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.
**Introduction**

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

A critical feature of this complexity is that resistant bacteria can be transmitted, so that the risk that an individual’s infection is antibiotic resistant depends on that individual’s antibiotic use (15,16) as well as the rates of antibiotic use among that individual’s contacts (17), such as their family members (18–20). This effect of resistance “spilling over” can be so strong that, for example, an individual in the hospital who has no recent antibiotic use may have a higher risk of antibiotic resistance than an individual in the community with a high antibiotic use rate (21). The same spillover phenomenon occurs 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 $\rho$ 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 (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 \( \varepsilon \) 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 \( \tau_{\text{int}} \) 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 \( \varepsilon \) 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 \( n_{\text{super}} \) “super-populations” representing geographic regions. Each super-population has \( n_{\text{sub}} \) 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 \( \varepsilon_{\text{sub}} \), 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 \( \varepsilon_{\text{sub}} \) 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 \( \tau_{i} \) 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 \( \beta \)-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
infections during 2011-2014. Third, we used the European Center for Disease Prevention and Control’s (ECDC) ESAC-Net antimicrobial consumption database (51) and EARS-Net Surveillance Atlas of Infectious Disease (52) 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.

Use-resistance associations by scale of aggregation

To test the idea that use-resistance associations are stronger when analyzing larger populations, presumably by decreasing spillover, we measured use-resistance associations when US states were aggregated into the 9 Census divisions or 4 Census regions and when European countries were aggregated into the 4 United Nations geoscheme sub-regions (53). Aggregate antibiotic use rates were computed as the population-weighted mean antibiotic use (Supplemental Methods). Aggregate resistance values were computed by summing the numerator number of resistant isolates and the denominator number of total isolates. Use-resistance associations were measured by logistic regression. Confidence intervals on the regression fits were evaluated using 1,000 bootstrap replications.

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 \textit{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:

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

where $i$ indexes the pairs of units, $\Delta \text{LO}(\rho)$ 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 $\epsilon$ 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
pathogen-antibiotic-dataset combination (Figure 3, Supplemental Figures 3). However, similar to the theoretical prediction (Figure 2b), associations were similar when measured across the original geographic units or across regional aggregations of those units (Supplemental Figure 4).

Using the observational data, we evaluated whether use-resistance associations between pairs of US states or European countries were weaker for adjacent pairs than for non-adjacent pairs, as occurred for some parameterizations in theoretical simulations (Figure 2c). We found no evidence for differences in the use-resistance associations among adjacent pairs compared to non-adjacent pairs (Figure 4, Supplemental Figure 5, Supplemental Table 2).

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. However, consistent with at least one previous study (40), empirical data did not provide robust evidence that aggregating US states or European countries into regions yielded stronger use-resistance associations. Furthermore, the same difference in antibiotic use between a pair of US states or European countries was associated with similar differences in antibiotic resistance between the units in the pair regardless of whether the units were physically adjacent or not. These results suggest that spillover at the level of US states and European countries is not
substantially stronger than spillover at regional scales. Thus, outpatient stewardship experiments at the level of US states may have effect sizes similar to those that would be achieved in a national intervention. States may serve as accurate pilot populations for designing national interventions.

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 (31,56), and we used only a limited number of determinants of resistance besides antibiotic use in our distance analysis.

Second, decreases in the use of an antibiotic may not necessarily lead to declines in resistance to that antibiotic in a target pathogen (13,27,57,58). We do not address co-resistance and cross-selection (59,60), and we assumed that resistance equilibrates on a timescale comparable to the 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 (61–64), but the expected delay between a perturbation to antibiotic use and the resulting change in resistance remains a subject of active study (14,61,65,66).

Third, we only considered geographical populations. Although people within a US state interact more often with other residents of that state than with residents of other states,
geography averages over important dimensions of population structure like age (67),
sexual networks (68), and race/ethnicity (69). Use-resistance relationships measured
across geographical units may be different from those that appear among
geographically-proximate populations with dissimilar antibiotic use rates, such as the
sexes (70) and racial/ethnic groups (71).

A final caveat is that our data sources limited us to analyzing geographical populations
at or larger than the scale of US states or European countries. Previous research has
shown that spillover is important for individuals (17–20), and the results of this study
suggest that US states and European countries do not have substantially stronger
spillover than larger regions, but the importance of spillover at smaller scales remains
unclear. Depending on the epidemiology of bacterial transmission and the distribution of
antibiotic use within the targeted populations, 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 for a particular pathogen and antibiotic.

We suggest 3 lines of investigation that could help address the knowledge gap about
the important of spillover at levels between individuals and US states or 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 (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.
References

1. Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: final report and recommendations. 2016.

2. Public Health England. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR). 2014.

3. Public Health Agency of Sweden, National Veterinary Institute. Consumption of antibiotics and occurrence of antibiotic resistance in Sweden.

4. US Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2013. 2013.

5. US Centers for Medicare & Medicaid Services. A Field Guide to Antibiotic Stewardship in Outpatient Settings. A Field Guide to Antibiotic Stewardship in Outpatient Settings July 2018. 2018.

6. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. JAMA. 2016 Nov 22;316(20):2115.

7. Dantes R, Mu Y, Hicks LA, Cohen J, Bamberg W, Beldavs ZG, et al. Association between Outpatient Antibiotic Prescribing Practices and Community-Associated Clostridium difficile Infection. Open Forum Infect Dis. 2015 Aug 11;ofv113.

8. Sanchez G V., Fleming-Dutra KE, Roberts RM, Hicks LA. Core Elements of Outpatient Antibiotic Stewardship. MMWR Recomm Rep. 2016 Nov 11;65(6):1–12.

9. Dellit TH, Owens RC, McGowan JE, Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis Off Publ Infect Dis Soc Am. 2007 Jan 15;44(2):159–77.

10. Vellinga A, Murphy AW, Hanahoe B, Bennett K, Cormican M. A multilevel analysis of trimethoprim and ciprofloxacin prescribing and resistance of uropathogenic Escherichia coli in general practice. J Antimicrob Chemother. 2010 Jul;65(7):1514–20.

11. Livermore DM. The 2018 Garrod Lecture: Preparing for the Black Swans of resistance. J Antimicrob Chemother. 2018 Nov 1;73(11):2907–15.

12. Turnidge J, Christiansen K. Antibiotic use and resistance--proving the obvious. Lancet Lond Engl. 2005 Feb;365(9459):548–9.
13. Arason VA, Gunnlaugsson A, Sigurdsson JA, Erlendsdottir H, Gudmundsson S, 
Kristinsson KG. Clonal Spread of Resistant Pneumococci Despite Diminished 
Antimicrobial Use. Microb Drug Resist. 2002 Sep;8(3):187–92.

14. Lipsitch M. The rise and fall of antimicrobial resistance. Trends Microbiol. 2001 
Sep;9(9):438–44.

15. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic 
prescribing in primary care on antimicrobial resistance in individual patients: 
systematic review and meta-analysis. BMJ. 2010 May 18;340:c2096.

16. Harbarth S, Harris AD, Carmeli Y, Samore MH. Parallel analysis of individual and 
aggregated data on antibiotic exposure and resistance in gram-negative bacilli. Clin 
Infect Dis. 2001;33:1462–8.

17. Lipsitch M. Measuring and Interpreting Associations between Antibiotic Use and 
Penicillin Resistance in Streptococcus pneumoniae. Clin Infect Dis. 2001 Apr 
1;32(7):1044–54.

18. Hannah EL, Angulo FJ, Johnson JR, Haddadin B, Williamson J, Samore MH. Drug-
resistant Escherichia coli, Rural Idaho. Emerg Infect Dis. 2005 Oct;11(10):1614–7.

19. Kalter HD, Gilman RH, Moulton LH, Cullotta AR, Cabrera L, Velapatiño B. Risk 
factors for antibiotic-resistant Escherichia coli carriage in young children in Peru: 
community-based cross-sectional prevalence study. Am J Trop Med Hyg. 2010 
May;82(5):879–88.

20. Samore MH, Magill MK, Alder SC, Severina E, Morrison-De Boer L, Lyon JL, et al. 
High rates of multiple antibiotic resistance in Streptococcus pneumoniae from 
healthy children living in isolated rural communities: association with cephalosporin 
use and intrafamilial transmission. Pediatrics. 2001 Oct;108(4):856–65.

21. Lipsitch M, Samore MH. Antimicrobial use and antimicrobial resistance: a 
population perspective. Emerg Infect Dis. 2002;8:347–54.

22. Cooper BS, Medley GF, Stone SP, Kibbler CC, Cookson BD, Roberts JA, et al. 
Methicillin-resistant Staphylococcus aureus in hospitals and the community: Stealth 
dynamics and control catastrophes. Proc Natl Acad Sci. 2004 Jul 6;101(27):10223–
8.

23. MacFadden DR, Fishman DN, Hanage WP, Lipsitch M. The Relative Impact of 
Community and Hospital Antibiotic Use on the Selection of Extended-Spectrum 
Beta-lactamase-Producing Escherichia coli. Clin Infect Dis [Internet]. 2018 [cited 
2018 Nov 29]; Available from: https://www.ncbi.nlm.nih.gov/pubmed/30462185

24. Knight GM, Costelloe C, Deeny SR, Moore LSP, Hopkins S, Johnson AP, et al. 
Quantifying where human acquisition of antibiotic resistance occurs: a 
mathematical modelling study. BMC Med. 2018 23;16(1):137.
25. Seppälä H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, et al. The Effect of Changes in the Consumption of Macrolide Antibiotics on Erythromycin Resistance in Group A Streptococci in Finland. N Engl J Med. 1997 Aug 14;337(7):441–6.

26. Kristinsson KG. Effect of antimicrobial use and other risk factors on antimicrobial resistance in pneumococci. Microb Drug Resist Larchmt N. 1997;3(2):117–23.

27. Hennessy TW, Petersen KM, Bruden D, Parkinson AJ, Hurlburt D, Getty M, et al. Changes in Antibiotic-Prescribing Practices and Carriage of Penicillin-Resistant Streptococcus pneumoniae: A Controlled Intervention Trial in Rural Alaska. Clin Infect Dis. 2002 Jun 15;34(12):1543–50.

28. Schechner V, Temkin E, Harbarth S, Carmeli Y, Schwaber MJ. Epidemiological interpretation of studies examining the effect of antibiotic usage on resistance. Clin Microbiol Rev. 2013 Apr;26(2):289–307.

29. O’Brien KS, Emerson P, Hooper P, Reingold AL, Dennis EG, Keenan JD, et al. Antimicrobial resistance following mass azithromycin distribution for trachoma: a systematic review. Lancet Infect Dis [Internet]. 2018 Oct 3 [cited 2018 Nov 7]; Available from: http://www.sciencedirect.com/science/article/pii/S1473309918304444

30. Bell BG, Schellevis F, Stoberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis. 2014 Jan 9;14:13.

31. MacFadden DR, McGough SF, Fisman D, Santillana M, Brownstein JS. Antibiotic resistance increases with local temperature. Nat Clim Change. 2018 Jun;8(6):510–4.

32. Olesen SW, Barnett ML, MacFadden DR, Brownstein JS, Hernández-Díaz S, Lipsitch M, et al. The distribution of antibiotic use and its association with antibiotic resistance. eLife [Internet]. 2018 Dec 18 [cited 2018 Dec 19];7. Available from: https://elifesciences.org/articles/39435

33. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. The Lancet. 2005 Feb 12;365(9459):579–87.

34. van de Sande-Bruinsma N, Grundmann H, Verloo D, Tiemersma E, Monen J, Goossens H, et al. Antimicrobial drug use and resistance in Europe. Emerg Infect Dis. 2008 Nov;14(11):1722–30.

35. Garcia-Rey C, Aguilar L, Baquero F, Casal J, Dal-Re R. Importance of local variations in antibiotic consumption and geographical differences of erythromycin and penicillin resistance in Streptococcus pneumoniae. J Clin Microbiol. 2002 Jan;40:159–64.
36. Bergman M, Nyberg ST, Huovinen P, Paakkari P, Hakanen AJ, and the Finnish Study Group for Antimicrobial Resistance. Association between Antimicrobial Consumption and Resistance in Escherichia coli. Antimicrob Agents Chemother. 2009 Mar 1;53(3):912–7.

37. MacDougall C, Powell JP, Johnson CK, Edmond MB, Polk RE. Hospital and community fluoroquinolone use and resistance in Staphylococcus aureus and Escherichia coli in 17 US hospitals. Clin Infect Dis. 2005 Aug 15;41:435–40.

38. Vellinga A, Tansey S, Hanahoe B, Bennett K, Murphy AW, Cormican M. Trimethoprim and ciprofloxacin resistance and prescribing in urinary tract infection associated with Escherichia coli: a multilevel model. J Antimicrob Chemother. 2012 Oct 1;67(10):2523–30.

39. Donnan PT, Wei L, Steinke DT, Phillips G, Clarke R, Noone A, et al. Presence of bacteriuria caused by trimethoprim resistant bacteria in patients prescribed antibiotics: multilevel model with practice and individual patient data. BMJ. 2004 May 29;328(7451):1297.

40. Priest P, Wise R, Yudkin P, McNulty C, Mant D. Antibacterial prescribing and antibacterial resistance in English general practice: cross sectional study. BMJ. 2001 Nov 3;323(7320):1037–41.

41. García-Rey C, Martín-Herrero JE, Baquero F. Antibiotic consumption and generation of resistance in Streptococcus pneumoniae: the paradoxical impact of quinolones in a complex selective landscape. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2006 May;12 Suppl 3:55–66.

42. Openshaw S. The modifiable areal unit problem. Geo Books; 1984. (Concepts and Techniques in Modern Geography).

43. Vellinga A, Bennett K, Murphy AW, Cormican M. Principles of multilevel analysis and its relevance to studies of antimicrobial resistance. J Antimicrob Chemother. 2012 Oct;67(10):2316–22.

44. Davies NG, Flasche S, Jit M, Atkins KE. Within-host dynamics explain patterns of antibiotic resistance in commensal bacteria. bioRxiv. 2018 Jan 3;217232.

45. Lehtinen S, Blanquart F, Croucher NJ, Turner P, Lipsitch M, Fraser C. Evolution of antibiotic resistance is linked to any genetic mechanism affecting bacterial duration of carriage. Proc Natl Acad Sci. 2017 Jan 31;114(5):1075–80.

46. Blanquart F, Lehtinen S, Lipsitch M, Fraser C. The evolution of antibiotic resistance in a structured host population. J R Soc Interface. 2018 Jun;15(143).

47. Truven Health MarketScan Database. Commercial Claims and Encounters. Ann Arbor, MI; 2015.
476 48. MacFadden DR, Fisman D, Andre J, Ara Y, Majumder MS, Bogoch II, et al. A Platform for Monitoring Regional Antimicrobial Resistance, Using Online Data Sources: ResistanceOpen. J Infect Dis. 2016 Dec 1;214(suppl_4):S393–8.

479 49. US Centers for Disease Control and Prevention. Patient Safety Atlas - Outpatient Antibiotic Use [Internet]. [cited 2018 Oct 25]. Available from: https://gis.cdc.gov/grasp/PSA/indexAU.html

50. US Centers for Disease Control and Prevention. Patient Safety Atlas - Antibiotic Resistance [Internet]. [cited 2018 Oct 25]. Available from: https://gis.cdc.gov/grasp/PSA/AboutTheData.html

51. European Centre for Disease Prevention and Control. Antimicrobial consumption database [Internet]. European Centre for Disease Prevention and Control. [cited 2018 Oct 25]. Available from: http://ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database

52. European Centre for Disease Prevention and Control. Surveillance Atlas of Infectious Diseases [Internet]. [cited 2018 Oct 25]. Available from: https://atlas.ecdc.europa.eu/public/index.aspx

53. United Nations Statistics Division. Standard country or area codes or statistical use [Internet]. New York: United Nations; 1999. Report No.: M No. 49. Available from: https://unstats.un.org/unsd/methodology/m49/

54. Venables WN, Ripley BD. Modern applied statistics with S [Internet]. 4th ed. New York: Springer; 2002. Available from: www.stats.ox.ac.uk/pub/MASS4

55. R Core Team. R: A language and environment for statistical computing [Internet]. Vienna; 2018. Available from: www.R-project.org

56. Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. Lancet Planet Health. 2018 Sep;2(9):e398–405.

57. Sundqvist M, Geli P, Andersson DI, Sjölund-Karlsson M, Runehagen A, Cars H, et al. Little evidence for reversibility of trimethoprim resistance after a drastic reduction in trimethoprim use. J Antimicrob Chemother. 2010 Feb;65(2):350–60.

58. Enne VI, Livermore DM, Stephens P, Hall LM. Persistence of sulphonamide resistance in Escherichia coli in the UK despite national prescribing restriction. Lancet Lond Engl. 2001 Apr 28;357(9265):1325–8.

59. Pouwels KB, Freeman R, Muller-Pebody B, Rooney G, Henderson KL, Robotham JV, et al. Association between use of different antibiotics and trimethoprim resistance: going beyond the obvious crude association. J Antimicrob Chemoth. 2018;
Tedijanto C, Olesen SW, Grad YH, Lipsitch M. Estimating the proportion of bystander selection for antibiotic resistance among potentially pathogenic bacterial flora. Proc Natl Acad Sci. 2018 Dec 18;115(51):E11988–95.

Olesen SW, Torrone EA, Papp JR, Kirkcaldy RD, Lipsitch M, Grad YH. Azithromycin Susceptibility Among Neisseria gonorrhoeae Isolates and Seasonal Macrolide Use. J Infect Dis [Internet]. 2018 [cited 2018 Nov 6]; Available from: http://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jy551/5098400

Dagan R, Barkai G, Givon-Lavi N, Sharf AZ, Vardy D, Cohen T, et al. Seasonality of Antibiotic-Resistant Streptococcus pneumoniae That Causes Acute Otitis Media: A Clue for an Antibiotic-Restriction Policy? J Infect Dis. 2008 Apr 15;197(8):1094–102.

Sun L, Klein EY, Laxminarayan R. Seasonality and Temporal Correlation between Community Antibiotic Use and Resistance in the United States. Clin Infect Dis. 2012 Sep 1;55(5):687–94.

Blanquart F, Lehtinen S, Fraser C. An evolutionary model to predict the frequency of antibiotic resistance under seasonal antibiotic use, and an application to Streptococcus pneumoniae. Proc R Soc B. 2017 May 31;284(1855):20170679.

Dingle KE, Didelot X, Quan TP, Eyre DW, Stoesser N, Golubchik T, et al. Effects of control interventions on Clostridium difficile infection in England: an observational study. Lancet Infect Dis. 2017 Apr;17(4):411–21.

McCormick AW, Whitney CG, Farley MM, Lynfield R, Harrison LH, Bennett NM, et al. Geographic diversity and temporal trends of antimicrobial resistance in Streptococcus pneumoniae in the United States. Nat Med. 2003 Apr;9(4):424–30.

Mossong J, Hens N, Jit M, Beutels P, Auranen K, Nikolajczyk R, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med. 2008 Mar 25;5(3):e74.

Garett G, Hughes J, Anderson R, Stoner B, Aral S, Whittington W, et al. Sexual mixing patterns of patients attending sexually transmitted diseases clinics. Sex Transm Dis. 1996;23(3):248–57.

Newman MEJ. Mixing patterns in networks. Phys Rev E Stat Nonlin Soft Matter Phys. 2003 Feb;67(2 Pt 2):026126.
Olesen SW, Grad YH. Racial/Ethnic Disparities in Antimicrobial Drug Use, United States, 2014–2015. Emerg Infect Dis [Internet]. 2018 [cited 2018 Nov 6];24(11). Available from: https://wwwnc.cdc.gov/eid/article/24/11/18-0762_article

Charu V, Zeger S, Gog J, Bjørnstad ON, Kissler S, Simonsen L, et al. Human mobility and the spatial transmission of influenza in the United States. PLoS Comput Biol. 2017;13(2):e1005382.
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Figures and figure legends

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

(a) Schematic of the 2-population WHN 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). As interaction strength ($\epsilon$, horizontal axis) increases, the difference in antibiotic resistance between the two populations decreases. (c) The same pattern holds for a stronger intervention ($\Delta \tau = 0.15$). Compare Supplemental Figure 1, which shows the analogous results for the D-types model.
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 ($\varepsilon_{\text{sub}}$) 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.
Figure 3. **Use-resistance associations when regionally aggregated.** Panels show use-resistance relationships for 3 pathogen-antibiotic combinations in the MarketScan/ResistanceOpen dataset. Points represent geographic units of analysis at different aggregation levels (black, US states; green, US Census divisions; orange, US Census regions). Curves show logistic regression fits. Shaded regions show 95% bootstrap confidence intervals. Compare Figure 2b, which shows that theoretical models predict the same use-resistance associations across aggregated and unaggregated data. Compare also Supplemental Figure 3, which shows analogous results using the other datasets.
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.