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:

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

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 θ 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

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 θ, 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

$$at = \beta 0 + \beta 1 * t + {}_{\varepsilon}.$$

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.).

Data

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

$$kt = dtrt,$$

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 jth year ($j = 1 .. 5$) during the widespread implementation of stewardship was specified as

$$bt = b0(1 - 0.2j \bullet 51.7\%).$$

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 *Bacteremia* *Pneumonia* *UTI*	—	point value specified	Zilberberg et al. 2017
q	Proportion of cases treated by prescription of carbapenems *Bacteremia* *Pneumonia* *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	
θ	Relative fitness of the resistant strain compared to the susceptible strain	$\theta < 1$	point value specified	Di Luca et al. 2016
ρ	Scaling factor for the susceptible fitness constant	—	no prior specification	
r_0	Initial resistance frequency	$0 < r_0 < 1$	no prior specification	
μ_i	Mean value of the relative fitness for transformant i	i in [1, 5]	Point value	Zilberberg et al. 2017
σ_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.