The distribution of antibiotic use and its association with antibiotic resistance

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Abstract

Antibiotic use is a primary driver of antibiotic resistance. However, antibiotic use can be distributed in different ways in a population, and the association between the distribution of use and antibiotic resistance has not been explored. Here we tested the hypothesis that repeated use of antibiotics has a stronger association with population-wide antibiotic resistance than broadly-distributed, low-intensity use. First, we characterized the distribution of outpatient antibiotic use across US states, finding that antibiotic use is uneven and that repeated use of antibiotics makes up a minority of antibiotic use. Second, we compared antibiotic use with resistance for 72 pathogen-antibiotic combinations across states. Finally, having partitioned total use into extensive and intensive margins, we found that intense use had a weaker association with resistance than extensive use. If the use-resistance relationship is causal, these results suggest that reducing total use and selection intensity will require reducing broadly-distributed, low-intensity use.

Introduction

Antibiotic use is a primary driver of antibiotic resistance, and reducing antibiotic use is a central strategy for combatting resistance (1, 2). Understanding the relationship between antibiotic use and antibiotic resistance is therefore critical for the design of rational antibiotic stewardship strategies. Multiple studies have identified cross-sectional relationships between antibiotic use and resistance, especially across European countries and US states (3–9). In general, these studies compare total outpatient antibiotic use with population-level resistance. However, antibiotic use is generally not evenly distributed. A study of outpatient prescribing in the UK found that 30% of patients were prescribed at least one antibiotic per year, with the top 9% of patients receiving 53% of all antibiotics (10). A study of beneficiaries of Medicare, a national health insurance program that covers that vast majority of Americans 65 and older, found that the proportion of beneficiaries who take antibiotics varies by US state and drug class (11). In some cases, antibiotic courses can last for months or even years (12, 13). Because antibiotic use is uneven, total use does not distinguish between broad use—many people receiving a few prescriptions—and intense use—a few people receiving many prescriptions (14).

It stands to reason that the distribution of antibiotic use, not just total use, could have an effect on resistance (15). There are a few studies of the relationship between repeated antibiotic exposure on antibiotic resistance (16–22), and it remains unclear whether broad use or intense use is associated with population-level resistance. For example, if a first course of antibiotics given to an antibiotic-naive patient clears most of the susceptible bacteria they carry, then a second course in the same patient will have only a small effect, since most susceptible bacteria were already eliminated. Giving that second course to a different, antibiotic-naive patient instead would have a

75 greater effect on population-level resistance. On the other hand, multiple courses given to a
76 single patient might have a synergistic effect on resistance.
77
78 The goal of this study was to test the hypothesis that intense antibiotic use has a stronger
79 association with population-level resistance than broad, low-level antibiotic use. We used an
80 ecological design to compare the distribution of antibiotic use with antibiotic resistance.
81 Although an ecological design is potentially subject to confounders and cannot definitively test
82 for the causal effect of the distribution of use on resistance at the individual level, ecological
83 studies of use and resistance are the most feasible design for studying the relationship between
84 antibiotic use and population-level resistance, and the results of ecological designs play an
85 important role in developing antibiotic stewardship policies (23, 24).
86
87 To test this hypothesis, we first characterized the distribution of outpatient antibiotic use in two
88 US nationwide pharmacy prescription claims databases, Truven Health MarketScan Research
89 Database (25) and Medicare, both covering 2011-2014. We considered only outpatient antibiotic
90 prescribing, which accounts for 80-90% of total medical antibiotic use in the UK and Sweden
91 (26, 27) and is presumed to account for a similar fraction in the US (28). Unlike antibiotic sales
92 data and nationwide healthcare surveys (29), MarketScan and Medicare claims data, which have
93 previously been used to characterize variations in antibiotic use (11, 30–32), provide longitudinal
94 prescribing information about individual people, which can distinguish between many people
95 getting a few prescriptions and a few people getting many prescriptions. We characterized the
96 distribution of antibiotic use across US states by partitioning annual total use as the sum of
97 annual first use—individuals' first pharmacy fill for an antibiotic in a calendar year—and annual

repeat use—pharmacy fills beyond individuals' first ones in a calendar year. Second, we compared annual total antibiotic use with antibiotic resistance as measured in ResistanceOpen, a US nationwide sample of antibiotic susceptibility reports, for 2012-2015 (i.e., lagged by one year (8, 33)), evaluating the relationship between use and resistance across US states for 72 pathogen-antibiotic combinations. Finally, we evaluated whether annual first use and annual repeat use are differently associated with population-level resistance.

Results

Antibiotic use is not evenly distributed

Our analysis included 99.8 million outpatient pharmacy antibiotic prescription fills among 62.4 million unique people, approximately 20% of the US population, during 2011-2014 using the MarketScan database (25). In 2011, 34% of people received an antibiotic, and 10% of people received 57% of all antibiotic prescriptions. This distribution varied by population but was similar across data years (Figure 1 - Figure Supplement 1). To characterize the distribution of specific antibiotics, we grouped individual antibiotic generic formulations into drug groups based on their chemical structures and mechanisms of action (Supplementary File 1 - Table 1). For all drug groups, most people had zero prescriptions for that antibiotic in a given year, but antibiotics differed in their distributions (Figure 1).

We next examined the distribution of antibiotic use for each drug group and US state. To quantify the distribution of antibiotic use, we labeled each antibiotic pharmacy claim as "first" if it was the first pharmacy fill for that drug group made by that individual in that calendar year, and "repeat" if it was a second, third, etc. fill for an antibiotic in the same drug group made by

121 the same individual in the same calendar year. An individual's first and repeat claims in a
122 calendar year add up to their total number of claims for that year. We then partitioned
123 population-level annual total use, measured as pharmacy fills per 1,000 members per year, into
124 the sum of annual first use, measured as first fills per 1,000 members per year, and repeat use,
125 measured as repeat fill per 1,000 members per year, for each drug group and US state. Annual
126 first use of a drug group is equivalent to the proportion of the population taking an antibiotic in
127 that group in that year.
128
129 Total use varied between drug groups and across states (Figure 2). Annual repeat use made up a
130 steady one-quarter to one-third of annual total use across drugs and states, with the exception of
131 tetracyclines, for which high repeat use was associated with young adults (Figure 2 – Figure
132 Supplements 1 and 2), probably for acne treatment. This distribution of first and repeat use is
133 distinct from the pattern predicted by the single-parameter Poisson and geometric distributions
134 (Figure 2), but the ratio of first use to repeat use for each drug was nearly constant across US
135 Census regions (Figure 2 – Figure Supplement 3). Thus, the higher antibiotic use in the Southern
136 states (11, 34) is primarily attributable to a greater proportion of people taking antibiotics, not
137 because those who receive antibiotics receive more of them.
138
139 *Landscape of correlations between total use and resistance across pathogens and antibiotics*
140 To verify that our antibiotic use and resistance data sources could be used to distinguish the
141 associations of first use and repeat use with antibiotic resistance, we first measured the landscape
142 of Spearman correlations between total use and antibiotic resistance for multiple pathogens and
143 antibiotics (3–8). To measure antibiotic resistance, we used a US nationwide sample of hospital

144 antibiotic susceptibility reports (35), which included resistance of 38 pathogens to 37 antibiotics
145 in 641 antibiotic susceptibility reports from 230 organizations (hospitals, laboratories, and
146 surveillance units) spread over 44 US states. Although most organizations contributing antibiotic
147 susceptibility reports were hospitals, hospital antibiotic susceptibility reports are biased toward
148 community-acquired organisms (36, 37), and studies often compare hospital antibiotic
149 susceptibility reports with community antibiotic use (38).
150
151 Because the epidemiology and pharmacology of each pathogen-antibiotic combination is unique,
152 each combination could have a unique use-resistance relationship (15). We therefore aggregated
153 antibiotic resistance into the same drug groups with which we aggregated antibiotic use
154 (Supplementary File 1 – Table 1) and evaluated the 72 pathogen-antibiotic combinations that
155 were adequately represented in the antibiotic resistance data (see Methods). Across those 72
156 combinations, correlation coefficients ranged from –32% to 64% (Figure 3, Supplementary File
157 1 - Table 2). The strongest correlation (Spearman's ρ = 64%, 95% CI 41 to 80%) was between
158 macrolide use and the proportion of *Streptococcus pneumoniae* isolates that were macrolide
159 nonsusceptible (Figure 4). Correlation coefficients were mostly positive (median correlation
160 coefficient 21%, IQR 8 to 34%). Use-resistance correlations involving macrolides, quinolones,
161 and cephalosporins were more positive than those for nitrofurantoin, and correlations involving
162 quinolones were more positive than those for trimethoprim/sulfamethoxazole (pairwise Mann-
163 Whitney tests, two-tailed, FDR = 0.05). Coefficients were not significantly more positive for any
164 particular pathogen.
165

166 Because isolates from older adults are disproportionately represented in antibiotic susceptibility
167 reports (39), we suspected that population-wide resistance might, in some cases, correlate better
168 with antibiotic use among older adults. We therefore queried outpatient pharmacy antibiotic
169 claims records from individuals 65 and older on Medicare (see Methods). When antibiotic use
170 among Medicare beneficiaries was substituted for antibiotic use as measured in the MarketScan
171 data (Figure 2 – Figure Supplement 2), correlation coefficients were similar (Supplementary File
172 1 – Tables 2 and 3). Conversely, children are the primary carriers for some pathogens (e.g.,
173 *Streptococcus pneumoniae* (40)), so we suspected that resistance might, in other cases, better
174 correlate with children's antibiotic use. Restricting the antibiotic use data to members at most 15
175 years old (Figure 2 – Figure Supplement 2) again yielded similar coefficients (Supplementary
176 File - Tables 2 and 3). Thus, the landscape of correlations we observed was mostly robust to the
177 exact population and data source.
178
179 We also evaluated the sensitivity of the results to the measurement of antibiotic use, substituting
180 days supply of antibiotic for number of pharmacy fills, and the geographic level of the analysis,
181 by aggregating the Medicare use data and resistance data at the level of the 306 hospital referral
182 regions intended to approximate regional health care markets (41) (Supplementary File – Tables
183 2 and 3). The absolute values of the correlation coefficients were slightly closer to zero when
184 using days supply rather than fills (Wilcoxon test, two-tailed; pseudomedian difference in
185 absolute correlation coefficient 1.9 percentage points, 95% CI 0.72 to 3.1) and substantially
186 closer to zero when using hospital referral regions rather than states as the units of analysis (6.1
187 percentage points, 95% CI 3.0 to 9.1).
188

Lack of evidence for more positive association with repeat use

Having examined the landscape of the relationships between total use and resistance across pathogen-antibiotic combinations, we set out to test the hypothesis that repeat use has a stronger association with resistance than first use. For each pathogen-antibiotic combination, we performed a multiple regression predicting proportion nonsusceptible from first use and repeat use (Figure 5). First use and repeat use are highly correlated in some cases (Supplementary File - - Table 4) which will widen the confidence intervals on the regression coefficients but should not introduce bias (42). Regression coefficients for first use were more often positive than negative (54 of 72 [75%]; binomial test, 95% CI 63 to 84%). That is, first use was positively associated with resistance when controlling for repeat use. In contrast, regression coefficients for repeat use were more often negative than positive (44 of 72 [61%]; binomial test, 95% CI 49 to 72%). That is, repeat use was negatively associated with resistance when controlling for first use.

We evaluated the sensitivity of this result to age group, data source, metric of antibiotic use, and geographic unit of analysis, as described above. In all cases, regression coefficients for first use in the multiple regression were more likely to be positive than negative, while regression coefficients for repeat use were more likely to be negative than positive (Supplementary File 1 - Table 5). For certain pathogens and antibiotics, resistance could presumably accumulate in an individual over many years (18, 21), so we also computed alternate measures of first and repeat use by considering only individuals who were included in the MarketScan data for each year of 2011-2014, and we labeled an antibiotic fill as first use only if it was the first fill for that drug group made by that individual in the entire four-year period. In that analysis, a similar proportion of regression coefficients for first use were positive (69%, 95% CI 57 to 80%) and regression

coefficients for repeat use were equally likely to be positive or negative (53%, 95% CI 41 to 65%).

Discussion

Landscape of use-resistance relationships

We used US nationwide datasets measuring antibiotic use in 60 million individual and antibiotic resistance in 3 million bacterial isolates to analyze relationships between antibiotic use and resistance, examining 72 pathogen-antibiotic combinations simultaneously, using identical data sources and analytical methods across combinations. Although previous studies have examined multiple pathogen-antibiotic combinations, usually no more than 5 pathogens or antibiotics are considered at once (3, 4, 8). We found that correlations between total use and resistance were mostly positive, that certain drugs tended to have more positive correlations, but that there was no clear pattern by organism (6). The overall landscape of correlations was mostly robust to the age groups studied and the geographic scale of the analysis, although correlations were somewhat weaker when conducting analysis at smaller geographic scales (8, 43–45). We used outpatient antibiotic use as the predictor of resistance because 80-90% of antibiotic use occurs in the outpatient setting (28) and because most antibiotic pressure on pathogens is due to "bystander selection", in which the patient is treated for some reason other than an infection caused by that pathogen (46).

The correlations we observed between total antibiotic use and population-wide antibiotic resistance were noticeably weaker than those in highly cited European studies but comparable to those from other analyses of European data. For example, for *S. pneumoniae* and macrolides,

Goossens *et al*. (3) reported a Spearman's ρ of 83% and García-Rey *et al.* (4) reported 85%, while we found 62% and van de Sande-Bruinsma *et al*. (8) reported a median of 56%. These studies all used similar statistical methods, so the differences in the results must be due to some other factors (e.g., data quality, range of antibiotic use, distribution of antibiotic use, or pathogen biology). Correlations between *E. coli* resistance and use of β-lactams, cephalosporins, trimethoprim/sulfamethoxazole, and quinolones were similar to those reported in studies of use and resistance in UK primary care groups (43, 44).

The most notable difference, however, between our study and previous results from Europe is for *S. pneumoniae* and β-lactams: Goossens *et al*. (3) report a Spearman's ρ of 84%, but we found no relation (–11%, 95% CI –41 to 22%). We propose that the narrow variation in β-lactam use across US states, approximately two-fold between the highest- and lowest-using states, obscures a correlation that is more apparent in Europe, where there is a four-fold variation between the highest- and lowest-using countries (3). Thus, our results and those from Goossens *et al*. may be consistent with respect to the underlying biology. We also note that, when reproducing the methodology from a US study (47) of the use-resistance relationship for β-lactams and *S. pneumoniae* (dichotomizing states as high- or low-prescribing and computing the odds ratio of resistance), we find a consistent point estimate but with wider confidence intervals (1.15, 95% CI 0.75 to 1.76).

Our study design may limit the interpretability of the landscape of use-resistance relationships. First, like the leading European studies using EARS-Net and US studies using the Centers for Disease Control and Prevention Active Bacterial Core surveillance, we compare population-wide

outpatient antibiotic use with antibiotic susceptibility reports from hospitals. The degree to which hospital antibiotic susceptibility reports represent community infections is debated (36, 38). For example, if outpatient antibiotic use selects for resistance among community-acquired infections, and hospital antibiograms reflect data from community-acquired infections as well as unrelated inpatient resistance patterns, then the correlations we measure would be biased toward weaker associations. Furthermore, antibiotic use and resistance in the community setting is not completely independent of use and resistance in the hospital setting (48), and our approach does not account for any relationship between the two.

Second, antibiotic resistance is temporally dynamic, and our cross-sectional approach assumes that antibiotic use is autocorrelated across years (49) or resistance changes slowly (50). If use does cause resistance, and use and resistance changed meaningfully over the course of the study, then the correlations we measured by aggregating over all years would be biased toward weaker associations.

Third, because of the limitations in statistical power, we did not address the possibility that use of one antibiotic can select for resistance to another antibiotic (51, 52). Notably, use of one antibiotic can select for resistance to another antibiotic if the dominant clones of that species are resistant to both (51). In that case, if the use rates of the two drugs are correlated across states, then the apparent relationship between one drug and resistance to that drug would be biased upward. Furthermore, because the palette of antibiotic use varies by country (53), and different pathogen strains circulate in different populations, the univariate associations we observed

between use of an antibiotic and resistance to that antibiotic in the US may not be applicable in other geographies.

Finally, like in other studies of antibiotic use, we did not address patient adherence, and typical approaches to address adherence using claims data (54) are problematic when the intended duration of treatment is not clear. The measured correlation would then be biased if, for example, poor patient adherence increased resistance and patient adherence were correlated with antibiotic use.

Distribution of antibiotic use and antibiotic resistance

We described the distribution of antibiotic use across drug groups and US states, finding that 34% of the study population took an antibiotic in a year, and 10% of the population had 57% of the antibiotic fills in that year, similar to results from the UK (10), although this distribution varied by population (Figure 1 – Figure Supplement 1). By partitioning annual total use into annual first use and annual repeat use, we were able to show that, for each drug, annual first use makes up the majority of annual total use and that variations in annual first use explain more variance in annual total use than do variations in annual repeat use. We also found that first use tends to have a positive association with resistance when controlling for repeat use, while repeat use tends to have negative or associations with resistance when controlling for first use. This result held across sensitivity analyses.

If these associations are causal, that is, if outpatient first and repeat antibiotic use select for resistance among community-acquired pathogens, then our results would imply that antibiotic

303 resistance in the outpatient setting is due more to first use, which tended to have positive
304 associations with resistance, than to repeat use. In contrast to proposals to focus on intense
305 antibiotic users for combatting resistance (10), this situation would imply that preventing
306 marginal prescriptions among patients whose indications are borderline-appropriate or
307 inappropriate for antibiotics may be the more effective tactic for reducing the prevalence of
308 resistance mechanisms already established in the US.
309
310 There are limitations to the interpretability of these results. First, as mentioned above, there is a
311 potential mismatch between the sources of the antibiotic use and antibiotic resistance data.
312
313 Second, although antibiotic use is a major driver of antibiotic resistance, the observed results
314 may not be causal. Factors beyond antibiotic use, like population density, play a role in antibiotic
315 resistance (2, 9). Even if antibiotic use and resistance are causally related, it may be that
316 resistance affects antibiotic use. For example, if resistance to a drug is high, treatment using that
317 drug is more likely to fail, discouraging repeated use, so that high resistance lead to decreased
318 repeat use (36, 43, 51). Ecological studies like this one do not directly address causality, and
319 further work is needed to distinguish between different causal pathways.
320
321 Third, the observed population-level relationships between antibiotic use and resistance need not
322 also hold for the relationship between an individual's first and repeat antibiotic use and the risk
323 of a resistant infection in that individual. Any comparisons between our population-level results
324 and individual-level studies would need to account for the difference between our population-

level measures of first and repeat antibiotic use and the individual-level timing of antibiotic use and measurements of resistance.

Fourth, controlling for factors beyond antibiotic use could alter the apparent relationship between antibiotic use and resistance. In particular, we speculate that controlling for patient morbidity, which we did not address in this population-level analysis, would amplify the observed result, that first use tends to have a more positive association with antibiotic resistance than repeat use. We expect that morbid individuals have more repeat antibiotic use. We also expect that morbid individuals visit the hospital more often, putting them at higher risk of antibiotic resistant infections regardless of their antibiotic use. Thus, we speculate that repeat use causes resistance and also is a predictor of morbidity, which is associated with resistance. Failing to control for morbidity thus biases the association between repeat use and resistance toward more positive values. Conversely, controlling for morbidity would decrease the measured relationships between repeat use and resistance, amplifying our central result.

Fifth, we defined first and repeat use with respect to the calendar year, while it may be that some other timescale is the appropriate one for this analysis. Although our central result held when re-defining first and repeat use with respect to a four-year period (Supplementary File 1 - Table 5), it may be that, say, repeat use within an individual on a time-scale shorter than a year is an important determinant for risk of resistance in that individual. Our study does not distinguish between repeat use that occurs across year boundaries, which is presumably important for relating individuals' antibiotic use with their risk of resistance.

348 Finally, we note that first use and repeat use are only one set of many ways of measuring the
349 distribution of antibiotic use. For example, 10 repeat uses could mean 1 person with 10 repeat
350 uses or 10 people with 1 repeat use each. The first and repeat use metrics cannot distinguish
351 between these two cases, and it may be that some other measure of the distribution of antibiotic
352 use would yield different results.
353
354 In conclusion, we find that population-wide antibiotic use and population-wide resistance
355 appears to be more closely linked with broadly-distributed, low-intensity use rather than with
356 intensity of use. Ultimately, accurate models predicting the emergence and spread of antibiotic
357 resistance will require more careful characterizations of who gets what antibiotic (55), what
358 selection pressure that places on pathogens, how those pathogens are transmitted, and in whom
359 they manifest as infections (56). An ideal study would compare the complete history of an
360 individual's outpatient and inpatient antibiotic exposure with clinical microbiology data from
361 that same individual, cross-referenced against population-level factors, among a representative,
362 nationwide sample of individuals. Individual-level results could then also be compared with
363 mechanistic models of resistance to draw inferences about within-host effects of antibiotic use
364 (57, 58), and the role of co-occurring resistance and correlated antibiotic use could be addressed.
365 In the absence of such a dataset, these ecological, associative results provide a guide to the
366 development of antibiotic stewardship policy.
367

Methods

Study population and antibiotic use

MarketScan (25) data covering 2011-2014 were used to identify insurance plan members and characterize their outpatient antibiotic use. To ensure quality of the antibiotic use distribution data, only members who were on their insurance plan for 12 months during a given year were included. Prescription fills for oral and injected antibiotics were identified by generic formulation (Supplementary File 1 - Table 6) and drug forms (Supplementary File 1 - Table 7). We treated multiple fills on the same day for the same generic formulation with the same refill code as a single prescription fill. In the main analysis, antibiotic use was measured using fills, rather than days supply of drug, because some previous research has suggested that prescriptions better correlate with resistance (33) and that this choice is probably not detrimental (8, 49). The specific generic drugs were grouped into antibiotic drug groups designed to correspond to the antibiotic resistance drug groups described below (Supplementary File 1 - Table 1). All measures of antibiotic use were computed for each year 2011 to 2014, and the mean for each value across the 4 years was reported and used in analyses of the use-resistance relationship.

Antibiotic use among Medicare beneficiaries was measured as previously described (59). Briefly, we considered fee-for-service beneficiaries at least 65 years old among and with 12 months of enrollment in Medicare Part B and Part D among a 20% sample of beneficiaries for each of 2011-2014. The Medicare data, which provides the zip code for each beneficiary, were also aggregated at the level of hospital referral region (41), using the 2011 zip code to region crosswalk. MarketScan data do not include zip code-level resolution.

391 This study was deemed exempt from review by the institutional review board at the Harvard T.
392 H. Chan School of Public Health.
393
394 *Antibiotic resistance*
395 Antibiotic resistance prevalences for common bacterial pathogens were identified from
396 ResistanceOpen, a previously developed database of spatially localized patterns of antibiotic
397 resistance (35). This continuously updated database contains antibiotic resistance data from
398 online sources during 2012 to 2015. At the time of analysis, the resistance data consisted of
399 approximately 86,000 records, each indicating the fraction of isolates of an organism that were
400 nonsusceptible to a particular drug in a particular antibiotic susceptibility report ("antibiogram").
401 The median number of isolates corresponding to each record was 93, but records had up to
402 75,000 associated isolates. 7 records (<0.01%) with missing numbers of isolates were excluded.
403 In antibiograms that separated *S. aureus* into MRSA and MSSA, resistance of aggregate *S.*
404 *aureus* to individual drugs was taken as the average of the MRSA and MSSA records, weighted
405 by number of isolates. MRSA and MSSA were not considered as separate species in any
406 analysis.
407
408 The specific antibiotics used in antibiotic resistance assays were grouped into antibiotic drug
409 groups (Supplementary File 1 - Table 1) designed to correspond to the antibiotic use groups. If
410 resistance to more than one antibiotic in a drug group was reported for a particular pathogen in a
411 particular antibiogram, resistance to that drug group for that pathogen in that antibiogram was
412 computed as the mean of the resistances measured for the antibiotics in that group, weighted by
413 the number of isolates. The proportion of nonsusceptible isolates in a state for a particular

414 pathogen-antibiotic combination was computed as the average of the proportions from each
415 contributing antibiogram in that state, weighted by number of isolates.
416
417 *Statistical methods*
418 Antibiotic use and resistance were compared using Spearman correlations and multiple linear
419 regressions. Of the 887 pathogen-antibiotic combinations present in the data, we analyzed the 72
420 combinations that were present in at least 34 states. This excluded 21% of the pathogen-
421 antibiotic-antibiogram combinations. We established the cut-off for number of states because
422 80% power to detect a Pearson correlation coefficient of magnitude 0.55 at $\alpha = 0.01$ under a two-
423 sided hypothesis requires at least 34 samples. (Although we report Spearman correlations, there
424 is no straightforward power calculation methodology for Spearman correlations, and we used the
425 Pearson power calculation as an approximation.) We aggregated data across all years, rather than
426 comparing use and resistance in each year, because of the sparse of the resistance data: of 2,767
427 pathogen-antibiotic-state combinations in the data, only 182 have data for all four years. No
428 pathogen-antibiotic combination had more than 4 states with data for all 4 years. Confidence
429 intervals on correlation coefficients were computed using the Fisher transformation and normal
430 approximation method. Multiple comparisons were accounted for using the Benjamini-Hochberg
431 false discovery rate (FDR) (60). Multiple regressions predicted proportion of isolates
432 nonsusceptible from first use and repeat use.
433
434 *Data availability*
435 State-level, aggregate antibiotic use and resistance data used in the main analyses are in Figure 3
436 – Source data 1 and 2. We do not own and cannot publish disaggregated MarketScan or

Medicare data. MarketScan data are available by commercial license from Truven Health (marketscan.truvenhealth.com). Medicare data are available from ResDAC (www.resdac.org). ResDAC requires an application ensuring that requesting researchers comply with Common Rule, HIPAA, and CMS security and privacy requirements. Disaggregated ResistanceOpen data are restricted due to hospitals' privacy concerns. ResistanceOpen data are available by request from HealthMap (www.resistanceopen.org).

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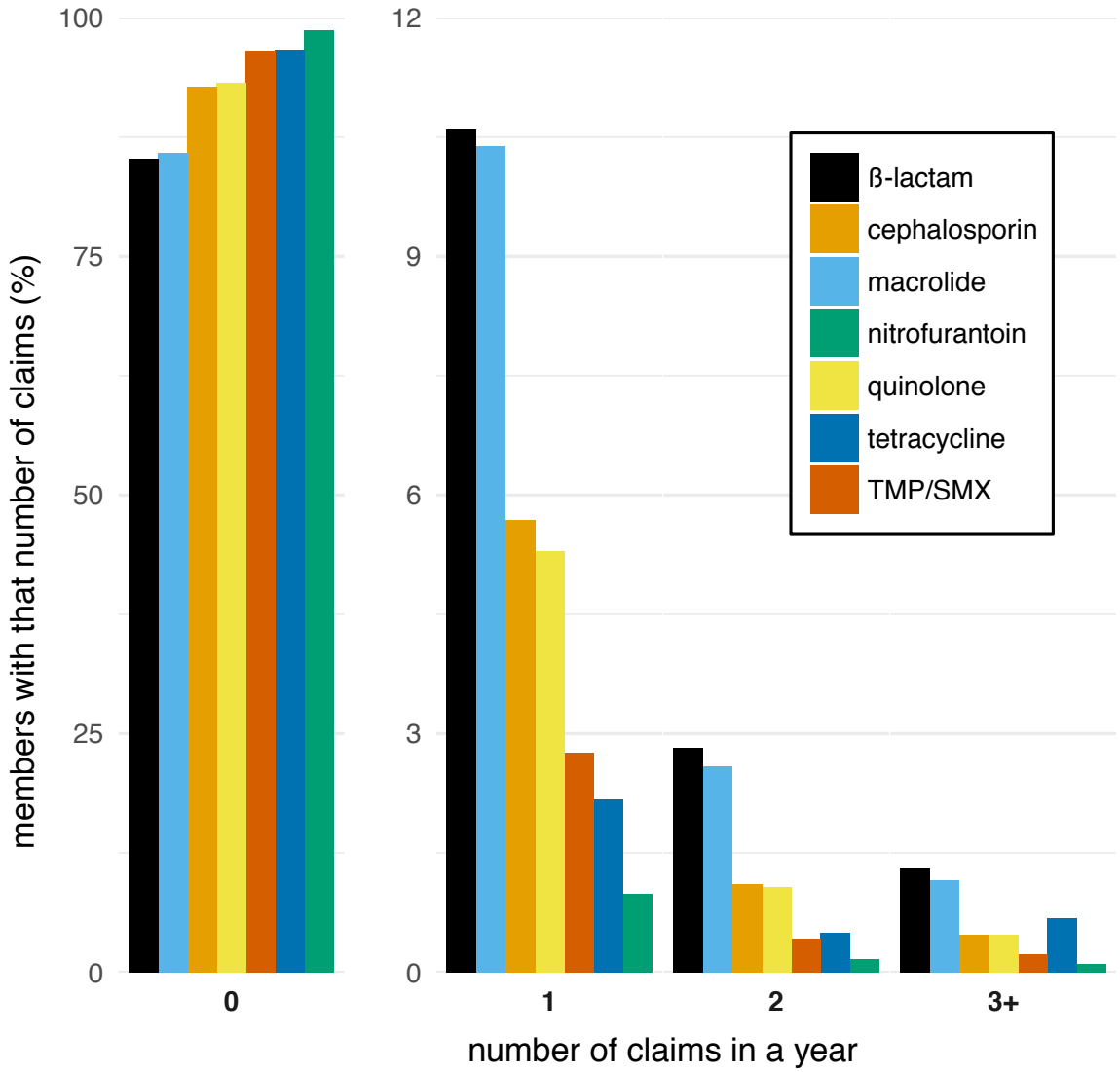
450 **Figures**

451

452 Figure 1. **The distribution of antibiotic use within individuals.** Bars indicate the proportion of

453 members in the MarketScan data with different numbers of prescription fills in 2011 for each of

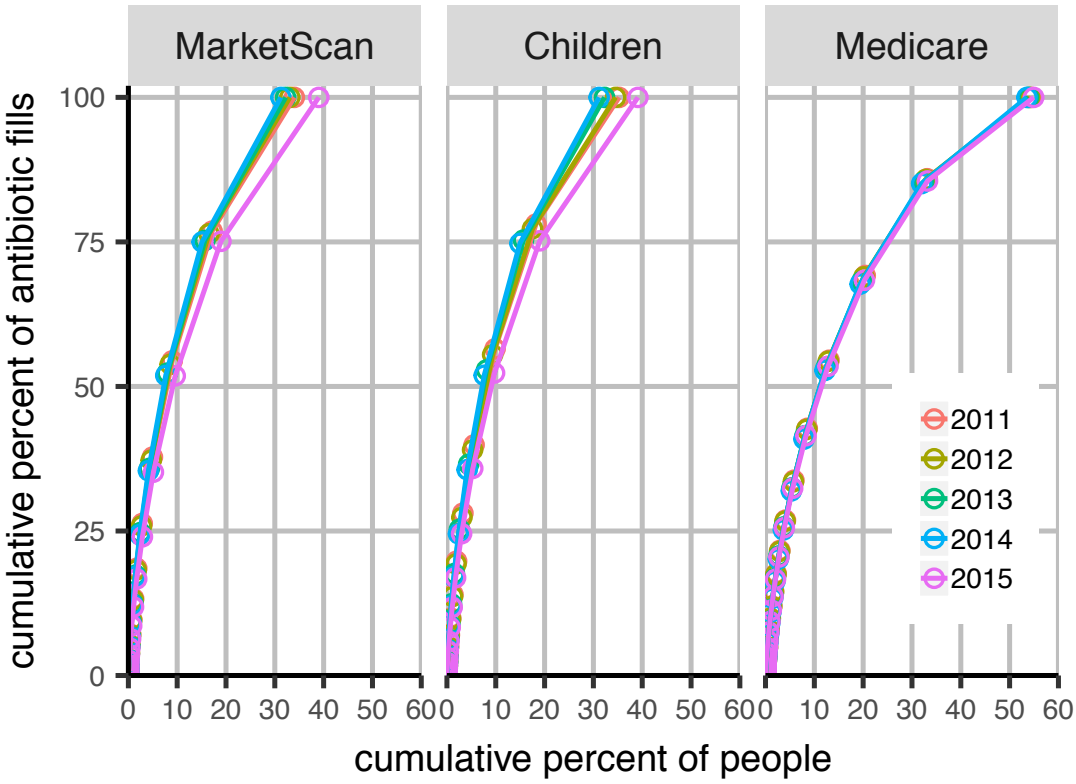
454 the drug groups. TMP/SMX: trimethoprim/sulfamethoxazole.



455

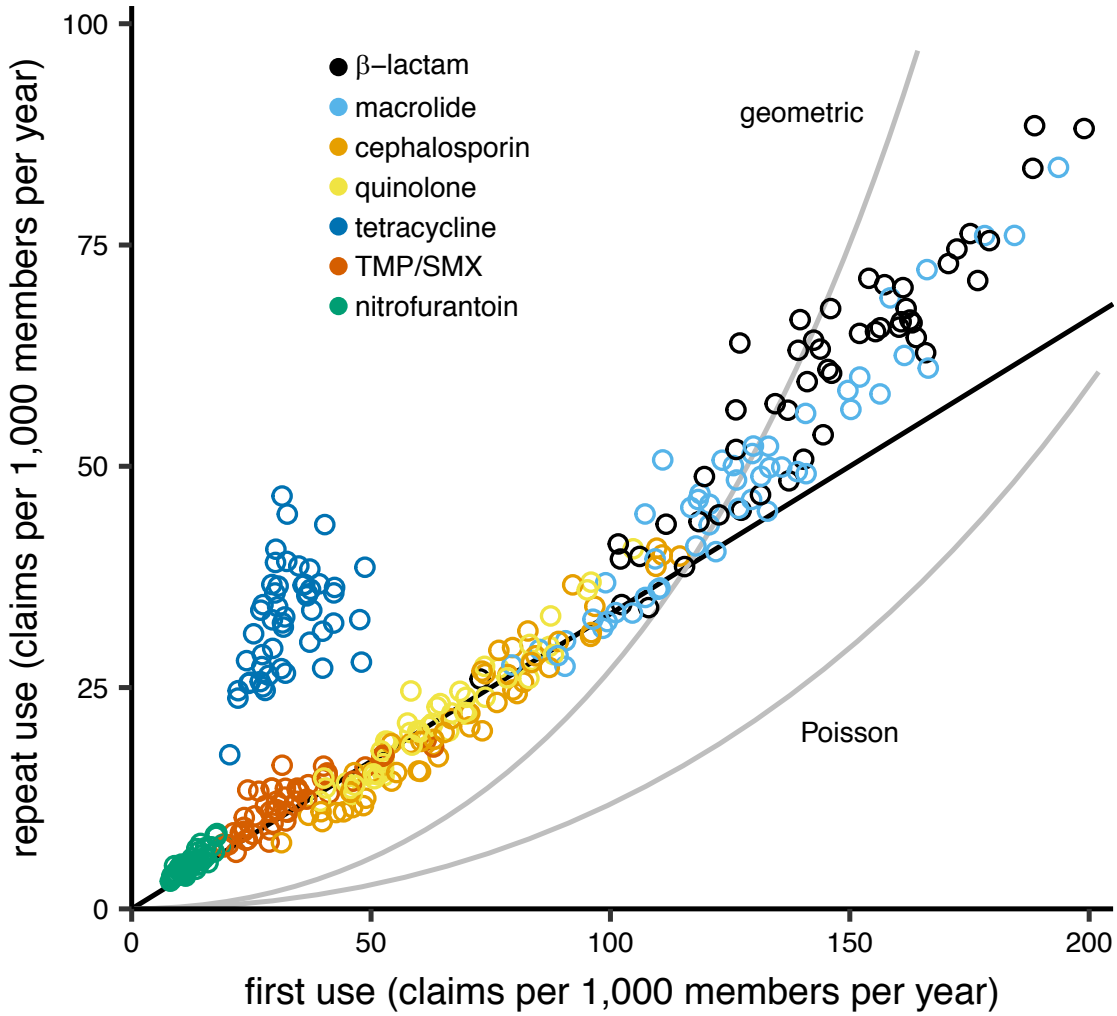
456

457 Figure 1 - Figure Supplement 1. **Cumulative distribution of antibiotic use.** Each point
458 represents a group of people with a certain number of associated claims for any antibiotic,
459 starting at the left with the members with the greatest number of claims. The upper-right line
460 segment shows members with 1 claim, the next segment shows members with 2 claims, etc.
461 Colors indicate data years. Panels indicate study population. MarketScan: main data set.
462 Children: MarketScan data including only members 15 and younger.



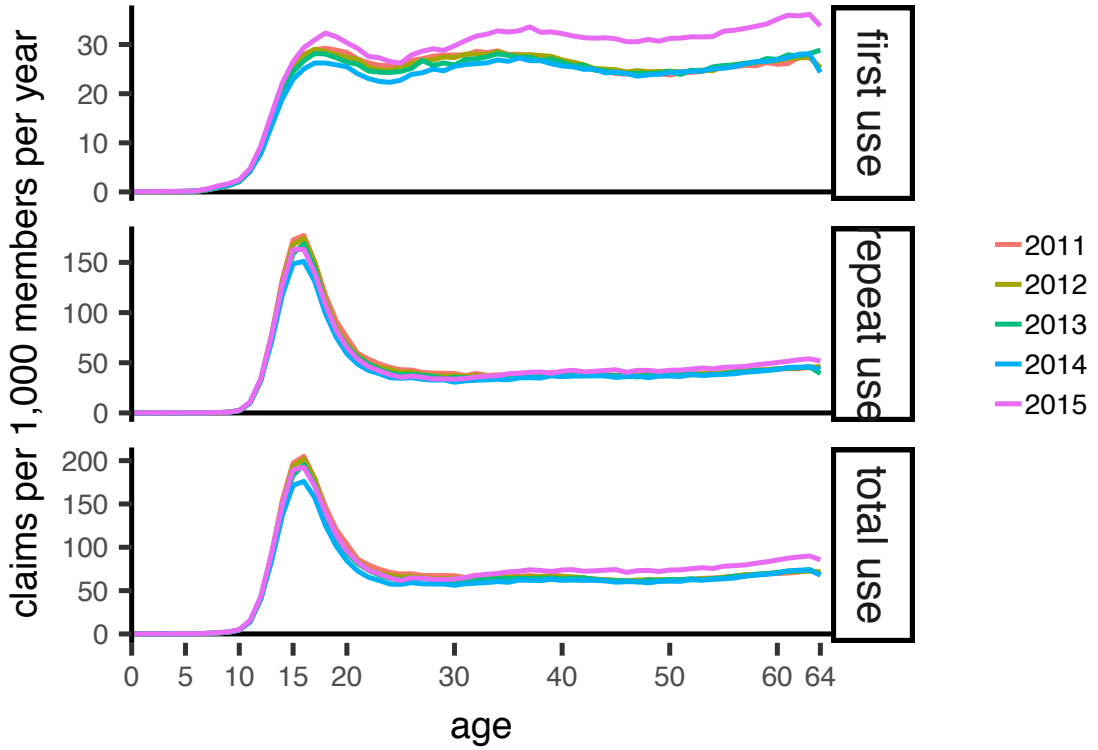
463
464

Figure 2. **The distribution of antibiotic use across US states.** Each point indicates first use and repeat use of a single drug group in a single US state (averaged over the data years). Points falling on the black line have three times as much first use as repeat use (i.e., repeat use is one-quarter of total use). The curves show the relationships between first use and repeat use expected from the Poisson and geometric distributions. TMP/SMX: trimethoprim/sulfamethoxazole.



472 Figure 2 – Figure Supplement 1. **Distribution of tetracycline use by age.** Colors indicate data

473 years.



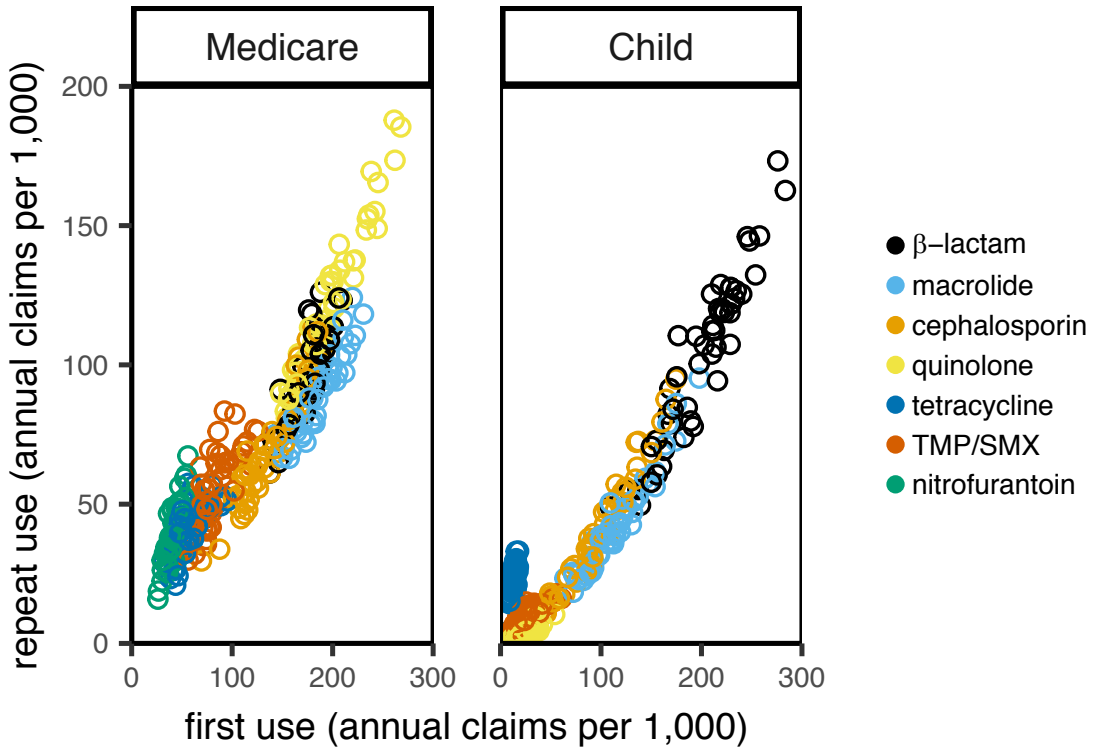
474

475

476 Figure 2 – Figure Supplement 2. **Distribution of antibiotic use by population.** Each point

477 represents average use of a drug group in a state across data years. Children: MarketScan data

478 including only members 15 and younger.



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481 Figure 2 – Figure Supplement 3. **Distribution of antibiotic use by region.** Each point shows use
482 for a drug group in a state, averaged over data years. Colors indicate US Census region (red,
483 South; light red, Midwest; gray, Northeast; black, West). Line shows unweighted linear best fit.

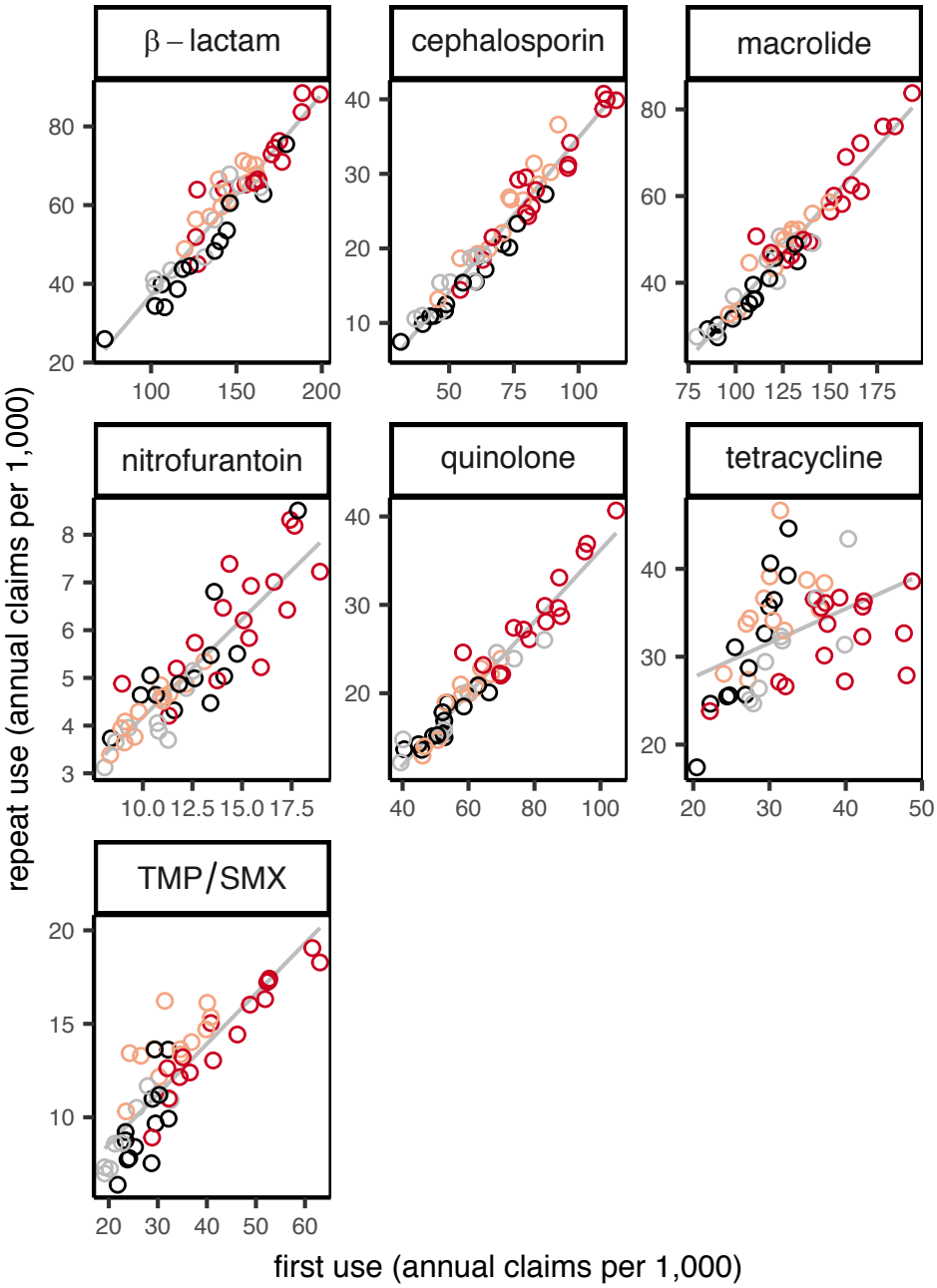

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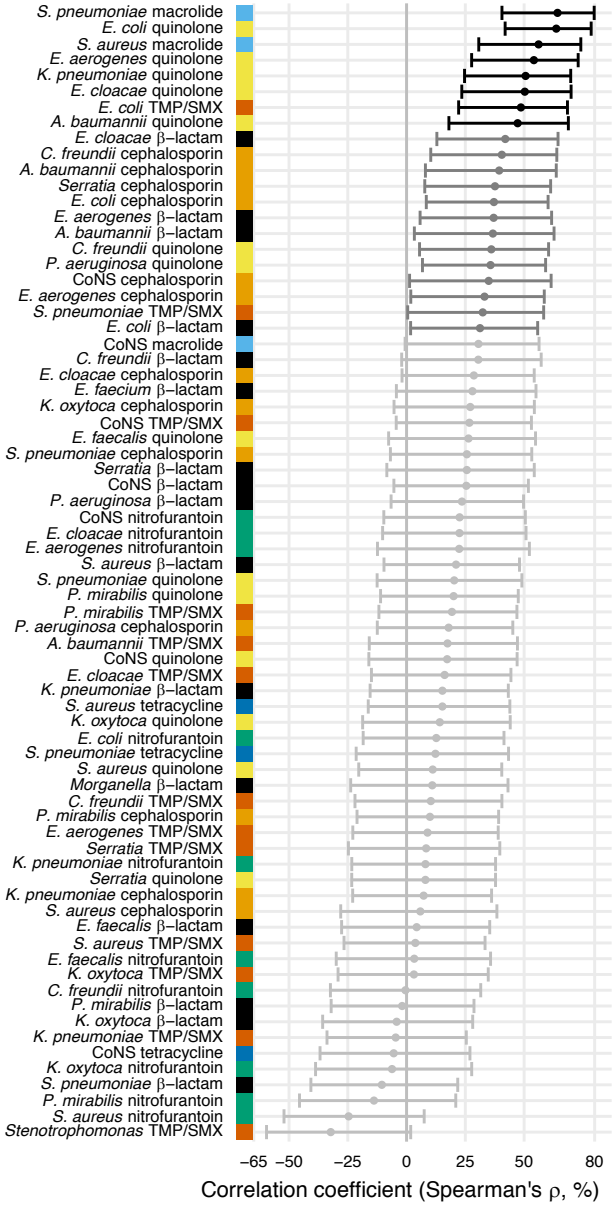
Figure 3. **Correlations between total antibiotic use and resistance are biased toward positive values.** Error bars show 95% confidence intervals. The color strip visually displays the drug groups. Statistical significance is indicated by color of the points (black, significant at FDR = 0.05, two-tailed; dark gray, significant at $\alpha = 0.05$, two-tailed; light gray, not significant). TMP/SMX: trimethoprim/sulfamethoxazole. CoNS: coagulase-negative *Staphylococcus*.



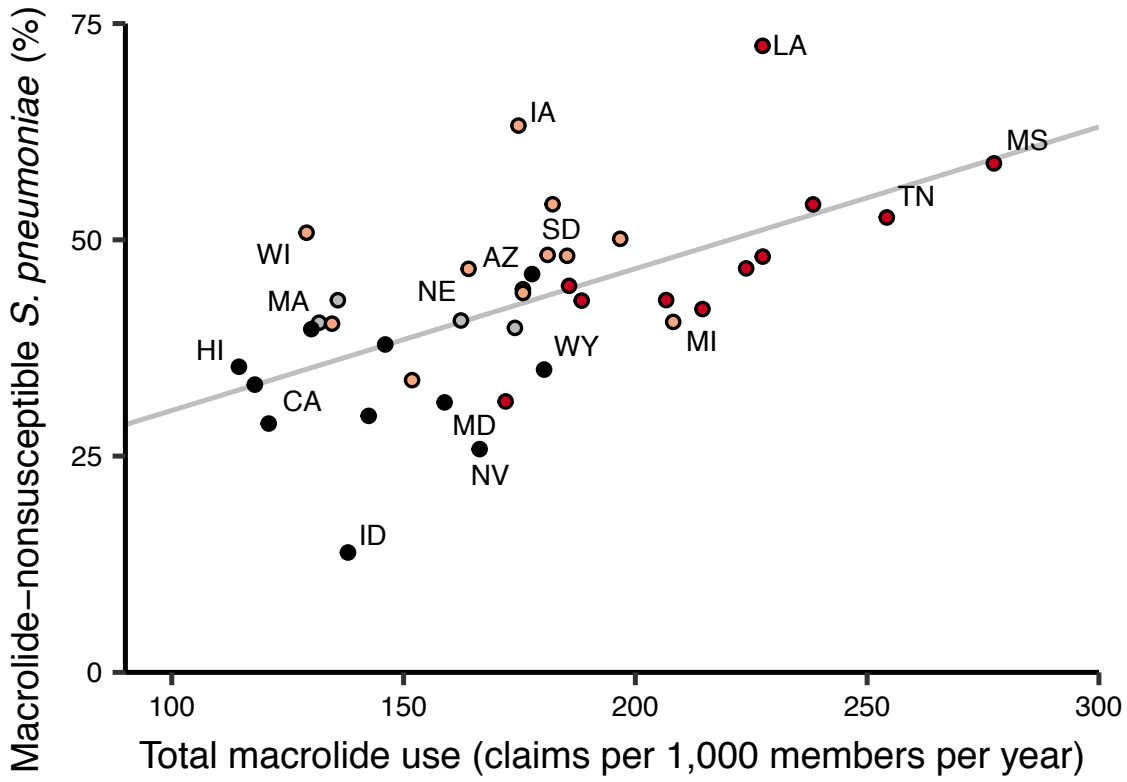
493 Figure 3 – Source data 1. **Antibiotic use data.** For each data source (MarketScan or Medicare),
494 data subset or population among MarketScan records, state (with masked ID), and drug group,
495 annual first and repeat claims per 1,000 members. Main: main data set. Children: members at
496 most 15 years old. Days supply: first and repeat use are reported as days supply, not claims.
497 Multiyear: among members in the data for all 4 data years.
498
499 Figure 3 – Source data 2. **Antibiotic resistance data.** For each adequately-represented pathogen
500 and drug group (see Methods) and state (with masked ID matching the antibiotic use data), the
501 proportion of isolates collected in that state susceptible to that drug.
502
503

504 Figure 4. **Total macrolide use and macrolide resistance among *Streptococcus pneumoniae***

505 **correlate across US states.** Labels indicate selected states. Colors indicate US Census region

506 (red, South; light red, Midwest; gray, Northeast; black, West). Line shows unweighted linear best

507 fit. Southern states have highest macrolide use and resistance.



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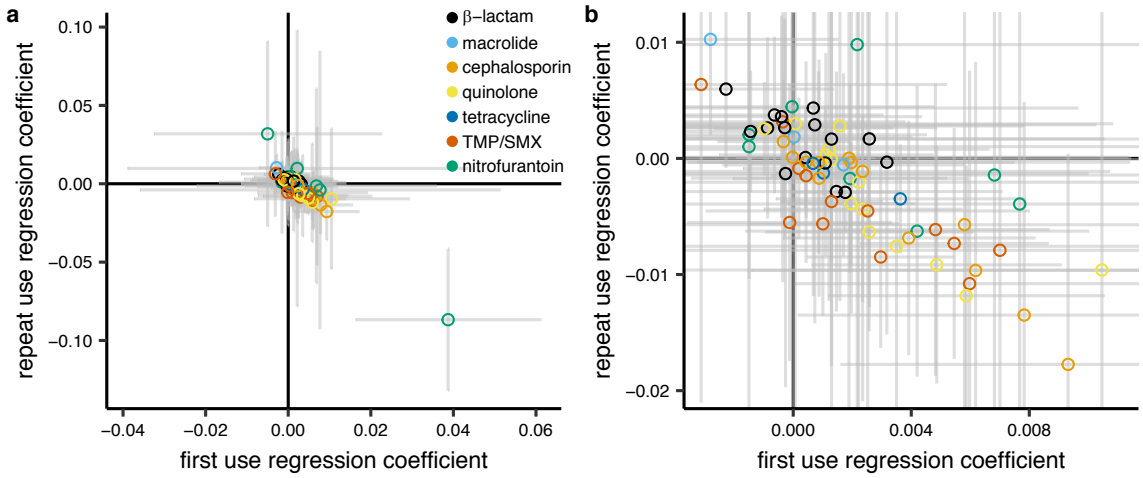
510 Figure 5. **Repeat use tends to be negatively associated with resistance when controlling for**
511 **first use.** Each point represents a pathogen-antibiotic combination. The position of the point
512 shows the two coefficients from the multiple regression. The units of the coefficients are
513 proportion resistant per annual claim per 1,000 people. Color indicates drug group. Error bars
514 show 95% CIs. (*a*) All data. (*b*) Same data, showing only the center cluster of points.



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517 **Supplementary File 1.** Supplemental tables.

518

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