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Adverse Events Associated with Prolonged Antibiotic Use

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Abstract

Purpose—The Infectious Diseases Society of America and US CDC recommend 60 days of ciprofloxacin, doxycycline or amoxicillin for anthrax prophylaxis. It is not possible to determine severe adverse drug event (ADE) risks from the few people thus far exposed to anthrax

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prophylaxis. This study's objective was to estimate risks of severe ADEs associated with long-term ciprofloxacin, doxycycline and amoxicillin exposure using 3 large databases: one electronic medical record (General Practice Research Database) and two claims databases (UnitedHealthcare, HMO Research Network).

Methods—We include office visit, hospital admission and prescription data for 1/1/1999–6/30/2001. Exposure variable was oral antibiotic person-days (pds). Primary outcome was hospitalization during exposure with ADE diagnoses: anaphylaxis, phototoxicity, hepatotoxicity, nephrotoxicity, seizures, ventricular arrhythmia or infectious colitis.

Results—We randomly sampled 999,773, 1,047,496 and 1,819,004 patients from Databases A, B and C respectively. 33,183 amoxicillin, 15,250 ciprofloxacin and 50,171 doxycycline prescriptions continued 30 days. ADE hospitalizations during long-term exposure were not observed in Database A. ADEs during long-term amoxicillin were seen only in Database C with 5 ADEs or 1.2(0.4–2.7) ADEs/100,000 pds exposure. Long-term ciprofloxacin showed 3 and 4 ADEs with 5.7(1.2–16.6) and 3.5(1.0–9.0) ADEs/100,000 pds in Databases B and C, respectively. Only Database B had ADEs during long-term doxycycline with 3 ADEs or 0.9(0.2–2.6) ADEs/100,000 pds. For most events, the incidence rate ratio, comparing >28 vs. 1–28 pds exposure was <1, showing limited evidence for cumulative dose-related ADEs from long-term exposure.

Conclusions—Long-term amoxicillin, ciprofloxacin and doxycycline appears safe, supporting use of these medications if needed for large-scale post-exposure anthrax prophylaxis.

Keywords

Anti-infective agents; Anthrax prevention and control; Health services research; Databases; Bioterrorism

Recent concerns regarding the potential for intentional release of bioterrorism agents, particularly regarding the threat of anthrax exposure, have drawn attention to the possible need for large-scale post-exposure antibiotic prophylaxis. Treatment choices should reflect a balance between the expected benefits and risks of alternative treatment strategies. As data are limited regarding treatments' relative effectiveness in preventing infection, the anticipated risks related to each agent's use should play an important role in developing treatment recommendations.

For adult and pediatric post-exposure anthrax prophylaxis, the Infectious Diseases Society of America and the U.S. Centers for Disease Control and Prevention (CDC) recommend a 60-day course of ciprofloxacin, doxycycline, or amoxicillin.^{1–3} A recent study reported that amoxicillin was the third most common drug implicated in adverse drug events (ADEs) treated in U.S. emergency departments, and tetracyclines account for approximately 0.5% of ADEs.⁴ However, most antimicrobial drug use is of short duration; antibiotic courses for acute infections typically range up to fourteen days duration,^{5, 6} and data are limited regarding the safety of long-term antibiotics. The risk of some adverse outcomes may be proportional to the duration of antibiotic exposure, resulting from cumulative dose effects. Antibiotic-associated diarrhea might fit this model. Conversely, other adverse event risks could fall over time, for example because of depletion of susceptible individuals in the treatment population.^{7–9} Allergic reactions might fit this model.

Case studies of individuals offered anthrax prophylaxis following the Fall 2001 bioterrorist attack suggest that minor adverse events are common and frequently result in therapy discontinuation, although they are not always attributable to antimicrobial therapy.^{10, 11} It is much more difficult to estimate the risk of rare but life-threatening adverse events,¹² and whether they increase with exposure time. Premarketing studies are not usually designed to reveal risks under 1/1000 exposed individuals;^{13–15} postmarketing data come mostly from anecdotal reporting and do not provide population-based risk estimates.^{15–17}

Electronic medical record (EMR) and administrative databases provide an opportunity to evaluate these risks on a larger scale. While minor ADEs may not be reliably documented, these data should have better sensitivity and specificity for severe adverse events such as hospitalizations.^{12, 18} This study uses data from 3 large observational databases to estimate risks of long-term exposure to amoxicillin, ciprofloxacin, and doxycycline. Our objectives are to describe and compare the frequency of hospitalizations for severe adverse events temporally linked to long-term antibiotic use in the three databases, and to determine if risks of severe ADEs increase with prolonged use.

Methods

We used a retrospective cohort design to describe antibiotic use and temporally associated adverse events and event rates in one EMR and two administrative claims databases. Data on outpatient visits, hospital admissions and medication dispensings were obtained regarding a sample of patients from each database, using the study time period January 1, 1999 through June 30, 2001. Our exposure variable was person-time of exposure to one of the three oral antibiotics of interest: amoxicillin, ciprofloxacin, and doxycycline, and our outcomes included adverse events during antibiotic exposure severe enough to result in hospitalization.

Databases

The General Practice Research Database (GPRD)—The GPRD is the world's largest primary care observational database, containing electronic medical record data from a population-based UK patient sample. The version of the GPRD used in this study covers almost 5% of the UK population and is representative of the UK's age, sex, and geographic distribution.^{19, 20} Approximately 98% of the UK population is registered with a general practitioner, who is responsible for almost the entirety of the patient's medical care. The GPRD records demographics, visits for acute conditions, medical diagnoses, hospital admissions, new and repeat prescriptions, mortality, and cause of death. Since 1995, diagnoses are recorded with Read diagnostic codes, and prescriptions using NHS Prescription Pricing Authority codes. Practitioners are trained in data entry; their data quality is reviewed²¹ and has shown good validity regarding documented diagnoses,^{22, 23} prescriptions,²³ and specialist information.²⁴ We used data from a 50% random sample from the active GPRD patients on January 1, 2000.

Center for Health Care Policy and Evaluation (CHCPE): UnitedHealthcare (UHC) health plans—The UnitedHealth Group health plans are IPA model or Independent Practice Associations that contract with networks of physicians, pharmacies

and facilities. Most plan members are commercially-insured through employers; membership also includes Medicaid and Medicare beneficiaries. UHC data include provider, facility and pharmacies claims submitted to obtain payment for health care services rendered. A research database organizes administrative data from 12 U.S. health plans, supporting health services and evaluation studies.²⁵ We sampled medical and pharmacy claims for a 50% random sample of patients active on January 1, 2000, from each of 8 geographically diverse plans, across all plans.

HMO Research Network (HMORN)—The nine HMORN organizations in this database provide health care for individuals across the U.S..²⁶ The HMOs serve Medicaid and Medicare beneficiaries as well as commercially insured members, and represent a variety of managed care organizational models including staff model, group, network, and Independent Practice Association Systems. The HMORN Center for Education and Research on Therapeutics (CERT) has developed techniques for linking records across its member organizations. The membership, demographic, pharmacy dispensing and claims files have been described elsewhere and used for other studies.^{26, 27} For this study, each of the nine HMORN CERT HMOs provided data for approximately representative 200,000 individuals.

Antibiotic Exposure

Duration of single prescriptions—We prepared a drug code set representing the three oral antibiotics of interest. The list of selected drugs was reviewed; topical and parenteral antibiotics were excluded.

The unit of analysis was exposure-days. The duration of antibiotic exposure was calculated for each drug dispensed to each subject. We used the “days supply” field to determine the prescription duration in UHC and HMORN. As the GPRD does not reliably include the “days supply” field, for the GPRD we used the total number of pills dispensed divided by the daily dose, calculated from dosing directions, to calculate an expected duration. Durations for liquid formulations often could not be calculated in the GPRD because the amount dispensed was sometimes recorded as “one vial” or “one bottle.” In this case, whenever the result of total amount dispensed/daily dose yielded a value <1, we discarded that prescription. Similarly, we discarded prescriptions <1 day duration from UHC and HMORN data.

We assumed that the number of prescribed treatment days was equivalent to the duration of antibiotic exposure. We excluded single antibiotic prescriptions with calculated durations >365 days, but did not exclude combinations of prescriptions that led to >365 exposure days.

Duration of cumulative exposure—To calculate a cumulative duration for each antibiotic, we combined sequential prescriptions of the same drug, ignoring gaps > 7 days between prescriptions. We assumed the day following the last day of the first prescription was the first day of the next prescription. When a new prescription for the same antibiotic was dispensed before the calculated end of the prior prescription, we assumed the second prescription began the day after the last day of the first prescription. Gaps >7 days between the last day of one antibiotic prescription and the first day of a second antibiotic prescription

(the same or different antibiotic) indicated a distinct antibiotic exposure. We explored the impact of different gap windows on our results by completing analyses for shorter (e.g., ignore gaps <3 days) and longer windows (e.g., ignore gaps <10 days).

In cases when a new prescription for a different antibiotic was dispensed prior to the calculated end of the prior prescription, we assumed that the first prescription ended on the day of the second prescription and the second prescription started on that day. In the extreme example when two different antibiotics were dispensed on the same day, we classified this as a mixed prescription; we did not include days when subjects were exposed to more than one antibiotic of interest.

Duration categories—Antibiotic exposure was defined two ways: 1) number of continuous days on drug, and 2) dichotomized into 2 exposure time periods,⁸ 1–28 days vs. >28 days. Twenty-eight days was chosen as the upper bound to define short- vs. long-term antibiotic exposure. This upper limit, similar to that used by previous authors to define long-term therapy,¹⁵ will approximate conditions of long-term post-exposure antibiotic prophylaxis.

Outcomes

Our primary outcome was serious adverse events associated with prolonged antibiotic exposure, defined as >28 days compared with short-term exposure, defined as 1–28 days. We defined serious events as those resulting in hospitalization, excluding ambulatory care and emergency department events unless they resulted in hospitalization.¹² Specific event categories were based on reviews of study medication drug inserts, FDA adverse event reports, and consensus opinion of the study authors. The event categories of interest included: anaphylaxis, hepatotoxicity, infectious colitis, nephrotoxicity, phototoxicity, seizures, and ventricular arrhythmias. We assigned GPRD Read discharge diagnosis codes using the following approach: First, we reviewed all Read codes using a search engine provided by the company that maintains the database, identifying codes corresponding to the categories of interest. Next, we reviewed hospitalizations for GPRD patients and identified codes falling under one of the seven categories above. The combination of these two approaches yielded a final set of Read codes of interest.

Conversion of Read to ICD-9 codes was accomplished by manual review of the ICD-9CM source book using key words from the identified GPRD Read codes. These lists of ICD-9 codes were reviewed by investigators at all three sites (Appendix).

For our primary analysis, we restricted endpoints to those resulting in hospitalization during antibiotic exposure. In secondary analyses, we expanded the window by up to seven days from the last antibiotic prescription date to assess any delayed adverse events. Medical record review was not performed.

Analysis

Our analysis focused on individual exposures as the unit of analysis. We created frequency tables for the population distribution for each data set. For each duration category, we

calculated the number of unique exposures, stratifying by database and the three antibiotics of interest.

We calculated the incidence rate for each type of ADE for each antibiotic exposure duration category, analyzing antibiotic exposure as a dichotomous variable, (1–28 days vs. >28 days), stratifying by each drug of interest.

Drug-related risk depends on population exposure-time; risk may not be constant over time. This can be addressed by considering incidence rate, dividing the number of events by follow-up population-time, and quantifying rates separately for various time intervals of continued exposure.^{8, 28, 29} For each exposure category, we calculated the total number of person-days within that exposure category. We then calculated an incidence rate for each exposure category as the total number of adverse events occurring within that time window divided by the total number of person days within that window. Incidence rates for each endpoint were calculated for each drug with 95% confidence intervals based on the Poisson distribution. We calculated the overall incidence rate for any adverse event resulting in hospitalization and event type-specific rates (eg., nephrotoxicity, hepatotoxicity, etc.).

Finally, we calculated an incidence rate ratio (IRR), the ratio of the incidence rate on exposure >28 days vs. the incidence rate on exposure from days 1–28, with 95% confidence intervals.³⁰ We looked for specific IRRs > 1 as signals that the incidence of adverse events was increasing as duration on antibiotics increased.

Analyses were completed with SAS version 8.2 (SAS Institute Inc., Cary, NC) and STATA version 9.2 (StataCorp LP, College Station, TX) software. In order to preserve some anonymity of specific data sources, we present the results identifying the data sources only as databases A, B, and C. Because all subjects within the databases were de-identified, the study was determined to be exempt from Institutional Review Board approval.

Results

Study Population

Distribution of subjects and person-years was relatively even across the three databases. From Database A, we sampled 999,773 subjects, representing 2.2 million person-years of observation time. From Database B, we sampled 1,047,496 subjects, representing 2.1 million person-years, and from Database C, we sampled 1,819,004 subjects, representing almost 3.3 million person-years (Table 1).

Antibiotic Exposure

Table 1 summarizes the subject exposure to study drugs, and Table 2 summarizes the frequency of antibiotic prescriptions for each study drug in each database. Amoxicillin accounted for over three times the number of prescriptions compared with ciprofloxacin and doxycycline combined, and accounted for a greater portion of antibiotic prescriptions in Database A compared with the other databases.

The Figure summarizes the distribution of cumulative exposure time for each of the antibiotics in each database; 33,183 of amoxicillin, 15,250 of ciprofloxacin, and 50,171 of doxycycline prescriptions continued >30 days. Using longer or shorter gap windows to define subsequent prescriptions had minimal impact on calculated exposure time distribution (data not shown).

Adverse Events

Table 3 summarizes the overall adverse event rates for each antibiotic, comparing 1–28 days vs. >28 days of exposure, expressed as events per 100,000 person-days of exposure. Ciprofloxacin had the greatest short-term risk of adverse events, 3.6–16.9 per 100,000 person-days. Adverse events >28 days of exposure were not observed in Database A. ADEs during long-term amoxicillin exposure were seen only in Database C with 5 total ADE hospitalizations or 1.2 (0.4–2.7) ADEs per 100,000 person-days of exposure. Long-term ciprofloxacin showed 3 total ADE's or 5.7 (1.2–16.6) ADEs per 100,000 person-days exposure in Database B, and 4 total ADE's with a rate of 3.5 (1.0–9.0) ADEs per 100,000 person-days exposure in Database C. Only Database B had ADEs during long-term doxycycline with 3 total ADEs or 0.9 (0.2–2.6) ADEs per 100,000 person-days of exposure. Expanding the exposure window by up to 7 days from the last date of antibiotic prescription to assess any delayed adverse events did not have a significant impact on results (data not shown).

Finally, we stratified the antibiotic-specific adverse events by specific adverse event type (Table 4). There were no adverse events after prolonged use from Database A; this table includes prescriptions from Databases B and C only. Ciprofloxacin had the highest adverse event risk with short-term use over all adverse event types. For most specific types of adverse events, the IRRs comparing > 28 days to 1–28 days of exposure were 0 or < 1. Among the few exceptions, for amoxicillin comparing long- vs. short-term antibiotic use, the IRR was 2.7 (0.70–8.4) for seizure risk in Database C, but there were no seizures observed in Database B after 28 exposure days. Similarly, amoxicillin had an IRR of 1.8 (0.18–10.51) for a hypersensitivity event with long-term vs. short-term use in Database C but again, no hypersensitivity events after long-term use were observed in Database B.

Discussion

Long-term amoxicillin, ciprofloxacin, and doxycycline use appears safe; there do not appear to be large increased adverse events risks associated with prolonged exposure. Most long-term use involved doxycycline. Ciprofloxacin shows the highest risk of adverse events per 100,000 person days of exposure among these drugs, but the risk does not appear to increase after 28 exposure days. Amoxicillin was the only drug to show any indication of increased adverse event risk with prolonged use for seizures and perhaps hypersensitivity, and only in one of three databases; the other two databases had no adverse events in these categories with prolonged amoxicillin use. While amoxicillin is the third most common drug implicated in emergency department visits for ADEs,⁴ amoxicillin is very common compared with other antibiotic use, and overall its use is associated with very low frequency

of serious adverse events, with rates 2.0 events per 100,000 person days of exposure for short- or long-term use.

These reassuring results support long-term antibiotic use if large-scale anthrax prophylaxis is needed. The data can also help us begin to assess the risks of long-term antibiotics for other indications, including osteomyelitis, prosthetic device infection, abscesses, etc., however studies including more clinical comorbidity data would be helpful to more fully understand the risks involving a potentially medically complex patient cohort.

We could have misclassified some antibiotic exposures as exposed when they were truly unexposed. GPRD data describe antibiotics prescribed, while UHC and HMORN data describe drugs dispensed. Patients do not fill 100% of their prescriptions,³¹ and there is no valid way for us to estimate the portion of prescribed GPRD antibiotics that were dispensed. And we do not know which patients were adherent to the prescribed medications.

Only temporally associated hospitalizations for previously-described medication adverse events were assessed. Claims-based data may be more sensitive than EMR data for severe adverse event outcomes, as they are less likely to need to be entered manually, but less sensitive than EMR data for medications dispensed (if no claim is filed), and less specific for outcomes, which may not be coded precisely. Within this context, it is reassuring that results from these three databases are relatively similar regarding severe adverse events. Less severe adverse events are a common reason for antibiotic prophylaxis discontinuation,¹¹ but were not included in this study. Claims-based and EMR data are likely to be both less sensitive and less specific for minor adverse events;¹⁸ future studies could explore the best way to best ascertain those risks.

Our analysis uses exposure time as the unit of analysis, not individual patient. In this observational study, individual exposures would not be randomized; they could be clustered by subject, provider, and practice, and influenced by subjects' clinical histories. However, given our largely negative findings of no increased risk of adverse events from prolonged antibiotic use, it is unlikely that more clinical information regarding individual patients would have changed our conclusions.

Our use of IRRs with observational data, comparing incidence risks over separate time intervals of continued exposure, is most valid when we can assume no previous occurrence of drug-related adverse events.²⁸ Since a history of a severe adverse drug event with a specific antibiotic is usually considered a contraindication to recurrent use of that antibiotic, the assumption should be valid for this study. Our IRR confidence intervals are based upon relatively few events and are quite wide. A larger long-term exposed population would be necessary for definitive conclusions. Although for some events, we cannot exclude a higher rate of adverse events than reported, the number of person-years included in this study is quite large, and the low number of adverse events is actually reassuring.

Most adverse events occurred during the first 28 days of therapy. This analysis is not based upon only first-users; subjects with previous adverse events associated with study drug use may not have been as likely to have been re-exposed during the time period of this study, a phenomenon known as "depletion of susceptibles."⁹ We did not do medical record review

and could not validate medication adherence, outcome codes or the possible contribution of competing causes of adverse events; we also have no comparison group without antibiotic exposure so we cannot attribute a definitive causal relationship between antibiotic exposure and concurrent adverse events.

In conclusion, risk of severe adverse events during exposure to the three antibiotics recommended for post-exposure anthrax prophylaxis, amoxicillin, ciprofloxacin, and doxycycline, does not appear to increase over time with prolonged exposure. These findings support the use of these medications if the need is determined for implementation of post-exposure anthrax prophylaxis or potentially other long term uses. As any short- and long-term risks are proportional to the frequency of medication use, any decision to implement large-scale antibiotic prophylaxis will need to balance the risks of exposure to anthrax (or another biologic agent) vs. the adverse event risks from antibiotic prophylaxis described here.

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Key points

- There are no large increased risks of adverse drug events associated with long-term antibiotic exposure.
- These results support long-term anoxicillin, ciprofloxacin and doxycycline use if needed for large-scale post-exposure anthrax prophylaxis

Figure.

Distribution of Drug Exposure Time for Each Antibiotic Drug

Table 1

Age and gender distribution of subjects exposed to study drugs

Drug	Frequency (%)		
	Database A N=999,773 (2,221,756 person-years)	Database B N=1,047,496 (2,062,454 person-years)	Database C N=1,819,004 (3,295,242 person-years)
Amoxicillin			
Male	81,618 (42.4)	120,352 (44.9)	138,485 (42.8)
Female	110,890 (57.6)	147,778 (55.1)	185,212 (57.2)
0 to 6 years	17,134 (8.9)	50,903 (19.0)	75,313 (23.3)
7 to 17 years	20,153 (10.5)	57,400 (21.4)	59,693 (18.4)
18 to 64 years	113,868 (59.2)	155,347 (57.9)	164,249 (50.7)
65+ years	41,353 (21.5)	4480 (1.7)	24,442 (7.6)
Ciprofloxacin			
Male	8111 (42.8)	24,876 (39.3)	36,187 (41.4)
Female	10,858 (57.2)	38,385 (60.7)	51,146 (58.6)
0 to 6 years	30 (0.2)	115 (0.2)	70 (0.1)
7 to 17 years	333 (1.8)	1246 (2.0)	1792 (2.1)
18 to 64 years	11,633 (61.3)	58,579 (92.6)	63,138 (72.3)
65+ years	6973 (36.8)	3321 (5.3)	22,333 (25.6)
Doxycycline			
Male	4575 (37.1)	19,534 (42.2)	35,828 (39.7)
Female	7750 (62.9)	26,800 (57.8)	54,392 (60.3)
0 to 6 years	0	78 (0.2)	28 (<0.1)
7 to 17 years	520 (4.2)	3253 (7.0)	6578 (7.3)
18 to 64 years	9936 (80.6)	41,526 (89.6)	69,558 (77.1)
65+ years	1869 (15.2)	1477 (3.2)	14,056 (15.6)

Table 2

Total numbers of unique prescriptions for each study drug

Study Drug	Database A		Database B		Database C		TOTAL	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Amoxicillin	289,689	87.2	454,386	74.9	518,385	67.9	1,262,460	74.2
Ciprofloxacin	26,122	7.9	87,175	14.3	120,357	15.8	233,654	13.7
Doxycycline	16,279	4.9	65,321	10.8	124,086	16.3	205,686	12.1

Table 3
Incidence rates for Any Serious Adverse Event resulting in hospitalization, 1–28 days vs. >28 days Exposure Duration

Drug	Database	Duration of Exposure (days)					
		1–28 days			> 28 days		
		# of events	duration of exposure (person-days)	events per 100,000 person days (95% CI)	# of events	duration of exposure (person-days)	events per 100,000 person days (95% CI)
Amoxicillin	Database A	40	1,911,936	2.1 (1.5–2.8)	0	65,848	0 (0–5.6)
Amoxicillin	Database B	87	4,406,578	2.0 (1.6–2.4)	0	115,226	0 (0–3.2)
Amoxicillin	Database C	53	5,476,031	1.0 (0.7–1.3)	5	432,933	1.2 (0.4–2.7)
Ciprofloxacin	Database A	7	194,279	3.6 (1.4–7.4)	0	31,072	0 (0–11.9)
Ciprofloxacin	Database B	140	826,243	16.9 (14.3–20.0)	3	52,772	5.7 (1.2–16.6)
Ciprofloxacin	Database C	71	1,126,877	6.3 (4.9–8.0)	4	113,777	3.5 (1.0–9.0)
Doxycycline	Database A	1	213,094	0.5 (0.01–2.8)	0	166,091	0 (0.01–2.6)
Doxycycline	Database B	27	1,026,386	2.6 (1.7–3.8)	3	343,184	0.9 (0.2–2.6)
Doxycycline	Database C	2	1,755,595	0.1 (0.01–0.4)	0	678,416	0 (0–0.5)

Table 4

Incidence Rates and Incidence Rate Ratios, by type of Adverse Event, 1–28 days vs. >28 days Exposure Duration for Each Study Antibiotic

Toxicity	Drug	Incidence Rate per 1,000,000 person-days exposure			IRR (95% c.i.)		
		1–28 days exposure		>28 days exposure		>28 days exposure vs. 1–28 days exposure	
		Database B	Database C	Database B	Database C	Database B	Database C
Hypersensitivity	Amoxicillin	2.3	1.3	0	2.3	0.0 (0.002–10.6)	1.8 (1.8–10.51)
	Ciprofloxacin	12.1	0.9	0	0	0.0 (0.0007–4.3)	0.0 (0.004–57.6)
	Doxycycline	3.9	0	0	0	0.0 (0.0003–2.4)	0.0 (0.004–1676.3)
Pseudomembranous Colitis	Amoxicillin	0.9	4	0	2.3	0.0 (0.004–30.6)	0.6 (0.06–2.9)
	Ciprofloxacin	18.2	17.7	0	8.8	0.0 (0.0005–2.8)	0.5 (0.05–2.5)
	Doxycycline	1	0	0	0	0.0 (0.001–17.4)	0.0 (0.004–1676.3)
Hepatic Toxicity	Amoxicillin	1.4	0.5	0	0	0.0 (0.003–18.9)	0.0 (0.002–14.6)
	Ciprofloxacin	20.6	6.2	18.9	0	0.9 (0.09–4.7)	0.0 (0.0007–4.1)
	Doxycycline	0	0	0	0	0.0 (0.005–1937.4)	0.0 (0.004–1676.3)
Renal Toxicity	Amoxicillin	1.6	0.4	0	0	0.0 (0.001–8.7)	0.0 (0.003–25.3)
	Ciprofloxacin	48.4	9.8	0	8.8	0.0 (0.0002–0.91)	0.9 (0.09–4.8)
	Doxycycline	3.9	0	2.9	0	0.7 (0.07–5.1)	0.0 (0.004–1676.3)
Ventricular Arrhythmias	Amoxicillin	7.3	0.4	0	0	0.0 (0.0006–3.1)	0.0 (0.003–25.3)
	Ciprofloxacin	33.9	9.8	37.9	8.8	1.1 (0.22–3.8)	0.9 (0.09–4.8)
	Doxycycline	6.8	0	5.8	0	0.9 (0.16–3.6)	0.0 (0.004–1676.3)
Seizures	Amoxicillin	4.8	2.6	0	6.9	0.0 (0.0009–4.8)	2.7 (0.70–8.4)
	Ciprofloxacin	29	17.7	0	8.8	0.0 (0.0003–1.7)	0.5 (0.05–2.5)
	Doxycycline	8.8	0.6	0	0	0.0 (0.0002–0.93)	0.0 (0.001–15.0)
Phototoxicity	Amoxicillin	0.5	0.5	0	0	0.0 (0.001–76.5)	0.0 (0.002–14.6)
	Ciprofloxacin	2.4	0.9	0	0	0.0 (0.003–31.3)	0.0 (0.004–57.6)
	Doxycycline	1.9	0.6	0	0	0.0 (0.0006–6.0)	0.0 (0.001–15.0)