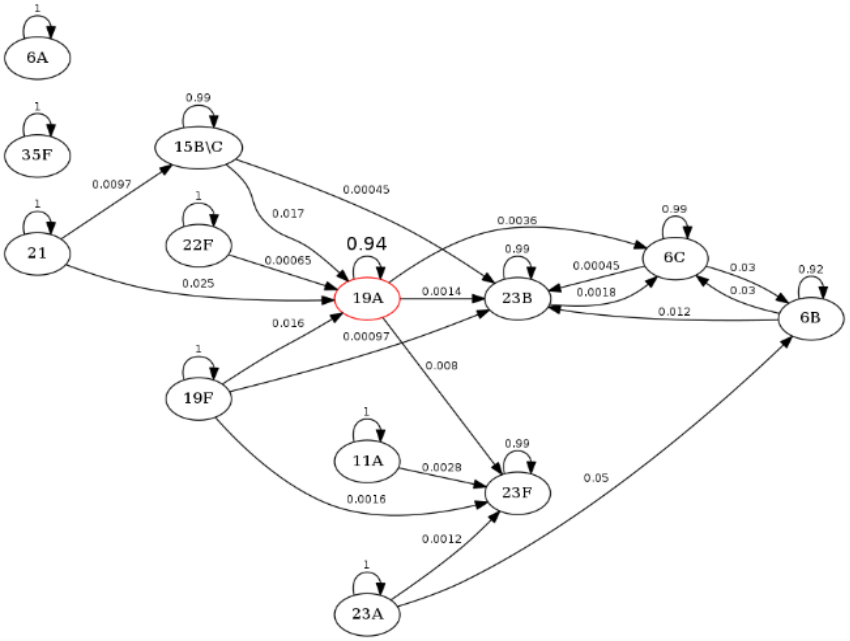
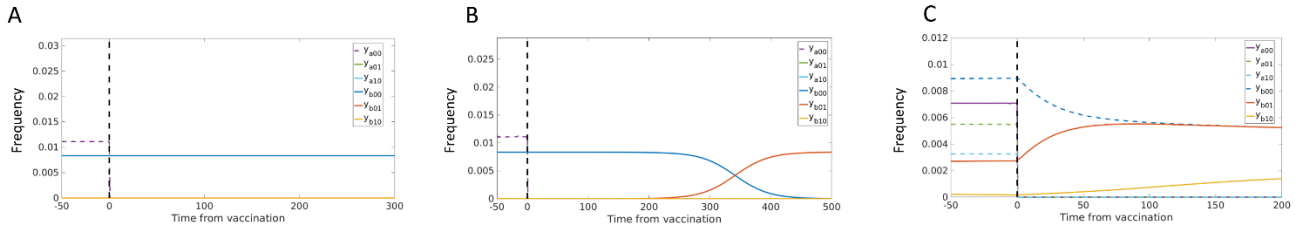
Figure S1: Admixture analysis using BAPS on antibiotic resistance-associated genes on data taken from Gladstone et al., 2015. Arrows represent statistically significant admixture events, with arrow directions defining origin and destination of admixed alleles, and numbers representing the fraction of alleles contributed from source to receiving serotype.



<u>Figure S2:</u> Time series of two-antibiotic dynamics. (A) Exclusion of resistance ($\gamma = 1, R_0^{01} = R_0^{10} = 1.98$). **(B)** Exclusion of sensitive type post-vaccination ($\gamma = 1, R_0^{01} = 2.006$). **(C)** Coexistence post-vaccination ($\gamma = 0.7, R_0^{10} = 1.996$). For all panels $\psi = 0.9$, and $R_0^a = 3, R_0^b = 2$ when not mentioned otherwise.



Supplementary Information S1

Model

We will start by writing the model presented in the main text for one bi-allelic resistance gene and one bi-allelic serotypes locus. Then we will extend it to multiple serotypes and finally to multiple serotypes and multiple resistance genes.

S1.a – Two-locus model

Each strain genotype is defined by the tuple (i, j), where i determines serotype and j the antibiotic resistance allele, respectively. Let $i \in (a, b), j \in (s, r)$. We will denote by $y_{ij}$the proportion of individuals currently infected by strain i, j; z_i and Z_{i} will be the proportion of the population previously exposed to serotype i and previously **or** currently exposed to serotype i, respectively; $Y_{i,j}$ and $V_{i,j}$ will refer to primary and secondary infections with strain i, j, respectively.

For example, the proportion of individuals infected by susceptible bacteria of serotype a is y_S; the proportion individuals previously exposed to serotype a is given by z_a.

Let z_a be the frequency of individuals who have been infected with antigenic type a, and y_{ar} contain all individuals currently infected with ar:

$$y_{as} = Y_{as} + Y_{asbs} + V_{as}$$

$$y_{ar} = Y_{ar} + Y_{arbr} + V_{ar}$$

The ODEs for the variables are given below.

Resistant a types:

$$\frac{dY_{ar}}{dt} = \lambda_{ar} Y_s - (\sigma + \lambda_{br}) Y_{ar} + Y_{as}\sigma * p$$

$$\frac{dY_{arbr}}{dt} = \lambda_{ar} Y_{br} + \lambda_{br} Y_{ar} - \sigma Y_{arbr} + Y_{asbs}\sigma * p$$

$$\frac{dV_{ar}}{dt} = \lambda_{ar} Z_b - \sigma V_{ar} + V_{as}\sigma * p$$

Where σ is the rate of infection clearance; μ is the host removal rate; p is the probability of resistance acquisition; $\lambda_{i,j}$ is the force of infection, determined by $y_{i,j}\beta_{i,j}$, and $\beta_{i,j}$is the transmission rate of strain i, j.

From the formulation above we have that

$$\frac{dy_{ar}}{dt} = \frac{dY_{ar}}{dt} + \frac{dY_{arbr}}{dt} + \frac{dV_{ar}}{dt} = \lambda_{ar} S - \lambda_{br} Y_{ar} - \sigma Y_{ar} + Y_{as}\sigma * p + \lambda_{ar} Y_{br} + \lambda_{br} Y_{ar} - \sigma Y_{arbr} + Y_{asbs}\sigma * p + \lambda_{ar} Z_b - \sigma V_{ar} + V_{as}\sigma * p =$$

$$\lambda_{ar}(S + Y_{br} + Z_b) - \sigma\left(\underbrace{Y_{ar} + Y_{arbr} + V_{ar}}_{y_{ar}}\right) + p\left(\sigma\left(\underbrace{Y_{asbs} + Y_{as} + V_{as}}_{y_{as}}\right)\right)$$

$$= \lambda_{ar}(S + Y_{br} + Z_b) - \sigma y_{ar} + p\,\sigma y_{as}$$

Using the equations from Watkins et al. we get that

$$S + Y_{br} + Z_b = 1 - z_a - Y_{bs} = 1 - z_a - y_{bs}\big(1 - (z_a - y_{ar})\big)$$

and thus

$$\frac{dy_{ar}}{dt} = \lambda_{ar}\Big(1 - z_a - y_{bs}\big(1 - (z_a - y_{ar})\big)\Big) - \sigma y_{ar} + p\,\sigma y_{as}$$

For the susceptible types we get:

$$\frac{dY_{as}}{dt} = \lambda_{as}S - (\sigma + \lambda_{bs})Y_{as}$$

$$\frac{dY_{asbs}}{dt} = \lambda_{as}Y_{bs} + \lambda_{bs}Y_{as} - \sigma Y_{asbs}$$

$$\frac{dV_{as}}{dt} = \lambda_{as}Z_b - \sigma V_{as}$$

Which yields

$$\frac{dy_{as}}{dt} = \frac{dY_{as}}{dt} + \frac{dY_{asbs}}{dt} + \frac{dV_{as}}{dt} = \lambda_{as}S - (\sigma + \lambda_{bs})Y_{as} + \lambda_{as}Y_{bs} + \lambda_{bs}Y_{as} - \sigma Y_{asbs} + \lambda_{as}Z_b - \sigma V_{as}$$

$$= \lambda_{as}\left(\underbrace{S + Y_{bs} + Z_b}_{1 - z_a - Y_{br}}\right) - \sigma\left(\underbrace{Y_{as} + Y_{asbs} + V_{as}}_{y_{as}}\right)$$

Again, using the equations from Watkins et al. we get that

$$S + Y_{bs} + Z_b = 1 - z_a - Y_{br} = 1 - z_a - y_{br}\big(1 - (z_a - y_{as})\big)$$

And thus

$$\frac{dy_{as}}{dt} = \lambda_{as}\Big(1 - z_a - y_{br}\big(1 - (z_a - y_{as})\big)\Big) - \sigma y_{as}$$

For the fraction of individuals who have been infected with a:

$$\frac{dz_a}{dt} = \lambda_{as}(1 - z_a - Y_{br}) + \lambda_{ar}(1 - z_a - Y_{bs}) - \mu z_a$$

And again using the equations from Watkins et al. we get that

$$\frac{dz_a}{dt} = \lambda_{as}\left(1 - z_a - y_{br}\left(1 - (z_a - y_{as})\right)\right) + \lambda_{ar}\left(1 - z_a - y_{bs}\left(1 - (z_a - y_{ar})\right)\right) - \mu z_a$$

We can introduce $0 \leq \gamma \leq 1$ as the serotype specific immunity, where $\gamma = 1$ indicates complete immunity from infection with serotypes an individual was previously infected with (as in the previously shown equations) and $\gamma = 0$ stands for no such immunity.

We introduce the parameter $0 \leq \psi_s \leq 1$ to represent the probability that an individual carrying a susceptible strain of pneumococci will suppress co-infection by a resistant strain, due to the fitness cost of antibiotic resistance. Analogously, represent the probability that a host carrying a resistant strain will suppress infection by any strain not resistant to the same antibiotic by $0 \leq \psi_r \leq 1$. This parameter is nullified in the main text, but remained in the analysis for the sake of generality. When we add ψ_s and ψ_r the equations take the following form:

$$\frac{dY_{as}}{dt} = \lambda_{as}S - (\sigma + \lambda_{bs} + (1 - \psi_s)\lambda_{br})Y_{as}$$

$$\frac{dY_{asbs}}{dt} = \lambda_{as}Y_{bs} + \lambda_{bs}Y_{as} - \sigma Y_{asbs}$$

$$\frac{dY_{asbr}}{dt} = \psi_r\lambda_{as}Y_{br} + (1 - \psi_s)\lambda_{br}Y_{as} - \sigma Y_{asbr}$$

$$\frac{dV_{as}}{dt} = \lambda_{as}Z_b - \sigma V_{as}$$

$$\begin{aligned}\frac{dy_{as}}{dt} = \frac{dY_{as}}{dt} + \frac{dY_{asbs}}{dt} + \frac{dV_{as}}{dt} + \frac{dY_{asbr}}{dt} \\ = \lambda_{as}S - (\sigma + \lambda_{bs} + (1 - \psi_s)\lambda_{br})Y_{as} + \lambda_{as}Y_{bs} + \lambda_{bs}Y_{as} - \sigma Y_{asbs} + \lambda_{as}Z_b - \sigma V_{as} \\ + \psi_r\lambda_{as}Y_{br} + (1 - \psi_s)\lambda_{br}Y_{as} - \sigma Y_{asbr} =\end{aligned}$$

$$\lambda_{as}\left(\underbrace{S + Y_{bs} + Z_b}_{1 - z_a - Y_{br}}\right) - \sigma\left(\underbrace{Y_{as} + Y_{asbs} + Y_{asbr} + V_{as}}_{y_{as}}\right) + (1 - \psi_r)\lambda_{as}Y_{br}$$

$$= \lambda_{as}\left(1 - z_a - \psi_r y_{br}\left(1 - (z_a - y_{as})\right)\right) - \sigma y_{as}$$

Adding the serotype specific immunity term yields:

$$\frac{dy_{ar}}{dt} = \lambda_{ar}\left(1 - y_{ar} - \gamma(z_a - y_{ar}) - \psi_s y_{bs}\left(1 - (z_a - y_{ar})\right)\right) - \sigma y_{ar} + p\sigma y_{as}$$

$$\frac{dy_{as}}{dt} = \lambda_{as}\left(1 - y_{as} - \gamma(z_a - y_{as}) - \psi_r y_{br}\left(1 - (z_a - y_{as})\right)\right) - \sigma y_{as}$$

$$\frac{dz_a}{dt} = \lambda_{as}\left(1 - y_{as} - \gamma(z_a - y_{as}) - \psi_r y_{br}\left(1 - (z_a - y_{as})\right)\right) + \lambda_{ar}\left(1 - y_{ar} - \gamma(z_a - y_{ar}) - \psi_s y_{bs}\left(1 - (z_a - y_{ar})\right)\right) - \mu z_a$$

S1.b – General number of serotype alleles

For three serotype alleles we will have:

$$\frac{dY_{as}}{dt} = \lambda_{as}S - (\sigma + \lambda_{bs} + \lambda_{cs})Y_{as}$$

$$\frac{dY_{asbs}}{dt} = \lambda_{as}Y_{bs} + \lambda_{bs}Y_{as} - \sigma Y_{asbs}$$

$$\frac{dY_{ascs}}{dt} = \lambda_{as}Y_{cs} + \lambda_{cs}Y_{as} - \sigma Y_{ascs}$$

$$\frac{dV_{as}^{b}}{dt} = \lambda_{as}Z_b - \sigma V_{as}^{b}$$

$$\frac{dV_{as}^{c}}{dt} = \lambda_{as}Z_c - \sigma V_{as}^{c}$$

$$\frac{dV_{as}^{bc}}{dt} = \lambda_{as}Z_{bc} - \sigma V_{as}^{bc}$$

$$\frac{dy_{as}}{dt} = \frac{dY_{as}}{dt} + \frac{dY_{asbs}}{dt} + \frac{dY_{ascs}}{dt} + \frac{dV_{as}^{b}}{dt} + \frac{dV_{as}^{c}}{dt} + \frac{dV_{as}^{bc}}{dt} = \cdots$$
$$= \lambda_{as}\left(\underbrace{S + Y_{bs} + Y_{cs} + Z_b + Z_c + Z_{bc}}_{1 - z_a - Y_{br} - Y_{cr}}\right)$$
$$- \sigma_s\left(\underbrace{Y_{as} + Y_{asbs} + Y_{ascs} + V_{as}^{b} + V_{as}^{c} + V_{as}^{bc}}_{y_{as}}\right)$$

Now extending the equations from Watkins et al., we will use the approximation

$$1 - z_a - Y_{bs} - Y_{cs} \approx 1 - z_a - y_{br}\left(1 - (z_a - y_{as})\right)(1 - (z_c - y_{cs})\,) - y_{cr}\left(1 - (z_a - y_{as})\right)\left(1 - (z_b - y_{bs})\right)$$

$$\frac{dy_{as}}{dt} = \lambda_{as}\big(1 - z_a - y_{br}\left(1 - (z_a - y_{as})\right)(1 - (z_c - y_{cs})\,) - y_{cr}\left(1 - (z_a - y_{as})\right)\left(1 - (z_b - y_{bs})\right)\,\big) - \sigma y_{as}$$

If we want to add γ and ψ we will have

$$\frac{dy_{as}}{dt} = \lambda_{as}\big(1 - y_{as} - \gamma(z_a - y_{as}) - \psi_r y_{br}\left(1 - (z_a - y_{as})\right)(1 - (z_c - y_{cs})\,) - \psi_r y_{cr}\left(1 - (z_a - y_{as})\right)\left(1 - (z_b - \mathrm{y}_{bs})\right)\,\big) - \sigma y_{as}$$

And eventually for any number of alleles:

$$\frac{dy_{is}}{dt} = \lambda_{is}\left(1 - y_{is} - \gamma\psi(z_i - y_{is}) - \psi_r \sum_{j\neq i} y_{jr}\left(\prod_{k\neq j}(1 - (z_k - y_{ks}))\right)\right) - \sigma y_{is}$$

S1.b – General number of resistance loci

Let us assume that there are $\mathcal{N}$ binary resistance loci and hence $2^{\mathcal{N}}$ resistance profiles. We can denote $y_{aj}, 0 \leq j \leq 2^{\mathcal{N}}$, as each of the resistance types, where j is the resistance types' index. We assume that any resistance type can be switched to any other resistance type and weigh the probability of this transition as we will.

For two resistance loci we observe equations for the double-resistant type

$$\frac{dY_{arr}}{dt} = \lambda_{arr}S - (\sigma + \lambda_{brr})Y_{arr} + Y_{ass}\sigma p + Y_{ars}\sigma p + Y_{asr}\sigma p$$

$$\frac{dY_{arrbrr}}{dt} = \lambda_{arr}Y_{brr} + \lambda_{brr}Y_{arr} - \sigma Y_{arbr} + (Y_{assbss}\sigma p + Y_{arsbrs}\sigma p + Y_{asrbsr}\sigma p)$$

$$\frac{dV_{arr}}{dt} = \lambda_{arr}Z_b - \sigma V_{arr} + (V_{ass}\sigma p + V_{ars}\sigma p + V_{asr}\sigma p)$$

$$\frac{dy_{arr}}{dt} = \frac{dY_{arr}}{dt} + \frac{dY_{arrbrr}}{dt} + \frac{dV_{arr}}{dt}$$

The only difference for the resistant types when multiple loci are considered is the resistance acquisition term:

$$\sigma p\left(\underbrace{Y_{ass} + Y_{ars} + Y_{asr} + Y_{assbss} + Y_{arsbrs} + Y_{asrbsr} + V_{ass} + V_{ars} + V_{asr}}_{y_{a\cdot} - y_{arr}}\right)$$

Where we denote $y_{a\cdot}$ as the sum of resistance types with serotype a.

Now, we can weigh the probability of transitioning to any resistance type (including retaining the same type) while keeping the sum of resistance acquisition in the system constant.

Proof:

Assume we assign probabilities of resistance acquisition from type j to all types q such that $\sum_{0\leq q\leq 2^{\mathcal{N}}} \omega_j^q = 1$. The sum of resistance acquisition terms for all i serotypes is

$$\sum_{0\le j\le 2^{\mathcal{N}}} p\sigma\left(\sum_{0\le q\ne j\le 2^{\mathcal{N}}} y_{iq}\,\omega_q^j\right) = p\sigma\left(\sum_{0\le j\le 2^{\mathcal{N}}}\left(\sum_{0\le q\ne j\le 2^{\mathcal{N}}} y_{ij}\,\omega_j^q\right)\right)$$

$$= p\sigma\left(\sum_{0\le j\le 2^{\mathcal{N}}} y_{ij}\left(\sum_{0\le q\ne j\le 2^{\mathcal{N}}} \omega_j^q\right)\right) = p\sigma\left(\sum_{0\le j\le 2^{\mathcal{N}}} y_{ij}\right)$$

Therefore, weighing the probability of acquiring different resistance profiles does not change the overall resistance acquisition rate. Note that we can also set $\sum_{0\le q\le 2^{\mathcal{N}}}\omega_k^q = 0$ for any k (e.g. for an all-resistant strain), and then the equations still remain correct if we remove the contribution of strain k the initial summation.

Finally, the general form of multiple serotypes and multiple binary resistance loci will be:

$$\frac{dy_{ij}}{dt} = \lambda_{ij}\left(1 - y_{ij} - \gamma\psi(z_i - y_{ij}) - \psi_r\sum_{l\ne i}\sum_{k\ne j} y_{lk}\left(\frac{\psi_s}{\psi_r}\right)^{I_{k=s}}\prod_{h\ne l}\left(1-(z_h - \sum_{m\ne k} y_{hm})\right)\right) - \sigma_j y_{ij}$$

$$+ p_j\sigma_j\left(\sum_{\forall q\ne j} y_{iq}\,\omega_q^j\right)$$

$$\frac{dz_i}{dt} = \sum_{\forall q}\lambda_{iq}\left(1 - y_{iq} - \gamma\psi(z_i - y_{iq}) - \psi_r\sum_{l\ne i}\sum_{k\ne q} y_{lk}\left(\frac{\psi_s}{\psi_r}\right)^{I_{k=s}}\prod_{h\ne l}\left(1-(z_h - \sum_{m\ne k} y_{hm})\right)\right) - \mu z_i$$

Where $I_{k=s}$ is the indicator function defined by

$$I_{k=s}\begin{cases}1 & if\ resistance\ profile\ k\ is\ the\ completely\ susceptile\ type\\ 0 & else\end{cases}$$

and the term $\left(\frac{\psi_s}{\psi_r}\right)^{I_{k=s}}$ determines whether we will change the current multiplication by the incompatibility factor ψ_r to ψ_s.

References

Gladstone, R.A., et al., Five winters of pneumococcal serotype replacement in UK carriage following PCV introduction. Vaccine, 2015. 33(17).

Watkins, E.R., et al., Vaccination Drives Changes in Metabolic and Virulence Profiles of Streptococcus pneumoniae. PLoS Pathogens, 2015. 11(7)

Supplementary Information S2

We analyse the scenario of a two serotypes and one antibiotic resistance locus. For convenience, resistant strains are marked by r, while susceptible strains are marked by s.

For the simple case of two bi-allelic loci we can obtain the equilibrium values by solving the following system of differential equations when all derivatives are constrained to zero:

(E.s1)

$$\frac{dy_{ar}}{dt} = \lambda_{ar}\left(1 - y_{ar} - \gamma(z_a - y_{ar}) - \psi_s y_{bs}\left(1 - (z_a - y_{ar})\right)\right) - \sigma y_{ar}$$

$$\frac{dy_{as}}{dt} = \lambda_{as}\left(1 - y_{as} - \gamma(z_a - y_{as}) - \psi_r y_{br}\left(1 - (z_a - y_{as})\right)\right) - \sigma y_{as}$$

$$\frac{dy_{br}}{dt} = \lambda_{br}\left(1 - y_{br} - \gamma(z_b - y_{br}) - \psi_s y_{as}\left(1 - (z_b - y_{br})\right)\right) - \sigma y_{br}$$

$$\frac{dy_{bs}}{dt} = \lambda_{bs}\left(1 - y_{bs} - \gamma(z_b - y_{bs}) - \psi_r y_{ar}\left(1 - (z_b - y_{bs})\right)\right) - \sigma y_{bs}$$

$$\frac{dz_a}{dt} = \lambda_{as}\left(1 - y_{as} - \gamma(z_a - y_{as}) - \psi_r y_{br}\left(1 - (z_a - y_{as})\right)\right) + \lambda_{ar}\left(1 - y_{ar} - \gamma(z_a - y_{ar}) - \psi_s y_{bs}\left(1 - (z_a - y_{ar})\right)\right) - \mu z_a$$

$$\frac{dz_b}{dt} = \lambda_{bs}\left(1 - y_{bs} - \gamma(z_b - y_{bs}) - \psi_r y_{ar}\left(1 - (\mathrm{z}_b - y_{bs})\right)\right) + \lambda_{br}\left(1 - y_{br} - \gamma(z_b - y_{br}) - \psi_s y_{as}\left(1 - (z_b - y_{br})\right)\right) - \mu z_b$$

Let us define $\alpha_{ij} \coloneqq \left(1 - y_{ij} - \gamma(z_i - y_{kl}) - \psi_r y_{kl}\left(1 - \left(z_i - y_{ij}\right)\right)\right), i \neq k, j \neq l.$

At equilibrium $\sigma y_{ij} = \lambda_{ij}(\alpha_{ij})$ and also $\mu z_i = \lambda_{is}(\alpha_{is}) + \lambda_{ir}(\alpha_{ir})$.

Therefore

$$\textbf{(E.s2)}\ \boldsymbol{z_i = \frac{\sigma}{\mu}(y_{ir} + y_{is})}$$

Assumption (I): for simplicity, we take $\psi_r = 0$.

Also, we define $\frac{\beta_{is}}{\sigma} = R_0^s$ and $\frac{\beta_{ir}}{\sigma} = R_0^r$.

S2.a – Post-vaccination dynamics

Under this scenario $y_{as} = \mathrm{y}_{ar} \approx 0$, so the values of ψ are irrelevant.

Therefore (relying on assumption (I)) we are reduced to two linear equations when finding the equilibrium values:

(E.s3)

$$\beta_{br} y_{br}\left(1 - y_{br} - \gamma(z_b - y_{br})\right) - \sigma y_{br} = 0$$

$$\beta_{bs} y_{bs}\left(1 - y_{bs} - \gamma(z_b - y_{bs})\right) - \sigma y_{bs} = 0$$

If $\gamma = 1$ (E.s3) reduces to

$$y_{br}(1 - z_b) = \frac{1}{R_0} y_{br}$$

$$y_{bs}(1 - z_b) = \frac{1}{R_0^r} y_{bs}$$

And either $y_{br} = y_{bs}$ for $R_0^s = R_0^r$ or one of the two strains competitively excludes the other.

Furthermore, since no interaction occurs between the strains, the strain with the higher reproductive number will be dominant.

In the case where $y_{br} \neq 0$, $y_{bs} \neq 0$ and $\gamma \neq 1$, we have

(E.s4)

$$\left(1 - y_{br} - \gamma(z_b - y_{br})\right) = \frac{\sigma}{\beta_{br}}$$

$$\left(1 - y_{bs} - \gamma(z_b - y_{bs})\right) = \frac{\sigma}{\beta_{bs}}$$

Summing (E.s4) yields

$2 - (y_{bs} + y_{br})(1 - \gamma) + \gamma z_b = \frac{1}{R_0^s} + \frac{1}{R_0^r}$ and therefore (using (E.s2))

(E.s5) $$z_b = \frac{\left(1 - \frac{1}{2}\left(\frac{1}{R_0^s} + \frac{1}{R_0^r}\right)\right)}{\frac{\mu}{2\sigma}(1-\gamma) + \gamma}$$

We observe that (E.s5) can help us derive a lower bound on γ values, as we have to keep $z_b < 1$. Assuming that $R_0^r \geq R_0$ and that $\frac{\mu}{2\sigma} \ll \gamma$ we get that

(E.s6) $$\gamma > \left(1 - \frac{1}{R_0^r}\right)$$

We can also subtract equation (E.s4) to get

$$1 - y_{br} - \gamma(z_b - y_{br}) - 1 + y_{bs} + \gamma(z_b - y_{bs}) = \frac{1}{R_0^r} - \frac{1}{R_0^s}$$

$$-\gamma(y_{bs} - y_{br}) + y_{bs} - y_{br} = \frac{1}{R_0^r} - \frac{1}{R_0^s}$$

$$(1 - \gamma)(y_{bs} - y_{br}) = \frac{1}{R_0^r} - \frac{1}{R_0^s}$$

$$y_{bs} - y_{br} = \frac{1}{1 - \gamma}\left(\frac{1}{R_0^r} - \frac{1}{R_0^s}\right)$$

Therefore, **if a polymorphic equilibrium exists**, it will satisfy $y_{bs} > y_{br} \Leftrightarrow R_0^s > R_0^r$ and the discrepancy between the strain frequencies increases with γ (note the similarity of the result to results obtained in Gupta et al. 1994). We can see that high values of γ relative to $\frac{1}{R_0^r} - \frac{1}{R_0^s}$ preclude a polymorphic equilibrium, and specifically $\gamma = 1$ is precluded, as explained above. Finally, if $R_0^r = R_0^S$ we get that any equilibrium value is possible, and the system is therefore only neutrally stable for any equilibrium values, which have to satisfy $\frac{\sigma}{\mu}(y_{ir} + y_{is}) = \frac{\mu}{\sigma}\left(1 - \frac{1}{R_0^s}\right)$.

S2.b – Pre-vaccination dynamics

Assumption (I): we will assume $\beta_{as} = \beta_{bs}$ and $\beta_{ar} = \beta_{br}$ (so we can vary the transmission of resistant relative to susceptible strains, but keep the transmission between serotypes constant for simplicity). This yields that pre-vaccination, we have that $y_{ir} = y_{jr}, y_{is} = y_{js}$.

Now we again examine the equilibrium equations. For ar we have

$$y_{ar} + \gamma(z_a - y_{ar}) + \psi y_{bs}\big(1 - (z_a - y_{ar})\big) = 1 - \frac{1}{R_0^r}$$

Using assumption (I) we can replace the b types with a types and get

$$y_{ar} + \gamma(z_a - y_{ar}) + \psi y_{as}\big(1 - (z_a - y_{ar})\big) = 1 - \frac{1}{R_0^r}$$

For as we have

$$y_{as} + \gamma(z_a - y_{as}) = 1 - \frac{1}{R_0^s}$$

Subtracting the two equations yields

$$(y_{as} - y_{ar})(1 - \gamma) - \psi y_{as}\big(1 - (z_a - y_{ar})\big) = \frac{1}{R_0^r} - \frac{1}{R_0^s}$$

When $\gamma < 1$ we have that

$$y_{as} - y_{ar} = \frac{1}{1 - \gamma}\left(\left(\frac{1}{R_0^r} - \frac{1}{R_0^s}\right) + \psi y_{as}\big(1 - (z_a - y_{ar})\big)\right)$$

So the factors determining the sign of $y_{as} - y_{ar}$ are

$$\left(\frac{1}{R_0^r} - \frac{1}{R_0^s}\right) + \psi y_{as}\big(1 - (z_a - y_{ar})\big)$$

As expected, if $R_0^r \leq R_0$ then $y_{ar} < y_{as}$. However, if $R_0^r > R_0^s$ and $\psi > 0$ then equilibria where either one of the resistant strains has higher frequency than the other are possible. In the scenario where $\mathrm{R}_0^r > R_0$, we know that y_{ar} would be the dominating strain post-vaccine (with the difference between the strains given by $y_{as} - y_{ar} = \frac{1}{1-\gamma}\left(\frac{1}{R_0^r} - \frac{1}{R_0^s}\right)$), so let us find parameter ranges where it is being suppressed to lower frequency pre-vaccine. We can start by finding the parameter ranges where the two strains are at equal frequency:

$$y_{as} - y_{ar} = 0 \Rightarrow \frac{1}{1-\gamma}\left(\left(\frac{1}{R_0^r} - \frac{1}{R_0^s}\right) + \psi y_{as}\left(1 - (z_a - y_{ar})\right)\right) = 0$$

Using the equal frequency, we can estimate $z_a \approx \frac{1}{\gamma}\left(1 - \frac{1}{2}\left(\frac{1}{R_0^s} + \frac{1}{R_0^r}\right)\right)$and use (1) to have that $y_{ar} = y_{as} = \frac{1}{2}\frac{\mu}{\sigma\gamma}\left(1 - \frac{1}{2}\left(\frac{1}{R_0^s} + \frac{1}{R_0^r}\right)\right)$. Plugging this into our equation we get:

$$\frac{1}{1-\gamma}\left(\left(\frac{1}{R_0^r} - \frac{1}{R_0^s}\right) + \psi y_{as}\left(1 - (z_a - y_{ar})\right)\right) =$$

$$\frac{1}{1-\gamma}\left(\left(\frac{1}{R_0^r} - \frac{1}{R_0^s}\right) + \frac{\psi}{2}\frac{\mu}{\sigma\gamma}\left(1 - \frac{1}{2}\left(\frac{1}{R_0^s} + \frac{1}{\mathrm{R}_0^r}\right)\right)\left(1 - \left(\frac{1}{\gamma}\left(1 - \frac{2}{R_0^s + R_0^r}\right) - \frac{1}{2}\frac{\mu}{\sigma\gamma}\left(1 - \frac{1}{2}\left(\frac{1}{R_0^s} + \frac{1}{R_0^r}\right)\right)\right)\right)\right)$$

And comparing this to zero (with $\gamma \neq 1$) we have the conditions

$$\text{(E.s5)}\ \psi = \frac{\frac{2\gamma\sigma}{\mu}\left(\frac{1}{R_0^s} - \frac{1}{R_0^r}\right)}{\left(1 - \frac{1}{2}\left(\frac{1}{R_0^s} + \frac{1}{R_0^r}\right)\right)\left(1 - \left(\frac{1}{\gamma}\left(1 - \frac{1}{2}\left(\frac{1}{R_0^s} + \frac{1}{R_0^r}\right)\right) - \frac{1}{2}\frac{\mu}{\sigma\gamma}\left(1 - \frac{1}{2}\left(\frac{1}{R_0^s} + \frac{1}{\mathrm{R}_0^r}\right)\right)\right)\right)}$$

So if the right-hand expression is larger than ψ, then $\mathrm{y_{ar}} > \mathrm{y_{as}}$. Since the difference between reproductive numbers allowing for suppression of $\mathrm{y_r}$ pre-vaccination is not very large, and $\mu \ll \sigma\gamma$ we can approximate (E.s5) to have a more comprehensible sense of the relationship between R_0^r and ψ:

$$\text{(E.s6)}\ \psi \approx \frac{\frac{2\gamma\sigma}{\mu}\left(\frac{1}{R_0^s} - \frac{1}{R_0^r}\right)}{\left(1 - \frac{1}{R_0^s}\right)\left(1 - \left(\frac{1}{\gamma}\left(1 - \frac{1}{R_0^s}\right)\right)\right)}$$

We derive this curve is with respect to γ:

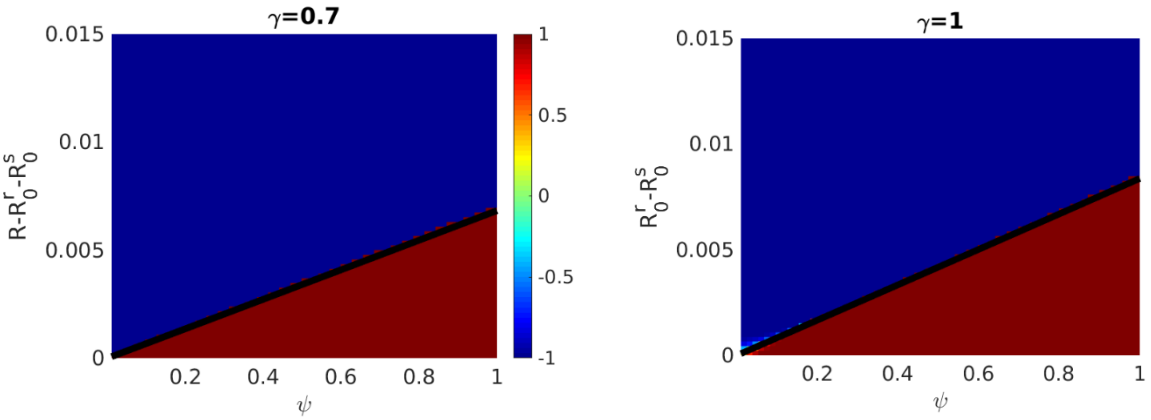
$$\frac{\partial\left(\frac{\frac{2\gamma\sigma}{\mu}\left(\frac{1}{R_0^s} - \frac{1}{R_0^r}\right)}{\left(1 - \frac{1}{R_0^s}\right)\left(1 - \left(\frac{1}{\gamma}\left(1 - \frac{1}{R_0^s}\right)\right)\right)}\right)}{\partial\gamma} = \frac{\frac{2\sigma}{\mu}\left(\frac{1}{R_0^s} - \frac{1}{R_0^r}\right)}{\left(1 - \frac{1}{R_0^s}\right)\left(1 - \left(\frac{1}{\gamma}\left(1 - \frac{1}{R_0^s}\right)\right)\right)}\gamma\frac{\left(\gamma - 2\left(1 - \frac{1}{R_0^s}\right)\right)}{\left(\gamma - \left(1 - \frac{1}{R_0^s}\right)\right)^2}$$

And the expression is always negative when $\gamma < 2\left(1 - \frac{1}{R_0^s}\right)$. For any $R_0^s \geq 2$ the derivative is always negative(as $\gamma \leq 1$) implying that higher γ values allow for increased ranges of R_0^r under which $y_{as} > y_{ar}$ pre-vaccination, because $\mathrm{y_{as}}$ supresses co-infection by $\mathrm{y_{ar}}$ and reduces its frequency. For $1 <$

$R_0^S < 2$ the derivative switches sign at $\gamma = 2\left(1 - \frac{1}{R_0^S}\right)$ and increasing γ over this threshold actually decreases the range of $\mathrm{R_0^r}$ where $y_{as} > y_{ar}$. We note that under low γ values there is little competitive exclusion, so resistance surge could occur outside this parameter range (as seen in the main text in Figure. 2).

Our solution assumes $\gamma \neq 1$, as this will completely preclude co-existence of both strains and rather create competitive exclusion. However, our solution with $\gamma = 1$ is continuous with respect to predicting the switch of $sign(y_{as} - y_{ar})$ as can be seen when comparing it to numerical simulations below.

Below we plot the parameter ranges where susceptible and resistant strain outcompete each other pre-vaccination. We plot the inhibition of co-infection by the susceptible strain (ψ) against the basic reproductive number of the resistant strain ($\mathrm{R_0^r}$), where the basic reproductive number of the susceptible strain is held at $\mathrm{R_0} = 2$. Yellow regions are the parameter range where $\mathrm{y_s} > \mathrm{y_r}$ pre vaccination, whereas blue regions mark the opposite. Red line is the approximation to the range where $y_s = y_r$, given by (E.s6). We plot two strain specific immunity values (γ). Note that throughout this parameter space the resistant strain will be the dominant one post vaccination, due to it's superior reproductive number, and completely excluding y_s when $\gamma = 1$.



References

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