Large variation in association between seasonal antibiotic use and resistance across multiple bacteria and antibiotic classes

Daphne Sun[1], Stephen M. Kissler[1], Sanjat Kanjilal[2,3,4], Scott W. Olesen[1], Marc Lipsitch[1], Yonatan H. Grad[1,3]

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

dssun@g.harvard.edu

Introduction

Understanding the relationship between antibiotic use and resistance is critical for informing effective stewardship strategies to reduce the growing burden of antibiotic resistance. However, how this relationship varies across diverse pathogens and antibiotics remains unclear.

Here, we leverage existing seasonal variations in antibiotic use to evaluate the seasonal relationship between use and resistance across 5 antibiotic classes and 3 species in Boston, Massachusetts.

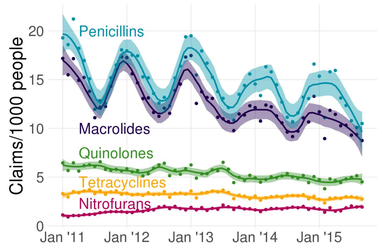


Figure 1. Outpatient antibiotic prescribing rates in Boston, MA from 2011 to 2015.

Methods

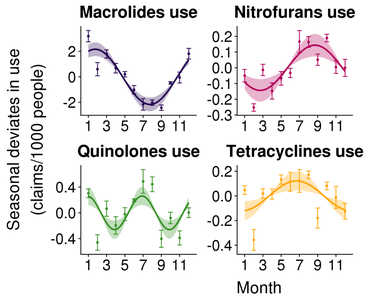
We compared outpatient antibiotic use data for Boston, MA residents obtained from the Massachusetts All Payers Claims Database (2011-2015) **[1]** to resistance data obtained from two major Boston-area hospitals from 2007-2019 for 131,815 *E. coli*, 47,208 *S. aureus*, and 27,237 *K. pneumoniae* isolates. We determined the amplitude and phase of seasonality in use and resistance by fitting these data to the following sinusoidal models with a fixed 6- or 12-month period **[2]**.

Use model: $$a_i \sim A_{use}\cos[\omega(t_i - P_{use})] + B_{y(i)}t_i + C_{y(i)} \quad (1)$$

Resistance model: $$y_i \sim A_{MIC}\cos[\omega(t_i - P_{MIC})] + B_{h(i)}t_i + C_{h(i)} \quad (2)$$

where a_i is the reported claims/1000 people during month t_i, y_i is the $\log_2$-transformed MIC and t_i is the month of collection of the i^{th} isolate, A_{use} and A_{MIC} are the amplitudes of seasonality, ω is the frequency of seasonality where $\omega = \frac{2\pi}{period}$, P_{use} and P_{MIC} are the phases of seasonality, $B_{y(i)}$ and $C_{y(i)}$ are the within-year slope and intercept terms for use, and $B_{h(i)}$ and $C_{h(i)}$ are the within hospital/year slope and intercept terms for resistance.

Antibiotic use is seasonal with varied peaks



Use of all 5 antibiotic classes showed significant amplitudes of seasonality after Benjamini-Hochberg correction. Use of each class peaked at different times during the year.

Figure 2. Sinusoidal model fits for antibiotic use by class. Points indicate the monthly mean seasonal deviates in use. Shaded regions indicate the 95% CI on the amplitude.

Antibiotic resistance peaks in the winter or spring

Resistance in 10 of 15 species-antibiotic combinations showed a significant amplitude of seasonality after Benjamini-Hochberg correction (indicated by asterisks in Fig. 3). In all 10 combinations, resistance almost always peaked in the winter to early spring, despite varied patterns of use across antibiotic classes.

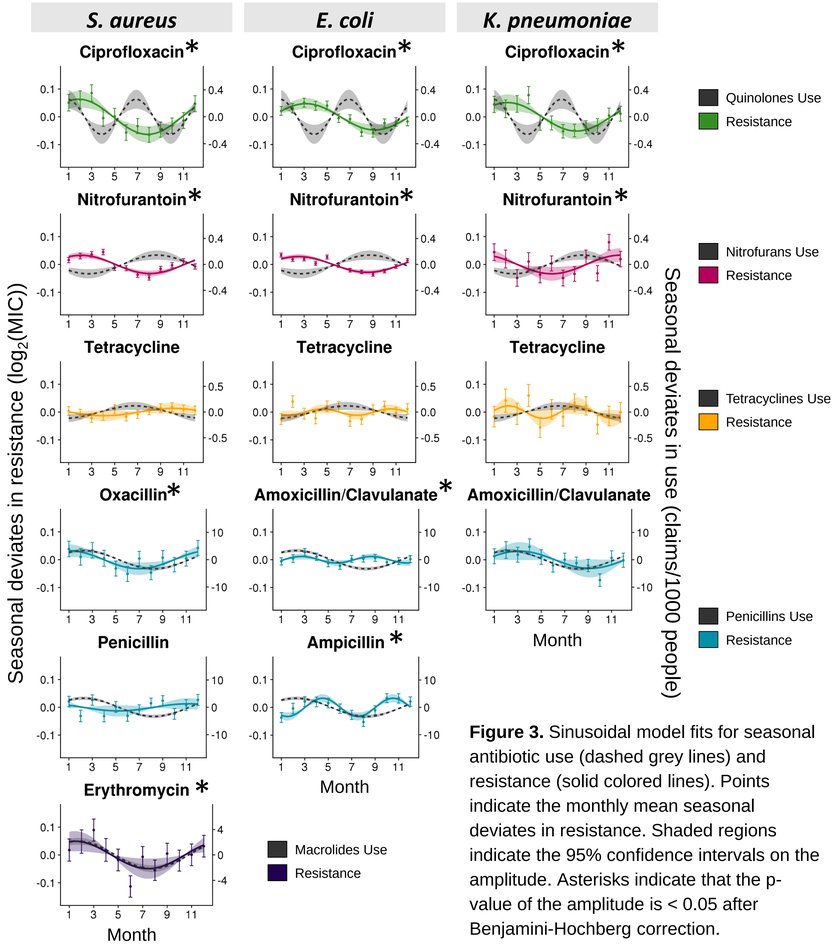


Figure 3. Sinusoidal model fits for seasonal antibiotic use (dashed grey lines) and resistance (solid colored lines). Points indicate the monthly mean seasonal deviates in resistance. Shaded regions indicate the 95% confidence intervals on the amplitude. Asterisks indicate that the p-value of the amplitude is < 0.05 after Benjamini-Hochberg correction.

Seasonal resistance is most strongly correlated with use of winter-peaking antibiotics

Resistance to every antibiotic, regardless of class, in all three species was most positively correlated with use of winter-peaking classes, penicillins and macrolides.

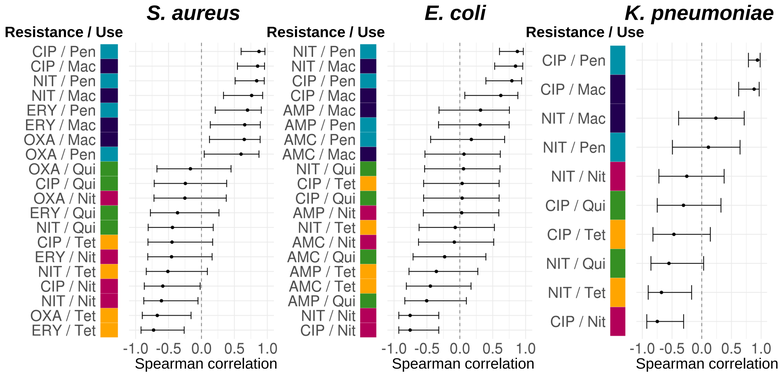


Figure 4. Spearman's rank correlations calculated between the monthly mean seasonal deviates in use and resistance for all cognate and non-cognate pairs of use classes and target antibiotics. Error bars indicate the 95% confidence intervals.

Conclusion

The association between seasonal antibiotic use and resistance varied widely across species-antibiotic combinations. While antibiotic use peaked at different times of the year, resistance always peaked in the winter to spring and was most strongly correlated with seasonal use of penicillins and macrolides. This finding suggests that stewardship strategies will not be equally effective across all species and antibiotics and underscores the need to broaden our understanding of the use-resistance relationship and identify factors that influence its strength.

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Affiliations: **[1]** Harvard T.H. Chan School of Public Health, Boston, MA, USA. **[2]** Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA. **[3]** Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. **[4]** Massachusetts General Hospital, Boston, MA, USA.

References: **[1]** Massachusetts All Payer Claims Database. https://www.chiamass.gov/ma-apcd. **[2]** Olesen SW, Torrone EA, Papp JR, Kirkcaldy RD, Lipsitch M, Grad YH, *J Infect Dis*. 2019.