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Original Investigation | Allergy

Association Between Removal of a Warning Against Cephalosporin Use in Patients With Penicillin Allergy and Antibiotic Prescribing

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Abstract

IMPORTANCE Electronic health records (EHRs) often include default alerts that can influence physician selection of antibiotics, which in turn may be associated with a suboptimal choice of agents and increased antibiotic resistance.

OBJECTIVE To examine whether removal of a default alert in the EHR to avoid cephalosporin use in patients with penicillin allergies is associated with changes in cephalosporin dispensing or administration in these patients.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study of a natural experiment included data on patients who had received antibiotic treatment in the hospital or outpatient setting in 2 regions of a large, integrated health system in California from January 1, 2017, to December 31, 2018. Of 4 398 792 patients, 4 206 480 met the eligibility criteria: enrollment in the health system during antibiotic use, availability of complete demographic data, and use of antibiotics outside of the washout period.

INTERVENTIONS OR EXPOSURES Oral or parenteral antibiotics dispensed or administered after removal of an EHR alert to avoid cephalosporin use in patients with a recorded penicillin allergy.

MAIN OUTCOMES AND MEASURES Probability that an antibiotic course was a cephalosporin. A multinomial logistic regression model was used to examine the change in rates of cephalosporin use before and after an EHR penicillin allergy alert was removed in 1 of the study regions. Temporal changes in use rates were controlled for by comparing changes in cephalosporin use among patients with or without a penicillin allergy at the site that removed the warning and among patients at a comparison site that retained the warning. Regression models were used to examine adverse events.

RESULTS Of the 4 206 480 patients who met all inclusion criteria, 2 465 849 (58.6%) were women; the mean (SD) age was 40.5 (23.2) years. A total of 10 652 014 antibiotic courses were administered or dispensed, divided approximately evenly between the period before and after removal of the warning. Before removal of an alert in the electronic health record system to avoid prescribing of cephalosporins to patients with a penicillin allergy at 1 of the 2 sites, 58 228 courses of cephalosporins (accounting for 17.9% of all antibiotic use at the site) were used among patients with a penicillin allergy; after removal of the alert, administration or dispensing of cephalosporins increased by 47% compared with cephalosporin administration or dispensing among patients without a penicillin allergy at the same site and patients at the comparison site that retained the warning (ratio of ratios of odds ratios [RROR], 1.47; 95% CI, 1.38-1.56) . No significant differences in anaphylaxis (9 total cases), new allergies (RROR, 1.02; 95% CI, 0.93-1.12), or treatment failures (RROR, 1.02; 95% CI, 0.99-1.05) were found at the course level. No significant differences were found in all-cause mortality (ratio of ratios of rate ratios [RRRR], 1.03; 95% CI, 0.94-1.13), hospital

(continued)

Key Points

Question Is removal of a warning to avoid cephalosporin use in patients with penicillin allergies associated with an increase in cephalosporin dispensing or administration?

Findings In this cohort study of 4 398 792 patients who had received antibiotic treatment, after an alert in the electronic health record system to avoid prescribing of cephalosporins to patients with a penicillin allergy was removed at 1 of 2 health system sites, cephalosporin dispensing or administration increased significantly among patients with a penicillin allergy at that site compared with patients without a penicillin allergy at the same site and patients at the comparison site that retained the warning.

Meaning In this study, removal of a warning in the electronic health record to avoid cephalosporin use in patients with penicillin allergies was associated with increased dispensing and administration of cephalosporin.

+ Supplemental content

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Abstract (continued)

days (RRRR, 1.04; 95% CI, 0.99-1.10), and new infections (*Clostridioides difficile*: RRRR, 1.02; 95% CI, 0.84-1.22; methicillin-resistant *Staphylococcus aureus*: RRRR, 0.87; 95% CI, 0.75-1.00; and vancomycin-resistant *Enterococcus*: RRRR, 0.82; 95% CI, 0.55-1.22) at the patient level.

CONCLUSIONS AND RELEVANCE In this cohort study, removal of a warning in the electronic health record to avoid cephalosporin use in patients with penicillin allergies was associated with increased administration and dispensing of cephalosporin. This simple and rapidly implementable system-level intervention may be useful for improvement in antibiotic stewardship.

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Introduction

Increases in drug-resistant organisms are a global threat, and thus antibiotic stewardship is a critical priority.[1] Approaches to antibiotic stewardship include both reducing unnecessary use of antibiotics and choosing the most appropriate agents. β-Lactams are the preferred treatment for many common pathogens, such as group A and B *Streptococcus* species, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Staphylococcus aureus*.[2] β-Lactams are also the preferred prophylactic agents for dental procedures and many other surgical procedures.[3] Physicians may, however, choose a second-line antibiotic in the presence of drug allergies or potential cross-reactivity with β-lactams.[4-6]

Point-of-care alerts to inform prescribing decisions by physicians and to enhance patient safety have been among the reasons for use of electronic health records (EHRs). In response to Meaningful Use requirements issued by the Office of the National Coordinator for Health Information Technology, many EHRs include an imbedded function to warn against prescribing cephalosporins to patients with a penicillin allergy.[7-9] This warning is not consistent with current evidence.[2] For example, no clinically significant immunologic cross-reactivity between penicillin and cephalosporins has been shown.[10,11] Furthermore, avoiding β-lactams when they are the drug of choice is associated with worse outcomes, such as increased risk of surgical site infections,[5,12,13] nephrotoxicity,[14] and *Clostridioides difficile* infection.[15] In addition, use of second-line antibiotic classes in patients with penicillin allergies may be associated with other adverse effects, decreased safety, and antimicrobial resistance.[4,6,16]

In December 2017, after a review of the literature and clinical deliberations among leaders in infectious diseases in the Southern California Permanente Medical Group, Kaiser Permanente Southern California removed a warning in its EHR to avoid prescribing cephalosporins to patients with a penicillin allergy. In the current study, we examined the association of this change with choice of antibiotic, incidence of antibiotic allergy, incidence of cephalosporin-associated anaphylaxis, and rate of penicillin allergy–associated morbidities in patients with a penicillin allergy.

Methods

This retrospective cohort study of a natural experiment included members enrolled in either Kaiser Permanente Southern California or Kaiser Permanente Northern California health plans who received antibiotic treatment between January 1, 2017, and December 31, 2018. Kaiser Permanente Southern California, which removed the alert, was the intervention site, and Kaiser Permanente Northern California, which did not remove the EHR alert, was the comparison site for the natural experiment. The institutional review boards of both sites approved this study and waived the requirement for informed consent because the research involved no more than minimal risk to participants, the waiver would not adversely affect participants' rights and welfare, the research could not practically be carried out without the waiver, and participants were provided with additional pertinent

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information after participation. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[17] Additional details are provided in the eMethods in the Supplement.

At each site, a difference-in-differences[18] design comparing changes in the cohort of patients allergic to penicillin with changes in the cohort of patients without penicillin allergy was used. Our focus was on understanding the changes in prescribing patterns and monitoring for adverse effects after removal of the EHR alert. Together, the health plans cover approximately 9 million members who receive care at 36 hospitals and 491 outpatient facilities from more than 17 000 physicians. The enrolled populations are broadly representative of the general population in California.[19,20]

Data Sources

Data were extracted from existing health plan and care delivery sources, including membership records, integrated claims, ambulatory and hospital-based EHRs, and other administrative data. We calculated baseline patient characteristics using data starting from January 1, 2016, and extracted outcome data through January 31, 2019, to allow for follow-up time to measure outcomes for courses of antibiotics started through December 31, 2018.

Study Definitions

We included all oral and parenteral antibiotic treatment courses dispensed or administered to enrolled members in the ambulatory or hospital setting for 12 antibiotic categories: penicillin, cephalosporin, other β-lactams, clindamycin, macrolides, metronidazole, nitrofurantoin, quinolones, sulfonamides, tetracyclines, vancomycin, and other antibiotics (a detailed list is provided in eTable 1 in the Supplement). Antibiotic use that occurred outside membership periods was excluded. We combined periods of exposure into the same course of antibiotic use if they involved the same drug by the same route and were separated by less than 2 days. The earliest date that the antibiotic was dispensed or administered was used to assign each course to the period before (January 1, 2017-December 12, 2017) or after (December 28, 2017-December 31, 2018) the change in the alert on December 20, 2017; we excluded data on antibiotics dispensed or administered in the 7 days before and 7 days after the change in the alert. The patient's penicillin allergy status was ascertained on the day before the start date of each antibiotic course.

We used any entry in the EHR allergy field to define the presence of a drug allergy. We did not require confirmed IgE-mediated or T-cell–mediated hypersensitivity. Although misclassification of penicillin allergy status in the EHR can occur,[21] we used the presence of an allergy record in the EHR to define *allergy* because this record triggers the automated warning that was being studied. We extracted complete histories of antibiotic allergies to identify periods of allergies to antibiotics in the 12 categories during the study. New antibiotic allergies were defined as new allergy records after use of an antibiotic in the same category within 30 days of the start of the treatment course.

Potential cases of cephalosporin-associated anaphylaxis in patients with a penicillin allergy were identified with *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes T78.2 or T88.6 recorded on the same day that a course of parenteral cephalosporins was started or within 1 day of starting a course of oral cephalosporins. Each potential case was manually audited by chart review (E.M. and W.W.C. for the intervention site and M.T.N. for the comparison site) to determine whether it met the current diagnostic criteria for antibiotic-associated anaphylaxis.[22] As a proxy for antibiotic treatment failure, we used the start of a new course of antibiotics in a different category within 30 days of the start of a course of monotherapy.[16]

The rate of days spent in the hospital (hereafter *hospital days*) per person-year was defined as the number of days in the period that the patient spent in the hospital (including time contributed by the emergency department and observation days that were linked to an inpatient admission) divided by the total member-days in the period. The rate of new infections per person-year was defined as patients having 1 or more new *C difficile*, methicillin-resistant *S aureus* (MRSA), or vancomycin-resistant *Enterococcus* (VRE) infections during the period. We selected these infections a priori based

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on prior studies[4,23,24] and clinical input. Infections were identified based on positive laboratory results or diagnoses from encounters in the hospital or outpatient setting. *ICD-10* diagnosis codes starting with A04.7 were used to identify *C difficile* infection; A41.02, A49.02, B95.62, or J15.212 were used to identify MRSA infection; and Z16.21 and Z16.22 were used to identify VRE infection. Infections were considered new if there were no indications of VRE or MRSA infection in the prior 30 days or *C difficile* infection in the prior 90 days.

We defined comorbidities using the diagnoses included in the Charlson Comorbidity Index.[25] We defined hospital encounters for surgery or labor and delivery using diagnosis-related group codes.

Statistical Analysis

The primary outcome was the category of antibiotic use measured by the change in the probability of cephalosporin use among patients with a penicillin allergy at the intervention site after the removal of the warning. We used a multinomial logistic regression model with the 12 antibiotic categories as the outcome. Generalized estimating equation–based adjustments to the SEs were performed using an independent working correlation matrix (details are provided in the eMethods in the Supplement). For each course of antibiotic treatment, the model included an indicator for site, period (before or after removal of the alert), and presence or absence of a penicillin allergy. The model included these main effects, as well as all 2-way interactions and the 3-way interaction. Patient sex, age, and self-reported race/ethnicity and the age-sex interaction were included as covariates in the model to adjust for differences between the sites.

This model simultaneously controlled for temporal effects using 2 comparison populations. First, we examined the change in cephalosporin prescriptions among patients without penicillin allergies, which should have been unaffected by the removal of the warning. This was an adjusted ratio of odds ratios (RORs) calculation. Second, we examined the equivalent RORs for the comparison site to further control for temporal changes in antibiotic use. The outcome was formulated as a ratio of these 2 RORs (RROR) and was modeled with multinomial logistic regression. The regression coefficient for the 3-way interaction represents the change in antibiotic prescribing as the natural log of the RROR. We fit models for all courses and fit separate models for oral and parenteral courses.

We calculated several secondary outcomes to explore whether removal of the warning was associated with patient outcomes. At the treatment-course level, we examined anaphylaxis, new antibiotic allergies, and antibiotic treatment failure. At the patient level, we assessed all-cause mortality, hospital days, and new infections per person-year. Regression models for the secondary outcomes used the same independent variables and interactions as in the model for the primary outcome. The details of the models for secondary outcomes varied, but all were formulated using the ROR approach described for the primary outcome. Course-level outcomes were RRORs, and patient-level outcomes were ratios of ratios of rate ratios (RRRRs). Dimensions of the differences included the model distributions and link functions, criteria for including courses and person-time, consideration of different cephalosporin generations, and membership criteria. More details are given in the eMethods and eTable 3 in the Supplement.

In addition, we fit separate models for the secondary outcomes that included the penicillin allergy indicator only as a main effect but not in interactions with other independent variables. These models estimated the extent to which patients with a penicillin allergy had a higher rate of the adverse outcome than patients without a penicillin allergy.

We tested the sensitivity of the results for the primary outcome after adding covariates to the models, including indicators for allergies to other antibiotic categories, the diagnosis group associated with the course, and the presence of individual comorbidities at the start of the course and indicators that the course occurred during a hospitalization for surgery or labor and delivery. We tested how the results changed when the main variables interacted with the other covariates as well as after adding effect modification of the 3-way interaction by adding the 4-way interactions with age, sex, and race/ethnicity. In addition, we tested whether the results were sensitive to different

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variable definitions by assigning the penicillin allergy on the date when the treatment was first dispensed or administered (rather than the day before) and including only each patient's first or last course in the model. Analyses were conducted using SAS, version 7.1 (SAS Institute).

Results

We identified 4 398 792 unique patients with antibiotic use during the study period. Of these, 143 606 (3.3%) were excluded because they were not enrolled at the time of their antibiotic use; 281 (0.01%) were excluded owing to missing or inconsistent birth date, sex, or death date; and 48 425 (1.1%) were excluded because their antibiotic use occurred during the washout period. Thus, 4 206 480 patients (2 252 525 at the intervention site and 1 953 955 at the comparison site) were included in the analysis: 2 465 849 (58.6%) were women, 1 827 714 (43.4%) were non-Hispanic White, and the mean (SD) age was 40.5 (23.2) years at the start of the study period. Patient demographics differed between the 2 sites; members at the intervention site were younger, more likely to be Black or Hispanic, and less likely to be Asian or White (**Table 1**). The crude mortality rate at the comparison site was higher than that at the intervention site (1.8% [34 485 deaths] vs 1.5% [32 734 deaths]), which is consistent with previously published studies.[26,27] Patients contributed a mean (SD) of 2.5 (2.7) treatment courses to the study, and 9.4% of patients had a penicillin allergy at the start of the study period.

We included 10 652 014 antibiotic courses in the analysis (**Table 2**); 51.8% were in the period after removal of the alert, 18.0% were parenteral courses, and 12.1% were dispensed or administered to patients with a documented penicillin allergy (eTable 4 in the Supplement). Cephalosporin use (as a fraction of all antibiotic use) increased among patients with a penicillin allergy at the intervention

Table 1. Characteristics of the 4 206 480 Patients Included in the Study

Characteristic	Patients, No. (%)	
	Intervention site (n = 2 252 525)	Comparison site (n = 1 953 955)
Sex		
Female	1 320 984 (58.6)	1 144 865 (58.6)
Male	931 541 (41.4)	809 090 (41.4)
Age at study start, y		
Mean (SD)	39.9 (23.1)	41.2 (23.2)
Median (IQR)	40 (22-58)	41 (23-59)
Race/ethnicity		
American Indian or Alaska Native (non-Hispanic)	23 944 (1.1)	25 883 (1.3)
Asian or Pacific Islander (non-Hispanic)	216 343 (9.6)	337 055 (17.3)
Black (non-Hispanic)	203 047 (9.0)	149 368 (7.6)
Hispanic	801 339 (35.6)	342 225 (17.5)
White (non-Hispanic)	847 734 (37.6)	979 980 (50.2)
Other race/ethnicity[a]	160 118 (7.1)	119 444 (6.1)
Penicillin allergy at study start	201 293 (8.9)	192 534 (9.9)
Died during study	32 734 (1.5)	34 485 (1.8)
Continuously enrolled during study	1 839 686 (81.7)	1 615 251 (82.7)
≥1 Oral course of antibiotic treatment	2 144 346 (95.2)	1 835 996 (94.0)
≥1 Parenteral course of antibiotic treatment	502 280 (22.3)	437 959 (22.4)
Antibiotic treatment courses, No.		
Mean (SD)	2.6 (2.7)	2.5 (2.6)
Median (IQR)	2 (1-3)	2 (1-3)
Received antibiotic treatment in the period before warning removal	1 420 320 (63.1)	1 216 371 (62.3)
Received antibiotic treatment in the period after warning removal	1 496 480 (66.4)	1 274 700 (65.2)

Abbreviation: IQR, interquartile range.

[a] Other race/ethnicity indicates not specified, unknown, or patient declined to state.

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site from 17.9% of courses in the period before removal of the alert to 27.0% of courses in the period after removal of the alert (Table 2). As cephalosporin use increased, use of some categories of antibiotics decreased in the period after removal of the alert. For example, among patients with penicillin allergy at the intervention site, use of clindamycin decreased from 13.7% to 11.4% and use of quinolones decreased from 12.8% to 10.5%. The same general pattern was present for oral and parenteral courses (eTable 5 in the Supplement). Most cephalosporin courses (71.7%) were first generation (eTables 2 and 6 in the Supplement), and the increase in use was mainly in this generation (eTable 7 in the Supplement). The change in rates of use of cephalosporin, clindamycin, or quinolones at the comparison site before vs after removal of the alert was smaller; among patients with penicillin allergy, cephalosporin use increased from 15.3% to 16.2%, clindamycin use increased from 14.0% to 14.2%, and quinolone use decreased from 14.7% to 14.2%.

We found a significant increase of 47% in cephalosporin use among patients with penicillin allergy at the intervention site compared with patients in the other groups (RROR, 1.47; 95% CI, 1.38-1.56). The RRORs for the 12 antibiotic categories are shown in the **Figure** and in eTables 8-10 in the Supplement. The RRORs for other categories generally decreased or stayed the same in the period after removal of the alert. The exception was metronidazole (RROR, 1.10; 95% CI, 1.03-1.18), but this result appeared to be an artifact of ratios of small numbers (Table 2). The change in oral

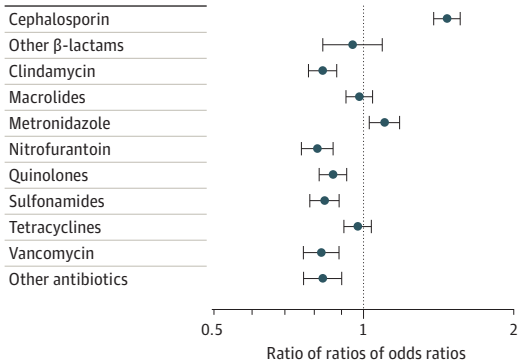
Table 2. Patterns of Antibiotic Use by Antibiotic Category, Study Period, Penicillin Allergy Status, and Study Site

	Antibiotic treatment courses dispensed or administered, %							
	Intervention site				Comparison site			
	No allergy		Allergy		No allergy		Allergy	
Antibiotic category	Before[a]	After[b]	Before[a]	After[b]	Before[a]	After[b]	Before[a]	After[b]
Antibiotic treatment courses, No.	2 480 535	2 679 107	324 856	349 847	2 029 273	2 174 367	297 710	316 319
Penicillin	29.5	29.5	2.1	2.2	29.8	29.5	2.0	2.1
Cephalosporin	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
Other β-lactams	0.2	0.2	0.5	0.4	0.2	0.2	1.0	0.8
Clindamycin	2.6	2.5	13.7	11.4	2.2	2.2	14.0	14.2
Macrolides	12.5	12.2	19.9	18.3	13.6	12.8	19.0	17.4
Metronidazole	4.8	4.9	5.4	5.5	4.1	4.5	5.1	5.1
Nitrofurantoin	2.5	2.8	4.3	3.9	3.1	3.4	4.2	4.6
Quinolones	7.9	7.3	12.8	10.5	7.8	7.3	14.7	14.2
Sulfonamides	4.6	4.3	7.4	5.8	4.5	4.2	7.0	6.7
Tetracyclines	7.2	7.3	11.4	11.4	8.0	8.5	12.7	13.9
Vancomycin	1.2	1.3	2.6	2.0	1.5	1.5	2.9	2.9
Other antibiotics	1.2	1.2	1.8	1.5	1.6	1.5	2.1	2.1

[a] One year before removal of the penicillin allergy warning from the electronic health record.

[b] One year after removal of the penicillin allergy warning from the electronic health record.

Figure. Multinomial Logistic Regression of Changes in Antibiotic Use Among Patients With Penicillin Allergies



Odds ratio of a patient with penicillin allergy receiving a course of antibiotic treatment, by category, at the intervention site before vs after removal of a warning against cephalosporin use from the electronic health record compared with odds ratios of patients without a penicillin allergy and those at the comparison site receiving the treatment in those periods. Whiskers indicate 95% CIs; vertical line represents a ratio of ratios of rate ratios of 1.0, indicating no change in antibiotic use (compared with other groups) after the removal of the warning.

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cephalosporin use was similar to the main result calculated for all courses, with an RROR of 1.51 (95% CI, 1.41-1.61) (eTable 9 in the Supplement). The crude increase in the rate of prescribing of parenteral cephalosporins (from 35.5% to 54.3%) among patients with penicillin allergy at the intervention site was larger than that for oral cephalosporins (from 14.2% to 21.1%), but the RROR was smaller (1.29; 95% CI, 1.10-1.51) because of a concurrent increase in use of parenteral cephalosporins at the comparison site.

The difference in the rates of anaphylaxis among individuals with penicillin allergies who used cephalosporin between the sites was not significant. The results for the other course-level outcome calculations are summarized in **Table 3**. New allergies and antibiotic treatment failure were more likely to occur among patients with a penicillin allergy than among those without a penicillin allergy (eTables 11-15 in the Supplement). The RRORs for these outcomes were not statistically significant when calculated with all courses (new allergies, 1.02 [95% CI, 0.93-1.12]; treatment failure, 1.02 [95% CI, 0.99-1.05]) or when calculated separately including only oral courses (new allergies, 1.00 [95% CI, 0.91-1.10]; treatment failure, 1.02 [95% CI, 0.99-1.06]) or parenteral courses (new allergies, 1.23 [95% CI, 0.94-1.61]; treatment failure, 0.96 [95% CI, 0.90-1.03]). Furthermore, patients with a penicillin allergy at the intervention site who used a cephalosporin had a similar rate of new cephalosporin allergies within 30 days during the 2 periods (1.0% of courses in the period before removal of the alert and 0.9% of courses in the period after removal of the alert) (eTable 11 in the Supplement).

The RRRR was not significantly different from 1 for all-cause mortality (1.03; 95% CI, 0.94-1.13), hospital days (1.04; 95% CI, 0.99-1.10), or new *C difficile* (1.02; 95% CI, 0.84-1.22), MRSA (0.87; 95% CI, 0.75-1.00), or VRE (0.82; 95% CI, 0.55-1.22) infection among all patients (**Table 4**). The RRRRs were also not significantly different when the hospital day and new infection calculations were limited to only patients who received parenteral courses. Patients with penicillin allergies had worse outcomes, and the outcomes generally improved after removal of the alert in each patient group (eTables 16-19 in the Supplement).

The results were robust to several sensitivity analyses (eTable 20 in the Supplement). The effect size was generally larger in the more complicated models, although the 95% CIs overlapped with the 95% CIs from the main model (eTable 20 in the Supplement). In models that included all courses, the value of the RROR of interest ranged from 1.46 to 1.64. For models that included only oral or only parenteral courses, the RROR values ranged from 1.52 to 1.71 and 1.20 to 1.37, respectively (eTable 20 in the Supplement). The model with effect modification by age, sex, and race/ethnicity suggested that the change in the warning was associated with fewer changes in antibiotic use patterns for patients younger than 18 years (RROR, 0.7; 95% CI, 0.6-0.9).

Table 3. Antibiotic Treatment Course–Level Outcome Results for All Patients and Patients With vs Without Penicillin Allergies

Outcome	All courses	Oral courses	Parenteral courses
New antibiotic allergy within 30 d			
Crude RROR	1.02	1.00	1.23
RROR from binomial logistic regression model (95% CI)	1.02 (0.93-1.12)	1.00 (0.91-1.10)	1.23 (0.94-1.61)
Overall OR for patients with vs without penicillin allergy (95% CI)	1.62 (1.58-1.66)	1.58 (1.54-1.62)	1.91 (1.79-2.05)
Treatment failure within 30 d			
Crude RROR	1.02	1.02	0.96
RROR from binomial logistic regression model (95% CI)	1.02 (0.99-1.05)	1.02 (0.99-1.06)	0.96 (0.90-1.03)
Overall OR for patients with vs without penicillin allergy (95% CI)	1.10 (1.10-1.11)	1.10 (1.10-1.11)	1.18 (1.16-1.21)

Abbreviations: OR, odds ratio; RROR, ratio of ratios of odds ratios.

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Discussion

In this retrospective cohort study of a natural experiment, cephalosporin use increased from 17.9% to 27.0% among patients at the intervention site, where the warning not to prescribe cephalosporins to patients with a penicillin allergy was removed, compared with a change from 15.3% to 16.2% at the comparison site, which retained the warning. This translated to a statistically significant increase in cephalosporin use at the intervention site (RROR, 1.47; 95% CI, 1.38-1.56) during the period after removal of the penicillin allergy warning. We found no significant differences in the rates of anaphylaxis, allergies to new antibiotic classes, antibiotic treatment failure, all-cause mortality, hospital days, and new infections after the change.

Although the rate of adverse outcomes did not increase after removal of the warning, patients with penicillin allergy experienced worse outcomes in general than did those with no penicillin allergy. These results are consistent with prior studies[16,28] suggesting higher rates of new antibiotic allergies among patients with a penicillin allergy who receive any antibiotic compared with patients without a penicillin allergy. The results are also consistent with prior studies showing higher rates of infection[16,23,28] and mortality[16,29] among patients with a penicillin allergy.

Removal of the penicillin allergy warning in the EHR represents a simple and rapidly implementable system-level intervention to potentially improve antibiotic stewardship. In addition, removal of an unsupported warning in the EHR may be associated with reduced alert fatigue among clinicians.[7] This study's findings may encourage other health care systems to remove the warning, which may improve antibiotic stewardship.

Limitations

This study has limitations. Because it was a retrospective study, we cannot rule out that unmeasured confounders may explain some of the associations. We attempted to control for this by using a before-and-after design and making comparisons with changes in the 2 patient groups that were

Table 4. Person-Level Outcome Results for All Patients and Patients With vs Without Penicillin Allergies

Outcomes	All patients	Patients receiving parenteral treatment
All-cause mortality		
Crude RRRR	1.02	NA
RRRRs from Poisson regression model (95% CI)[a]	1.03 (0.94-1.13)	NA
Overall rate for patients with vs without penicillin allergy (95% CI)	1.03 (1.01-1.06)	NA
Hospital days		
Crude RRRR	1.04	1.05
RRRR from Poisson regression model (95% CI)	1.04 (0.99-1.10)	1.05 (0.99-1.11)
Overall rate for patients with vs without penicillin allergy (95% CI)	1.09 (1.08-1.11)	1.12 (1.10-1.14)
New *Clostridioides difficile* infection		
Crude RRRR	1.02	1.01
RRRR from Poisson regression model (95% CI)	1.02 (0.84-1.22)	1.02 (0.82-1.26)
Overall rate for patients with vs without penicillin allergy (95% CI)	1.23 (1.17-1.29)	1.17 (1.11-1.24)
New MRSA infection		
Crude RRRR	0.87	0.88
RRRR from Poisson regression model (95% CI)	0.87 (0.75-1.00)	0.88 (0.73-1.05)
Overall rate for patients with vs without penicillin allergy (95% CI)	1.06 (1.02-1.10)	1.14 (1.09-1.20)
New VRE infection		
Crude RRRR	0.82	0.77
RRRR from Poisson regression model (95% CI)	0.82 (0.55-1.22)	0.78 (0.51-1.18)
Overall rate for patients with vs without penicillin allergy (95% CI)	1.39 (1.26-1.53)	1.38 (1.24-1.53)

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable; RRRR, ratio of ratios of rate ratios; VRE, vancomycin-resistant *Enterococcus*.

[a] Details are provided in the eMethods in the Supplement.

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unaffected by the removal of the warning (those at the comparison site, where the warning was not changed, and those at the intervention site who did not have a penicillin allergy, to whom the warning did not apply). Although we adjusted the results for basic confounders, it is possible that unmeasured patient characteristics were contributing biases. In addition, although none of the changes in the secondary outcomes were statistically significant, the 95% CIs were generally large enough to include at least a 10% increase or decrease in each outcome. Thus, we cannot rule out the possibility that removing the warning was associated with changes in patient outcomes.

Conclusions

In this cohort study, removal of a warning in the EHR to avoid cephalosporin use in patients with penicillin allergies was associated with increased prescribing of cephalosporins and decreased prescribing of some second-line antibiotics. Overall rates of adverse antibiotic-associated reactions or specific serious cephalosporin-associated morbidities were similar before and after removal of the warning. Removing the warning was not associated with a reduction in the known morbidities associated with an unconfirmed penicillin allergy. Greater attention should be given to the accuracy with which patients are labeled as having a penicillin allergy.[30]

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Administrative, technical, or material support: Nguyen, Davis, McGlynn.

Supervision: Macy, Adams, McGlynn.

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

Macy E, McCormick T, Adams J, et al.

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

eMethods. Additional methodology details

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eTable 2. Classification of cephalosporin antibiotics by generation

eTable 3. Definitions and modeling strategies for secondary outcomes

eTable 4. Descriptive statistics for courses in the analysis

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

Macy E, McCormick T, Adams J, et al.

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

Macy E, McCormick T, Adams J, et al.

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

Macy E, McCormick T, Adams J, et al.

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

Macy E, McCormick T, Adams J, et al.

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

Macy E, McCormick T, Adams J, et al.

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

Macy E, McCormick T, Adams J, et al.

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

Macy E, McCormick T, Adams J, et al.

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

Macy E, McCormick T, Adams J, et al.

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

Macy E, McCormick T, Adams J, et al.

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

Macy E, McCormick T, Adams J, et al.

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

Macy E, McCormick T, Adams J, et al.

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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Supplementary Online Content

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. *JAMA Netw Open*. 2021;4(4):e218367. doi:10.1001/jamanetworkopen.2021.8367

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Association between removing a warning to avoid cephalosporin use in patients with penicillin allergy and antibiotic prescribing

Supplementary Appendix

Macy E, McCormick T, Adams J, et al.

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eMethods. Additional Methodology Details

Study Population

Study inclusion and exclusion criteria were as follows:

- Inclusion:
  - Members enrolled in KPSC (the intervention site) or KPNC (the comparison site) who received any oral or parenteral antibiotic (dispensed/administered) listed in eTable 1 between January 1, 2017 and December 31, 2018
- Exclusion:
  - Antibiotics dispensed/administered during the wash out period (the 7 days before and 7 days after the December 20, 2017 change in the alert)
  - Antibiotics dispensed/administered outside of a membership period
  - Patients with missing birth date or gender
  - Patients with birth date after the date of the first prescription, administration, or dispense (which suggested an inaccurate birth date).
  - Patients with death date before the first administration or dispense (which suggested an inaccurate death date).

Antibiotic Names and Categories

The list of 144 antibiotic generic and class names used to identify relevant medication and allergy records is shown in eTable 1.

Study Definitions

Antibiotic Use

Periods of exposure to outpatient dispenses were calculated based on the dispense date and the days' supply, after adjusting sequential dispenses for stockpiled supply. Missing values of days' supply of outpatient medications were set to 1 day, and missing prescription dates were set to the date of the administration or dispense.

When two different antibiotics were administered in combination, they were considered to be two concurrent courses. For each course, we identified the date of the earliest prescription and the date of the earliest administration or dispense (the course start date). If any prescriptions in the course were associated with a diagnosis code, the earliest diagnosis code was used as the indication for the whole course.

For all courses, detailed route descriptions were categorized as either "oral" or "parenteral" to allow separate analyses by route of administration.

Anaphylaxis

We used ICD codes as described in the manuscript to identify potential cases of anaphylaxis. We included any outpatient coding of the relevant diagnoses on the same day as a parenteral course or within one day of an oral course of cephalosporin. For diagnoses that were coded during a hospitalization, it was not possible to determine from the secondary data the date on which the diagnosis occurred. Therefore, we included as potential cases all those coded during hospital or Emergency Department (ED) encounters that started within the same day as the start of a course of parenteral cephalosporin or within 1 day of a course of oral cephalosporin, or cases coded during a hospital stay that overlapped with the start of a course of a cephalosporin. Potential cases were confirmed by chart review, as described in the manuscript.

New Antibiotic Allergy

The calculations for new antibiotic allergies included courses for which the patient had at least 30 days of membership after the course start date, and included new allergy records and membership data through January 2019. The outcome was defined as a binary indicator for any new allergy records in the same antibiotic category during the 30-day follow-up window. New allergy records that appeared in the follow-up windows for multiple courses were assigned to the course(s) on the most recent date. If two courses in the same category started on the same date, the new allergy record was attributed to both (this accounted for approximately 2% of new allergy events).

Antibiotic Treatment Failure

The calculations for antibiotic treatment failure included courses of antibiotic monotherapy for which the patient had at least 30 days of membership in the analysis period after the course start date and included new courses of

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antibiotics through December 2018. A course was considered to be monotherapy if it was the only course of antibiotics that the patient started on the date. For this calculation, cephalosporin generations 1, 2, and 3 (or higher) were treated as different categories of antibiotics (see eTable 2 for the mapping of cephalosporin generic names to generations). If a new course of antibiotics started in the follow-up window of multiple courses, it was considered treatment failure only for the most recent course; and the outcome was a binary indicator for the presence of any treatment failure events in the follow-up window.

All-Cause Mortality

The all-cause mortality calculation included person-time starting at the earliest course start date in the period (to avoid immortal time bias) and ended at the earlier of the period end or the death date. Age was calculated as of the first course start date in the period, and penicillin allergy status was assessed as of the day before.

Hospital Days

The hospital days per person-year calculation included all periods of membership during the analysis period as person-time and included all hospital encounters during these member periods. Membership periods and hospital stays were separated into days in the pre and post periods, and days with and without a penicillin allergy record.

New Infections

The calculations for each new infection type (*C. diff*, MRSA, and VRE) were carried out separately. Person-time was calculated from the first course date in the period until the earlier of the end of the period or the end of the membership period. The date associated with a lab result was the specimen collection date. The date associated with an outpatient or ED diagnosis was the encounter date. The date associated with a hospital diagnosis with an inpatient admission was the encounter end date, unless the diagnosis was flagged as being present on admission (in which case it was associated with the encounter start date). Diagnoses and lab results from encounters in the three months before the start of the analysis period were included to determine whether infections in January-March 2017 were new. Because a person could have recurrent infections, the outcome was defined as a binary indicator of zero vs. one or more infections during the period.

Variables Used in Sensitivity Analyses

For the sensitivity analyses, dates of the onset of the individual comorbidities in the Charlson index, as well as hypertension and hyperlipidemia, were extracted based on ICD-10 diagnosis codes from hospital and outpatient encounters. We extracted Diagnosis-Related Group (DRG) data for hospital encounters that overlapped with course time periods, and used the DRG and Major Diagnostic Category (MDC) codes to identify courses that occurred during hospitalizations that included surgeries or labor and delivery. Encounters in Hospital Ambulatory Surgery (HAS) were also counted as surgery encounters.

Statistical Analyses

Summary

A high-level summary of the outcome definitions and modeling strategies used in all main analyses is presented in eTable 3.

All models in the main analyses of the primary and secondary outcomes included the following variables:

- Main effects:
    - site (intervention or comparison)
    - period (pre or post)
    - penicillin allergy status
    - all two-way interactions of the above
    - the three-way interaction of the above (the coefficient on this interaction term is the logarithm of the RROR or RRRR of interest in each model)
- Covariates:
    - Sex
    - Age
    - race/ethnicity
    - the age-sex interaction

We adjusted for race/ethnicity in the multivariate analyses because of known differences between the patient populations of the two sites. Race and ethnicity are self-reported as part of routine data capture within the EHR. We

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categorized the self-reported race/ethnicity values from the EHR into six categories (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian/Pacific Islander, non-Hispanic Black, Hispanic, non-Hispanic White, and other). Other race/ethnicity includes those for whom race/ethnicity is unknown.

Modeling of the Primary Outcome

The primary outcome was change in antibiotic use, estimated at the course level. We used a generalized logistic regression model with penicillin as the reference level in the modeling of the primary outcome. The resulting estimate is an RROR representing the probability that a course of antibiotics will be cephalosporin.

Modeling of the Secondary Outcomes

We did not model probability of anaphylaxis because of small numbers (total of 68 potential cases, of which 9 were confirmed). To assess statistical significance of the anaphylaxis outcome (course level), we used Poisson regression on a person-level dataset with course count as an offset to calculate a chi-squared test with three degrees of freedom (based on two regions and two time periods).

We modeled all other secondary outcomes with binary logistic regression or Poisson regression, as described below. We also completed sensitivity analyses that are described below; the study findings did not change based on these models.

- New antibiotic allergies: we used binary logistic regression models to calculate the RROR for a new allergy in the same antibiotic category within 30 days of the start of a course of antibiotics, combining all antibiotic categories.
- Treatment failure: we used binary logistic regression models to calculate the RROR for the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy, combining all antibiotic categories.
- Mortality: crude mortality rates were directly standardized to the age, gender, and race/ethnicity distribution of the full intervention site pre period population. Separately, we used Poisson regression to estimate the change in all-cause mortality rates as a RRRR. As a sensitivity analysis, we fit a second model that included indicators for the presence of comorbidities (described above) as of the first course start in the period.
- Hospital Days: we used Poisson regression to estimate the change in hospital days as an RRRR. Because the same person could contribute both oral and parenteral courses to the analysis, this calculation could not be done separately for oral and parenteral courses. Instead, the model was also fit separately for patients who contributed parenteral courses to the analysis. As sensitivity analyses, we fit models that included indicators for the presence of comorbidities (described above) and with a more flexible negative binomial distribution.
- New Infections: we used logistic regression with a complementary log-log link to calculate the change in new infection rates as RRRRs (*C. diff*, MRSA, and VRE). The models were also fit separately for patients who contributed parenteral courses to the analysis. As a sensitivity analysis, we recalculated the new infection outcomes without censoring at the first membership gap.

Modeling of Outcomes for Patients with and Without Penicillin Allergies

We fit additional models of the secondary outcomes to estimate the odds ratio (or rate ratio) of the outcome for patients with penicillin allergies vs. patients without penicillin allergies. The independent variables in these models were the same as in the main outcome models except that they did not include interactions involving the penicillin allergy indicator. That is, the models included region, period, the region-period interaction, penicillin allergy status, sex, age, race/ethnicity, and the age-sex interaction.

Calculation of Confidence Intervals

For all model results reported with confidence intervals, Generalized Estimating Equations (GEEs) were used to fit models with a random 20% subset of the patients to estimate a multiplicative correction factor for standard errors related to patient-level correlations (since patients often contributed multiple courses in the analysis). This correction factor was used to increase the size of 95% confidence intervals for the full model results. Running these models on 100% of the data was computationally infeasible. The correction factors for most outcomes ranged from 1.0-1.2. The exception was the hospital days outcome, where the correction factor ranged from 4.3-4.4. We considered the possibility that correlations at a higher level of aggregation might also affect standard error and confidence interval calculations. To explore this, we fit alternative models that included fixed effects for medical office building area.

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These geographic units correspond to the area around medical office buildings in the delivery system. The alternative models produced standard errors that were nearly the same as our main analyses.

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Supplementary Tables

eTable 1. Antibiotic names and categories

Generic or class name	Category
AMDINOCILLIN	Penicillin
AMIKACIN	Other antibiotics
AMINOGLYCOSIDES	Other antibiotics
AMOXICILLIN	Penicillin
AMPICILLIN	Penicillin
AZITHROMYCIN	Macrolide
AZTREONAM	Other beta-lactam
CAPREOMYCIN	Other antibiotics
CARBAPENEMS	Other beta-lactam
CARBENICILLIN	Penicillin
CEFACLOR	Cephalosporin
CEFADROXIL	Cephalosporin
CEFAMANDOLE	Cephalosporin
CEFAZOLIN	Cephalosporin
CEFDINIR	Cephalosporin
CEFDITOREN	Cephalosporin
CEFEPIME	Cephalosporin
CEFIXIME	Cephalosporin
CEFMETAZOLE	Cephalosporin
CEFONICID	Cephalosporin
CEFOPERAZONE	Cephalosporin
CEFOTAXIME	Cephalosporin
CEFOTETAN	Cephalosporin
CEFOXITIN	Cephalosporin
CEFPODOXIME	Cephalosporin
CEFPROZIL	Cephalosporin
CEFTAROLINE	Cephalosporin
CEFTAZIDIME	Cephalosporin
CEFTIBUTEN	Cephalosporin
CEFTIZOXIME	Cephalosporin
CEFTOLOZANE	Cephalosporin
CEFTRIAXONE	Cephalosporin
CEFUROXIME	Cephalosporin
CEPHALEXIN	Cephalosporin
CEPHALOSPORINS	Cephalosporin
CEPHALOTHIN	Cephalosporin
CEPHAPIRIN	Cephalosporin
CEPHRADINE	Cephalosporin
CHLORAMPHENICOL	Other antibiotics
CHLORTETRACYCLINE	Tetracycline
CINOXACIN	Quinolone
CIPROFLOXACIN	Quinolone
CLARITHROMYCIN	Macrolide
CLINDAMYCIN	Clindamycin
CLOFAZIMINE	Other antibiotics
CLOXACILLIN	Penicillin
COLISTIMETHATE	Other antibiotics
COLISTIN	Other antibiotics

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Generic or class name	Category
CO-TRIMOXAZOLE	Sulfonamide
CYCLOSERINE	Other antibiotics
DALBAVANCIN	Other antibiotics
DALFOPRISTIN	Other antibiotics
DAPSONE	Other antibiotics
DAPTOMYCIN	Other antibiotics
DELAFLOXACIN	Quinolone
DEMECLOCYCLINE	Tetracycline
DICLOXACILLIN	Penicillin
DIHYDROSTREPTOMYCIN	Other antibiotics
DIRITHROMYCIN	Macrolide
DORIPENEM	Other beta-lactam
DOXYCYCLINE	Tetracycline
ENOXACIN	Quinolone
ERTAPENEM	Other beta-lactam
ERYTHROMYCIN	Macrolide
ERYTHROMYCIN ETHYLSUCCINATE + SULFISOXAZOLE ACETYL	Macrolide and Sulfonamide
ETHAMBUTOL	Other antibiotics
ETHIONAMIDE	Other antibiotics
FIDAXOMICIN	Other antibiotics
FOSFOMYCIN	Other antibiotics
FURAZOLIDONE	Other antibiotics
GATIFLOXACIN	Quinolone
GEMIFLOXACIN	Quinolone
GENTAMICIN	Other antibiotics
GRAMICIDIN	Other antibiotics
GREPAFLOXACIN	Quinolone
IMIPENEM	Other beta-lactam
ISONIAZID	Other antibiotics
KANAMYCIN	Other antibiotics
LEVOFLOXACIN	Quinolone
LINCOMYCIN	Other antibiotics
LINEZOLID	Other antibiotics
LORACARBEF	Cephalosporin
MACROLIDES	Macrolide
MEROPENEM	Other beta-lactam
METHACYCLINE	Tetracycline
METHICILLIN	Penicillin
METRONIDAZOLE	Metronidazole
MEZLOCILLIN	Penicillin
MINOCYCLINE	Tetracycline
MONOBACTAMS	Other beta-lactam
MOXALACTAM	Cephalosporin
MOXIFLOXACIN	Quinolone
NAFCILLIN	Penicillin
NALIDIXIC ACID	Quinolone
NETILMICIN	Other antibiotics
NITROFURAN	Nitrofurantoin
NITROFURANTOIN	Nitrofurantoin
NORFLOXACIN	Quinolone
NOVOBIOCIN	Other antibiotics

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Generic or class name	Category
OFLOXACIN	Quinolone
OLEANDOMYCIN	Macrolide
ORITAVANCIN	Other antibiotics
OXACILLIN	Penicillin
OXYQUINOLONE	Quinolone
OXYTETRACYCLINE	Tetracycline
PAROMOMYCIN	Other antibiotics
PEN G	Penicillin
PENICILLIN	Penicillin
PIPERACILLIN	Penicillin
POLYMYXIN	Other antibiotics
PYRAZINAMIDE	Other antibiotics
QUINOLONES	Quinolone
QUINUPRISTIN	Other antibiotics
RIFABUTIN	Other antibiotics
RIFAMPICIN	Other antibiotics
RIFAMPIN	Other antibiotics
RIFAMYCINS	Other antibiotics
RIFAPENTINE	Other antibiotics
RIFAXIMIN	Other antibiotics
ROLITETRACYCLINE	Tetracycline
SPARFLOXACIN	Quinolone
SPECTINOMYCIN	Other antibiotics
STREPTOMYCIN	Other antibiotics
SULFA (SULFONAMIDE ANTIBIOTICS)	Sulfonamide
SULFACYTINE	Sulfonamide
SULFADIAZINE	Sulfonamide
SULFADOXINE	Sulfonamide
SULFAMETHIZOLE	Sulfonamide
SULFAMETHOXAZOLE	Sulfonamide
SULFAPYRIDINE	Sulfonamide
SULFATHIAZOLE	Sulfonamide
SULFISOXAZOLE	Sulfonamide
TEDIZOLID	Other antibiotics
TELAVANCIN	Other antibiotics
TELITHROMYCIN	Macrolide
TETRACYCLINE	Tetracycline
TICARCILLIN	Penicillin
TIGECYCLINE	Tetracycline
TINIDAZOLE	Other antibiotics
TOBRAMYCIN	Other antibiotics
TRIMETHOPRIM	Sulfonamide
TRIMETREXATE	Other antibiotics
TROVAFLOXACIN MESYLATE	Quinolone
VANCOMYCIN	Vancomycin

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eTable 2. Classification of cephalosporin antibiotics by generation

Generation	Generic
1	CEFADROXIL
1	CEFAZOLIN
1	CEPHALEXIN
2	CEFACLOR
2	CEFOTETAN
2	CEFOXITIN
2	CEFPROZIL
2	CEFUROXIME
3	CEFDINIR
3	CEFIXIME
3	CEFOTAXIME
3	CEFPODOXIME
3	CEFTAZIDIME
3	CEFTIBUTEN
3	CEFTRIAXONE
4	CEFEPIME
5	CEFTAROLINE
5	CEFTOLOZANE

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eTable 3. Definitions and modeling strategies for secondary outcomes

	Outcome	Description	Model	Additional notes
Course-level outcomes: **Models calculate ODDS RATIOS**	Change in Antibiotic Use	Probability that a course of antibiotics will be cephalosporin.	Multinomial logistic regression to calculate an RROR.	Primary outcome.
	Anaphylaxis	Counts of occurrence of anaphylaxis attributable to cephalosporin use, after a patient with a penicillin allergy uses a course of cephalosporin. Anaphylaxis must be coded on the same day as a parenteral course or within one day of the start of an oral course.	Not modeled due to small numbers.	This is the only outcome in the analysis that was limited to courses of cephalosporin among patients with penicillin allergies (this is the only outcome that involved manual chart review).
	New Antibiotic Allergy	Probability of a new allergy record in the same antibiotic category, within 30 days of the start of a course of antibiotics.	Binomial logistic regression to calculate an RROR.	Events are assigned to the most recent course only.
	Antibiotic Treatment Failure	Probability of the start of a course of antibiotics in a different category, within 30 days of the start of a course of monotherapy.	Binomial logistic regression to calculate an RROR.	Monotherapy is defined as being the only course of antibiotics that a patient starts on a date. Events are assigned to the most recent course only.
Person-level outcomes: **Models calculate RATE RATIOS**	Mortality	All-cause mortality per person year.	Poisson regression to calculate an RRRR.	Person-time starts at the first course in the period (pre or post) and ends at death or the end of the period - no membership criterion.

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	Hospital Days	Days in the hospital during an encounter that involves an inpatient admit, per person-year.	Poisson regression to calculate an RRRR.	Person-time includes all member days during the period (pre or post), including time before the first course.
	New Infection	Rate of one or more new C. diff, MRSA, or VRE infections per person-year.	Binomial logistic regression with a complementary log-log link, to calculate an RRRR.	Person time starts at the first course in the period (pre or post) and ends at the end of the period or the first membership gap, whichever happens first. An infection is new if there are no indications in the preceding 90 days (for C. diff) or 30 days (for MRSA or VRE).

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eTable 4. Descriptive statistics for courses in the analysis

	Intervention	Comparison
Courses in the analysis	5,834,345	4,817,669
Courses in post period (%)	51.9	51.7
Courses that include any administrations (%)	20.1	21.9
Courses that include ED administrations (%)	3.9	6.6
Courses that include back-office administrations (%)	1.6	0.1
Courses that include any outpatient dispenses (%)	81.0	79.8
Courses that include a surgery encounter (%)	7.6	8.9
Courses that include a labor and delivery encounter (%)	1.3	1.6
Courses of penicillins (%)	26.4	26.1
Courses of cephalosporins (%)	25.7	23.0
Courses of other beta-lactams (%)	0.2	0.3
Courses of clindamycin (%)	3.7	3.7
Courses of macrolides (%)	13.1	13.8
Courses of metronidazole (%)	5.0	4.4
Courses of nitrofurantoin (%)	2.8	3.4
Courses of quinolones (%)	8.1	8.4
Courses of sulfonamides (%)	4.7	4.6
Courses of tetracyclines (%)	7.7	8.9
Courses of vancomycin (%)	1.4	1.7
Courses of any other antibiotics (%)	1.3	1.6
Oral courses (%)	82.7	81.2
Parenteral courses (%)	17.3	18.8
Any antibiotic allergy at start of course (%)	22.1	24.3
Allergies to more than 1 class (%)	6.0	6.9
Allergy to penicillins (%)	11.6	12.7
Allergy to cephalosporins (%)	2.6	2.6
Allergy to other beta-lactams (%)	0.0	0.1
Allergy to clindamycin (%)	0.9	0.8
Allergy to macrolides (%)	2.3	2.7
Allergy to metronidazole (%)	0.5	0.5
Allergy to nitrofurantoin (%)	0.8	0.7
Allergy to quinolones (%)	2.0	2.3
Allergy to sulfonamides (%)	8.0	9.3
Allergy to tetracyclines (%)	1.6	1.9
Allergy to vancomycin (%)	0.3	0.4

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Allergy to any other antibiotic(s) (%)	0.3	0.4
Courses with any associated diagnosis (%)	75.6	64.7
First course dx category is Bone and joint (%)	0.6	0.4
First course dx category is Dental (%)	0.4	0.4
First course dx category is GI (%)	4.5	2.3
First course dx category is GU (%)	2.3	1.7
First course dx category is Infection (%)	0.1	0.1
First course dx category is Non-GI cancer (%)	0.3	0.1
First course dx category is Obstetric (%)	0.5	0.1
First course dx category is Pre-op (%)	1.2	0.3
First course dx category is Pulmonary (%)	3.6	3.2
First course dx category is Sepsis (%)	0.5	0.4
First course dx category is Sinus (%)	7.0	5.9
First course dx category is Skin infection (%)	8.4	7.8
First course dx category is URI (%)	15.8	13.2
First course dx category is UTI (%)	12.8	11.0
First course dx category is Other (%)	17.5	18.0
Courses with no associated diagnosis (%)	24.4	35.3

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eTable 5. Patterns of antibiotic use, by category, before and after warning was removed in the intervention site, by penicillin allergy status and region, for oral and parenteral courses separately

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Antibiotic courses	2,055,836	2,211,703	268,460	286,967	1,656,224	1,765,551	238,368	252,964
	Penicillin (%)	32.9	33.0	2.3	2.4	33.0	32.8	2.0	2.1
	Cephalosporin (%)	18.8	19.3	14.2	21.1	16.5	17.2	12.2	12.6
	Other beta-lactams (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Clindamycin (%)	2.6	2.6	13.1	12.2	2.2	2.2	12.9	13.3
	Macrolides (%)	14.4	14.0	23.3	21.4	16.0	15.0	23.1	21.2
	Metronidazole (%)	4.7	4.8	4.9	4.9	3.9	4.4	4.7	4.7
	Nitrofurantoin (%)	3.0	3.4	5.3	4.8	3.8	4.2	5.2	5.7
	Quinolones (%)	8.7	8.1	13.1	11.2	8.3	7.8	14.1	13.6
	Sulfonamides (%)	5.5	5.2	9.0	7.1	5.5	5.1	8.8	8.3
	Tetracyclines (%)	8.4	8.6	13.5	13.6	9.4	10.0	15.3	16.8
	Vancomycin (%)	0.2	0.2	0.4	0.4	0.3	0.3	0.4	0.5
	Other antibiotics (%)	0.8	0.8	1.0	0.9	1.0	1.0	1.2	1.3
Parenteral courses	Antibiotic courses	424,699	467,404	56,396	62,880	373,049	408,816	59,342	63,355
	Penicillin (%)	13.1	13.0	1.3	1.4	15.4	15.6	1.9	1.9
	Cephalosporin (%)	59.7	60.1	35.5	54.3	55.5	55.7	27.6	30.3
	Other beta-lactams (%)	1.1	1.1	3.1	2.5	1.3	1.1	4.9	3.8
	Clindamycin (%)	2.2	2.2	16.5	7.5	2.2	2.1	18.5	17.7
	Macrolides (%)	3.3	3.4	3.5	3.9	2.7	2.9	2.2	2.2
	Metronidazole (%)	5.8	5.9	7.9	8.2	4.7	4.8	6.7	7.0
	Nitrofurantoin (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quinolones (%)	4.0	3.6	11.4	7.1	5.6	5.2	17.1	16.6

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	Sulfonamides (%)	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.1
	Tetracyclines (%)	1.1	1.2	1.4	1.5	1.9	2.4	2.2	2.5
	Vancomycin (%)	6.1	6.2	13.4	9.7	6.8	6.7	13.1	12.5
	Other antibiotics (%)	3.5	3.3	6.0	3.8	3.8	3.6	5.6	5.3

The change in overall cephalosporin use was present in oral and parenteral courses separately, although the categories of antibiotics whose use decreased for patients in the intervention site with penicillin allergies differed slightly for the two routes. Both routes showed decreases in the use of clindamycin, macrolides, and quinolones. Oral sulfonamides, parenteral vancomycin, and parenteral “other antibiotics” also showed decreases.

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eTable 6. Generation of cephalosporin courses in the analysis

Generation	Courses	% of cephalosporin courses
1	1,870,309	71.7%
2	135,925	5.2%
3	581,278	22.3%
4	21,795	0.8%
5	332	0.01%
All cephalosporins	2,609,639	100%

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eTable 7. Change in cephalosporin use by generation (all courses)

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Total courses	2,480,535	2,679,107	324,856	349,847	2,029,273	2,174,367	297,710	316,319
Fraction of courses that are:								
Cephalosporin (%)	25.8	26.4	17.9	27.0	23.7	24.4	15.3	16.2
1st generation (%)	18.4	18.8	9.6	16.2	18.0	18.6	8.6	9.1
2nd generation (%)	1.6	1.6	1.7	2.6	0.8	0.8	0.8	0.9
3rd generation (%)	5.6	5.8	6.3	7.8	4.7	5.0	5.6	5.9
4th generation (%)	0.2	0.2	0.4	0.5	0.1	0.1	0.3	0.3
5th generation (%)	0.003	0.003	0.003	0.005	0.003	0.003	0.006	0.003

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eTable 8. Ratios of ratios of odds ratios for changes in antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from Table 2)	**From multinomial logistic regression (95% CI)**
Cephalosporin	1.47	1.47 (1.38-1.56)
Other beta-lactams	0.95	0.95 (0.83-1.09)
Clindamycin	0.83	0.83 (0.77-0.88)
Macrolides	0.99	0.98 (0.92-1.04)
Metronidazole	1.12	1.10 (1.03-1.18)
Nitrofurantoin	0.82	0.81 (0.75-0.87)
Quinolones	0.87	0.87 (0.81-0.92)
Sulfonamides	0.84	0.83 (0.78-0.89)
Tetracyclines	0.98	0.97 (0.91-1.04)
Vancomycin	0.82	0.82 (0.76-0.89)
Other antibiotics	0.83	0.83 (0.76-0.90)

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eTable 9. Ratios of ratios of odds ratios for changes in oral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.51	1.51 (1.41-1.61)
Other beta-lactams		
Clindamycin	0.94	0.93 (0.86-1.00)
Macrolides	1.00	0.99 (0.93-1.06)
Metronidazole	1.16	1.13 (1.05-1.23)
Nitrofurantoin	0.84	0.82 (0.76-0.89)
Quinolones	0.92	0.92 (0.85-0.98)
Sulfonamides	0.86	0.85 (0.79-0.91)
Tetracyclines	1.00	0.98 (0.92-1.05)
Vancomycin	1.05	1.05 (0.88-1.25)
Other antibiotics	0.99	0.98 (0.87-1.10)

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eTable 10. Ratios of ratios of odds ratios for changes in parenteral antibiotic use for patients with penicillin allergies

	Ratio of ratios of odds ratios	
	Crude (from eTable 5)	From multinomial logistic regression (95% CI)
Cephalosporin	1.28	1.29 (1.10-1.51)
Other beta-lactams	0.83	0.84 (0.69-1.02)
Clindamycin	0.42	0.42 (0.36-0.50)
Macrolides	1.03	1.04 (0.86-1.27)
Metronidazole	0.92	0.92 (0.78-1.10)
Nitrofurantoin		
Quinolones	0.62	0.62 (0.53-0.74)
Sulfonamides	1.58	1.57 (0.70-3.49)
Tetracyclines	0.97	0.99 (0.79-1.23)
Vancomycin	0.69	0.70 (0.59-0.82)
Other antibiotics	0.63	0.63 (0.52-0.75)

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eTable 11. Fraction of courses with a new allergy within 30 days

	Intervention				Comparison			
Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Penicillin (%)	0.64	0.61	1.00	1.02	0.85	0.78	1.29	1.05
Cephalosporin (%)	0.33	0.31	0.96	0.90	0.36	0.37	1.06	1.00
Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
Clindamycin (%)	0.95	0.93	0.82	0.74	1.03	1.11	0.98	0.79
Macrolides (%)	0.21	0.17	0.34	0.33	0.21	0.16	0.35	0.33
Metronidazole (%)	0.34	0.35	0.50	0.59	0.40	0.37	0.52	0.60
Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
Quinolones (%)	0.55	0.57	0.94	0.96	0.72	0.78	1.16	1.09
Sulfonamides (%)	1.80	1.60	2.59	2.55	1.76	1.81	2.40	2.54
Tetracyclines (%)	0.41	0.39	0.76	0.67	0.46	0.42	0.85	0.81
Vancomycin (%)	0.74	0.76	0.78	0.92	0.78	0.83	0.80	0.99
Other antibiotics (%)	0.21	0.29	0.37	0.38	0.34	0.40	0.50	0.54
Total (%)	0.52	0.49	0.87	0.82	0.61	0.59	0.95	0.90

In total, 10,475,367 courses (98% of all courses in the analysis) had 30 days of follow-up and were included in the new allergy calculations. We identified 61,566 courses with a new allergy record in the same category within 30 days, corresponding to an overall new allergy rate of 0.6%. New allergy rates varied by antibiotic category and were more likely for patients that had a penicillin allergy, but generally decreased slightly in the post period. These general trends appeared in the data for all courses, as well as for oral and parenteral courses separately.

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eTable 12. Fraction of oral and parenteral courses with a new allergy within 30 days

		Intervention				Comparison			
	Penicillin allergy flag status	**No allergy**		**Allergy**		**No allergy**		**Allergy**	
	Period	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Oral courses	Penicillin (%)	0.66	0.63	1.01	1.05	0.89	0.81	1.40	1.07
	Cephalosporin (%)	0.40	0.37	1.16	1.10	0.46	0.48	1.27	1.19
	Other beta-lactams (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Clindamycin (%)	1.02	0.98	0.97	0.77	1.14	1.21	1.20	0.96
	Macrolides (%)	0.21	0.17	0.34	0.32	0.21	0.16	0.35	0.34
	Metronidazole (%)	0.38	0.40	0.57	0.73	0.45	0.42	0.62	0.70
	Nitrofurantoin (%)	0.51	0.48	0.88	0.77	0.51	0.52	0.97	0.73
	Quinolones (%)	0.54	0.58	0.93	0.94	0.71	0.76	1.17	1.13
	Sulfonamides (%)	1.80	1.60	2.59	2.56	1.76	1.81	2.39	2.53
	Tetracyclines (%)	0.41	0.40	0.77	0.68	0.48	0.42	0.87	0.83
	Vancomycin (%)	0.24	0.22	0.23	0.52	0.23	0.15	0.11	0.74
	Other antibiotics (%)	0.29	0.43	0.60	0.53	0.48	0.55	0.71	0.74
	Total (%)	0.57	0.53	0.94	0.88	0.67	0.64	1.02	0.96
Parenteral courses	Penicillin (%)	0.35	0.33	0.89	0.74	0.44	0.45	0.80	0.95
	Cephalosporin (%)	0.22	0.20	0.55	0.53	0.22	0.24	0.67	0.66
	Other beta-lactams (%)	0.46	0.56	0.64	0.14	0.62	0.52	0.65	0.34
	Clindamycin (%)	0.52	0.65	0.26	0.50	0.56	0.65	0.35	0.28
	Macrolides (%)	0.19	0.20	0.33	0.54	0.32	0.20	0.34	0.08
	Metronidazole (%)	0.14	0.16	0.30	0.19	0.24	0.18	0.22	0.30
	Nitrofurantoin (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Quinolones (%)	0.61	0.51	0.95	1.05	0.80	0.91	1.12	0.96
	Sulfonamides (%)	1.09	0.52	0.00	0.00	2.86	1.54	7.50	5.00
	Tetracyclines (%)	0.17	0.18	0.00	0.35	0.14	0.33	0.17	0.21
	Vancomycin (%)	0.84	0.86	0.86	0.99	0.89	0.96	0.89	1.03
	Other antibiotics (%)	0.12	0.14	0.19	0.22	0.17	0.21	0.32	0.35
	Total (%)	0.29	0.27	0.53	0.56	0.34	0.36	0.65	0.61

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eTable 13. Odds ratios of new allergy within 30 days

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	0.96	0.97 (0.94-1.00)	0.95	0.96 (0.93-0.99)	1.06	1.06 (0.97-1.15)
Intervention, no penicillin allergy flag, post vs. pre	0.94	0.95 (0.93-0.98)	0.94	0.95 (0.93-0.98)	0.96	0.96 (0.88-1.05)
Comparison, penicillin allergy flag, post vs. pre	0.95	0.95 (0.90-1.01)	0.95	0.95 (0.89-1.01)	0.94	0.94 (0.80-1.10)
Intervention, penicillin allergy flag, post vs. pre	0.94	0.95 (0.90-1.01)	0.94	0.94 (0.89-1.00)	1.05	1.05 (0.88-1.25)
Ratio ratios of odds ratios, Intervention/Comparison	1.02	1.02 (0.93-1.12)	1.00	1.00 (0.91-1.10)	1.23	1.23 (0.94-1.61)

The crude post/pre odds ratio for each combination of region and penicillin allergy status was smaller than 1 in most cases, consistent with the observation that the overall rate of new allergies decreased in the post period.

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eTable 14. Crude odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

Route	Site	Penicillin allergy flag	Outcome odds		
			Pre	Post	Post/Pre
All Courses	Comparison	No	0.141	0.140	1.00
		Yes	0.175	0.176	1.00
	Intervention	No	0.152	0.151	0.99
		Yes	0.192	0.194	1.01
Oral	Comparison	No	0.122	0.121	0.99
		Yes	0.152	0.152	1.00
	Intervention	No	0.135	0.133	0.99
		Yes	0.170	0.172	1.01
Parenteral	Comparison	No	0.323	0.321	1.00
		Yes	0.406	0.408	1.00
	Intervention	No	0.345	0.342	0.99
		Yes	0.458	0.438	0.96

Of the courses with 30 days of follow-up, 8,177,655 (77% of all courses) were monotherapy and were included in the treatment failure calculations. We identified 1,072,038 courses with treatment failure events, corresponding to an overall rate of 13.1%. Treatment failure rates were higher for patients with penicillin allergies and after parenteral courses.

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eTable 15. Odds ratios of antibiotic treatment failure within 30 days of a course of monotherapy

	All courses		Oral courses		Parenteral courses	
	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)	Crude odds ratio	Odds ratio from binomial logistic regression (95% CI)
Comparison, no penicillin allergy flag, post vs. pre	1.00	0.99 (0.98-1.00)	0.99	0.99 (0.98-1.00)	1.00	0.99 (0.97-1.01)
Intervention, no penicillin allergy flag, post vs. pre	0.99	0.98 (0.98-0.99)	0.99	0.98 (0.97-0.99)	0.99	0.99 (0.97-1.01)
Comparison, penicillin allergy flag, post vs. pre	1.00	1.00 (0.98-1.02)	1.00	0.99 (0.97-1.01)	1.00	1.00 (0.96-1.05)
Intervention, penicillin allergy flag, post vs. pre	1.01	1.00 (0.99-1.02)	1.01	1.01 (0.99-1.03)	0.96	0.96 (0.92-1.01)
Ratio of odds ratios, Intervention/Comparison	1.02	1.02 (0.99-1.05)	1.02	1.02 (0.99-1.06)	0.96	0.96 (0.90-1.03)

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eTable 16. Crude and standardized mortality rates by penicillin allergy status and region

			Mortality rate per 1000 person-years		Post/pre rate ratio
Site	**Penicillin allergy flag**	**Period**	**Crude**	**Standardized**	
Comparison	no	pre	19.2	18.9	0.97
		post	18.8	18.3	
	yes	pre	29.5	19.5	0.97
		post	29.2	19.0	
Intervention	no	pre	15.3	16.2	0.98
		post	15.2	15.8	
	yes	pre	23.4	16.5	1.00
		post	24.4	16.6	

The crude overall mortality rate was 18.0 per 1,000 person-years. The rate decreased slightly in the post period in both regions, and was higher for patients in the comparison site and patients with penicillin allergies.

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eTable 17. Crude rate of hospital days per person year

Site	Penicillin allergy flag	All patients			Patients with parenteral courses		
		Pre	Post	Post/Pre	Pre	Post	Post/Pre
Comparison	no	0.48	0.47	0.99	1.81	1.86	1.03
	yes	0.63	0.61	0.96	2.21	2.21	1.00
Intervention	no	0.46	0.45	0.99	1.65	1.69	1.03
	yes	0.57	0.57	1.00	1.96	2.05	1.04

The crude overall rate of hospital days was 0.48 days per person-year. The rates were higher for patients with penicillin allergies and for patients with any parenteral courses in the analysis.

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eTable 18. Crude rates of new infections per 1,000 person years

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	2,424	2,552	4.10	3.87	0.94
		yes	505	528	6.59	6.20	0.94
	Intervention	no	2,811	2,947	4.02	3.71	0.92
		yes	559	587	6.79	6.36	0.94
MRSA	Comparison	no	5,140	5,287	8.69	8.02	0.92
		yes	719	774	9.39	9.09	0.97
	Intervention	no	6,245	6,760	8.94	8.52	0.95
		yes	906	883	11.01	9.57	0.87
VRE	Comparison	no	466	384	0.79	0.58	0.74
		yes	124	101	1.62	1.19	0.73
	Intervention	no	503	574	0.72	0.72	1.01
		yes	141	129	1.71	1.40	0.82

We identified 12,913 new C. diff infections, 26,714 new MRSA infections, and 2,422 new VRE infections during the analysis period, which correspond to overall rates of 4.2 new C. diff infections, 8.7 new MRSA infections, and 0.79 new VRE infections per 1,000 person-years. The infection rates decreased slightly in the post period in both regions and were higher for patients with penicillin allergies.

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eTable 19. Crude rates of new infections for patients with parenteral courses of antibiotics

	Site	Penicillin allergy flag	New infections		Rate per 1,000 person-years		
			Pre	Post	Pre	Post	Post/Pre
C. diff	Comparison	no	1,818	1,874	12.2	11.3	0.92
		yes	361	377	16.4	15.5	0.95
	Intervention	no	2,108	2,130	11.8	10.6	0.90
		yes	407	423	17.8	16.6	0.93
MRSA	Comparison	no	2,805	2,936	18.9	17.7	0.94
		yes	479	519	21.8	21.4	0.98
	Intervention	no	3,608	4,017	20.2	19.9	0.99
		yes	582	594	25.5	23.3	0.91
VRE	Comparison	no	422	356	2.84	2.15	0.76
		yes	115	95	5.22	3.92	0.75
	Intervention	no	472	547	2.64	2.72	1.03
		yes	131	115	5.74	4.51	0.79

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eTable 20. Ratios of ratios of odds ratios for change in cephalosporin use for patients with penicillin allergies from sensitivity analyses

	RROR from multinomial logistic regression (95% CI)		
Sensitivity analysis	**All courses**	**Oral courses**	**Parenteral courses**
Result from model in main analysis (for comparison)	1.47 (1.38-1.56)	1.51 (1.41-1.61)	1.29 (1.10-1.51)
Model including only each person's first course	1.64 (1.47-1.84)	1.71 (1.53-1.92)	1.34 (0.99-1.81)
Model including only each person's last course	1.56 (1.40-1.75)	1.54 (1.38-1.73)	1.37 (1.03-1.81)
Model with allergy status as of course start date (rather than day before)	1.46 (1.37-1.55)	1.52 (1.41-1.63)	1.20 (1.03-1.41)
Model with additional covariates	1.58 (1.48-1.68)	1.59 (1.48-1.70)	1.36 (1.16-1.59)
Model with additional interactions	1.53 (1.44-1.63)	1.57 (1.46-1.68)	1.30 (1.10-1.52)

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