The Impact of Carbapenem-Sparing Interventions on the Evolution of Resistance in *Pseudomonas aeruginosa* in the United States

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Background

Carbapenem resistance (CR) among *P. aeruginosa* infections is a pressing public health concern in the United States. Therapeutic alternatives for CR infections are limited. Implementation of a key antimicrobial stewardship intervention such as formulary restriction, which is one of the many stewardship strategies, can minimize selection pressure for resistance. We evaluate the consequent impact of this intervention for carbapenems on Bacteremia, Pneumonia, and UTI patients infected with *Pseudomonas aeruginosa* in the United States.

Methods

We developed a Malthusian population-genetic model of selection for CR. Increases in CR were modeled as a consequence of inappropriate prescription. Inappropriate prescription was estimated from a retrospective cohort study of inappropriate empiric treatment,[1] and future projections were based on historical resistance frequencies and yearly carbapenem (CBP) consumption associated with *P. aeruginosa* bacteremia. We projected peak *P. aeruginosa* CR frequencies and cumulative CR cases from 2020–2040. We compared scenarios without any carbapenem restriction to those in which carbapenem usage was decreased linearly to 51.7% of levels at implementation, as achieved in previous AMSP,[2] with 5-year rollouts starting in 2020 (early) or 2030 (late).

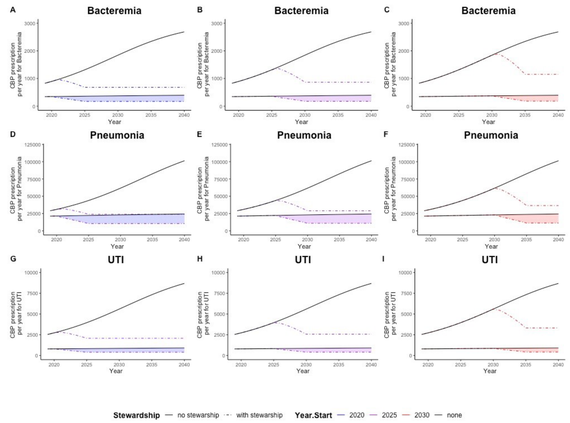
Results

Table 1. Projected Carbapenem Resistance Frequencies Among *P. aeruginosa* Cases in 2040

Stewardship Start Year	Bacteremia	Pneumonia	UTI
Never[a]	86.0%	75.6%	89.6%
2020	23.2%	19.9%	23.6%
2025	28.7%	23.5%	30.1%
2030	36.6%	28.6%	39.4%

[a]Under a theoretical scenario without any antibiotic restriction.

Figure 1. Overall and Inappropriate CBP prescription for *P. aeruginosa* under Status Quo vs. Stewardship Interventions



Overall and inappropriate CBP prescription across US under status quo (grey solid line) and under stewardship interventions beginning in 2025 (dot-dashed blue line), 2030 (dot-dashed purple line), and 2035 (dot-dashed red line) to treat a *P. aeruginosa* infection causing bacteremia (**A–C**), pneumonia (**D–F**), and UTI (**G–I**), implemented in 2025 (**A, D, G**), 2030 (**B, E, H**), or 2035 (**C, F, I**), projected assuming constancy of the 2011 prevalence of pneumonia, bacteremia, and UTI (HCUP), and of levels of carbapenem prescriptions (CDDEP).

Model

- For a given pathogen, the resistance frequency at time t, $r(t)$, starting at initial frequency r_0 can be modeled as:

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

where m is the Malthusian selection coefficient.[3,4]

- Selective pressure from inappropriate antibiotic prescription increases the relative fitness of resistant bacteria,[5] therefore we assume that the selection coefficient m is time dependent: $m_y = \rho \times a_y - \theta$

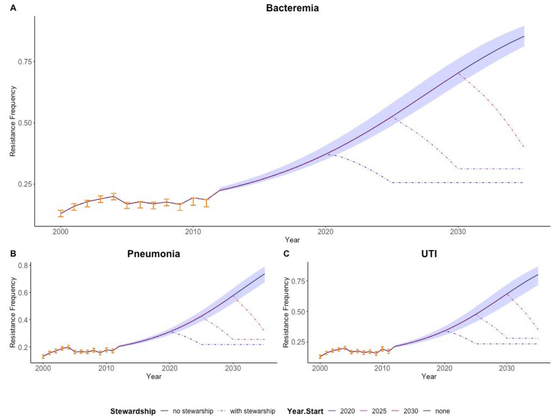
where ρ is a fitted parameter that conveys the degree to which selection is affected by counterproductive prescription, a_y quantifies the amount of counterproductive prescription for the year y, and θ is the difference between the exponential growth rate of susceptible bacteria and the exponential growth rate of resistant bacteria in the absence of antibiotics.

- Resistance per year (r_y for the year y) can be computed recursively: $r_y = (1 - (1 - 1/r(n))e^{-m_y/2})^{-1}$

$$r(n) = (1 - (1 - 1/r_{y-1})e^{-m_{y-1}/2})^{-1}$$

where $y = y_0 + n$, n is a natural number, y_0 represents the initial year, the time $t = 0$ corresponds to the first day of the year y_0, the time unit is years, and r_y is measured at the middle of the year y.

Figure 2. Observed and Projected Carbapenem Resistance Frequencies for *P. aeruginosa*



Observed resistance frequencies and 95% confidence intervals (orange circles and error bars) spanning 2000–2011, and model fit (black line) and 95% confidence interval (blue bands) for projected carbapenem resistance frequencies spanning 2000–2035, and observed frequencies (orange points) among *P. aeruginosa* cases with bacteremia (**A**), pneumonia (**B**), and UTI (**C**) under *status quo*.

Table 2. Prevented Cases of Carbapenem-resistant *P. aeruginosa* Infection in the US Between 2025 and 2040

Stewardship Start Year	Bacteremia	Pneumonia	UTI
2020	29,600	1,051,600	110,300
2025	23,500	867,000	88,600
2030	15,200	600,000	58,700

Conclusions

- Antimicrobial stewardship is a coordinated program that promotes the appropriate use of antimicrobials with the objective of decreasing antimicrobial resistance and eventually improving patient outcomes. Our study establishes, for the first time, spatially-averaged national-scale impacts of carbapenem restriction as a part of antibiotic stewardship programs that are developed to balance public health and individual medicine
- We demonstrate that timely restriction of carbapenem consumption could markedly reduce future CR in *P. aeruginosa* bacteremia patients. Implementing early carbapenem restriction should be expected to result in a lower ultimate frequency of CR and a lower number of cumulative cases of resistant infections, thereby decreasing the overall burden of CR cases that will be encountered in the future

References

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Parameterization and Model Fitting

Data

References

Presented at IDWeek 2020; October 21-25, 2020.