**Within-host competition determines vaccine impact on antibiotic resistance**

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**Abstract |** Vaccines could help mitigate the burden of antibiotic-resistant infections by preventing people from contracting infections in the first place. But the long-term impact of vaccines upon antibiotic resistance is unclear, because we do not know how vaccination may itself alter selection for resistance. This lack of clarity is compounded by uncertainty over which mechanisms drive resistance evolution in bacteria. Specifically, there is disagreement over what stably maintains observed patterns of coexistence between resistant and sensitive strains over time. Using a mathematical modelling framework, we show that contemporary patterns of penicillin resistance in the commensal pathogen *Streptococcus pneumoniae* across Europe can be explained either by within-host competition, by diversifying selection for bacterial carriage duration, or by within-country heterogeneity in treatment rates. However, these alternative mechanisms vary considerably in their predictions of the impact of vaccine interventions. Specifically, we identify the testable hypothesis that the outcome of within-host competition between sensitive and resistant strains critically determines whether vaccination promotes or inhibits the evolution of resistance. These predictions vary for settings differing in carriage prevalence and treatment rates. Hence, calibration to pathogen- and country-specific data is required for evidence-based policy.

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 (PCV) has seemingly borne out these advantages. Administering PCV to young children has substantially reduced pneumococcal disease (*5–8*) and decreased demand for antibiotic therapy, largely by reducing cases of otitis media requiring treatment (*5*, *9*). But because PCV targets only a fraction of the ~100 known pneumococcal serotypes, the niche it has vacated has been filled by non-vaccine serotypes, and pneumococcal carriage has returned to pre-vaccine levels (*10*, *11*). Concomitantly, disease caused by non-vaccine serotypes (*12*) and the level of resistance among non-vaccine serotypes (*5*, *13*) have risen in many settings. Concern over serotype replacement—along with the high cost of manufacturing PCV—has spurred development of "universal" whole-cell or protein-based pneumococcal vaccines protecting against all serotypes, which are now in clinical trials (*14*).

However, it is unclear how universal vaccination may itself impact upon the evolution of antibiotic resistance in *S. pneumoniae*. While mathematical models are a useful tool for generating predictions from nonlinear transmission dynamics (*15*, *16*), existing models focus on serotype-specific vaccines and, even then, disagree over the expected impact of vaccination on resistance evolution (*17–23*). Comparing and interpreting the results of these models is hampered by the fact that none starts from a position of recapitulating contemporary, large-scale patterns of antibiotic resistance. The main challenge in replicating these patterns lies in identifying the mechanisms that maintain long-term coexistence between sensitive and resistant strains across a wide range of antibiotic treatment rates, like those seen across Europe and the United States (*24*, *25*). Robust predictions of the long-term impact of vaccination on resistant pneumococcal disease require a mechanistic understanding of these patterns.

Here, we identify eight hypotheses that have been proposed to explain coexistence between sensitive and resistant strains of pathogenic bacteria. We find that four of these hypotheses are consistent with empirical patterns of penicillin resistance in the commensal pathogen *Streptococcus pneumoniae* (pneumococcus) across 27 European countries. Then, we show that each of these four models make different predictions for the impact of vaccination upon the long-term evolution of antibiotic resistance. In particular, we show that whether vaccination promotes or inhibits resistance evolution depends upon the nature of within-host competition between sensitive and resistant strains. We demonstrate how our predictions can be applied more generally by extending our model to high-carriage settings. Our work emphasizes that an understanding of the mechanisms that govern resistance evolution is crucial for predicting the potential for using vaccines to manage antibiotic resistance.

## Results

**Four models of resistance evolution.** Using a literature search, we identify eight candidate mechanisms that have been hypothesised to maintain coexistence between sensitive and resistant bacterial strains. We find that four of these mechanisms could plausibly reproduce patterns of coexistence as seen in *S. pneumoniae* (Table 1). Accordingly, we embed these four mechanisms in the following model framework of pneumococcal transmission. Our model calculates the country-specific equilibrium frequency of resistance in pneumococci circulating among children under five years of age—the age group responsible for the majority of pneumococcal carriage (*26*). We assume that hosts mix randomly within a population, with each host making effective contact with another random host at rate $\beta$ per month, thereby potentially acquiring a carried strain (either sensitive or resistant) from the contacted host. With probability $c$, resistant strains fail to transmit, where $c$ represents the transmission cost of resistance (*27*, *28*). We model importation of strains from outside a country at a low, constant rate $\psi$, assuming that with probability $\rho$ (equal to the average resistance frequency in Europe) an imported strain is resistant. A host naturally clears all carried strains at rate $u$, and is exposed to antibiotic therapy at a country-specific rate $\tau$, which clears the host of sensitive strains only. We assume that the treatment rate is independent of carriage status (*29*). In the absence of any mechanism maintaining coexistence between sensitive and resistant cells, competitive exclusion is expected—in other words, either resistant or sensitive strains are expected to go to fixation in the population (*24*, *30*). Each of the four models builds upon this framework and invokes an alternative mechanism for maintaining coexistence.

## Table 1. Mechanisms for maintaining coexistence

| Mechanism | Mode of action | Modelled in this study? | Consistent with empirical patterns? |
|---|---|---|---|
| **Within-host competition (A: transmission cost)** | Within-host competition creates frequency-dependent selection for resistance (*24*, *25*, *31–33*) | Yes | ✓ |
| **Within-host competition (B: growth cost)** | " | Yes | ✓ |
| **Diverse subtypes** | Subtypes maintained by diversifying selection differ in propensity for resistance (*34*) | Yes | ✓ |
| **Treatment variation** | Assortatively-mixing subpopulations differ in treatment rates (*24*, *35–38*) | Yes | ✓ |
| **Treated class** | Individuals currently in treatment maintain resistant strains (*24*, *32*, *35*, *39*) | No: Only supports a small amount of coexistence (*24*) | |
| **Separate niches** | Sensitive and resistant strains exploit separate niches (*40*, *41*) | No: Resistant and sensitive strains are known to occupy the same niches (*30*) | |
| **Mutation pressure** | Mutation-selection balance maintains intermediate resistance frequency (*38*, *41*, *42*) | No: De novo acquisition of resistance in *S. pneumoniae* is not frequent enough (*24*) | |
| **Prescription feedback** | Doctors reduce prescribing of a drug as resistance to it increases (*38*, *39*) | No: Does not explain how coexistence is maintained over a range of different treatment rates | |

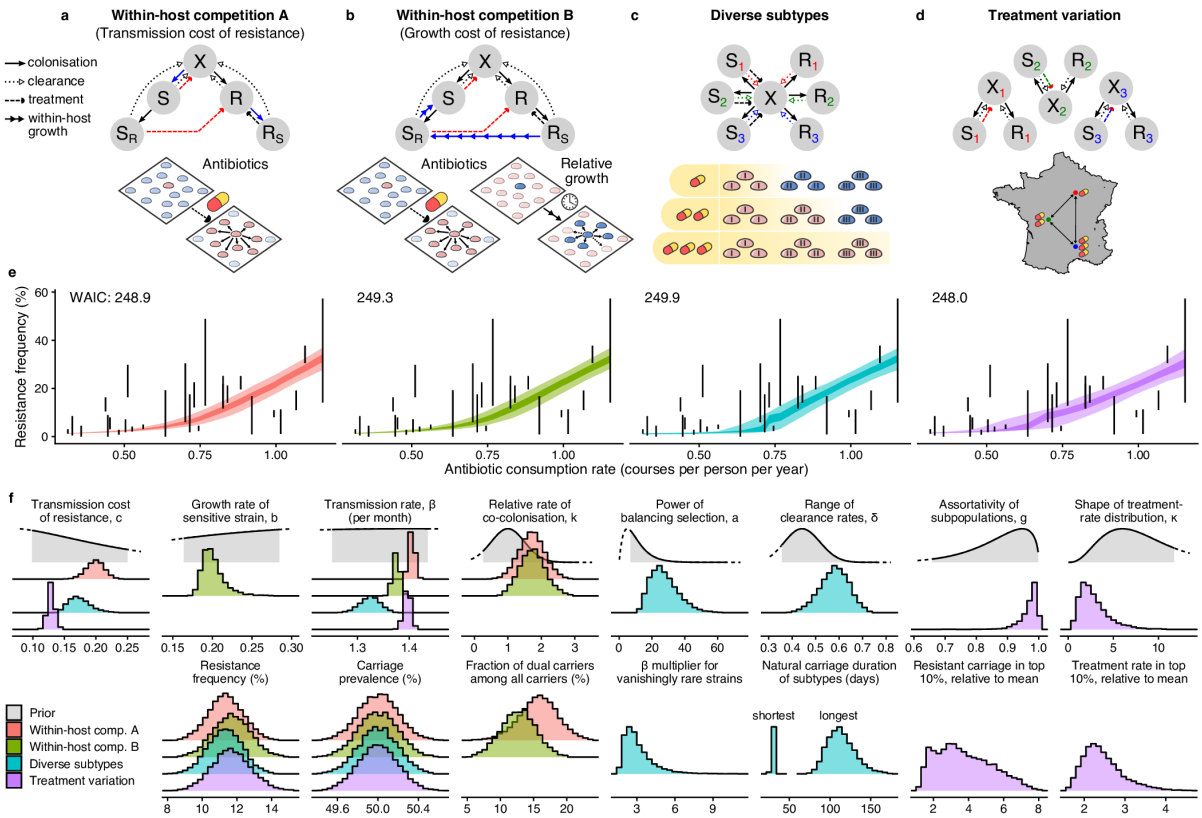


**Fig. 1. Four models of resistance evolution. (a–d)** We contrast four models, whose structures are shown here. The mechanism promoting coexistence in each model is illustrated. See Methods for model implementation details. **(e)** Model fits with associated WAIC. Vertical lines show the 95% HDIs for the reported proportion of invasive *S. pneumoniae* isolates that are resistant to penicillin plotted against the antibiotic consumption rate in under-5s. Ribbons show the 50% and 95% HDIs for resistance prevalence from each fitted model. **(f)** 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.

In the first two "Within-host competition" models (Fig. 1a&b), individuals can be colonised by both sensitive and resistant strains. Antibiotic treatment benefits resistant strains by clearing away their sensitive competitors. This benefit is more pronounced when resistant strains are rare, because when rare they tend to compete more with common sensitive strains than with other rare resistant strains. This creates frequency-dependent selection for resistance that can maintain coexistence (*25*). The "Within-host competition A" model assumes that only antibiotic therapy mediates within-host competition, while the "Within-host competition B" model assumes that sensitive strains can gradually outcompete resistant strains within the host in the absence of antibiotics, which occurs at rate $b$ (*25*). We assume that there is no transmission cost of resistance in this latter model ($c = 0$), with the within-host growth advantage $b$ of sensitive strains accounting completely for the cost of resistance. Accordingly, the two models primarily differ in how the cost of resistance is presumed to operate. The key parameter governing coexistence in these two models is $k$, the relative rate of co-colonisation compared to primary colonisation.

In the third "Diverse subtypes" model, pneumococci are divided into subtypes ("D-types") (*34*) that vary in their mean duration of natural carriage. Diversifying selection acting on the D-type locus ensures that all subtypes are maintained in circulation despite the variability in carriage duration. In turn, the variability in carriage duration causes resistance to be selected in some subtypes, but not others (Fig. 1c). What D-types correspond to is not explicitly specified by this model, but serotype variation is one candidate. For example, if host immunity promotes antigenic diversity through acquired immunity to capsular serotypes, and different 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 strains that have a prolonged duration of carriage. Long-lasting serotypes will tend to evolve resistance, while shorter-lived serotypes will tend not to—a pattern observed in *S. pneumoniae* (*34*). This model assumes that individuals already carrying pneumococcus cannot be co-colonised. The parameters governing coexistence in this model are $a$, the strength of diversifying selection on strain type, and $\delta$, the variability between subtypes in clearance rate.

Finally, in the "Treatment variation" model, heterogeneity in the consumption of antibiotics between subpopulations of hosts within a country maintains coexistence (*24*, *35*, *36*) (Fig. 1d). Subpopulations in which consumption is high tend to promote resistance, and subpopulations in which consumption is low tend to inhibit resistance. Provided that the interchange of strains between high-consumption and low-consumption groups is not too frequent, a stable, intermediate frequency of resistance can be maintained across the whole population. Again, co-colonisation is not modelled. Subpopulations within a country could correspond to geographical regions, socioeconomic strata, host age and risk classes, or a combination of these. The key parameters governing coexistence in this model are $\kappa$, which measures the variability in antibiotic consumption between subpopulations, and $g$, the relative rate at which contact between hosts is made within rather than between subpopulations, a measure of 'assortativity'. Full details of all model implementations are provided in the Methods.

**All models can reproduce observed patterns of resistance.** The European Centre for Disease Prevention and Control (ECDC) monitors antibiotic consumption and resistance evolution across European countries for 26 combinations of drug and bacterial species (*13*, *43*). 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. Overall, resistance tends to be more common in countries where more antibiotics are consumed (*44*), and the fraction of invasive isolates that are resistant is maintained at a stable, intermediate level over time (*25*). Fitting models to data from multiple countries allows one to rule out models that cannot reproduce this large-scale pattern (*25*).

We use Bayesian inference to independently fit the four models to ECDC data for community penicillin consumption and penicillin resistance in *S. pneumoniae* across 27 European countries, with an assumed 50% carriage prevalence in children under five years (*11*, *26*). We assume that countries only differ in treatment rate and reported resistance frequency, with other model parameters shared across countries. We find that each model can fit equally well to the empirical data (Fig. 1e, ΔWAIC < 2.0) and recover plausible posterior parameter distributions (Fig. 1f).

**Models differ in the predicted impact of vaccination.** Using our four fitted models, we predict the impact of two alternative vaccines that each reduce carriage prevalence by a different mode (Fig. 2). We model an "acquisition-blocking" vaccine that prevents pneumococcal acquisition with probability $\varepsilon_a$, and a "clearance-accelerating" vaccine that shortens the duration of pneumococcal carriage by a fraction $\varepsilon_c$, reflecting alternative modes of acquired immunity that might be elicited by a pneumococcal vaccine (*45*, *46*). For simplicity, we assume that all children under five are vaccinated and refer to $\varepsilon_a$ or $\varepsilon_c$ as the vaccine efficacy. To compare vaccines with antibiotic stewardship, we also evaluate the impact of reducing the rate of antibiotic therapy by a fraction $\varepsilon_s$.

We report the effect of each intervention on carriage prevalence and on resistance frequency (Fig. 2). As expected, pneumococcal carriage prevalence is decreased by both vaccines, and is moderately increased by antibiotic stewardship (Fig. 2a), with consistent effects across models.

In contrast, predictions for resistance frequency vary across both models and vaccine types (Fig. 2b). The acquisition-blocking vaccine selects strongly against resistance in the "Within-host competition A" model because by lowering transmission, it reduces co-colonisation and thus decreases within-host competition, which in this model benefits the resistant strain (Fig. 2d). Conversely, in "Within-host competition B", within-host competition typically benefits the sensitive strain, and so the vaccine strongly promotes resistance (Fig. 2d). This mirrors our previous finding that increased transmission of strains modulates resistance evolution through its impact upon within-host competition (*25*). In the "Diverse subtypes" and "Treatment variation" models, the acquisition-blocking vaccine has a relatively minor inhibiting effect upon resistance. This stems from vaccines having a relatively greater impact upon transmission in populations (whether countries or subpopulations within a country) where carriage is lower, leading to variability between populations in the interplay between transmission and importation that have a mild impact upon resistance evolution. All of these effects are also seen for the clearance-accelerating vaccine, which has an additional resistance-inhibiting effect across all models, because a shorter duration of carriage — whether natural or vaccine-induced — selects against resistance (Fig. 2d) (*34*). Antibiotic stewardship selects against resistance, as expected.

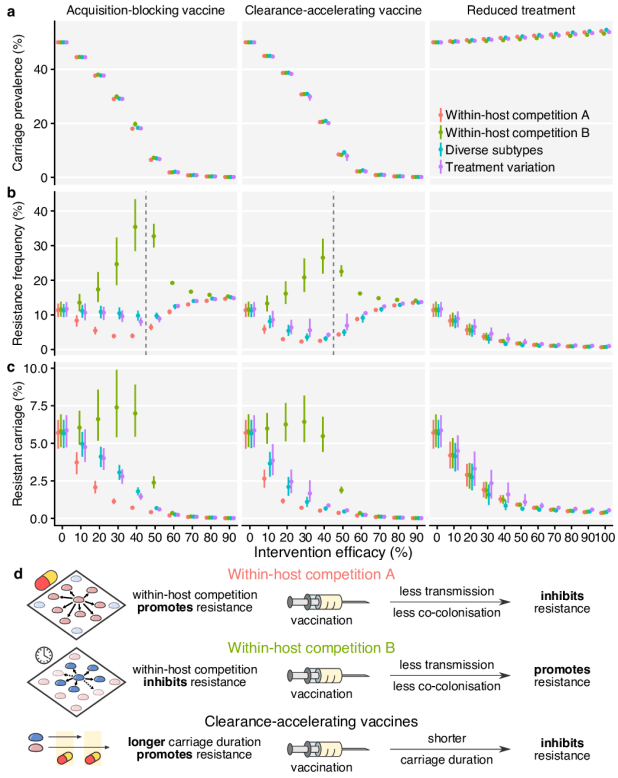


**Fig. 2. Impact of interventions.** Points give the mean, and vertical bars give the 95% HDI, for **(a)** carriage prevalence, **(b)** resistance frequency, and **(c)** resistant carriage under different interventions. Note that as vaccines reduce within-country transmission to near zero ($\varepsilon \geq 50\%$; dashed line), carriage is increasingly dominated by imported strains, which have a resistance frequency of 14%, the empirical average across Europe. **(d)** Illustration of the strongest forces selecting for greater or lesser resistance across models.

The predicted resistant carriage (Fig. 2c) is the product of carriage prevalence and resistance frequency. Note that under the "Within-host competition B" model, vaccination at intermediate efficacy is expected to marginally increase the overall rate of resistant carriage. In other models, vaccination always reduces resistant carriage, particularly under the "Within-host competition A" model.

**Implications for policy.** Reducing inappropriate antibiotic use is currently the primary means of managing resistance. Accordingly, we evaluate the average reduction in antibiotic use which is equivalent, in terms of reducing resistant carriage, to a rollout of each vaccine for increasing vaccine efficacies (Fig 3a). We find that the relative effect of reducing inappropriate antibiotic use and introducing a vaccine is considerably dependent on the underlying model. For example, the vaccine efficacy required to achieve the equivalent of a 15% reduction in antibiotic consumption—the current target for antibiotic stewardship in the UK (*48*)—is lowest in the "Within-host competition A" model ($\varepsilon_a = 11\%$; $\varepsilon_c = 7\%$) and highest under the "Within-host competition B" model ($\varepsilon_a = 47\%$; $\varepsilon_c = 45\%$). Of interest for clinical trials is the length of time that is expected for vaccine-mediated changes in resistance to occur; we find that it takes 5–10 years for the full effects of resistance evolution to be seen (Fig. 3b).

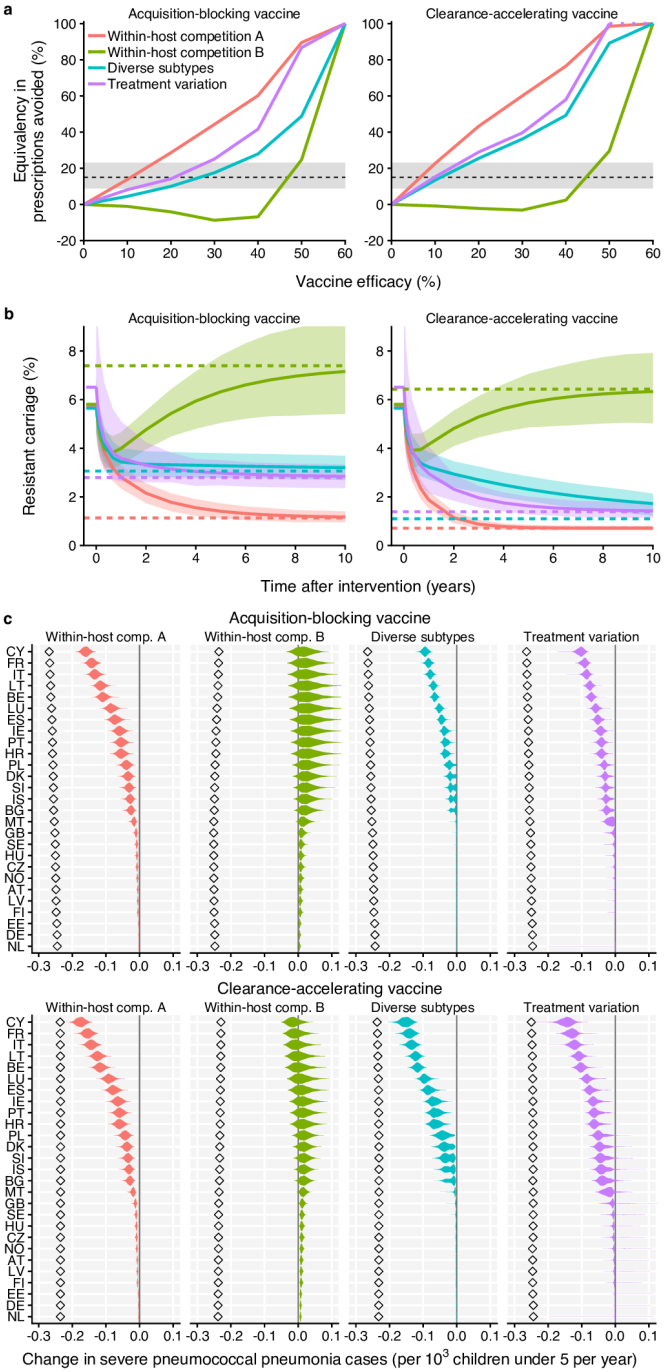


**Fig. 3. Policy implications. (a)** Median equivalent reduction in prescription rate across four models of resistance evolution, in terms of their efficacy at reducing the incidence of resistant pneumococcal carriage. This demonstrates the vaccine efficacy required to achieve a similar decrease in resistant carriage to a given reduction in antibiotic prescription rates. The impact on overall pneumococcal carriage is not considered here. The shaded bar shows an 8.8–23.1% reduction in prescriptions, an estimate of the percentage of prescriptions which are clinically inappropriate in the UK (*47*). The dashed line shows a 15% reduction in prescriptions, which has recently been announced as a target by the UK government (*48*). **(b)** The impact of vaccination is not immediate, but takes about 5–10 years, depending upon the model. Dashed lines show equilibrium resistant carriage after vaccination at 30% efficacy, while solid lines and ribbons show mean and 95% HDIs. **(c)** Per-country impact of vaccines. Countries reporting to ECDC are ordered from lowest (NL) to highest (CY) reported rate of penicillin consumption. Open diamonds show the change in all pneumococcal pneumonia cases, while filled distributions show the change in resistant cases.

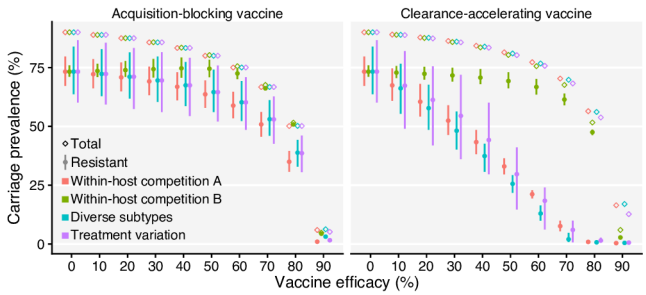


**Fig. 4. Vaccine impact in a high-burden setting.** Adjusting fitted models to be consistent with a high-burden setting yields different predictions for vaccine impact, highlighting both the increased challenges and greater opportunities for resistance management via vaccination.

We also evaluate the impact of each intervention on a national level, focusing on the concrete outcome of childhood pneumococcal pneumonia cases (Methods). While interventions have a consistent impact from country to country on the total pneumonia case rate, the impact on resistant pneumonia cases is greatest in those countries where resistance is highest (Fig. 3c).

**Vaccination in a high-burden setting.** High carriage and resistance rates are observed in some settings. For example, a 90% pneumococcal carriage rate, with 81.4% of isolates resistant to penicillin, has been observed among children under five in western Kenya (*49*). This increased carriage rate may be partly attributable to a longer average duration of carriage in this setting, consistent with a 71.4-day mean duration of natural pneumococcal carriage measured in Kilifi, eastern Kenya (*50*) (Supplementary Material). To model a similar high-burden setting, we adjust model parameters estimated from European data: decreasing the rate of natural clearance to 71.4 days$^{-1}$, increasing the transmission rate to generate a 90% carriage prevalence, increasing the treatment rate to yield a resistance frequency of 81.4%, and ignoring strain importation ($\psi = \rho = 0$), while keeping other parameters ($c$, $b$, $k$, $a$, $\delta$, $g$, and $\kappa$) the same. In relative terms, a comparatively greater vaccine efficacy is needed to reduce the rate of resistant cases, particularly under the "Within-host competition B" model (Fig. 4). However, vaccination is expected to have a comparatively greater impact in absolute terms because of a comparatively higher rate of disease in such settings: for example, Kenya is estimated to have an 8.8-fold higher rate of severe pneumococcal pneumonia than the average in Europe (*51*).

## Conclusions

We have identified four mechanisms that can explain patterns of penicillin resistance in *S. pneumoniae* across Europe. These mechanisms are not mutually exclusive, but the relative importance of each will have a substantial impact upon predictions for resistance evolution under vaccination. In particular, the "directionality" of within-host competition—that is, whether, on average, within-host competition benefits resistant or sensitive strains—has a substantial impact upon whether immunisation selects for a

decrease or an increase in antibiotic resistance in the long term. This directionality will 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 sensitive and resistant strains of *S. pneumoniae* only, competition between serotypes (*23*) and among other nasopharyngeal colonisers will also impact upon resistance evolution, and determining the importance of these other sources of within-host competition is crucial.

We have also shown that the mode of vaccine protection—whether acquisition-blocking or clearance-accelerating—is important. Whole-cell and purified-protein pneumococcal vaccines may induce antibody-mediated humoral immunity, CD4+ T helper-17 cell-mediated immunity, or both (*45*, *46*). By modelling both modes of vaccine action, we have highlighted that clearance-accelerating vaccines have special potential for preventing the spread of resistance.

Our focus has been on the impact of the four identified mechanisms *per se* upon resistance evolution. 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. We have assumed that antibiotic treatment rates among pneumococcal carriers remains constant after the introduction of a vaccine, even though treatment rates dropped in many settings following PCV introduction (*5*, *9*). However, for a universal pneumococcal vaccine that reduces antibiotic treatment rates because it reduces carriage and thereby prevents antibiotic-treatable disease, any reduction in treatment will only occur among individuals who, because of vaccine protection, are not pneumococcal carriers, all else being equal. Accordingly, it might be expected that treatment rates in carriers would remain equally high among those individuals for whom vaccine protection has failed.

A highly efficacious next-generation pneumococcal vaccine can indeed reduce the overall burden of antibiotic-resistant pneumococcal disease. However, the long-term effect of a vaccine with intermediate efficacy upon resistance is less certain, as vaccine impact depends crucially upon the mechanisms that drive 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 resistant infections.

## Methods

*Mechanisms driving resistance.* We conducted a literature search to identify mechanisms through which an intermediate frequency of resistance can be maintained across a host population. We searched PubMed using the terms: (AMR OR ABR OR ((antimicrobial OR antibiotic) AND resist*)) AND ((model OR modelling OR modeling) AND (dynamic* OR transmi* OR mathematical)) AND (coexist* OR intermediate). This yielded 93 papers (Supplementary Material). We included all papers containing a dynamic host-to-host pathogen transmission model analysing both sensitive and resistant strains with stable coexistence as an outcome of the model. From the 11 studies meeting this criterion, we identified seven unique mechanisms. Four of these we ruled out because of implausibility or because previous work shows that the mechanism does not bring about substantial coexistence, leaving four mechanisms (Table 1).

*Model framework.* We analyse the evolution of antibiotic resistance by tracking the transmission of resistant and sensitive bacterial strains among hosts in a population using 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). Model dynamics within a country are captured by

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

where $\lambda_S = \beta S + \psi(1-\rho)$ is the force of infection of the sensitive strain, $\lambda_R = \beta(1-c)R + \psi\rho$ is the force of infection of the resistant strain, $\beta$ is the transmission rate, $c$ is the transmission cost of antibiotic resistance, $u$ is the rate of natural clearance, $\tau$ is the treatment rate, $\psi$ is the rate of importation, and $\rho$ is the fraction of imported strains that are resistant. The models we compare in this paper extend this simple model.

The "within-host competition" models (*25*) 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

$$\begin{aligned} \mathrm{d}S/\mathrm{d}t &= \lambda_S X - (u + \tau)S - k\lambda_R S + b_0 b S_R \\ \mathrm{d}S_R/\mathrm{d}t &= k\lambda_R S - (u + \tau)S_R + bR_S - b_0 b S_R \\ \mathrm{d}R_S/\mathrm{d}t &= k\lambda_S R - (u + \tau)R_S - bR_S \\ \mathrm{d}R/\mathrm{d}t &= \lambda_R X - uR - k\lambda_S R + \tau(S_R + R_S) \\ X &= 1 - S - R - S_R - R_S\,, \end{aligned} \qquad (2)$$

where $\lambda_S = \beta(S + S_R) + \psi(1-\rho)$ is the force of infection of the sensitive strain, $\lambda_R = \beta(1-c)(R + R_S) + \psi\rho$ is the force of infection of the resistant strain, $k$ is the rate of co-colonisation relative to primary colonisation, $b$ is the within-host growth benefit of sensitivity, and $b_0$ is the rate of the $S_R \rightarrow S$ transition relative to the $R_S \rightarrow S_R$ transition. "Within-host competition A" assumes the cost of resistance is incurred by reduced transmission potential ($b = 0$ and $c > 0$), while "Within-host competition B" assumes that the cost of resistance is incurred through decreased within-host growth ($b > 0$ and $c = 0$).

The "Diverse subtypes" 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 (*34*). Dynamics within a country are

$$\begin{aligned} dS_d/dt &= q_d\lambda_{S,d}X - (u_d + \tau)S_d \\ dR_d/dt &= q_d\lambda_{R,d}X - u_dR_d \\ X &= 1 - \Sigma_d\,(S_d + R_d) \end{aligned} \qquad (3)$$

where $\lambda_{S,d} = \beta S_d + \psi(1-\rho)/D$ is the force of infection of the sensitive strain of D-type $d$, $\lambda_{R,d} = \beta(1-c)R_d + \psi\rho/D$ is the force of infection of the resistant strain of D-type $d$, $q_d = (1 - \frac{S_d+R_d}{\Sigma_j\,(S_j+R_j)} + \frac{1}{D})^a$ is the strength of diversifying selection for D-type $d \in \{1,2,\ldots,D\}$ and $u_d = u\left(1 + \delta\left(2\frac{d-1}{D-1} - 1\right)\right)$ is the clearance rate for D-type $d$ (*34*).

Finally, the "Treatment variation" model extends the simple model (eq. 1) by structuring the population into multiple subpopulations that exhibit different rates of antibiotic treatment and make contact with each other at unequal rates (*21*, *26*, *27*, *38*). In each country, we model $N$ representative subpopulations indexed by $i \in \{1,2,\ldots,N\}$, where we assume $N = 10$. Dynamics within a country are

$$\begin{aligned} dS_i/dt &= \lambda_{S,i}X - (u + \tau_i)S \\ dR_i/dt &= \lambda_{R,i}X - uR \\ X_i &= 1 - S_i - R_i \end{aligned} \qquad (4)$$

where $\lambda_{S,i} = \beta\,(\Sigma_j\, w_{ij}S_j) + \psi(1-\rho)$ is the force of infection of the sensitive strain in subpopulation $i$, $\lambda_{R,i} = \beta(1-c)\,(\Sigma_j\, w_{ij}S_j) + \psi\rho$ is the force of infection of the resistant strain in subpopulation $i$, and $w_{ij}$ is the "who acquires infection from whom" matrix, capturing the relative rate of contact by group-$i$ individuals to group-$j$ individuals. We assume that $w_{ij} = g + (1-g)/N$ when $i = j$, and $w_{ij} = (1 - g)/N$ when $i \neq j$, such that $g$ is the assortativity of subpopulations. Finally, 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.

*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*, *43*). We use data from 2007, because changes in pneumococcal resistance reporting standards for some countries after this year hamper the comparability of ECDC data points. We assume 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 5 DDD in the population at large correspond to one treatment course for a child under 5 years of age.

Our model framework tracks carriage of *S. pneumoniae* among children aged 0-5 years, the age group driving both transmission and disease. In European countries, we assume that the prevalence of pneumococcal carriage in under-5s is 50% (*11*, *26*) and the average duration of carriage is 47 days (*52*, *53*). We calculate the average incidence of *S. pneumoniae*-caused severe pneumonia requiring hospitalisation as 610 per million children under 5 per year (*51*) across the European countries in our data set. To match model predictions to a high-burden setting, we increase the duration of carriage to 71.4 days; increase the transmission rate by a factor of 3.61 (Within-host competition A), 3.20 (Within-host competition B), 3.62 (Diverse subtypes), or 3.49 (Treatment variation) so that carriage prevalence reaches 90.0%; and increase the antibiotic consumption rate to 1.138, 5.887, 1.458, or 1.670 courses per person per year, respectively, so that resistance prevalence reaches 81.4%. See Supplementary Material for details of calculations relating to pneumococcal carriage and disease.

We use Bayesian inference via differential evolution Markov chain Monte Carlo (*54*) to identify model parameters that are consistent with empirical data. 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.

We adopt $c \sim Beta(\alpha = 1.5, \beta = 8.5)$, $b \sim Gamma(\kappa = 2, \theta = 0.5)$, $\beta \sim Gamma(\kappa = 5, \theta = 0.35)$, $k \sim Normal(\mu = 1, \sigma = 0.5)$, $a \sim Gamma(\kappa = 2, \theta = 5)$, $\delta \sim Beta(\alpha = 20, \beta = 25)$, $g \sim Beta(\alpha = 10, \beta = 1.5)$, and $\kappa \sim Gamma(\kappa = 4, \theta = 2)$ as weakly informative prior distributions for model fitting. We set the unexplained between-country variation in resistance frequency σ to 0.06 across all models based on a preliminary round of model fitting with σ as a free parameter, and set the rate of importation ψ to 0.0075 per month based on rates of travel within the EU. See Supplementary Material for MCMC diagnostics.

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

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