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

Short title: Geography of outpatient stewardship interventions

Scott W. Olesen[1], Marc Lipsitch[1,2], Yonatan H. Grad[1,3]

1 Department of Immunology and Infectious Diseases, Harvard T. H. Chan School of Public Health, Boston, Massachusetts 02115

2 Center for Communicable Disease Dynamics, Harvard T. H. Chan School of Public Health, Boston, Massachusetts 02115

3 Division of Infectious Diseases, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115

Correspondence:
Yonatan Grad
Harvard T. H. Chan School of Public Health
665 Huntington Ave, Building 1, Room 715, Boston, Massachusetts 02115
617 432 2275
ygrad@hsph.harvard.edu

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 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 (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 τ_{int} than a control population with use rate τ_{cont}. To determine how spillover affects the intervention's measured outcome, we modulated the proportion ε 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 ε 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 β-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

138 and Prevention's (CDC) National Healthcare Safety Network (NHSN) (34). The Xponent
139 data includes state-level data on US quinolone use during 2011-2014. NHSN includes
140 state-level data on quinolone resistance among *E. coli* catheter-associated urinary tract
141 infections during 2011-2014. Third, we used the European Center for Disease
142 Prevention and Control's (ECDC) ESAC-Net antimicrobial consumption database (35)
143 and EARS-Net Surveillance Atlas of Infectious Disease (36) for 2011-2015. The ESAC-
144 Net data includes country-level outpatient antibiotic use data provided by WHO and
145 Ministries of Health from member countries. The EARS-Net data includes country-level
146 resistance data. In the observational data, we quantified antibiotic use as yearly
147 treatments per capita and resistance as the proportion of collected isolates that were
148 non-susceptible. Further details about preparation of these data sources and their
149 availability are in the Supplemental Methods.
150
151 We excluded the *S. pneumoniae* resistance to β-lactams in US states from the analysis
152 because, in previous work using the same primary datasets, the point estimate for the
153 use-resistance relationship was negative (37).
154
155 *Use-resistance relationships by populations' adjacency*
156 To test the theoretical prediction that the same difference in antibiotic use will be
157 associated with smaller differences in antibiotic resistance when two populations (US
158 states or European countries) have stronger interactions, we tested whether the use-
159 resistance association is weaker in adjacent pairs of populations, which presumably
160 have more cross-population contacts, compared to non-adjacent populations. Two

161 populations were considered adjacent if they share a land or river border (Supplemental
162 Methods).
163
164 We quantified the use-resistance association as the percentage point difference in
165 resistance (proportion of non-susceptible isolates) divided by the difference in antibiotic
166 use. We summarized use-resistance associations among adjacent pairs and non-
167 adjacent pairs of populations using the median value. Because use-resistance
168 relationships between pairs of populations are correlated, we used the jackknife method
169 to compute confidence intervals on the difference in medians between groups.
170
171 In a sensitivity analysis, to account for the possibility that the use-resistance association
172 is not well-described using the simple difference in resistance proportions, we use the
173 log odds ratio of resistance as the numerator in the use-resistance association.
174
175 *Use-resistance relationships by adjacency, accounting for confounders*
176 We expected that analyzing use-resistance associations by adjacency might artificially
177 inflate the signal for spillover because determinants of antibiotic resistance aside from
178 antibiotic use are spatially correlated. For example, if temperature affects levels of
179 resistance (24), then the fact that adjacent populations tend to have similar climates
180 may cause those populations to have more similar resistances, mimicking spillover. To
181 partially account for these other determinants of resistance, we performed robust linear
182 regressions predicting the use-resistance relationship from adjacency (dichotomous
183 variable) as well as the differences in population density (38), per capita income (39),

184 and mean temperature (24) between the two populations (Supplemental Methods).
185 Regressions were computed using the *rlm* function in the MASS package (40) in R.
186 Confidence intervals on the adjacency-use interaction coefficient were computed using
187 the jackknife method described above.
188
189 *Use-resistance associations by commuting fraction*
190 Because adjacency might be too coarse measure of populations' interactions to detect
191 spillover, we repeated the analyses above, replacing the dichotomous adjacency
192 variable with "commuting fraction", which we defined as the number of individuals who
193 commute between the areas divided by the total number of workers in those two areas
194 (Supplemental Methods). We expected that this might be a better approximation of the
195 mathematical parameter ε, the fraction of a population's contacts that are in the other
196 population, that was varied in the theoretical models of use and resistance.
197
198 Simulations and observational analyses were made using R (version 3.5.1) (41).
199
200
201 **Results**
202 In simulations of two populations, representing an intervention and control group,
203 interactions between the two groups attenuated the effect of the intervention (Figure 1).
204 With increasing interaction strength, the same intervention, that is, the same difference
205 in antibiotic use between the populations, was associated with a smaller difference in
206 antibiotic resistance. The difference in resistance between populations increases with

207 the difference in antibiotic use (Figure 1d), but the use-resistance association,
208 measured as the ratio of the difference in resistance to the difference in use, depends
209 strongly on the interaction strength (Figure 1e). Thus, spillover between populations
210 attenuates the measured use-resistance association.
211
212 The use-resistance association was sensitive to ε, the proportion of each population's
213 contacts that are in the other population, but depended on choice of the mathematical
214 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
216 European countries (Supplemental Figure 2), the use-resistance association declined
217 by less than 1% with the WHN model but up to 20% for the "D-types" model. For $\varepsilon =$
218 1%, the use-resistance declined by approximately 30% in the WHN model and more
219 than 60% in the "D-types" model. In other words, the models predict that as few as 1%
220 of contacts need to be across populations, rather than within populations, to cause the
221 observed effect of an antibiotic stewardship intervention to shrink by one-third, or even
222 half.
223
224 To test whether spillover is important at the scale of US states or European countries,
225 we measured use-resistance associations between pairs of populations in 6
226 combinations of pathogen species, antibiotic class, and data source (Figure 2). We
227 reasoned that, if spillover is relevant at these geographic scales, pairs of states or
228 countries with stronger interactions would have detectably weaker use-resistance
229 associations.

230

231 We first tested whether pairs of physically adjacent populations (e.g., Massachusetts
232 and Connecticut) had weaker use-resistance associations than non-adjacent
233 populations (e.g., Massachusetts and Alaska). In 5 of 6 pathogen/antibiotic/dataset
234 combinations, the median use-resistance association was smaller among adjacent
235 populations than among non-adjacent populations (Figure 3). In 2 cases, the confidence
236 interval on the ratio of use-resistance associations among adjacent populations,
237 compared to non-adjacent populations, did not include zero (Supplemental Table 2).
238 First, for *S. pneumoniae* resistance to macrolides in the MarketScan/ResistanceOpen
239 dataset, use-resistance associations were 27% weaker (95% CI 6% to 49%) among
240 adjacent states compared to non-adjacent states. Second, for *E. coli* resistance to
241 quinolones in the Xponent/NHSN dataset, use-resistance associations were 50%
242 weaker (95% CI 27% to 73%) among adjacent states compared to non-adjacent states.
243 Results were similar when using a different metric of the use-resistance association
244 (Supplemental Table 3).
245

246 We next checked that determinants of antibiotic resistance aside from antibiotic use
247 were not artificially amplifying spillover, making differences in the use-resistance
248 association between adjacent and non-adjacent pairs larger. We performed robust
249 regressions, predicting the use-resistance association from adjacency while controlling
250 for the differences in other covariates that are established determinants of resistance
251 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

298 is associated with factors beyond antibiotic use (24,42), and we used only a limited
299 number of determinants of resistance besides antibiotic use in our analyses.
300
301 Second, decreases in the use of an antibiotic may not necessarily lead to declines in
302 resistance to that antibiotic in a target pathogen (10,43–45). We do not address co-
303 resistance and cross-selection (46,47), and we assumed that resistance equilibrates on
304 a timescale comparable to an intervention. Previous research has shown that resistance
305 among *E. coli*, *S. pneumoniae*, *N. gonorrhoeae* and other organisms can respond to
306 changes in antibiotic use on the timescale of months (48–51), but the expected delay
307 between a perturbation to antibiotic use and the resulting change in resistance remains
308 a subject of active study (11,48,52,53).
309
310 Finally, analyses based on administrative entities like US states, although logistically
311 attractive “laboratories” of stewardship, will always be difficult to interpret because
312 administrative entities average over important dimensions of population structure like
313 age (54), sexual networks (55), and race/ethnicity (56). Thus, use-resistance
314 associations measured across states and countries may be different from those that
315 appear among geographically-proximate populations with dissimilar antibiotic use rates,
316 such as the sexes (57) and racial/ethnic groups (58). We might have come to different
317 conclusions about the role of spillover if we used different types of populations for
318 analysis.
319

320 We suggest 3 lines of investigation that could refine our understanding about the role of
321 spillover at levels of US states and European countries. First, further mathematical
322 modeling studies with more realistic structuring of the host population might articulate
323 more detailed theoretical expectations about the relationship between intervention scale
324 and spillover. For example, models could be parameterized with epidemiological
325 information about individuals' contacts and travel patterns, as has been done for other
326 infectious diseases (59). Second, meta-analysis of existing studies of use-resistance
327 relationships (23,60,61), both experimental and observational, could potentially
328 determine the empirical relationship between intervention population size and the
329 importance of spillover. This kind of meta-analysis might reveal that populations other
330 than US states are feasible "laboratories" for stewardship policy: it may be that cities,
331 daycares, schools, workplaces, or even families represent the optimal trade-off between
332 logistical feasibility and the accuracy of measured effect size. Finally, future
333 experimental outpatient antibiotic stewardship interventions should make careful and
334 deliberate decisions about the sizes and interconnectedness of the populations they
335 target. We hope that a better understanding of spillover will allow stewardship
336 interventions made by state and city health departments can be used to develop an
337 evidence-based national antibiotic stewardship policy.
338

339 **References**

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

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

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

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

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

350 6. Dellit TH, Owens RC, McGowan JE, Gerding DN, Weinstein RA, Burke JP, et al.
351 Infectious Diseases Society of America and the Society for Healthcare
352 Epidemiology of America guidelines for developing an institutional program to
353 enhance antimicrobial stewardship. Clin Infect Dis Off Publ Infect Dis Soc Am.
354 2007 Jan 15;44(2):159–77.

355 7. Vellinga A, Murphy AW, Hanahoe B, Bennett K, Cormican M. A multilevel analysis
356 of trimethoprim and ciprofloxacin prescribing and resistance of uropathogenic
357 Escherichia coli in general practice. J Antimicrob Chemother. 2010 Jul;65(7):1514–
358 20.

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

361 9. Turnidge J, Christiansen K. Antibiotic use and resistance--proving the obvious.
362 Lancet Lond Engl. 2005 Feb;365(9459):548–9.

363 10. Arason VA, Gunnlaugsson A, Sigurdsson JA, Erlendsdottir H, Gudmundsson S,
364 Kristinsson KG. Clonal Spread of Resistant Pneumococci Despite Diminished
365 Antimicrobial Use. Microb Drug Resist. 2002 Sep;8(3):187–92.

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

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

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

374 14. Lipsitch M. Measuring and Interpreting Associations between Antibiotic Use and
375 Penicillin Resistance in Streptococcus pneumoniae. Clin Infect Dis. 2001 Apr
376 1;32(7):1044–54.

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

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

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

387 18. Gottesman B-S, Low M, Almog R, Chowers M. Quinolone Consumption by Mothers
388 Increases Their Children's Risk of Acquiring Quinolone-Resistant Bacteriuria. Clin
389 Infect Dis [Internet]. 2019 Aug 29 [cited 2019 Dec 2]; Available from:
390 https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciz858/5556473

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

393 20. Cooper BS, Medley GF, Stone SP, Kibbler CC, Cookson BD, Roberts JA, et al.
394 Methicillin-resistant Staphylococcus aureus in hospitals and the community: Stealth
395 dynamics and control catastrophes. Proc Natl Acad Sci. 2004 Jul 6;101(27):10223–
396 8.

397 21. MacFadden DR, Fishman DN, Hanage WP, Lipsitch M. The Relative Impact of
398 Community and Hospital Antibiotic Use on the Selection of Extended-Spectrum
399 Beta-lactamase-Producing Escherichia coli. Clin Infect Dis [Internet]. 2018 [cited
400 2018 Nov 29]; Available from: https://www.ncbi.nlm.nih.gov/pubmed/30462185

401 22. Knight GM, Costelloe C, Deeny SR, Moore LSP, Hopkins S, Johnson AP, et al.
402 Quantifying where human acquisition of antibiotic resistance occurs: a
403 mathematical modelling study. BMC Med. 2018 23;16(1):137.

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

407 24. MacFadden DR, McGough SF, Fisman D, Santillana M, Brownstein JS. Antibiotic
408 resistance increases with local temperature. Nat Clim Change. 2018 Jun;8(6):510–
409 4.

25. Olesen SW, Barnett ML, MacFadden DR, Brownstein JS, Hernández-Diaz 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

26. 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.

27. 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.

28. Davies NG, Flasche S, Jit M, Atkins KE. Within-host dynamics shape antibiotic resistance in commensal bacteria. Nat Ecol Evol. 2019 Mar;3(3):440–9.

29. 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.

30. 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).

31. Truven Health MarketScan Database. Commercial Claims and Encounters. Ann Arbor, MI; 2015.

32. 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.

33. 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

34. 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

35. 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

36. 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

37. 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 2019 Sep 23];7. Available from: https://elifesciences.org/articles/39435

38. Franco BE, Altagracia Martínez M, Sánchez Rodríguez MA, Wertheimer AI. The determinants of the antibiotic resistance process. Infect Drug Resist. 2009;2:1–11.

39. Harbarth S, Samore MH. Antimicrobial Resistance Determinants and Future Control. Emerg Infect Dis. 2005 Jun;11(6):794–801.

40. 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

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

42. 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.

43. 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.

44. 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.

45. 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.

46. Pouwels KB, Freeman R, Muller-Pebody B, Rooney G, Henderson KL, Robotham JV, et al. Association between use of different antibiotics and trimethoprimresistance: going beyond the obvious crude association. J Antimicrob Chemoth. 2018;

47. 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.

48. 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/jiy551/5098400

481 49. Dagan R, Barkai G, Givon-Lavi N, Sharf AZ, Vardy D, Cohen T, et al. Seasonality
482 of Antibiotic-Resistant Streptococcus pneumoniae That Causes Acute Otitis Media:
483 A Clue for an Antibiotic-Restriction Policy? J Infect Dis. 2008 Apr 15;197(8):1094–
484 102.

485 50. Sun L, Klein EY, Laxminarayan R. Seasonality and Temporal Correlation between
486 Community Antibiotic Use and Resistance in the United States. Clin Infect Dis.
487 2012 Sep 1;55(5):687–94.

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

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

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

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

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

503 56. Newman MEJ. Mixing patterns in networks. Phys Rev E Stat Nonlin Soft Matter
504 Phys. 2003 Feb;67(2 Pt 2):026126.

505 57. Hicks LA, Bartoces MG, Roberts RM, Suda KJ, Hunkler RJ, Taylor TH, et al. US
506 Outpatient Antibiotic Prescribing Variation According to Geography, Patient
507 Population, and Provider Specialty in 2011. Clin Infect Dis. 2015 May
508 1;60(9):1308–16.

509 58. Olesen SW, Grad YH. Racial/Ethnic Disparities in Antimicrobial Drug Use, United
510 States, 2014–2015. Emerg Infect Dis [Internet]. 2018 [cited 2018 Nov 6];24(11).
511 Available from: https://wwwnc.cdc.gov/eid/article/24/11/18-0762_article

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

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

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

523

524

Disclaimers

The views and opinions of the authors expressed herein do not necessarily state or reflect those of the ECDC. The accuracy of the authors' statistical analysis and the findings they report are not the responsibility of ECDC. ECDC is not responsible for conclusions or opinions drawn from the data provided. ECDC is not responsible for the correctness of the data and for data management, data merging and data collation after provision of the data. ECDC shall not be held liable for improper or incorrect use of the data.

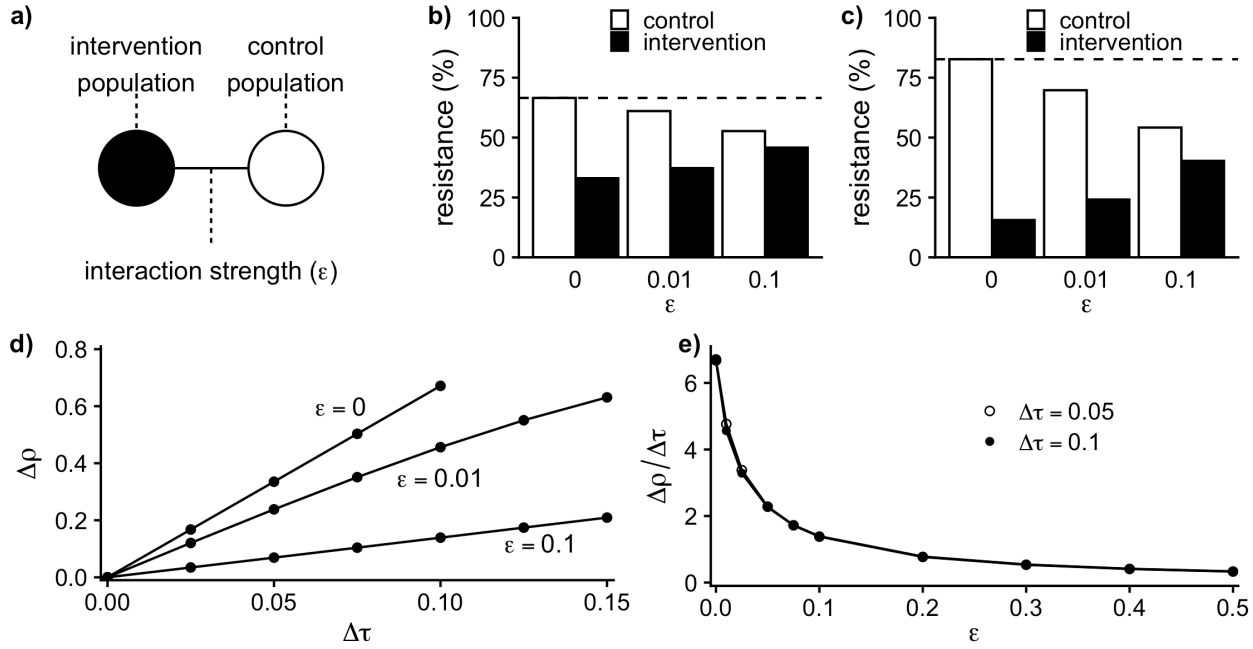
Funding

This work was supported by the National Institutes of Health (grant number U54GM088558 to ML). The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

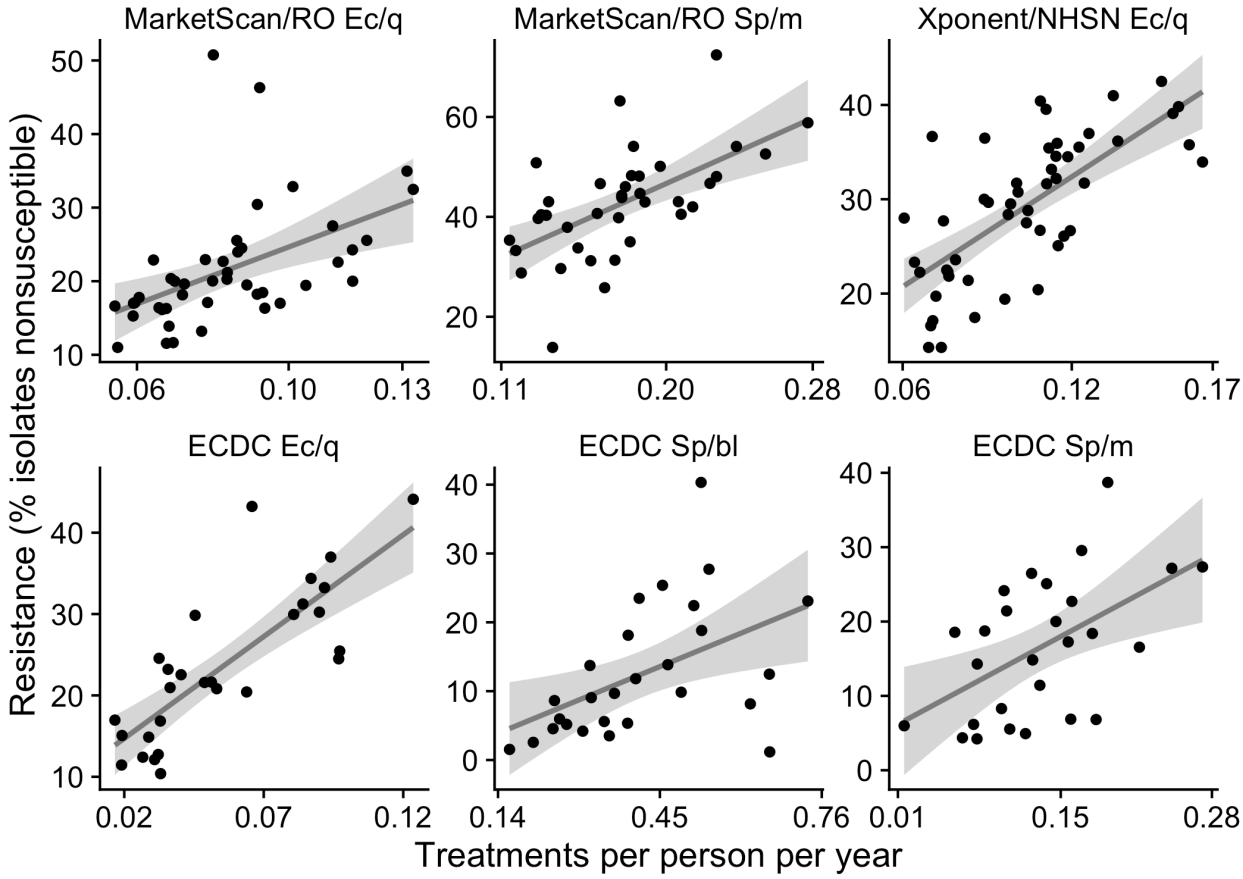
Acknowledgements

We thank Dr. Stephen M. Kissler for helpful comments on the manuscript.

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 (ε, 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 ε and is mostly independent of the difference in antibiotic use $\Delta\tau$.



557 Figure 2. **Use-resistance relationships across US states and European countries.**
558 Each point represents antibiotic use and resistance in a US state (top row) or European
559 country (bottom row). Lines show simple linear regression best fit. Gray areas show
560 95% confidence interval. Ec/q: *E. coli* and quinolones. Sp/m: *S. pneunomiae* and
561 macrolides. Sp/bl: *S. pneumoniae* and β-lactams. RO: ResistanceOpen. ECDC:
562 European CDC.



563
564

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. pneunomiae* and macrolides. Sp/bl: *S. pneumoniae* and β-lactams. RO: ResistanceOpen. ECDC: European CDC.

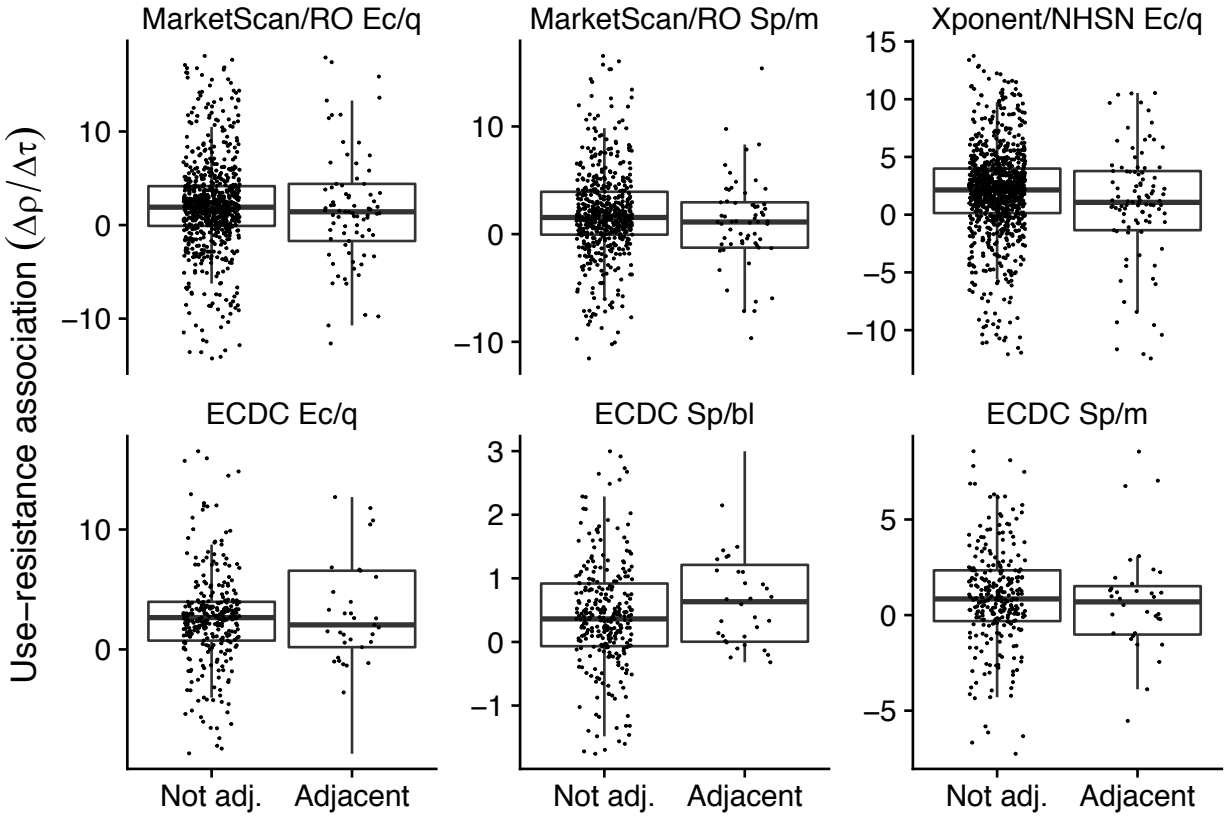
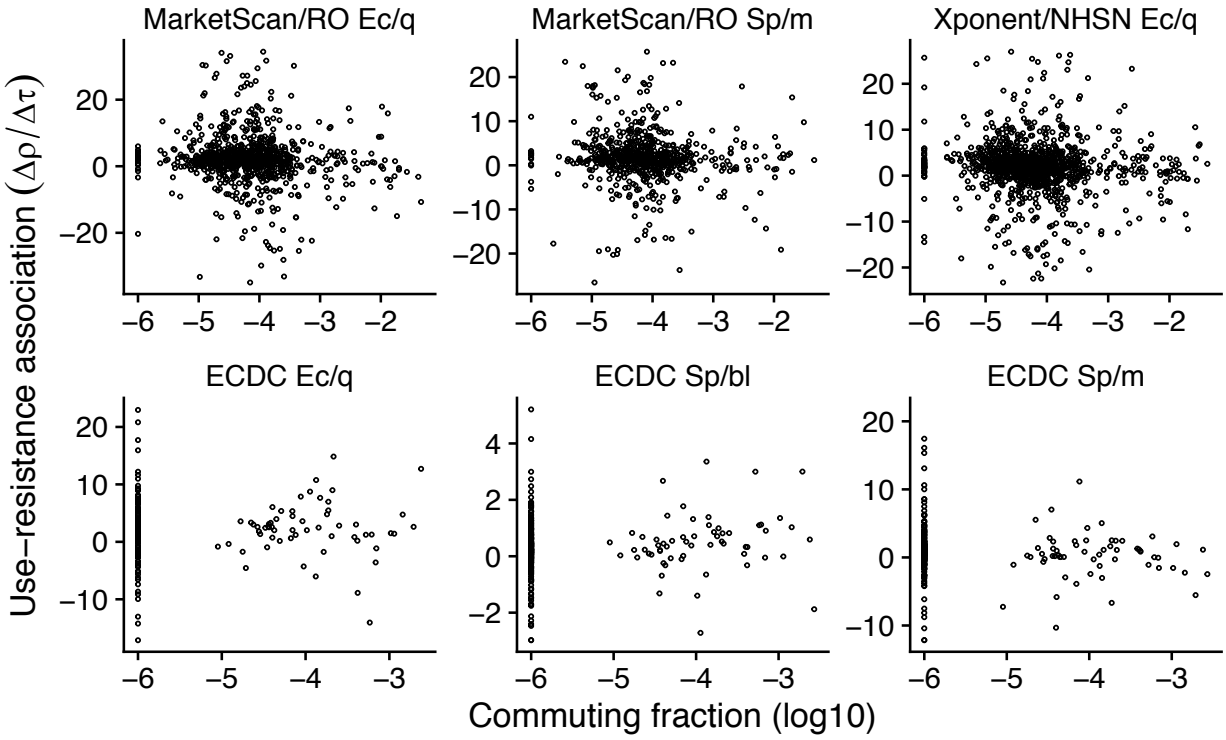



Figure 4. **Use-resistance associations by proportion of commuters.** Each point represents the use-resistance association in a pair of US states (top row) or European countries (bottom row), the same pairs as shown in Figure 3, arranged by "commuting fraction", defined as the proportion of people who 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. pneunomiae* and macrolides. Sp/bl: *S. pneumoniae* and β-lactams. RO: ResistanceOpen. ECDC: European CDC.