The potential for “spillover” in outpatient antibiotic stewardship interventions among US states

Short title: Geography of outpatient stewardship interventions

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Abstract

Antibiotic stewardship combats antibiotic resistance by reducing inappropriate antibiotic use. Stewardship policy should be guided by experimental stewardship interventions. However, the design and interpretation of stewardship interventions is subject to “spillover”, in which the transmission of microbes between the control and intervention population reduces the intervention’s measured effect. Small-scale stewardship experiments may therefore underestimate the effect of a larger-scale implementation. Here, we aimed to quantify the effect of spillover on state-level outpatient antibiotic stewardship interventions to determine if states are feasible "laboratories" for designing national policy. First, we used dynamical models of antibiotic resistance to predict the effects of spillover, finding that if even 1% of residents' interactions are between, rather than within, US states, the measured effect of a state-wide stewardship intervention could be reduced by as much as 50%. Then, we quantified spillover in observational antibiotic use and resistance data from US states and European countries for 3 pathogen-antibiotic combinations. We found that these cross-sectional data were insufficiently powered to detect even the large spillover effect sizes predicted by the mathematical models. We were unable to rule out the possibility that state-level changes in antibiotic use, either increases or reductions, may lead to substantially smaller changes in antibiotic resistance than if those changes took place nationwide. We suggest that well-designed, controlled interventions, couple with more sophisticated modeling and analysis, with could help determine spillover’s policy ramifications.
Introduction

Antibiotic resistance is a major threat to public health (1). Outpatient antibiotic use, which accounts for approximately 80% of human antibiotic use (2,3), is considered a principal driver of antibiotic resistance in the community (4), and antibiotic stewardship aims to mitigate antibiotic resistance (5–7) by reducing antibiotic use. US national stewardship policy should be guided by evidence from experimental stewardship interventions at smaller scales. For example, the results of interventions at the scale of US states could be used to inform the design of national policy. However, antibiotic resistance is a complex, temporally dynamic phenomenon (8–11), making the design and interpretation of stewardship interventions challenging.

A key feature of antibiotic resistance is that it can be transmitted from person to person, so that one person’s risk of an antibiotic resistant infection depends on that person’s antibiotic use (12,13) as well as the rates of antibiotic use among that person’s contacts (14). For example, one person’s use of antibiotics increases the risk of an antibiotic resistant infection among their family members (15–18). As an extreme example, hospitalized patients with no recent antibiotic use can have a higher risk of resistance than people in the community who use many antibiotics (19) because, in general, rates of antibiotic use and resistance among hospitalized patients are high. A change in an individual’s use of antibiotics is therefore not an accurate predictor of the change in antibiotic resistance that would follow from the same change in use if it occurred among a larger group of people. Likewise, an intervention targeting a group of people might have different effects depending on that population’s interactions with other populations.
For example, if antibiotic use in one hospital changes, resistance might not change as expected because resistant or susceptible bacteria can be transmitted, or “spill over”, to that hospital’s patients in the community or in other hospitals.

The effect of susceptibility and resistance “spilling over” between populations during stewardship interventions could theoretically be reduced by using larger populations. Smaller populations tend to have more transmission with the surrounding populations compared with larger populations, which tend to have more contacts within populations, rather than between populations. Thus, the problem of “spillover” is mitigated when studying larger populations. However, even hospitals are subject to spillover, as the level of resistance in one hospital appears to be affected by resistance levels in nearby hospitals as well as by antibiotic use rates in the surrounding communities (20–22). It is therefore possible that even hospitals may be too small and too subject to spillover to be accurate “laboratories” for stewardship.

We hypothesized that stewardship interventions at the level of US states, which are large populations with relatively independent public health policies, may be subject to substantially lower levels of spillover than individual-level or even hospital-level interventions. We evaluated this hypothesis using mathematical models and cross-sectional data of antibiotic use and resistance. First, we use mathematical models of antibiotic use and resistance to make quantitative predictions about the effect of spillover between US states and European countries. Second, we search for signals of spillover in observational data of antibiotic use and resistance in US states and
European countries. We chose to include European countries because, although our goal was to evaluate whether states are accurate "laboratories" for US national policy, the association between antibiotic use and antibiotic resistance has been previously characterized in many ecological studies at the level of US states (23–25) and European countries (26,27). Furthermore, many European countries are roughly similar in size to US states and might provide useful context for any US results.

**Methods**

*Dynamical model of antibiotic resistance*

To examine how interactions between populations could theoretically affect the association between antibiotic use and resistance, we use the within-host neutrality (WHN) mathematical model presented by Davies *et al.* (28) and described in the Supplemental Methods. Briefly, the model predicts the prevalence $\rho$ of antibiotic resistance that results from an antibiotic use rate $\tau$ in a single, well-mixed population. To verify that conclusions drawn from the WHN model are not specific to the model structure, we repeated all analyses with the “D-types” model of use and resistance (29). We selected these two models because they demonstrate coexistence between sensitive and resistant strains at equilibrium over a wide parameter space. Parameter values and simulation methodology for both models are in the Supplemental Methods. In the simulations, antibiotic use is measured as monthly treatments per capita and resistance as the proportion of colonized hosts carrying resistant strains.
We adapted the WHN model, using a structured host population approach inspired by Blanquart et al. (30), to simulate a stewardship experiment in which an intervention population has a lower antibiotic use rate $\tau_{\text{int}}$ than a control population with use rate $\tau_{\text{cont}}$. To determine how spillover affects the intervention’s measured outcome, we modulated the proportion $\varepsilon$ of each population’s contacts that are in the other population. For $\varepsilon = 0$, the populations are completely separate. For $\varepsilon = 0.5$, contacts across populations are just as likely as contacts within populations (Supplemental Methods). We varied $\varepsilon$ between 0 and 0.50, and we varied the difference in use $\Delta \tau = \tau_{\text{cont}} - \tau_{\text{int}}$ between 0 and 0.15 treatments per person per month while fixing the average use $\frac{1}{2}(\tau_{\text{cont}} + \tau_{\text{int}})$ at 0.125.

Observational data

In this study, we examined antibiotic use and resistance for 3 pathogen-antibiotic combinations: *S. pneumoniae* and macrolides, *S. pneumoniae* and $\beta$-lactams, and *Escherichia coli* and quinolones. We considered these 3 combinations because they are the subject of many modeling (28,29) and empirical studies (12,23).

Observational data were drawn from 3 sources. First, we used MarketScan (31) and ResistanceOpen (32) as previously described (25). The MarketScan data includes outpatient pharmacy antibiotic prescription claims for 62 million unique people during 2011-2014. ResistanceOpen includes antibiotic resistance data collected during 2012-2015 from 230 hospitals, laboratories, and surveillance units in 44 states. Second, we used the QuintilesIMS Xponent database (33) and the US Centers for Disease Control
and Prevention’s (CDC) National Healthcare Safety Network (NHSN) (34). The Xponent data includes state-level data on US quinolone use during 2011-2014. NHSN includes state-level data on quinolone resistance among E. coli catheter-associated urinary tract infections during 2011-2014. Third, we used the European Center for Disease Prevention and Control’s (ECDC) ESAC-Net antimicrobial consumption database (35) and EARS-Net Surveillance Atlas of Infectious Disease (36) for 2011-2015. The ESAC-Net data includes country-level outpatient antibiotic use data provided by WHO and Ministries of Health from member countries. The EARS-Net data includes country-level resistance data. In the observational data, we quantified antibiotic use as yearly treatments per capita and resistance as the proportion of collected isolates that were non-susceptible. Further details about preparation of these data sources and their availability are in the Supplemental Methods.

We excluded the S. pneumoniae resistance to β-lactams in US states from the analysis because, in previous work using the same primary datasets, the point estimate for the use-resistance relationship was negative (37).

Use-resistance relationships by populations’ adjacency

To test the theoretical prediction that the same difference in antibiotic use will be associated with smaller differences in antibiotic resistance when two populations (US states or European countries) have stronger interactions, we tested whether the use-resistance association is weaker in adjacent pairs of populations, which presumably have more cross-population contacts, compared to non-adjacent populations. Two
populations were considered adjacent if they share a land or river border (Supplemental Methods).

We quantified the use-resistance association as the percentage point difference in resistance (proportion of non-susceptible isolates) divided by the difference in antibiotic use. We summarized use-resistance associations among adjacent pairs and non-adjacent pairs of populations using the median value. Because use-resistance relationships between pairs of populations are correlated, we used the jackknife method to compute confidence intervals on the difference in medians between groups.

In a sensitivity analysis, to account for the possibility that the use-resistance association is not well-described using the simple difference in resistance proportions, we use the log odds ratio of resistance as the numerator in the use-resistance association.

Use-resistance relationships by adjacency, accounting for confounders

We expected that analyzing use-resistance associations by adjacency might artificially inflate the signal for spillover because determinants of antibiotic resistance aside from antibiotic use are spatially correlated. For example, if temperature affects levels of resistance (24), then the fact that adjacent populations tend to have similar climates may cause those populations to have more similar resistances, mimicking spillover. To partially account for these other determinants of resistance, we performed robust linear regressions predicting the use-resistance relationship from adjacency (dichotomous variable) as well as the differences in population density (38), per capita income (39),
and mean temperature (24) between the two populations (Supplemental Methods).

Regressions were computed using the \textit{rlm} function in the MASS package (40) in R.

Confidence intervals on the adjacency-use interaction coefficient were computed using
the jackknife method described above.

Use-resistance associations by commuting fraction

Because adjacency might be too coarse measure of populations’ interactions to detect
spillover, we repeated the analyses above, replacing the dichotomous adjacency
variable with “commuting fraction”, which we defined as the number of individuals who
commute between the areas divided by the total number of workers in those two areas
(Supplemental Methods). We expected that this might be a better approximation of the
mathematical parameter \( \varepsilon \), the fraction of a population’s contacts that are in the other
population, that was varied in the theoretical models of use and resistance.

Simulations and observational analyses were made using R (version 3.5.1) (41).

Results

In simulations of two populations, representing an intervention and control group,
interactions between the two groups attenuated the effect of the intervention (Figure 1).

With increasing interaction strength, the same intervention, that is, the same difference
in antibiotic use between the populations, was associated with a smaller difference in
antibiotic resistance. The difference in resistance between populations increases with
the difference in antibiotic use (Figure 1d), but the use-resistance association,

measured as the ratio of the difference in resistance to the difference in use, depends

strongly on the interaction strength (Figure 1e). Thus, spillover between populations

attenuates the measured use-resistance association.

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212 The use-resistance association was sensitive to \( \varepsilon \), the proportion of each population’s

contacts that are in the other population, but depended on choice of the mathematical

model of use-resistance association (Supplemental Table 1, Supplemental Figure 1).

215 For values as small as \( \varepsilon = 10^{-4} \), a typical level of interaction between two US states or

European countries (Supplemental Figure 2), the use-resistance association declined

by less than 1\% with the WHN model but up to 20\% for the “D-types” model. For \( \varepsilon = 
1\% \), the use-resistance declined by approximately 30\% in the WHN model and more

than 60\% in the “D-types” model. In other words, the models predict that as few as 1\%

of contacts need to be across populations, rather than within populations, to cause the

observed effect of an antibiotic stewardship intervention to shrink by one-third, or even

half.

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To test whether spillover is important at the scale of US states or European countries,

we measured use-resistance associations between pairs of populations in 6

combinations of pathogen species, antibiotic class, and data source (Figure 2). We

reasoned that, if spillover is relevant at these geographic scales, pairs of states or

countries with stronger interactions would have detectably weaker use-resistance

associations.
We first tested whether pairs of physically adjacent populations (e.g., Massachusetts and Connecticut) had weaker use-resistance associations than non-adjacent populations (e.g., Massachusetts and Alaska). In 5 of 6 pathogen/antibiotic/dataset combinations, the median use-resistance association was smaller among adjacent populations than among non-adjacent populations (Figure 3). In 2 cases, the confidence interval on the ratio of use-resistance associations among adjacent populations, compared to non-adjacent populations, did not include zero (Supplemental Table 2).

First, for *S. pneumoniae* resistance to macrolides in the MarketScan/ResistanceOpen dataset, use-resistance associations were 27% weaker (95% CI 6% to 49%) among adjacent states compared to non-adjacent states. Second, for *E. coli* resistance to quinolones in the Xponent/NHSN dataset, use-resistance associations were 50% weaker (95% CI 27% to 73%) among adjacent states compared to non-adjacent states. Results were similar when using a different metric of the use-resistance association (Supplemental Table 3).

We next checked that determinants of antibiotic resistance aside from antibiotic use were not artificially amplifying spillover, making differences in the use-resistance association between adjacent and non-adjacent pairs larger. We performed robust regressions, predicting the use-resistance association from adjacency while controlling for the differences in other covariates that are established determinants of resistance levels. Results were almost identical when including these covariates (Supplemental
Table 4), suggesting that these spatially-correlated covariates of resistance are not driving the spillover signal we observed.

Finally, we checked whether adjacency was too coarse a measure for interactions between populations by replacing the dichotomous adjacency variable with a continuous variable, the “commuting fraction”, defined as the proportion of residents of a pair of populations that commute to the other population (Figure 4). In 2 dataset/pathogen/antibiotic combinations, the confidence interval around the spillover signal did not include zero (Supplemental Table 5). First, for *E. coli* resistance to quinolones in the MarketScan/ResistanceOpen dataset, a modest commuting fraction comparable to the effect of adjacency ($10^{-4}$) was associated with a 0.9% decrease (95% CI 0.5% to 1.3%) in use-resistance associations, compared to pairs of states with no inter-state commuters. Second, *S. pneumoniae* resistance to macrolides in the ECDC dataset, that same commuting fraction was associated with a 12% decrease (95% CI 3% to 20%) in use-resistance associations.

**Discussion**

We used theoretical models to show that interactions between a control and intervention group can attenuate the reduction in antibiotic resistance expected from an antibiotic stewardship intervention. The quantitative relationship between the extent of inter-population interactions and the attenuation of the use-resistance association was dependent on the precise theoretical model used. However, we found that, in two
models of the use-resistance association, having on the order of 1% of interactions between a control and intervention population was sufficient to attenuate the observed effect of theoretical stewardship intervention by 50%, relative to a situation where the two populations were completely isolated. Thus, in theory, even small numbers of interactions could lead to a substantial underestimation of the potential reduction in antibiotic resistance that would follow from a reduction in antibiotic use, compared to the same reduction in use implemented in a completely isolated population.

In observational antibiotic use and resistance data in 3 pathogen-antibiotic combinations across 3 datasets, we found that point estimates of the spillover effect varied from as small as 1% to as large as 50%. In general, however, the confidence intervals on these estimates were wide, encompassing zero in most cases. We therefore did not find strong evidence to support our hypothesis, that spillover would have minimal effects at the level of US states. In fact, our results suggest that an experimental stewardship intervention conducted at the level of a US states might underestimate, by as much as 50%, the effect that the same intervention would have on resistance if it were implemented at a national scale. It is unclear if US states can be used as accurate “laboratories” of the effects of national stewardship policy.

Our study has multiple limitations. First, we used observational data to address questions about the design of outpatient stewardship interventions, which requires interpreting the theoretical results and ecological data as if the association between antibiotic use and resistance were causal and deterministic. In fact, antibiotic resistance
is associated with factors beyond antibiotic use (24,42), and we used only a limited number of determinants of resistance besides antibiotic use in our analyses.

Second, decreases in the use of an antibiotic may not necessarily lead to declines in resistance to that antibiotic in a target pathogen (10,43–45). We do not address co-resistance and cross-selection (46,47), and we assumed that resistance equilibrates on a timescale comparable to an intervention. Previous research has shown that resistance among *E. coli*, *S. pneumoniae*, *N. gonorrhoeae* and other organisms can respond to changes in antibiotic use on the timescale of months (48–51), but the expected delay between a perturbation to antibiotic use and the resulting change in resistance remains a subject of active study (11,48,52,53).

Finally, analyses based on administrative entities like US states, although logistically attractive “laboratories” of stewardship, will always be difficult to interpret because administrative entities average over important dimensions of population structure like age (54), sexual networks (55), and race/ethnicity (56). Thus, use-resistance associations measured across states and countries may be different from those that appear among geographically-proximate populations with dissimilar antibiotic use rates, such as the sexes (57) and racial/ethnic groups (58). We might have come to different conclusions about the role of spillover if we used different types of populations for analysis.
We suggest 3 lines of investigation that could refine our understanding about the role of spillover at levels of US states and European countries. First, further mathematical modeling studies with more realistic structuring of the host population might articulate more detailed theoretical expectations about the relationship between intervention scale and spillover. For example, models could be parameterized with epidemiological information about individuals’ contacts and travel patterns, as has been done for other infectious diseases (59). Second, meta-analysis of existing studies of use-resistance relationships (23,60,61), both experimental and observational, could potentially determine the empirical relationship between intervention population size and the importance of spillover. This kind of meta-analysis might reveal that populations other than US states are feasible “laboratories” for stewardship policy: it may be that cities, daycares, schools, workplaces, or even families represent the optimal trade-off between logistical feasibility and the accuracy of measured effect size. Finally, future experimental outpatient antibiotic stewardship interventions should make careful and deliberate decisions about the sizes and interconnectedness of the populations they target. We hope that a better understanding of spillover will allow stewardship interventions made by state and city health departments can be used to develop an evidence-based national antibiotic stewardship policy.
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Disclaimers

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Figure 1. **Interactions between populations attenuate the effect of interventions.**

(a) Schematic of the 2-population model. (b) Results of simulations of the 2-population WHN model for a modest intervention (difference in antibiotic use between populations $\Delta \tau = 0.05$ monthly treatments per capita; average of control and intervention treatment rates 0.125). As interaction strength ($\epsilon$, horizontal axis) increases, the difference in antibiotic resistance between the two populations decreases. Dotted line shows resistance level in populations before the intervention. (c) The same pattern holds for a stronger intervention ($\Delta \tau = 0.1$, same average treatment rate). (d) In general, the difference in resistance between populations ($\Delta \rho$, vertical axis) increases with the difference in antibiotic use ($\Delta \tau$, horizontal axis). (e) However, in the WHN model, the use-resistance relationship ($\Delta \rho / \Delta \tau$, vertical axis) depends mostly on the interaction strength $\epsilon$ and is mostly independent of the difference in antibiotic use $\Delta \tau$. 

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Figure 2. **Use-resistance relationships across US states and European countries.**

Each point represents antibiotic use and resistance in a US state (top row) or European country (bottom row). Lines show simple linear regression best fit. Gray areas show 95% confidence interval. Ec/q: *E. coli* and quinolones. Sp/m: *S. pneumoniae* and macrolides. Sp/bl: *S. pneumoniae* and β-lactams. RO: ResistanceOpen. ECDC: European CDC.
Figure 3. **Use-resistance relationships by adjacency.** Each point represents the use-resistance association in a pair of the US states (top row) or European countries (bottom row) shown in Figure 2, arranged by whether the pair of states or countries is physically adjacent. Physically adjacent populations tend to have weaker use-resistance associations. For visual clarity, the vertical axes are truncated to show only the central 90% of data points. Ec/q: *E. coli* and quinolones. Sp/m: *S. pneumoniae* and macrolides. Sp/bl: *S. pneumoniae* and β-lactams. RO: ResistanceOpen. ECDC: European CDC.
Figure 4. **Use-resistance associations by proportion of commuters.** Each point represents the use-resistance association in a pair of US states (top row) or European countries (bottom row), the same pairs as shown in Figure 3, arranged by “commuting fraction”, defined as the proportion of people who live in one population and commute to the other. For visual clarity, the horizontal axes are truncated to show only 95% of the data points. Pairs of populations reported as having no inter.population commuting are shown at $10^{-6}$. **Ec/q**: *E. coli* and quinolones. **Sp/m**: *S. pneumoniae* and macrolides. **Sp/bl**: *S. pneumoniae* and β-lactams. **RO**: ResistanceOpen. **ECDC**: European CDC.