Outpatient antibiotic stewardship interventions: geographic scale and associations between antibiotic use and resistance

Short title: Geographical scales of outpatient stewardship interventions

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Abstract

Background: Antibiotic stewardship interventions aim to combat antibiotic resistance by reducing inappropriate antibiotic use. One obstacle to the rational design of outpatient stewardship programs is that small-scale pilot experiments that aim to reduce antibiotic resistance by reducing antibiotic use may produce results that are systematically different from results observed in larger-scale implementations. Here, we investigate the relationship between geographic scale and the effect of reductions in antibiotic use.

Methods and findings: First, we show that dynamical models of antibiotic resistance exhibit "spillover", such that resistance in an intervention population is partly due to antibiotic use in surrounding populations, which attenuates the intervention's effect size. Second, using observational antibiotic use and resistance data from US states and European countries for 3 pathogen-antibiotic combinations, we show that use-resistance associations are robust to aggregation above the level of US states or European countries. Finally, we did not detect differences in the strength of use-resistance associations measured between pairs of adjacent states or countries, which presumably have stronger spillover, compared to the associations among non-adjacent pairs.

Conclusions: These results imply that interventions at the level of US states will yield effect sizes that can be used to estimate the effects of regional or national interventions.

47

48 **Introduction**

49 Antibiotic resistance is a major threat to public health (1). Outpatient antibiotic use,
50 which accounts for approximately 80% of all human antibiotic use (2,3), is considered a
51 principal driver of antibiotic resistance in the community (4). Antibiotic stewardship
52 initiatives reduce antibiotic use with the goal of lowering healthcare costs (5), preventing
53 adverse drug events (6,7), and mitigating antibiotic resistance (8–10). Rational design of
54 stewardship initiatives requires quantitative models that predict the outcome of an
55 intervention. It is relatively simple to predict what reduction in antibiotic use is required
56 to achieve a target reduction in monetary costs or adverse events: each avoided
57 antibiotic prescription prevents the cost of that prescription and the risk of an adverse
58 event from that prescription. In contrast, quantitative predictions about how a reduction
59 in antibiotic use will affect antibiotic resistance are more challenging because resistance
60 is a complex, temporally dynamic phenomenon (11–14).

61

62 A critical feature of this complexity is that resistant bacteria can be transmitted, so that
63 the risk that an individual's infection is antibiotic resistant depends on that individual's
64 antibiotic use (15,16) as well as the rates of antibiotic use among that individual's
65 contacts (17), such as their family members (18–20). This effect of resistance "spilling
66 over" can be so strong that, for example, an individual in the hospital who has no recent
67 antibiotic use may have a higher risk of antibiotic resistance than an individual in the
68 community with a high antibiotic use rate (21). The same spillover phenomenon occurs
69 at the level of populations, such that resistance in a hospital can be affected by

resistance in nearby hospitals or by antibiotic use in the surrounding community (22–24).

If resistance spills over into an outpatient stewardship intervention population from surrounding populations not affected by the intervention, the effect on antibiotic resistance in the intervention population may be smaller than it would be if the intervention population were completely isolated, because spillover from the surrounding population is not changed by the intervention. Conversely, an outpatient stewardship intervention targeting a small population might underestimate the effect that a certain reduction in antibiotic use would have when applied to a larger population.

As the population targeted by the intervention increases, the amount of bacterial transmission and resistance spillover into the population presumably decreases relative to the amount of transmission within the population, thus also mitigating the spillover effect and providing ever more accurate predictions of an intervention's effect. It is unclear if stewardship interventions at small scales can accurately inform the design of interventions targeting larger populations. For example, an intervention at the level of a city may not provide results that can be projected to predict the effects of that intervention implemented at the level of a US state, which in turn may or may not be an accurate prediction of a nationwide intervention's effect.

Ideally, one could determine what population size is sufficiently large to mitigate spillover by consulting the results of randomized, controlled experiments that measure

how a reduction in antibiotic use affects resistance for the relevant pathogen and antibiotic. In practice, interventions are often not controlled (25,26). Only a few population-level, randomized experiments modulating antibiotic use have been conducted (27,28), and many of those were intentional increases in antibiotic use as part of mass drug administrations (29).

In contrast, the association between antibiotic use and antibiotic resistance has been characterized in many observational studies, including ecological studies at the level of US states (30–32), European countries (33,34), and smaller geographical areas (35–37). However, even for observational data, it is not clear what kinds of populations should be used to minimize the spillover problem (38,39). For example, larger geographical areas would be expected to have less spillover. Aggregating smaller geographical units into larger units for the purposes of analysis might therefore average over the relevant scales of transmission, producing stronger correlations between use and resistance (32,40). Conversely, it has been suggested that analyses at smaller geographic scales may be more likely to detect relationships between use and resistance (10), possibly because aggregating over larger areas obscures important variations in use or resistance (41). In principle, multilevel models with individual-level data can account for correlations between geographical units, but the selection of the units will still affect the results (28,42,43) and few studies of antibiotic use and resistance have assessed the sensitivity of the results to the choice of population used in the analysis.

In this study, we aim to determine whether outpatient stewardship experiments at the level of US states or European countries can be expected to provide accurate estimates of the effect that the same reduction in antibiotic use would have if applied over a larger area, indicating that interventions in smaller populations can be used to predict the effect of an intervention in a larger population. First, we show that the spillover effect does occur in mathematical models of antibiotic use and resistance, and we measure how interactions between theoretical populations attenuate use-resistance associations. Second, we look for empirical evidence that spillover has a measurably different effect at scales above US states or European countries.

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*. (44) and described in the Supplemental Methods. Briefly, the model predicts the prevalence ρ of antibiotic resistance that results from an antibiotic use rate τ 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 (45). Parameter values and simulation methodology for both models are in the Supplemental Methods. In the simulations, antibiotic use as monthly treatments per capita and resistance as the proportion of colonized hosts carrying resistant strains.

We adapted the WHN model to include multiple, interacting populations using a structured host population approach inspired by Blanquart *et al.* (46). Interactions between populations are modulated by the proportion ε of a population's contacts that are in other populations. For $\varepsilon = 0$, each population is completely separate. For $\varepsilon = 1$, contacts across populations are just as likely as contacts within populations (Supplemental Methods).

We simulated a situation in which an intervention population has a lower antibiotic use rate τ_{int} than a control population with use rate $\tau_{\text{cont}} > \tau_{\text{int}}$. To measure how contacts between the two populations affect the intervention's effect size, we varied three parameters, setting ε to each of the values 0.00, 0.01, 0.10, 0.25, and 0.50; and setting $(\tau_{\text{cont}}, \tau_{\text{int}})$ to (0.15, 0.10) or (0.20, 0.05) treatments per person per month.

Mathematical models with nested population structure

To examine the effect of population structure on associations between antibiotic use and resistance, we further adapted the multi-population model to include a nested population structure with $n_{\text{super}} \times n_{\text{sub}}$ populations. The populations are grouped into n_{super} "super-populations" representing geographic regions. Each super-population has n_{sub} constituent subpopulations, each representing a smaller geographic area like a US state or European country. Populations within a super-population interact according to the parameter ε_{sub}, while populations in different super-populations interact according to $\varepsilon_{\text{super}} \leq \varepsilon_{\text{sub}}$ (Figure 1a, Supplemental Methods). The inequality encodes the idea that

US states within a region will interact more strongly with one another than with states in other regions, for example.

To measure the effect of population structure on use-resistance associations, we set $n_{\text{super}} = n_{\text{sub}} = 4$ and varied three parameters, setting ε_{sub} to 0.00, 0.01, 0.10, and 0.50; $\varepsilon_{\text{super}}$ to the same values, subject to $\varepsilon_{\text{super}} \leq \varepsilon_{\text{sub}}$; and setting τ_i to a range of values between 0.05 and 0.20 treatments per person per month (Supplemental Table 1).

Observational data

In this study, we examined antibiotic use and resistance for 3 pathogen-antibiotic combinations: *S. pneumoniae* and macrolides, *S. pneumoniae* and β-lactams, and *Escherichia coli* and quinolones. We considered these 3 combinations because they are the subject of many modeling (44,45) and empirical studies (15,30).

Observational data were drawn from 3 sources. First, we used MarketScan (47) and ResistanceOpen (48) as previously described (32). 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 (49) and the US Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN) (50). 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

185 infections during 2011-2014. Third, we used the European Center for Disease
186 Prevention and Control's (ECDC) ESAC-Net antimicrobial consumption database (51)
187 and EARS-Net Surveillance Atlas of Infectious Disease (52) for 2011-2015. The ESAC-
188 Net data includes country-level outpatient antibiotic use data provided by WHO and
189 Ministries of Health from member countries. The EARS-Net data includes country-level
190 resistance data. In the observational data, we quantified antibiotic use as yearly
191 treatments per capita and resistance as the proportion of collected isolates that were
192 non-susceptible. Further details about preparation of these data sources and their
193 availability are in the Supplemental Methods.
194
195 *Use-resistance associations by scale of aggregation*
196 To test the idea that use-resistance associations are stronger when analyzing larger
197 populations, presumably by decreasing spillover, we measured use-resistance
198 associations when US states were aggregated into the 9 Census divisions or 4 Census
199 regions and when European countries were aggregated into the 4 United Nations
200 geoscheme sub-regions (53). Aggregate antibiotic use rates were computed as the
201 population-weighted mean antibiotic use (Supplemental Methods). Aggregate
202 resistance values were computed by summing the numerator number of resistant
203 isolates and the denominator number of total isolates. Use-resistance associations were
204 measured by logistic regression. Confidence intervals on the regression fits were
205 evaluated using 1,000 bootstrap replications.
206
207 *Use-resistance relationships by adjacency*

To test the idea that the same difference in antibiotic use will be associated with smaller differences in antibiotic resistance when the two populations have stronger interactions, we tested whether the use-resistance association is weaker for geographic units (US states or European countries) that are physically adjacent to one another. Two units were considered adjacent if they share a land or river border (Supplemental Methods). We performed robust linear regressions (Tukey's bisquare) predicting the log odds ratio of resistance between two units. Regressions were computed using the *rlm* function in the MASS package (54) in R (version 3.5.1) (55). Predictors in the model were the differences in antibiotic use, population density, per capita income, and mean temperature (31) between the two units (Supplemental Methods). The model also included an interaction term between antibiotic use and adjacency, which allows adjacent pairs of geographic units to have a different use-resistance association from non-adjacent pairs:

$$\Delta\mathrm{LO}(\rho)_i = \beta_\tau(\Delta\tau)_i + \beta_{\tau a}(\Delta\tau)_i a_i + \beta_{\mathrm{dens}}\Delta\mathrm{dens}_i + \beta_{\mathrm{income}}\Delta\mathrm{income}_i + \beta_{\mathrm{temp}}\Delta\mathrm{temp}_i + \varepsilon_i$$

where *i* indexes the pairs of units, ΔLO(ρ) is the log odds ratio of resistance between the two units $\Delta\tau$ is the difference in antibiotic use, *a* is a flag for whether the units in the pair are adjacent, and ε is the error term. Confidence intervals on the regression fits were evaluated using 1,000 bootstrap replications resampling the geographic units and assembling new lists of pairs in each replication.

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 difference in antibiotic use between the populations was associated with a smaller difference in antibiotic resistance. Similar results held for the D-types model (Supplemental Figure 1).

In simulations of nested populations, with state-like populations grouped into region-like "super-populations", interactions within super-populations modulate use-resistance associations within super-populations, while interactions across super-populations modulate the use-resistance association across all populations (Figure 2a). When aggregating the populations into super-populations, the use-resistance associations across all super-populations are similar to the associations across all populations (Figure 2b). However, analysis of pairs of populations can detect the within-super-population interactions (Figure 2c) because pairs of populations from different super-populations tend to have differences in resistance that scale with their differences in antibiotic use, while pairs in the same super-population tend to have much smaller differences in resistance for the same differences in antibiotic use. Similar results were observed in the D-types model (Supplemental Figure 2).

In observational data of antibiotic use and resistance for 3 pathogen-antibiotic combinations, we found that aggregating geographic units (US states or European countries) into regional units (US Census division, US Census regions, or European regions) produced similar use-resistance associations. Associations varied by

253 pathogen-antibiotic-dataset combination (Figure 3, Supplemental Figures 3). However,
254 similar to the theoretical prediction (Figure 2b), associations were similar when
255 measured across the original geographic units or across regional aggregations of those
256 units (Supplemental Figure 4).
257
258 Using the observational data, we evaluated whether use-resistance associations
259 between pairs of US states or European countries were weaker for adjacent pairs than
260 for non-adjacent pairs, as occurred for some parameterizations in theoretical
261 simulations (Figure 2c). We found no evidence for differences in the use-resistance
262 associations among adjacent pairs compared to non-adjacent pairs (Figure 4,
263 Supplemental Figure 5, Supplemental Table 2).
264
265
266 **Discussion**
267 We used theoretical models to show that interactions between a control and intervention
268 group can attenuate the reduction in antibiotic resistance expected from an antibiotic
269 stewardship intervention. However, consistent with at least one previous study (40),
270 empirical data did not provide robust evidence that aggregating US states or European
271 countries into regions yielded stronger use-resistance associations. Furthermore, the
272 same difference in antibiotic use between a pair of US states or European countries
273 was associated with similar differences in antibiotic resistance between the units in the
274 pair regardless of whether the units were physically adjacent or not. These results
275 suggest that spillover at the level of US states and European countries is not

276 substantially stronger than spillover at regional scales. Thus, outpatient stewardship
277 experiments at the level of US states may have effect sizes similar to those that would
278 be achieved in a national intervention. States may serve as accurate pilot populations
279 for designing national interventions.
280
281 Our study has multiple limitations. First, we used observational data to address
282 questions about the design of outpatient stewardship interventions, which requires
283 interpreting the theoretical results and ecological data as if the association between
284 antibiotic use and resistance were causal and deterministic. In fact, antibiotic resistance
285 is associated with factors beyond antibiotic use (31,56), and we used only a limited
286 number of determinants of resistance besides antibiotic use in our distance analysis.
287
288 Second, decreases in the use of an antibiotic may not necessarily lead to declines in
289 resistance to that antibiotic in a target pathogen (13,27,57,58). We do not address co-
290 resistance and cross-selection (59,60), and we assumed that resistance equilibrates on
291 a timescale comparable to the intervention. Previous research has shown that
292 resistance among *E. coli*, *S. pneumoniae*, *N. gonorrhoeae* and other organisms can
293 respond to changes in antibiotic use on the timescale of months (61–64), but the
294 expected delay between a perturbation to antibiotic use and the resulting change in
295 resistance remains a subject of active study (14,61,65,66).
296
297 Third, we only considered geographical populations. Although people within a US state
298 interact more often with other residents of that state than with residents of other states,

299 geography averages over important dimensions of population structure like age (67),
300 sexual networks (68), and race/ethnicity (69). Use-resistance relationships measured
301 across geographical units may be different from those that appear among
302 geographically-proximate populations with dissimilar antibiotic use rates, such as the
303 sexes (70) and racial/ethnic groups (71).
304
305 A final caveat is that our data sources limited us to analyzing geographical populations
306 at or larger than the scale of US states or European countries. Previous research has
307 shown that spillover is important for individuals (17–20), and the results of this study
308 suggest that US states and European countries do not have substantially stronger
309 spillover than larger regions, but the importance of spillover at smaller scales remains
310 unclear. Depending on the epidemiology of bacterial transmission and the distribution of
311 antibiotic use within the targeted populations, it may be that cities, daycares, schools,
312 workplaces, or even families represent the optimal trade-off between logistical feasibility
313 and the accuracy of measured effect size for a particular pathogen and antibiotic.
314
315 We suggest 3 lines of investigation that could help address the knowledge gap about
316 the important of spillover at levels between individuals and US states or European
317 countries. First, further mathematical modeling studies with more realistic structuring of
318 the host population might articulate more detailed theoretical expectations about the
319 relationship between intervention scale and spillover. For example, models could be
320 parameterized with epidemiological information about individuals' contacts and travel
321 patterns, as has been done for other infectious diseases (72). Second, meta-analysis of

existing studies of use-resistance relationships (28–30), both experimental and observational, might determine how increasing population scales are associated with increasing use-resistance associations. Finally, future experimental outpatient antibiotic stewardship interventions should make careful and deliberate decisions about the sizes and interconnectedness of the populations they target. The results of this study suggest that outpatient interventions can be effective at scales smaller than US states. We hope this means that outpatient stewardship can be effectively addressed by more organizations, such as state and city health departments.

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573 **Figures and figure legends**

574

575 Figure 1. **Interactions between populations attenuate the effect of interventions.**
576 (*a*) Schematic of the 2-population WHN model. (*b*) Results of simulations of the 2-
577 population WHN model for a modest intervention (difference in antibiotic use between
578 populations $\Delta\tau$ = 0.05 monthly treatments per capita). As interaction strength (ε,
579 horizontal axis) increases, the difference in antibiotic resistance between the two
580 populations decreases. (*c*) The same pattern holds for a stronger intervention ($\Delta\tau$ =
581 0.15). Compare Supplemental Figure 1, which shows the analogous results for the D-
582 types model.

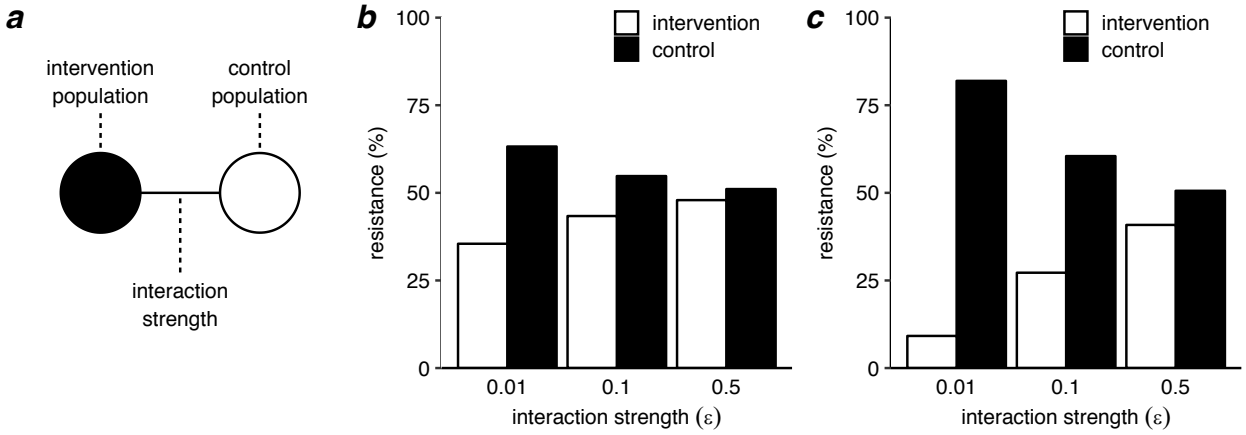

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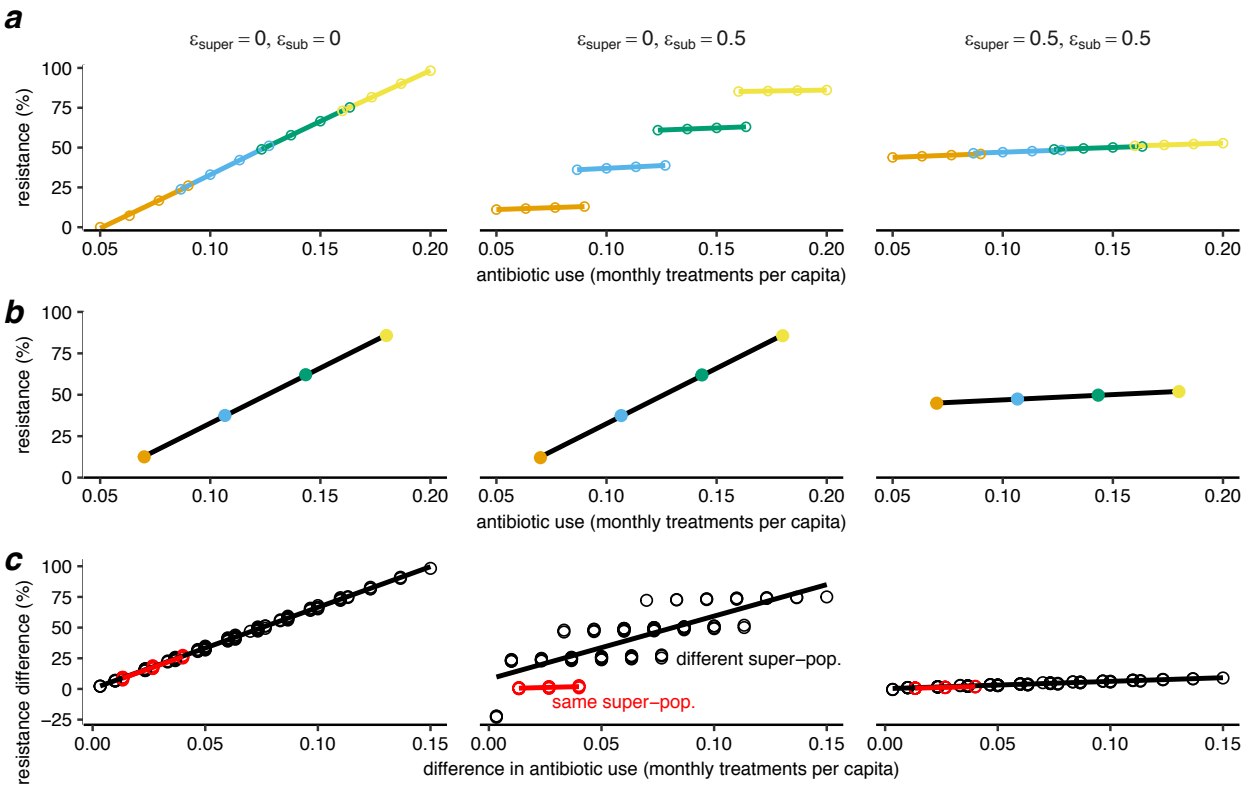
Figure 2. **Theoretical use-resistance associations with regional population structure.** (*a*) Results of simulations of nested population simulations using the WHN model for 3 parameter sets (panel columns). Populations (circles) in the same super-population (color) interact more strongly (ε_{sub}) with populations in the same super-population than with other populations ($\varepsilon_{\text{super}} \leq \varepsilon_{\text{sub}}$). Lines show linear best fit within each super-population. (*b*) Points show the populations in panel *a* but aggregated into super-populations. Each super-population's use and resistance is the mean of its constituent populations' values. Lines show linear best fit across super-populations. (*c*) Each point represents a pair of populations from panel *a*. Points' positions represent the differences in antibiotic use and resistance between the populations in the pair. Colors indicate whether the two populations are in the same super-population. Lines show best fit among the same-super-population and different-super-population pairs. Compare Supplemental Figure 2, which shows the analogous results for the D-types model.



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599 Figure 3. **Use-resistance associations when regionally aggregated.** Panels show
600 use-resistance relationships for 3 pathogen-antibiotic combinations in the
601 MarketScan/ResistanceOpen dataset. Points represent geographic units of analysis at
602 different aggregation levels (black, US states; green, US Census divisions; orange, US
603 Census regions). Curves show logistic regression fits. Shaded regions show 95%
604 bootstrap confidence intervals. Compare Figure 2b, which shows that theoretical
605 models predict the same use-resistance associations across aggregated and
606 unaggregated data. Compare also Supplemental Figure 3, which shows analogous
607 results using the other datasets.

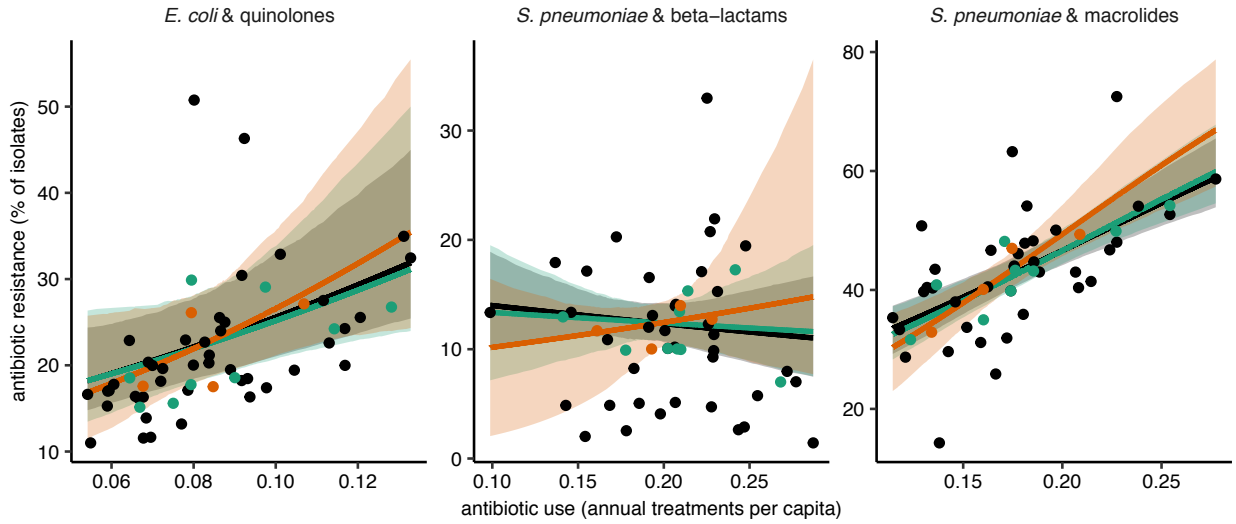

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Figure 4. **Use-resistance relationships by adjacency.** Each point represents a pair of US states. The point's position represents the difference in use of macrolides between the two states (horizontal axis) and the difference in macrolide resistance among *S. pneumoniae* between the states (log odds ratio) using the MarketScan/ResistanceOpen data, shown in one of the panels of Figure 3. The point's color indicates whether the states are physically adjacent (red = adjacent, black = not adjacent). Lines show predictions from robust linear regressions on the adjacent and non-adjacent pairs, using the indicated difference in antibiotic use and mean values for the other model predictors. Shaded areas indicate regressions' 95% bootstrap confidence intervals. Compare Figure 2c, which shows that adjacency effects can be detected in theoretical models. Compare also Supplemental Figure 5, which shows analogous results for other pathogen-antibiotic combinations and other datasets.