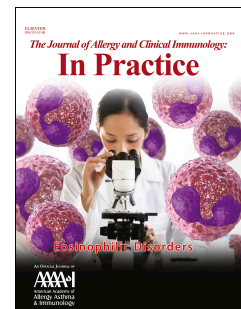


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Adverse reactions associated with penicillins, carbapenems, monobactams, and
clindamycin: A retrospective population-based study

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Parenteral

Penicillin

Serious cutaneous adverse reaction

Abbreviations:

ADR adverse drug reaction

Cdiff *Clostridioides difficile*

DRESS drug eruption with eosinophilia and systemic symptoms

EHR electronic health record

ICD-9 International classification of disease, ninth revision

ICD-10 International classification of disease, tenth revision

KPSC Kaiser Permanente Southern California

SCAR serious cutaneous adverse reaction

SJS Stevens-Johnson Syndrome

TEN toxic epidermal necrolysis

This article will restrict the word “allergy” to mean a confirmed clinically significant IgE-mediated acute-onset hypersensitivity. When “*allergy*” is used it will refer to what is noted in a medical record pertaining to an adverse reaction or intolerance associated with the previous use of a specific medication or medication class that has not been confirmed.

70

71 Highlight Box:

72 1. What is already known about this topic?

73 Penicillin is the most common antibiotic *allergy* reported.

74 2. What does this article add to our knowledge?

75 Penicillin-class antibiotic-associated anaphylaxis is much rarer than
76 previously reported. There is a wide range in the rate that new *allergy* is
77 reported after various penicillin-class antibiotic exposures in males and
78 females.

79 3. How does this study impact current practice management guidelines?

80 Accurate data on the risks of penicillin-associated anaphylaxis and other
81 serious non-cephalosporin beta-lactam- and clindamycin-associated
82 adverse reactions will support penicillin *allergy* delabeling efforts and
83 hopefully lead to more appropriate antibiotic use.

84

Abstract

Background: Limited population-based data on penicillin-, carbapenem-, monobactam-, and clindamycin-associated reported adverse reactions exists.

Objective: Collect data on penicillin, carbapenem, monobactam, and clindamycin usage and associated adverse reactions.

Methods: Data from 1-1-2009 to 12-31-2017 in Kaiser Permanente Southern California was collected.

Results: There were 6,144,422 unique individuals, mean age 33.6 ± 21.1 years, 52.2% females, with at least one healthcare visit during the 9-year study interval, for a total of 37,387,313 patient-years of follow-up. This population was exposed to 5,617,402 courses of oral penicillins, 370,478 courses of parenteral penicillins, 59,645 courses of parenteral carbapenems or monobactams, 817,232 courses of oral clindamycin, and 215,880 courses of parenteral clindamycin. New penicillin *allergies* were reported more commonly after parenteral (0.85%) compared to oral (0.74%) exposures ($p < 0.0001$).

There were 22 cases (1 in 255,320) of oral penicillin-associated anaphylaxis and 3 cases (1 in 123,792) of parenteral penicillin-associated anaphylaxis ($p < 0.001$). There were 2 clindamycin-associated anaphylaxis cases, 1 (1 in 817,232) oral and 1 (1 in 215,880) parenteral. There were 2 (1 in 2,993,940) penicillin-associated SCAR cases, but both also had co-trimoxazole co-exposure within 45 days. There was 1 (1 in

1,033,112) clindamycin-associated SCAR. *Clostridioides difficile* infection was more common after parenteral exposures, and with extended-spectrum penicillins, beta lactamase combinations, carbapenems, monobactam, and clindamycin exposures compared to oral penicillins or clindamycin.

Conclusions: Only 1/1543 (0.065%) oral and 1/1030 (0.097%) parenteral penicillin-associated *allergy* reports were confirmed to be anaphylaxis. *Clostridioides difficile* was more common after parenteral versus oral penicillin, carbapenem, monobactam, and clindamycin exposures, and with broader spectrum antibiotic exposures.

Introduction

The epidemiology of new *allergy* reports, anaphylaxis, serious cutaneous adverse reactions (SCAR)s, drug eruption with eosinophilia and systemic symptoms (DRESS), nephropathy, and *Clostridioides difficile* (Cdiff) infections, associated with oral and parenteral exposures to penicillins and several antibiotics commonly used when penicillin *allergy* is present, carbapenems, monobactams, and clindamycin (Figure 1), are incompletely understood. Most previous reports have been restricted to relatively small populations, or specific sub-groups, such as hospitalized individuals or individuals referred to specialized drug hypersensitivity evaluation centers, and have not provided concurrent data on carbapenems, monobactams, or clindamycin.¹ We have previously reported on the frequency and severity of adverse reactions associated with oral and parenteral cephalosporin use in a portion, those with at least one visit between 1-1-2010 to 12-31-2012, of the Kaiser Permanente Southern California (KPSC) population that is used for this report.² We have previously demonstrated that there is no clinically significant cross-reactivity between different cephalosporins and between penicillins and cephalosporins based on therapeutic exposure data.^{3,4} We also showed that cephalosporin-associated anaphylaxis is very rare (95% confidence intervals, 1 in 1,428,571 to 1 in 96,154 for oral exposures and 1 in 200,000 to 1 in 35,971 for parenteral exposures) and cephalosporin-associated SCARs are even rarer.² We noted that Cdiff infections, particularly with 3rd or higher generation cephalosporins, and nephropathy are significant manifestations of cephalosporin-associated morbidity.²

Penicillins are still one of the most commonly used antibiotic families in the United States and the most common drug *allergy* reported.^{4,5} About 8-10% of individuals using healthcare in the United States carry an unconfirmed penicillin *allergy* label, with higher rates reported in females and with increasing age.^{4,5} Only a small fraction, much less than 1 in 100 per year, of penicillin *allergies* are ever confirmed by skin testing or oral challenges.⁶ Based on data collected by the Center for Disease Control and Prevention (CDC) there were about 392 outpatient courses of beta-lactams dispensed per 1000 individuals in 2016, with a large state-by-state variation.⁷ There was an average of about 278 courses of penicillins, about 114 courses of cephalosporins, and only about 1 course of monobactams and carbapenems combined dispensed per 1000 individuals in 2016.⁷ Macrolides are the second most commonly used antibiotic family in the United States with about 148 outpatient courses, 139 of which were azithromycin, dispensed per 1000 people in 2016.⁷

All antibiotic use is associated with a potential for side effects and true IgE-mediated allergy or other immunologically-mediated hypersensitivity only accounts for a small minority of reported adverse reactions.⁸ Accurate data on the relative risks of serious or benign adverse reactions associated with penicillin and the commonly used alternatives, carbapenem, monobactam, and clindamycin, use can help clinicians and patients make more informed decisions on penicillin allergy delabeling strategies and optimize antibiotic use.⁶ Knowing that the rate of serious penicillin-associated reactions is extremely low may help make patients and clinicians more comfortable when

163 performing direct oral amoxicillin challenges to confirm current penicillin-class antibiotic
164 tolerance in penicillin “allergic” individuals with low-risk histories.^{4,8}

165

Methods

The KPSC Institutional Review Board reviewed this project. All individuals with any KPSC healthplan coverage, who also had at least one KPSC healthplan visit during the 9-year period from 1-1-2009 through 12-31-2017 were identified. These individuals were considered active healthplan members and are the subjects of this study. The index visit was defined as the first visit during the study interval, if their healthplan membership post-dated 1-1-2009. KPSC currently cares for over 4 million healthplan members, an ethnically diverse group that represents slightly more than 1% of the United States population. Visits included all outpatient, emergency room, electronic, and hospital visits. The Kaiser Permanente Healthcare Program nationally uses a single comprehensive electronic health record (EHR), called Health Connect, EPIC Systems Corporation, Verona, Wisconsin, that contains all outpatient, inpatient, and pharmacy data.

All active healthplan members who received at least one course of a non-cephalosporin beta-lactam antibiotic or clindamycin were identified directly out of our EHR data. Data was collected on clindamycin to compare to previously published reports comparing relative rates of amoxicillin and clindamycin-associated serious adverse reactions.⁹ The route of each penicillin, carbapenem, monobactam, or clindamycin administration, oral or parenteral, was determined. The number of days of antibiotic use was determined for each course. This allowed for the calculation of antibiotic-specific exposure days per 1000 active healthplan members per year.

189

190 The population prevalence of penicillin, carbapenem, monobactam, and clindamycin
191 *allergies*, reported in the EHR, was determined based on active *allergy* entries of active
192 healthplan members on 12-31-2017. All reported drug-associated adverse reactions
193 are grouped under the “Allergy” tab of the EHR. The incidence of new penicillin,
194 carbapenem, monobactam, and clindamycin *allergies* per antibiotic exposure were
195 determined by identifying all relevant antibiotic exposures and noting new antibiotic
196 *allergy* reports within 30 days of the start of each exposure. Penicillin exposures in
197 individuals with an active penicillin *allergy* on the date of exposure were also specifically
198 identified and those who still carried an active penicillin *allergy* 30 days later were
199 identified. These cases were reviewed to determine if there were any episodes of
200 anaphylaxis associated with these apparent inappropriate exposures.

201

202 The most common general diagnosis categories associated with each oral penicillin use
203 were identified by their linkage to specific ICD-9 and ICD-10 coding and were
204 determined to be: upper respiratory infections (URIs) [ICD-9 460.x, 462.x, 466.x, ICD-10
205 J00.x, J02.x, J20.x, J21.x], sinusitis [ICD-9 461.x, 473.x, ICD-10 J01.x, J32.x], urinary
206 tract infections (UTIs) [ICD-9 599.0, ICD-10 N39.0], skin and soft tissue infections
207 (SSTIs) [ICD-9 680.x through 686.x, ICD-10 L02.x through L05.x, L08.x], lung infections
208 [ICD-9 480.x through 488.x, 490.x, 491.x, 494.x, ICD-10 J09.x through J18.x, J40.x,
209 J41.x, J47.x], and other bacterial infections [ICD-9 041.9, ICD-10 A49.9, B96.89].

210

A course of an antibiotic was defined as any administration of a specific antibiotic by one specific route and any temporally associated administrations of the exact antibiotic by the same route, with 36 or fewer hours between administrations. Baseline study subject drug *allergies* were noted at the index visit plus two days to allow completion of EHR charting. The overall population prevalence of reported antibiotic *allergies* in the EHR was determined on 12-31-2017. The active drug *allergies* noted in the EHR for each individual at the start of each course of any specific antibiotic were determined. New specific antibiotic *allergies* noted in the medical record within 30 days of the start of a specific antibiotic course were attributed to that course. Any clinically significant IgE, IgG, or T-cell mediated adverse drug reactions would be expected to be manifest within 5 days and thus could be attributed to that course. Most antibiotic-associated serious delayed onset reactions, including any SCAR or DRESS, should also be captured by using a 30-day follow-up period after the start of each antibiotic course. New cases of antibiotic-associated Cdiff were identified if they occurred within 90 days of any antibiotic course initiation.

Individuals with possible antibiotic-induced anaphylaxis were identified by screening for individuals with a diagnosis of anaphylaxis (ICD-9 995.0, ICD-10 T78.2XXA, T88.6XXA) coded within 1 day of the start of an antibiotic course. The EHR of potential cases were then manually reviewed by two physicians, EHL and EM, who had to agree with the determination, to ensure the coded anaphylaxis diagnosis was supported by clinical findings and met the current working definition.¹⁰

All individuals with possible serious cutaneous adverse reactions (SCAR)s were initially screened for by identifying all individuals for whom a diagnosis of Stevens-Johnson Syndrome (SJS) (ICD-9 695.13, ICD-10 L51.1) or toxic epidermal necrolysis (TEN) (ICD-9 695.15, ICD-10 L12.3x, L51.2) was made within 30 days of starting each antibiotic course. The EHR of potential SCAR cases were manually reviewed by two physicians, EHL and EM, who had to agree with the determination, to ensure the coded diagnosis was supported by clinical findings.¹¹

Laboratory data on eosinophilia and elevated liver enzymes were collected to compare to previously published data on potential cases of DRESS.¹² Potential DRESS cases were identified by either a DRESS codes, ICD-9 995.27 or ICD-10 L27.0, entered into the EHR within 30 days of the start of an antibiotic course, or a combination of a newly elevated alanine aminotransferase > 100 U/L and a complete blood count with more than 500 eosinophils per μ L occurring within 30 days of the start of an antibiotic course.

Individuals with possible antibiotic-associated nephropathy were identified by screening for new increases of more than 3.0 mg/dL in serum creatinine, within 30 days of starting the implicated antibiotic course, and no history of increased serum creatinine levels (> 1.3 mg/dL) or chronic kidney disease (ICD-9 codes 580 through 589 or 250.4) in the preceding 90 days.²

New cases of antibiotic-associated clinically significant Cdiff defined by the combination of clinical symptoms of diarrhea recorded in the EHR, any new positive laboratory test,

toxin or polymerase chain reaction (PCR) for Cdiff, and a code of ICD-9 8.45 or ICD-10 A04.7x, made with 90 days of a penicillin, carbapenem, monobactam, or clindamycin administration were identified.²

All individuals who died within 1 day of starting an antibiotic course were identified. All deaths within 30 days of a penicillin, carbapenem, monobactam, or clindamycin administration were also identified. Any deaths associated with anaphylaxis were screened for.

In general, descriptive statistics were performed. The mean and standard deviation were calculated for continuous variables as well as number and percentage for categorical variables. Select demographic characteristics including age at the start and end of the study interval and years of health plan coverage were presented in mean and standard deviation, and further stratified by gender. The prevalence of the specific antibiotic allergy (or antibiotic use) was calculated as a percentage of the total of specific antibiotic allergy (or antibiotic use) among active health plan members with at least one visit in the study period. The prevalence for males or females was calculated similarly as the total of men or women who had specific antibiotic allergy (or antibiotic use) was divided by the active male or female members in the study period. The days of specific antibiotic group use per 1000 members at a given year was calculated. The annual trends in the specific antibiotic group use over time were plotted in the figures. Non-linear trends were investigated using generalized additive models. Additionally, the rates of serious adverse events were calculated using the denominators of total courses

280 for specific antibiotic group and route. We used SAS 9.4/SAS Enterprise Guide 5.2
281 (SAS Institute Inc, Cary, North Carolina) for all analyses.

282

Results

There were 7,449,076 total unique individuals with any KPSC healthplan coverage during the 9-year period from 1-1-2009 through 12-31-2017, but only 6,144,422 (82.5%) used any healthplan services and served as the study subjects for this report. There were 535,613 (14.3%) of females and 768,867 (20.7%) of males who had no health plan visits. There were 3,204,922 (52.2%) female and 2,939,427 (47.8%) male study subjects with at least 1 healthcare visit during the study interval. Study subjects had a total of 37,387,313 patient-years of healthplan coverage during the 9-year study period. The demographics of the study subjects are displayed in Table 1.

There were 7,156,621 total courses of penicillins, carbapenems, monobactams, or clindamycin prescribed to 3,153,462 unique individuals, see Table 1. There were 5,652,158 total courses of oral penicillins given to 3,048,815 unique individuals with 33,950 (0.60%) new penicillin *allergies* reported. There were 440,253 total courses of parenteral penicillins given to 341,784 unique individuals with 3,089 (0.70%) new penicillin *allergies* reported ($p < 0.0001$). There were 817,232 total courses of oral clindamycin given to 525,013 unique individuals with 8,605 (1.05%) new clindamycin *allergies* reported. There were 197,998 total courses of parenteral clindamycin given to 155,614 unique individuals with only 1,417 (0.72%) new clindamycin *allergies* reported ($p < 0.0001$).

The specific antibiotic groups used per year are noted in Table 2 along with the days of antibiotic exposure per 1000 active healthplan members per year. Aminopenicillins, including amoxicillin, ampicillin, and amoxicillin or ampicillin combinations, accounted for 90.5% of all penicillin courses. There were significant downward trends in aminopenicillin, native penicillin, and other penicillins use over the study interval, see Figures 1a to 1c. Carbapenem and monobactam use trended higher, see Figure 1d. Clindamycin use was flat for most of the study interval but increased in 2016 and 2017, see Figure 1e.

The coded indications for which oral penicillin-class antibiotics were prescribed are noted in Table 3 by study year. There were significant downward trends in oral penicillin-class antibiotic use days per 1000 active healthplan members per year for upper respiratory, sinus, and lung infections, see Figures 2a through 2f. Skin and soft tissue infection use was stable. There were significant increases in oral penicillin-class antibiotic usage for urinary tract infections and otherwise unspecified “bacterial infections”.

Supplemental tables E1a and E1b display the rates of new antibiotic *allergy* reports made within 30 days of the start of each specific oral and parenteral non-cephalosporin beta-lactam and clindamycin antibiotic usage by gender. For all oral antibiotics, except for amoxicillin, females reported higher *allergy* incidence rates. Oral clindamycin and dicloxacillin had the highest *allergy* incidence rates followed by aminopenicillins and then native penicillins. Overall parenteral ampicillin-sulbactam, nafcillin, oxacillin, and

piperacillin-tazobactam were associated with higher new allergy incidence rates. Parenteral clindamycin had an intermediate allergy incidence rate, which interestingly was low than the rate noted with oral clindamycin exposures. Parenteral carbapenems and monobactams had the lowest *allergy* incidence rates. Females again had higher *allergy* incidence rates with most parenteral exposures, with the notable exceptions of nafcillin, oxacillin, and penicillin G.

Tables 4a and 4b display the rates of new *allergy* reports within 30 days per course along with the rates of serious adverse events including anaphylaxis, SCARs, DRESS, nephropathy, Cdiff, and deaths. Among oral penicillins there were significantly higher rates of new *allergy* reports with dicloxacillin compared to penicillin and aminopenicillins. Among parenteral penicillins the lowest *allergy* incidence was noted with native penicillins, intermediate rates with ampicillin/sulbactam or piperacillin/tazobactam, and the highest rates with nafcillin or oxacillin.

There were 22 cases (1 in 255,320 exposures) of oral penicillin-associated anaphylaxis and 3 cases (1 in 123,792 exposures) of parenteral penicillin-associated anaphylaxis ($p < 0.001$), see Tables 4a and 4b. There were 2 clindamycin-associated anaphylaxis cases, 1 (1 in 817,232) oral and 1 (1 in 215,880) parenteral. Parenteral penicillin-associated anaphylaxis is more likely than oral ($p < 0.001$). We did not identify any cases of carbapenem or monobactam-associated anaphylaxis. We noted a very high relative rate of anaphylaxis associated with dicloxacillin (1 in 20,525 exposures). Only 22 of 33,950 (0.065%) of new penicillin *allergy* reports after oral exposures were confirmed to

be anaphylaxis. This compares to 3 of 3,089 (0.097%) of new *allergy* reports after parenteral penicillin exposures. There were no cases of penicillin- or clindamycin-associated anaphylaxis noted in individuals with an active penicillin or clindamycin *allergy* respectively at the time of the exposure.

There were 2 (1 in 2,993,940) confirmed penicillin-associated SCAR cases, but both also had co-trimoxazole co-exposure within 45 days, see Tables 4a and 4b. There was 1 (1 in 1,033,112) confirmed parenteral clindamycin-associated TEN, who also had co-trimoxazole co-exposure. There was one individual (1 in 49,651) who had confirmed SJS within 30 days of starting a carbapenem.

There were 2 cases (1 in 2,155,400) of oral amoxicillin-associated, 2 cases (1 in 430,397) of amoxicillin/clavulanate-associated, and 1 case (1 in 817,232) of oral clindamycin-associated DRESS within 30 days of starting the antibiotic. There were 5 cases (1 in 25,085) of ampicillin or ampicillin/sulbactam-associated, 31 cases (1 in 6,250) of parenteral amoxicillin/clavulanate- or piperacillin/tazobactam-associated, 2 cases (1 in 4,116) of nafcillin or oxacillin-associated, 15 cases (1 in 2,035) of carbapenem or monobactam-associated, and 2 cases (1 in 98,999) of parenteral clindamycin-associated DRESS within 30 days of starting the antibiotic.

New onset antibiotic-associated nephropathy was much more common with extended-spectrum parenteral antibiotics, compared to oral narrow-spectrum penicillins, see Table 4b. The highest rates were seen with piperacillin-tazobactam, carbapenems, and

monobactams ranging from 0.11% to 0.13% per course, over 10-fold higher than the rate noted with parenteral penicillins, 0.008%.

Cdiff is more common after parenteral extended-spectrum penicillins and beta lactamase combinations (1 in 25), carbapenems and monobactam (1 in 13), and parenteral clindamycin exposure (1 in 71), compared to oral penicillin (1 in 1,831), oral extended-spectrum penicillins (1 in 867), or oral clindamycin (1 in 177) exposures, see Tables 4a and 4b.

Deaths were much more common after parenteral compared to oral antibiotic exposures, see Tables 4 and 4b. We were unable to identify any deaths directly attributed to penicillin-, carbapenem-, monobactam-, or clindamycin-associated anaphylaxis.

Discussion

This reports helps address one of the unmet needs noted recently by Torres and coworkers, namely good population-based data on penicillin *allergy*.¹⁷ We noted a wider variation in the incidence of newly reported *allergy* after specific penicillin class antibiotic exposures, by gender, than is often appreciated. We noted overall rates from 0.4% per exposure with penicillin V to 1.3% per exposure with dicloxacillin. It is also well known that only a small minority of these new *allergies* will be confirmed to be clinically-significant immunologically-mediated hypersensitivity after testing.^{6,8} We once again show that oral non-cephalosporin beta-lactams have on average lower *allergy* incidence rates compared to parenteral exposures. We are the first to report that oral clindamycin exposures result in significantly higher rates of new *allergy* reports compared to parenteral clindamycin exposures. We once again show that women have a higher penicillin *allergy* population prevalence, in this cohort of individuals using healthcare in Southern California. Women also note higher or equivalent new *allergy* incidence rates after all oral penicillin-class antibiotic exposures. We are the first to report that males have higher *allergy* incidence rates after parenteral oxacillin, penicillin G, or penicillin G procaine exposures. We also note that oral ampicillin, amoxicillin, or native penicillin exposures result in significantly lower *allergy* incidence rates than amoxicillin/clavulanate or dicloxacillin exposures for both males and females.

Antibiotic use over the study interval showed a downward trend in the use of penicillin-class antibiotics, and upward trend in the use of alternatives such as clindamycin,

carbapenem, or monobactams. Our study confirms the findings of Baggs and coworkers in 2016 that shows similar national inpatient trends in the United States from 2006 to 2012 with respect to the increasing use of extended-spectrum penicillins and carbapenem, though clindamycin use was relatively stable in their report.¹⁴ The uptick in clindamycin usage we noted in 2016 and 2017 deserves further study.

Our study provides a comprehensive look at the epidemiology of anaphylaxis, as well as other adverse drug reactions, in a large population-based cohort. Our observed rate of penicillin-associated anaphylaxis with parenteral and oral penicillin exposures was lower than previous studies, which were not confirmed by EHR or chart review. It is always possible that anaphylaxis is under recognized and then under coded, but if it is not mentioned in the EHR, it cannot affect future healthcare decisions. Galvao and coworkers in 2013 reviewed 8 studies that included 2,108,117 patients treated with parenteral benzathine benzylpenicillin between 1954 and 2012. They identified 54 cases (0.0026%) [1 in 39,039] of probable anaphylaxis resulting in 4 (7.4%) deaths.¹ Dhopeswarkar and co-workers in 2019 used an EHR system in an 18-year study to determine EHR-reported anaphylaxis and found a rate of 45.9 per 10,000 patients for all penicillin antibiotics, with the most common causative drug as amoxicillin at 2 per 10,000 patients.¹⁵ However, other studies have shown confirmed anaphylaxis associated with oral amoxicillin has been rarely reported, and fatal anaphylaxis with oral amoxicillin extremely rare. In a UK survey on endocarditis prophylaxis, Lee and coworkers in 2007 found only 1 case of fatal oral-amoxicillin associated anaphylaxis over 100 million treatment courses.¹⁶ Thornhill and co-workers in 2015 reported 0 fatal

reactions per 3 million prescriptions for amoxicillin used as endocarditis prophylaxis.⁹ We believe our data showing the low rates of penicillin- and in particular, amoxicillin-associated anaphylaxis, provides additional support for the safety of using an oral amoxicillin challenge as the reference standard test for determination of current penicillin tolerance in individuals with a low-risk history.^{8,13}

We noted an unexpectedly high rate of *allergy* and anaphylaxis associated with oral dicloxacillin use, a semi-synthetic penicillin in the isoxazoloxy penicillin group which includes oxacillin, cloxacillin, and flucloxacillin. This finding deserves further study. Kennard and coworkers in 2019 reported on UK retrospective cohort of 108 patients referred for evaluation of suspected flucloxacillin hypersensitivity. They showed that 33 of the patients were confirmed with immediate hypersensitivity, one-third had elevations in mast cell tryptase consistent with anaphylaxis, and 17.6% were categorized as having had severe reactions involving hypotension, hypoxia, or neurologic compromise.¹⁷

Similar to our past study on cephalosporin-associated adverse reactions, our study showed clindamycin-associated anaphylaxis is extremely rare and rather, Cdiff is the most common severe clindamycin-related adverse reaction.^{2,9} There have only been 3 previously reported cases of possible clindamycin-associated anaphylaxis.¹⁸

The upward trend in clindamycin usage at the end of our study interval relative to penicillin usage is concerning. A higher rate of clindamycin-associated versus

cephalosporin-associated adverse reactions was noted, 1.5% versus 0.6%, in penicillin allergic children given antibiotics for surgical prophylaxis.¹⁹ Thornhill and co-workers reported in 2015 a much higher rate of fatal and serious outcomes when clindamycin was used instead of amoxicillin for endocarditis prophylaxis, 13 fatal and 149 serious non-fatal reactions for clindamycin versus no fatal and 22.62 serious non-fatal reactions with amoxicillin per one million exposures.⁹

We noted the highest rates of Cdiff after parenteral carbapenem, monobactam, and piperacillin-tazobactam exposures, all higher than after parenteral clindamycin. These same antibiotic groups had the highest all-cause death rates within 1 and 30 days per exposure. Overall parenteral exposures had higher rates of Cdiff and all-cause death rates within 1 and 30 days compared to oral exposure, reflecting the underlying morbidity of the patients being treated. The higher rates of Cdiff can be partially explained by the anaerobic coverage of these drug, leading to increased disruption of the normal gut flora.²⁰ Our study, however, contrasts with a recent study showing the highest rates of Cdiff with clindamycin (reporting odds ratio 46.95), followed by monobactams (reporting odds ratio 29.97), penicillin-beta lactamase inhibitor combinations (reporting odds ratio 20.05), and carbapenems (reporting odds ratio 19.16).²¹ This study also noted high rates of Cdiff with 3rd and 4th generation cephalosporins, as we have noted previously.²

Severe delayed cutaneous hypersensitivity reactions including SJS, TEN and DRESS can cause significant patient morbidity. Our study found that SCARs like SJS and TEN

are extremely rare with both non-cephalosporin beta-lactams and clindamycin. Co-trimoxazole co-exposure was present within 45 days for the cases we identified. Among antibiotic-associated cases of SJS/TEN, co-trimoxazole and other sulfonamide antibiotics are commonly implicated and clindamycin has rarely been implicated.²⁰⁻²² However, co-exposure with other antibiotics are common given the degree of skin involvement and risk of infection, and often the culprit drug is difficult to assess via retrospective record review. One study found that the relative risk of non-sulfonamide antibiotic-related SJS/TEN was reduced when infection was controlled for in the analysis.²⁰

DRESS syndrome is most commonly associated with anticonvulsant agents and allopurinol, though has been reported with antibiotics including beta-lactams^{23,24}. We used a 30-day window after the start of the antibiotic exposure to identify potential DRESS cases because the mean latency for antibiotic-associated DRESS, 17 to 20 days, is significantly less than the up to 6 weeks noted for anticonvulsants or other non-antibiotic medications.²⁷ It is possible that we missed some cases. We found that the incidence of DRESS is overall low, with a few suspected cases of clindamycin-, carbapenem-, and monobactam-associated DRESS, which were not formally confirmed by chart review. Previous studies have estimated an approximate frequency of 1 in 1,000 to 1 in 10,000 antibiotic exposures, but a study of 824 patients receiving outpatient parenteral antibiotics found a higher frequency of DRESS with 1 in 100 affected, most commonly associated with vancomycin.^{12, 23} In a systematic review of 172 cases in the literature of DRESS, a total of 44 different drugs were associated, but

only one reported case in a patient associated with amoxicillin-clavulanic acid. Since then, there have been a few case reports of clindamycin-associated and meropenem-associated DRESS.²⁸⁻³⁰

Past studies on penicillin-associated adverse reactions have been limited to select populations with low quality of evidence and did not distinguish between oral and parenteral exposures.¹ A strength of our study was that by examining a population covered with a comprehensive electronic medical record, we were able to achieve a high degree of consistency in our audits, capture all clinically significant penicillin, other non-cephalosporin beta-lactam, and clindamycin use, and categorize other clinically significant antibiotic-associated adverse reactions. It is very unlikely a patient would receive care outside of our system and our EHR would not capture the data because the outside entity would bill for the services.

Our large population-based cohort and number of patient-years of follow up, including all inpatient and outpatient encounters, make our findings widely generalizable and adds valuable knowledge to the epidemiology of adverse drug reactions. A limitation of our study is its reliance on diagnoses and documentation from all health care providers. As we have previously noted, if it is not documented in the EHR, it cannot affect future treatment decisions. In our audit of cases of anaphylaxis and SCARs, we found that these were significantly over-coded. Many cases had anaphylaxis coded on the same day an antibiotic was given, but it referred to a historical event and was coded so a treating physician could refill an epinephrine injector. Anaphylaxis may potentially be

under-coded with true anaphylaxis given some other diagnoses such as “drug allergy” or “hypotension”; however, we did not have the resources to manually review every possible case.

We found that antibiotic-associated nephropathy was relatively rare with the highest rates of only about 1 in 1000 exposures being associated with parenteral piperacillin-tazobactam, carbapenems, and monobactams, all antibiotics frequently given to critically ill patients with multisystem disease. These patients also had 30-day all-cause death rates in the 15 to 20% range.

The antibiotic stewardship activities of our health plan over the past decade appears to be making an impact. We did not study in this report the effect that penicillin allergy delabeling has had on antibiotic usage patterns. Overall non-cephalosporin beta-lactam use has fallen significantly. After a relatively constant rate of clindamycin use from 2009 to 2015, there has been an unexpected, and currently unexplained, uptick in clindamycin usage in 2016 and 2017. This warrants further investigation. The total non-cephalosporin beta-lactam and clindamycin combined usage days/1000 members/years has fallen by 225 (9.3%) from 2417 in 2009 to 2192 in 2017. Based on data collected by the Center for Disease Control and Prevention (CDC), there was an average of about 278 courses of penicillins dispensed per 1000 Americans in 2016, with each course typically lasting 7 to 10 days, which gives an estimate of 1946 to 2780 penicillin-class antibiotic usage days/1000 members/year.⁷ In comparison, we noted

only 1731 penicillin-class antibiotic usage days/1000 active healthplan members/year in 2016.

Unconfirmed penicillin *allergy* leads healthcare providers to prescribe alternative, often broader spectrum, antibiotics such as carbapenems, monobactams, 3rd or higher generation cephalosporins, or clindamycin – all of which are associated with higher rates of serious adverse reactions than narrow spectrum penicillin.^{2,31} Comprehensive population-based data on serious antibiotic-associated adverse reaction rates can help providers and patients make more informed decisions on optimal antibiotic use and encourage more penicillin allergy delabeling.

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680 Table 1 Population demographics

	Male	Female	Total
Unique health-plan members between 1-1-2009 and 12-31-2017. N (%)	3,708,284 (49.8%)	3,740,535 (50.2%)	7,449,076
Active health-plan members with at least one visit between 1-1-2009 and 12-31-2017. N (%)	2,939,427 (47.8%)	3,204,922 (52.2%)	6,144,422
Active healthplan members on 1-1-2009. N (%)	1,441,866 (47.5%)	1,593,272 (52.5%)	3,035,184
Active healthplan members on 12-31-2017. N (%)	2,135,578 (47.6%)	2,352,119 (52.4%)	4,487,733
Average age at start of coverage or on 1-1-2009 (whichever is later). Mean $\pm$ SD years	33.0 $\pm$ 21.1	34.1 $\pm$ 21.1	33.6 $\pm$ 21.1
Average age on 12-31-2017.	38.6 $\pm$ 21.5	39.7 $\pm$ 21.5	39.2 $\pm$ 21.5

Mean $\pm$ SD years			
Average years of healthplan coverage. Mean $\pm$ SD.*	5.1 $\pm$ 3.1	5.1 $\pm$ 3.1	5.1 $\pm$ 3.1
Total patient years of follow-up. N (%)	17,530,743 (46.9%)	19,856,211 (53.1%)	37,387,313
Antibiotic allergy prevalence on 12-31-2017 in members with at least one visit between 1-1-2009 and 12-31-2017			
Penicillin N (%)	215,241 (7.3%)	350,130 (10.9%)	565,375 (9.2%)
Carbapenem N (%)	193 (0.007%)	258 (0.008%)	451 (0.007%)
Monobactam N (%)	32 (0.001%)	69 (0.002%)	101 (0.001%)
Clindamycin N (%)	6,305 (0.2%)	16,531 (0.52%)	22,836 (0.4%)
Antibiotic Class Exposures			
Unique individuals with at least one visit between 1-1-2009 and 12-31-	1,134,655 (38.6%)	1,395,404 (43.5%)	2,530,071 (41.2%)

2017 and any penicillin exposure N (%) [total courses]	[2,655,192]	[3,437,202]	[6,092,411]
Unique individuals with at least one visit between 1-1-2009 and 12-31-2017 and any carbapenem or monobactam exposure N (%) [total courses]	12,379 (0.4%) [22,419]	15,157 (0.5%) [26,557]	27,537 (0.4%) [48,980]
Unique individuals with at least one visit between 1-1-2009 and 12-31-2017 and any clindamycin exposure N (%) [total courses]	248,412 (8.5%) [408,270]	347,438 (10.8%) [606,955]	595,854 (9.7%) [1,015,230]

681

682 *(maximum possible = 9)

683

684 Table 2: Penicillin class, other non-cephalosporin beta-lactam, and clindamycin use over time

685

	Aminopenicillins**	Penicillin	All other penicillins	Carbapenem or Monobactam	Clindamycin
2009					
Unique individuals exposed	443,165	62,241	18,142	2,191	77,446
[Courses]	[571,704]	[69,285]	[23,678]	[3,470]	[98,974]
(Antibiotic days/1000 members*/year)	(1,918)	(188)	(48)	(6)	(257)
2010					
Unique individuals exposed	434,324	61,247	19,125	2,646	80,147
[Courses]	[560,076]	[67,927]	[24,689]	[4,169]	[102,558]
(Antibiotic days/1000 members*/year)	(1,843)	(184)	(48)	(7)	(263)
2011	448,504	60,399	20,285	3,112	83,350

Unique individuals exposed [Courses] (Antibiotic days/1000 members*/year)	[575,835] (1,783)	[66,943] (168)	[25,737] (45)	[4,711] (7)	[106,478] (259)
2012 Unique individuals exposed [Courses] (Antibiotic days/1000 members*/year)	428,692 [544,931] (1,632)	53,261 [59,153] (143)	20,603 [25,928] (43)	3,391 [5,150] (7)	83,907 [106,687] (252)
2013 Unique individuals exposed [Courses] (Antibiotic days/1000 members*/year)	451,588 [576,355] (1,677)	51,904 [57,403] (132)	20,443 [25,690] (39)	3,423 [5,210] (6)	82,979 [104,972] (243)
2014	440,364	53,657	22,413	3,793	86,230

Unique individuals exposed [Courses] (Antibiotic days/1000 members*/year)	[558,357] (1,565)	[59,486] (130)	[28,462] (40)	[5,813] (7)	[109,238] (262)
2015 Unique individuals exposed [Courses] (Antibiotic days/1000 members*/year)	491,467 [629,552] (1,679)	52,293 [57,923] (120)	23,283 [29,365] (38)	4,184 [6,319] (7)	90,690 [114,861] (265)
2016 Unique individuals exposed [Courses] (Antibiotic days/1000 members*/year)	495,306 [628,787] (1,580)	52,610 [58,511] (115)	24,146 [30,571] (36)	4,481 [7,161] (8)	102,814 [131,071] (371)
2017	513,087	51,087	23,145	4,565	107,621

Unique individuals exposed [Courses] (Antibiotic days/1000 members*/year)	[650,541] (1,589)	[56,742] (113)	[29,032] (34)	[7,006] (9)	[140,433] (447)
Overall p-value for antibiotic days/1000 members/year	p < 0.001	p < 0.001	p < 0.001	p = 916	p < 0.001 2009-2015: p = 0.899

686

687 *members = active health plan members with at least one visit in the year indicated

688 ** Including ampicillin, amoxicillin, and ampicillin or amoxicillin combinations

689

690 Table 3: Coded indications for oral penicillin[¥] class antibiotic use over time

691

	Upper Respiratory	Sinus	Lung	Skin and soft tissue	Bacterial	Urinary Tract
Relevant ICD-9 codes	460.x 462.x-466.x	461.x 473.x	480.x-488.x 490.x, 491.x 494.x	680.x-686.x	041.9	599.0
Relevant ICD-10 codes	J00.x, J02.x, J20.x, J21.x	J01.x, J32.x	J09.x-J18.x, J40.x, J41.x, J47.x	10 L02.x-L05.x, L08.x	A49.9, B96.89	N39.0
2009 Unique individuals exposed [Courses] (Antibiotic days/1000 members*/year)	102,316 [109,450] (375)	96,899 [108,252] (398)	29,405 [30,667] (104)	7,279 [7,709] (27)	225 [232] (1)	1,784 [1,851] (6)
2010 Unique individuals exposed [Courses]	93,075 [99,830] (337)	96,395 [108,012] (387)	26,133 [27,454] (92)	7,338 [7,779] (27)	431 [440] (2)	2,063 [2,162] (7)

(Antibiotic days/1000 members*/year)						
2011	86,186	105,174	24,298	7,594	1,485	2,514
Unique individuals exposed	[91,917]	[117,723]	[25,494]	[7,978]	[1,532]	[2,671]
[Courses]	(293)	(397)	(81)	(26)	(5)	(8)
(Antibiotic days/1000 members*/year)						
2012	72,145	92,084	21,197	7,997	3,579	2,514
Unique individuals exposed	[76,408]	[102,699]	[22,246]	[8,439]	[3,700]	[3,094]
[Courses]	(238)	(335)	(69)	(26)	(12)	(9)
(Antibiotic days/1000 members*/year)						
2013	75,872	103,403	24,018	8,007	5,005	3,002
Unique individuals exposed	[80,272]	[115, 375]	[25,149]	[8,466]	[5,194]	[3,168]
[Courses]	(244)	(364)	(76)	(26)	(16)	(9)
(Antibiotic days/1000 members*/year)						
2014	71,272	97,269	21,547	9,025	4,804	3,637
Unique individuals exposed	[75,266]	[108,736]	[22,741]	[9,569]	[4,950]	[3,910]
[Courses]	(223)	(331)	(68)	(28)	(14)	(10)
(Antibiotic days/1000 members*/year)						

2015						
Unique individuals exposed	80,028	113,795	28,658	9,800	6,120	4,173
[Courses]	[84,492]	[127,727]	[30,309]	[10,322]	[6,353]	[4,471]
(Antibiotic days/1000 members*/year)	(238)	(367)	(85)	(29)	(18)	(11)
2016						
Unique individuals exposed	69,727	114,030	26,854	10,947	7,562	4,088
[Courses]	[73,241]	[128,174]	[28,298]	[11,575]	[7,899]	[4,373]
(Antibiotic days/1000 members*/year)	(196)	(347)	(76)	(32)	(20)	(10)
2017						
Unique individuals exposed	71,712	122,170	26,603	11,420	7,975	4,953
[Courses]	[74,983]	[137,535]	[28,034]	[12,078]	[8,312]	[5,419]
(Antibiotic days/1000 members*/year)	(195)	(361)	(73)	(32)	(12)	(12)

692

693 *members = active health plan members with at least one visit in the year indicated

694 †Oral penicillin class antibiotics include ampicillin, amoxicillin, amoxicillin with clavulanic acid, dicloxacillin, and penicillin.

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696 Table 4a: Adverse reactions associated with oral penicillins, other non-cephalosporin beta-lactams and clindamycin in 2009 through
 697 2017

	Unique individuals exposed (Total courses)	New allergy reports within 30 days per course N (%)	Anaphylaxis per course N (%)	SCARs per course within 30 days N (%)	DRESS per course within 30 days N (%)	Nephropathy per course within 30 days N (%)	Cdiff per course within 90 days N (%)	Death within 1 day per course N (%)	Death within 30 days per course N (%)
Amoxicillin or Ampicillin	2,054,617 (4,310,799)	26,251 (0.61%)	16 (<0.001%)	1 (<0.001%)	2 (<0.001%)	234 (0.005%)	2,664 (0.062%)	50 (0.001%)	1,588 (0.037%)
Amoxicillin/ Clavulanate	611,484 (860,793)	4,911 (0.57%)	4 (<0.001%)	0	2 (<0.001%)	131 (0.015%)	3,173 (0.37%)	113 (0.013%)	3,155 (0.34%)
Penicillin	348,436 (348,436)	2,299 (0.52%)	0	0	0	16 (0.004%)	240 (0.055%)	1 (<0.001%)	94 (0.021%)
Dicloxacillin	34,278 (41,050)	489 (1.2%)	2 (0.005%)	0	0	5 (0.012%)	138 (0.34%)	3 (0.007%)	91 (0.22%)
Clindamycin	525,013	8,605	1	0	1	3	4,613	41	1,130

	(817,232)	(1.1%)	(<0.001%)		(<0.001%)	(0.004%)	(0.56%)	(0.005%)	(0.14%)
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698

699

700 Table 4b: Adverse reactions associated with parenteral penicillins, other non-cephalosporin beta-lactams and
 701 clindamycin in 2009 through 2017

	Unique individuals exposed (Total courses)	New <i>allergy</i> reports within 30 days per course N (%)	Anaphylaxis per course N (%)	SCARs per course within 30 days N (%)	DRESS per course within 30 days N (%)	Nephropathy per course within 30 days	C diff per course within 90 days N (%)	Death within 1 day per course N (%)	Death within 30 day per course N (%)
Ampicillin	76,965 (86,116)	173 (0.20%)	0	1 (0.001%)	3 (0.003%)	28 (0.033%)	1,302 (1.5%)	180 (0.21%)	2,063 (2.4%)
Ampicillin/ Sulbactam	34,320 (38,320)	203 (0.53%)	1 (0.003%)	0	2 (0.005%)	32 (0.084%)	1,119 (2.9%)	141 (0.37%)	2,036 (5.3%)
Penicillin	93,466 (113,830)	681 (0.60%)	0	0	0	9 (0.008%)	199 (0.18%)	20 (0.18%)	251 (0.22%)
Nafcillin or Oxacillin	6,076 (8,232)	222 (2.70%)	0	0	2 (0.024%)	5 (0.061%)	432 (5.3%)	71 (0.86%)	944 (11.5%)
Piperacillin/	130,957	1,810	2	0	31	249	12,845	4,399	29,393

tazobactam	(193,755)	(0.93%)	(0.001%)		(0.016%)	(0.13%)	(6.6%)	(2.3%)	(15.2%)
Carbapenems	21,716 (40,162)	198 (0.49%)	0	1 (0.002%)	9 (0.022%)	43 (0.11%)	4,057 (10.1%)	1,284 (3.2%)	8,166 (20.3%)
Monobactams	7,139 (8,818)	39 (0.44%)	0	0	6 (0.068%)	11 (0.13%)	605 (6.9%)	191 (2.2%)	1,253 (14.2%)
Clindamycin	155,614 (197,998)	1,417 (0.72%)	1 (0.001%)	1 (0.001%)	2 (0.001%)	36 (0.018%)	3,060 (1.5%)	358 (0.18%)	3,493 (1.76%)

702

Figure 1a: Amoxicillin and amoxicillin/clavulanate usage days/1000 members/year

Legend: Overall $p < 0.001$

Figure 1b: Penicillin usage days/1000 members/year

Legend: Overall $p < 0.001$

Figure 1c: Other penicillins usage days/1000 members/year

Legend: Overall $p < 0.001$

Figure 1d: Carbapenem or monobactam usage days/1000 members/year

Legend: Overall $p < 0.001$

Figure 1e: Clindamycin usage days/1000 members/year

Legend: Overall $p < 0.001$, 2009-2015: $p = 0.899$, 2016-2017: $p < 0.001$

Figure 2a: Upper respiratory infection coded indications associated with oral penicillin[¥]
usage days/1000 members/year

Figure 2b: Sinus infection coded indications associated with oral penicillin[¥] usage
days/1000 members/year

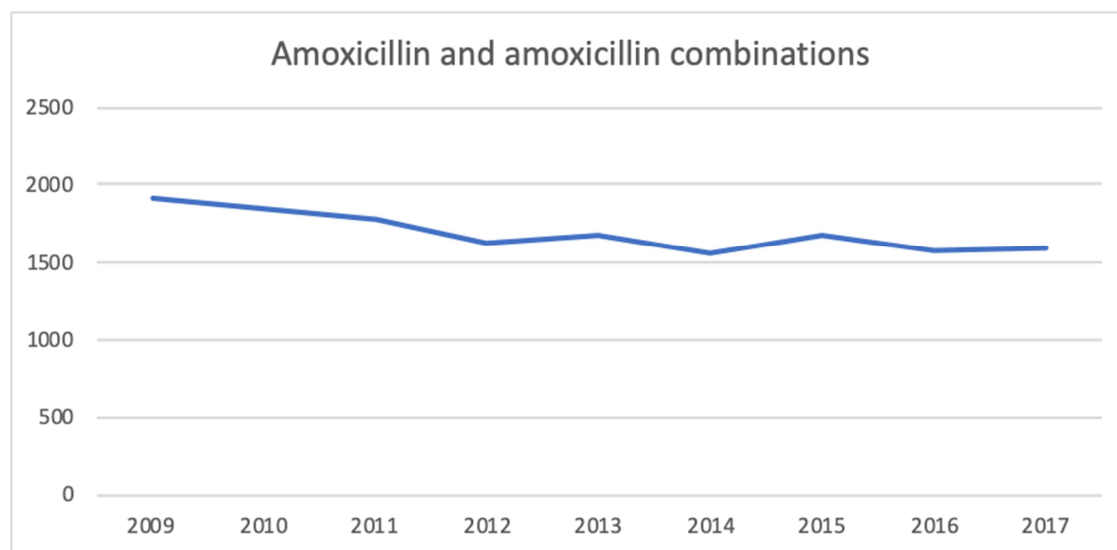
Figure 2c: Lung infection coded indications associated with oral penicillin[¥] usage
days/1000 members/year

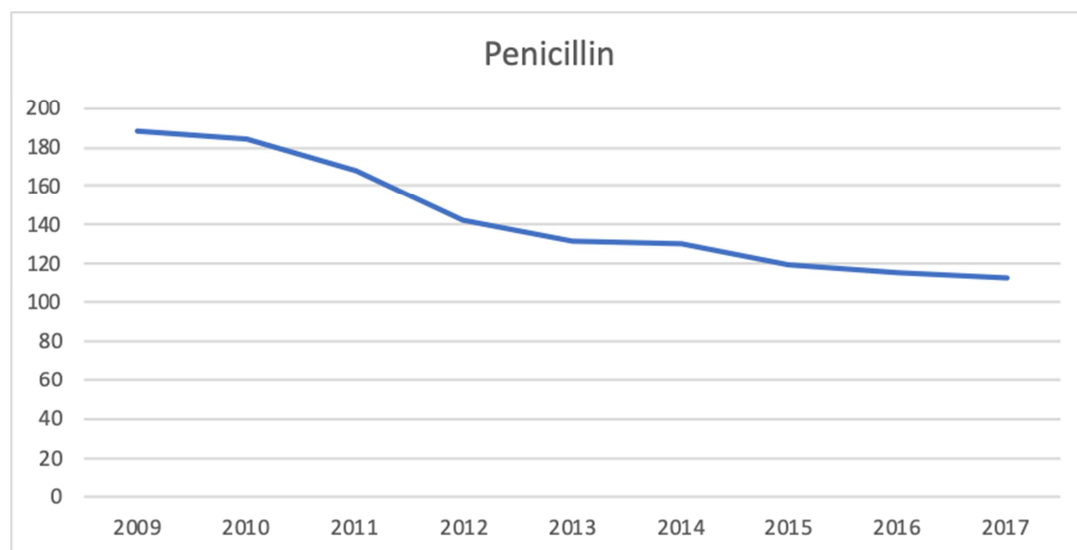
Figure 2d: Skin infection coded indications associated with oral penicillin[¥] usage
days/1000 members/year

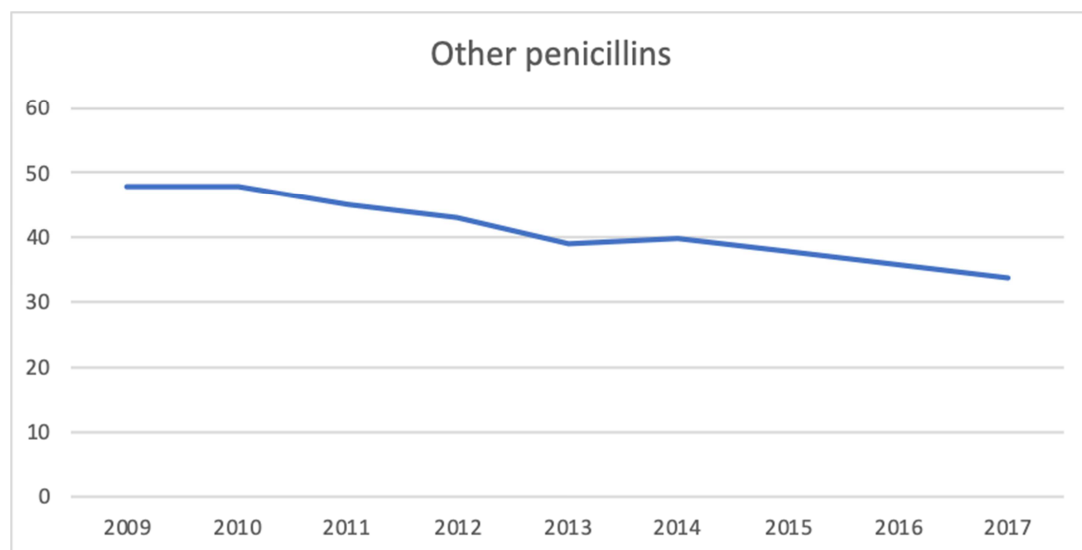
Figure 2e: Bacterial infection coded indications associated with oral penicillin[¥] usage
days/1000 members/year

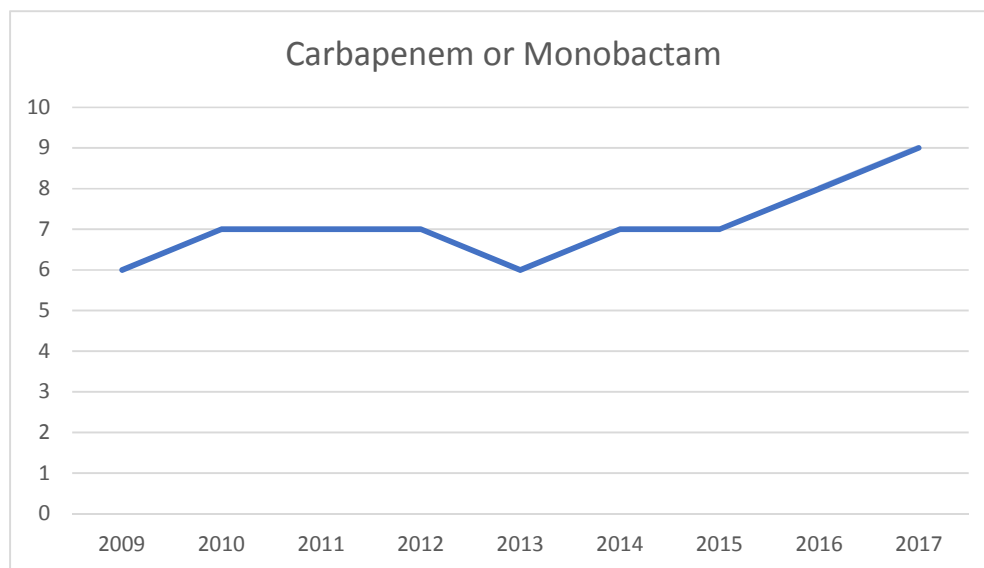
Figure 2f: Urinary tract infection coded indications associated with oral penicillin[¥]
days/1000 members/year

[¥] Oral penicillin class antibiotics include ampicillin, amoxicillin, amoxicillin with clavulanic
acid, dicloxacillin, and penicillin.

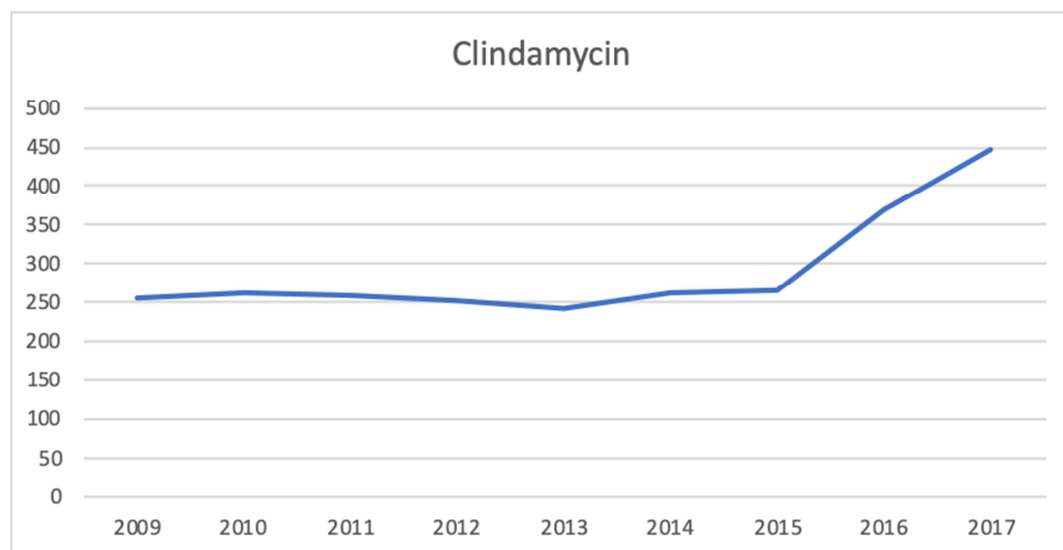






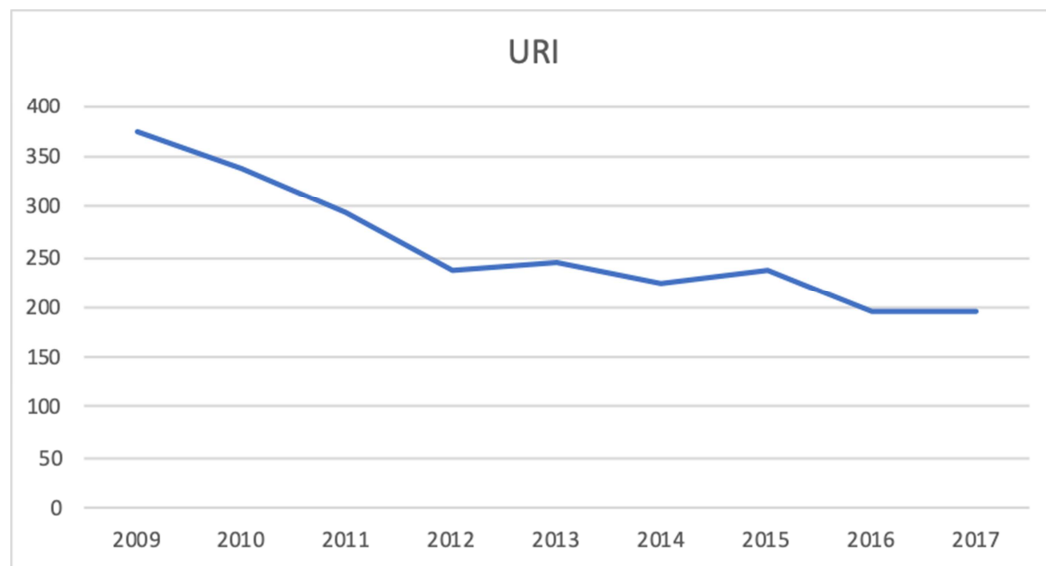


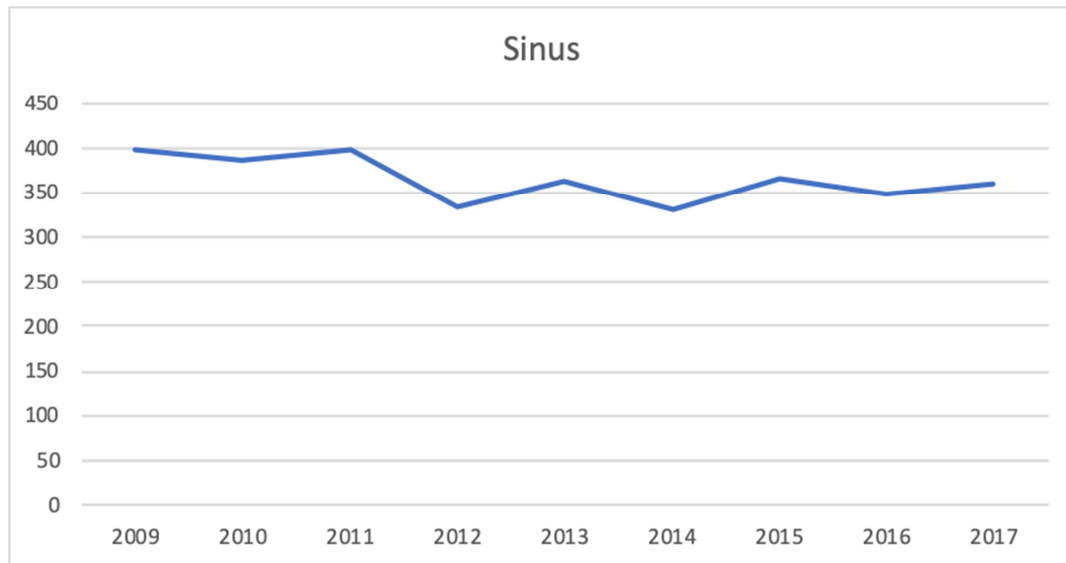
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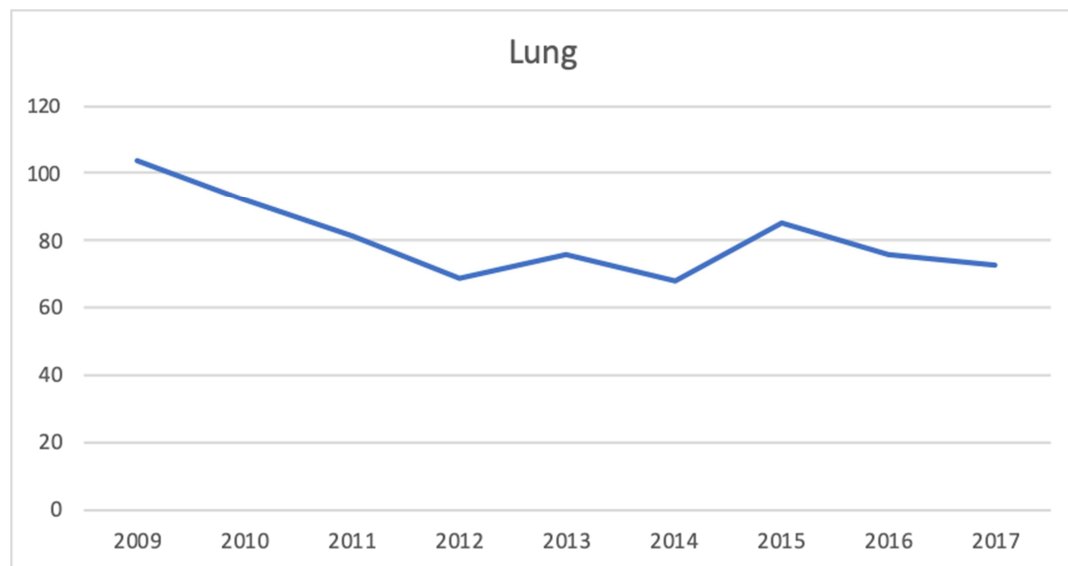


2

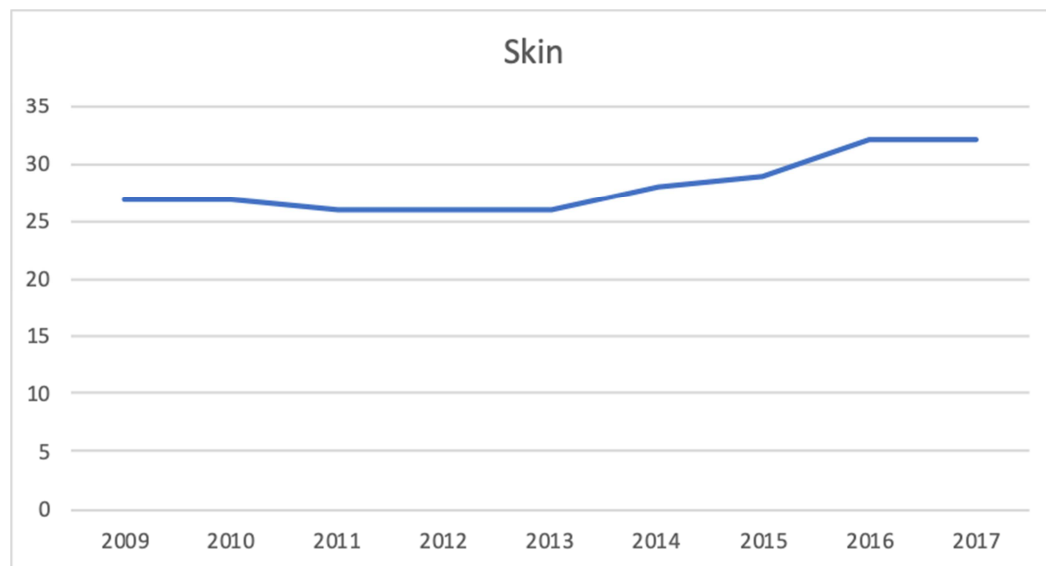
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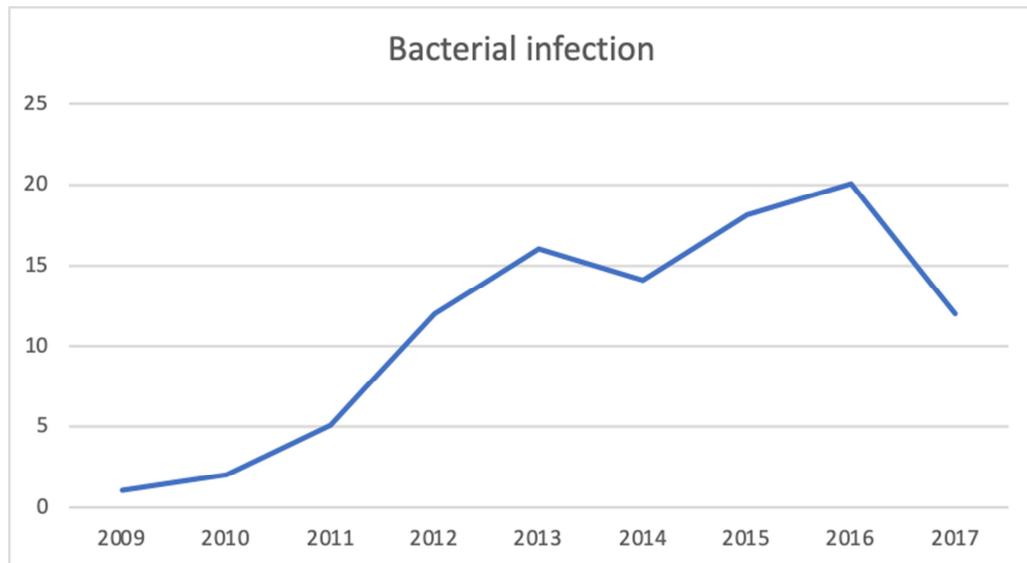


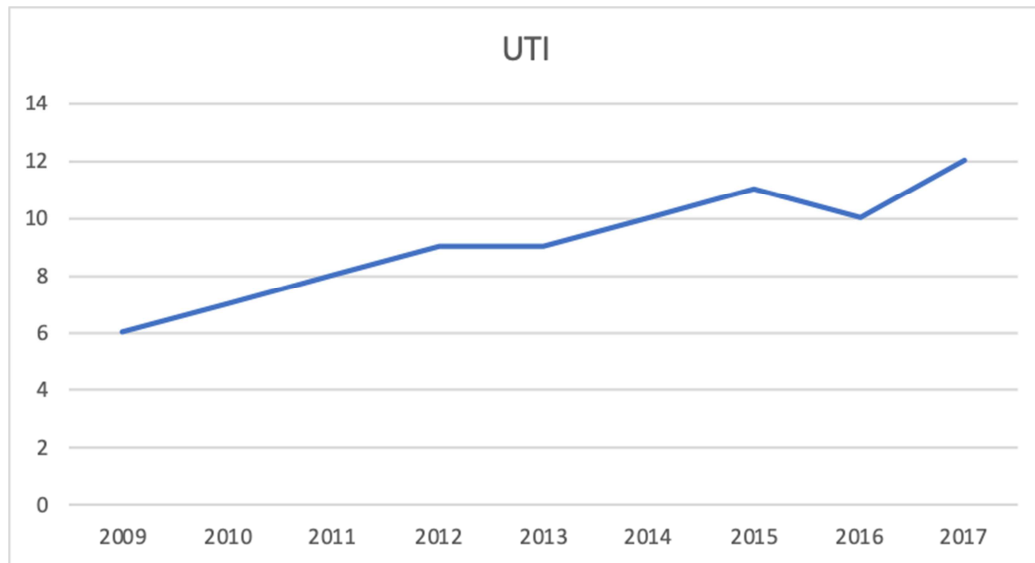




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Supplemental Table E1a Oral non-cephalosporin beta-lactam and clindamycin antibiotic use, population exposure, and new drug *allergy* noted within 30 days

Oral antibiotics	Courses used by females (Females exposed) [% exposed]*	New <i>allergy</i> reported within 30 days per course N (%) [§]	Course used by males (males exposed) [% exposed]*	New <i>allergy</i> within 30 days per course N (%) [§]
Amoxicillin	2,402,081 (1,129,988) [35%]	16,891 (0.70%)	1,873,980 (912,560) [31%]	13,050 (0.70%)
Amoxicillin/Clavulanate	473,614 (332,712) [10%]	4,329 (0.91%)	387,145 (278,744) [9.5%]	2,751 (0.71%)
Ampicillin	25,223 (20,151)	186 (0.74%)	9,500 (6,447)	50 (0.53%)

	[0.63%]		[0.22%]	
Clindamycin	482,526 (300,712) [9.4%]	5,736 (1.2%)	334,703 (224,298) [7.6%]	2,687 (0.80%)
Dicloxacillin	27,019 (22,942) [0.72%]	352 (1.3%)	14,031 (11,336) [0.39%]	123 (0.88%)
Penicillin V	254,512 (201,280) [6.3%]	1,517 (0.60%)	185,004 (147,156) [5.0%]	742 (0.40%)

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6 *percent of total health plan members exposed to the specific antibiotic

7 ^spercent of courses resulting in a new *allergy* report in the EHR within 30 days

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Supplemental Table E1b Parenteral non-cephalosporin beta-lactam and clindamycin antibiotic use, population exposure, and new drug *allergy* noted within 30 days

Parenteral Antibiotics	Courses used by females (Females exposed) [% exposed]*	New <i>allergy</i> reported within 30 days per course N (%) [§]	Course used by males (males exposed) [% exposed]*	New <i>allergy</i> within 30 days per course N (%) [§]
Ampicillin-sulbactam	19,087 (17,379) [0.54%]	231 (1.2%)	19,233 (16,941) [0.58%]	166 (0.86%)
Aztreonam	5,675 (4,698) [0.15%]	25 (0.44%)	3,140 (2,440) [0.083%]	12 (0.38%)
Clindamycin	124,429 (96,294)	918 (0.74%)	73,567 (59,318)	466 (0.63%)

	[3.0%]		[2.0%]	
Doripenem	17 (16) [<0.001%]	0	31 (30) [0.001%]	0
Ertapenem sodium	9,835 (6,001) [0.19%]	53 (0.54%)	7,201 (4,453) [0.15%]	33 (0.46%)
Imipenem-cilastatin	1,155 (854) [0.27%]	2 (0.17%)	1,132 (927) [0.032%]	3 (0.27%)
Meropenem	9,875 (6,353) [0.20%]	41 (0.42%)	10,915 (6,909) [0.24%]	40 (0.37%)
Nafcillin sodium	1,123 (903) [0.20%]	23 (2.0%)	1,637 (1,294) [0.044%]	49 (3.0%)

Oxacillin sodium	1,998 (1,517) [0.047%]	45 (2.3%)	3,474 (2,598) [0.09%]	91 (2.6%)
Penicillin G benzathine	23,080 (19,561) [0.61%]	157 (0.68%)	29,885 (21,242) [0.71%]	205 (0.69%)
Penicillin G potassium or Penicillin G sodium	65,210 (50,621) [1.6%]	2221 (0.40%)	2,801 (2,375) [0.072%]	63 (2.2%)
Penicillin G procaine	1,047 (1,020) [0.032%]	6 (0.57%)	817 (762) [0.026%]	5 (0.61%)
Piperacillin sodium- tazobactam	89,409 (62,441) [1.95%]	921 (1.03%)	104,328 (68,512) [2.33%]	770 (0.74%)

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14 *percent of total health plan members exposed to the specific antibiotic

15 §percent of courses resulting in a new *allergy* notation in the medical record within 30 day

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