## Parametrization and Model Fitting

*Population genetic model of antimicrobial resistance evolution*

To model the evolutionary trajectory and temporal dynamics of antimicrobial resistance in the context of inappropriate antibiotic prescription, we developed a spatially-averaged (US national scale) population genetic model. For a given pathogen, the resistance frequency at time $t$, $r(t)$, starting at initial frequency $r_0$ can be modeled as

$$r(t) = \frac{r_0 e^{mt}}{1 - r_0 + r_0 e^{mt}}, \quad (1)$$

where $m$ is the Malthusian selection coefficient (Hartl and Clark 2007; Johnsen et al. 2011). Selective pressure from inappropriate antibiotic prescription increases the relative fitness of resistant bacteria (Austin, Kristinsson, and Anderson 1999), therefore we assume that the constant $m$ is time dependent:

$$m = \rho * a * r_t + (\theta - 1), \quad (2)$$

where ρ is a fitted parameter that conveys the degree to which selection is affected by counter-productive prescription, $a_y$ quantifies the amount of counter-productive prescription for the year $y$, and $\theta$ is the difference between the exponential growth of susceptible bacteria and the exponential growth of resistant bacteria in the absence of antibiotics. Equation (1) can then be determined step-wise:

$$r(t) = \frac{r(y) e^{m_y t}}{1 - r(y) + r(y) e^{m_y t}}, \quad (3)$$

for $y \leq t < y - 1$, where the time unit $t$ represents the number of year(s) from 2000.

By taking the reciprocal of both sides and simplifying Eq. 1 to

$$\frac{1}{r_t} - 1 = \frac{\frac{1}{r_0} - 1}{e^{m*t}}, \quad (4)$$

the model can be further transformed into a generalized linear regression,

$$\ln\left(\frac{1}{r_t} - 1\right) = \ln\left(\frac{1}{r_0} - 1\right) - m * t. \quad (5)$$

*Parameterization*

To parameterize $\theta$, we calculated the average relative fitness of five strains of *E. coli* harboring newly acquired resistance plasmids (Di Luca et al. 2017). To account for variability among strains and uncertainty for each strain associated with this dataset, we iteratively sampled a fitness from each of the five strain-specific best-fit Normal error distributions, and then calculated the mean. One thousand stochastic iterations of probabilistic sensitivity were conducted and the 25th and 97.5th quantiles were taken to describe the 95% sensitivity interval.

Taking the carbapenem consumption over the time frame of the collected historical surveillance data over the 12 years from 2000–2011, the counter-productive carbapenem prescription used in the Malthusian selection coefficient equation (**Eq 2**) for estimating the parameters $\rho$and $\theta$was obtained using the fitted values of consumption onto the time variables

$$a_t = \beta_0 + \beta_1 * t + \epsilon \;..$$

Annual carbapenem consumption from 2000–2011 were obtained from the Center For Disease Dynamics, Economics & Policy (CDDEP) as at with a unit of daily doses per 1,000 individuals (DDD/1000). To obtain the annual inappropriate carbapenem consumption, we take the product of atand the proportion of prescription given inappropriately, $x$, where $x$ is calculated as the percentage of the inappropriate empiric treatment (IET) out of the total treatment number (both non-IET and IET) (Zilberberg et al. 2017).

We estimated the number of patients with bacteremia that are given inappropriate empiric treatment with a carbapenem,

$$y = N_t \times e \times x \times q \times p,$$

where $N_t$ is the population size each year (US Census Bureau n.d.); $e$ represents the incidence rate for bacteremia (Angus DC n.d.; Nielsen n.d.; Simmering et al. 2017); $p$ is the proportion of bacteremia attributed to *P. aeruginosa*, obtained from proportional breakdowns from hospital and national databases; $q$ is the proportion of bacteremia patients prescribed carbapenems; and $x$ is the proportion given inappropriate empiric treatment, defined as first-line antibiotic prescribed to a resistant pathogen, with failure to initiate appropriate treatment within two days of a positive culture (Zilberberg et al. 2017; **Table 1**).

US carbapenem consumption during 2000–2011 was previously quantified from national surveys of pharmaceutical sales (ResistanceMap - Antibiotic Use ). The surveillance approach shifted between 2012 and 2013, restricting our ability to draw on data beyond this time frame ("ResistanceMap - Antibiotic Resistance" n.d.).

<u>*Data*</u>

The number of resistant cases among bacteremia patients as a function of inappropriate carbapenem prescription at given year is computed as

$$k_t = d_t * r_t,$$

where $r_t$ is the resistance frequency at a given year, and $t$ is the year, indexed as $t = 1$ in 2000.

By the end of the five-year antibiotic stewardship program, we project a reduction in inappropriate prescription of carbapenems of 51.7% (Van Hollebeke et al. 2016), with a yearly proportional decreasing trend. The number of inappropriately prescribed cases at the $j$th year ($j = 1 \ldots 5$) during the widespread implementation of stewardship was specified as

$$b_t = b_0\,(1 - 0.2j * 51.7\%).$$

**Table 1**. Dynamic model parameters, definitions, constraints, priors, and sources of data.

| Parameter | Definition | Constraints | Prior distribution | Source |
|---|---|---|---|---|
| $c_y$ | Carbapenem prescription (in a given year) | — | annual point value specified | CDDEP[a] |
| $x$ | Proportion of inappropriate prescription<br>*Bacteremia*<br>*Pneumonia*<br>*UTI* | — | point value specified | Zilberberg et al. 2017 |
| $q$ | Proportion of cases treated by prescription of carbapenems<br>*Bacteremia*<br>*Pneumonia*<br>*UTI* | — | point value specified | Merck |
| $p$ | Proportion of bacteremia (pneumonia and UTI) attributed to *P. aeruginosa* | — | point value specified | Gaynes et al. 2005 (NHSN[b]) |
| $e$ | Incidence rate for bacteremia (pneumonia and UTI) | | point value specified | (Angus DC n.d.; Nielsen n.d.; Simmering et al. 2017) |
| $a$ | Inappropriate carbapenem prescription averaged t=1nat | | average value from historical data | |
| $a_t$ | Inappropriate carbapenem prescription after the 5-yr stewardship program complete | | point value estimated | |
| $\theta$ | Relative fitness of the resistant strain compared to the susceptible strain | $\theta < 1$ | point value specified | Di Luca et al. 2016 |
| $\rho$ | Scaling factor for the susceptible fitness constant | — | no prior specification | |
| $r_0$ | Initial resistance frequency | $0 < r_0 < 1$ | no prior specification | |
| $\mu_i$ | Mean value of the relative fitness for transformant *i* | *i* in [1, 5] | Point value | Zilberberg et al. 2017 |
| $\sigma_i$ | Standard deviation of the relative fitness for a given transformant | *i* in [1, 5] | Point value | Zilberberg et al. 2017 |
| $N_y$ | US population at year *y* | | annual point value specified | US Census Bureau |

[a]Center for Disease Dynamics Economics & Policy (http://resistancemap.cddep.org/)
[b]National Healthcare Safety Network (https://www.cdc.gov/nhsn/index.html)

*Model fitting*

Data from 2000–2011 on the pathogen *P. aeruginosa* and diagnosis-specific US carbapenem resistance from Merck were combined with a larger CDDEP dataset, which included pathogen-specific carbapenem resistance data in the US.

the least square estimates of which were used for expressing the unknown parameters. The initial resistance frequency $r_0$ can be assessed from the intercept, 1r0-1, and the slope corresponds to –$m$. From **Eq 2**, we calculated

$$\rho = \frac{-m - (\theta - 1)}{a_t}, \quad (7)$$

with $a_t$ obtained by linearly fitting the annual carbapenem consumption on the time variable $t$ and further projected into the future years.

To account for uncertainty within the resistance data, 1,000 trials were conducted and the 95% confidence interval was estimated.