**The Impact of Stewardship on the evolution of antibiotic resistance**

**Abstract**

The evolution and spread of antibiotic resistance compromises humanity’s ability to combat life-threatening diseases, such as tuberculosis and pneumonia. As the efficacy of many antibiotics has been progressively eroded, health care providers across the United States have been turning to broad-spectrum carbapenems as initial empiric therapy previously reserved for cases where first-line options have failed. Precariously, this expeditious use of carbapenem has fueled rising frequencies of resistance in this class of antibiotics. Retrospective analysis of hospital records has indicated that carbapenems are inappropriately used in a substantial number of cases. To determine the impact of stewardship programs that promote adherence to guidelines for appropriate carbapenem use, we developed a population genetic model of microbial evolution, calibrated to observed antibiotic resistance and carbapenem consumption. Projecting future mortality, we demonstrate the urgency of stewardship in order to maintain our current capacity to address the threats of microbial pathogenesis.

Antibiotic stewardship is challenged by the trade-off between short-term clinical care and sustainability of efficacious antibiotics.

Expediency can lead to To ensure the swiftest resolution of infections, the unnecessary prescription of second-line antibiotics has become widespread.

**Introduction**

Antibiotics revolutionized the treatment of myriad diseases, dramatically extending our lifespans [(Davies & Davies, 2010; Yoshikawa, 2002)](https://paperpile.com/c/8fpTGd/sNLC+hMPB). However, mounting antibiotic resistance poses a grave threat to global health [(Spellberg, 2014a; Spellberg, Bartlett, & Gilbert, 2013)](https://paperpile.com/c/8fpTGd/3KzaO+NxiY7). In some regions of the United States, the majority of bacterial pathogens are now resistant to first-line antibiotics (ref). In the wake of this crisis, it is becoming increasingly common to use carbapenems in initial empiric therapy because of their broad-spectrum efficacy and tolerability. As prescription of carbapenems has expanded, so too has carbapenem resistance. Resistance evolution has outpaced the development of novel antibiotics, exacerbating the severity of this public health challenge.

In the treatment of infections with carbapenem-resistant bacteria, hospitals often turn to multidrug therapy, which may include last-resort antibiotics like colistin and gentamicin [(Sbrana et al., 2012)](https://paperpile.com/c/8fpTGd/tWRp). Such antibacterial agents have traditionally been used sparingly, due to toxicity. As a result, less resistance against these drugs has developed [(Li et al., 2006)](https://paperpile.com/c/8fpTGd/voYZ), but such resistance would be expected to emerge as the last-resort antibiotics increasingly replace carbapenems. Rather than impose a blanket restriction on carbapenem use—a policy that is necessarily blind to the conditions of individual patients—several hospitals have initiated antibiotic stewardship programs. Such programs mandate approval of antibiotic prescription by a qualified steward prior to the administration of controlled drugs such as carbapenems. Such programs have been shown to reduce inappropriate prescription of carbapenems by as much as 52% [(Van Hollebeke et al., 2016)](https://paperpile.com/c/8fpTGd/wM2x). Carbapenem use, rates of antibiotic resistance, and drug costs drop significantly, without increases in mortality or length of stay [(Elligsen et al., 2012)](https://paperpile.com/c/8fpTGd/FZ76). One stewardship study conducted over the course of five years suggested that hospitals restricting carbapenems experienced significantly lower incidence rates of carbapenem-resistant *P. aeruginosa* for all five years [(Pakyz, Oinonen, & Polk, 2009)](https://paperpile.com/c/8fpTGd/q57K).

If current usage continues indefinitely, the effectiveness of carbapenems will be entirely eroded. Models of antibiotic resistance have not previously provided projections at national levels that address this long timescale and the associated health and economic outcomes. Here, we apply a population genetic model to carbapenem usage and resistance data among pneumonia, bacteremia and urinary tract infected (UTI) patients in the US infected with *P. aeruginosa*. We predict future resistance trends among this patient population, as well as the decline in levels of resistant microbe under nationwide stewardship programs initiated in 2020, 2025, or 2030. Our analysis reveals tension between individual and public health, as we find population-wide benefits of early stewardship initiation but patient-level incentives for carbapenem use.

**Methods**

*Mathematical model of carbapenem resistance evolution*

To model the evolutionary trajectory temporal dynamics of carbapenem resistance, we developed a population genetic model of carbapenem resistance. For a carbapenem resistant *P. aeruginosa* pathogen, the current resistance frequency *r* starting at initial frequency *r*0 can be modeled as:

, (1)

where *m* is the Malthusian selection coefficient [(Hartl & Clark, 2007; P. J. Johnsen et al., 2011)](https://paperpile.com/c/8fpTGd/EyXj+eOnNi). In the presence of carbapenem, the relative fitness of drug sensitivity is determined by *θ* and the frequency of inappropriate carbapenem prescription. Specifically, selective pressure from carbapenem prescription increases the relative fitness of resistant bacteria [(Austin, Kristinsson, & Anderson, 1999)](https://paperpile.com/c/8fpTGd/fFGz), such that

, (2)

where *⍴* conveys the amount that selection is affected by inappropriate carbapenem prescription,is a scaling factor and *a* is the amount of inappropriate carbapenem prescription in standard units. The parameters *⍴*, *θ* and *a* are all fixed over time, with *a* extracted from averaged historical surveillance data or projected based on scenarios of prescription. From Equations (1) and (2), frequency of resistance over time can be projected as

(3)

*Data*

We applied our model to two infectious diseases (pneumonia, bacteremia and UTI) caused by *Pseudomonas aeruginosa*, which is treated by carbapenems (Jary et al., 2012; Van Hollebeke et al., 2016) and that exhibit resistance to carbapenems in nosocomial settings (McLaughlin et al., 2013; Papp-Wallace et al., 2011; Zanetti et al., 2003). US carbapenem consumption was quantified during 2000–2012 by the Center for Disease Dynamics Economics & Policy (CDDEP), using the source from The Surveillance Network, USA. Consumption, in standard units, was estimated from national surveys of pharmaceutical sales. Inappropriate prescription for each diagnosis and pathogen was estimated using proportional breakdowns from hospital and national databases (**Table 1**). We define inappropriate prescription as first-line antibiotic prescribed to a resistant pathogen, with failure to initiate appropriate treatment within 2 days of a positive culture (Zilberberg et al. 2017). To match consumption year to yearly resistance data, the constant consumption data was inputted as

, (4)

where is inappropriate prescription at year t and is inappropriate prescription in the following

year.

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | Definition | Constraints | Prior distribution | Source |
| *c* | Carbapenem prescription (in a given year) | — | annual point value specified | CDDEPa |
| *ci* | Proportion of inappropriate prescription | — | point value specified | Zilberberg et al. 2017 |
| *cd* | Proportion of carbapenems prescribed to pneumonia, bacteremia, or UTI patients | — | point value specified | Merck |
| *cp* | Proportion of pneumonia, bacteremia, or UTI attributed to *P. aeruginosa* pathogen of interest | — | point value specified | Gaynes et al. 2005; NHSNb |
| *b* | Inappropriate carbapenem prescription  (*c* × *ci* × *cd* × *cp*) |  |  |  |
| *at* | Inappropriate carbapenem prescription averaged over two points  (½ × (*bt* + *bt*+1)) |  |  |  |
| *a* | Inappropriate carbapenem prescription averaged |  |  |  |
| *θ* | Relative fitness of the resistant strain compared to the susceptible strain (*kr / ks* ) | *θ* < 1 | point value specified | Di Luca et al. 2016 |
| *ρ* | Scaling factor for the susceptible fitness constant | — | no prior specification |  |
| *r0* | Initial resistance frequency | 0 < *r0*< 1 | no prior specification |  |
| *n* | Susceptible isolates for each pathogen (in a given year) |  | annual point value specified | CDDEPa |
| *k* | Resistant isolates for each pathogen and diagnosis given *p* |  | binomial distribution |  |

aCenter for Disease Dynamics Economics & Policy (http://resistancemap.cddep.org/)

bNational Healthcare Safety Network (https://www.cdc.gov/nhsn/index.html)

*Model fitting*

Data from 2000–2012 on pathogen- 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. *θ* was computed by averaging out the 1,000 simulated normal distributions with parameters inferred from Relative fitness of *E. coli* harboring newly acquired plasmids (Di Luca et al. 2016). The frequency of resistance predicted by the model **(Eq4)** was transformed into a generalized linear regression (**Eq 5**), the least square estimates of which were used for expressing the unknown parameters, *⍴* and *r0*

, (5)

where the slope of the regression corresponds to and the intercept is essentially .

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

*Results*

Our model recapitulates observed carbapenem resistance from 2000–2012 in the pathogen *P. aeruginosa* associated with pneumonia, bacteremia and UTI (Figure X). Since 2000, the frequency of resistance in patients diagnosed with pneumonia in the U.S. has increased from around XX% to around XX%, an increase captured by our model (Figure X). A similar increase of resistant strains from around XX% to XX% in patients with an indication of bacteremia and an increase from XX% to XX% in patients with UTI are also captured (Figure X).

Levels of carbapenem resistance from 2000–2014 are influenced year-to-year both by variable

increases in carbapenem usage for each disease, disease types (Figure X), and by epidemiological stochasticity. We projected a “status quo consumption” trajectory of the usage of carbapenems based on linear regression of inappropriate consumption from 2000–2012 for each disease (Figure X), as well as projecting trajectories in response to imposed reductions of carbapenem usage under a 5-year implementation of a program of nationwide stewardship commencing in 2020, 2025, or 2030. In our model, these reductions in inappropriate CBP prescription correspond directly to reductions in the number of patients prescribed CBPs (Table X).

A close up of a map

Description automatically generated

**Figure 1.** Actual (black line) for projected frequencies of carbapenem resistance in *P. aeruginosa* in patients with A) pneumonia, B) bacteremia and C) UTI under status quo and stewardship 2020 (dashed blue line), 2025 (dashed purple line), and 2030 (dashed red line) based on ≥1000 simulations with parameter values fit to sampled resistance frequencies.

Successful stewardship that reduces inappropriate usage of CBPs was projected to

markedly decrease resistance frequencies among all 3 disease, deterring

evolution of resistance that otherwise renders futile the therapeutic usage of CBPs (Figure X).

For indications of pneumonia, bacteremia and UTI, antibiotic stewardship was projected to yield

lower ultimate steady-state resistance frequencies of XXX than of XXX diseases.

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| --- | --- | --- | --- | --- | --- | --- |
| **Table 2.** Yearly discounted resistance frequency of among *P. aeruginosa* infected diseases pneumonia (left), bacteremia (middle) and UTI (right) patients with/out stewardship beginning in 2020, 2025, and 2030. | | | | | | |
| **Stewardship start year** | ***P. aeruginosa*** | | | | | |
| Pneumonia | | Bacteremia | | UTI | |
| Stewardship | - | + | - | + | - | + |
| 2020 | 0.459 | 0.207 | 0.349 | 0.257 | 0.282 | 0.164 |
| 2025 | 0.631 | 0.252 | 0.467 | 0.332 | 0.361 | 0.179 |
| 2030 | 0.797 | 0.317 | 0.613 | 0.437 | 0.469 | 0.201 |
|  | | | | | | |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 3.** Yearly discounted resistance cases number of among *P. aeruginosa* infected diseases pneumonia (left), bacteremia (middle) and UTI (right) patients with/out stewardship beginning in 2020, 2025, and 2030. | | | | | | | | | |
| **Stewardship start year** | ***P. aeruginosa*** | | | | | | | | |
| Pneumonia | | | Bacteremia | | | UTI | | |
| Stewardship | - | + | #Saved cases | - | + | #Saved cases | - | + | #Saved cases |
| 2020 | 47900 | 21594 | 1157561 | 976 | 511 | 23410 | 2365 | 1378 | 17030 |
| 2025 | 68150 | 27219 | 937882 | 1353 | 603 | 19245 | 3142 | 1558 | 13632 |
| 2030 | 88823 | 35282 | 632721 | 1832 | 731 | 13516 | 4205 | 1804 | 9202 |
|  | | | | | | | | | |

*Discussion*

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