# Modeling the effect of vaccination on selection for antibiotic resistance in *S. pneumoniae*

Nicholas G. Davies[1*], Stefan Flasche[1], Mark Jit[1,2], Katherine E. Atkins[1,3]

1. Centre for Mathematical Modelling of Infectious Diseases; Vaccine Centre; and Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK.
2. Modelling and Economics Unit, Public Health England, London, UK.
3. Centre for Global Health, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK.
* Corresponding author E-mail: nicholas.davies@lshtm.ac.uk.

**Overline: Bacterial infections**

**One sentence summary:** Bacterial competition and diversity may influence selection for antibiotic-resistant bacteria after vaccination.

**Accessible Summary:**

Using mathematical modelling, we show that the association between penicillin consumption and penicillin non-susceptibility in *Streptococcus pneumoniae* across 27 European countries can be explained by four different models of antibiotic resistance evolution, out of nine potential models we identified by searching the literature. Each model encapsulates an alternative hypothesis for why antibiotic-sensitive and antibiotic-resistant bacterial strains coexist in the same population. We show that, depending upon the model, vaccination can either inhibit or promote the spread of antibiotic resistance. Our work suggests testable hypotheses to help predict or explain changes in antibiotic resistance following the introduction of new vaccines.

**Abstract**

Vaccines against bacterial pathogens can protect recipients from becoming infected with potentially antibiotic-resistant pathogens. But by altering the selective balance between antibiotic sensitive and resistant bacterial strains, vaccines may also suppress—or spread—antibiotic resistance among unvaccinated individuals. Predicting the outcome of vaccination requires knowing what drives selection for drug-resistant bacterial pathogens and what maintains the circulation of both antibiotic-sensitive and antibiotic-resistant strains of bacteria. Using mathematical modeling and data from 2007 on penicillin consumption and penicillin non-susceptibility in *S. pneumoniae* invasive isolates from 27 European countries, we show that the frequency of penicillin resistance in *Streptococcus pneumoniae* (pneumococcus) 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 antibiotic-resistant and sensitive *S. pneumoniae* strains. We used our calibrated models to predict the impact of non-serotype-specific pneumococcal vaccination upon the prevalence of *S. pneumoniae* carriage, incidence of disease, and frequency of *S. pneumoniae* antibiotic resistance. We found that the relative strength and directionality of competition between drug resistant and sensitive pneumococcal strains was the most important determinant of whether vaccination would promote, inhibit, or have little effect upon the evolution of antibiotic resistance. Finally, we show that country-specific differences in pathogen transmission substantially altered the predicted impact of vaccination, highlighting that policies for managing antibiotic resistance with vaccines must be tailored to a specific pathogen and setting.

## Introduction

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 has seemingly borne out these advantages. Administering pneumococcal conjugate vaccines to young children has substantially reduced disease caused by *S. pneumoniae* (*5–8*)—a

common asymptomatic bacterial coloniser of the nasopharynx that can cause pneumonia, meningitis and other infections when invasive. Administration of pneumococcal conjugate vaccines has decreased demand for antibiotic therapy, largely by reducing cases of otitis media (*5*, *9*). But because pneumococcal conjugate vaccine formulations target only a fraction of the ~100 known pneumococcal serotypes, the niche vacated by vaccine-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 *S. pneumoniae* non-vaccine serotypes (*12*) and the proportion of non-vaccine-type infections exhibiting antibiotic resistance (*5*, *13*) have increased in many settings. Concern over serotype replacement, along with the high cost of manufacturing pneumococcal conjugate vaccines, has spurred the development of "universal" (non-serotype-specific) whole-cell or protein-based pneumococcal vaccines protecting against all pneumococcal 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.

It remains unclear, however, how universal vaccination itself may impact 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 antibiotic-sensitive and antibiotic-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 drug-resistant pneumococcal disease require a mechanistic understanding of these patterns.

## Results

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

A mathematical 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 (Fig. S1). One feature 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 antibiotic 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 that maintains coexistence between them (*25*, *29*).

By conducting a literature search, we identified nine such potential mechanisms (*25*, *26*, *30–41*) that fall into two broad classes. In one class, coexistence is maintained by environmental or genetic diversity that effectively creates separate niches for resistant and sensitive strains, preventing them 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 antibiotic resistance. Thus, extrinsically-imposed diversity and frequency-dependent competition are two key forces maintaining stability in antibiotic resistance evolution. We suggest that four of the nine identified mechanisms for maintaining coexistence are biologically plausible for *S. pneumoniae* (Table 1).

**Four models of antibiotic resistance evolution.**

To compare these four mechanisms, we embedded 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 assumed this treatment rate is independent of carriage status (*46*) and we did not explicitly track disease progression in hosts.

Under the "Treatment diversity" and "Pathogen diversity" models, extrinsically-maintained diversity among hosts or among pathogens prevents competitive exclusion by keeping antibiotic-resistant and sensitive strains from fully competing with each other. In the "Treatment diversity" model (Fig. 1A), heterogeneity in the consumption of antibiotics between host subpopulations within a country maintains coexistence (*25*, *34*, *35*). These subpopulations could correspond to geographical regions, socioeconomic strata, host age and risk classes, or a combination of these. Provided that transmission between high-consumption (resistance-promoting) and low-consumption (resistance-inhibiting) subpopulations is not too frequent, an intermediate frequency of resistance can be maintained across the whole population. Because coexistence is maintained by assortative mixing between subpopulations differing in antibiotic use, the key parameters governing coexistence in this model are κ, the variability in antibiotic consumption between subpopulations, and *g*, the relative rate at which within-country contact is made within subpopulations rather than between them (Fig. S2).

In the "Pathogen diversity" model (Fig. 1B), pneumococci are divided into subtypes ("D-types") (*38*) that vary in their mean duration of natural carriage. All else being equal, the D-type with the longest carriage duration would be expected to competitively exclude all other strains; the model assumes that diversifying selection acting on the D-

type locus keeps all subtypes in circulation. What D-types correspond to is not explicitly specified by this model, but one candidate is serotype variation. For example, if antigenic diversity is promoted by host acquired immunity to capsular serotypes, and serotypes tend to differ in their intrinsic ability to evade clearance by the immune system, then intermediate resistance can be maintained because selection for resistance tends to be greater in serotypes that have a longer duration of carriage (*38*). Long-lasting serotypes will tend to evolve resistance, while shorter-lived serotypes will tend not to—a pattern observed in *S. pneumoniae* (*38*) and reproduced by this model (Fig. S3). The parameters governing coexistence in this model are $a$, the strength of diversifying selection on the D-type locus, and $\delta$, the variability between subtypes in clearance rate.

Under the "Treatment competition" and "Growth competition" models, coexistence is maintained by within-host competition between sensitive and resistant strains. In these models, hosts can be co-colonised by multiple strains. Then, competition between strains within the host niche determines which strain is transmitted to other potential hosts (*26*). The "Treatment competition" model (Fig. 1C) assumes that antibiotic therapy mediates within-host competition, such that when a co-colonised host takes antibiotics (*i.e.*, at rate $\tau$), the sensitive strains are cleared and only the resistant strains are transmitted to other hosts. The "Growth competition" model (Fig. 1D) has both treatment-mediated and growth-mediated competition: in the presence of antibiotics, resistant strains still outcompete co-colonising sensitive strains, whereas in the absence of antibiotics, sensitive strains gradually outcompete co-colonising resistant strains at rate $b$. We assumed that there is no transmission cost of resistance in this latter model (*i.e.*, $c = 0$); instead, the within-host growth advantage $b$ of sensitive strains accounts for the cost of resistance. In these competition models, resistant strains have an advantage in antibiotic-mediated competition, and sensitive strains have an advantage in growth-mediated competition. These alternative forms of within-host competition can both promote coexistence because rare strains can more consistently exploit a competitive advantage over common strains, thus creating negative frequency-dependent selection for resistance (*26*). The key parameter governing coexistence in these two models is $k$, the relative rate of co-colonisation compared to primary colonisation.

In all four models, we assume that contact between individuals is assortative by country, such that with probability *f*, contact is with a random person from the same country, and with probability 1 – *f*, contact is with a random person from any country. We implement these models using systems of ordinary differential equations. All four models (*25*, *26*, *38*) are structurally neutral (*25*, *29*), meaning that any coexistence exhibited by the models is accounted for by the specified biological mechanism rather than by any bias in the logical structure of the model that generates coexistence "for free" (*29*). Additionally, whereas the within-host competition models capture co-colonisation using a simplified subset of only 2 "mixed-carriage" states ($S_R$ and $R_S$, Fig. 1A, B), we have previously shown (*26*) that this is equivalent to a more complex individual-based model with an arbitrary number of mixed-carriage states.

**All four models reproduce observed patterns of antibiotic resistance.**

The European Centre for Disease Prevention and Control (ECDC) monitors antibiotic consumption and resistance evolution across European countries (*13*, *28*). These data capture a natural experiment in resistance evolution: for each monitored drug and pathogen, each country reports a different rate of antibiotic consumption in the community and exhibits a different frequency of resistance among invasive bacterial isolates. By fitting models to this multi-country data set, we can potentially rule out models that cannot reproduce the large-scale patterns that are observed. We used Bayesian inference to fit the model-predicted equilibrium frequency of resistance to the reported frequency of penicillin non-susceptibility in *S. pneumoniae* across 27 European countries, assuming a 50% carriage prevalence (*11*, *42*) and a carriage duration of 47 days (*47*, *48*) in children under five years old. We began by assuming that countries only differ by their reported treatment rate—where we define a treatment course as equivalent to $z = 5$ defined daily doses of penicillin—with other model parameters shared across countries.

Strikingly, each model fits equally well to the empirical relationship between resistance and antibiotic use (Widely Applicable Information Criteria are similar across all models; Fig. 2A) and recovers plausible posterior parameter distributions (Fig. 2B; Fig. S4). That is, the empirical data do not distinguish between the four alternative mechanisms of resistance evolution we have identified. Later, we relax the assumption that only the

treatment rate varies between countries, allowing us to capture additional between-country variation in antibiotic resistance not explained by population-wide penicillin consumption.

**Mechanisms of resistance evolution determine the impact of vaccination on antibiotic-resistant disease.**

To determine the impact of universal vaccination on pneumococcal disease, we considered three outcomes. The first is the impact of the vaccine upon the prevalence of pneumococcal carriage. The second is the vaccine impact upon the frequency of penicillin resistance among circulating pneumococcal strains remaining after vaccination. The third is the impact of the vaccine upon the prevalence of antibiotic-resistant pneumococcal carriage—*i.e.*, the prevalence of carriage multiplied by the frequency of penicillin resistance. Given that all four models are equally capable of recapitulating observed patterns of penicillin resistance in *S. pneumoniae*, our aim was to determine whether the mechanism maintaining stability in antibiotic resistance evolution—frequency-dependent competition or extrinsically-imposed diversity—matters when forecasting the impact of interventions for managing antibiotic resistance.

We consider two alternative non-serotype-specific vaccines: an "acquisition-blocking" vaccine, which prevents carriage from being established with probability $\varepsilon_a$, and a "clearance-accelerating" vaccine, which shortens the duration of carriage by a fraction $\varepsilon_c$. Both vaccines reduce pneumococcal transmission through alternative modes of host immunity that might be elicited by a whole-cell or protein-based universal pneumococcal vaccine. Analogously to naturally-acquired serotype-independent pneumococcal immunity (*49*), the protective effect of whole-cell vaccines manifests as accelerated clearance (*50*); it is unclear whether protein-based vaccines would block pneumococcal acquisition—as pneumococcal conjugate vaccines do—or accelerate clearance as whole-cell vaccines do (*51*). We refer to $\varepsilon_a$ or $\varepsilon_c$ as the vaccine efficacy, and for simplicity, we assume that all children under five years old have vaccine protection, as would be established by an infant vaccination programme rolled out across Europe. In order to compare these vaccines with an alternative intervention of antibiotic

stewardship, we also evaluated the impact of reducing the rate of penicillin prescribing by a fraction $\varepsilon_s$.

We found that both vaccines have a similar impact upon pneumococcal carriage prevalence, regardless of whether competition or diversity maintains stability in resistance evolution (Fig. 3A). Specifically, as the vaccine efficacy $\varepsilon_a$ or $\varepsilon_c$ increases, carriage decreases, with the elimination of pneumococcal carriage occurring at a vaccine efficacy between 50 and 60%. Reducing antibiotic prescribing moderately increases pneumococcal carriage, such that carriage prevalence increases to approximately 54% across all countries when penicillin prescribing is eliminated completely.

The mechanism of resistance evolution, however, has a substantial impact upon whether vaccines increase or decrease the frequency of antibiotic resistance in *S. pneumoniae* in the long term (Fig. 3B). In the "Treatment diversity" and "Pathogen diversity" models, the acquisition-blocking vaccine has relatively little impact upon the frequency of resistance, because administering a universal pneumococcal vaccine to all individuals does not substantially alter the distribution of antibiotic use or of heritable variation in clearance rates. By contrast, in the within-host competition models, vaccination has a substantial impact upon resistance evolution because by reducing pneumococcal circulation, vaccines decrease the rate at which strains encounter each other within hosts, and hence strongly decrease competition between pneumococcal strains. Specifically, the acquisition-blocking vaccine selects strongly against resistance in the "Treatment competition" model: given that antibiotic-mediated within-host competition benefits the resistant strain in this model, the vaccine works against this competitive advantage and therefore inhibits antibiotic resistance. Conversely, in the "Growth competition" model, growth-mediated competition benefits the sensitive strain, and so by reducing competition, vaccination tends to promote antibiotic resistance. These results expand upon our previous finding that the rate of co-colonisation modulates antibiotic resistance evolution through its impact upon within-host competition (*26*).

The clearance-accelerating vaccine exhibits similarly divergent impacts across mechanisms of antibiotic resistance evolution. However, compared with the acquisition-blocking vaccine, it also has an additional resistance-inhibiting effect across all models, because a shorter duration of carriage—whether natural or vaccine-induced—selects against resistance (*38*). This suggests that vaccines that accelerate natural clearance have a particular potential for managing antibiotic-resistant infections. As expected, reducing the rate of penicillin prescribing selects against resistance, exhibiting a similar impact across all four models.

The impact on antibiotic-resistant pneumococcal carriage (Fig. 3C), which combines changes in the prevalence of carriage and changes in the frequency of resistance, can be treated as a proxy for the incidence of antibiotic-resistant infections. Overall, under the "Growth competition" model, vaccination at intermediate efficacy is expected to increase the rate of antibiotic-resistant carriage, and hence the number of cases of resistant disease. In other models, vaccination always reduces resistant carriage, particularly under the "Treatment competition" model. A summary of the strongest vaccine impacts is shown in Fig. 3D.

**Evidence to inform health policy and vaccine clinical trials.**

For vaccines to be considered an efficient means of controlling antibiotic-resistant bacterial 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 antibiotic resistance evolution (Fig 4A); for example, the required vaccine efficacy is lowest under the "Treatment competition" model ($\varepsilon_a$ = 11% or $\varepsilon_c$ = 7%), and highest under the "Growth competition" model ($\varepsilon_a$ = 52% or $\varepsilon_c$ = 50%). A full comparison of vaccine and antibiotic stewardship interventions would require accounting for the economic cost of vaccines versus antibiotics, the wider range of antibiotic-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 clinical trials of pneumococcal vaccines, antibiotic 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 antibiotic resistance. Indeed, we found that it can take 5–10 years for antibiotic 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 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 antibiotic treatment rate in a given country. Focusing on the specific outcome of childhood pneumococcal pneumonia cases, we found that while interventions have a consistent impact from country to country on the total pneumonia case rate, the impact on antibiotic-resistant pneumonia cases is greatest in those countries where antibiotic use, and hence resistance, is highest (Fig. 4C). We focused on antibiotic-resistant carriage, but the realised public health benefits of any intervention targeting both antibiotic-resistant and antibiotic-sensitive strains will depend upon the relative health burden of susceptible versus non-susceptible *S. pneumoniae* infections; enumerating these comparative burdens is the subject of ongoing research (*55*).

**Vaccination in a high-burden setting.**

While our study has focused on the epidemiology of antibiotic-resistant *S. pneumoniae* in Europe, higher prevalences of carriage, disease, and resistance may be observed in lower-income settings, and it is desirable to know whether this could substantially alter predictions of vaccine impact. As an illustrative example, a 90% pneumococcal carriage

rate, with 81% of isolates resistant to penicillin, has been observed among children under five years old in western Kenya (*56*). This may be partly attributable to a longer average duration of carriage in this setting, as a 71-day mean duration of natural pneumococcal carriage has been measured in Kilifi, eastern Kenya (*57*).

To model a similar high-burden setting, we adjusted model parameters estimated from European data. Specifically, we increased the mean natural carriage duration, transmission rate, and treatment rate to match observed data, and ignored mixing with any other countries ($f = 1$), while keeping other parameters the same. We found that a comparatively greater vaccine efficacy is needed to reduce the prevalence of antibiotic-resistant pneumococcal carriage in a high-burden, high-resistance setting (Fig. 5). This is particularly true under the "Growth competition" model, because in this model resistant carriage only declines as total pneumococcal carriage declines, and it is particularly difficult to reduce overall carriage in a high-transmission setting. Simultaneously, vaccination may have a comparatively greater impact in high-burden settings because of a comparatively higher incidence of disease. For example, Kenya has been estimated to have an 8.8-fold higher incidence of severe pneumococcal pneumonia than the average in Europe (*58*).

**Accounting for additional between-country variation does not substantially alter predictions.**

Our focus thus far has been on the impact of the four identified mechanisms *per se* upon antibiotic resistance evolution, and accordingly we have focused on reproducing the positive association between treatment rate and resistance frequency rather than attempting to capture the additional variability in resistance frequency between countries not accounted for by the reported treatment rate alone (Fig. 2A). This additional variability may partially stem from differences in national testing and reporting practices, or between-country differences in the distribution of pneumococcal serotypes among invasive isolates (*59*). However, another possibility is that this additional variability in resistance results from systematic differences in pathogen biology or host behaviour across countries, which can be captured by our modeling framework.

To help identify which model parameters could account for this variability, we relaxed the assumption that only the treatment rate varies across countries, and performed Bayesian maximum *a posteriori* fitting, assuming one additional parameter ($c$, $b$, $\beta$, $u$, $f$, $z$, $g$, $\kappa$, $a$, $\delta$, or $k$) is free to vary between countries while other parameters are held constant. We found that additional variation in antibiotic resistance between countries can be explained by variation in certain other parameters, depending upon which model is used (Fig. 6A, B). Importantly, among those parameters for which additional variation between countries can explain the variation in resistance (Fig. 6C), predictions for the overall impact of vaccination remain similar, with the major differences between scenarios still attributable to the underlying mechanism of antibiotic resistance evolution (Fig. 6D; Figs. S5–S16). Models that could make more accurate country-specific predictions would need to account for the effects of demographic structure, differences in carriage prevalence and disease rates between settings, and variable vaccine protection among individuals.

## Discussion

Using mathematical modeling of penicillin consumption and penicillin non-susceptibility in *S. pneumoniae* invasive isolates, we have identified four mechanisms of antibiotic resistance evolution that can recapitulate the observed relationship between penicillin consumption and penicillin non-susceptibility in *S. pneumoniae* across Europe. These mechanisms are not mutually exclusive, but the relative importance of each may have an impact upon predictions of antibiotic resistance evolution after vaccination. In particular, the "directionality" of within-host competition—that is, whether, on average, within-host competition tends to benefit antibiotic-resistant or sensitive strains—strongly determines whether vaccination selects for a decrease or an increase in antibiotic resistance in the long term. This directionality may vary between pathogens, but is also sensitive to the antibiotic treatment rate, and so may also vary between settings. Although we have focused on competition between antibiotic-sensitive and resistant strains of *S. pneumoniae* only, competition between pneumococcal serotypes (*24*) and with other bacteria colonizing the nasopharynx will also impact antibiotic resistance evolution; determining the importance of these other sources of within-host competition is crucial.

A key finding of our models suggests that the mode of vaccine protection—whether acquisition-blocking or clearance-accelerating—has an appreciable impact upon antibiotic resistance evolution. Whole-cell and purified-protein pneumococcal vaccines may induce antibody-mediated humoral immunity, CD4+ T helper-17 cell-mediated immunity, or both, with the type of immunity mediating pneumococcal acquisition, carriage, and disease in ways that are still not fully understood (*49*–*51*). By modeling both modes of vaccine action, we have highlighted that clearance-accelerating vaccines may have increased potential for preventing the spread of antibiotic resistance, because in shortening the duration of asymptomatic carriage they limit the fitness advantage of antibiotic-resistant pathogens under selection pressure from antibiotic use.

We fitted our models to a "snapshot" of penicillin non-susceptible *S. pneumoniae* as observed across European countries in 2007, finding that each of the four models recapitulated the data equally well. This raises the question of what kind of data would be needed to distinguish among the four models. One possibility would be to consider trends of antibiotic resistance evolution over time. Indeed, the prevalence of penicillin non-susceptibility in *S. pneumoniae* remained largely stable in Europe between 2005–2017, a period which saw the incorporation of pneumococcal conjugate vaccines into the routine immunization schedules of most European countries (*60*). This could be viewed as favoring the "treatment diversity" and "pathogen diversity" mechanisms, which predict little change in antibiotic resistance evolution following vaccination. But because serotype replacement has largely negated any vaccine impact on the prevalence of nasopharyngeal pneumococcal carriage (*10*, *11*), it is not clear that we would be able to detect any effects of competition-mediated antibiotic resistance evolution following a serotype-specific vaccine such as pneumococcal conjugate vaccine—particularly given the complexity of detecting vaccine-attributable changes in resistance in a population-level ecological study that would be confounded both by serotype replacement and by other changes in antibiotic resistance evolution that might be expected to occur at a national level over the course of multiple years. However, it is known that the prevalence of pneumococcal carriage declines substantially with age (*42*). Therefore, it might be possible to detect a signal of within-host competition between antibiotic-sensitive and resistant strains by comparing the relative prevalence

of antibiotic-resistant pneumococcal carriage in younger versus older hosts, provided that other differences could be controlled for.

Under the "Treatment diversity" and "Pathogen diversity" models, we have argued that universal pneumococcal vaccination will have little impact upon the long-term evolution of antibiotic resistance because it does not change the sources of diversity that modulate antibiotic resistance evolution. Nonetheless, it is possible to target vaccines such that this diversity is harnessed to manage antibiotic resistance: high-resistance serotypes could be targeted with a serotype-specific vaccine, or high-treatment subpopulations could be targeted for vaccination in order to more effectively manage resistance. Indeed, vaccination does have an additional inhibiting effect upon antibiotic resistance in our models because of the latter effect. This inhibition occurs because the vaccine has a relatively greater impact upon transmission in populations where the prevalence of pneumococcal carriage is already low, which in our models occurred in countries or subpopulations with more antibiotic consumption. Given that these populations drive antibiotic resistance more strongly, the vaccine's comparatively greater impact in these populations tends to moderately inhibit antibiotic resistance overall. We note that while previous work (*38*) has suggested that antibiotic resistance evolution under a "Pathogen diversity" model results in a "stepped" resistance pattern in which D-types are either fully sensitive or fully resistant at equilibrium, we find that small amounts of mixing between populations can smooth out this pattern and allow intermediate rates of resistance within subtypes (Fig. S2). Finally, while we have framed "Treatment competition" and "Growth competition" as two distinct alternatives, they can instead be viewed as endpoints on a continuum, with possible models of resistance evolution for which both $c > 0$ and $b > 0$ lying between them. The impact of vaccination on antibiotic resistance in such a model would depend upon the relative importance of treatment-mediated and growth-mediated competition.

These are some of the limitations to our study. We have focused on prevalence (the fraction of individuals who are carriers) rather than incidence (the rate of new carriage episodes) of nasopharyngeal carriage in presenting our findings. There is evidence that pneumococcal disease progression is more likely to occur shortly after nasopharyngeal acquisition (*61*), suggesting that incidence may be more relevant than prevalence for predicting disease outcomes. Notably, recent modeling work has suggested that clearance-accelerating vaccines could increase rates of pneumococcal

489 acquisition, if carriage is protective against new acquisition (due to, e.g., a founder
490 effect) (*62*). More work is required to clarify the links between acquisition, carriage, and
491 disease across competing models of pneumococcal transmission. Additionally, we have
492 assumed that antibiotic treatment rates among pneumococcal carriers remains constant
493 after the introduction of a vaccine, even though treatment rates dropped in many
494 settings following the introduction of pneumococcal conjugate vaccine (*5*, *9*). However,
495 for a universal pneumococcal vaccine that reduces antibiotic treatment rates because it
496 reduces carriage and thereby prevents antibiotic-treatable disease, any reduction in
497 treatment will only occur among individuals who, because of vaccine protection, are not
498 pneumococcal carriers, all else being equal. It might then be expected that treatment
499 rates in pneumococcal carriers would remain equally high among those individuals for
500 whom vaccine protection has failed—although physicians may be less inclined to
501 prescribe antibiotics for respiratory tract infection more generally after the
502 introduction of a new pneumococcal vaccine. Finally, we have focused on modeling data
503 from children under 5 years old only. We would not expect incorporating age structure
504 to lead to qualitatively different results, but age-related maturation of the immune
505 system has been shown to be important for maintaining the circulation of
506 pneumococcal serotypes (*49*) which, in turn, is a key driver of resistance evolution in
507 the "pathogen diversity" model.
508 Our work helps to resolve the question: What explains the persistent coexistence
509 between antibiotic-resistant and sensitive strains of *S. pneumoniae*? (*25*) by
510 demonstrating that multiple mechanisms are capable of explaining trends of antibiotic
511 resistance across European countries. Given that there is empirical support for within-
512 host competition between antibiotic-sensitive and resistant pathogen strains (*63*–*66*),
513 heritable differences in the propensity for resistance within species (*38*, *67*), and
514 within-country heterogeneity in antibiotic consumption rates (*68*–*70*), all of these
515 mechanisms likely contribute to this pattern. Our results contextualize previous
516 mathematical studies that have variously suggested that serotype-specific vaccination
517 may increase (*24*), decrease (*22*) or have no impact upon (*18*) the frequency of
518 antibiotic resistance in *S. pneumoniae*. Whereas the potential for vaccination to promote
519 antibiotic resistance because of competition between sensitive and resistant strains has
520 been described previously (*24*), we have shown that vaccination can either promote or
521 inhibit antibiotic resistance depending upon the directionality of within-host

competition. Whereas vaccines targeting highly-resistant serotypes can decrease antibiotic resistance (*22*), we have shown that a serotype-independent vaccine promoting accelerated natural clearance can decrease resistance across all circulating subtypes. And where single-population models have found no long-term impact of vaccination on antibiotic resistance frequency (*18*), we have shown that in multi-population models, vaccination can inhibit resistance if it has a larger impact in subpopulations that consume more antibiotics. The direction and magnitude of this effect would depend upon variation in vaccine uptake, vaccine efficacy, and pathogen transmission among subpopulations, and we have not systematically explored this variation here.

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

## Materials and Methods

*Study design.*

This study comprised four parts: (1) A literature search used to identify plausible mechanisms through which coexistence can be maintained between antibiotic-sensitive and resistant pneumococcal strains across a range of antibiotic treatment rates; (2) a mathematical modeling study embedding these mechanisms of antibiotic resistance evolution in four models of pneumococcal transmission; (3) 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; (4) a vaccine impact analysis using these fitted models to forecast the impact of a universal pneumococcal vaccine. We used data from 2007 because changes in pneumococcal resistance reporting standards for some countries after this year would hamper the between-country comparability of data (*71*). Our objectives were to identify the mechanisms potentially responsible for maintaining coexistence between antibiotic-resistant and sensitive pneumococci in Europe, and to determine whether the

impact of vaccination on the evolution of antibiotic resistance depends upon which mechanism is assumed to operate.

*Literature search for mechanisms driving antibiotic 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 (Table S1). We included all papers containing a dynamic host-to-host pathogen transmission model analysing both antibiotic-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 showed that the mechanism does not bring about substantial coexistence, leaving four mechanisms (Table 1).

*Model framework.*

We analysed 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 $\lambda_S$ is the force of infection of the sensitive strain, $\lambda_R$ is the force of infection of the resistant strain, $c$ is the transmission cost of resistance, $u$ is the rate of natural clearance, and $\tau$ 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

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

where we assume that treatment rates of subpopulations within a country approximately follow a gamma distribution with shape parameter $\kappa$ and mean treatment rate $\tau$. 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 $\kappa$ 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

$$\begin{aligned} dS_d/dt &= q_d\lambda_{S,d}X - (u_d + \tau)S_d \\ dR_d/dt &= q_d(1 - c)\lambda_{R,d}X - u_dR_d \end{aligned}$$

$$X = 1 - \Sigma_d (S_d + R_d) \quad (3)$$

where $q_d$ is the strength of diversifying selection for D-type $d \in \{1,2,\dots,D\}$ 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 $\delta$ 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

$$\begin{aligned}
dS/dt &= \lambda_S X - (u + \tau)S - k(1 - c)\lambda_R S + b_0 S_R \\
dS_R/dt &= k(1 - c)\lambda_R S - (u + \tau)S_R + bR_S - b_0 S_R \\
dR_S/dt &= k\lambda_S R - (u + \tau)R_S - bR_S \\
dR/dt &= (1 - c)\lambda_R X - uR - k\lambda_S R + \tau(S_R + R_S) \\
X &= 1 - S - R - S_R - R_S\,, \quad (4)
\end{aligned}$$

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 $\lambda_A = \beta\left(f A_{\text{tot}|m} + (1 - f)\sum_{\ell=1}^{M} h_\ell A_{\text{tot}|\ell}\right)$, where $\beta$ is the transmission rate, $f$ is the between-country assortativity, $h_\ell$ is the relative population size of country $m$ (such that $\sum_\ell h_\ell =$

1), and $A_{\text{tot}|\ell}$ is the total carriage of strain $A$ in country $\ell$. The probability with which individuals contact an individual from another country, 1 – $f$, captures those contacts made with individuals from another country in either one's home country or a foreign country. In equation 2, the force of infection of a particular strain $A$ in subpopulation $i$ of country $m$ is $\lambda_{\text{A},i} = \beta\left(f\left(gA_{\text{tot}|m,i} + (1-g)\sum_{j=1}^{N}\frac{1}{N}A_{\text{tot}|m,j}\right) + (1-f)\sum_{\ell=1}^{M}\sum_{j=1}^{N}\frac{h_\ell}{N}A_{\text{tot}|\ell,j}\right)$, where $g$ is the within-country assortativity and $A_{\text{tot}|\ell,j}$ is the total carriage of strain $A$ in subpopulation $j$ of country $\ell$.

*Data and model fitting.*

We extracted community penicillin consumption and penicillin non-susceptibility in *S. pneumoniae* invasive isolates from databases made available by the ECDC (*13*, *28*). We assumed that community penicillin consumption drives penicillin resistance, that antibiotic consumption is independent of whether an individual is colonised by pneumococcus, and that resistance among invasive bacterial isolates is representative of resistance among circulating strains more broadly. Countries report community penicillin consumption in defined daily doses (DDD) per thousand individuals per day. To transform this bulk consumption rate into the rate at which individuals undertake a course of antibiotic therapy, we analysed prescribing data from eight European countries, estimating that, on average, 5 DDD in the population at large correspond to one treatment course for a child under 5 years of age. This conversion rate varies between countries (Table S3), but since the data are incomplete (8 of 27 countries) we have not explicitly accounted for this variability in our main model fitting results.

Our model framework tracks carriage of *S. pneumoniae* among children less than 5 years old, the age group driving both transmission and disease. In European countries, we assumed that the prevalence of pneumococcal carriage in under-5s is 50% (*11*, *42*) and the average duration of carriage is 47 days (*47*, *48*). We calculated the average incidence of *S. 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 Tables S4, S5, and S6 for details of calculations relating to pneumococcal carriage duration and disease incidence.

We used 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 $\tau_m$ 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 $\theta$ is then

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

where $P(\theta)$ is the prior probability of parameters $\theta$ 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 $\tau, r, n$ given model parameters $\theta$. 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 $\rho$. 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 adopted $c \sim \text{Beta}(\alpha = 1.5, \beta = 8.5)$, $b \sim \text{Gamma}(\kappa = 2, \theta = 0.5)$, $\beta \sim \text{Gamma}(\kappa = 5, \theta = 0.35)$, $g \sim \text{Beta}(\alpha = 10, \beta = 1.5)$,

$\kappa \sim \text{Gamma}(\kappa = 4, \theta = 2)$, $a \sim \text{Gamma}(\kappa = 2, \theta = 5)$, $\delta \sim \text{Beta}(\alpha = 20, \beta = 25)$, 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 fitted 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 increased the duration of carriage to 71.4 days; increased 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 reached 90.0%; and increased the antibiotic consumption rate to 1.670, 1.458, 1.138, or 5.887 courses per person per year, respectively, so that resistance prevalence reached 81.4%.

*Vaccine impact analysis*

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 antibiotic resistance frequency.*

We began by finding the maximum *a posteriori* model fits according to the likelihood and prior distributions for each of the four models of antibiotic resistance evolution. This identified the following parameter values for each model. "Treatment diversity": $\beta = 1.41$, $c = 0.124$, $g = 0.976$, and $\kappa = 2.22$. "Pathogen diversity": $\beta = 1.33$, $c = 0.191$, $a = 10.8$, and $\delta = 0.608$. "Treatment competition": $\beta = 1.42$, $c = 0.191$, and $k = 1.64$. "Growth competition": $\beta = 1.39$, $b = 0.195$, and $k = 1.61$. Then, we performed 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 used 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 used 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 antibiotic 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.

*Statistics used in this study.*

We used Bayesian inference, via Markov chain Monte Carlo techniques, in this study. We summarized the resulting posterior distributions using means and highest density intervals (HDIs), which differ from equal-tailed credible intervals in that they estimate the most compact region of support that contains a given proportion (e.g., 95%) of the posterior density.

**Supplementary Materials**

**Fig. S1–S16**

**Table S1–S8.**

## References and Notes


1. J. O'Neill, "Vaccines and alternative approaches: reducing our dependence on antimicrobials" (2016), (available at http://amr-review.org/sites/default/files/Vaccines and alternatives_v4_LR.pdf).
2. M. Lipsitch, R. Siber, How Can Vaccines Contribute to Solving the Antimicrobial Resistance Problem ? **7**, 1–8 (2016).
3. K. E. Atkins, M. Lipsitch, Can antibiotic resistance be reduced by vaccinating against respiratory disease? *Lancet Respir. Med.* **6**, 820–821 (2018).
4. J. P. Sevilla, D. E. Bloom, D. Cadarette, M. Jit, M. Lipsitch, Toward economic evaluation of the value of vaccines and other health technologies in addressing AMR. *Proc. Natl. Acad. Sci.* **115**, 12911–12919 (2018).
5. K. P. Klugman, S. Black, Impact of existing vaccines in reducing antibiotic resistance: Primary and secondary effects. *Proc. Natl. Acad. Sci.* **115**, 12896–12901 (2018).
6. M. H. Kyaw, R. Lynfield, W. Schaffner, A. S. Craig, J. Hadler, A. Reingold, A. R. Thomas, L. H. Harrison, N. M. Bennett, M. M. Farley, R. R. Facklam, J. H. Jorgensen, J. Besser, E. R. Zell, A. Schuchat, C. G. Whitney, Effect of Introduction of the Pneumococcal Conjugate Vaccine on Drug-Resistant Streptococcus pneumoniae. *N. Engl. J. Med.* **354**, 1455–1463 (2006).
7. D. Thorrington, N. Andrews, J. Stowe, E. Miller, A. J. van Hoek, Elucidating the impact of the pneumococcal conjugate vaccine programme on pneumonia, sepsis and otitis media hospital admissions in England using a composite control. *BMC Med.* **16**, 1–14 (2018).
8. C. Chen, F. Cervero Liceras, S. Flasche, S. Sidharta, J. Yoong, N. Sundaram, M. Jit, Effect and cost-effectiveness of pneumococcal conjugate vaccination: a global modelling analysis. *Lancet Glob. Heal.* **7**, e58–e67 (2019).
9. K. J. Wilby, D. Werry, A review of the effect of immunization programs on antimicrobial utilization. *Vaccine*. **30**, 6509–6514 (2012).
10. W. P. Hanage, J. A. Finkelstein, S. S. Huang, S. I. Pelton, A. E. Stevenson, K. Kleinman, V. L. Hinrichsen, C. Fraser, Evidence that pneumococcal serotype replacement in Massachusetts following conjugate vaccination is now complete. *Epidemics*. **2**, 80–84 (2010).

11. S. Flasche, A. J. Van Hoek, E. Sheasby, P. Waight, N. Andrews, C. Sheppard, R. George, E. Miller, Effect of pneumococcal conjugate vaccination on serotype-specific carriage and invasive disease in England: a cross-sectional study. *PLoS Med.* **8**, e1001017 (2011).
12. J. A. Lewnard, W. P. Hanage, Making sense of differences in pneumococcal serotype replacement. *Lancet Infect. Dis.* **3099** (2019), doi:10.1016/s1473-3099(18)30660-1.
13. European Centre for Disease Prevention and Control, Antimicrobial consumption rates by country (2018), (available at http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/esac-net-database/Pages/Antimicrobial-consumption-rates-by-country.aspx).
14. World Health Organization, WHO vaccine pipeline tracker (2019), (available at https://www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/).
15. G. L. Masala, M. Lipsitch, C. Bottomley, S. Flasche, Exploring the role of competition induced by non-vaccine serotypes for herd protection following pneumococcal vaccination. *J. R. Soc. Interface*. **14** (2017), doi:10.1098/rsif.2017.0620.
16. K. E. Atkins, E. I. Lafferty, S. R. Deeny, N. G. Davies, J. V. Robotham, M. Jit, Use of mathematical modelling to assess the impact of vaccines on antibiotic resistance. *Lancet Infect. Dis.* **18**, e204–e213 (2018).
17. K. E. Atkins, S. Flasche, Vaccination to reduce antimicrobial resistance. *Lancet Glob. Heal.* **6**, e252 (2018).
18. L. Temime, D. Guillemot, P. Y. Boëlle, Short- and long-term effects of pneumococcal conjugate vaccination of children on penicillin resistance. *Antimicrob. Agents Chemother.* **48**, 2206–2213 (2004).
19. L. Temime, P. Y. Boëlle, A. J. Valleron, D. Guillemot, Penicillin-resistant pneumococcal meningitis: High antibiotic exposure impedes new vaccine protection. *Epidemiol. Infect.* **133**, 493–501 (2005).
20. L. Opatowski, L. Temime, E. Varon, R. Leclerc, H. Drugeon, P.-Y. Boëlle, D. Guillemot, Antibiotic Innovation May Contribute to Slowing the Dissemination of Multiresistant Streptococcus pneumoniae: The Example of Ketolides. *PLoS One*. **3**, e2089 (2008).

21. T. Van Effelterre, M. R. Moore, F. Fierens, C. G. Whitney, L. White, S. I. Pelton, W. P. Hausdorff, A dynamic model of pneumococcal infection in the United States: Implications for prevention through vaccination. *Vaccine*. **28**, 3650–3660 (2010).
22. M. D. De Cellès, M. Pons-Salort, E. Varon, M. A. Vibet, C. Ligier, V. Letort, L. Opatowski, D. Guillemot, Interaction of vaccination and reduction of antibiotic use drives unexpected increase of pneumococcal meningitis. *Sci. Rep.* **5**, 1–11 (2015).
23. P. K. Mitchell, M. Lipsitch, W. P. Hanage, Carriage burden, multiple colonization and antibiotic pressure promote emergence of resistant vaccine escape pneumococci. *Philos. Trans. R. Soc. B Biol. Sci.* **370**, 3–9 (2015).
24. U. Obolski, J. Lourenço, C. Thompson, R. Thompson, A. Gori, S. Gupta, Vaccination can drive an increase in frequencies of antibiotic resistance among nonvaccine serotypes of Streptococcus pneumoniae. *Proc. Natl. Acad. Sci.* **115**, 3102–3107 (2018).
25. C. Colijn, T. Cohen, C. Fraser, W. Hanage, E. Goldstein, N. Givon-Lavi, R. Dagan, M. Lipsitch, What is the mechanism for persistent coexistence of drug-susceptible and drug-resistant strains of *Streptococcus pneumoniae*? *J. R. Soc. Interface*. **7**, 905–919 (2010).
26. N. G. Davies, S. Flasche, M. Jit, K. E. Atkins, Within-host dynamics shape antibiotic resistance in commensal bacteria. *Nat. Ecol. Evol.* (2019), doi:10.1038/s41559-018-0786-x.
27. H. Goossens, M. Ferech, R. Vander Stichele, M. Elseviers, Outpatient antibiotic use in Europe and association with resistance: A cross-national database study. *Lancet*. **365**, 579–587 (2005).
28. European Centre for Disease Prevention and Control, Data from the ECDC Surveillance Atlas - Antimicrobial resistance (2016), (available at https://ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc).
29. M. Lipsitch, C. Colijn, T. Cohen, W. P. Hanage, C. Fraser, No coexistence for free: Neutral null models for multistrain pathogens. *Epidemics*. **1**, 2–13 (2009).
30. P. Rodrigues, M. G. M. Gomes, C. Rebelo, Drug resistance in tuberculosis-a reinfection model. *Theor. Popul. Biol.* **71**, 196–212 (2007).
31. O. Patterson-Lomba, B. M. Althouse, G. M. Goerg, L. Hébert-Dufresne, Optimizing Treatment Regimes to Hinder Antiviral Resistance in Influenza across Time

884 Scales. *PLoS One*. **8**, 1–11 (2013).
885 32. I. M. Hastings, Complex dynamics and stability of resistance to antimalarial drugs.
886 *Parasitology*. **132**, 615–624 (2006).
887 33. R. Sergeev, C. Colijn, T. Cohen, Models to understand the population-level impact
888 of mixed strain M. tuberculosis infections. *J. Theor. Biol.* **280**, 88–100 (2011).
889 34. F. Blanquart, S. Lehtinen, M. Lipsitch, C. Fraser, The evolution of antibiotic
890 resistance in a structured host population. *J. R. Soc. Interface*. **15** (2018),
891 doi:10.1098/rsif.2018.0040.
892 35. M. S. Krieger, A. L. Hill, Long-term coexistence and regional heterogeneity of
893 antibiotic-resistant infections reproduced by a simple spatial model. *bioRxiv*. **14**,
894 469171 (2018).
895 36. R. Kouyos, E. Klein, B. Grenfell, Hospital-Community Interactions Foster
896 Coexistence between Methicillin-Resistant Strains of Staphylococcus aureus. *PLoS*
897 *Pathog.* **9** (2013), doi:10.1371/journal.ppat.1003134.
898 37. M. F. Boni, M. W. Feldman, Evolution of Antibiotic Resistance By Human and
899 Bacterial Niche Construction. *Evolution (N. Y).* **59**, 477 (2006).
900 38. S. Lehtinen, F. Blanquart, N. J. Croucher, P. Turner, M. Lipsitch, C. Fraser, Evolution
901 of antibiotic resistance is linked to any genetic mechanism affecting bacterial
902 duration of carriage. *Proc. Natl. Acad. Sci.* **114**, 1075–1080 (2017).
903 39. D. J. Austin, K. G. Kristinsson, R. M. Anderson, The relationship between the
904 volume of antimicrobial consumption in human communities and the frequency
905 of resistance. *Proc. Natl. Acad. Sci.* **96**, 1152–1156 (1999).
906 40. A. B. Beams, D. J. A. Toth, K. Khader, F. R. Adler, Harnessing intra-host strain
907 competition to limit antibiotic resistance: mathematical model results. *Bull. Math.*
908 *Biol.* **78**, 1828–1846 (2016).
909 41. K. Græsbøll, S. S. Nielsen, N. Toft, L. E. Christiansen, How fitness reduced,
910 antimicrobial resistant bacteria survive and spread: A multiple pig - multiple
911 bacterial strain model. *PLoS One*. **9** (2014), doi:10.1371/journal.pone.0100458.
912 42. D. Bogaert, A. Van Belkum, M. Sluijter, A. Luijendijk, R. De Groot, H. C. Rümke, H. A.
913 Verbrugh, P. W. M. Hermans, Colonisation by *Streptococcus pneumoniae* and
914 *Staphylococcus aureus* in healthy children. *Lancet*. **363**, 1871–1872 (2004).
915 43. D. M. Weinberger, V. E. Pitzer, G. Regev-Yochay, N. Givon-Lavi, R. Dagan,
916 Association between the Decline in Pneumococcal Disease in Unimmunized

Adults and Vaccine-Derived Protection Against Colonization in Toddlers and Preschool-Aged Children. *Am. J. Epidemiol.* **188**, 160–168 (2019).

44. D. I. Andersson, The biological cost of mutational antibiotic resistance: any practical conclusions? *Curr. Opin. Microbiol.* **9** (2006), pp. 461–465.

45. D. I. Andersson, D. Hughes, Antibiotic resistance and its cost: Is it possible to reverse resistance? *Nat. Rev. Microbiol.* **8**, 260–271 (2010).

46. C. Tedijanto, S. Olesen, Y. Grad, M. Lipsitch, Estimating the proportion of bystander selection for antibiotic resistance among potentially pathogenic bacterial flora. *Proc Natl Acad Sci USA*. **115**, E11988–E11995 (2018).

47. L. Högberg, P. Geli, H. Ringberg, E. Melander, M. Lipsitch, K. Ekdahl, Age- and serogroup-related differences in observed durations of nasopharyngeal carriage of penicillin-resistant pneumococci. *J. Clin. Microbiol.* **45**, 948–952 (2007).

48. A. Melegaro, N. J. Gay, G. F. Medley, Estimating the transmission parameters of pneumococcal carriage in households. *Epidemiol. Infect.* **132**, 433–441 (2004).

49. S. Cobey, M. Lipsitch, Niche and neutral effects of acquired immunity permit coexistence of pneumococcal serotypes. *Science (80-. ).* **335**, 1376–1380 (2012).

50. R. Malley, P. W. Anderson, Serotype-independent pneumococcal experimental vaccines that induce cellular as well as humoral immunity. *Proc. Natl. Acad. Sci. U. S. A.* **109**, 3623–3627 (2012).

51. S. P. Jochems, J. N. Weiser, R. Malley, D. M. Ferreira, The immunological mechanisms that control pneumococcal carriage. *PLoS Pathog.* **13**, 1–14 (2017).

52. UK Department of Health and Social Care, "Tackling antimicrobial resistance 2019 to 2024: the UK's 5-year national action plan" (2019), (available at https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024).

53. B. S. Buckley, N. Henschke, H. Bergman, B. Skidmore, E. J. Klemm, G. Villanueva, C. Garritty, M. Paul, Impact of vaccination on antibiotic usage: a systematic review and meta-analysis. *Clin. Microbiol. Infect.* **In press** (2019), doi:10.1016/j.cmi.2019.06.030.

54. A. Von Gottberg, L. De Gouveia, S. Tempia, V. Quan, S. Meiring, C. Von Mollendorf, S. A. Madhi, E. R. Zell, M. Stat, J. R. Verani, K. L. O'Brien, C. G. Whitney, K. P. Klugman, C. Cohen, Effects of vaccination on invasive pneumococcal disease in South Africa. *N. Engl. J. Med.* **371**, 1889–1899 (2014).

55. A. Cassini, L. D. Högberg, D. Plachouras, A. Quattrocchi, A. Hoxha, G. S. Simonsen, M. Colomb-Cotinat, M. E. Kretzschmar, B. Devleesschauwer, M. Cecchini, D. A. Ouakrim, T. C. Oliveira, M. J. Struelens, C. Suetens, D. L. Monnet, R. Strauss, K. Mertens, T. Struyf, B. Catry, K. Latour, I. N. Ivanov, E. G. Dobreva, A. Tambic Andraševic, S. Soprek, A. Budimir, N. Paphitou, H. Žemlicková, S. Schytte Olsen, U. Wolff Sönksen, P. Märtin, M. Ivanova, O. Lyytikäinen, J. Jalava, B. Coignard, T. Eckmanns, M. Abu Sin, S. Haller, G. L. Daikos, A. Gikas, S. Tsiodras, F. Kontopidou, Á. Tóth, Á. Hajdu, Ó. Guólaugsson, K. G. Kristinsson, S. Murchan, K. Burns, P. Pezzotti, C. Gagliotti, U. Dumpis, A. Liuimiene, M. Perrin, M. A. Borg, S. C. de Greeff, J. C. Monen, M. B. Koek, P. Elstrøm, D. Zabicka, A. Deptula, W. Hryniewicz, M. Caniça, P. J. Nogueira, P. A. Fernandes, V. Manageiro, G. A. Popescu, R. I. Serban, E. Schréterová, S. Litvová, M. Štefkovicová, J. Kolman, I. Klavs, A. Korošec, B. Aracil, A. Asensio, M. Pérez-Vázquez, H. Billström, S. Larsson, J. S. Reilly, A. Johnson, S. Hopkins, Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect. Dis.* **19**, 56–66 (2019).

56. M. Kobayashi, L. M. Conklin, G. Bigogo, G. Jagero, L. Hampton, K. E. Fleming-Dutra, M. Junghae, M. da G. Carvalho, F. Pimenta, B. Beall, T. Taylor, K. F. Laserson, J. Vulule, C. Van Beneden, L. Kim, D. R. Feikin, C. G. Whitney, R. F. Breiman, Pneumococcal carriage and antibiotic susceptibility patterns from two cross-sectional colonization surveys among children aged <5 years prior to the introduction of 10-valent pneumococcal conjugate vaccine - Kenya, 2009-2010. *BMC Infect. Dis.* **17**, 1–12 (2017).

57. M. Lipsitch, O. Abdullahi, A. D'Amour, W. Xie, D. M. Weinberger, E. Tchetgen Tchetgen, J. A. G. Scott, Estimating rates of carriage acquisition and clearance and competitive ability for pneumococcal serotypes in Kenya with a Markov transition model. *Epidemiology*. **23**, 510–519 (2012).

58. I. Rudan, K. L. O'Brien, H. Nair, L. Liu, E. Theodoratou, S. Qazi, I. Luksic, C. L. F. Walker, R. E. Black, H. Campbell, Child Health Epidemiology Reference Group, Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. *J. Glob. Health*. **3**, S114-010401 (2013).

59. A. N. Torné, J. G. Dias, C. Quinten, F. Hruba, M. C. Busana, P. L. Lopalco, A. J. A. Gauci, L. Pastore-Celentano, M. Sabbe, J. Verhaegen, M. Koliou, D. Pieridou-Bagkatzouni, P. Křižovà, J. Kozakova, J. Motlova, P. Valentiner-Branth, L. Lambertsen, T. Georgakopoulou, H. Humphreys, T. Melillo, P. Caruana, M. Knol, H. de Merkel, K. Elberse, D. Frimann, A. Skoczynska, W. Hryniewicz, A. Kuch, I. Paradowska-Stankiewicz, M. Pana, M. Vitek, V. Učakar, B. H. Normark, T. Lepp, M. Slack, P. A. Waight, European enhanced surveillance of invasive pneumococcal disease in 2010: Data from 26 European countries in the post-heptavalent conjugate vaccine era. *Vaccine*. **32**, 3644–3650 (2014).

60. M. Tin Tin Htar, D. Christopoulou, H. J. Schmitt, Pneumococcal serotype evolution in Western Europe. *BMC Infect. Dis.* **15**, 1–10 (2015).

61. B. Simell, K. Auranen, H. Käyhty, D. Goldblatt, R. Dagan, K. L. O'Brien, The fundamental link between pneumococcal carriage and disease. *Expert Rev. Vaccines*. **11**, 841–855 (2012).

62. S. Flasche, A. Guilder, Using a mathematical model to assess the potential effects of a new vaccine approach that targets enhanced clearance of pneumococcal carriage. (2018).

63. M. C. Negri, M. Lipsitch, J. Blázquez, B. R. Levin, F. Baquero, Concentration-dependent selection of small phenotypic differences in TEM beta-lactamase-mediated antibiotic resistance. *Antimicrob. Agents Chemother.* **44**, 2485–91 (2000).

64. A. R. Wargo, S. Huijben, J. C. de Roode, J. Shepherd, A. F. Read, Competitive release and facilitation of drug-resistant parasites after therapeutic chemotherapy in a rodent malaria model. *Proc. Natl. Acad. Sci.* **104**, 19914–19919 (2007).

65. N. Wale, D. G. Sim, M. J. Jones, R. Salathe, T. Day, A. F. Read, Resource limitation prevents the emergence of drug resistance by intensifying within-host competition. *Proc. Natl. Acad. Sci.*, 201715874 (2017).

66. J. A. Lewnard, P. A. Tähtinen, M. K. Laine, L. Lindholm, J. Jalava, P. Huovinen, M. Lipsitch, A. Ruohola, Impact of antimicrobial treatment for acute otitis media on carriage dynamics of penicillin-susceptible and penicillin–non-susceptible Streptococcus pneumoniae. *J. Infect. Dis.*, jiy343 (2018).

67. S. Lehtinen, F. Blanquart, M. Lipsitch, C. Fraser, On the evolutionary ecology of multidrug resistance in bacteria. *PLoS Pathog.* **15**, 1–22 (2019).

68. M. Filippini, G. Masiero, K. Moschetti, Socioeconomic determinants of regional differences in outpatient antibiotic consumption: Evidence from Switzerland. *Health Policy (New. York).* **78**, 77–92 (2006).
69. D. Koller, F. Hoffmann, W. Maier, K. Tholen, R. Windt, G. Glaeske, Variation in antibiotic prescriptions: Is area deprivation an explanation? Analysis of 1.2 million children in Germany. *Infection*. **41**, 121–127 (2013).
70. M. Di Martino, A. Lallo, U. Kirchmayer, M. Davoli, D. Fusco, Prevalence of antibiotic prescription in pediatric outpatients in Italy: The role of local health districts and primary care physicians in determining variation. A multilevel design for healthcare decision support. *BMC Public Health*. **17**, 1–8 (2017).
71. M. C. Goossens, B. Catry, J. Verhaegen, Antimicrobial resistance to benzylpenicillin in invasive pneumococcal disease in Belgium, 2003-2010: The effect of altering clinical breakpoints. *Epidemiol. Infect.* **141**, 490–495 (2013).
72. S. Cobey, E. B. Baskerville, C. Colijn, W. Hanage, C. Fraser, M. Lipsitch, Host population structure and treatment frequency maintain balancing selection on drug resistance. *J. R. Soc. Interface*. **14**, 20170295 (2017).
73. A. Pottegård, A. Broe, R. Aabenhus, L. Bjerrum, J. Hallas, P. Damkier, Use of antibiotics in children: A danish nationwide drug utilization study. *J. Pediatr. Infect. Dis.* **34**, e16–e22 (2015).
74. W. V. Kern, K. De With, K. Nink, M. Steib-Bauert, H. Schröder, Regional variation in outpatient antibiotic prescribing in Germany. *Infection*. **34**, 269–273 (2006).
75. C. Ter Braak, A Markov Chain Monte Carlo version of the genetic algorithm Differential Evolution: Easy Bayesian computing for real parameter spaces. *Stat. Comput.* **16**, 239–249 (2006).
76. Eurostat (2019), (available at https://ec.europa.eu/eurostat/home?).
77. T. Smieszek, K. B. Pouwels, F. C. K. Dolk, D. R. M. Smith, S. Hopkins, M. Sharland, A. D. Hay, M. V Moore, J. V Robotham, Potential for reducing inappropriate antibiotic prescribing in English primary care. *J. Antimicrob. Chemother.* **73**, ii36–ii43 (2018).

**Acknowledgements**

*Funding:* N.G.D., M.J. and K.E.A. were funded by the National Institute for Health Research Health Protection Research Unit in Immunisation at the London School of Hygiene and Tropical Medicine in partnership with Public Health England. The views expressed are those of the authors and not necessarily those of the NHS, National Institute for Health Research, Department of Health or Public Health England. S.F. was supported by a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and Royal Society (grant number 208812/Z/17/Z).

*Author contributions:* All authors designed the study. N.G.D. performed the analyses with input from K.E.A., M.J., and S.F. The paper was written by N.G.D. and K.E.A. with input from M.J. and S.F.

*Competing interests:* The authors declare no competing interests.

**Data and Materials Availability:** All data and code used in this study have been deposited to Zenodo with DOI 10.5281/zenodo.5116454.

## Figures

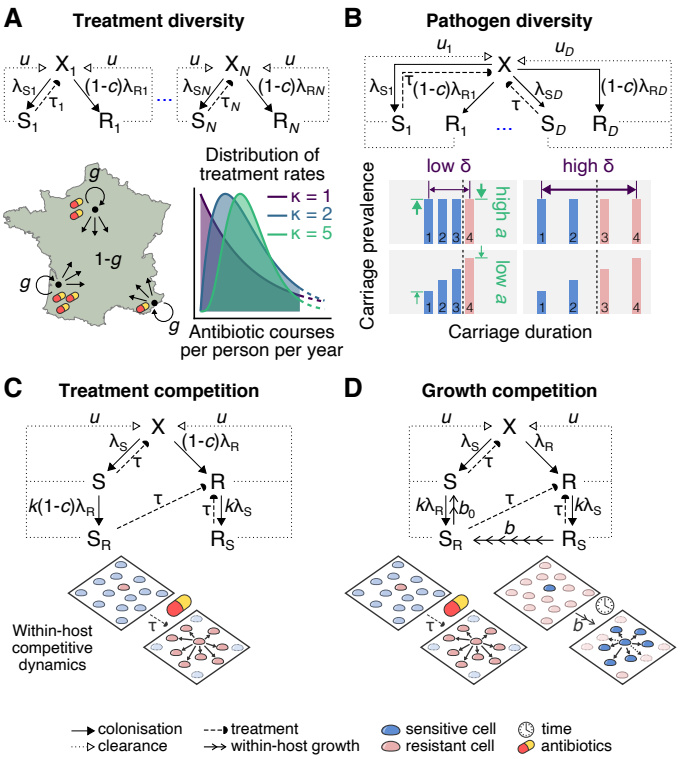


**Fig. 1. Four models of antibiotic resistance evolution.** This figure illustrates the four mechanisms that this study identifies as potential explanations for the association between penicillin consumption and penicillin non-susceptibility in *Streptococcus pneumoniae* across 27 European countries. Each mechanism is captured by a different mathematical model, the structure and key features of which are illustrated here. In the diagrams above, X hosts are uncolonised, S hosts are colonised with the antibiotic-sensitive strain and R hosts are colonised with the antibiotic-resistant strain. Force-of-infection terms $\lambda_A$ 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 $\tau$ is the rate of antibiotic treatment. **(A)** "Treatment diversity" model: Each country is split into subpopulations varying in treatment rate $\tau_i$, 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 antibiotic sensitive and resistant strains. **(B)** "Pathogen diversity" model: 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 antibiotic resistance, so that overall, both antibiotic sensitive and resistant strains can circulate. **(C)** "Treatment competition" model: 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 antibiotic treatment-mediated within-host competition. **(D)** "Growth competition" model: 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 $f$.

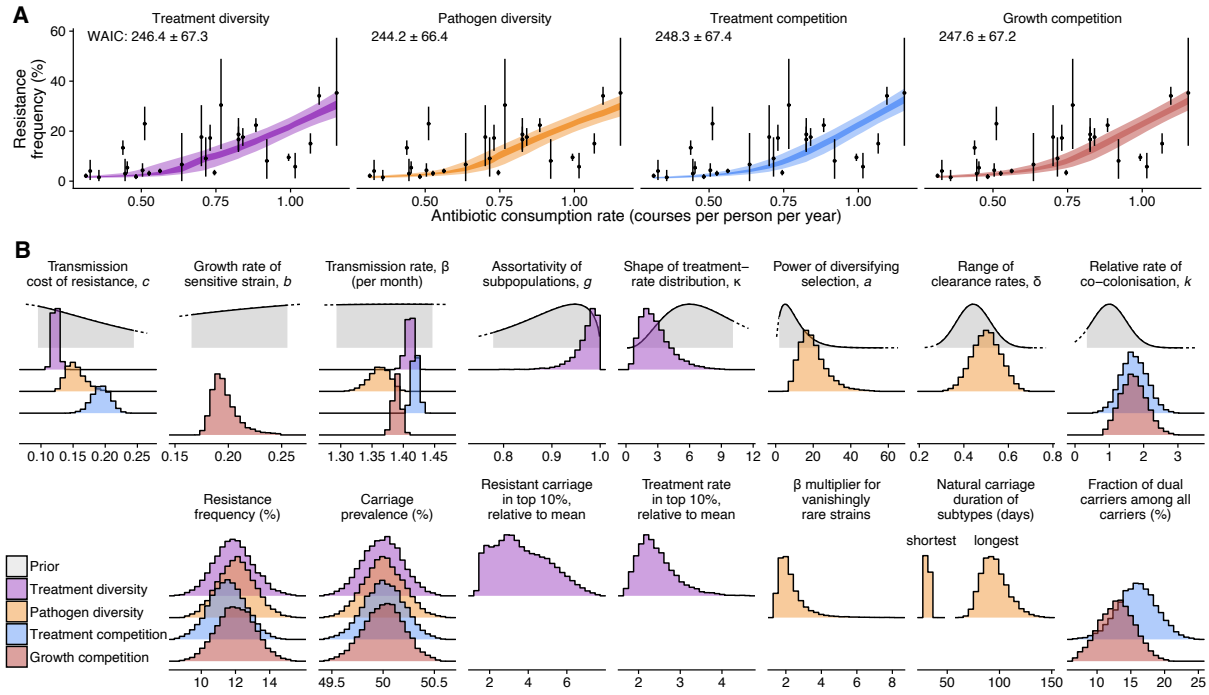


**Fig 2. Four models reproduce patterns of antibiotic resistance in *S. pneumoniae* in Europe. (A)** Model fits with associated Widely Applicable Information Criteria (WAIC, ± standard error) for the four models presented in Figure 1: Treatment diversity, Pathogen diversity, Treatment competition, Growth competition. 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 children under five years of age for 27 countries (source: European Centre for Disease Prevention and Control). Ribbons show the 50% and 95% HDIs for antibiotic 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.

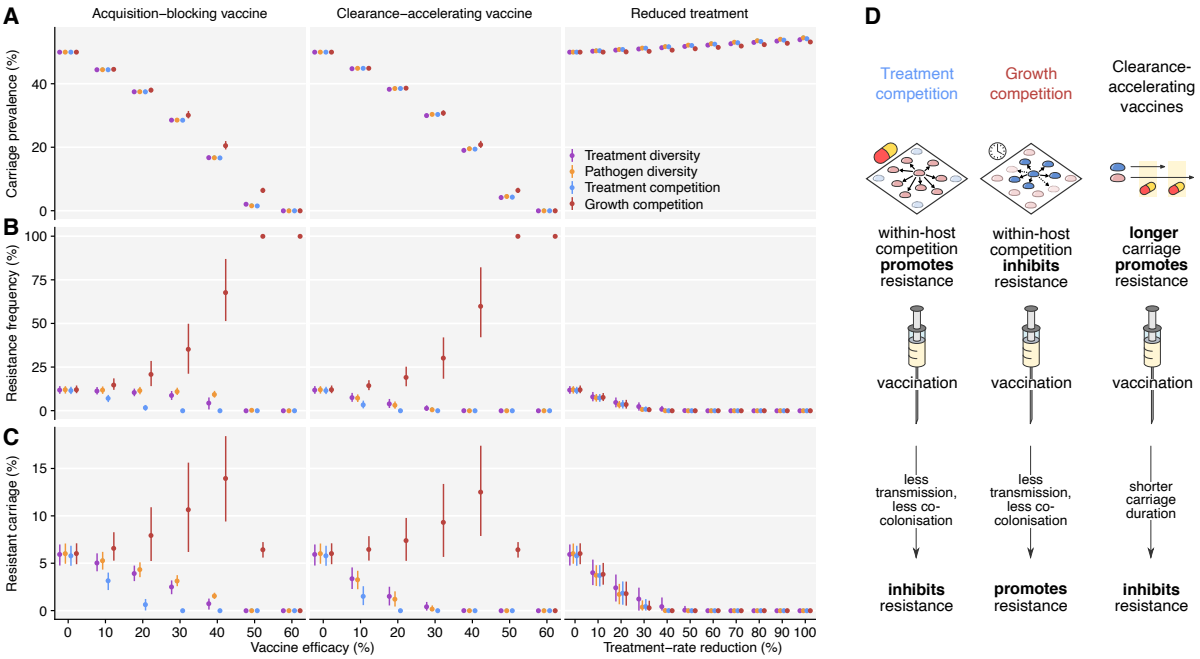


**Fig. 3. Impact of vaccination and antibiotic treatment on model outcomes.** Shown is the impact of vaccination with an acquisition-blocking vaccine or a clearance-accelerating vaccine, or reduced antibiotic treatment on **(A)** pneumococcal carriage prevalence, **(B)** antibiotic resistance frequency, and **(C)** antibiotic-resistant pneumococcal carriage (mean and 95% HDI) in the four models. **(D)** Illustration of the strongest forces selecting for greater or lesser antibiotic resistance across the four models.

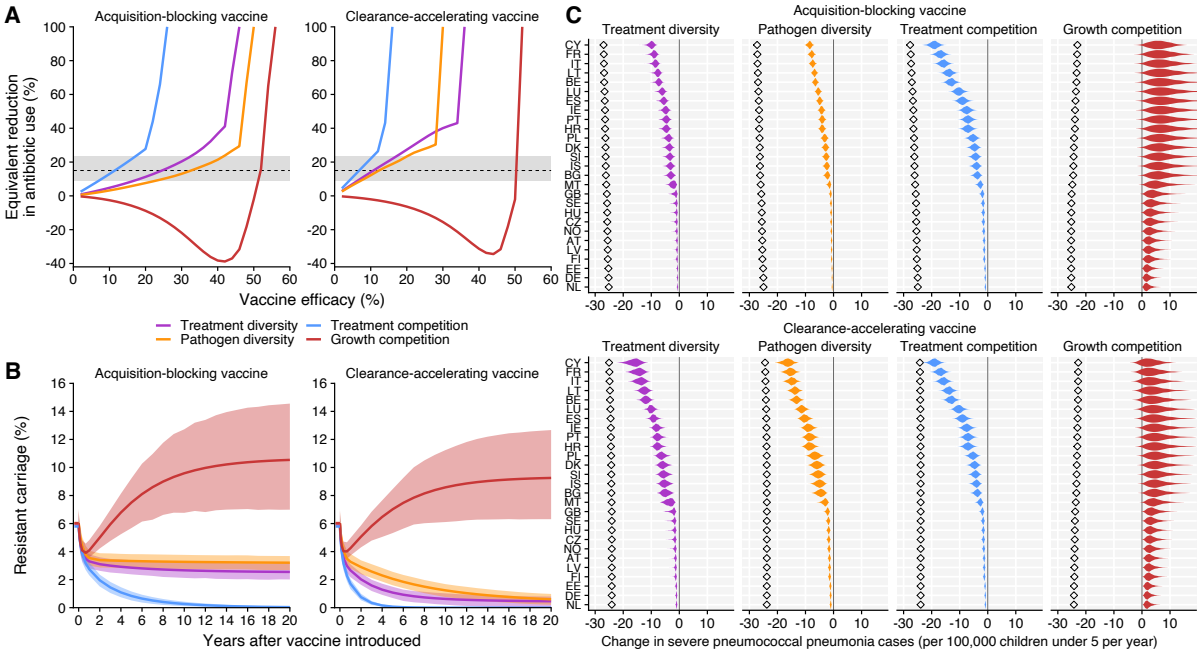


**Fig. 4. Policy considerations of the four models. (A)** Shown is the median equivalent reduction in prescribing antibiotics across the four models of antibiotic resistance evolution, in terms of vaccine efficacy at reducing the prevalence of resistant pneumococcal carriage. This demonstrates the vaccine efficacy required to achieve a similar decrease in antibiotic-resistant pneumococcal 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 in the UK which are clinically unnecessary (*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 on antibiotic resistance evolution, 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 is shown. European 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; filled distributions show the change in antibiotic-resistant pneumonia cases.

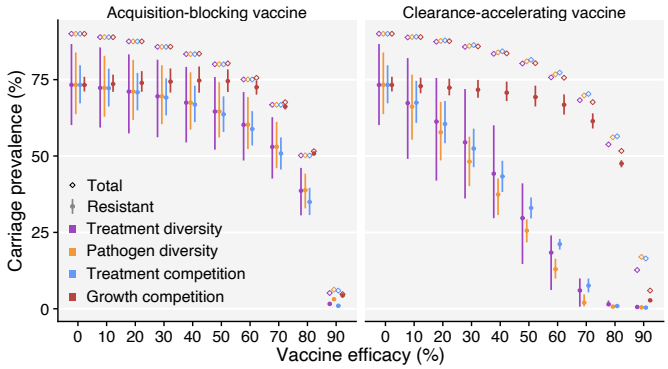


**Fig. 5. Vaccine impact in a high-burden setting.** Our study focuses on patterns of antibiotic consumption and resistance observed in European countries, and shows that the alternative mechanisms that could explain these patterns each yield differing predictions for how vaccination might impact upon selection for antibiotic resistance. However, these predictions depend upon the epidemiological situation in a given country. Indeed, adjusting the four fitted models to be consistent with a higher-burden setting, as is often observed in lower-income countries, yields different predictions for the impact of acquisition-blocking and clearance-accelerating vaccines on antibiotic resistance evolution (shown: mean and 95% HDI).

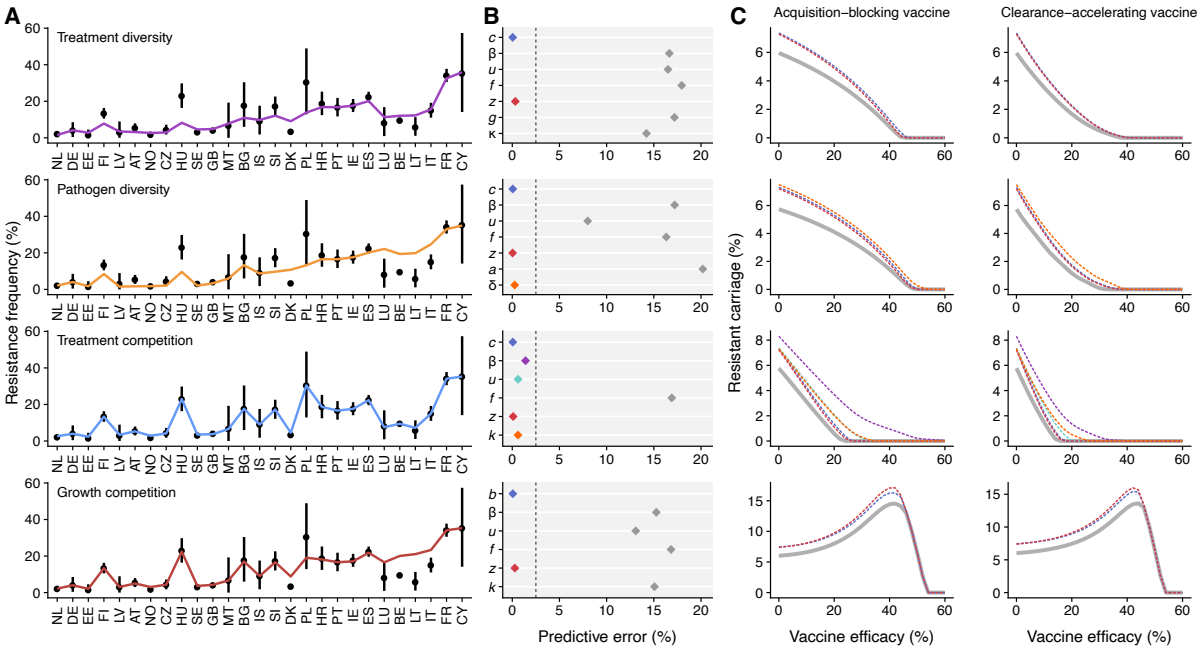


**Fig 6. Explaining additional between-country variation in antibiotic resistance frequency.** Allowing model parameters to vary across countries captures additional between-country variation in antibiotic resistance frequency not captured by variation in the antibiotic treatment rate. For example, **(A)** 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 antibiotic resistance frequency and 95% HDI for each country). **(B)** Depending upon which parameter is allowed to vary, the four 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 colors in panel B.

1177 **Table 1. Mechanisms for maintaining coexistence of antibiotic-resistant and**

1178 **sensitive *S. pneumoniae***

| | 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** | Within-host competition creates frequency-dependent selection for resistance (*25*, *26*, *32*, *33*, *40*) | ✓ 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 |

1179
1180

Supplementary Materials for

# Modeling the effect of vaccination on selection for antibiotic resistance in *S. pneumoniae*

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

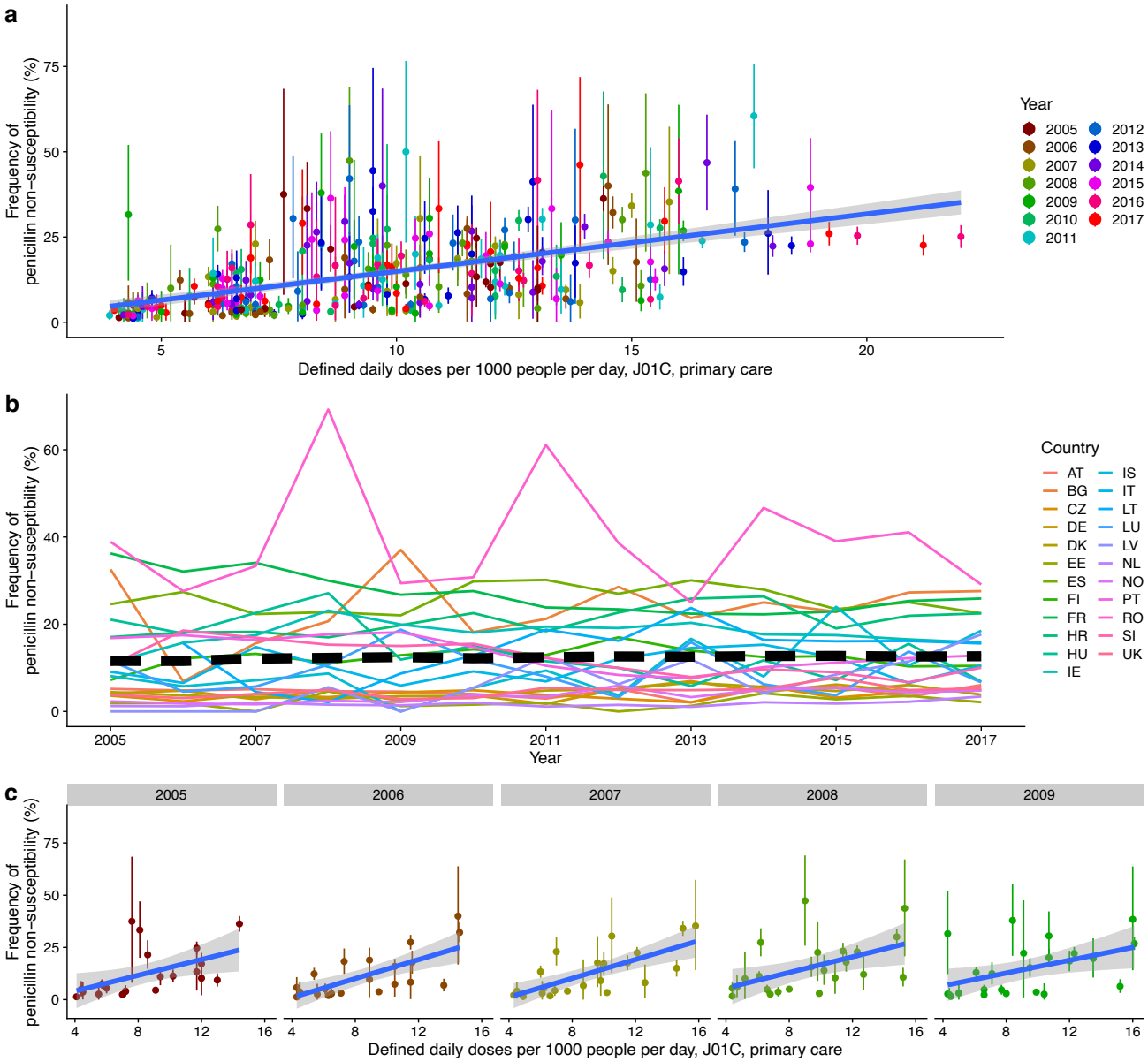


**Fig. S1. Patterns of penicillin non-susceptibility across European countries, 2005–2017. (a)** The frequency of penicillin non-susceptibility in pneumococcal isolates (mean and 95% HDI) increases with the primary care consumption of penicillins, ATC class J01C (least-squares linear regression $\beta = 0.0168, F(1,344) = 148.5, P < 2.2 \times 10^{-16}$). 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

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

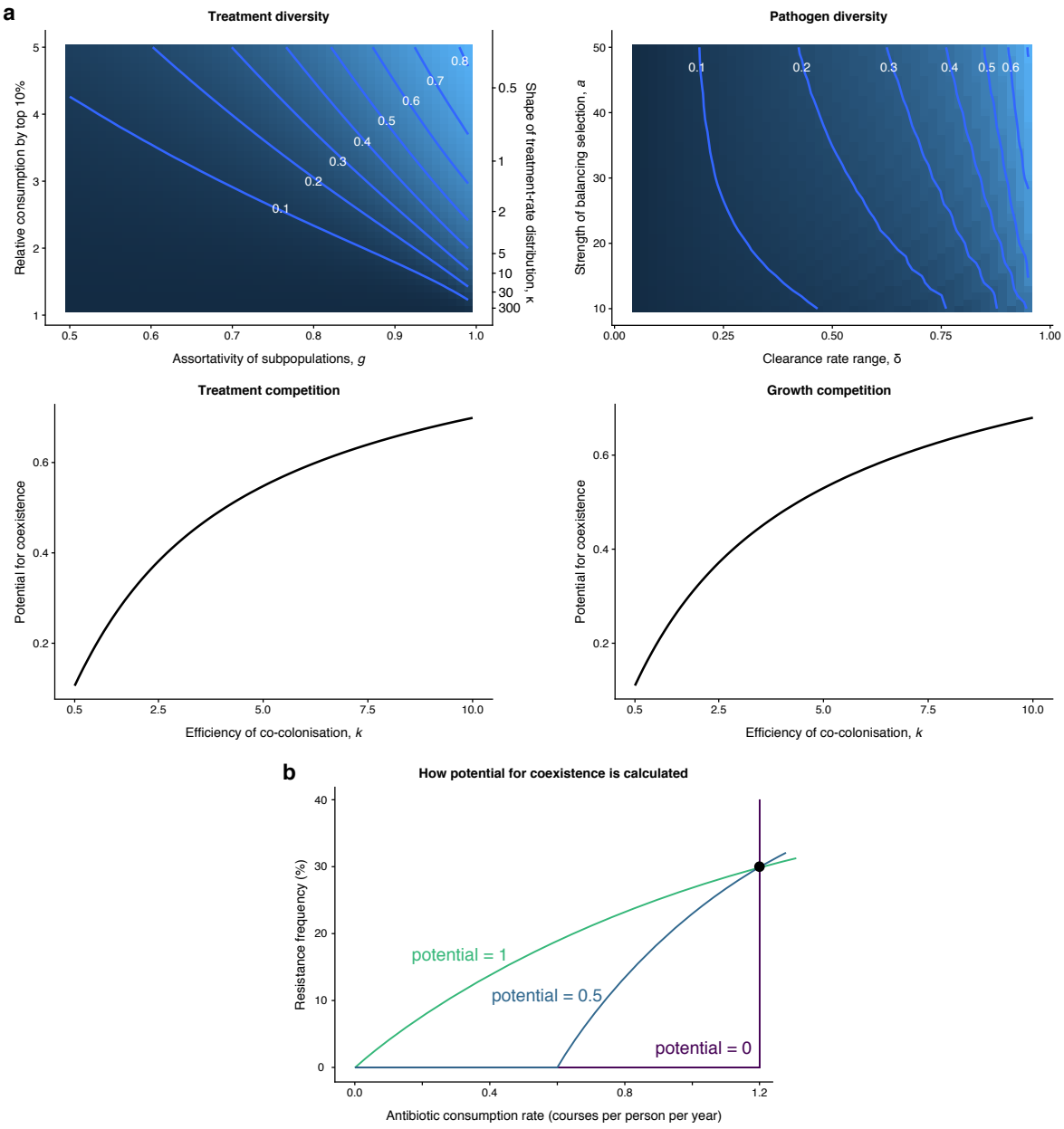


**Fig. S2. Impact of key parameters upon the potential for coexistence in each model. (a)** Potential for coexistence for each model, depending upon key parameters. In the top two panels, darker colours represent lower potential for coexistence while lighter colours represent higher potential for coexistence. **(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 $g$, $\kappa$, $\delta$, $a$, 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.

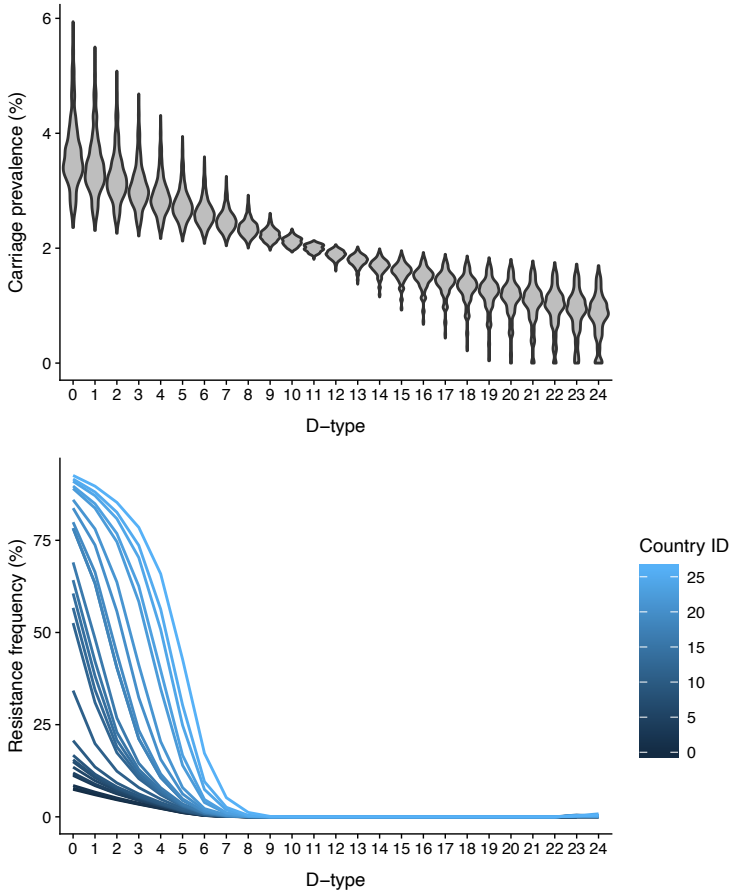


**Fig. S3. Carriage and resistance of D-types in the "Pathogen diversity" model.** This verifies that the D-types with the highest prevalence of carriage (averaged over all countries, above) also exhibit the highest resistance frequency (separated by country, below), and shows that at equilibrium, D-types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

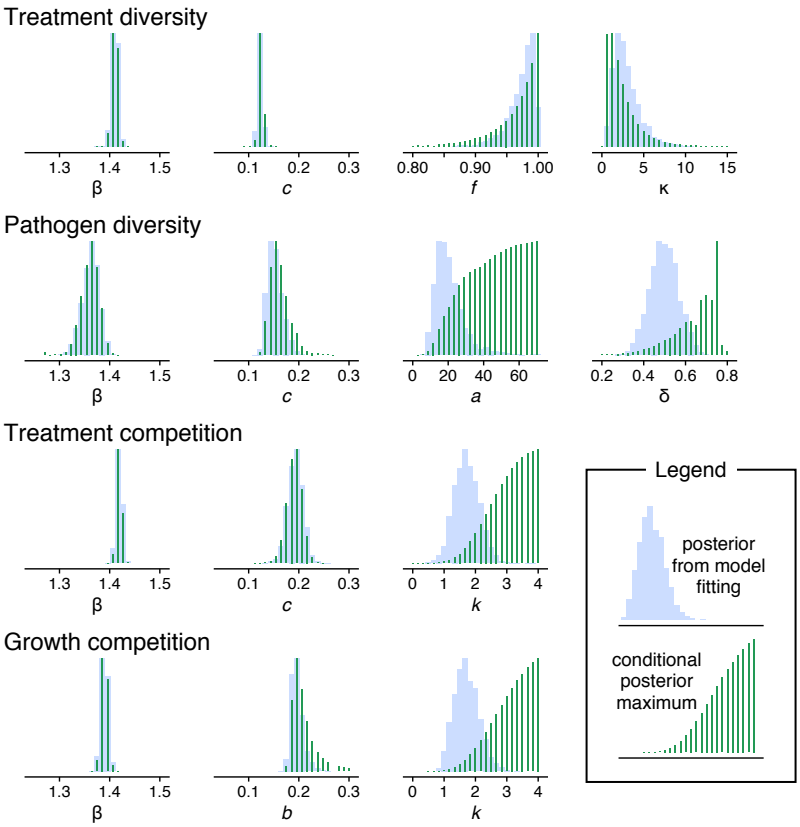


**Fig. S4. Comparison of inferred model posteriors and conditional posterior maxima for each parameter.** The conditional posterior maximum (green bars) is obtained by fixing the parameter of interest at a specific value, then allowing the other parameters to assume their maximum *a posteriori* values 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 $\delta$ 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.

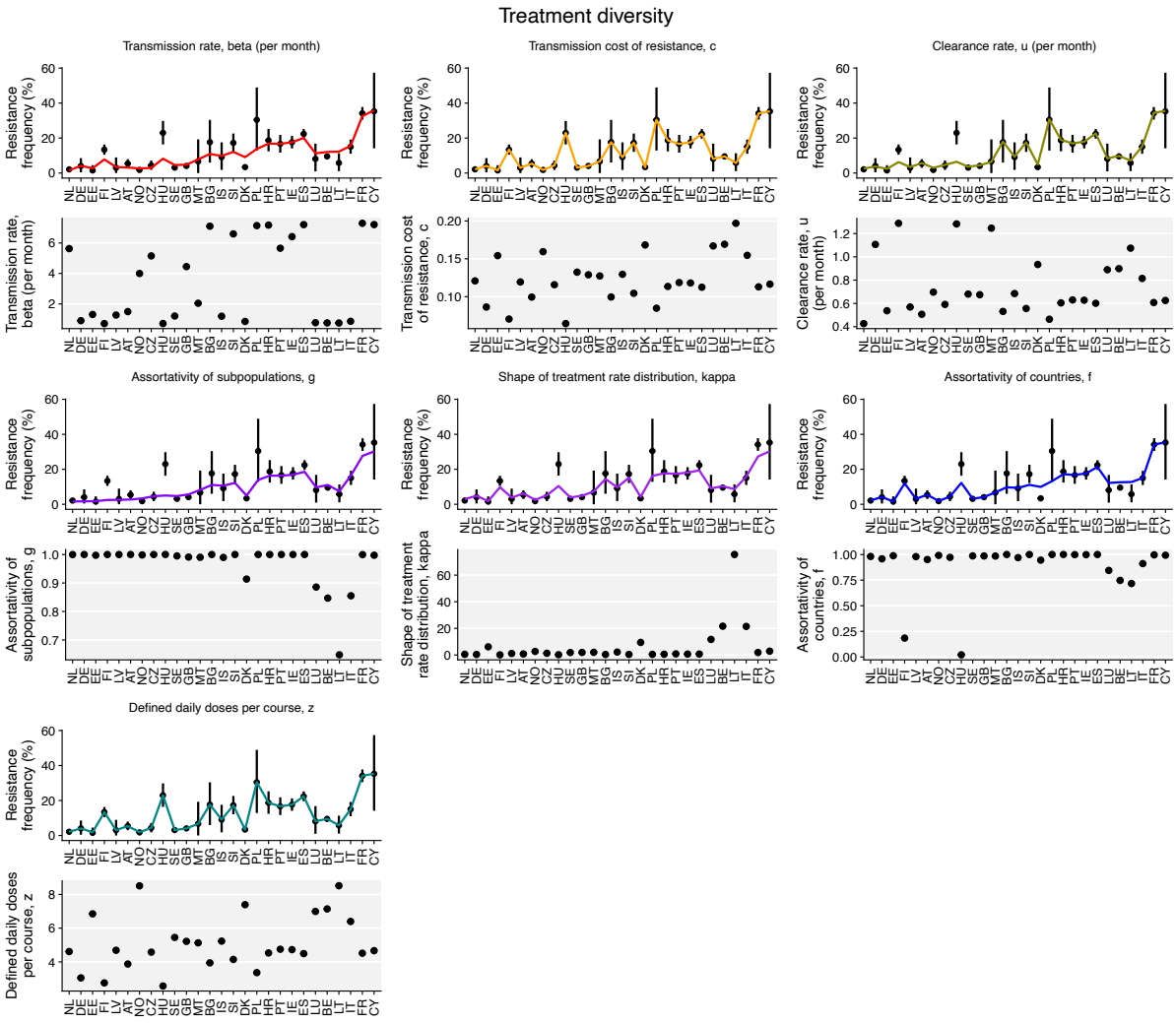


**Fig. S5. Varying-parameter fits for the "Treatment diversity" model.** Maximum *a posteriori* fits for the "Treatment diversity" model allowing one parameter to vary between countries. Parameters *c* and *z* can capture the additional variation in resistance frequency between countries.

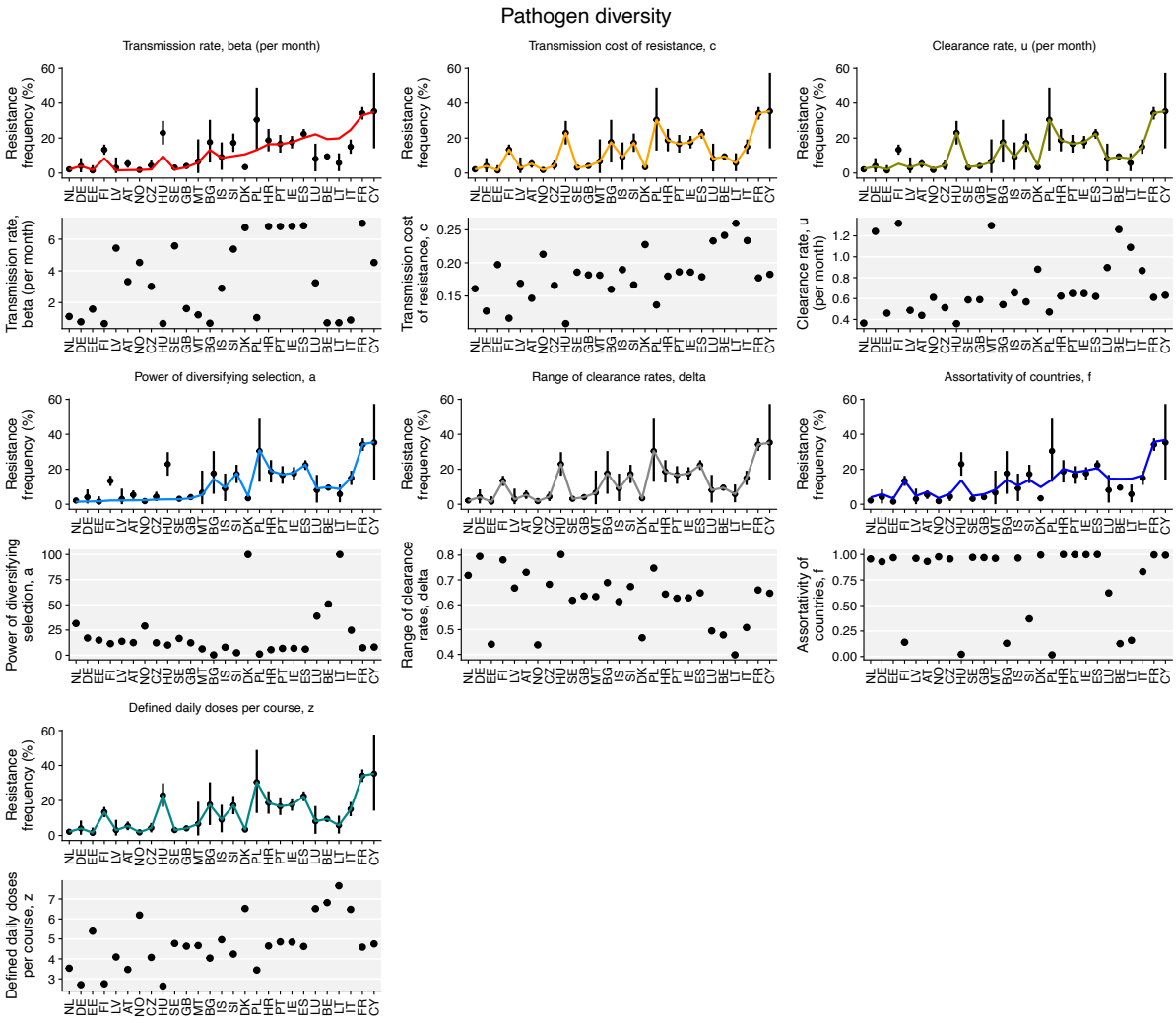


**Fig. S6. Varying-parameter fits for the "Pathogen diversity" model.** Maximum *a posteriori* fits for the "Pathogen diversity" model allowing one parameter to vary between countries. Parameters *c*, δ, and *z* can capture the additional variation in resistance frequency between countries.

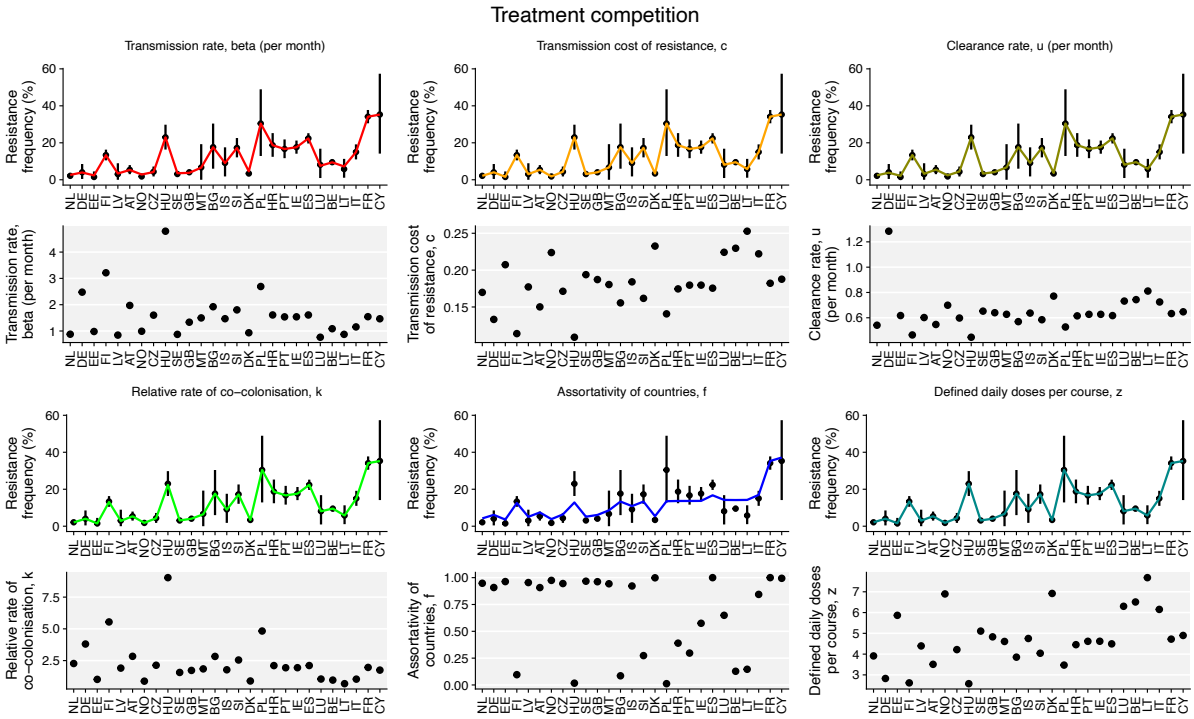


**Fig. S7. Varying-parameter fits for the "Treatment competition" model.** Maximum *a posteriori* fits for the "Treatment competition" model allowing one parameter to vary between countries. Parameters β, *c*, *u*, *k*, and *z* can capture the additional variation in resistance frequency between countries.

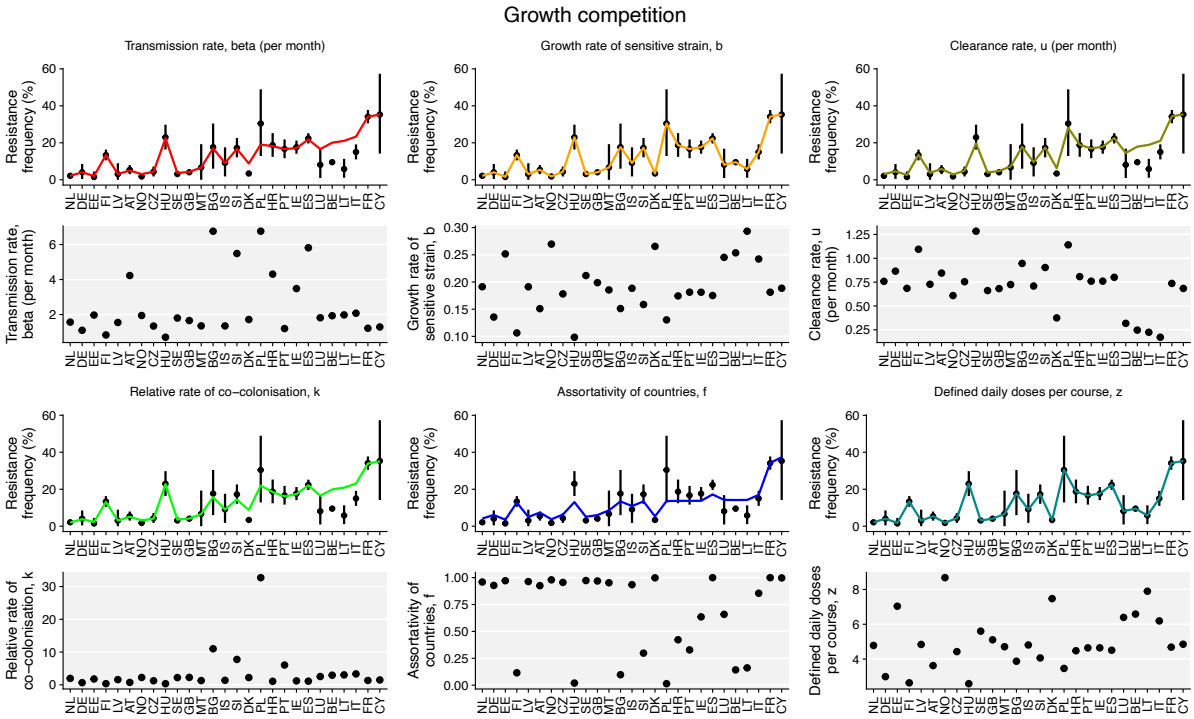


**Fig. S8. Varying-parameter fits for the "Growth competition" model.** Maximum *a posteriori* fits for the "Growth competition" model allowing one parameter to vary between countries. Parameters *b* and *z* can capture the additional variation in resistance frequency between countries.

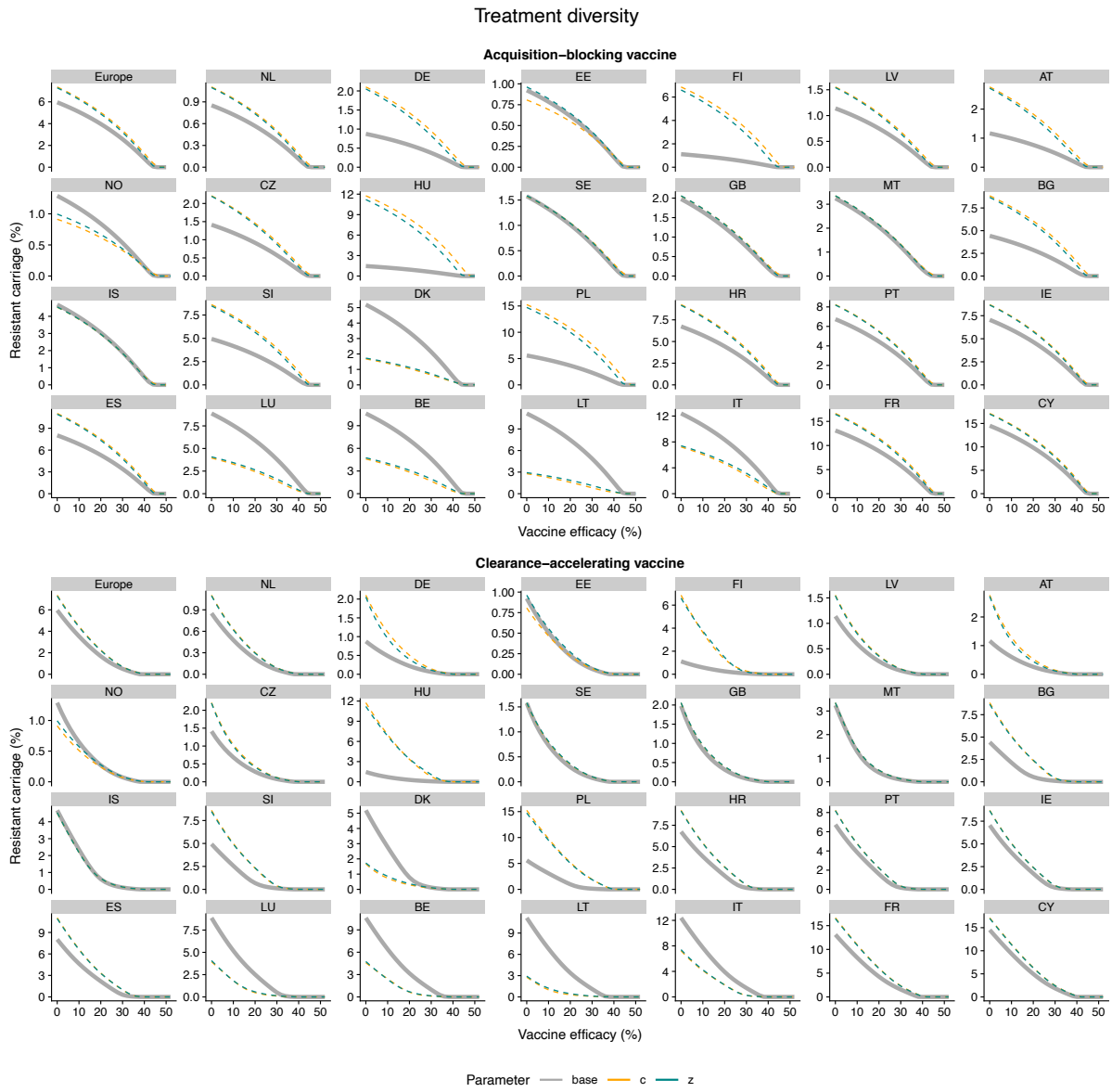


**Fig. S9. Vaccine impact for the "Treatment diversity" model, varying parameters *c* and *z*.** Impact of vaccination under the "Treatment diversity" model, for those parameters able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared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

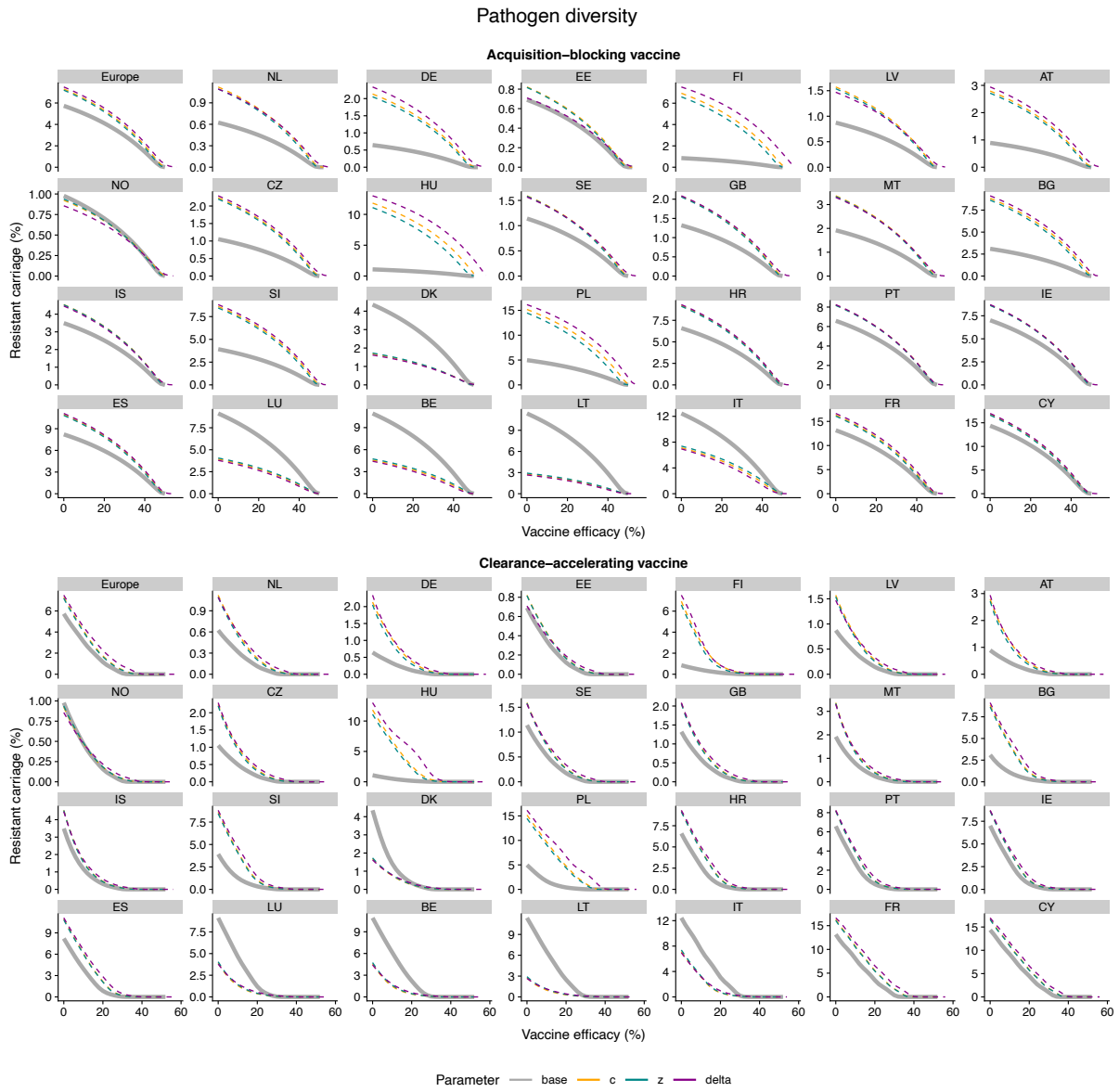


**Fig. S10. Vaccine impact for the "Pathogen diversity" model, varying parameters *c*, δ, and *z*.** Impact of vaccination under the "Pathogen diversity" model, for those parameters able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared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

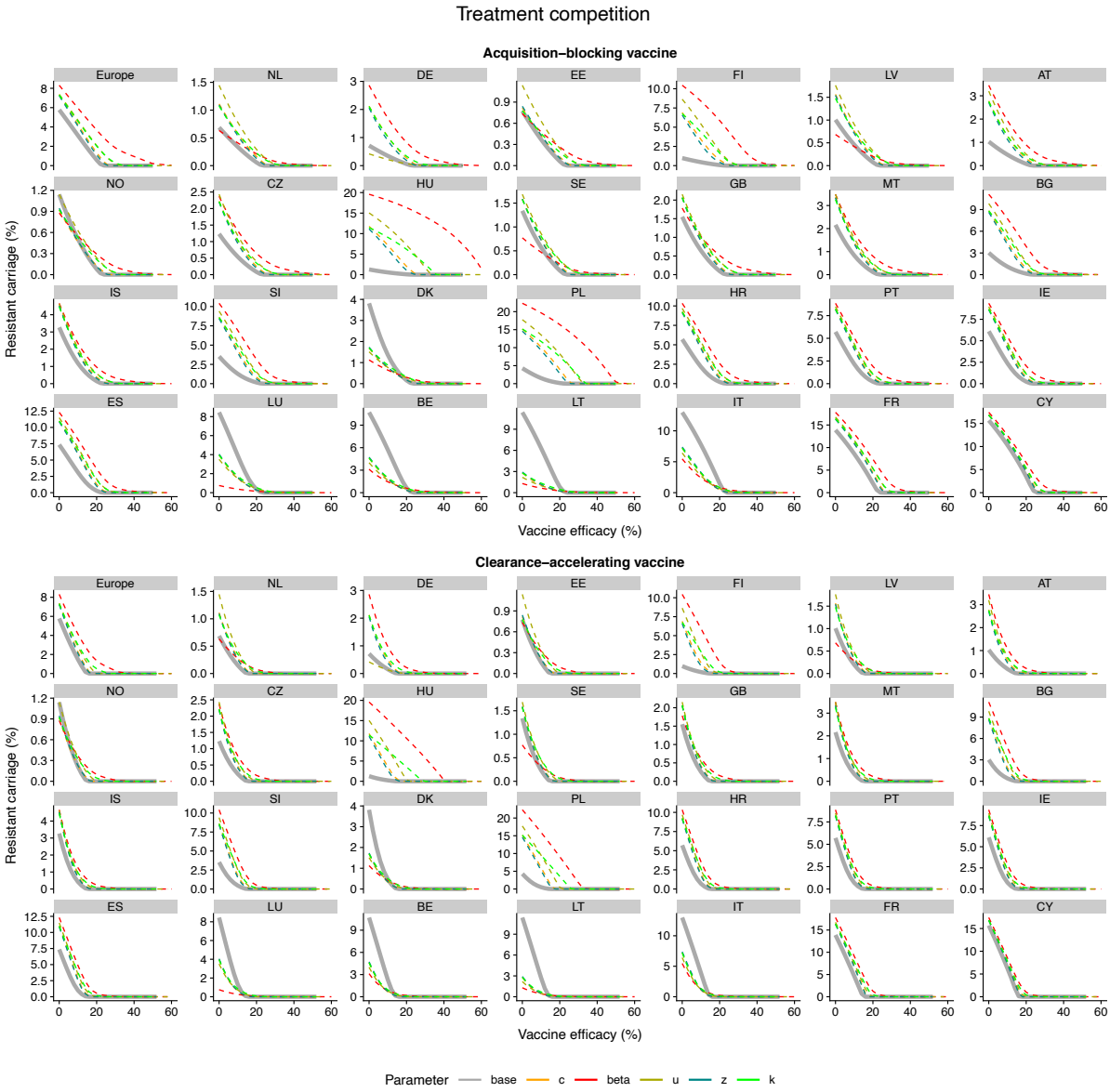


**Fig. S11. Vaccine impact for the "Treatment competition" model, varying parameters *β*, *c*, *u*, *k*, and *z*.** Impact of vaccination under the "Treatment competition" model, for those parameters able to capture the between-country variation in resistance frequency. The base model fit (thick grey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

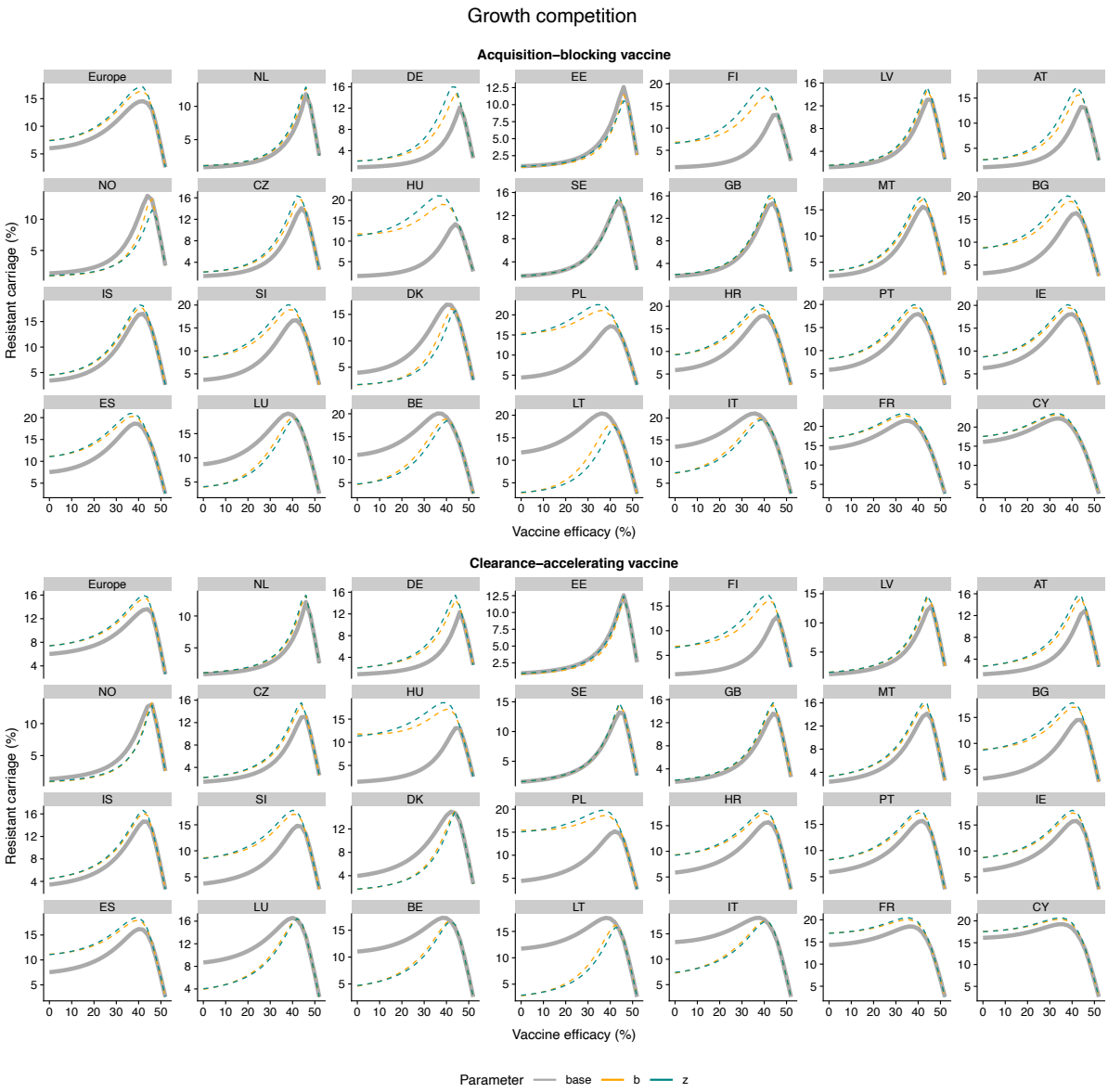


**Fig. S12. Vaccine impact for the "Growth competition" model, varying parameters *b* and *z*.** Impact of vaccination under the "Growth competition" model, for those parameters able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared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

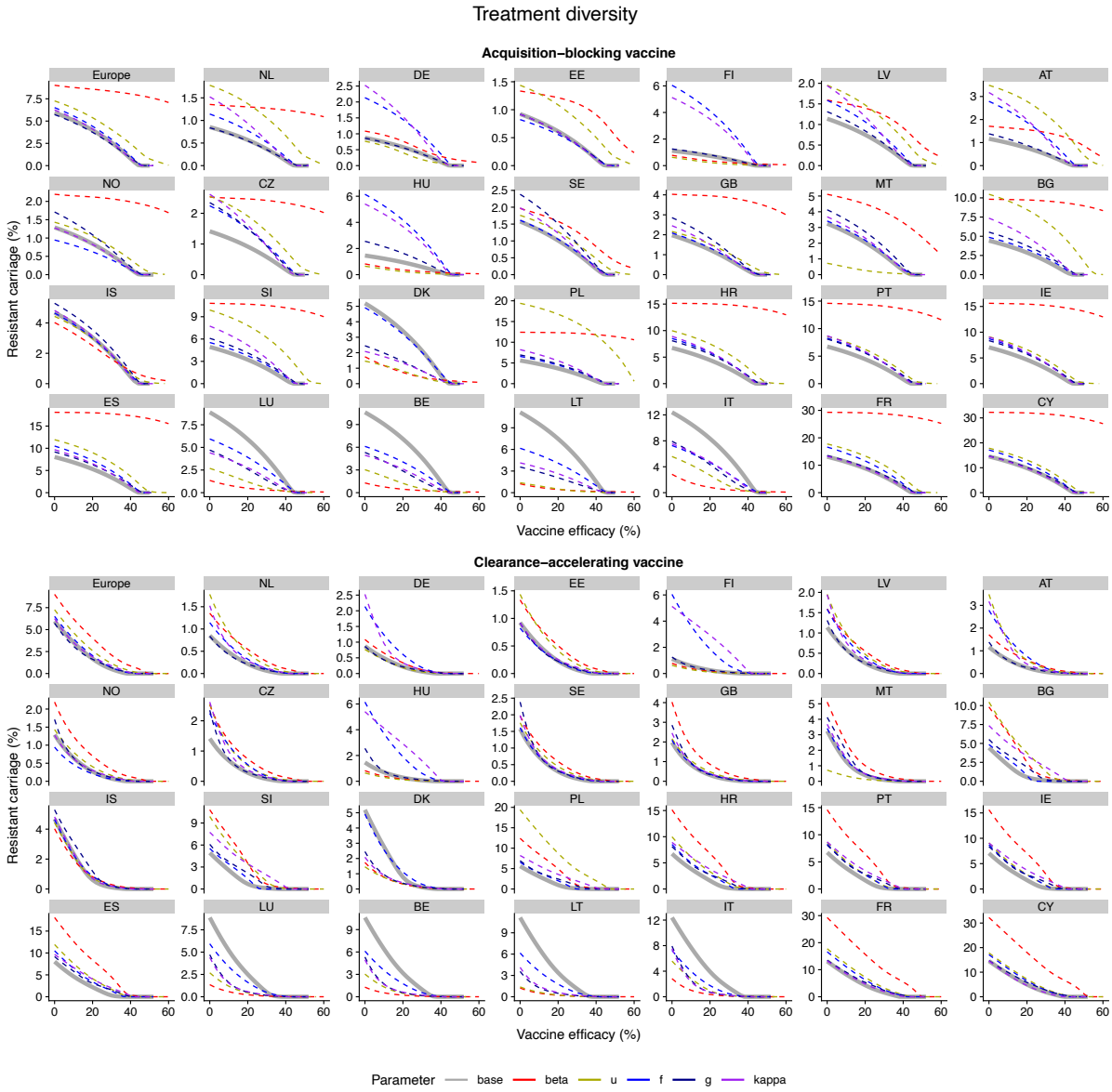


**Fig. S13. Vaccine impact for the "Treatment diversity" model, varying other parameters.** Impact of vaccination under the "Treatment diversity" model, for those parameters *not* able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared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

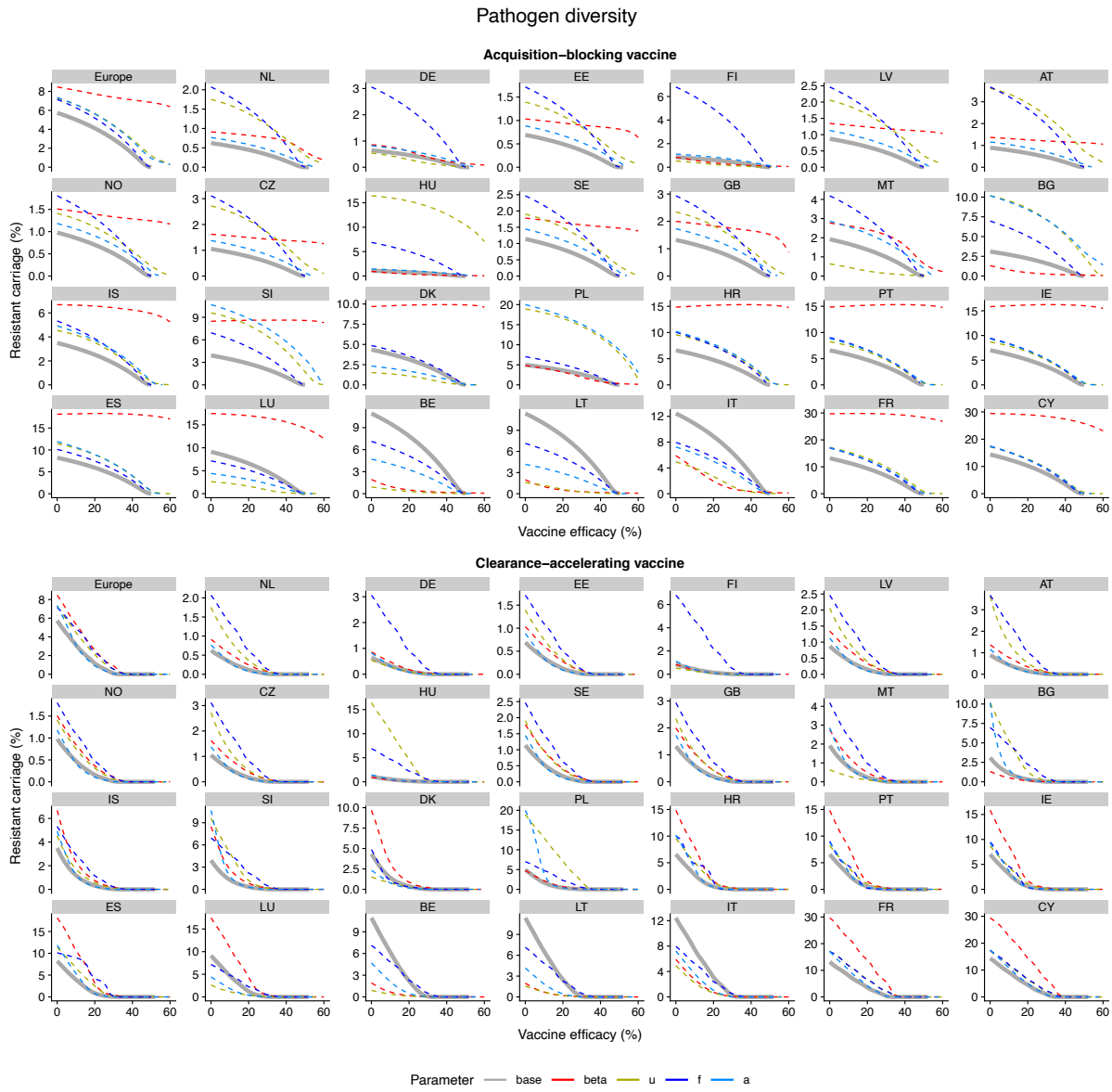


**Fig. S14. Vaccine impact for the "Pathogen diversity" model, varying other parameters.** Impact of vaccination under the "Pathogen diversity" model, for those parameters *not* able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared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

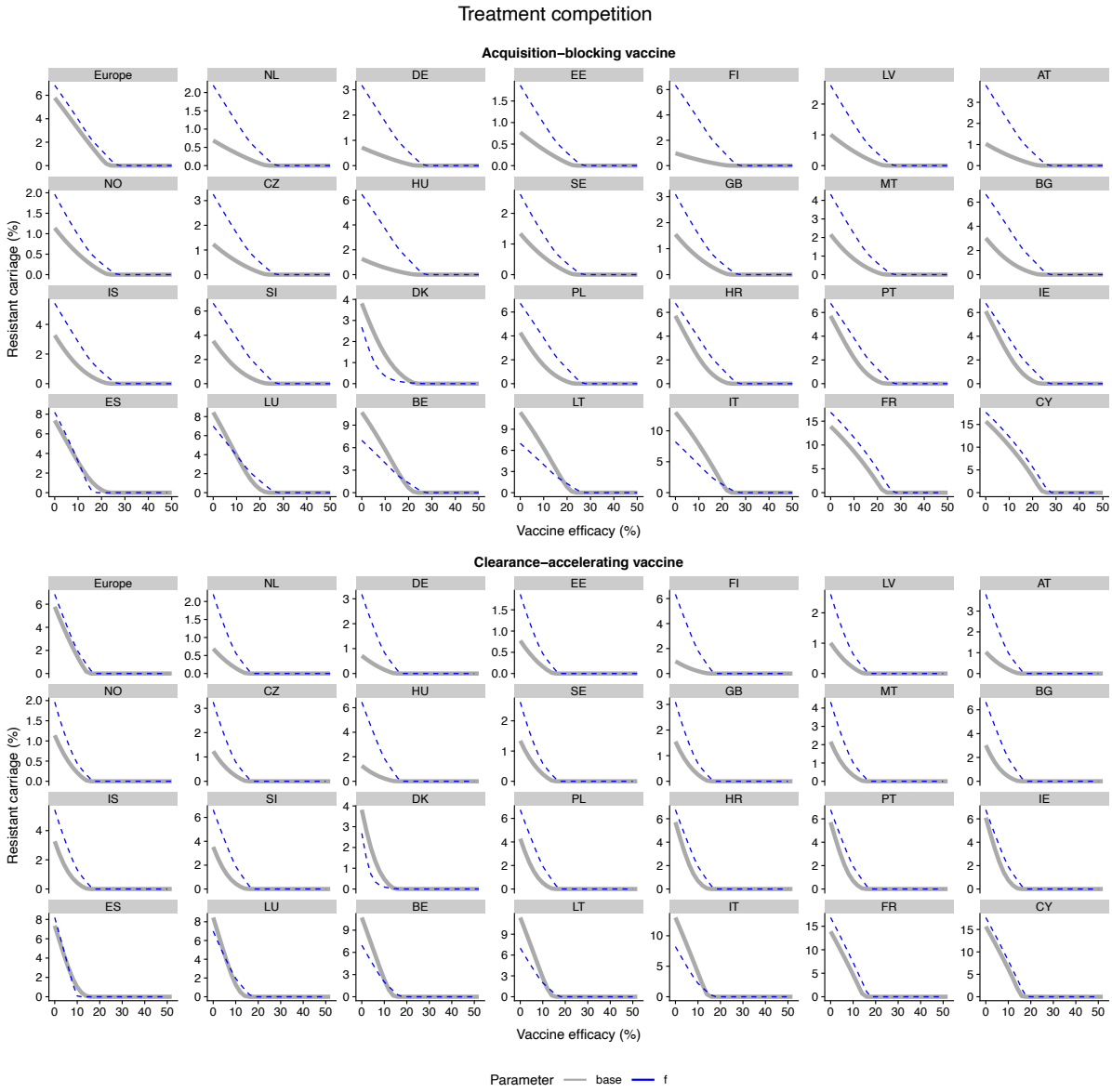


**Fig. S15. Vaccine impact for the "Treatment competition" model, varying other parameters.** Impact of vaccination under the "Treatment competition" model, for those parameters *not* able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is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

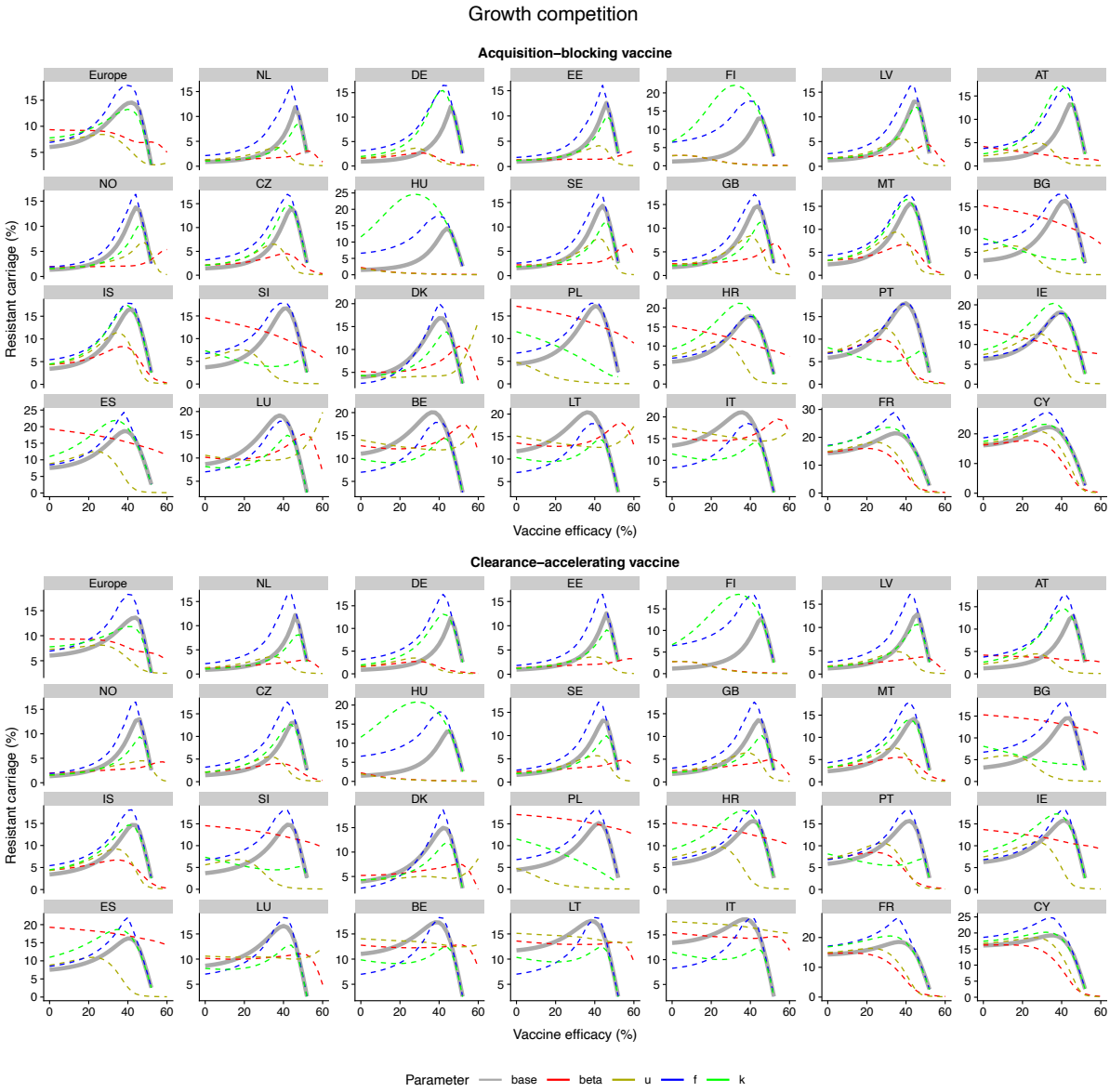


**Fig. S16. Vaccine impact for the "Growth competition" model, varying other parameters.** Impact of vaccination under the "Growth competition" model, for those parameters *not* able to capture the between-country variation in resistance frequency. The base model fit (thick grey solid line) is compared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

**Tables S1–S8**

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

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

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

*Table S3. Penicillin consumption* — Calculation of the mean number of defined daily doses of penicillin corresponding to a single treatment course for children under 5 years old in European countries.

*Table S4. Carriage duration (Europe)* — Calculation of mean pneumococcal carriage duration for children under 5 years old in European settings.

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

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

*Table S7. Priors for model fitting* — Table describing prior distributions assumed for fitted model parameters.

*Table S8. MCMC diagnostics* — Widely Applicable Information Criteria (WAIC), Leave-One-Out Information Criteria (LOOIC), effective posterior sample size and Gelman-Rubin diagnostics for Bayesian inference model fitting using Markov chain Monte Carlo.