WEB APPENDIX

Differential equation formulations

Super Infection Model

$$\begin{aligned}
\frac{dS}{dt} &= -\beta_w(I_w + qI_{wz})S - \beta_z(I_z + qI_{wz})S + \gamma(1-\epsilon)I_w + \gamma'\epsilon I_w + \gamma I_z \\
\frac{dI_w}{dt} &= \beta_w S(I_w + qI_{wz}) - \beta_z I_w(I_z + qI_{wz}) - \gamma(1-\epsilon)I_w - \gamma'\epsilon I_w + \gamma I_{wz} \\
\frac{dI_z}{dt} &= \beta_z S(I_z + qI_{wz}) - \beta_w I_z(I_w + qI_{wz}) - \gamma I_z + (1-\epsilon)\gamma I_{wz} + \epsilon\gamma' I_{wz} \\
\frac{dI_{wz}}{dt} &= \beta_w I_z(I_w + qI_{wz}) + \beta_z I_w(I_z + qI_{wz}) - (1-\epsilon)\gamma I_{wz} - \epsilon\gamma' I_{wz} - \gamma I_{wz}
\end{aligned}$$

Exclusive Infection Model

$$\begin{aligned}
\frac{dS}{dt} &= -\beta_w I_w S - \beta_z I_z S + \gamma(1-\epsilon)I_w + \gamma'\epsilon I_w + \gamma I_z \\
\frac{dIw}{dt} &= \beta_w S I_w - \gamma(1-\epsilon)I_w - \gamma'\epsilon I_w \\
\frac{dIz}{dt} &= \beta_z S I_z - \gamma I_z
\end{aligned}$$

The R_0 of this model is the larger of either: $\frac{\beta_w}{\gamma(1-\epsilon)+\gamma'\epsilon}$ or $\frac{\beta_z}{\gamma}$

Replacement Infection Model

$$\begin{aligned}
\frac{dS}{dt} &= -\beta_w I_w S - \beta_z I_z S + \gamma(1-\epsilon)I_w + \gamma'\epsilon I_w + \gamma I_z \\
\frac{dIw}{dt} &= \beta_w S I_w - \gamma(1-\epsilon)I_w - \gamma'\epsilon I_w + (\beta_w - \beta_z)I_w I_z \\
\frac{dIz}{dt} &= \beta_z S I_z - \gamma I_z + (\beta_z - \beta_w)I_w I_z
\end{aligned}$$

Note, when $\beta_w > \beta_z$, the sensitive strain may replace the resistant one. When $\beta_z > \beta_w$, the resistant strain may replace the sensitive strain. Regardless of

which, the above equations hold.

The R_0 of this model is either: $\frac{\beta_w}{\gamma(1-\epsilon)+\gamma'\epsilon}$ or $\frac{\beta_z}{\gamma}$. While the values of these R_0's are identical to those of the exclusive infection model,here the larger R_0 does not always win. When the R_0's are fairly close to one another, it is possible for the strain with the lower R_0 to outcompete the other, assuming it has a higher transmission rate (β); this result is the effect of the replacement infection. The replacement infection mechanism does not effectively tips the scales slightly towards one strain or the other in this manner.

Unidirectional Conversion Model

$$\begin{aligned}
\frac{dS}{dt} &= -\beta_w I_w S - \beta_z I_z S + \gamma(1-\epsilon)I_w + \gamma'\epsilon I_w + \gamma I_z \\
\frac{dIw}{dt} &= \beta_w S I_w - \gamma(1-\epsilon)I_w - \gamma'\epsilon I_w - \rho\epsilon I_w \\
\frac{dIz}{dt} &= \beta_z S I_z - \gamma I_z + \rho\epsilon I_w
\end{aligned}$$

Note, this model shows unidirectional conversion from sensitive to resistant. Another possibility for this model is for there to be resistant to sensitive conversion. Those equations are not shown.

The system-R_0 for this model is the larger of either $\frac{\beta_z}{\gamma}$ and $\frac{\beta_w}{\gamma(1-\epsilon)+\epsilon\gamma'+\epsilon\rho}$.

Bidirectional Conversion Model

$$\begin{aligned}
\frac{dS}{dt} &= -\beta_w I_w S - \beta_z I_z S + \gamma(1-\epsilon)I_w + \gamma'\epsilon I_w + \gamma I_z \\
\frac{dIw}{dt} &= \beta_w S I_w - \gamma(1-\epsilon)I_w - \gamma'\epsilon I_w - \rho\epsilon I_w + \phi(1-\epsilon)I_z \\
\frac{dIz}{dt} &= \beta_z S I_z - \gamma I_z + \rho\epsilon I_w - \phi(1-\epsilon)I_z
\end{aligned}$$

The system-R_0 for this model is the larger of either :

$$2\beta_w\beta_z/(\beta_w\gamma + \beta_z\gamma - \beta_z\epsilon\gamma + \beta_z\epsilon\gamma' + \beta_w\phi - \beta_w\epsilon\phi + \beta_z\epsilon\rho -$$
$$((\beta_w(\gamma + phi - \epsilon\phi) + \beta_z(\gamma - \epsilon\gamma + \epsilon(\gamma' + \rho)))^2 + 4\beta_w\beta_z((-1+\epsilon)\gamma^2 +$$
$$(-1+\epsilon)\epsilon\gamma'\phi - \gamma(\phi + \epsilon^2\phi + \epsilon(\gamma' - 2\phi + \rho))))^{\frac{1}{2}})$$

or:

$$2\beta_w\beta_z/(\beta_w\gamma + \beta_z\gamma - \beta_z\epsilon\gamma + \beta_z\epsilon\gamma' + \beta_w\phi - \beta_w\epsilon\phi + \beta_z\epsilon\rho +$$
$$((\beta_w(\gamma + phi - \epsilon\phi) + \beta_z(\gamma - \epsilon\gamma + \epsilon(\gamma' + \rho)))^2 + 4\beta_w\beta_z((-1+\epsilon)\gamma^2 +$$
$$(-1+\epsilon)\epsilon\gamma'\phi - \gamma(\phi + \epsilon^2\phi + \epsilon(\gamma' - 2\phi + \rho))))^{\frac{1}{2}})$$

Detailed discussion of results

Single strain

In the single strain model there is no competition between sensitive and resistant strains at any level. The bifurcation diagram summarizes this independence (Web Figure 2A); when either strain's R_0 falls below one, it goes extinct, and whenever either strain's R_0 is greater than one, it persists; when both strains have strain specific $R_0's$ that are either greater than or less than one, they either both persist or go extinct. The R_0's of each strain are

$$R_{0W} = \frac{\beta_w}{\gamma'\epsilon + \gamma(1-\epsilon)}, R_{0Z} = \frac{\beta_z}{\gamma} \tag{1}$$

This illustrates how the resistant strain's equilibrium prevalence is unaffected by population antibiotic treatment, while the sensitive agent's equilibrium prevalence gradually decreases with greater population antibiotic treatment. Therefore, only the sensitive strain exhibits a threshold effect as a function of population antibiotic treatment (Web Figure 1A).

Super infection

Compared to the single strain model, the super infection model dampens contagiousness of super-infected hosts. The presence of a second opposing strain in a population, either by itself or jointly present as I_{WZ}, consumes susceptibles that could have otherwise been consumed by the first strain alone. In the super infection model, there are regions where each strain persists on its own, both strains coexist, and where neither strain persists (Web Figure 2B). The region where both strains coexist is smaller compared to the single strain model structure. Now a strain will not necessarily persist when its strain-specific R_0 is greater than one. Only if both strains have similar R_0s will there be coexistence in a population. For example, where antibiotic use is very low, the sensitive strain persists alone. As antibiotic use increases, there is coexistence since the R_0s are similar. Above a threshold, the sensitive R_0 falls too low, and only the resistant strain persists (Web Figure 1B).

Exclusive infection

In the exclusive infection model where there is complete cross-immunity, there is no possibility of within-host coexistence; as a result there is also no population level coexistence assuming a stable equilibrium has been reached. Therefore, there are only regions where each strain persists on its own, and where both are extinct (Web Figure 2C). For low levels of population antibiotic treatment the sensitive strain I_W is present alone based on the assumption that the sensitive strain is more fit in the absence of antibiotics. When a population antibiotic treatment threshold is exceeded, the resistant strain has a selective advantage will outcompete the sensitive strain to persist alone (Web Figure 1C). This threshold is determined by comparing the R_0's of each strain; the strain with the greater R_0 wins out. If neither strain has an R_0 above one at the given population antibiotic treatment level, neither strain will persist.

Replacement infection

The replacement infection and exclusive infection bifurcation diagrams are identical; only one strain may exist at a time in a population at equilibrium (Web Figure 2D) because within-host strain coexistence is not allowed for either. The exclusive and replacement infection model structures do differ, however, in how antibiotic use affects R_0; i.e., the equilibrium prevalences of each strain differ. Compared with the exclusive infection model, the position of the threshold that determines which strain will persist in the replacement infection model is shifted, in this case to higher population antibiotic treatment levels (Web Figures 1C and 1D). This shift occurs because of how we formulated replacement infection to operate; due to its higher transmission rate only the sensitive strain is able to replace the resistant strain. Had replacement infection occurred in the opposite direction ($\beta_z > \beta_w$), the position of the population antibiotic treatment threshold would be lower, rather than higher.

Unidirectional conversion

In the unidirectional conversion model, resistant infections arise from both resistant transmission events and strain conversion events from the sensitive to the resistant strain. In contrast to the exclusive and replacement infection models, when there is persistence of the resistant strain there is always coexistence at the population level. However, similar to the exclusive and replacement infection models, the sensitive strain may dieout, leaving only the resistant strain. This is due to the conversion being unidirectional, where sensitive strains convert to resistant. However, the resistant strain may still go extinct when either: 1) the R_0's of both strains are less than one; or 2) there is no population antibiotic treatment and the resistant strain's R_0 is less than one. The sensitive strain will dieout when its strain-R_0 is less than the resistant R_0 (Web Figure 2E). This is illustrated in Web Figure 1E where increased antibiotic use decreases

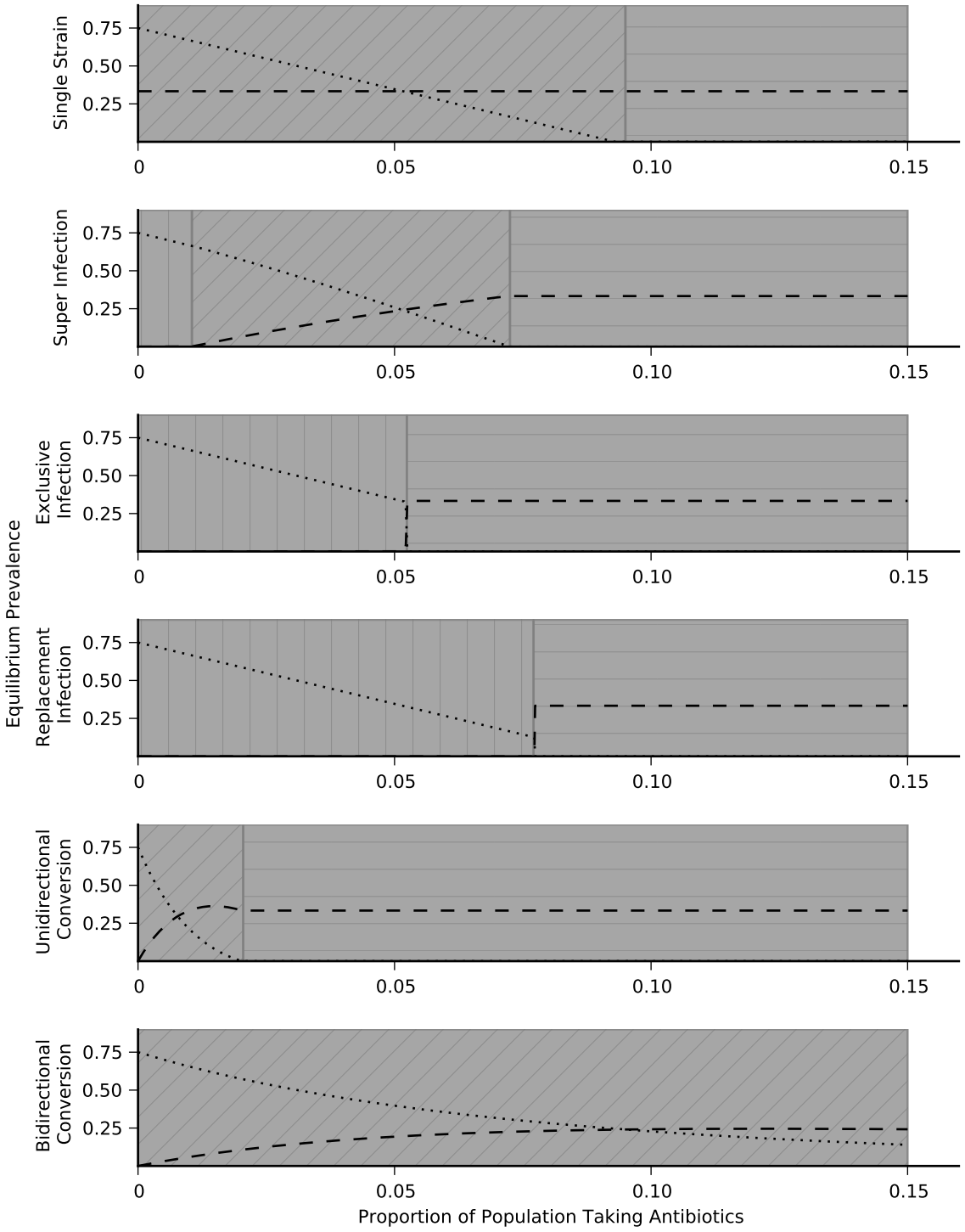
sensitive transmission relevant to resistant transmission. In order to determine whether one or both of the strains will dieout we can use R_0's as calculated in the single strain model (equation 1).

Bidirectional conversion

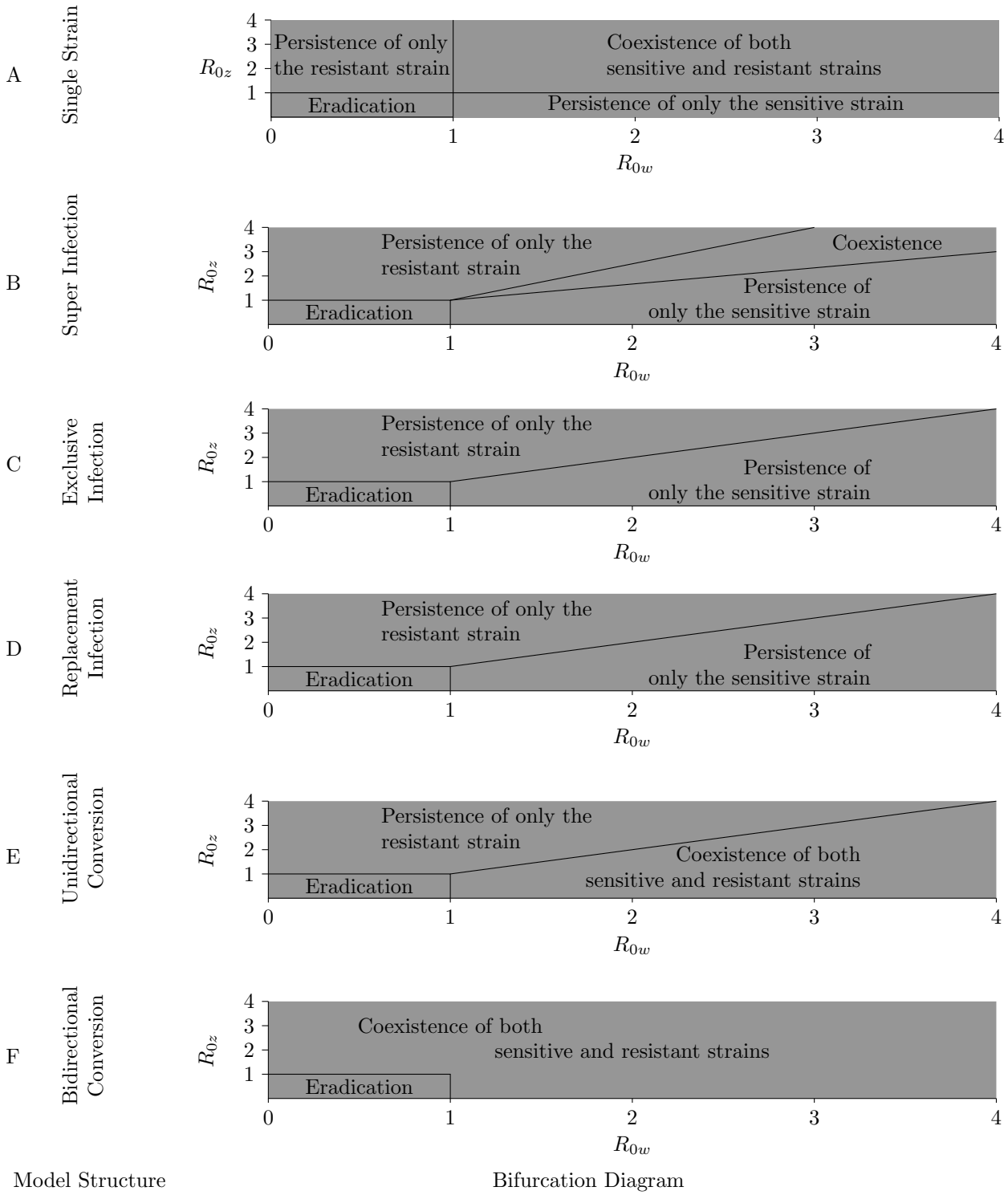
Similar to the unidirectional conversion model, within-host strain coexistence in the bidirectional conversion model is implicit, in the form of a majority-minority relationship. However, within-host strain conversion can now operate in both directions: sensitive conversion to resistant in the presence of antibiotics and resistant conversion to sensitive in the absence of antibiotics. As a result, the strain coexistence region is expanded (Web Figure 2F). Strain-specific R_0s are less useful than in the other model structures due to the strong interdependency, and a system-wide R_0 becomes important. As long as this system-$R_0 > 1$, both strains will coexist unless either 1) there is no population antibiotic treatment ($\epsilon = 0\%$), or 2) there is complete population antibiotic treatment ($\epsilon = 100\%$). At these boundary conditions, the conversion pathways (from sensitive to resistant or vice versa) may be shut down. When there is no population antibiotic treatment there is no selection for minority resistant strains among predominately sensitive strains, or vice versa. Therefore, except at the boundary conditions of treatment, stable presence of one strain indicates stable presence of the other since there is constant first order transition between each (Web Figure 1F).

Compound Model Structures

In practice, systems may have combinations of these six base model structures. For example, adding either unidirectional conversion (UC) or super infection (SI) mechanisms to a replacement infection model will allow for population coexistence where a system with only the replacement infection (RI) mechanism



Web Figure 1: Equilibrium prevalence across model structures.
Parameter values held constant across model forms (Table 1). Background hatching denotes regions of antibiotic treatment parameter space where vertical hatching indicates a region where only the antibiotic sensitive strain persists, diagonal hatching where both strains coexist, and horizontal hatching where only the antibiotic resistant strain persists.



Web Figure 2: Bifurcation diagrams of competition between antibiotic sensitive (I_W) and resistant (I_Z) strains for each model structure. Each axis represents a strain-specific R0, calculated in the absence of the competing strain (see Equation 1). Model structure alters the result of competition between sensitive and resistant strains across strain-specific transmission strength.

would not allow. So an RI + UC or RI +SI system would qualitatively look like Web Figure 4E or 4B respectively, but with shifted breakpoints. These breakpoints are shifted because of the RI mechanism.

Sensitivity Analyses

To examine how variability in the transmission rates of each strain affect our results shown in Web Figure 1, we conducted two sets of sensitivity analyses, where the transmission rates are assumed to be equal to one another, and where the transmission rates are assumed to be more dissimilar from one another.

Equal transmission rates

When the transmission rates of each strain are equivalent (i.e. when there is no fitness cost associated with antibiotic resistance), the competition between each strain is altered. The resistant strain now has a higher R_0 compared to the sensitive strain assuming there is antibiotic treatment. When there is no antibiotic treatment in the population (i.e. $\epsilon = 0.0$) the two strains have identical R_0's. Because of the lack of a fitness cost associated with antibiotic resistance, the resistant strain more often dominates and outcompetes the sensitive strain to extinction (Web Figure 3).

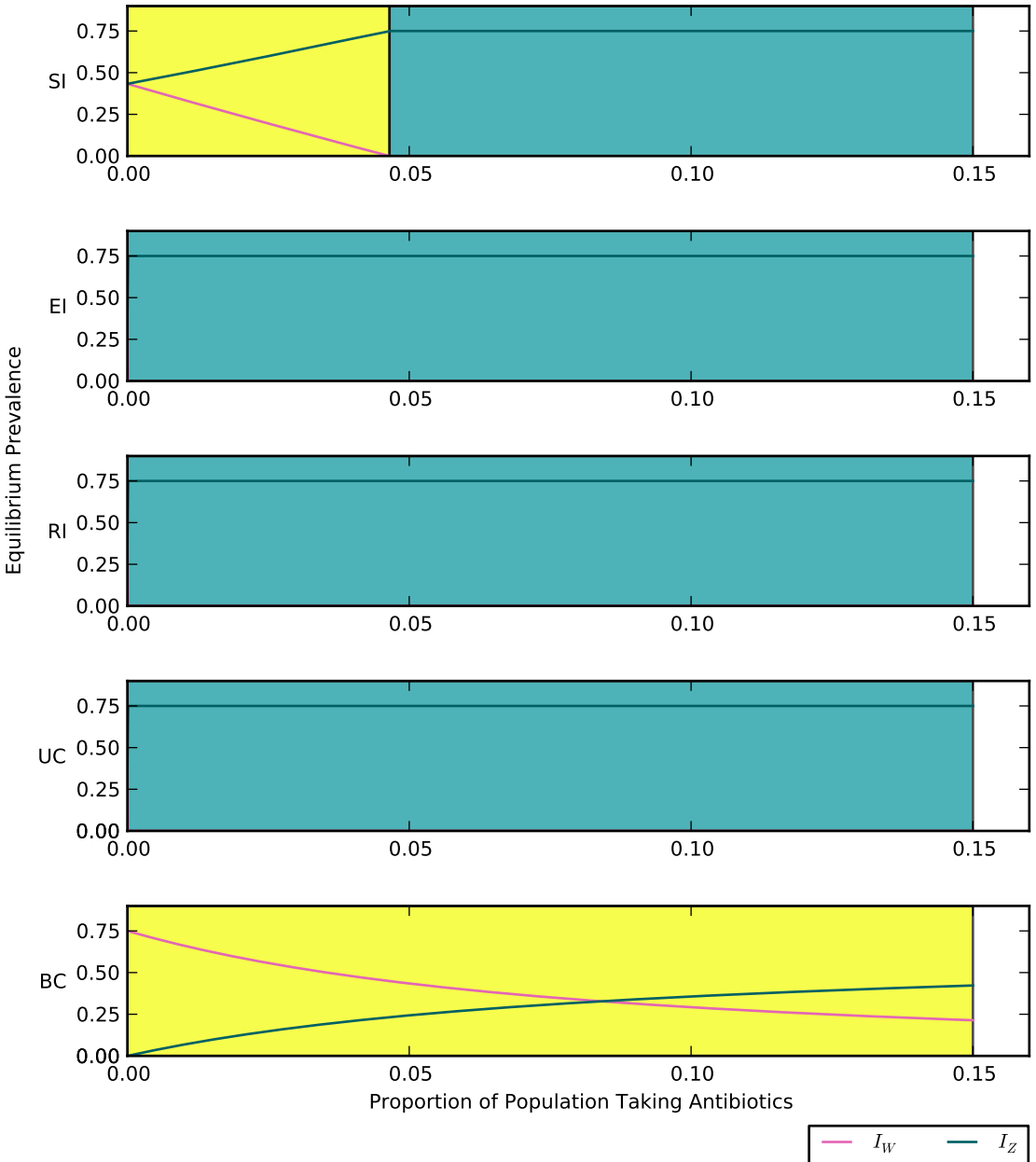
In the exclusive infection and replacement infection model structures where there is no possible population level strain coexistence, the resistant strain always wins out across the same spectrum of antibiotic use ($0.0 < \epsilon < 0.15$). In the unidirectional conversion model, where coexistence is possible, there is still none, because conversion is assumed to only operate from sensitive-to-resistant; however, this mechanism can only yield population coexistence when the sensitive strain R_0 is greater than the resistant one. Because this condition is not satisfied in this set of sensitivity analyses, there is no coexistence, and the resistant strain again dominates throughout. In the super infection model where

population level coexistence is also possible, we finally do observe some. Until the sensitive strain transmission becomes too weak (due to increased population level treatment), there is coexistence; above a threshold of treatment however, the sensitive strain transmission becomes too weak compared to the resistant strain to sustain coexistence of both strains. Finally, in the bidirectional conversion model, where there is both sensitive-to-resistant and resistant-to-sensitive conversion, we see coexistence of both strains throughout.

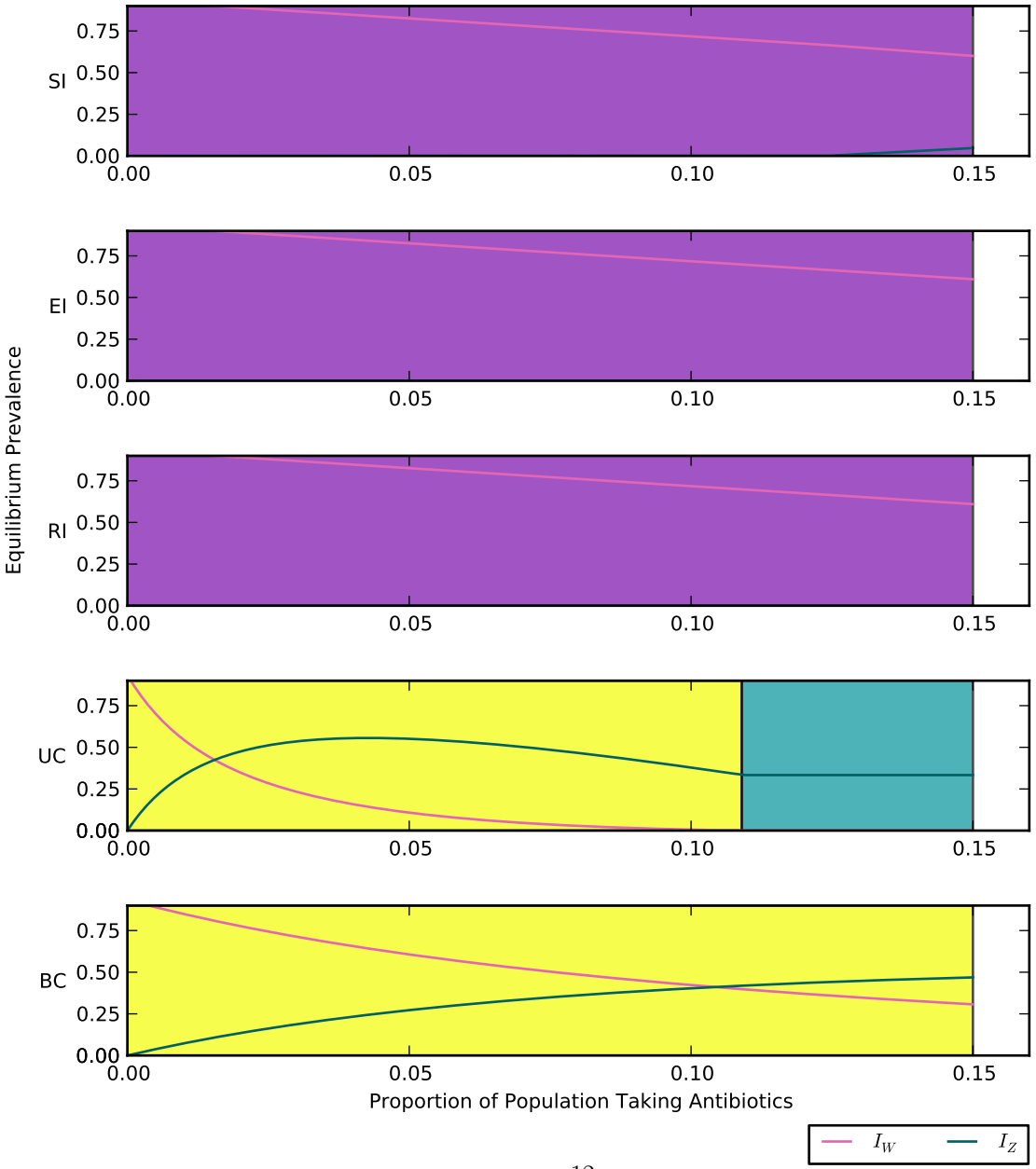
More dissimilar transmission rates

When the transmission rates of each strain are more dissimilar (i.e. when there is greater fitness cost associated with antibiotic resistance), the competition between each strain is altered. The sensitive strain now has a higher R_0 compared to the resistant strain. Because of the increased fitness cost the sensitive strain more often dominates and outcompetes the resistant strain to extinction (Web Figure 4).

In the exclusive infection and replacement infection model structures where there is no possible population level strain coexistence, the sensitive strain always wins out across the same spectrum of antibiotic use ($0.0 < \epsilon < 0.15$). In the super infection model where population coexistence is possible, there is none because the transmission of the sensitive strain is too strong; had the figure included regions of greater population antibiotic use, eventually the there would be coexistence of the strains, due to the sensitive strain becoming more weakly transmitted. In the unidirectional conversion model, where coexistence is also possible, there is coexistence at low and moderate treatment levels. Eventually however the combination of increased antibiotic treatment and conversion force the sensitive strain extinct at higher levels of treatment. Finally, in the bidirectional conversion model, where there is both sensitive-to-resistant and resistant-to-sensitive conversion, we see coexistence of both strains throughout.



Web Figure 3: Equilbrium prevalence across model structures with no fitness cost of resistance. Parameter values are from (Table 1), except for $\beta_w = 0.04$ and $\beta_z = 0.04$. Background color denotes regions of antibiotic treatment parameter space where violet indicates a region where only the antibiotic sensitive strain persists, aqua where only the antibiotic resistant strain persists, and yellow where both strains coexist.



Web Figure 4: Equilbrium prevalence across model structures with more fitness cost of resistance. Parameter values are from (Table 1), except for $\beta_w = 0.15$ and $\beta_z = 0.015$. Background color denotes regions of antibiotic treatment parameter space where violet indicates a region where only the antibiotic sensitive strain persists, aqua where only the antibiotic resistant strain persists, and yellow where both strains coexist.

Parameter	Explanation	Default Value	Unit
ϵ	Percent of population consuming antibiotics	Varied from 0% to 15%	percent
β_w	Transmission rate of the sensitive I_W strain	0.04	t^{-1}
β_z	Transmission rate of the resistant I_Z strain	0.015	t^{-1}
γ	Innate recovery rate	0.01	
γ'	Recovery rate from I_W assuming antibiotics are being consumed	0.1	t^{-1}
ρ	Conversion rate from I_W to I_Z assuming antibiotics are being consumed	0.5	t^{-1}
ϕ	Conversion rate from $I_Z$to I_W assuming antibiotcs are not being consumed	0.05	t^{-1}
q	Contagiousness of each strain in super-infected hosts	0.5	proportion

Table 1: Parameter symbol, description and values used to calculate equilibrium prevalence of sensitive and resistant strains for each model structure summarized in Figure 1