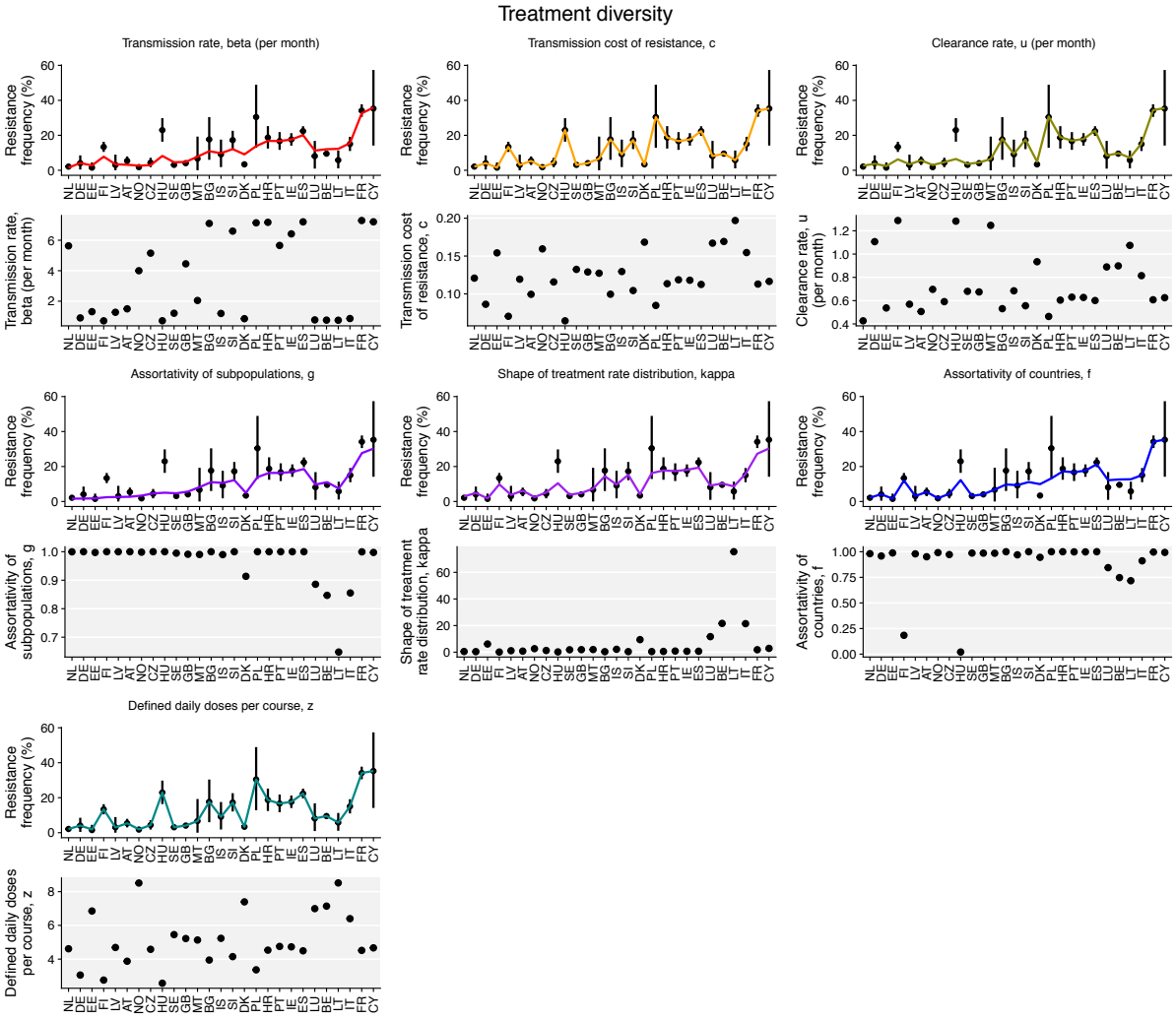


Supplementary Fig. 1. Patterns of penicillin non-susceptibility across European countries, 2005–2017. **(a)** The frequency of penicillin non-susceptibility in pneumococcal isolates (mean and 95% HDI) increases roughly linearly with the primary care consumption of penicillins (ATC class J01C). Data from Belgium after 2007 are excluded because of changes to the definition of non-susceptibility after this year. **(b)** The frequency of penicillin non-susceptibility has fluctuated in individual countries between 2005 and 2017, but the European population-weighted average (thick dashed line) has remained stable at roughly 12%.

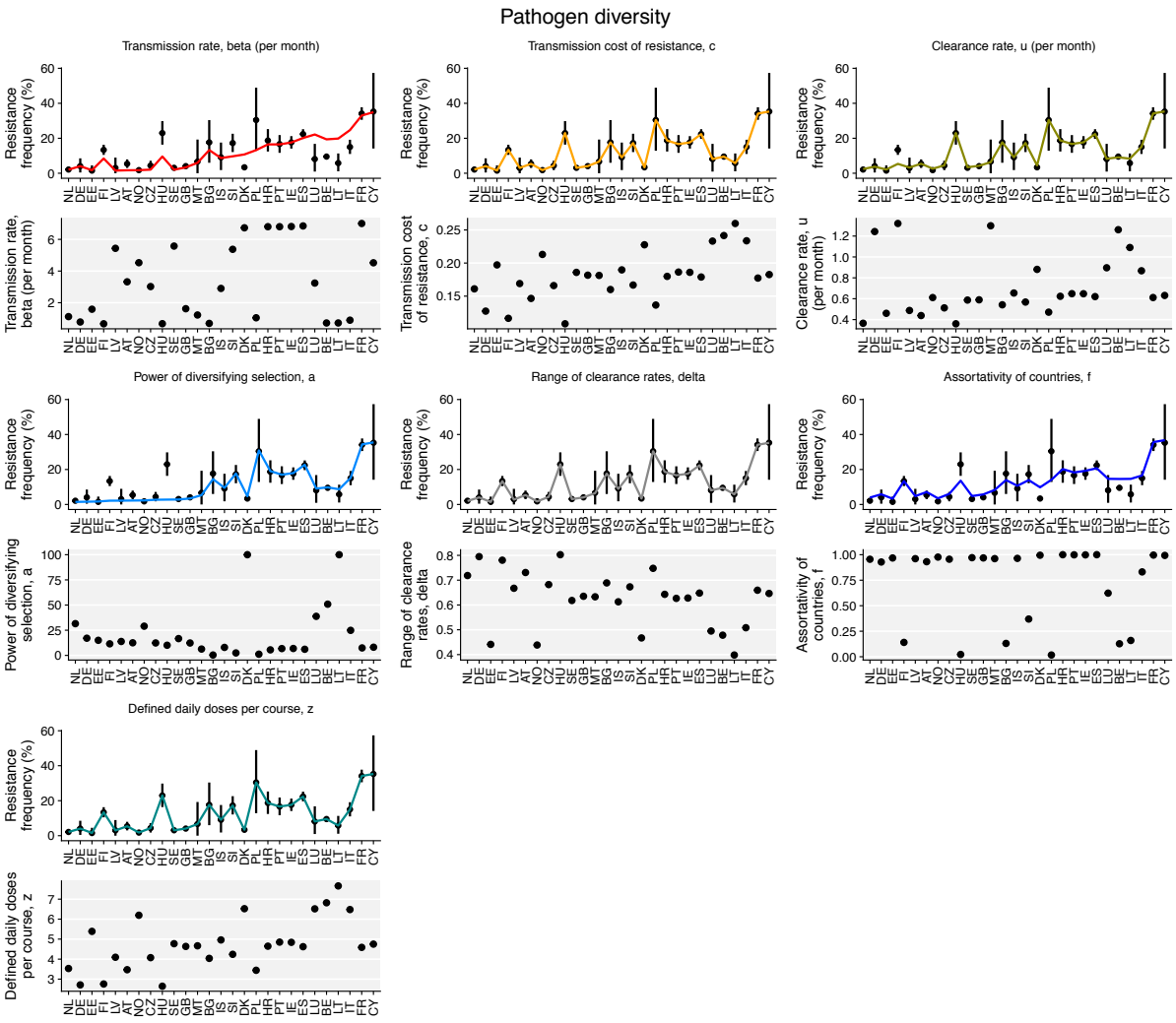


1098

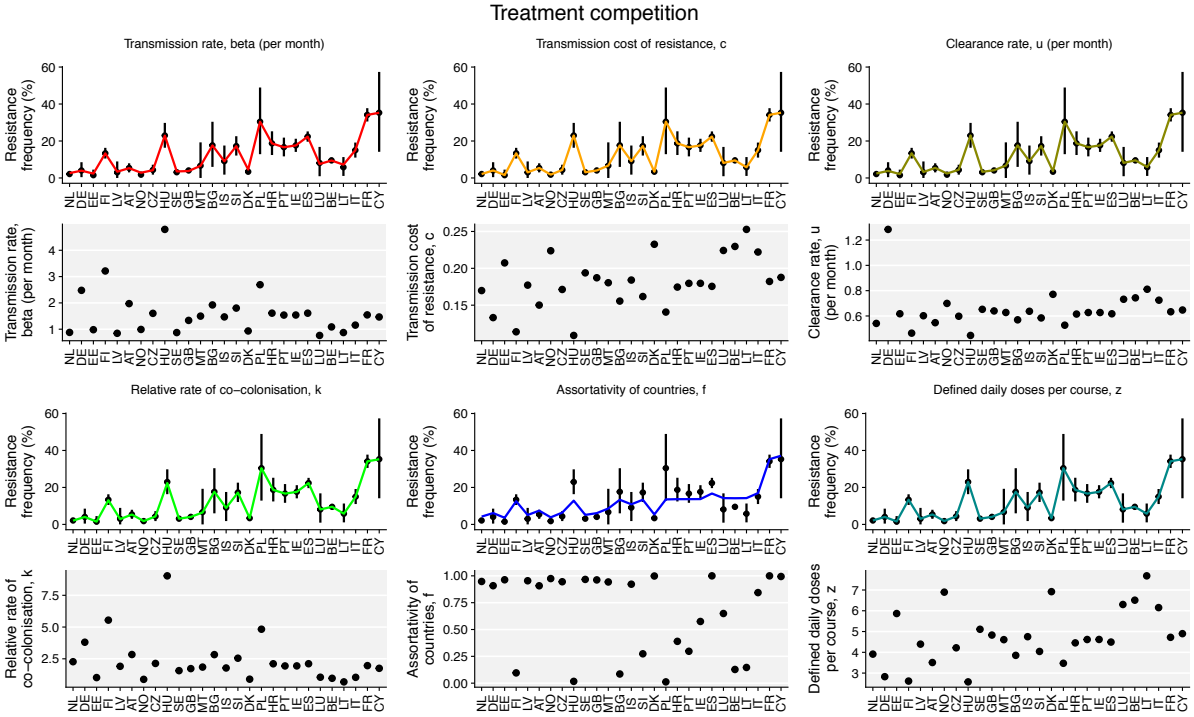
1099 **Supplementary Fig. 2.** Distribution of carriage prevalence and resistance frequency in
1100 the "Pathogen diversity" model. This verifies that the D-types with the highest
1101 prevalence of carriage (averaged over all countries, above) also exhibit the highest
1102 resistance frequency (separated by country, below), and shows that at equilibrium, D-
1103 types can exhibit intermediate frequencies of resistance.



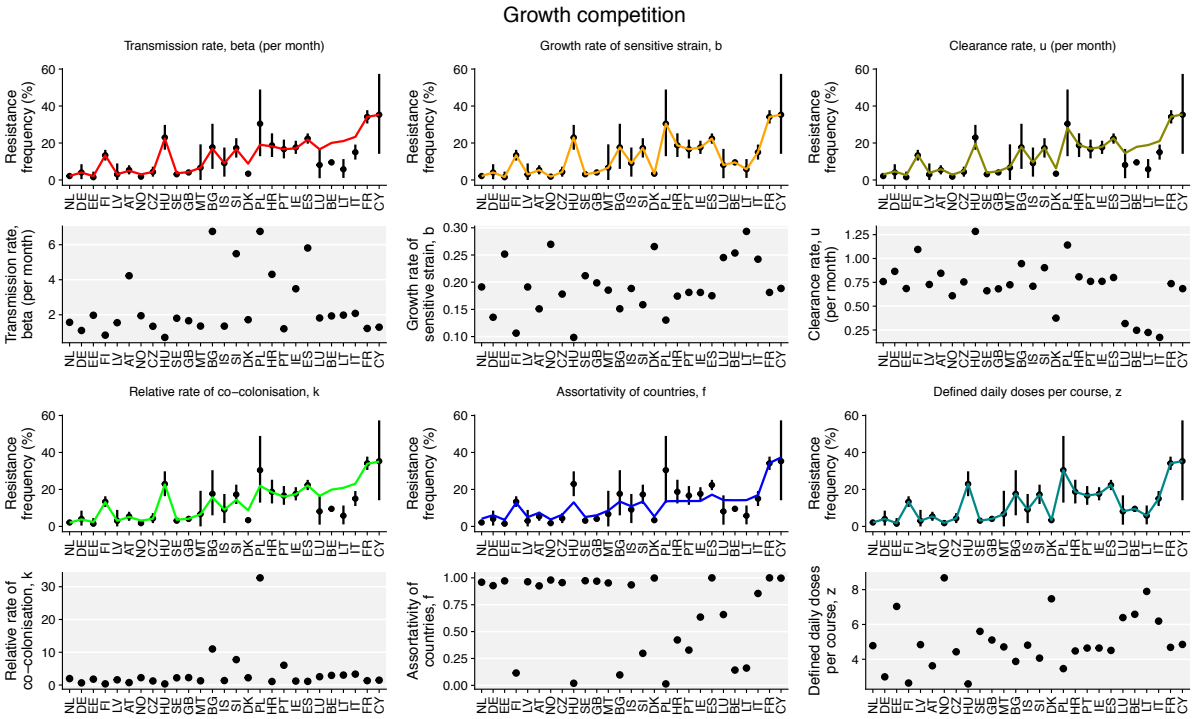
Supplementary Fig. 3. Maximum *a posteriori* fits for the "Treatment diversity" model allowing one parameter to vary between countries. Parameters *c* and *z* can capture the additional variation in resistance frequency between countries.



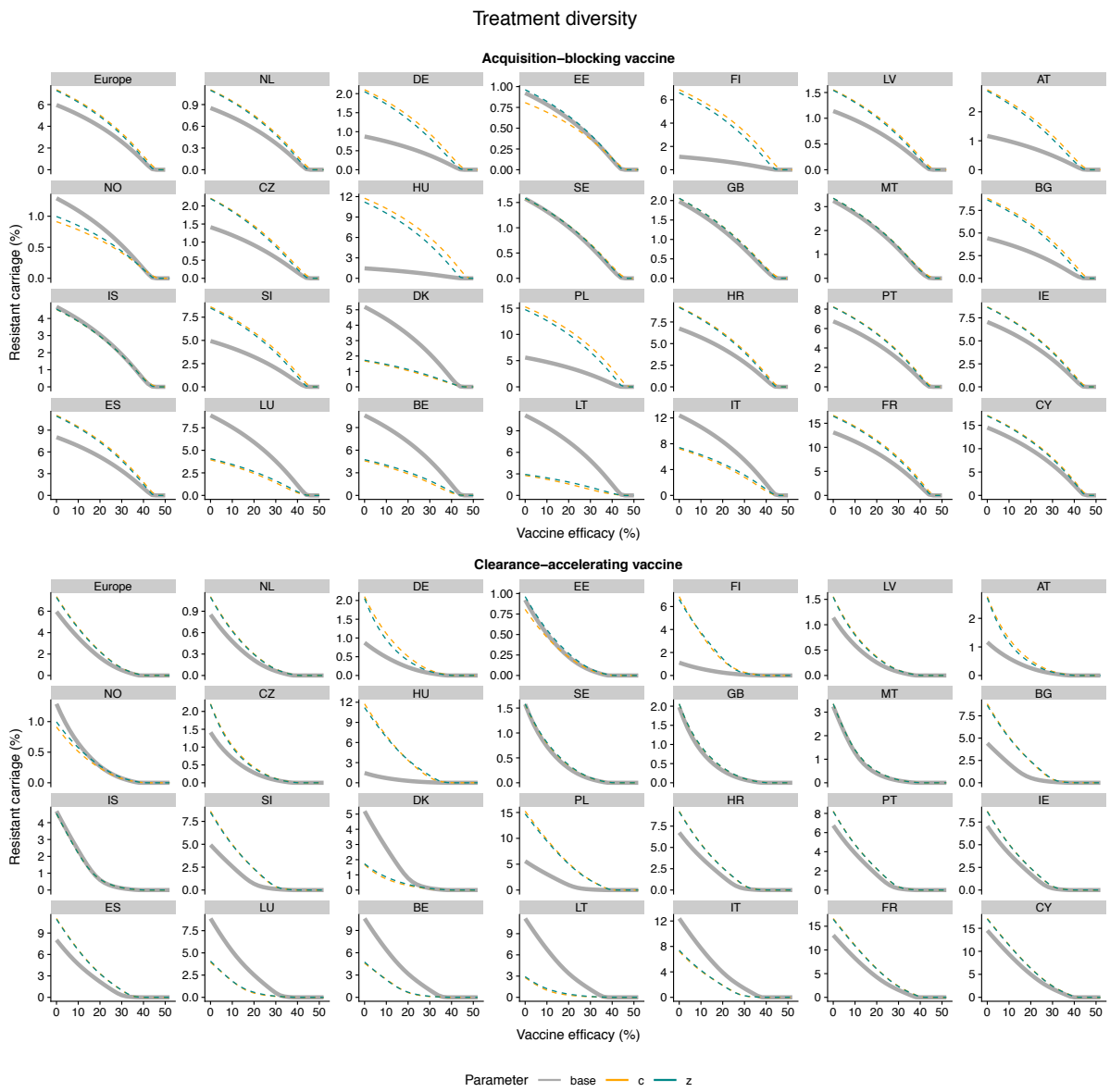
Supplementary Fig. 4. Maximum *a posteriori* fits for the "Pathogen diversity" model allowing one parameter to vary between countries. Parameters c, δ, and z can capture the additional variation in resistance frequency between countries.



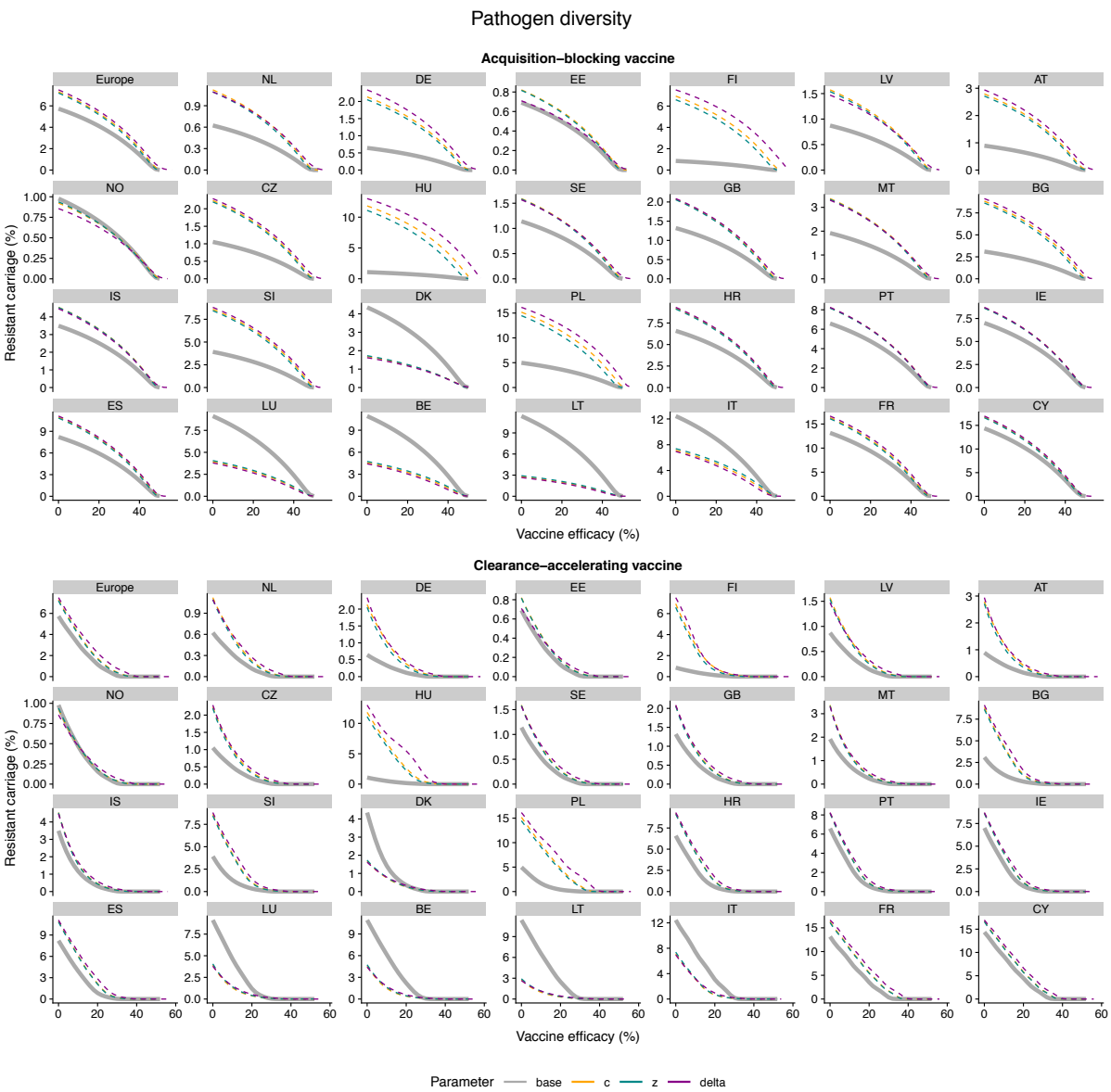
Supplementary Fig. 5. Maximum *a posteriori* fits for the "Treatment competition" model allowing one parameter to vary between countries. Parameters β, *c*, *u*, *k*, and *z* can capture the additional variation in resistance frequency between countries.



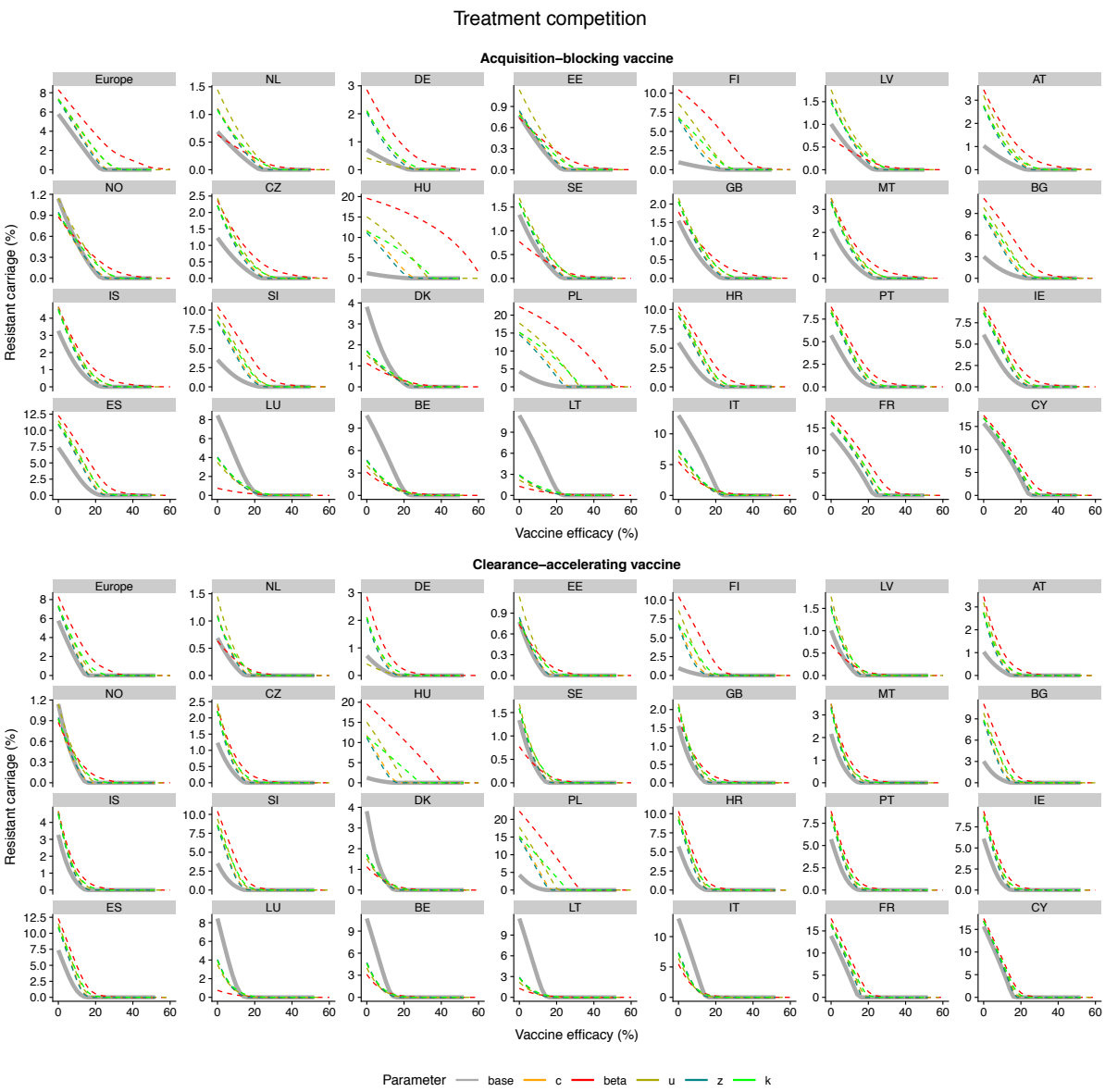
Supplementary Fig. 6. Maximum *a posteriori* fits for the "Growth competition" model allowing one parameter to vary between countries. Parameters *b* and *z* can capture the additional variation in resistance frequency between countries.



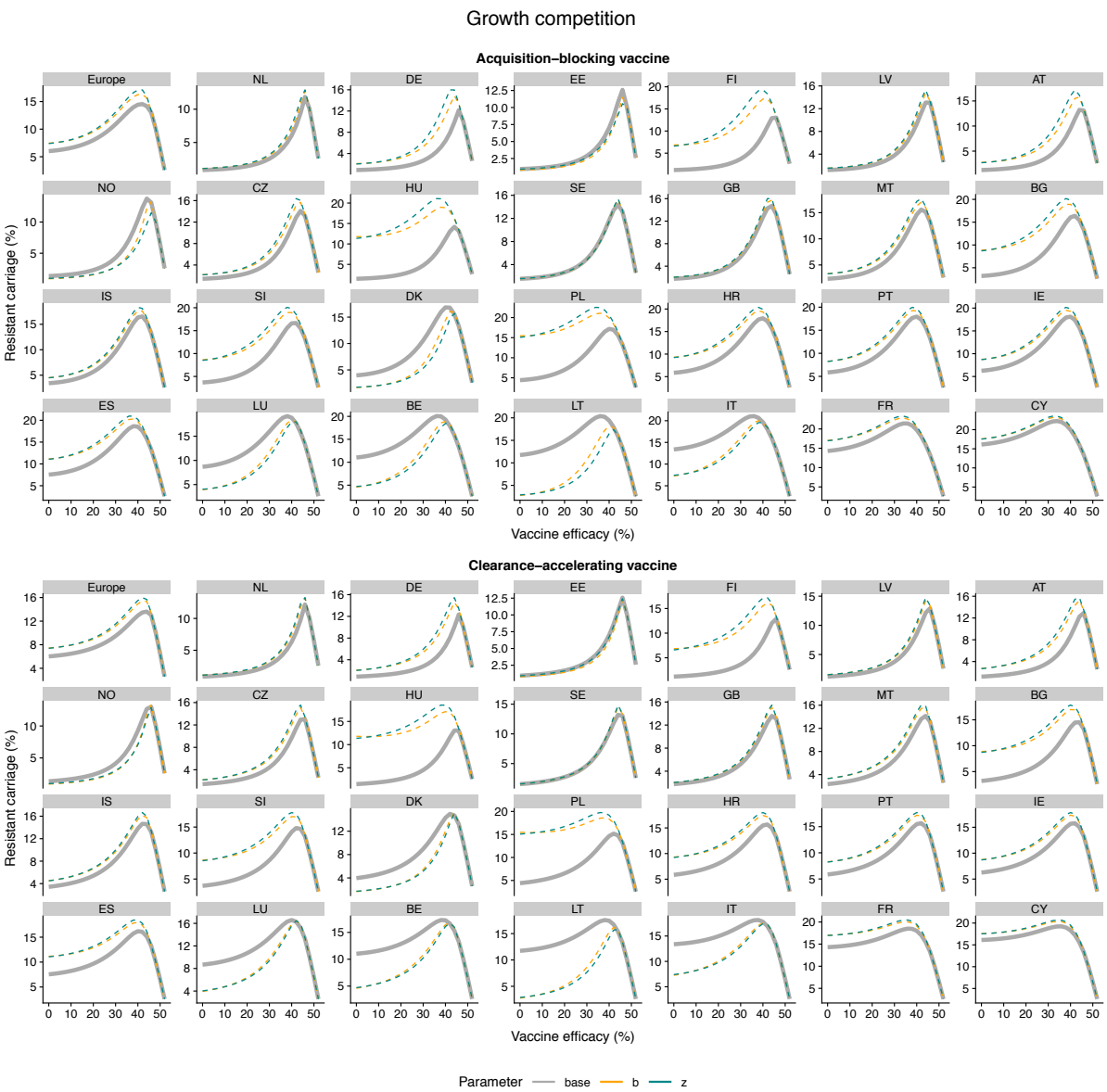
Supplementary Fig. 7. Impact of vaccination under the "Treatment diversity" model, for those parameters able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).



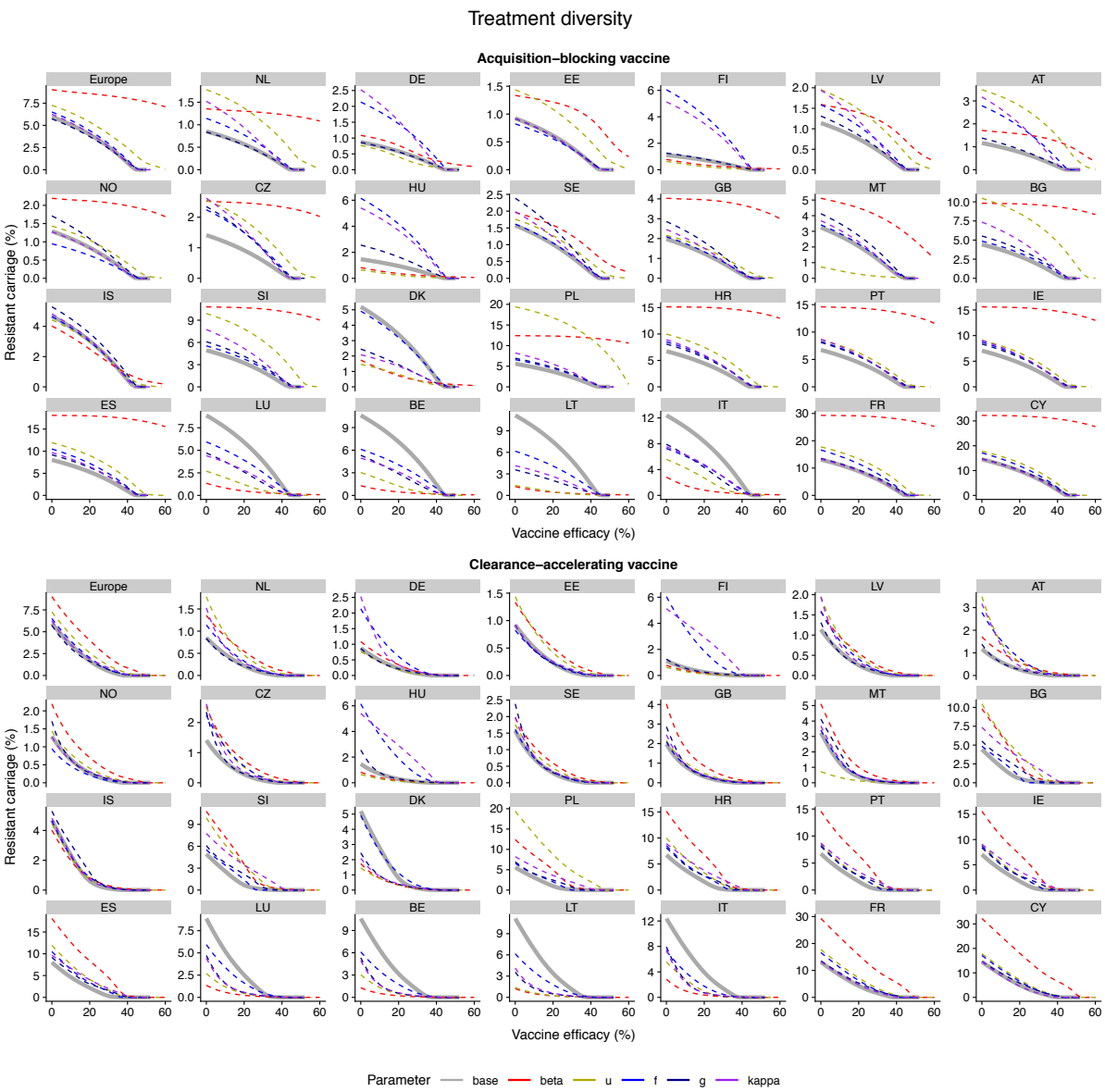
Supplementary Fig. 8. Impact of vaccination under the "Pathogen diversity" model, for those parameters able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).



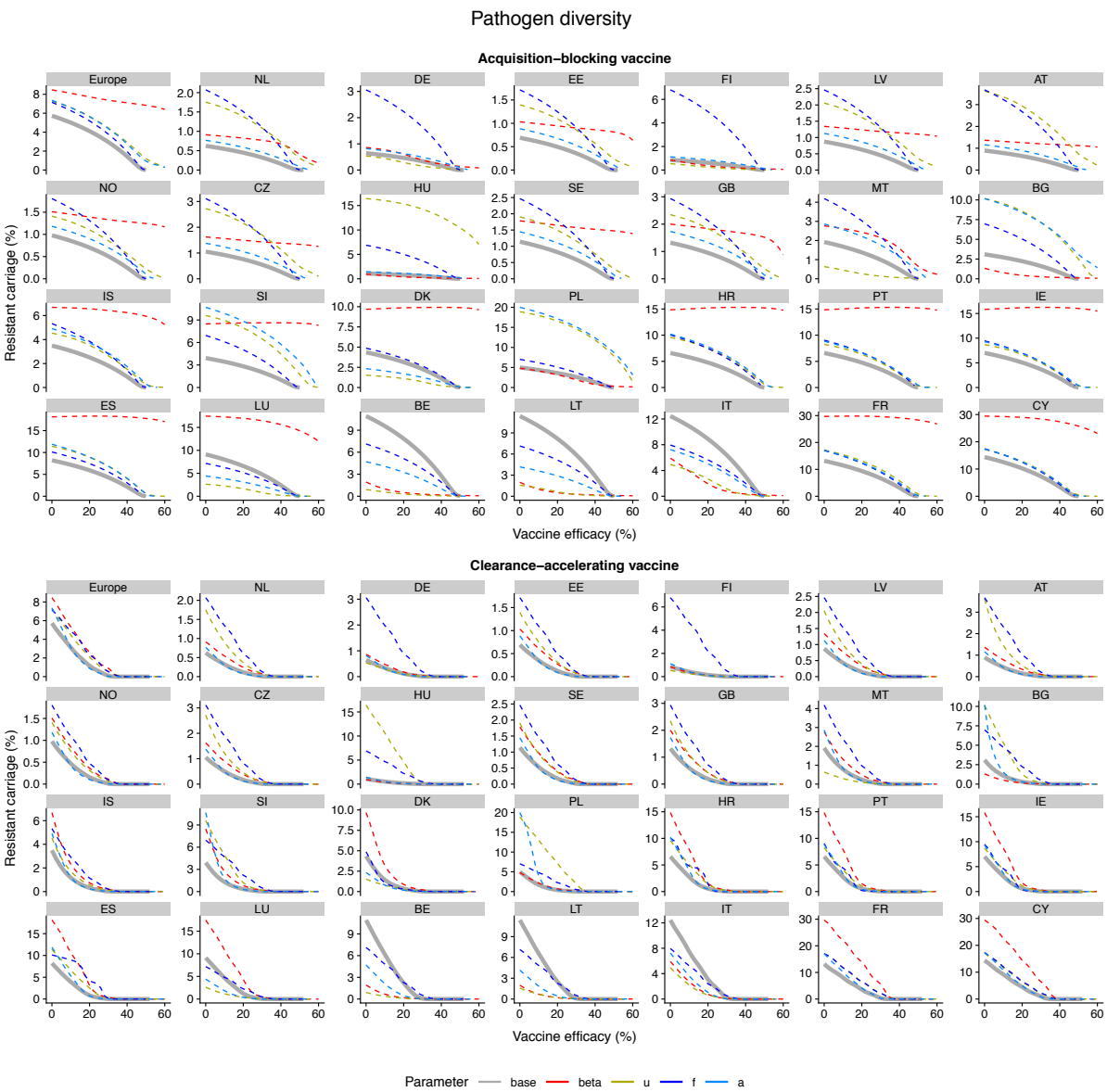
Supplementary Fig. 9. Impact of vaccination under the "Treatment competition" model, for those parameters able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).



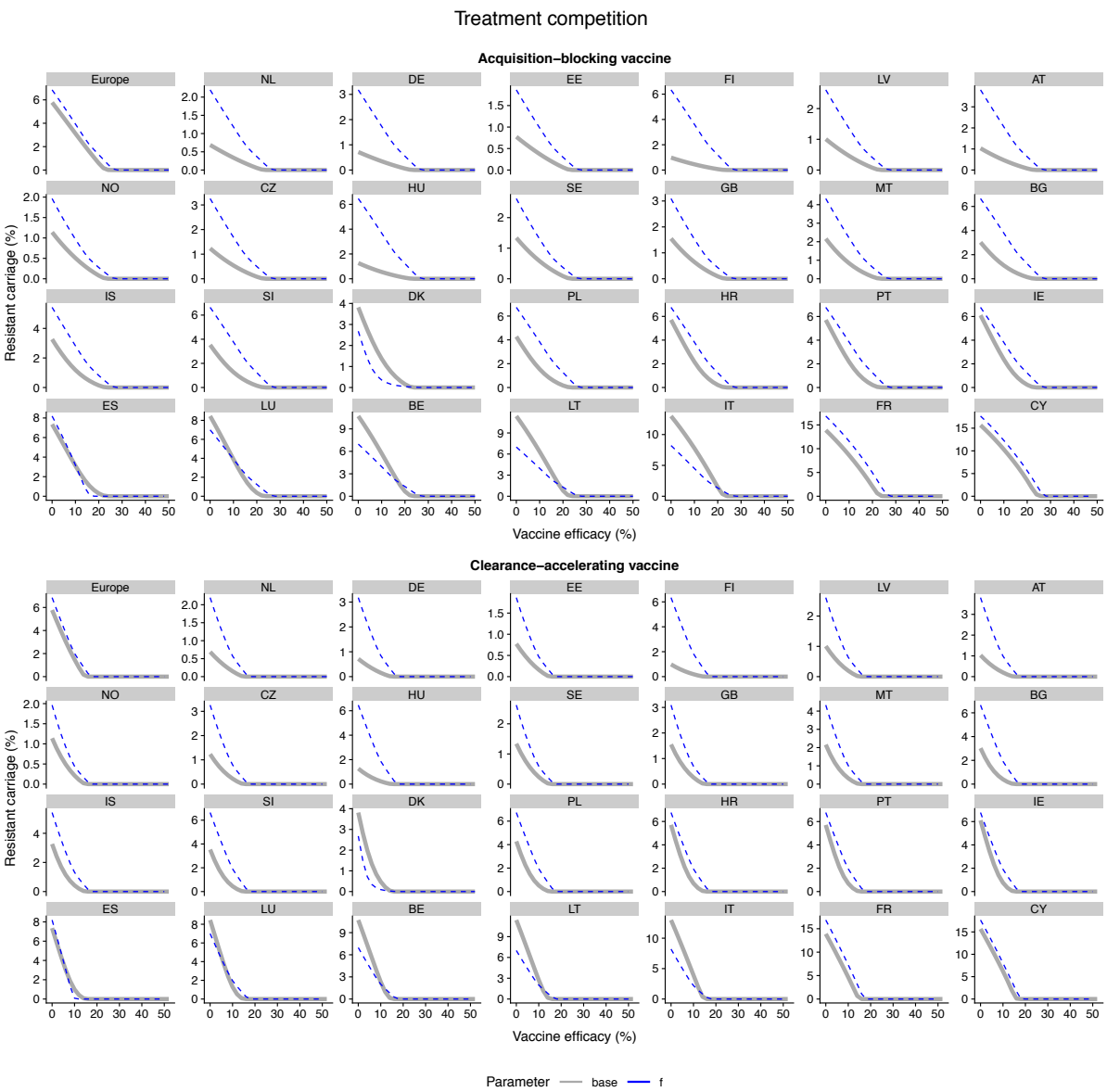
Supplementary Fig. 10. Impact of vaccination under the "Growth competition" model, for those parameters able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).



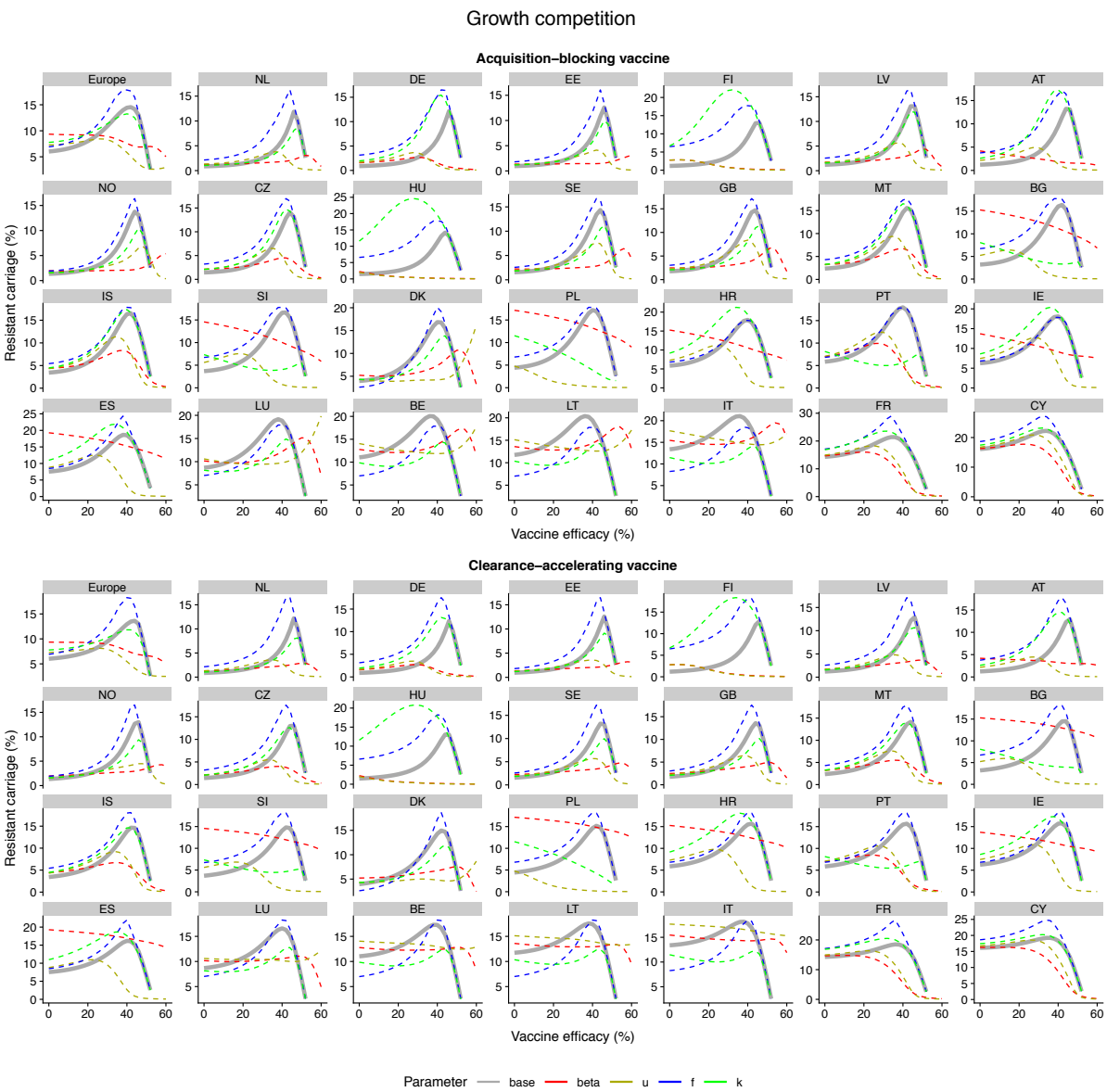
Supplementary Fig. 11. Impact of vaccination under the "Treatment diversity" model, for those parameters *not* able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).



Supplementary Fig. 12. Impact of vaccination under the "Pathogen diversity" model, for those parameters *not* able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).



Supplementary Fig. 13. Impact of vaccination under the "Treatment competition" model, for those parameters *not* able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).



Supplementary Fig. 14. Impact of vaccination under the "Growth competition" model, for those parameters *not* able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).