Stabilising effects of competition and diversity determine vaccine impact on antibiotic resistance evolution

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One sentence summary: Frequency-dependent competition and extrinsically-maintained diversity shape selection for antibiotic resistance following vaccination.

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 suppress—or spread—antibiotic resistance among unvaccinated individuals. Predicting the outcome requires knowing what drives selection for resistance in bacterial pathogens, and in particular, what maintains the circulation of both antibiotic-sensitive and resistant strains of bacteria. Using mathematical modelling, 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 frequency-dependent selection brought about by within-host competition between resistant and sensitive strains. We use our calibrated models to predict the impact of non-serotype-specific pneumococcal vaccination upon the prevalence of carriage, incidence of disease, and frequency of resistance for *S. pneumoniae*. We find that the relative strength and directionality of competition between resistant and sensitive pneumococcal strains is the most important determinant of whether vaccination promotes, inhibits, or has little effect upon the evolution of antibiotic resistance. Finally, we show that country-specific differences in pathogen transmission substantially alter the predicted impact of vaccination, highlighting that policies for managing resistance with vaccines must be tailored to a specific 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" (non-serotype-specific) whole-cell or protein-based pneumococcal vaccines protecting against all serotypes, some of which are now in early-stage clinical trials (*14*). If successful, universal pneumococcal vaccines could reduce the burden of pneumococcal disease without selecting for serotype replacement.

However, it is unclear how universal vaccination itself may impact upon the evolution of antibiotic resistance in *S. pneumoniae*, which is a concern given that vaccination is unlikely to eliminate pneumococcal carriage entirely (*15*). Mathematical models of bacterial transmission can be used to predict the impact of vaccination on antibiotic resistance (*16*, *17*), but existing models for *S. pneumoniae* 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 non-serotype-specific vaccination on resistant pneumococcal disease require a mechanistic understanding of these patterns.

Results

Stability in resistance evolution can be maintained by frequency-dependent competition or extrinsically-imposed diversity. 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

85 features for models to recapitulate (Fig. S1). One feature is spatial: the frequency of
86 penicillin non-susceptibility varies between countries, and is higher in countries where
87 more penicillin is consumed (*27*). The other is temporal: although in individual
88 countries, resistance fluctuates from year to year, the overall frequency across Europe
89 of penicillin non-susceptibility in pneumococcal isolates has remained steady at roughly
90 12% since consolidated records began in 2005 (*28*). These observations contradict
91 simple models of resistance evolution, which predict that intermediate frequencies of
92 resistance cannot be stably maintained in the long term: that is, either sensitive strains
93 will competitively exclude resistant strains, or resistant strains will competitively
94 exclude sensitive strains, unless there is some mechanism that maintains coexistence
95 between them (*25*, *29*).
96
97 By conducting a literature search, we identified nine such mechanisms (*25*, *26*, *30–41*)
98 that fall into two broad classes. In one class, coexistence is maintained by
99 environmental or genetic diversity that effectively creates separate niches for resistant
100 and sensitive strains, preventing them from completely overlapping in competition. In
101 the other class, competition between resistant and sensitive strains is itself the
102 stabilising factor that maintains coexistence, because resistant and sensitive strains
103 exhibit alternative competitive phenotypes that afford strains a competitive advantage
104 when rare, thus promoting negative frequency-dependent selection for resistance. Thus,
105 extrinsically-imposed diversity and frequency-dependent competition are two key
106 forces maintaining stability in resistance evolution. We find that four of the nine
107 identified mechanisms for maintaining coexistence are biologically plausible for *S.*
108 *pneumoniae* (Table 1).
109
110 **Four models of resistance evolution.** To compare these four mechanisms, we embed
111 each in a shared model framework of person-to-person transmission of nasopharyngeal
112 pneumococcal carriage. This framework tracks the country-specific frequency of
113 resistance in pneumococci circulating among children under five years old, the age
114 group that drives the majority of pneumococcal transmission and disease (*42*, *43*). We
115 assume that each individual makes effective contact with another random individual at
116 rate β, thereby potentially acquiring a strain (either sensitive or resistant) carried by
117 the contacted person. With probability *c*, resistant strains fail to transmit, where *c*

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

	Mechanism	Mode of action	Plausible mechanism for coexistence in *S. pneumoniae*?	Consistent with empirical patterns? (Fig. 2)
DIVERSITY	**Treatment diversity**	Assortatively-mixing subpopulations differ in treatment rates (*25*, *34–37*)	✓ Yes	✓ Yes
	Pathogen diversity	Subtypes maintained by diversifying selection differ in propensity for resistance (*38*)	✓ Yes	✓ Yes
	Treated class	Individuals currently in treatment maintain resistant strains (*25*, *34*, *39*, *40*)	✗ No: Only supports a small amount of coexistence (*25*)	■ N/A
	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
	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
	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
	Within-host competition: Growth competition	"	✓ Yes	✓ Yes
	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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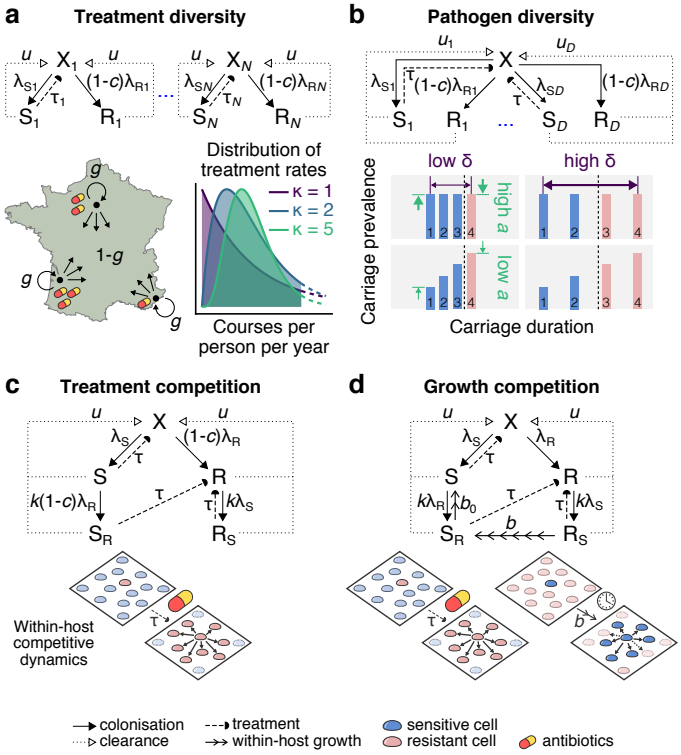

Fig. 1. Four models of resistance evolution. X hosts are uncolonised, S hosts are colonised with the sensitive strain and R hosts are colonised with the resistant strain. Force of infection terms λ_A are equal to the person-to-person contact rate β times the probability that a contacted individual carries strain *A*; *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, with treatment rates drawn from a gamma distribution with shape κ. Within a country, individuals assort with their own subpopulation with probability *g*; this assortative mixing among treatment-varying subpopulations allows coexistence between sensitive and resistant strains. **(b)** "Pathogen diversity": the pathogen comes in multiple subtypes maintained by diversifying selection, each with its own natural carriage duration u_d^{-1}. Diversifying selection is stronger (*i.e.*, more equalizing) as *a* increases, while carriage durations span a greater range as δ increases. Only those subtypes whose carriage duration exceeds a critical threshold (dashed line) are selected for resistance, so that overall, both sensitive and resistant strains can circulate. **(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). Dually-colonized hosts only transmit the dominant strain, so there is within-host competition between co-colonising strains. Population-level coexistence is maintained by treatment-mediated within-host competition. **(d)** "Growth competition": as in panel 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. Panels a–d illustrate alternative model dynamics for a single country; our full model framework tracks dynamics for 27 European countries simultaneously, which themselves mix with assortativity *f*.

147 represents the transmission cost of resistance (*44*, *45*). A carrier naturally clears all
148 strains at rate u, and is exposed to antibiotic therapy at a country-specific rate τ, which
149 clears the host of sensitive strains only. We assume this treatment rate is independent
150 of carriage status (*46*) and we do not explicitly track disease progression in hosts.
151
152 Under the "Treatment diversity" and "Pathogen diversity" models, extrinsically-
153 maintained diversity among hosts or among pathogens prevents competitive exclusion
154 by keeping resistant and sensitive strains from fully competing with each other. In the
155 "Treatment diversity" model (Fig. 1a), heterogeneity in the consumption of antibiotics
156 between host subpopulations within a country maintains coexistence (*25*, *34*, *35*). These
157 subpopulations could correspond to geographical regions, socioeconomic strata, host
158 age and risk classes, or a combination of these. Provided that transmission between
159 high-consumption (resistance-promoting) and low-consumption (resistance-inhibiting)
160 subpopulations is not too frequent, an intermediate frequency of resistance can be
161 maintained across the whole population. Because coexistence is maintained by
162 assortative mixing between subpopulations differing in antibiotic use, the key
163 parameters governing coexistence in this model are κ, the variability in antibiotic
164 consumption between subpopulations, and g, the relative rate at which within-country
165 contact is made within subpopulations rather than between them (Fig. S2).
166
167 In the "Pathogen diversity" model (Fig. 1b), pneumococci are divided into subtypes ("D-
168 types"(*38*)) that vary in their mean duration of natural carriage. All else equal, the D-
169 type with the longest carriage duration would be expected to competitively exclude all
170 other strains; the model assumes that diversifying selection acting on the D-type locus
171 keeps all subtypes in circulation. What D-types correspond to is not explicitly specified
172 by this model, but one candidate is serotype variation. For example, if antigenic
173 diversity is promoted by host acquired immunity to capsular serotypes, and serotypes
174 tend to differ in their intrinsic ability to evade clearance by the immune system, then
175 intermediate resistance can be maintained because selection for resistance tends to be
176 greater in serotypes that have a longer duration of carriage (*38*). Long-lasting serotypes
177 will tend to evolve resistance, while shorter-lived serotypes will tend not to—a pattern
178 observed in *S. pneumoniae* (*38*) and reproduced by this model (Fig. S3). The parameters

179 governing coexistence in this model are a, the strength of diversifying selection on the
180 D-type locus, and δ, the variability between subtypes in clearance rate.
181
182 Under the "Treatment competition" and "Growth competition" models, coexistence is
183 maintained by within-host competition between sensitive and resistant strains. In these
184 models, hosts can be co-colonised by multiple strains. Then, competition between
185 strains within the host niche determines which strain is transmitted to other potential
186 hosts (*26*). The "Treatment competition" model (Fig. 1c) assumes that antibiotic therapy
187 mediates within-host competition, such that when a co-colonised host takes antibiotics
188 (*i.e.*, at rate τ), the sensitive strains are cleared and only the resistant strains are
189 transmitted to other hosts. The "Growth competition" model (Fig. 1d) has both
190 treatment-mediated and growth-mediated competition: while in the presence of
191 antibiotics, resistant strains still outcompete co-colonising sensitive strains, in the
192 absence of antibiotics, sensitive strains gradually outcompete co-colonising resistant
193 strains at rate b. We assume that there is no transmission cost of resistance in this latter
194 model (*i.e.*, $c = 0$); instead, the within-host growth advantage b of sensitive strains
195 accounts for the cost of resistance. In these competition models, resistant strains have
196 an advantage in antibiotic-mediated competition, while sensitive strains have an
197 advantage in growth-mediated competition. These alternative forms of within-host
198 competition can both promote coexistence because rare strains can more consistently
199 exploit a competitive advantage over common strains, thus creating negative frequency-
200 dependent selection for resistance (*26*). The key parameter governing coexistence in
201 these two models is k, the relative rate of co-colonisation compared to primary
202 colonisation.
203
204 In all four models, we assume that contact between individuals is assortative by
205 country, such that with probability f, contact is with a random person from the same
206 country, and with probability $1 - f$, contact is with a random person from any country.
207 We implement these models using systems of ordinary differential equations. All four
208 models (*25*, *26*, *38*) are structurally neutral (*25*, *29*), meaning that any coexistence
209 exhibited by the models is accounted for by the specified biological mechanism rather
210 than by any bias in the logical structure of the model that generates coexistence "for
211 free" (*29*). Additionally, while the within-host competition models capture co-

212 colonisation using a simplified subset of only 2 "mixed-carriage" states (S_R and R_S, Fig.
213 1a&b), we have previously shown (*26*) that this is equivalent to a more complex
214 individual-based model with an arbitrary number of mixed-carriage states.
215
216 **All four models reproduce observed patterns of resistance.** The European Centre
217 for Disease Prevention and Control (ECDC) monitors antibiotic consumption and
218 resistance evolution across European countries (*13*, *28*). These data capture a natural
219 experiment in resistance evolution: for each monitored drug and pathogen, each
220 country reports a different rate of antibiotic consumption in the community and
221 exhibits a different frequency of resistance among invasive bacterial isolates. By fitting
222 models to this multi-country data set, we can potentially rule out models that cannot
223 reproduce the large-scale patterns that are observed. We use Bayesian inference to fit
224 the model-predicted equilibrium frequency of resistance to the reported frequency of
225 penicillin non-susceptibility in *S. pneumoniae* across 27 European countries, assuming a
226 50% carriage prevalence (*11*, *42*) and a carriage duration of 47 days (*47*, *48*) in children
227 under five years old. We begin by assuming that countries only differ by their reported
228 treatment rate—where we define a treatment course as equivalent to $z = 5$ defined daily
229 doses of penicillin—with other model parameters shared across countries.
230
231 Strikingly, each model fits equally well to the empirical relationship between resistance
232 and antibiotic use (all model WAICs are similar; Fig. 2a) and recovers plausible
233 posterior parameter distributions (Fig. 2b; Fig. S4). That is, the empirical data do not
234 distinguish between the four alternative mechanisms of resistance evolution we have
235 identified. Later, we relax the assumption that only the treatment rate varies between
236 countries, allowing us to capture additional between-country variation in resistance not
237 explained by population-wide penicillin consumption.
238
239 **Mechanisms of resistance evolution determine the impact of vaccination on**
240 **resistant disease.** To determine the impact of universal vaccination on pneumococcal
241 disease, we consider three outcomes. The first is the impact of the vaccine upon the
242 prevalence of pneumococcal carriage. The second is the vaccine impact upon the
243 frequency of penicillin resistance among circulating pneumococcal strains remaining
244 after vaccination. The third is the impact of the vaccine upon the prevalence of resistant

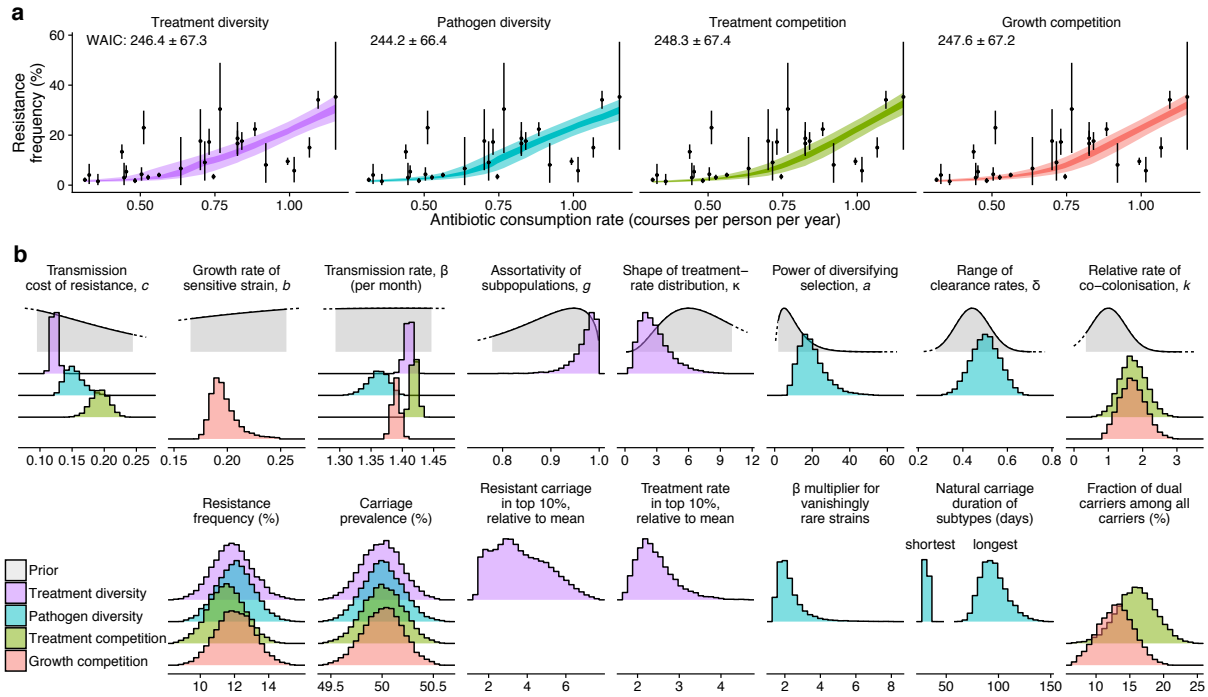

Fig 2. Four models reproduce patterns of resistance in *S. pneumoniae* in Europe. (a) Model fits with associated WAIC (± standard error). Points and vertical lines show the mean and 95% highest density intervals (HDIs) for the reported proportion of invasive *S. pneumoniae* isolates that are resistant 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.

254 pneumococcal carriage—*i.e.*, the prevalence of carriage multiplied by the frequency of
255 penicillin resistance. Since all four models are equally capable of recapitulating
256 observed patterns of penicillin resistance in *S. pneumoniae*, our aim is to determine
257 whether the mechanism maintaining stability in resistance evolution—frequency-
258 dependent competition or extrinsically-imposed diversity—matters when forecasting
259 the impact of interventions for managing resistance.
260
261 We consider two alternative non-serotype-specific vaccines: an "acquisition-blocking"
262 vaccine, which prevents carriage from being established with probability ε_a, and a
263 "clearance-accelerating" vaccine, which shortens the duration of carriage by a fraction
264 ε_c. Both vaccines reduce pneumococcal transmission through alternative modes of host
265 immunity that might be elicited by a whole-cell or protein-based universal
266 pneumococcal vaccine. Analogously to naturally-acquired serotype-independent
267 pneumococcal immunity (*49*), the protective effect of whole-cell vaccines manifests as
268 accelerated clearance (*50*); it is unclear whether protein-based vaccines would block
269 pneumococcal acquisition, like PCVs, or accelerate clearance (*51*). We refer to ε_a or ε_c as
270 the vaccine efficacy, and for simplicity, we assume that all children under five years old
271 have vaccine protection, as would be established by an infant vaccination programme
272 rolled out across Europe. In order to compare these vaccines with an alternative
273 intervention of antibiotic stewardship, we also evaluate the impact of reducing the rate
274 of penicillin prescribing by a fraction ε_s.
275
276 We find that both vaccines have a similar impact upon carriage prevalence, regardless
277 of whether competition or diversity maintains stability in resistance evolution (Fig. 3a).
278 Specifically, as the vaccine efficacy ε_a or ε_c increases, carriage decreases, with the
279 elimination of pneumococcal carriage occurring at a vaccine efficacy between 50 and
280 60%. Reducing antibiotic prescribing moderately increases pneumococcal carriage,
281 such that carriage prevalence increases to approximately 54% across all countries
282 when penicillin prescribing is eliminated completely.
283
284 However, the mechanism of resistance evolution has a substantial impact upon whether
285 vaccines increase or decrease the frequency of resistance in *S. pneumoniae* in the long
286 term (Fig. 3b). In the "Treatment diversity" and "Pathogen diversity" models, the

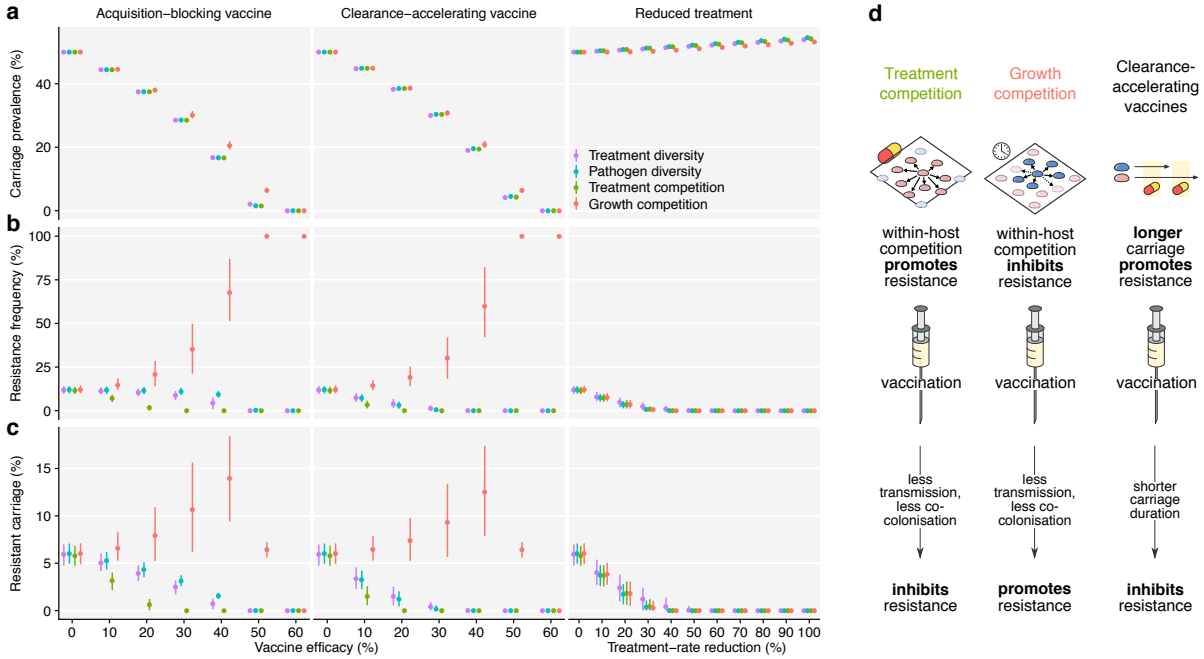

Fig. 3. Impact of interventions. Impact of vaccine and treatment interventions on **(a)** carriage prevalence, **(b)** resistance frequency, and **(c)** resistant carriage (mean and 95% HDI). **(d)** Illustration of the strongest forces selecting for greater or lesser resistance across models.

291 acquisition-blocking vaccine has relatively little impact upon the frequency of
292 resistance, because administering a universal pneumococcal vaccine to all individuals
293 does not substantially alter the distribution of antibiotic use or of heritable variation in
294 clearance rates. By contrast, in the within-host competition models, vaccination has a
295 substantial impact upon resistance evolution because by reducing pneumococcal
296 circulation, vaccines decrease the rate at which strains encounter each other within
297 hosts, and hence strongly decrease competition between pneumococcal strains.
298 Specifically, the acquisition-blocking vaccine selects strongly against resistance in the
299 "Treatment competition" model: since antibiotic-mediated within-host competition
300 benefits the resistant strain in this model, the vaccine works against this competitive
301 advantage and therefore inhibits resistance. Conversely, in the "Growth competition"
302 model, growth-mediated competition benefits the sensitive strain, and so by reducing
303 competition, vaccination tends to promote resistance. These results expand upon our
304 previous finding that the rate of co-colonisation modulates resistance evolution through
305 its impact upon within-host competition (*26*).
306
307 The clearance-accelerating vaccine exhibits similarly divergent impacts across
308 mechanisms of resistance evolution. However, compared with the acquisition-blocking
309 vaccine, it also has an additional resistance-inhibiting effect across all models, because a
310 shorter duration of carriage—whether natural or vaccine-induced—selects against
311 resistance (*38*). This suggests that vaccines that accelerate natural clearance have a
312 particular potential for managing resistant infections. As expected, reducing the rate of
313 penicillin prescribing selects against resistance, exhibiting a similar impact across all
314 four models.
315
316 The impact on resistant carriage (Fig. 3c), which combines changes in the prevalence of
317 carriage and changes in the frequency of resistance, can be treated as a proxy for the
318 incidence of resistant infections. Overall, under the "Growth competition" model,
319 vaccination at intermediate efficacy is expected to increase the rate of resistant carriage,
320 and hence the number of cases of resistant disease. In other models, vaccination always
321 reduces resistant carriage, particularly under the "Treatment competition" model. A
322 summary of the strongest vaccine impacts is shown in Fig. 3d.
323

Evidence to inform policy and vaccine trials. For vaccines to be considered an efficient means of controlling resistant infections, they must compare favourably to existing interventions, such as reducing inappropriate antibiotic use (*52*). The UK government has recently announced an initiative to reduce antibiotic consumption by 15% by the year 2024 (*52*). Our models predict that a 15% reduction in primary-care penicillin consumption would reduce carriage of penicillin-non-susceptible pneumococci from 6% to 3%. The vaccine efficacy required to yield the same effect varies considerably depending upon the mechanism of resistance evolution (Fig 4a); for example, the required vaccine efficacy is lowest under the "Treatment competition" model (ε_a = 11% or ε_c = 7%), and highest under the "Growth competition" model (ε_a = 52% or ε_c = 50%). A full comparison of vaccine and stewardship interventions would require accounting for the economic cost of vaccines versus antibiotics, the wider range of resistant pathogens that would be targeted by restrictions on antibiotic use, and any potential increase in pathogen circulation that might be brought about by inadvertent decreases in appropriate antibiotic use.

In randomized controlled trials of pneumococcal vaccines, resistance-related endpoints have routinely been evaluated over a follow-up period of between 6 months and 3.5 years after vaccination (*53*, *54*). If vaccine-induced changes in resistance evolution unfold over a considerably longer timescale, similarly-designed trials may not fully capture vaccine impact on resistance. Indeed, we find that it can take 5–10 years for resistance to stabilise following vaccination (Fig. 4b), and that short-term drops in resistance can be reversed—or even give way to increased resistance—in the long term. Moreover, a trial in which vaccination is not offered to a substantial fraction of the population would not capture the full impact of reduced pneumococcal circulation, which is what drives competition-mediated changes in resistance in our models. Finally, our analysis assumes that vaccines are administered to all recipients simultaneously. In the real world, where vaccination is likely to be be rolled out gradually, the full effect of vaccination would take even longer to observe.

The impact of vaccination at a national level varies depending upon the treatment rate in a given country. Focusing on the specific outcome of childhood pneumococcal pneumonia cases, we find that while interventions have a consistent impact from

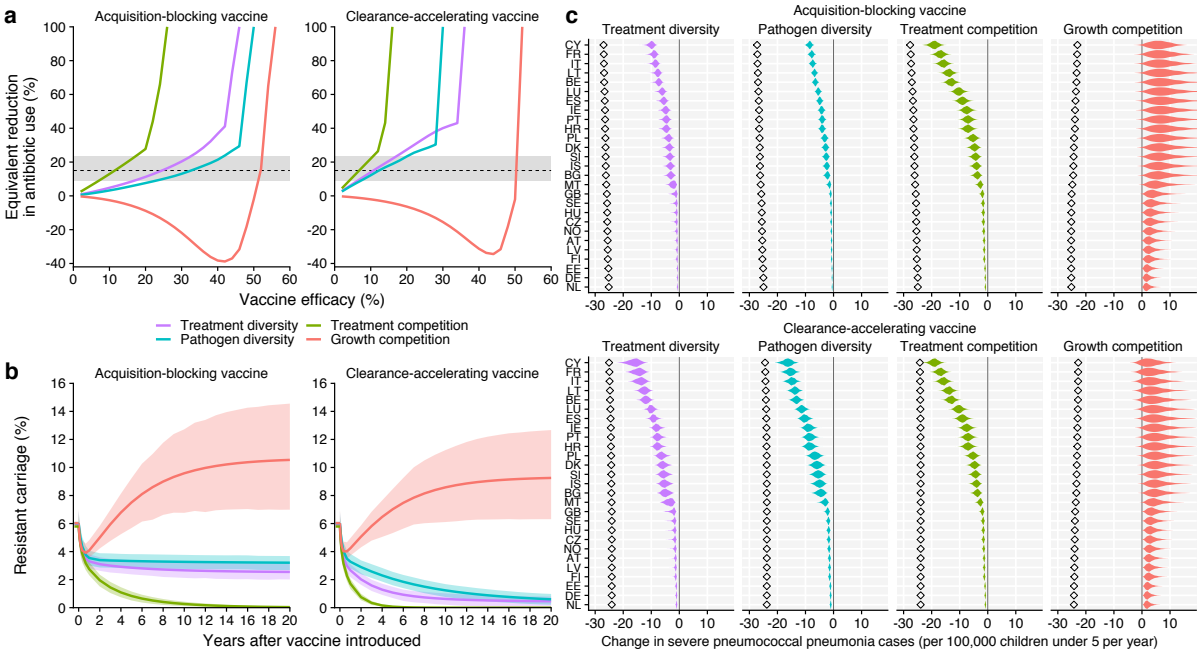

Fig. 4. Policy considerations. (a) Median equivalent reduction in prescribing across four models of resistance evolution, in terms of vaccine efficacy at reducing the prevalence of resistant pneumococcal carriage. This demonstrates the vaccine efficacy required to achieve a similar decrease in resistant 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 (*77*). 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.

372 country to country on the total pneumonia case rate, the impact on resistant pneumonia
373 cases is greatest in those countries where antibiotic use, and hence resistance, is highest
374 (Fig. 4c). We focus on resistant carriage, but the realised public health benefits of any
375 intervention targeting both resistant and sensitive strains will depend upon the relative
376 health burdens of susceptible versus non-susceptible *S. pneumoniae* infections;
377 enumerating these comparative burdens is the subject of ongoing research (*55*).
378
379 **Vaccination in a high-burden setting.** High prevalences of carriage, disease, and
380 resistance are often observed in low-income settings, and it is desirable to know
381 whether this could substantially alter predictions of vaccine impact. As an illustrative
382 example, a 90% pneumococcal carriage rate, with 81% of isolates resistant to penicillin,
383 has been observed among children under five years old in western Kenya (*56*). This may
384 be partly attributable to a longer average duration of carriage in this setting, as a 71-day
385 mean duration of natural pneumococcal carriage has been measured in Kilifi, eastern
386 Kenya (*57*).
387
388 To model a similar high-burden setting, we adjust model parameters estimated from
389 European data: increasing the mean natural carriage duration, transmission rate, and
390 treatment rate to match observed data, and ignoring mixing with any other countries (f
391 = 1), while keeping other parameters the same. We find that a comparatively greater
392 vaccine efficacy is needed to reduce the prevalence of resistant carriage in a high-
393 burden, high-resistance setting (Fig. 5). This is particularly true under the "Growth
394 competition" model, because in this model resistant carriage only declines as total
395 pneumococcal carriage declines, and it is particularly difficult to reduce overall carriage
396 in a high-transmission setting. Simultaneously, vaccination may have a comparatively
397 greater impact in high-burden settings because of a comparatively higher incidence of
398 disease: for example, Kenya has been estimated to have an 8.8-fold higher incidence of
399 severe pneumococcal pneumonia than the average in Europe (*58*).
400
401 **Accounting for additional between-country variation does not substantially alter**
402 **predictions.** Our focus thus far has been on the impact of the four identified
403 mechanisms *per se* upon resistance evolution, and accordingly we have focused on
404 reproducing the positive association between treatment rate and resistance frequency

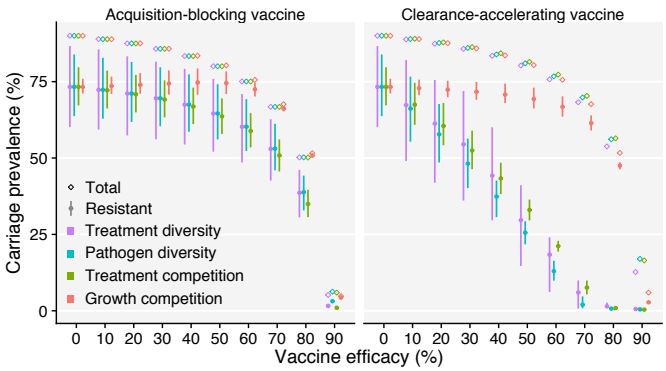

Fig. 5. Vaccine impact in a high-burden setting. Adjusting fitted models to be consistent with a high-burden setting yields different predictions for vaccine impact (mean and 95% HDI), highlighting both increased challenges and greater opportunities for resistance management via vaccination.

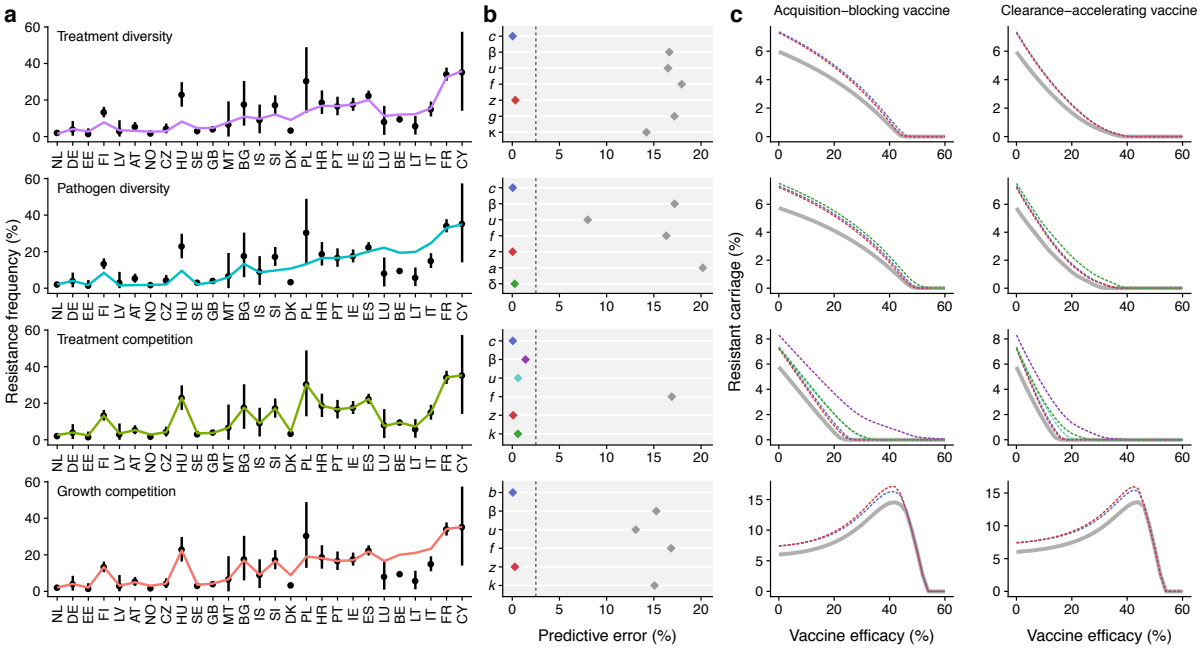

Fig 6. Explaining additional between-country variation in resistance frequency. Allowing model parameters to vary across countries captures additional between-country variation in resistance frequency not captured by variation in the treatment rate. For example, **(a)** allowing the transmission rate β to vary across countries can explain the variation in some but not all models (points and vertical lines show mean credible resistance frequency and 95% HDI for each country). **(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.

425 rather than attempting to capture the additional variability in resistance frequency
426 between countries not accounted for by the reported treatment rate alone (Fig. 2a). This
427 additional variability may partially stem from differences in national testing and
428 reporting practices, or between-country differences in the distribution of pneumococcal
429 serotypes among invasive isolates (*59*). However, another possibility is that this
430 additional variability in resistance results from systematic differences in pathogen
431 biology or host behaviour across countries which can be captured by our modelling
432 framework.
433
434 To help identify which model parameters could account for this variability, we relax the
435 assumption that only the treatment rate varies across countries, and perform Bayesian
436 maximum *a posteriori* fitting, assuming one additional parameter (c, b, β, u, f, z, g, κ, a, δ,
437 or k) is free to vary between countries while other parameters are held constant. We
438 find that additional variation in resistance between countries can be explained by
439 variation in certain other parameters, depending upon which model is used (Fig. 6a–b).
440 Importantly, among those parameters for which additional variation between countries
441 can explain the variation in resistance (Fig. 6c), predictions for the overall impact of
442 vaccination remain similar, with the major differences between scenarios still
443 attributable to the underlying mechanism of resistance evolution (Fig. 6d; Figs. S5–S16).
444 Models that could make more accurate country-specific predictions would need to
445 account for the effects of demographic structure, differences in carriage prevalence and
446 disease rates between settings, and variable vaccine protection among individuals.
447
448 **Discussion**
449
450 We have identified four mechanisms of resistance evolution that are capable of
451 recapitulating the observed relationship between penicillin consumption and penicillin
452 non-susceptibility in *S. pneumoniae* across Europe. These mechanisms are not mutually
453 exclusive, but the relative importance of each is predicted to have a substantial impact
454 upon predictions for resistance evolution under vaccination. In particular, the
455 "directionality" of within-host competition—that is, whether, on average, within-host
456 competition tends to benefit resistant or sensitive strains—strongly determines
457 whether vaccination selects for a decrease or an increase in antibiotic resistance in the

458 long term. This directionality may vary between pathogens, but is also sensitive to the
459 antibiotic treatment rate, and so may also vary between settings. Although we have
460 focused on competition between sensitive and resistant strains of *S. pneumoniae* only,
461 competition between serotypes (*24*) and with other bacteria colonizing the
462 nasopharynx will also impact upon resistance evolution, and determining the
463 importance of these other sources of within-host competition is crucial.
464
465 A key result of our models is that the mode of vaccine protection—whether acquisition-
466 blocking or clearance-accelerating—has an appreciable impact upon resistance
467 evolution. Whole-cell and purified-protein pneumococcal vaccines may induce
468 antibody-mediated humoral immunity, CD4+ T helper-17 cell-mediated immunity, or
469 both, with the type of immunity mediating pneumococcal acquisition, carriage, and
470 disease in ways that are still not fully understood (*49–51*). By modelling both modes of
471 vaccine action, we have highlighted that clearance-accelerating vaccines have increased
472 potential for preventing the spread of resistance, because in shortening the duration of
473 asymptomatic carriage they limit the fitness advantage of resistant pathogens under
474 selection pressure from antibiotic use.
475
476 We fit our models to a "snapshot" of penicillin non-susceptible *S. pneumoniae* as
477 observed across European countries in 2007, finding that each model recapitulated the
478 data equally well. This raises the question of what kind of data would be needed to
479 distinguish the models. One possibility would be to consider trends of resistance
480 evolution over time. Indeed, the prevalence of penicillin non-susceptibility in *S.*
481 *pneumoniae* remained largely stable in Europe between 2005–2017, a period which saw
482 the incorporation of PCV into the routine immunization schedules of most European
483 countries (*60*). This could be viewed as favouring the "diversity" mechanisms, which
484 predict little change in resistance evolution following vaccination. But because serotype
485 replacement has largely negated any vaccine impact on the prevalence of
486 nasopharyngeal pneumococcal carriage (*10*, *11*), it is not clear that we would be able to
487 detect any effects of competition-mediated resistance evolution following a serotype-
488 specific vaccine such as PCV—particularly given the complexity of detecting vaccine-
489 attributable changes in resistance in a population-level associational study that would
490 be confounded both by serotype replacement and by other changes in resistance

491 evolution that might be expected to occur at a national level over the course of multiple
492 years. However, it is known that the prevalence of pneumococcal carriage declines
493 substantially with age (*42*). Therefore, it might be possible to detect a signal of within-
494 host competition between sensitive and resistant strains by comparing the relative
495 prevalence of resistant pneumococcal carriage in younger versus older hosts, provided
496 that other differences could be controlled for.
497
498 Under the "Treatment diversity" and "Pathogen diversity" models, we have argued that
499 universal pneumococcal vaccination will have little impact upon the long-term
500 evolution of antibiotic resistance because it does not change the sources of diversity
501 that modulate resistance evolution. Nonetheless, it is possible to target vaccines such
502 that this diversity is harnessed to manage resistance: high-resistance serotypes could
503 be targeted with a serotype-specific vaccine, or high-treatment subpopulations could be
504 targeted for vaccination in order to more effectively manage resistance. Indeed,
505 vaccination does have an additional inhibiting effect upon resistance in our models
506 because of the latter effect. This inhibition occurs because the vaccine has a relatively
507 greater impact upon transmission in populations where the prevalence of carriage is
508 already low, which in our models occur in countries or subpopulations with more
509 antibiotic consumption. Since these populations drive resistance more strongly, the
510 vaccine's comparatively greater impact in these populations tends to moderately inhibit
511 resistance overall. We note that while previous work (*38*) has suggested that resistance
512 evolution under a "Pathogen diversity" model results in a "stepped" resistance pattern
513 in which D-types are either fully sensitive or fully resistant at equilibrium, we find that
514 small amounts of mixing between populations can smooth out this pattern and allow
515 intermediate rates of resistance within subtypes (Fig. S2). Finally, while we have framed
516 "Treatment competition" and "Growth competition" as two distinct alternatives, they
517 can instead be viewed as endpoints on a continuum, with possible models of resistance
518 evolution for which both $c > 0$ and $b > 0$ lying between them. The impact of vaccination
519 on resistance in such a model would depend upon the relative importance of treatment-
520 mediated and growth-mediated competition.
521
522 This analysis has necessarily made simplifying assumptions. We have focused on
523 prevalence (the fraction of individuals who are carriers) rather than incidence (the rate

524 of new carriage episodes) of nasopharyngeal carriage in presenting our findings. There
525 is evidence that pneumococcal disease progression is more likely to occur shortly after
526 nasopharyngeal acquisition (*61*), suggesting that incidence may be more relevant than
527 prevalence for predicting disease outcomes. Of particular note, recent modelling work
528 has suggested that clearance-accelerating vaccines can increase rates of pneumococcal
529 acquisition, if extended carriage is protective against new acquisition (*62*). However, it
530 is not obvious how to compare rates of carriage acquisition across the models examined
531 in this paper, particularly because co-colonisation is explicitly tracked in some but not
532 all models. More work is required to clarify the links between acquisition, carriage, and
533 disease across competing models of pneumococcal transmission. Additionally, we have
534 assumed that antibiotic treatment rates among pneumococcal carriers remains constant
535 after the introduction of a vaccine, even though treatment rates dropped in many
536 settings following PCV introduction (*5*, *9*). However, for a universal pneumococcal
537 vaccine that reduces antibiotic treatment rates because it reduces carriage and thereby
538 prevents antibiotic-treatable disease, any reduction in treatment will only occur among
539 individuals who, because of vaccine protection, are not pneumococcal carriers, all else
540 being equal. It might then be expected that treatment rates in carriers would remain
541 equally high among those individuals for whom vaccine protection has failed—although
542 physicians may be less inclined to prescribe antibiotics for respiratory tract infection
543 more generally after the introduction of a new pneumococcal vaccine. Finally, we have
544 focused on modelling children under 5 years old only. We would not expect
545 incorporating age structure to lead to qualitatively different results, but age-related
546 maturation of the immune system has been shown to be important for maintaining the
547 circulation of pneumococcal serotypes (*49*) which we have abstracted here.
548
549 Our work helps resolve the question: What explains the persistent coexistence between
550 resistant and sensitive strains of *S. pneumoniae*? (*25*) by demonstrating that multiple
551 mechanisms are capable of explaining trends of resistance across European countries.
552 Since there is empirical support for within-host competition between sensitive and
553 resistant pathogen strains (*63–66*), heritable differences in the propensity for resistance
554 within species (*38*, *67*), and within-country heterogeneity in antibiotic consumption
555 rates (*68–70*), all of these mechanisms likely contribute to this pattern. Our results
556 contextualize previous mathematical studies which have variously suggested that

557 serotype-specific vaccination may increase (*24*), decrease (*22*) or have no impact upon
558 (*18*) the frequency of resistance in *S. pneumoniae*. While the potential for vaccination to
559 promote resistance because of competition between sensitive and resistant strains has
560 been described previously (*24*), we have shown that vaccination can either promote or
561 inhibit resistance depending upon the directionality of within-host competition. While
562 vaccines targeting highly-resistant serotypes can decrease resistance (*22*), we have
563 shown that a serotype-independent vaccine promoting accelerated natural clearance
564 can decrease resistance across all circulating subtypes. And where single-population
565 models have found no long-term impact of vaccination on resistance frequency (*18*), we
566 have shown that in multi-population models, vaccination can inhibit resistance if it has
567 a larger impact in subpopulations that consume more antibiotics. The direction and
568 magnitude of this effect would depend upon variation in vaccine uptake, vaccine
569 efficacy, and pathogen transmission among subpopulations, and we have not
570 systematically explored this variation here.
571
572 A highly efficacious serotype-independent pneumococcal vaccine can indeed reduce the
573 overall burden of antibiotic-resistant pneumococcal infections. However, the long-term
574 effect upon resistance of a vaccine with intermediate efficacy is less certain, as vaccine
575 impact depends crucially upon the mechanisms that drive resistance evolution. Thus,
576 empirical investigation of pathogen competitive dynamics—and the impact of setting-
577 specific factors on these dynamics—is needed to make accurate predictions of vaccine
578 impact on resistant infections.
579
580 **Methods**
581
582 *Study design.* This study comprises four parts: a literature search used to identify
583 plausible mechanisms through which coexistence can be maintained between sensitive
584 and resistant pneumococcal strains across a range of antibiotic treatment rates; a
585 mathematical modelling study embedding these mechanisms of resistance evolution in
586 four models of pneumococcal transmission; a Bayesian statistical analysis to fit these
587 models to empirically observed frequencies of penicillin non-susceptibility and
588 community penicillin consumption across 27 European countries for the year 2007; and
589 a vaccine impact analysis using these fitted models to forecast the impact of a universal

590 pneumococcal vaccine. We use data from 2007 because changes in pneumococcal
591 resistance reporting standards for some countries after this year hamper the between-
592 country comparability of data (*71*). Our objectives were to identify the mechanisms
593 potentially responsible for maintaining coexistence between resistant and sensitive
594 pneumococci in Europe, and to determine whether the impact of vaccination on the
595 evolution of resistance depends upon which mechanism is assumed to operate.
596
597 *Mechanisms driving resistance.* We searched PubMed using the terms: (AMR OR ABR OR
598 ((antimicrobial OR antibiotic) AND resist*)) AND ((model OR modelling OR modeling)
599 AND (dynamic* OR transmi* OR mathematical)) AND (coexist* OR intermediate). This
600 yielded 93 papers (Table S1). We included all papers containing a dynamic host-to-host
601 pathogen transmission model analysing both sensitive and resistant strains with stable
602 coexistence as an outcome of the model. From the 11 studies meeting these criteria, we
603 identified nine unique mechanisms, two of which correspond to alternative
604 parameterisations of a within-host competition model. We ruled out four mechanisms
605 because of implausibility or because previous work shows that the mechanism does not
606 bring about substantial coexistence, leaving four mechanisms (Table 1).
607
608 *Model framework.* We analyse the evolution of antibiotic resistance by tracking the
609 transmission of resistant and sensitive bacterial strains among hosts in a set of M
610 countries indexed by $m \in \{1,2, \dots, M\}$ using systems of ordinary differential equations.
611
612 In a simple model, hosts can either be non-carriers (X), carriers of the sensitive strain
613 (S), or carriers of the resistant strain (R). Omitting country-specific subscripts m for
614 concision, model dynamics within a country are captured by
615
616 $$\mathrm{d}S/\mathrm{d}t = \lambda_S X - (u + \tau)S$$
617 $$\mathrm{d}R/\mathrm{d}t = (1 - c)\lambda_R X - uR$$
618 $$X = 1 - S - R\,, \qquad (1)$$
619
620 where λ_S is the force of infection of the sensitive strain, λ_R is the force of infection of the
621 resistant strain, c is the transmission cost of resistance, u is the rate of natural
622 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; a summary of all model parameters can be found in Table S2.

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*, *72*). 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

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

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. At the scale of individuals, antibiotic consumption is highly variable, with some people taking no antibiotics in a given year and others taking many courses of antibiotics (*73*); at regional scales, antibiotic consumption shows less extreme variability (*74*) and approaches a normal distribution. We use a gamma distribution to model variation in treatment rates among subpopulations because it can capture patterns at either of these scales, or scales in between.

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

$$\mathrm{d}S_d/\mathrm{d}t = q_d\lambda_{S,d}X - (u_d + \tau)S_d$$

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

where q_d is the strength of diversifying selection for D-type $d \in \{1,2,\ldots,D\}$ and u_d is the clearance rate for D-type d. We follow Lehtinen *et al.* (*38*) in defining $q_d = (1 - \frac{S_d+R_d}{\sum_{j=1}^{D}(S_j+R_j)} + \frac{1}{D})^a$ and $u_d = u\left(1 + \delta\left(2\frac{d-1}{D-1} - 1\right)\right)$, where a is the power of diversifying selection and δ is the range of clearance rates. 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

$$\mathrm{d}S/\mathrm{d}t = \lambda_S X - (u+\tau)S - k(1-c)\lambda_R S + b_0 S_R$$
$$\mathrm{d}S_R/\mathrm{d}t = k(1-c)\lambda_R S - (u+\tau)S_R + bR_S - b_0 S_R$$
$$\mathrm{d}R_S/\mathrm{d}t = k\lambda_S R - (u+\tau)R_S - bR_S$$
$$\mathrm{d}R/\mathrm{d}t = (1-c)\lambda_R X - uR - k\lambda_S R + \tau(S_R + R_S)$$
$$X = 1 - S - R - S_R - R_S\,, \qquad (4)$$

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 is the rate of the $S_R \rightarrow S$ transition. We follow Davies *et al.* (*26*) in setting $b_0 = 4b$. 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 $c = 0$).

In equations 1, 3 and 4, the force of infection of a particular strain A in country m is $\lambda_A = \beta\left(f A_{\mathrm{tot}|m} + (1-f)\sum_{\ell=1}^{M} h_\ell A_{\mathrm{tot}|\ell}\right)$, where β is the transmission rate, f is the between-

687 country assortativity, h_ℓ is the relative population size of country m (such that $\sum_\ell h_\ell =$
688 1), and $A_{\text{tot}|\ell}$ is the total carriage of strain A in country ℓ. The probability with which
689 individuals contact an individual from another country, 1 – f, captures those contacts
690 made with individuals from another country in either one's home country or a foreign
691 country. In equation 2, the force of infection of a particular strain A in subpopulation i of
692 country m is $\lambda_{\text{A},i} = \beta\left(f\left(gA_{\text{tot}|m,i} + (1-g)\sum_{j=1}^{N}\frac{1}{N}A_{\text{tot}|m,j}\right) + (1-\right.$
693 $\left.f)\sum_{\ell=1}^{M}\sum_{j=1}^{N}\frac{h_\ell}{N}A_{\text{tot}|\ell,j}\right)$, where g is the within-country assortativity and $A_{\text{tot}|\ell,j}$ is the
694 total carriage of strain A in subpopulation j of country ℓ.
695
696 *Data and model fitting.* We extracted community penicillin consumption and penicillin
697 non-susceptibility in *S. pneumoniae* invasive isolates from databases made available by
698 the ECDC (*13*, *28*). We assume that community penicillin consumption drives penicillin
699 resistance, that antibiotic consumption is independent of whether an individual is
700 colonised by pneumococcus, and that resistance among invasive bacterial isolates is
701 representative of resistance among circulating strains more broadly. Countries report
702 community penicillin consumption in defined daily doses (DDD) per thousand
703 individuals per day. To transform this bulk consumption rate into the rate at which
704 individuals undertake a course of antibiotic therapy, we analysed prescribing data from
705 eight European countries, estimating that, on average, 5 DDD in the population at large
706 correspond to one treatment course for a child under 5 years of age. This conversion
707 rate varies between countries (Table S3), but since the data are incomplete (8 of 27
708 countries) we have not explicitly accounted for this variability in our main model fitting
709 results.
710
711 Our model framework tracks carriage of *S. pneumoniae* among children aged 0–5 years,
712 the age group driving both transmission and disease. In European countries, we assume
713 that the prevalence of pneumococcal carriage in under-5s is 50% (*11*, *42*) and the
714 average duration of carriage is 47 days (*47*, *48*). We calculate the average incidence of *S.*
715 *pneumoniae*-caused severe pneumonia requiring hospitalisation as 610 per million
716 children under 5 per year (*58*) across the European countries in our data set. See Tables
717 S4, S5, and S6 for details of calculations relating to pneumococcal carriage duration and
718 disease incidence.

We use Bayesian inference via differential evolution Markov chain Monte Carlo (*75*) to identify model parameters that are consistent with empirical data while accounting for uncertainty in those estimates. 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, $T(x|\mu, \sigma) = \frac{\varphi(x|\mu,\sigma)}{(\Phi(1|\mu,\sigma) - \Phi(0|\mu,\sigma))}$, 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.

As prior distributions for parameter inference, 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 $k \sim \text{Normal}(\mu = 1, \sigma = 0.5)$. Priors for c, b, and β were chosen to be vague since these parameters are heavily constrained by the data we fit our models to. Priors for g, κ, a, δ, and k were chosen to keep parameters within biologically plausible ranges. Table S7 provides more detail on the choice of priors, and Fig. S4 shows which parameters are most strongly constrained by these prior beliefs.

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. We 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 for EU residents. Specifically, using Eurostat database tour_dem_tnw (*76*) we estimated that the average EU resident spent 1.5% of their nights abroad in 2007; this overestimates mixing because children under 5 travel less than the average person, but underestimates mixing because it does not account for contacts made with visitors to an individual's country of residence and because children may contract pneumococcal carriage from adults who travel, and so we kept the value of 1.5%. See Table S8 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.

Figs. S5–S8 show maximum *a posteriori* fits when allowing an additional parameter to vary freely between countries, along with the parameter values identified by model fitting. Figs. S9–S12 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). Figs. S13–S16 show the impact of vaccination for the remaining parameters.

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Fig. S1. Patterns of penicillin non-susceptibility across European countries, 2005–2017.
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Table S8. MCMC diagnostics.

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Code availability

C++ code used for model comparison is available at https://github.com/nicholasdavies/amr-competition-diversity.

1123 Supplementary Materials for

1124

1125 **Stabilising effects of competition and diversity**

1126 **determine vaccine impact on antibiotic resistance evolution**

1127

1128 Nicholas G. Davies, Stefan Flasche, Mark Jit, Katherine E. Atkins

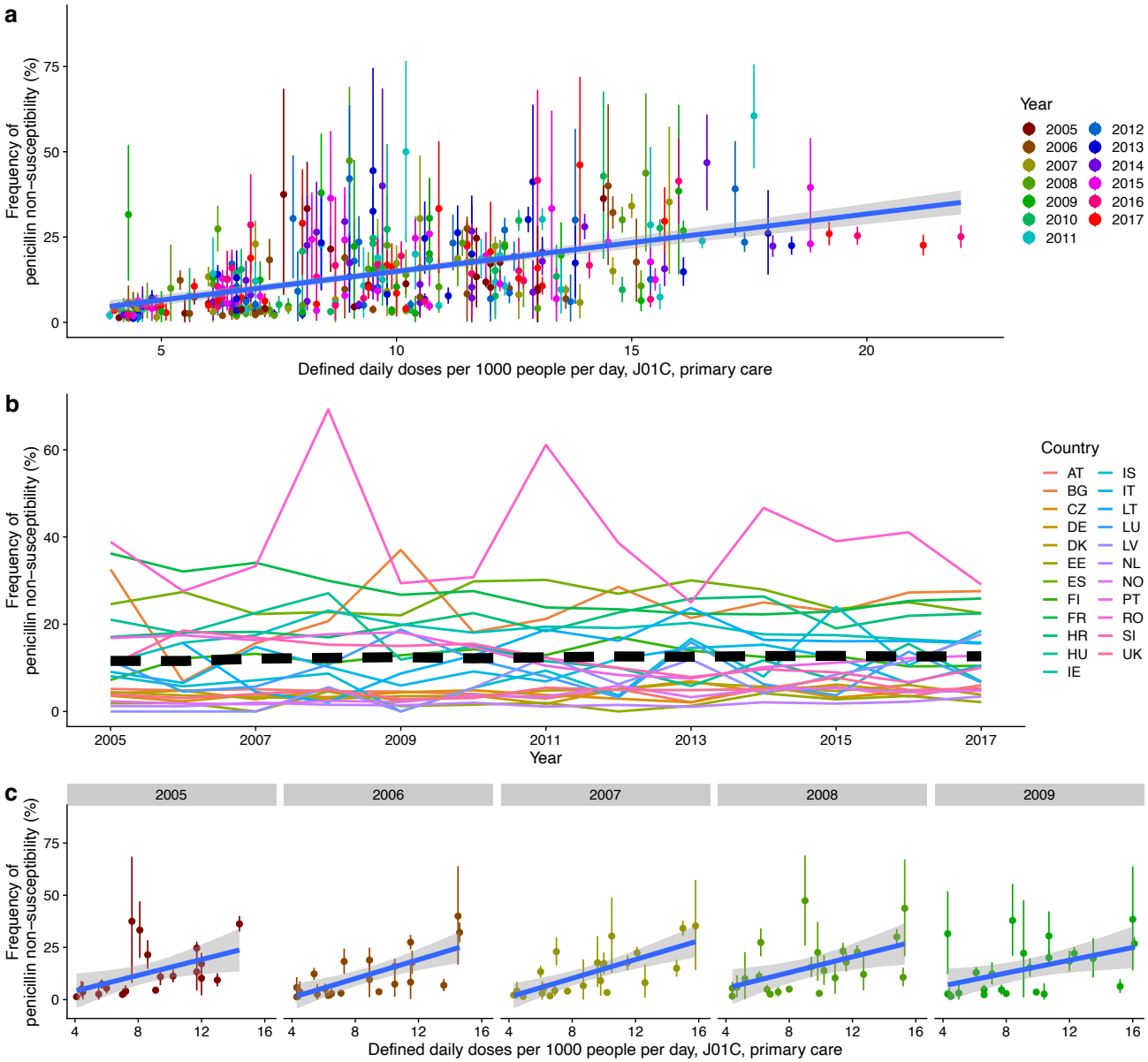

Fig. S1. Patterns of penicillin non-susceptibility across European countries, 2005–2017. (a) The frequency of penicillin non-susceptibility in pneumococcal isolates (mean and 95% HDI) increases with the primary care consumption of penicillins, ATC class J01C (least-squares linear regression $\beta = 0.0168, F(1,344) = 148.5, P < 2.2 \times 10^{-16}$). Data from Belgium after 2007 are excluded because of changes to the definition of penicillin 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%. **(c)** We fit our models to the prevalence of penicillin non-susceptibility in 2007. Despite the introduction of pneumococcal conjugate vaccines into many

1141 European national immunisation programmes starting in 2006, pneumococcal
1142 resistance appears to have been relatively stable over the time period 2005–2009:
1143 while mean penicillin non-susceptibility across European countries increased by 0.5%
1144 per year over this time period, and the slope of penicillin non-susceptibility on primary-
1145 care penicillin consumption decreased by 0.1%/DDD per year, neither of these changes
1146 are significant (least-squares linear regression: $F(1,3) = 0.64$, $P = 0.48$ and $F(1,3) = 1.48$,
1147 P = 0.31, respectively).
1148

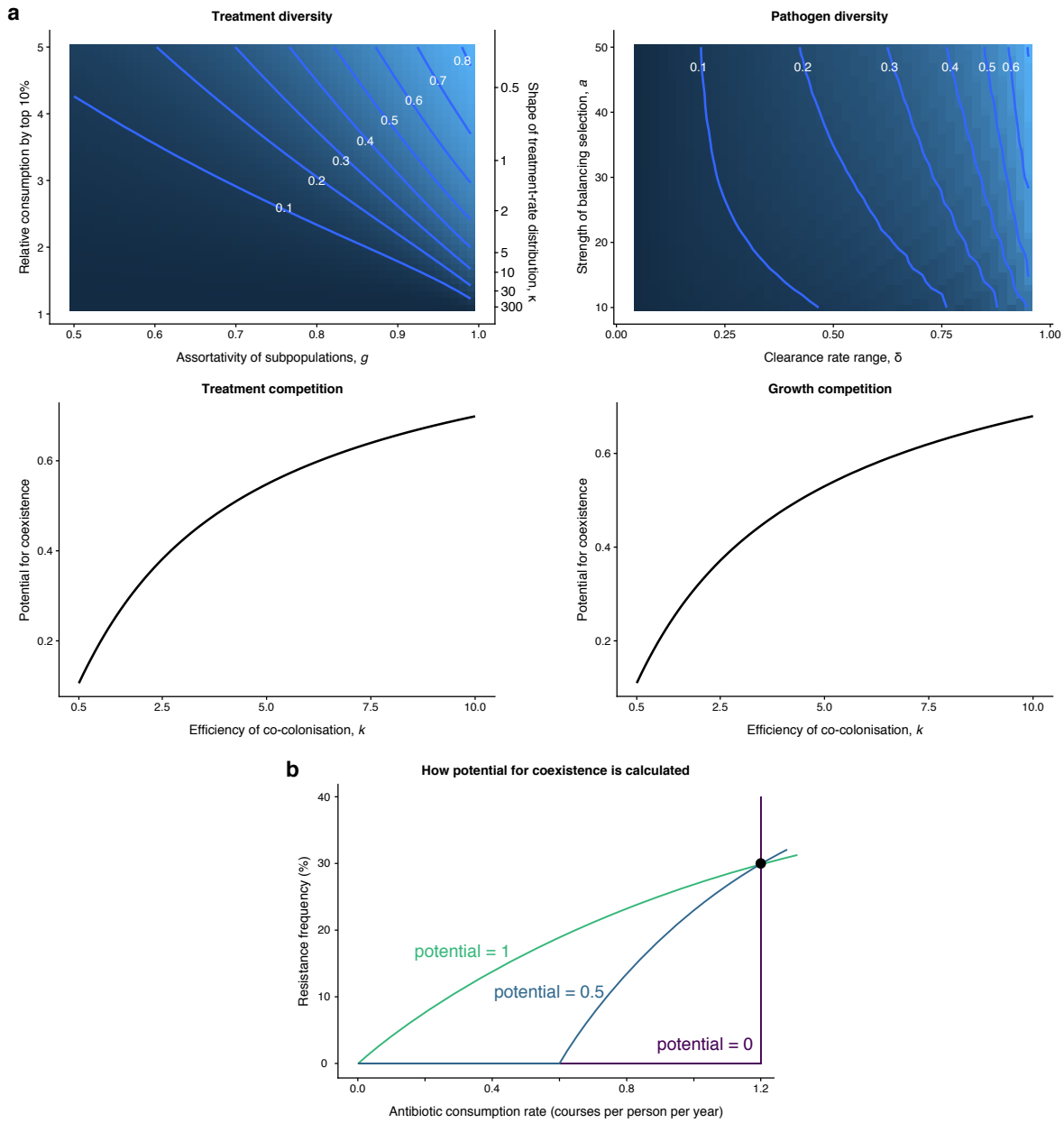

Fig. S2. Impact of key parameters upon the potential for coexistence in each model. (a) Potential for coexistence for each model, depending upon key parameters. In the top two panels, darker colours represent lower potential for coexistence while lighter colours represent higher potential for coexistence. **(b)** Schematic showing how to calculate the "potential for coexistence", an ad-hoc measurement of how much coexistence is exhibited by a given model under a given parameterisation. To find it, we set $\beta = 1.4$ months^{-1}, $u = 0.7$ months^{-1}, and set g, κ, δ, a, and k according to the values shown in the figure (panel a). We then numerically identify the value of c (or b for the "growth competition" model) which results in the equilibrium resistance frequency passing through exactly 30% for a single country in which the antibiotic consumption

rate is equal to $\tau = 1.2$ courses per person per year (black dot; these values are chosen to approximately match observations for *S. pneumoniae* in European countries). The potential for coexistence is the probability that the equilibrium resistance frequency is above 0 for a random treatment rate between $\tau = 0$ and $\tau = 1.2$ (in other words, it is the proportion of the curve that "lifts off" from the x-axis; see figure). By this definition, a model showing no coexistence has potential 0, while a model showing the maximum amount of coexistence has potential 1.

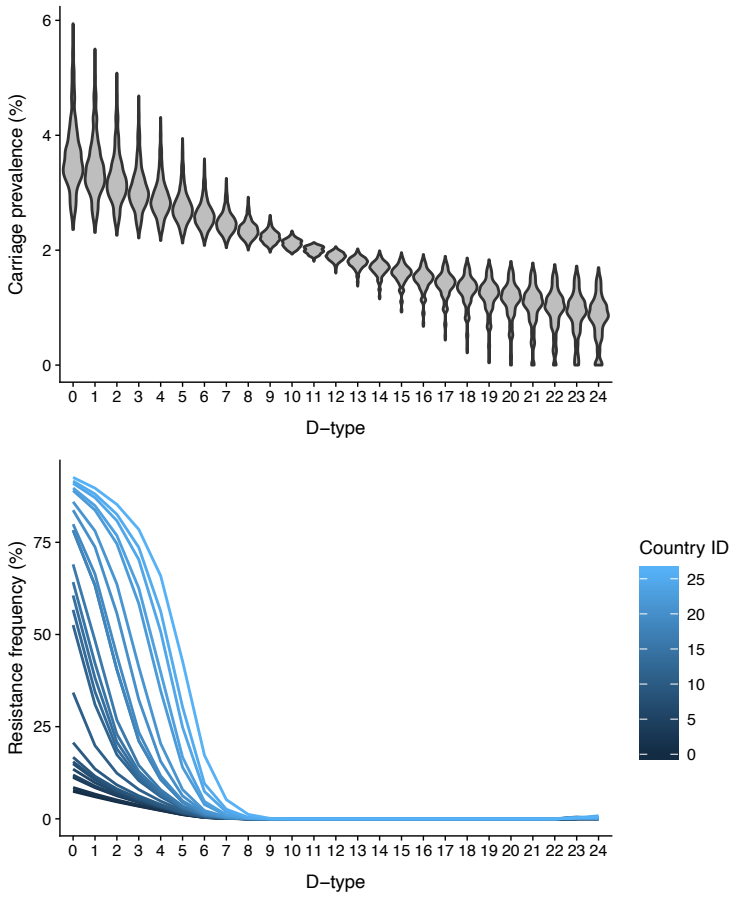

Fig. S3. Carriage and resistance of D-types in the "Pathogen diversity" model. This verifies that the D-types with the highest prevalence of carriage (averaged over all countries, above) also exhibit the highest resistance frequency (separated by country, below), and shows that at equilibrium, D-types can exhibit intermediate frequencies of resistance.

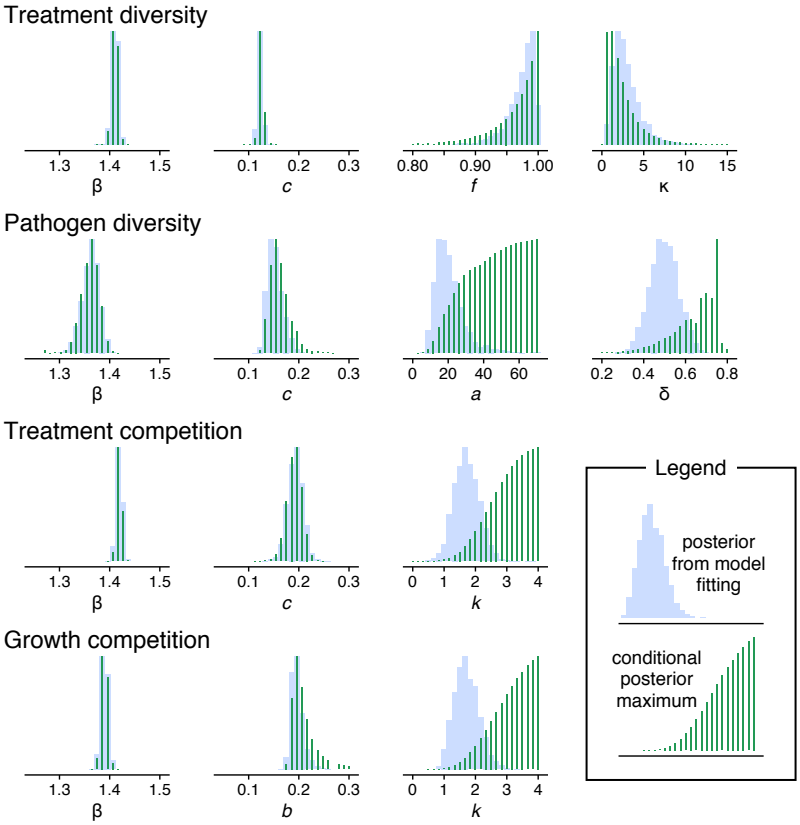

Fig. S4. Comparison of inferred model posteriors and conditional posterior maxima for each parameter. The conditional posterior maximum (green bars) is obtained by fixing the parameter of interest at a specific value, then allowing the other parameters to assume their maximum *a posteriori* values through numerical optimization of the model fit. This is repeated for multiple values of the parameter of interest. The position on the x-axis of the thin green bars shows these fixed values for the parameter of interest (chosen to "sweep" across the parameter range), while the height of the thin green bars is relative to the maximum posterior probability conditional on that fixed value. When the conditional posterior maximum (green bars) does not align with the posteriors from model fitting (blue bars, same as Fig. 2b, main text), this indicates that the prior distribution is strongly influencing the posterior distribution for a given parameter. This analysis shows that values inferred for a and δ under the "Pathogen diversity" model, and for k under the "Treatment competition" and "Growth competition" models, are strongly constrained by prior beliefs about plausible ranges for those parameters, while other parameters are less constrained.

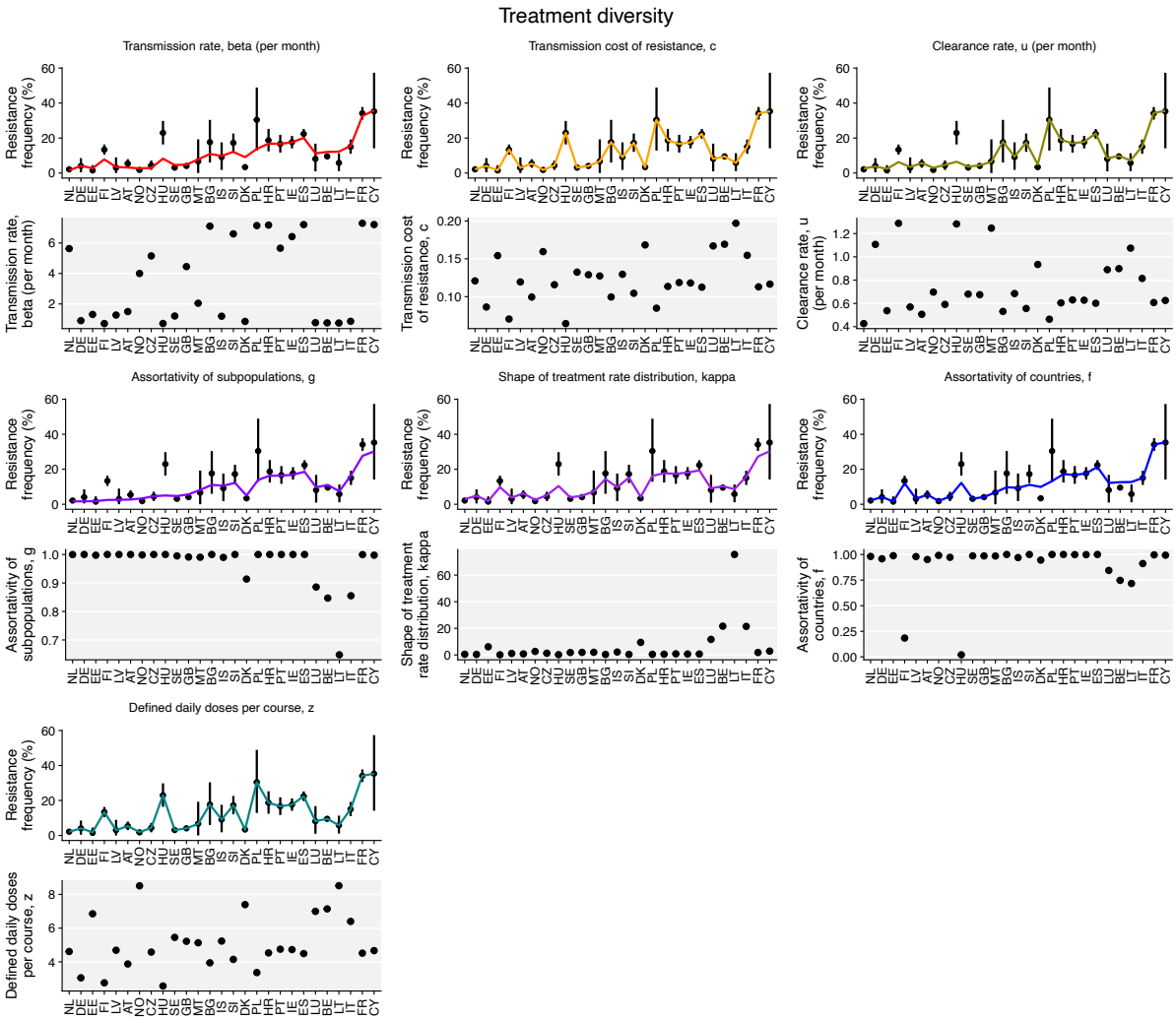

Fig. S5. Varying-parameter fits for the "Treatment diversity" model. Maximum *a posteriori* fits for the "Treatment diversity" model allowing one parameter to vary between countries. Parameters *c* and *z* can capture the additional variation in resistance frequency between countries.

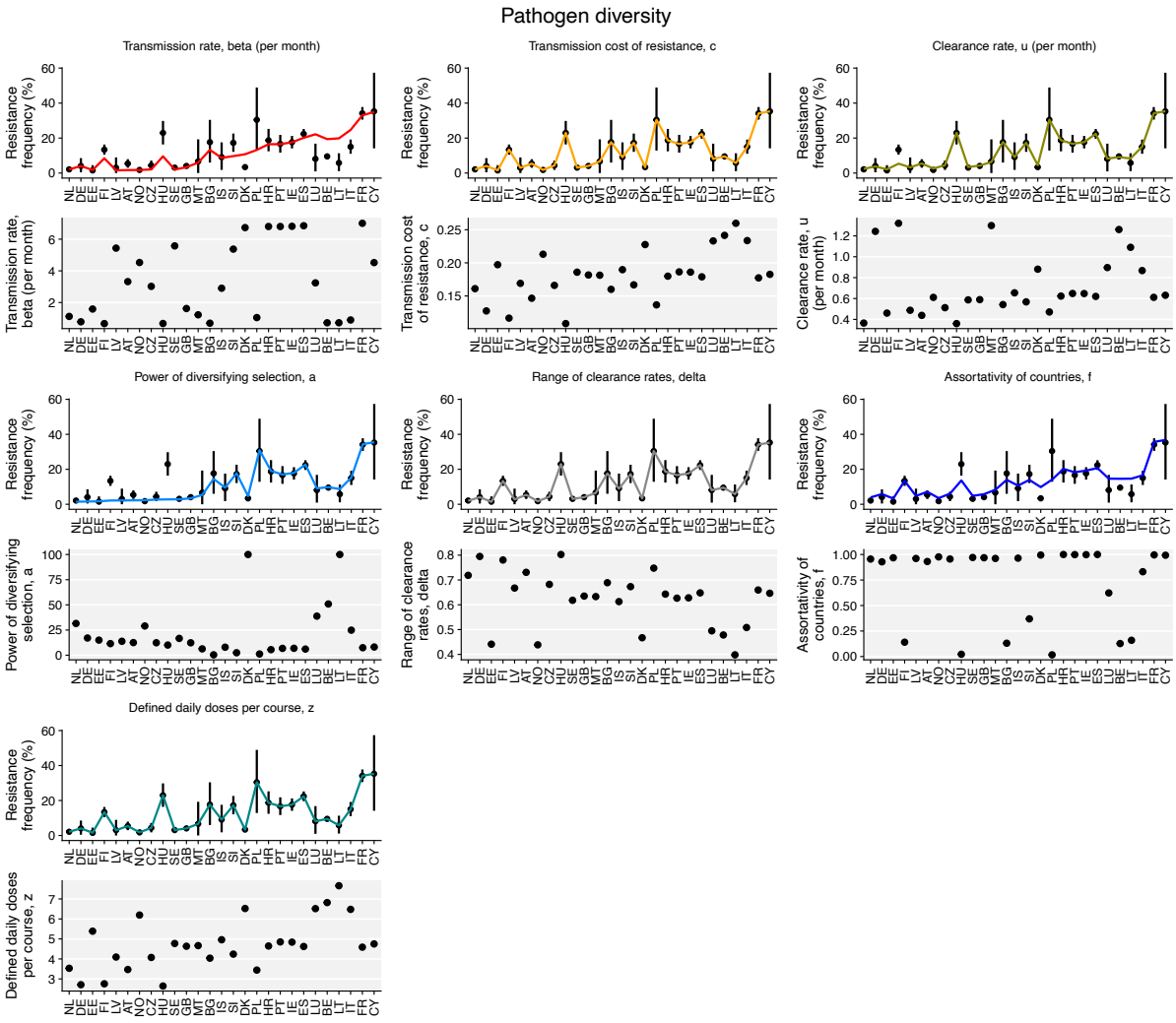

Fig. S6. Varying-parameter fits for the "Pathogen diversity" model. Maximum *a posteriori* fits for the "Pathogen diversity" model allowing one parameter to vary between countries. Parameters c, δ, and z can capture the additional variation in resistance frequency between countries.

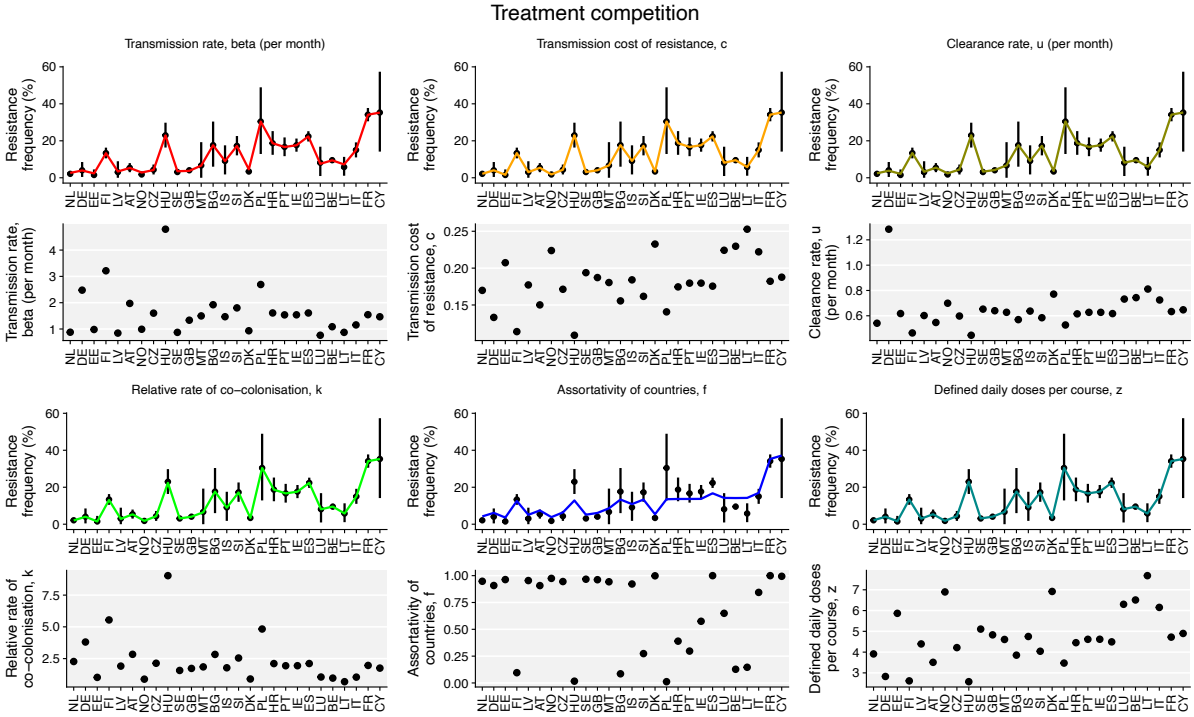

Fig. S7. Varying-parameter fits for the "Treatment competition" model. Maximum *a posteriori* fits for the "Treatment competition" model allowing one parameter to vary between countries. Parameters β, *c*, *u*, *k*, and *z* can capture the additional variation in resistance frequency between countries.

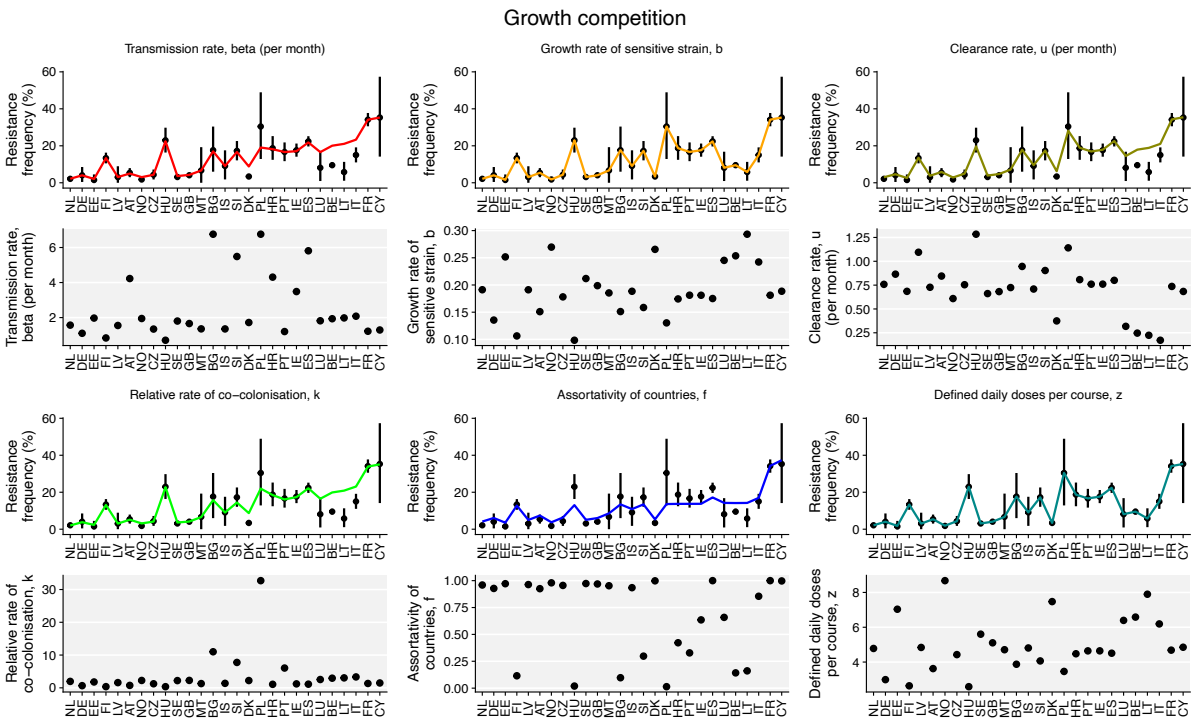

Fig. S8. Varying-parameter fits for the "Growth competition" model. Maximum *a posteriori* fits for the "Growth competition" model allowing one parameter to vary between countries. Parameters *b* and *z* can capture the additional variation in resistance frequency between countries.

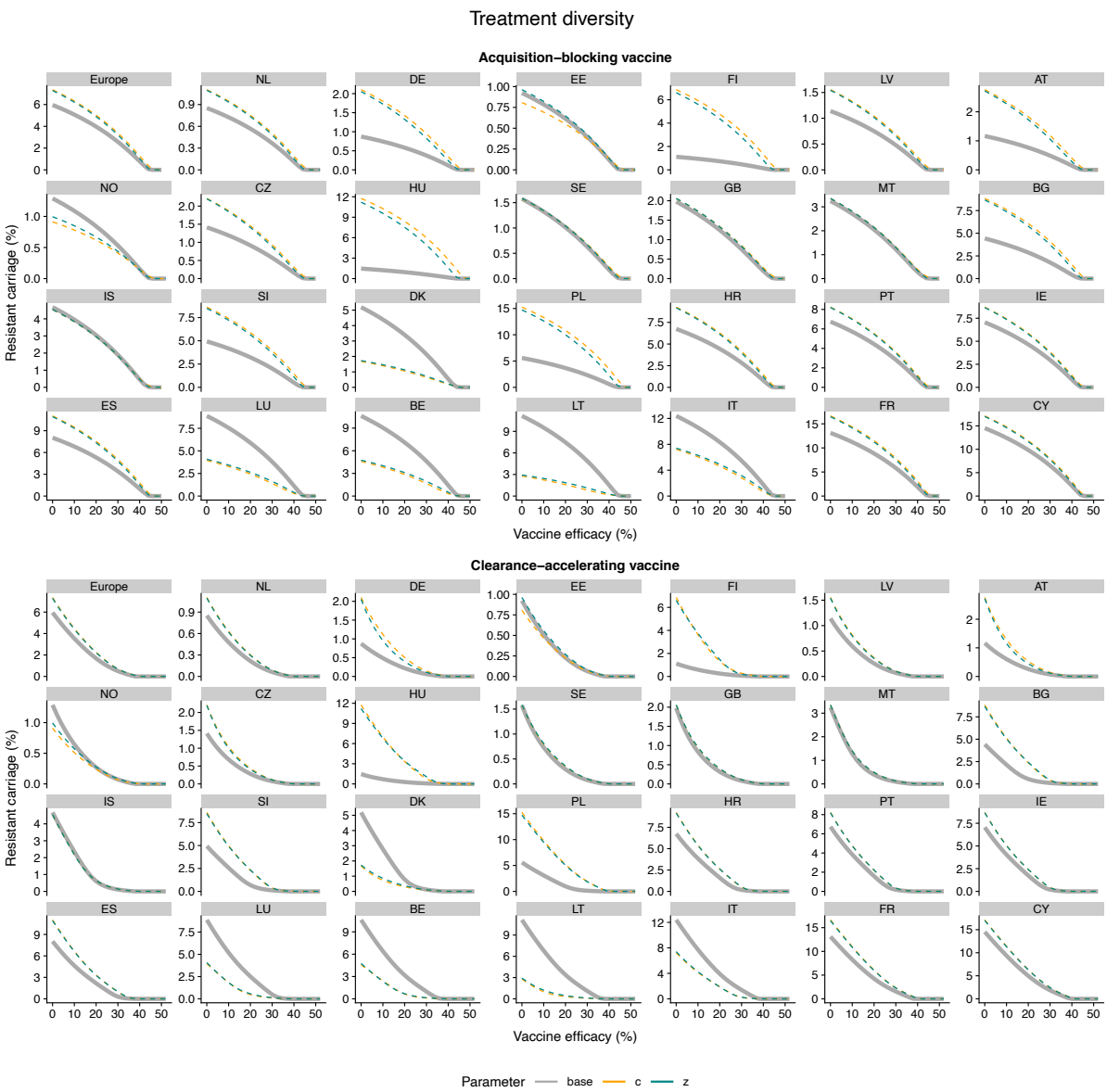

Fig. S9. Vaccine impact for the "Treatment diversity" model, varying parameters *c* and *z*. Impact of vaccination under the "Treatment diversity" model, for those parameters able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).

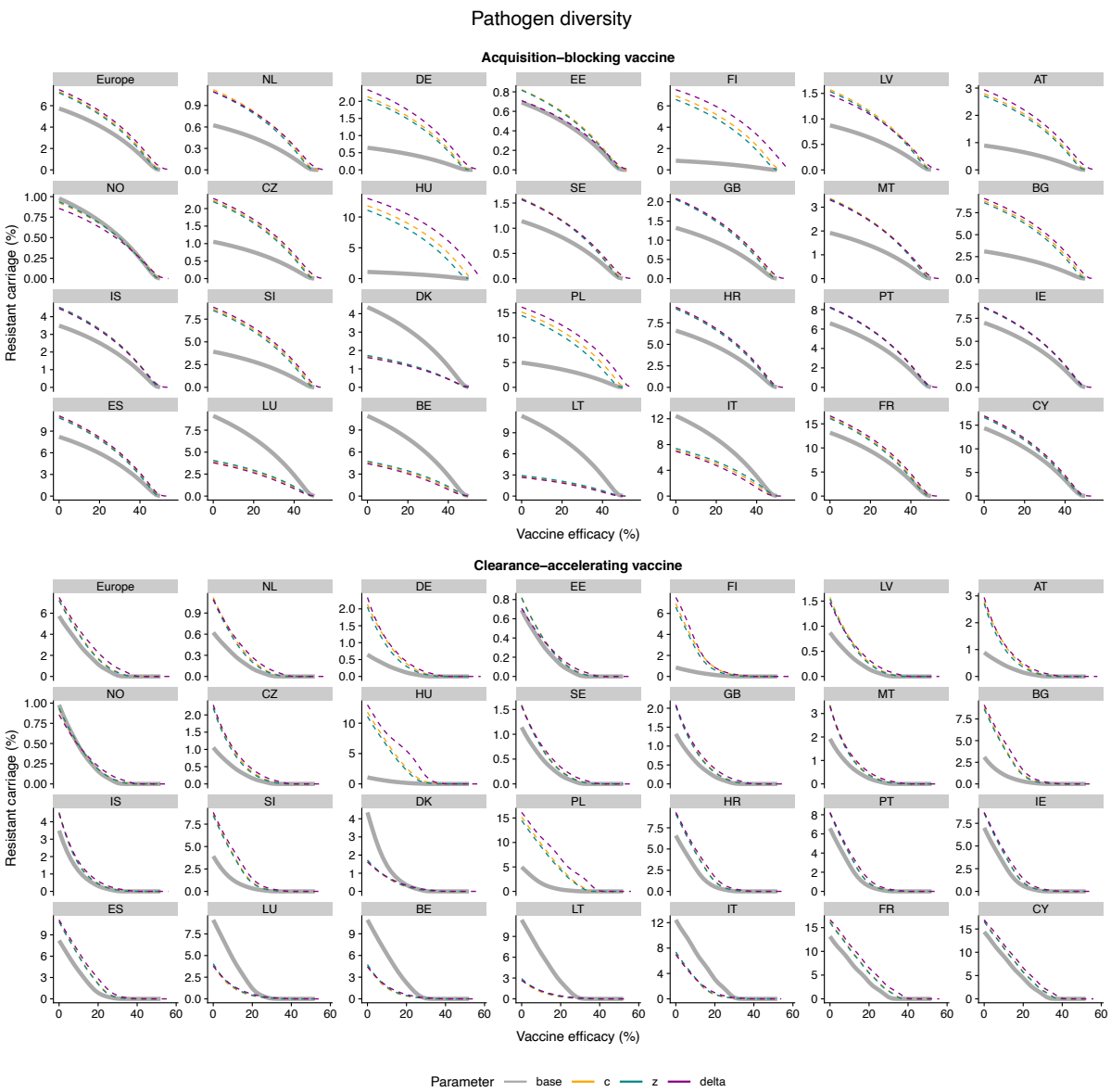

Fig. S10. Vaccine impact for the "Pathogen diversity" model, varying parameters *c*, δ, and *z*. Impact of vaccination under the "Pathogen diversity" model, for those parameters able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).

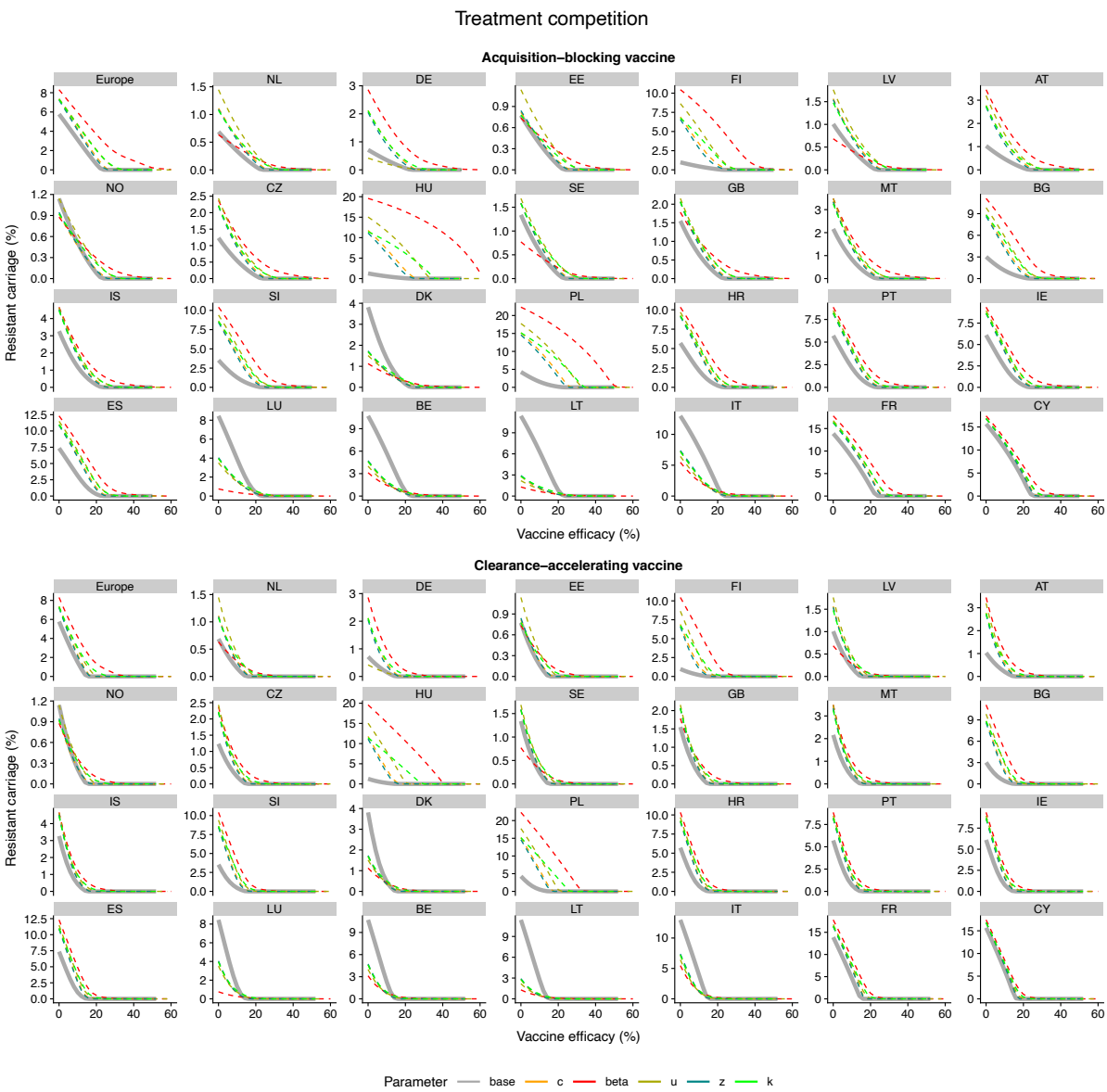

Fig. S11. Vaccine impact for the "Treatment competition" model, varying parameters *β, c, u, k,* and *z*. Impact of vaccination under the "Treatment competition" model, for those parameters able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).

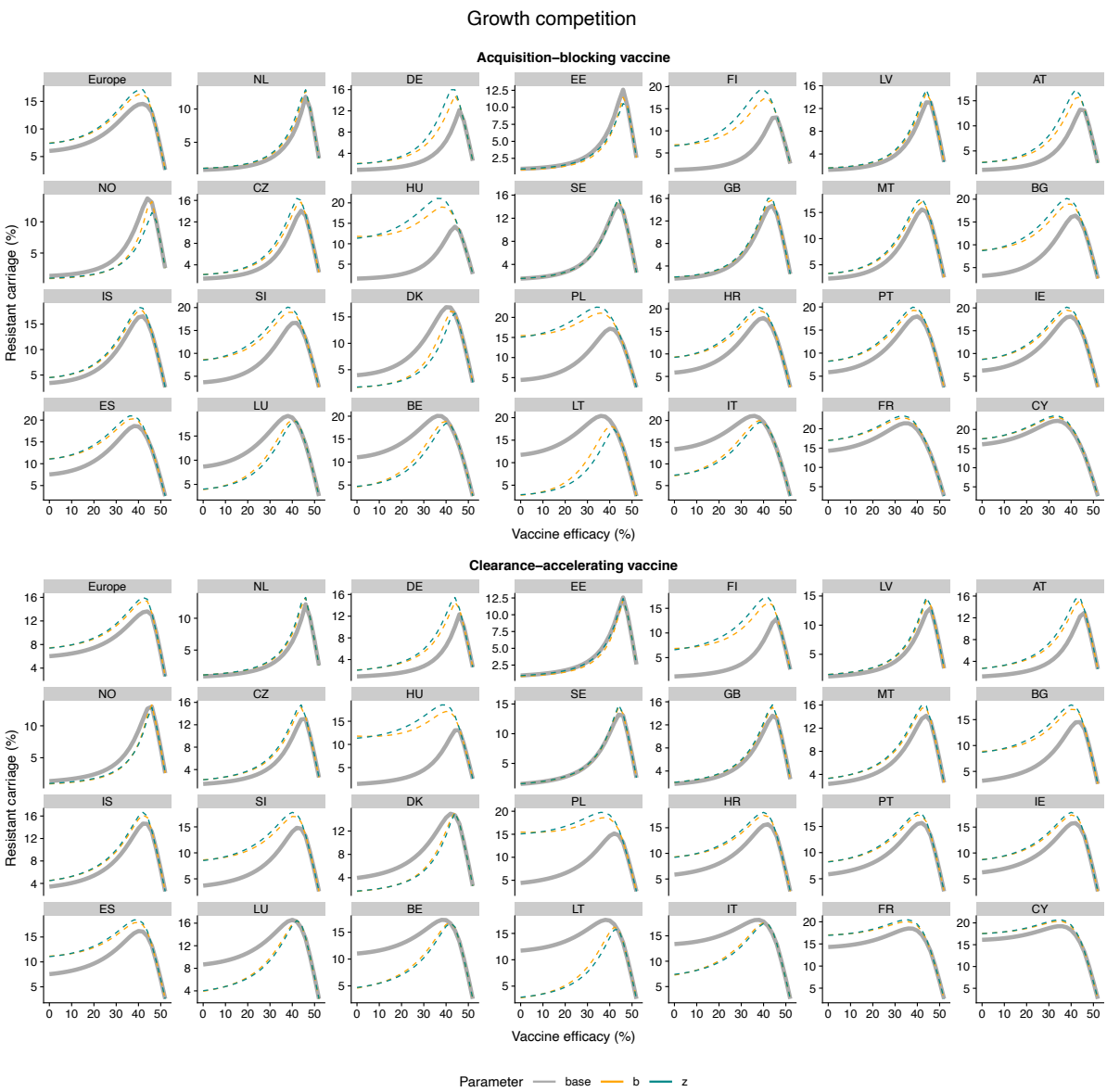

Fig. S12. Vaccine impact for the "Growth competition" model, varying parameters *b* and *z*. Impact of vaccination under the "Growth competition" model, for those parameters able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).

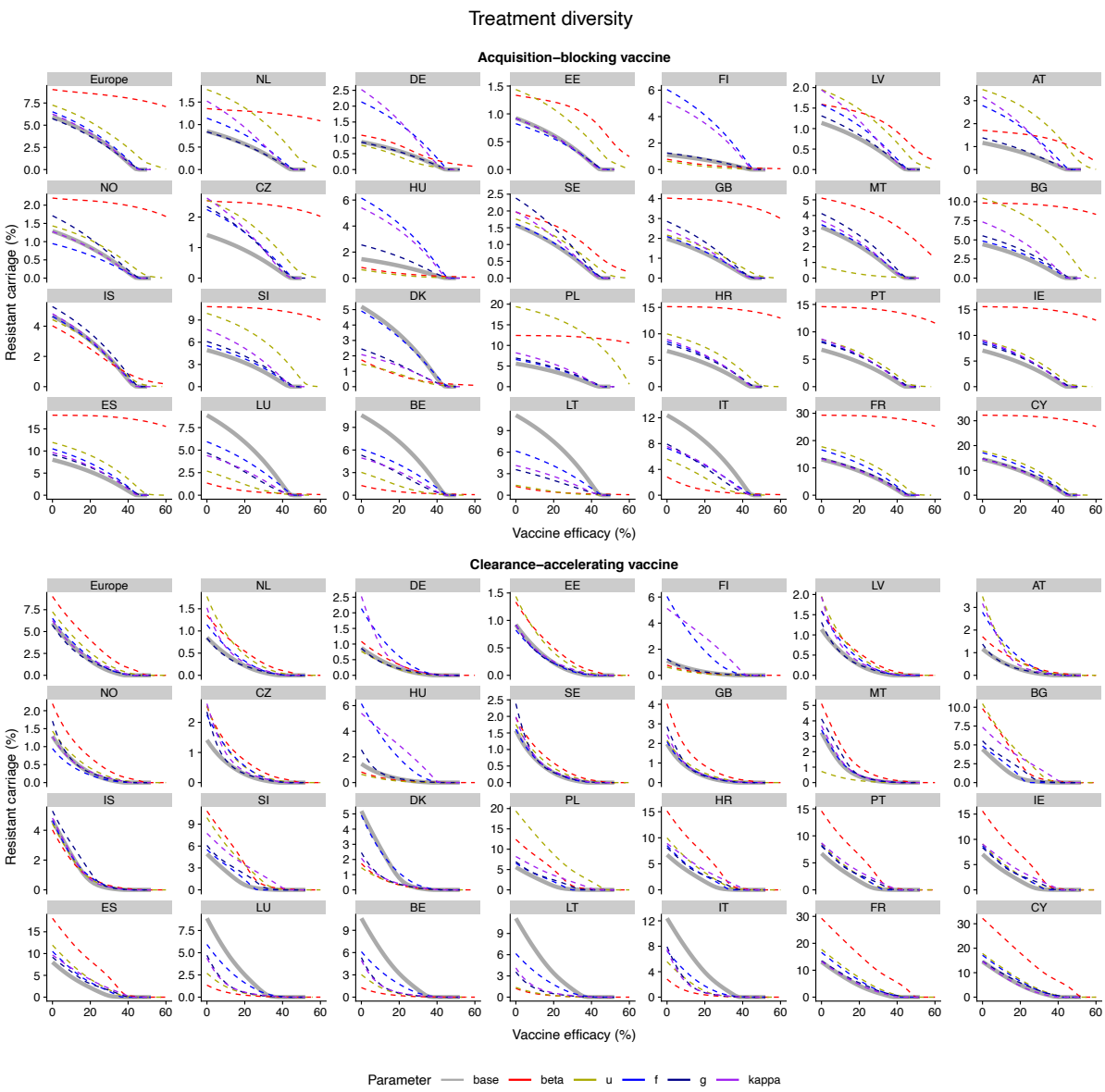

Fig. S13. Vaccine impact for the "Treatment diversity" model, varying other parameters. Impact of vaccination under the "Treatment diversity" model, for those parameters *not* able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).

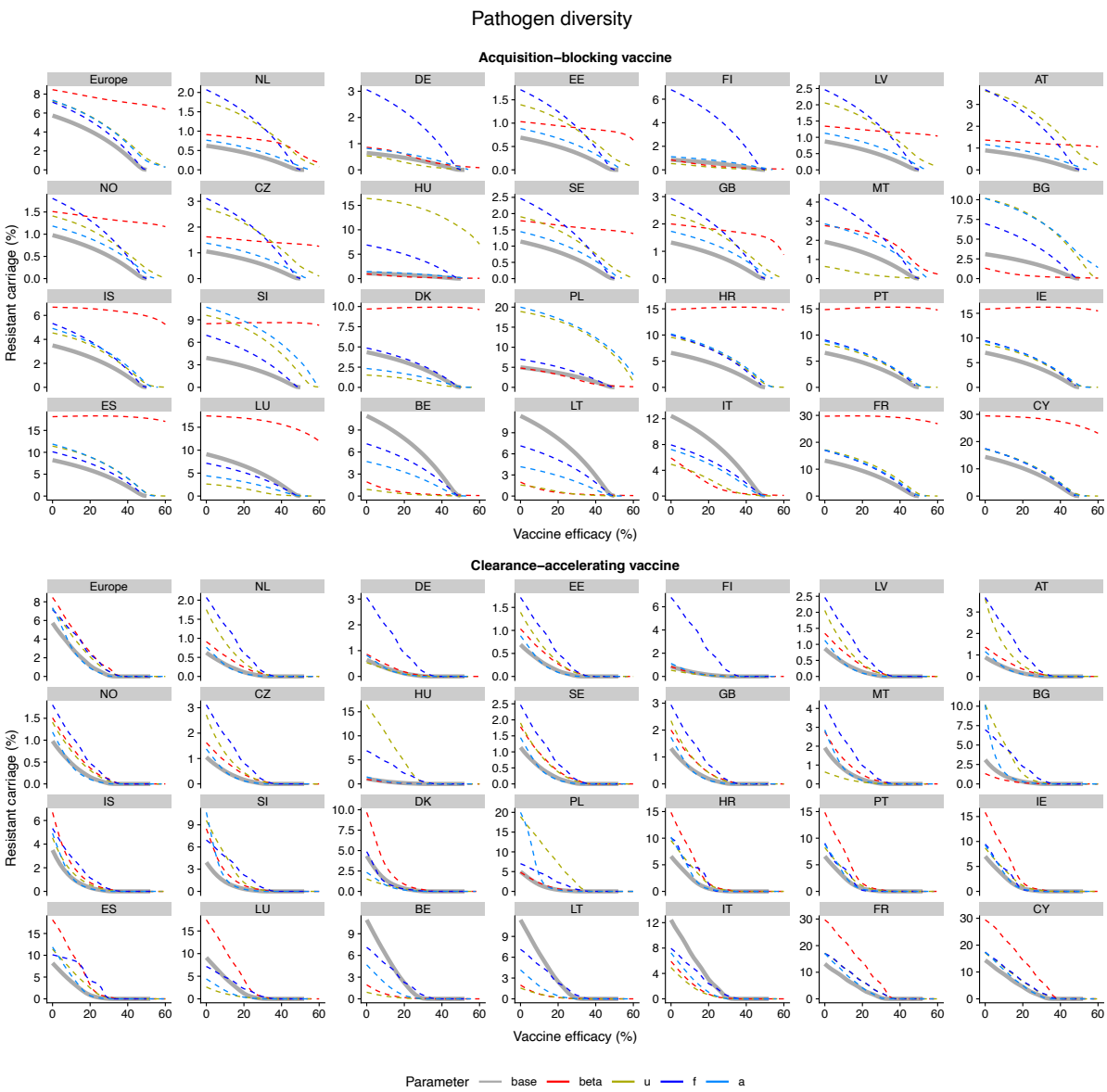

Fig. S14. Vaccine impact for the "Pathogen diversity" model, varying other parameters. Impact of vaccination under the "Pathogen diversity" model, for those parameters *not* able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).

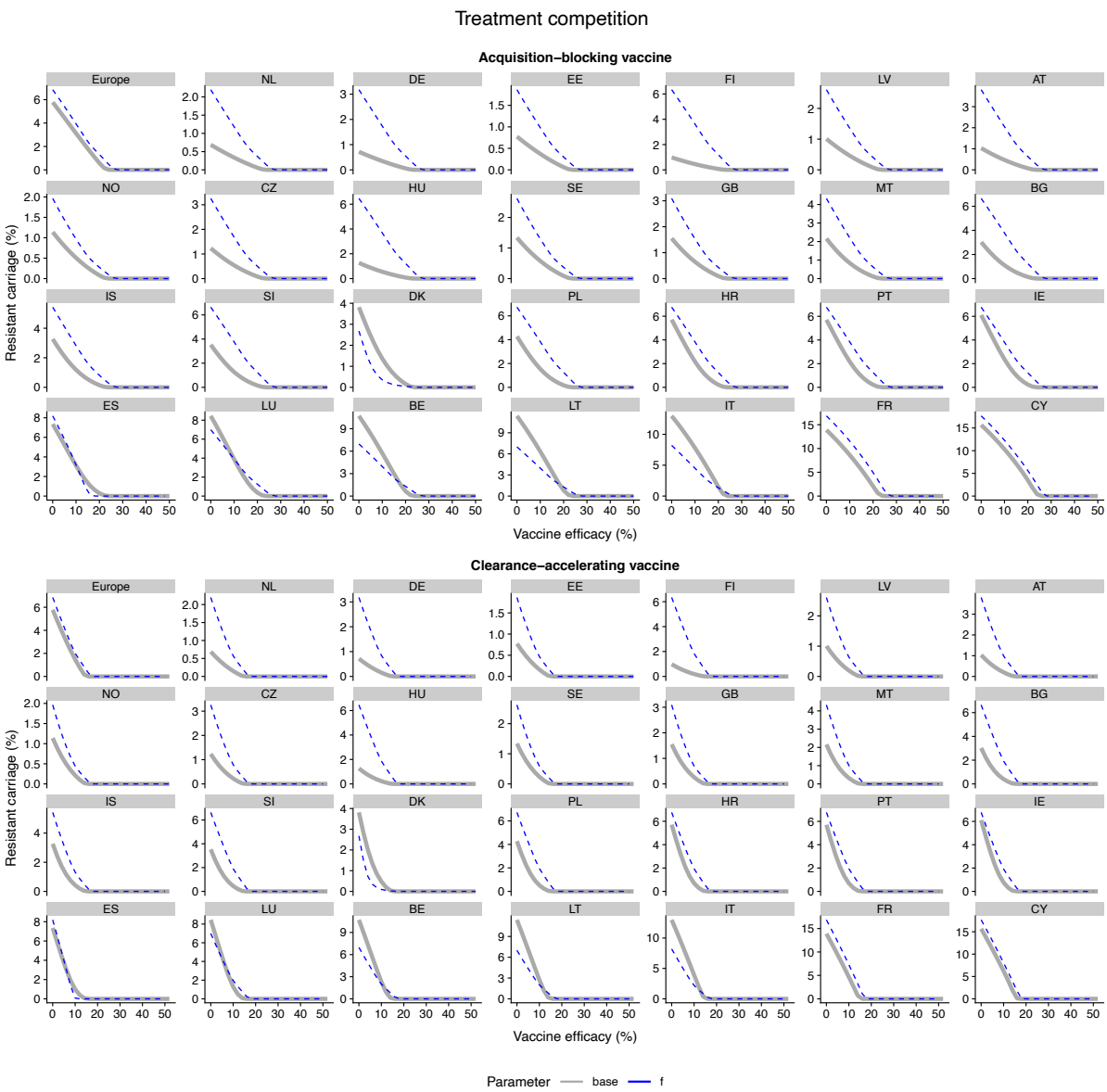

Fig. S15. Vaccine impact for the "Treatment competition" model, varying other parameters. Impact of vaccination under the "Treatment competition" model, for those parameters *not* able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).

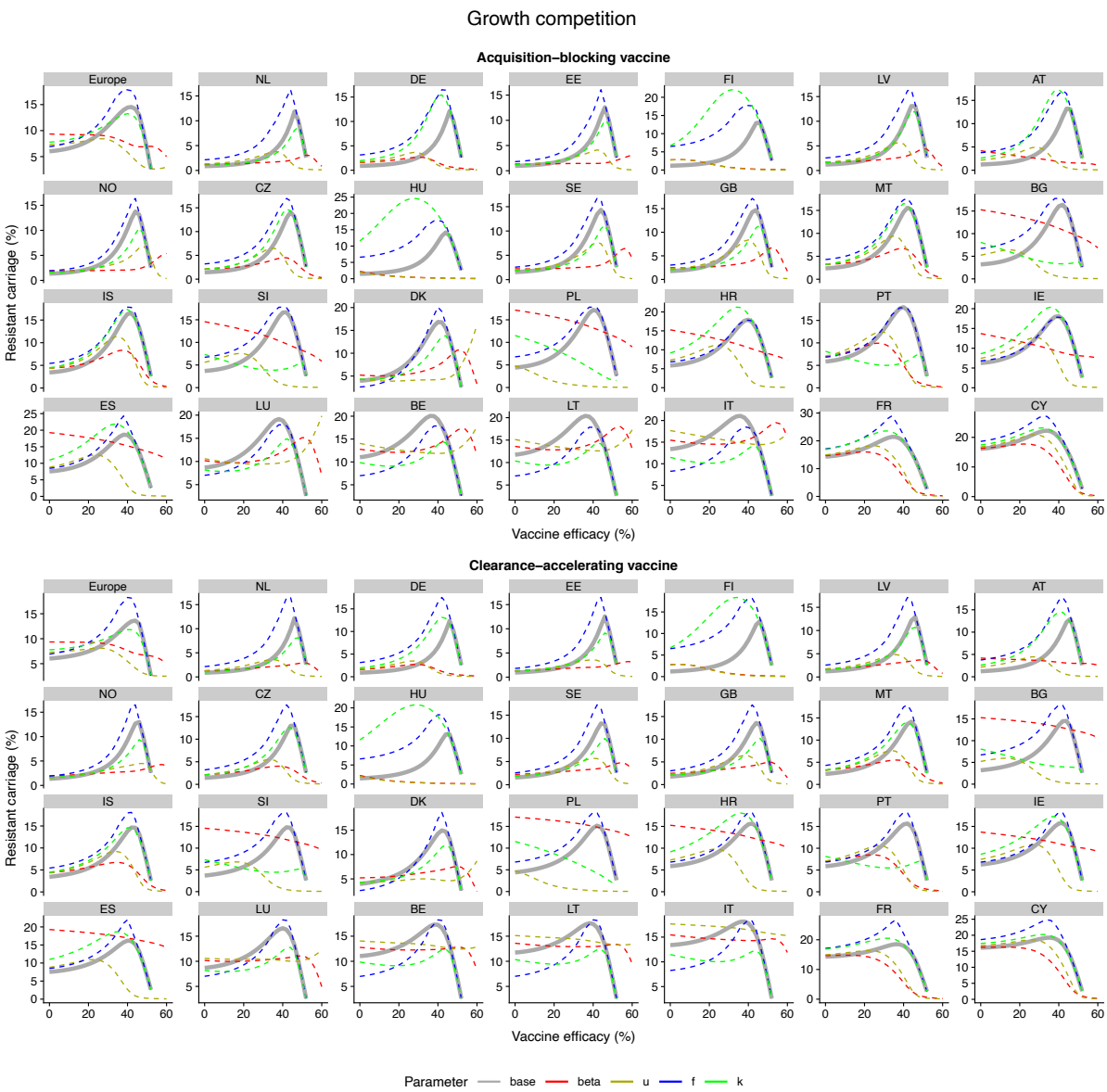

Fig. S16. Vaccine impact for the "Growth competition" model, varying other parameters. Impact of vaccination under the "Growth competition" model, for those parameters *not* able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared with the model fits in which parameters vary between countries (thin dashed lines).

1272 **Tables S1–S7**

1273

1274 These tables can be found in an Excel spreadsheet accompanying the article.

1275

1276 *Table S1. Literature review* — Details of the literature review used to identify
1277 mechanisms for maintaining coexistence between sensitive and resistant bacterial
1278 strains.

1279

1280 *Table S2. Summary of model parameters* — Table describing model parameters and
1281 assumed values or prior distributions for model fitting.

1282

1283 *Table S3. Carriage duration* — Calculation of mean pneumococcal carriage duration for
1284 children under 5 years old in European settings.

1285

1286 *Table S4. Penicillin consumption* — Calculation of the mean number of defined daily
1287 doses of penicillin corresponding to a single treatment course for children under 5
1288 years old in European countries.

1289

1290 *Table S5. Pneumococcal morbidity* — Calculation of the annual number of pneumococcal
1291 pneumonia cases in children under 5 in Europe and Kenya.

1292

1293 *Table S6. Carriage duration (Kilifi)* — Calculation of mean pneumococcal carriage
1294 duration for children under 5 years old in Kilifi, Kenya.

1295

1296 *Table S7. MCMC diagnostics* — Widely Applicable Information Criteria (WAIC), Leave-
1297 One-Out Information Criteria (LOOIC), effective posterior sample size and Gelman-
1298 Rubin diagnostics for Bayesian inference model fitting using Markov chain Monte Carlo.