National Estimates of Emergency Department Visits for Antibiotic Adverse Events Among Adults—United States, 2011–2015

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BACKGROUND: Detailed, nationally representative data describing high-risk populations and circumstances involved in antibiotic adverse events (AEs) can inform approaches to prevention.

OBJECTIVE: Describe US burden, rates, and characteristics of emergency department (ED) visits by adults for antibiotic AEs.

DESIGN: Nationally representative, public health surveillance of adverse drug events (National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance [NEISS-CADES]) and a nationally projected database of dispensed prescriptions (QuintilesIMS), 2011–2015.

PATIENTS: Antibiotic-treated adults (≥ 20 years) seeking ED care.

MAIN MEASURES: Estimated annual numbers and rates of ED visits for antibiotic AEs among outpatients treated with systemically administered antibiotics.

KEY RESULTS: Based on 10,225 cases, US adults aged ≥ 20 years made an estimated 145,490 (95% confidence interval, 115,279–175,701) ED visits for antibiotic AEs each year in 2011–2015. Antibiotics were implicated in 13.7% (12.3–15.2%) of all estimated adult ED visits for adverse drug events. Most (56.6%; 54.8–58.4%) antibiotic AE visits involved adults aged < 50 years, and 71.8% (70.4–73.1%) involved females. Accounting for prescriptions dispensed from retail and long-term care pharmacies, adults aged 20–34 years had twice the estimated rate of ED visits for oral antibiotic AEs compared with those aged ≥ 65 years (9.7 [7.6–11.8] versus 4.6 [3.6–5.7] visits per 10,000 dispensed prescriptions, respectively). Allergic reactions accounted for three quarters (74.3%; 70.0–78.6%) of estimated ED visits for antibiotic AEs. The three most frequently implicated antibiotic classes in ED visits for antibiotic AEs were oral sulfonamides (23.2%; 20.6–25.8%), penicillins (20.8%; 19.3–22.4%), and quinolones (15.7%; 14.2–17.1%). Per-prescription rates declined with increasing age group.

CONCLUSIONS: Antibiotics are a common cause of ED visits by adults for adverse drug events and represent an important safety issue. Quantifying risks of AEs from specific antibiotics for specific patient populations, such as younger adults, provides additional information to help clinicians assess risks versus benefits when making the decision to prescribe or not prescribe an antibiotic. AE rates may also facilitate communication with patients about antibiotic risks.

KEY WORDS: pharmaceutical care; patient safety; community health; primary care; evidence-based medicine.

J Gen Intern Med 33(7):1060–8
DOI: 10.1007/s11606-018-4430-x

BACKGROUND

Antibiotics are one of the most commonly prescribed medications in the USA.[1] In 2014, almost 200 million antibiotic prescriptions were written for adult outpatients aged ≥ 20 years, approximately five prescriptions for every six Americans.[2,3] Increased use of antibiotics is correlated with development of antibiotic resistance,[4,5] and the outpatient setting, which accounts for the majority of antibiotic expenditures,[6] has been identified as a target for interventions to improve quality of care.[7] Approximately one in ten adult outpatient visits results in an antibiotic prescription,[8] of which an estimated one third are unnecessary,[9] and even more may be inappropriate in antibiotic selection, dosing or duration.[8–12] Unnecessary prescribing of antibiotics has been attributed to both demand-side factors (e.g., patient expectations) and supply-side factors (e.g., clinician concerns about patient satisfaction and/or time constraints).[12–20]

In addition to long-term antibiotic resistance, the use of antibiotics causes acute adverse drug events.[21] Systemically administered antibiotics are the second most common cause of estimated emergency department (ED) visits for adverse drug events, accounting for one sixth of all estimated adverse drug event ED visits in the USA.[22,23] We assessed the frequency, rates, and clinical characteristics of adult ED visits for adverse events (AEs) from antibiotics in the USA to help inform efforts to encourage appropriate prescribing. Pediatric antibiotic AEs were assessed in a separate analysis.

Electronic supplementary material *The online version of this article (https://doi.org/10.1007/s11606-018-4430-x) contains supplementary material, which is available to authorized users.*

Received September 11, 2017
Revised February 7, 2018
Accepted March 20, 2018
Published online April 20, 2018

METHODS

Data Source and Collection Methods

National estimates of ED visits for antibiotic AEs by adults (aged ≥ 20 years) were obtained using 5 years of data (January 1, 2011 through December 31, 2015) from hospitals participating in the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project. NEISS-CADES is a nationally representative, size-stratified probability sample of hospitals with at least six beds and 24-h EDs (excluding psychiatric and penal institutions) in the USA and its territories. From 2011 through 2015, 55 to 62 hospitals participated in NEISS-CADES each year. As described previously,[24] trained abstractors at each participating hospital review clinical records of ED visits to identify clinician-diagnosed adverse drug events, reporting up to two implicated drugs and ten concomitant drugs. Abstractors also record narrative descriptions of the event, including preceding circumstances, clinician diagnoses, testing, treatments administered in the ED or by emergency medical services, and disposition. Narrative data are coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 9.1. Data collection is considered a public health surveillance activity and does not require human subjects review or institutional review board approval.[25]

To contextualize ED visit numbers relative to antibiotic exposure, national estimates of antibiotic prescriptions dispensed at outpatient retail and long-term care pharmacies were obtained from the 2011–2015 QuintilesIMS National Prescription Audit (NPA). NPA tracks national prescription trends and activity for pharmaceutical products; NPA aggregates prescription data from participating US pharmacies and uses a proprietary algorithm to project national-level estimates of dispensed outpatient prescriptions.[1] NPA data have previously been used to provide outpatient dispensed prescription estimates on a national level.[26] The NPA sample included pharmacy records from nearly 48,000 retail pharmacies across the USA, representing approximately 80% of all retail prescription activity from independent and chain pharmacies and pharmacies in food and mass merchandise stores, and an additional 1800 pharmacies serving long-term care facilities.[1]

Definitions

Antibiotic AE cases were defined as visits for problems the treating ED clinician explicitly attributed to the use of systemically administered antibiotics (excluding antitubercular agents). ED visits for AEs involving all other systemically administered medications (prescription and over-the-counter medications, dietary supplements, homeopathic products, and vaccines) were used as a comparison group. Systemically administered antibiotics and other medications were defined as medications administered by oral, injectable, rectal, sublingual, or transdermal routes.

For the purposes of this analysis, AEs were categorized as allergic reactions (immunologically mediated effects, including severe hypersensitivity reactions such as Stevens-Johnson syndrome), non-allergic adverse effects (undesirable pharmacologic or idiosyncratic effects at recommended doses), supratherapeutic effects of dose or intake of excess dose, or other effects (including those secondary to drug administration [e.g., choking on pill] or vaccination reactions). The MedDRA-coded narrative terms for each case were used to assign a single AE manifestation in a mutually exclusive and hierarchical manner based on severity; for example, a case involving anaphylactic respiratory distress and dyspepsia would be classified as a moderate-to-severe allergic reaction based on the anaphylaxis. Cases involving death in or prior to arrival in the ED and visits involving intentional self-harm, drug abuse, therapeutic failure, non-adherence, medication withdrawal, occupational exposure, and AEs from treatments received in the ED were not included. Cases usually diagnosed as antibiotic AEs only after the patient departs the ED (e.g., most *Clostridium difficile* infections) were not included.

Statistical Analysis

Cases were weighted based on inverse probability of selection, adjusted for non-response and hospital non-participation, and post-stratified to account for changes in the number of US ED visits each year.[27] Nationally estimated (projected) numbers and proportions, with corresponding 95% confidence intervals (CIs), were calculated using the SURVEYMEANS procedure in SAS 9.4 (SAS Institute, Cary, NC). Cumulative 5-year (2011–2015) estimates and corresponding CIs were divided by 5 to calculate average annual estimates and CIs, accounting for weighting and complex sample design. Cumulative estimates less than 1200, based on fewer than 20 cases, or with coefficients of variation greater than 30% were considered statistically unreliable and are noted.

Population rates of ED visits for antibiotic AEs were calculated by dividing the ED visit estimate (from NEISS-CADES) in each age group by the corresponding US Census Bureau bridged-race population estimates from the National Center for Health Statistics, Centers for Disease Control and Prevention.[28] Prescription-based rates of ED visits for antibiotic AEs were calculated by dividing the ED visit estimate (from NEISS-CADES) by the corresponding dispensed prescription estimate for retail and long-term care pharmacies (from NPA). Prescription-based rates were also calculated for specific drug products and patient demographics (age group, sex) for oral antibiotic classes with statistically reliable estimates. Accompanying 95% CIs for rate estimates were calculated incorporating the variance of the numerator (NEISS-CADES) estimates of ED visits for antibiotic AEs. Because of the large sample size (approximately 3.8 billion dispensed prescriptions annually), the variance of NPA estimates was considered negligible.

Table 1 US Emergency Department (ED) Visits Among Adults for Adverse Events (AEs) from Systemically Administered Medications, by Case Characteristics, 2011–2015

Case characteristic	Antibiotics			All other medications		
	Cases, no.	Annualized national estimate		Cases, no.	Annualized national estimate	
		No.	% (95% CI)		No.	% (95% CI)
Patient age (years)						
20–34	3500	48,073	33.0 (31.5–34.6)	10,270	129,493	14.2 (12.4–16.0)
35–49	2509	34,265	23.6 (22.3–24.8)	12,151	153,667	16.8 (15.2–18.4)
50–64	2288	33,223	22.8 (21.6–24.0)	18,318	228,645	25.0 (23.5–26.5)
≥65	1928	29,929	20.6 (18.8–22.3)	30,224	401,841	44.0 (39.5–48.4)
Patient sex*						
Female	7275	104,440	71.8 (70.4–73.1)	39,912	514,201	56.3 (54.4–58.2)
Number of implicated medications						
One	8707	125,756	86.4 (84.4–88.5)	60,133	781,097	85.5 (83.6–87.4)
Two or more	1518	19,734	13.6 (11.5–15.6)	10,830	132,549	14.5 (12.6–16.4)
AE type†						
Allergic reaction	7643	108,125	74.3 (70.0–78.6)	11,071	145,688	15.9 (14.0–17.9)
Adverse effect (non-allergic)	2365	34,687	23.8 (19.6–28.1)	23,139	296,290	32.4 (29.4–35.4)
Supratherapeutic effect or intake of excess dose	124	1524	1.0 (0.8–1.3)	34,588	442,483	48.4 (45.8–51.1)
Other	93	1154	0.8 (0.6–1.0)	2165	29,185	3.2 (2.8–3.6)
Documented medication error‡						
Yes	273	3466	2.4 (1.8–2.9)	9339	114,429	12.5 (10.4–14.7)
Disposition§						
Hospitalized	961	13,444	9.2 (7.1–11.4)	24,380	296,217	32.4 (26.8–38.0)
Treated/released or left against medical advice	9264	132,046	90.8 (88.6–92.9)	46,574	617,338	67.6 (62.0–73.1)
Total	10,225	145,490	N/A	70,963	913,646	N/A

Case counts and estimates are from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project, CDC. "Systemically Administered Medications" refers to medications administered by oral, injectable, rectal, sublingual, or transdermal routes
CI confidence interval, N/A not applicable
**Sex not reported for one case of ED visits for AEs from antibiotics*
†"Allergic reaction" refers to immunologically mediated effects; "adverse effect" refers to undesirable pharmacologic or idiosyncratic effects at recommended doses; "other" refers to other adverse effects secondary to drug administration (such as choking on tablet or pill) or vaccination reactions
‡Refers to drug prescribing, dispensing, or administration errors (e.g., wrong drug, wrong dose, wrong duration, wrong route, expired drug, or old prescription), administration of another individual's medication, or accidental needle stick
§Disposition not reported for nine cases of ED visits for AEs from all other systemically administered medications

RESULTS

Based on 10,225 NEISS-CADES cases, US adults aged ≥ 20 years made an estimated 145,490 (95% CI, 115,279–175,701) ED visits for AEs from antibiotics each year in 2011–2015, causing 13.7% (95% CI, 12.3–15.2%) of estimated adult ED visits for AEs from all systemically administered medications (Table 1). One third (33.0%) of estimated ED visits for antibiotic AEs involved adults 20 to 34 years of age, representing 27.1% (95% CI, 25.1–29.1%) of estimated ED visits for AEs from all systemically administered medications in young adults. Adults younger than 50 years of age were involved in over one half (56.6%) of estimated ED visits for AEs from antibiotics (95% CI, 54.8–58.4%), but less than a third (31.0%) of estimated ED visits for AEs from all other systemically administered medications (95% CI, 27.7–34.3%).

The population rate of estimated ED visits for AEs from antibiotics was similar for younger and older age groups (7.3 per 10,000 individuals aged 20–34 years [95% CI, 5.8–8.9] versus 6.7 per 10,000 individuals aged ≥ 65 years [95% CI, 5.1–8.3]). In contrast, the population rate of estimated ED visits for AEs from non-antibiotic, systemically administered medications increased significantly with age, from 19.7 per 10,000 individuals aged 20–34 years (95% CI, 16.0–23.4) to 90.0 per 10,000 individuals aged ≥ 65 years (95% CI, 61.2–118.9).

Accounting for prescribing frequency of oral antibiotics, young adults aged 20–34 years had twice the estimated rate of ED visits for AEs from oral antibiotics compared with those aged ≥ 65 years (9.7 visits per 10,000 dispensed prescriptions versus 4.6 visits per 10,000 dispensed prescriptions; 95% CI, 7.6–11.8 versus 3.6–5.7). The estimated rate of ED visits for AEs from oral antibiotics among females was 7.2 per 10,000 dispensed prescriptions (95% CI, 5.8–8.7), compared with 5.0 per 10,000 dispensed prescriptions among males (95% CI, 3.9–6.0) (Online Supplementary Table).

Females accounted for 71.8% of estimated ED visits for AEs from antibiotics, compared with 56.3% of visits due to AEs from non-antibiotics (Table 1). A single medication was almost always implicated in ED visits for antibiotic AEs (86.4%), and nearly all estimated ED visits for antibiotic AEs were attributed to oral preparations (96.9%; 95% CI, 96.2–97.6%). Allergic reactions were more common among ED visits for antibiotic AEs, compared with AEs

from non-antibiotics (74.3 versus 15.9%), and ED visits for antibiotic AEs less commonly had documented medication errors (2.4 versus 12.5%) or required hospitalization (9.2 versus 32.4%).

Antibiotic Classes Implicated in Adverse Events

The three most frequently implicated antibiotic classes in ED visits by adults for AEs were oral sulfonamides (23.2%), penicillins (20.8%), and quinolones (15.7%) (Table 2). Oral oxazolidinones (linezolid) accounted for just 0.2% of ED visits for antibiotic AEs but, accounting for dispensed prescriptions from retail and long-term care pharmacies, had the highest estimated rate of ED visits for AEs (19.9 ED visits per 10,000 dispensed prescriptions), followed by oral sulfonamides (19.4 ED visits per 10,000 dispensed prescriptions) and lincomycins (clindamycin) (13.2 ED visits per 10,000 dispensed prescriptions).

Antibiotic Drug Products Implicated in Adverse Events

Sulfamethoxazole/trimethoprim was the most commonly implicated oral antibiotic product across all age groups, accounting for between one fifth (19.7%) and one quarter (25.8%) of estimated ED visits for oral antibiotic AEs (Table 3). Amoxicillin was the second most commonly implicated oral antibiotic product among adults aged 20–34, 35–49, and 50–64 years, accounting for an estimated 14.6, 10.8, and 11.0% of visits, respectively, while among older adults aged ≥ 65 years, ciprofloxacin was the second most commonly implicated oral antibiotic product (12.2%).

Prescription-based estimated rates of ED visits for AEs from oral antibiotics generally decreased with increasing patient age group. For example, the estimated rate for oral sulfamethoxazole/trimethoprim was 29.7 (95% CI, 21.9–37.5) ED visits per 10,000 dispensed prescriptions among young adults aged 20–34 years, compared with 11.4 (95% CI, 8.4–14.4) per 10,000 dispensed prescriptions among older adults aged ≥ 65 years.

Moxifloxacin had the highest estimated rate of ED visits for AEs from oral antibiotics across all ages, at 30.1 ED visits per 10,000 dispensed prescriptions (95% CI, 20.2–40.0), a rate five to six times that of the oral fluoroquinolones ciprofloxacin and levofloxacin (5.8 and 5.7 ED visits per 10,000 dispensed prescriptions, respectively; 95% CI, 4.2–7.4 and 4.5–6.9). After moxifloxacin, oral antibiotics with the highest estimated rates were linezolid (19.9 ED visits per 10,000 dispensed prescriptions; 95% CI, 8.2–31.5), sulfamethoxazole/trimethoprim (19.1 ED visits per 10,000 dispensed prescriptions; 95% CI, 14.7–23.5), and clindamycin (13.2 ED visits per 10,000 dispensed prescriptions; 95% CI, 10.4–16.0).

Table 2 US Emergency Department (ED) Visits Among Adults for Adverse Events (AEs) from Antibiotics, by Drug Class, 2011–2015

Drug class*	Annualized national estimate		
	ED visits for AEs		Rate per 10,000 dispensed prescriptions
	No.	% (95% CI)	Rate (95% CI)
Oral antibiotics			
Sulfonamides	33,725	23.2 (20.6–25.8)	19.4 (14.9–23.8)
Penicillins	30,298	20.8 (19.3–22.4)	5.9 (4.6–7.1)
Quinolones	22,770	15.7 (14.2–17.1)	6.7 (5.1–8.2)
Cephalosporins	15,616	10.7 (9.7–11.8)	6.6 (5.1–8.2)
Lincomycins (clindamycin)	10,685	7.3 (6.5–8.2)	13.2 (10.4–16.0)
Macrolides	10,279	7.1 (6.3–7.8)	2.6 (1.9–3.3)
Tetracyclines	7391	5.1 (4.3–5.8)	4.3 (3.1–5.5)
Nitroimidazoles (metronidazole)	6159	4.2 (3.4–5.1)	7.4 (5.6–9.1)
Nitrofurans (nitrofurantoin)	3961	2.7 (2.3–3.1)	4.7 (3.6–5.7)
Oxazolidinones (linezolid)	336	0.2 (0.1–0.4)	19.9 (8.2–31.5)
Other or unspecified oral antibiotics†	7023	4.8 (4.0–5.7)	N/A
Injectable antibiotics			
Cephalosporins	1598	1.1 (0.8–1.4)	N/A§
Glycopeptides (vancomycin)	756	0.5 (0.3–0.7)	
Penicillins	1355	0.9 (0.6–1.3)	
Other injectable antibiotics‡	1133	0.8 (0.5–1.1)	

Estimates of ED visits for antibiotic AEs are from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project, CDC. Estimates of dispensed prescriptions (from retail and long-term care pharmacies) are from QuintilesIMS National Prescription Audit (2011–2015)

CI confidence interval, N/A not applicable

**ED visits that involve antibiotics from two different drug classes are included in estimates for each class*

†"Other or unspecified oral antibiotics" includes unspecified antibiotics, vancomycin, dapsone, rifaximin, trimethoprim, neomycin, rifabutin, and chloramphenicol

‡"Other injectable antibiotics" includes carbapenems, quinolones, lipopeptides (daptomycin), aminoglycosides, lincomycins (clindamycin), tetracyclines, sulfonamides, macrolides, monobactams (aztreonam), lipoglycopeptides (dalbavancin), oxazolidinones (linezolid), and pentamidine isethionate

§Rate estimates not calculated because outpatient dispensing of injectable antibiotics is less reliably measured from the denominator data source (prescriptions dispensed from retail and long-term care pharmacies)

Table 3 US Emergency Department (ED) Visits Among Adults for Adverse Events (AEs) from Oral Antibiotics, by Patient Age and Drug Product, 2011–2015

Oral antibiotic product*	Annualized national estimate			
	ED visits for AEs		Rate per 10,000 dispensed prescriptions	
	No.	% (95% CI)	Rate (95% CI)	NNH†
Age 20–34				
Sulfamethoxazole/trimethoprim	11,811	25.1 (21.2–28.9)	29.7 (21.9–37.5)	337
Amoxicillin	6876	14.6 (12.5–16.7)	9.3 (6.7–11.8)	1079
Cephalexin	4672	9.9 (7.7–12.1)	12.6 (8.6–16.7)	792
Azithromycin	3363	7.1 (6.1–8.1)	3.9 (2.9–5.0)	2541
Clindamycin	3219	6.8 (5.7–8.0)	17.6 (12.7–22.5)	568
Ciprofloxacin	2926	6.2 (4.9–7.5)	8.8 (6.1–11.6)	1131
Metronidazole	2716	5.8 (4.4–7.2)	8.9 (6.4–11.4)	1126
Doxycycline	2613	5.5 (4.2–6.9)	7.9 (5.1–10.7)	1265
Amoxicillin/clavulanate	2539	5.4 (4.3–6.5)	7.1 (4.8–9.4)	1415
Penicillin	2211	4.7 (3.8–5.6)	12.5 (9.4–15.5)	802
Levofloxacin	1025	2.2 (1.5–2.9)	10.0 (6.6–13.4)	1001
Nitrofurantoin	941	2.0 (1.4–2.6)	4.5 (2.7–6.2)	2243
Moxifloxacin	520	1.1 (0.7–1.5)	50.0 (30.2–69.8)	200
Clarithromycin	503	1.1 (0.6–1.6)	11.2 (5.1–17.3)	895
Other or unspecified oral antibiotics	2989	6.3 (5.2–7.5)	N/A	
Total for age group	47,120	N/A	N/A	
Age 35–49				
Sulfamethoxazole/trimethoprim	8617	25.8 (22.4–29.3)	21.6 (17.0–26.2)	464
Amoxicillin	3604	10.8 (9.4–12.2)	5.1 (4.1–6.2)	1948
Clindamycin	2929	8.8 (7.4–10.1)	15.2 (11.9–18.5)	658
Ciprofloxacin	2512	7.5 (5.1–10.0)	6.0 (3.9–8.1)	1667
Cephalexin	2411	7.2 (5.7–8.8)	6.7 (5.0–8.5)	1486
Amoxicillin/clavulanate	2302	6.9 (5.4–8.4)	5.2 (3.7–6.6)	1930
Azithromycin	1586	4.8 (3.8–5.7)	1.7 (1.1–2.2)	6057
Doxycycline	1453	4.4 (3.4–5.3)	4.4 (3.1–5.7)	2276
Levofloxacin	1405	4.2 (3.1–5.3)	6.7 (4.5–8.8)	1501
Metronidazole	1349	4.0 (2.9–5.2)	6.4 (4.2–8.5)	1570
Penicillin	1296	3.9 (3.0–4.8)	9.3 (6.5–12.1)	1079
Moxifloxacin	1043	3.1 (2.2–4.1)	42.5 (26.2–58.8)	236
Nitrofurantoin	803	2.4 (1.8–3.0)	5.3 (3.4–7.3)	1871
Cefuroxime	463	1.4 (0.7–2.1)	7.3 (3.2–11.4)	1372
Clarithromycin	434	1.3 (0.6–2.0)	6.0 (2.5–9.5)	1658
Other or unspecified oral antibiotics	2359	7.1 (5.2–9.0)	N/A	
Total for age group	33,340	N/A	N/A	
Age 50–64				
Sulfamethoxazole/trimethoprim	7232	22.7 (20.0–25.3)	16.1 (12.0–20.2)	621
Amoxicillin	3516	11.0 (9.2–12.9)	4.3 (3.2–5.4)	2322
Ciprofloxacin	3484	10.9 (8.9–12.9)	6.0 (4.3–7.7)	1667
Clindamycin	2750	8.6 (7.1–10.2)	11.8 (8.7–14.9)	847
Cephalexin	2553	8.0 (6.2–9.8)	5.8 (4.2–7.4)	1714
Amoxicillin/clavulanate	2289	7.2 (6.0–8.3)	4.8 (3.6–6.0)	2081
Azithromycin	1674	5.2 (4.1–6.4)	1.6 (1.1–2.2)	6082
Levofloxacin	1627	5.1 (4.2–6.0)	4.7 (3.3–6.1)	2127
Doxycycline	1320	4.1 (3.3–5.0)	3.4 (2.5–4.4)	2918
Metronidazole	1116	3.5 (2.5–4.5)	7.1 (5.2–9.0)	1404
Moxifloxacin	1043	3.3 (2.0–4.5)	25.9 (12.1–39.7)	386
Penicillin	966	3.0 (2.3–3.8)	6.9 (4.7–9.2)	1440
Nitrofurantoin	743	2.3 (1.6–3.0)	4.4 (2.8–5.9)	2298
Cefdinir	357	1.1 (0.7–1.6)	3.9 (2.2–5.6)	2545
Other or unspecified oral antibiotics	2317	7.3 (5.4–9.1)	N/A	
Total for age group	31,924	N/A	N/A	
Age ≥ 65				
Sulfamethoxazole/trimethoprim	5638	19.7 (17.6–21.8)	11.4 (8.4–14.4)	877
Ciprofloxacin	3491	12.2 (9.7–14.7)	4.3 (2.9–5.7)	2315
Levofloxacin	2494	8.7 (7.1–10.4)	5.1 (3.8–6.3)	1976
Amoxicillin	2318	8.1 (6.2–10.0)	3.3 (2.3–4.3)	3054
Cephalexin	2132	7.5 (5.9–9.0)	3.9 (2.6–5.1)	2596
Clindamycin	1788	6.2 (4.7–7.8)	8.9 (6.0–11.8)	1125
Nitrofurantoin	1474	5.2 (3.8–6.5)	4.6 (3.4–5.9)	2152
Amoxicillin/clavulanate	1407	4.9 (3.7–6.2)	3.8 (2.6–5.0)	2628
Azithromycin	1254	4.4 (3.4–5.3)	1.5 (1.0–2.0)	6641

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Table 3. (continued)

Oral antibiotic product*	Annualized national estimate			
	ED visits for AEs		Rate per 10,000 dispensed prescriptions	
	No.	% (95% CI)	Rate (95% CI)	NNH†
Moxifloxacin	1156	4.0 (2.7–5.4)	23.2 (13.7–32.8)	430
Metronidazole	978	3.4 (2.4–4.5)	6.1 (3.8–8.4)	1634
Doxycycline	946	3.3 (2.2–4.4)	2.6 (1.5–3.7)	3856
Cefdinir	486	1.7 (0.9–2.5)	5.9 (2.4–9.4)	1687
Penicillin	446	1.6 (0.7–2.4)	5.4 (2.1–8.8)	1845
Cefuroxime‡	431	1.5 (0.6–2.4)	3.6 (1.2–6.1)	2747
Clarithromycin	349	1.2 (0.7–1.8)	6.6 (3.0–10.2)	1516
Other or unspecified oral antibiotics	2809	9.8 (8.2–11.4)	N/A	
Total for age group	28,617	N/A	N/A	

Estimates of ED visits for antibiotic AEs are from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project, CDC. Estimates of dispensed prescriptions (from retail and long-term care pharmacies) are from QuintilesIMS National Prescription Audit (2011–2015)

CI confidence interval, N/A not applicable, NNH number needed to harm

**Drug products shown if implicated in > 1% of estimated ED visits for oral antibiotic AEs within each age group. ED visits that involve two different drug products are included in estimates for each product*

†Number needed to harm calculated as 10,000 multiplied by the reciprocal of the ED visit rate

‡Coefficient of variation for ED visit estimate > 30%

Adverse Event Manifestations

Mild allergic reactions (e.g., rash, pruritus) were the most commonly documented adverse event manifestation across all oral antibiotic classes (Table 4), and accounted for over two thirds of estimated visits involving sulfonamides (69.3%). Moderate-to-severe allergic reactions (e.g., anaphylaxis, angioedema) occurred in approximately one quarter of estimated ED visits for AEs involving oral quinolones (26.2%), and allergic reactions of any severity accounted for 87.2% (95% CI, 84.7–89.7%) of estimated ED visits for AEs involving oral sulfonamides. Gastrointestinal disturbance (e.g., nausea, diarrhea, abdominal pain) was documented in approximately one quarter of estimated visits involving oral nitroimidazoles (metronidazole) (28.3%), macrolides (27.0%), and tetracyclines (25.4%).

Oral sulfonamides had the highest estimated rates of ED visits for mild allergic reactions (13.4 visits per 10,000 dispensed prescriptions; 95% CI, 10.0–16.8) and moderate-to-severe allergic reactions (3.5 visits per 10,000 dispensed prescriptions; 95% CI, 2.6–4.3). While the overall rate of ED visits for moderate-to-severe allergic reactions to oral quinolones (1.7 visits per 10,000 dispensed prescriptions; 95% CI, 1.3–2.1) was lower than that for sulfonamides, moxifloxacin had significantly higher estimated rates of ED visits for moderate-to-severe allergic reactions (9.7 visits per 10,000 dispensed prescriptions; 95% CI, 5.9–13.4) compared with sulfonamides. The estimated rate of ED visits for moderate-to-severe allergic reactions to moxifloxacin was significantly higher than rates for the other oral quinolones levofloxacin (1.7 per 10,000 dispensed prescriptions; 95% CI, 1.3–2.2) and ciprofloxacin (1.3 per 10,000 dispensed prescriptions; 95% CI, 1.0–1.6).

DISCUSSION

Using nationally representative public health surveillance data, an estimated 145,490 ED visits were made by adults for antibiotic AEs annually from 2011 through 2015, making antibiotics a leading cause of AEs, accounting for approximately 14% of all ED visits by adults for AEs from systemically administered medications. These findings are similar to those from a decade ago,[21] highlighting the need for continued emphasis on avoiding acute adverse effects of antibiotics, in addition to the individual and community risks from antimicrobial resistance. Specific findings from this study include updated national estimates of the numbers and rates of ED visits for AEs from specific antibiotics stratified by patient age, which can be used by clinicians to optimize the risk-benefit assessment for patients.

The key to reducing the number of antibiotic AEs is avoiding unnecessarily prescribing antibiotics. Allergic reactions were the most common cause (74.3%) of ED visits by adults for antibiotic AEs, while supratherapeutic effects or excessive doses were the most common cause of AEs from other medications. Unlike supratherapeutic effects and overdoses which can be prevented by laboratory monitoring and appropriate dosing, most allergic reactions can only be prevented by avoiding exposure altogether.

Antibiotic adverse events are a particularly important issue for young adults. Young adults were involved in one third of antibiotic AE visits and had double the per-prescription rate of ED visits for antibiotic AEs compared with older adults (aged ≥ 65 years). Higher rates of antibiotic AEs among younger compared to older adults may be related to immune senescence decreasing the likelihood of allergic reactions as patients age.[29] Lower proportions of antibiotic ED visits among older adults are likely due to higher use of other medications with high rates of ED visits for AEs such as anticoagulants, diabetes drugs, and

Table 4 US Emergency Department (ED) Visits Among Adults for Adverse Events (AEs) from Oral Antibiotics, by Drug Class and AE Manifestation, 2011–2015

Oral antibiotic class*	Annualized national estimate			
	ED visits for AEs		Rate per 10,000 dispensed prescriptions	
	No.	% (95% CI)	Rate (95% CI)	NNH[¶]
Sulfonamides				
Mild allergic reaction[†]	23,359	69.3 (65.5–73.0)	13.4 (10.0–16.8)	746
Moderate-to-severe allergic reaction[‡]	6061	18.0 (14.5–21.4)	3.5 (2.6–4.3)	2873
Gastrointestinal disturbance[§]	2915	8.6 (6.1–11.2)	1.7 (1.0–2.3)	5974
Other or unspecified effect	868	2.6 (1.6–3.5)	0.5 (0.3–0.7)	20,060
Neurological or psychiatric effect[‖]	522	1.5 (1.0–2.1)	0.3 (0.2–0.4)	33,363
Penicillins				
Mild allergic reaction[†]	17,436	57.5 (52.5–62.6)	3.4 (2.7–4.0)	2958
Moderate-to-severe allergic reaction[‡]	6982	23.0 (20.5–25.6)	1.4 (1.1–1.6)	7385
Gastrointestinal disturbance[§]	4821	15.9 (11.6–20.2)	0.9 (0.5–1.3)	10,695
Other or unspecified effect	878	2.9 (1.9–3.9)	0.2 (0.1–0.3)	58,737
Neurological or psychiatric effect[‖]	–	–	–	–
Quinolones				
Mild allergic reaction[†]	9847	43.2 (38.9–47.5)	2.9 (2.2–3.6)	3469
Moderate-to-severe allergic reaction[‡]	5969	26.2 (21.6–30.8)	1.7 (1.3–2.1)	5723
Gastrointestinal disturbance[§]	4474	19.6 (12.8–26.5)	1.3 (0.7–1.9)	7635
Other or unspecified effect	1105	4.9 (3.7–6.0)	0.3 (0.2–0.4)	30,929
Neurological or psychiatric effect[‖]	1376	6.0 (4.2–7.9)	0.4 (0.3–0.5)	24,834
Cephalosporins				
Mild allergic reaction[†]	9265	59.3 (53.2–65.5)	3.9 (2.9–4.9)	2549
Moderate-to-severe allergic reaction[‡]	3382	21.7 (17.7–25.7)	1.4 (1.1–1.8)	6983
Gastrointestinal disturbance[§]	2296	14.7 (9.7–19.7)	1.0 (0.5–1.4)	10,286
Other or unspecified effect	426	2.7 (1.5–4.0)	0.2 (0.1–0.3)	55,475
Neurological or psychiatric effect[‖]	–	–	–	–
Lincomycins (clindamycin)				
Mild allergic reaction[†]	6351	59.4 (55.1–63.8)	7.8 (6.2–9.5)	1275
Moderate-to-severe allergic reaction[‡]	1862	17.4 (12.3–22.6)	2.3 (1.6–3.0)	4348
Gastrointestinal disturbance[§]	1930	18.1 (12.4–23.7)	2.4 (1.3–3.5)	4196
Other or unspecified effect	413	3.9 (2.2–5.5)	0.5 (0.3–0.7)	19,618
Neurological or psychiatric effect[‖]	–	–	–	–
Macrolides				
Mild allergic reaction[†]	4499	43.8 (38.3–49.2)	1.1 (0.8–1.5)	8709
Moderate-to-severe allergic reaction[‡]	2353	22.9 (18.8–27.0)	0.6 (0.5–0.8)	16,650
Gastrointestinal disturbance[§]	2775	27.0 (19.3–34.7)	0.7 (0.4–1.0)	14,116
Other or unspecified effect	426	4.1 (2.1–6.2)	0.1 (0.1–0.2)	91,956
Neurological or psychiatric effect[‖]	–	–	–	–
Tetracyclines				
Mild allergic reaction[†]	3516	47.6 (39.8–55.4)	2.0 (1.4–2.7)	4885
Moderate-to-severe allergic reaction[‡]	1164	15.8 (10.2–21.3)	0.7 (0.4–0.9)	14,752
Gastrointestinal disturbance[§]	1874	25.4 (19.0–31.7)	1.1 (0.6–1.6)	9167
Other or unspecified effect	561	7.6 (4.8–10.4)	0.3 (0.2–0.5)	30,621
Neurological or psychiatric effect[‖]	–	–	–	–
Nitroimidazoles (metronidazole)				
Mild allergic reaction[†]	2767	44.9 (37.6–52.2)	3.3 (2.4–4.2)	3016
Moderate-to-severe allergic reaction[‡]	1219	19.8 (14.9–24.7)	1.5 (1.1–1.9)	6842
Gastrointestinal disturbance[§]	1742	28.3 (20.9–35.7)	2.1 (1.2–3.0)	4789
Other or unspecified effect	271	4.4 (2.0–6.8)	0.3 (0.2–0.5)	30,840
Neurological or psychiatric effect[‖]	–	–	–	–
Nitrofurans (nitrofurantoin)				
Mild allergic reaction[†]	2220	56.0 (48.6–63.5)	2.6 (1.9–3.3)	3825
Moderate-to-severe allergic reaction[‡]	789	19.9 (14.5–25.4)	0.9 (0.6–1.2)	10,767
Gastrointestinal disturbance[§]	767	19.4 (12.7–26.0)	0.9 (0.5–1.3)	11,066
Other or unspecified effect	–	–	–	–
Neurological or psychiatric effect[‖]	–	–	–	–

Estimates of ED visits for antibiotic AEs are from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project, CDC. Estimates of dispensed prescriptions (from retail and long-term care pharmacies) are from QuintilesIMS National Prescription Audit (2011–2015). Unreliable estimates due to fewer than 20 surveillance cases are indicated by en dash (–) and not shown

CI confidence interval, N/A not applicable, NNH number needed to harm

**Adverse event manifestations were categorized in a mutually exclusive and hierarchical manner based on severity of presentation—for example, visits with both anaphylaxis and diarrhea would be classified as moderate-to-severe allergic reaction*

[†]*Includes dermatitis, drug eruption, erythema, flushing, localized or peripheral edema, pruritus, rash, and urticaria*

[‡]*Includes anaphylaxis, angioedema, erythema multiforme, exfoliative dermatitis, facial-pharyngeal-genital edema, hyperhidrosis or chills, hypersensitivity vasculitis, allergy-related respiratory compromise (e.g., bronchospasm, dyspnea, hyperventilation, tachypnea, throat tightness, wheezing), serum sickness, and Stevens-Johnson syndrome*

[§]*Includes abdominal discomfort, appetite change, constipation, diarrhea, dyspepsia, gastrointestinal irritation (e.g., enteritis, colitis, pancreatitis), gastrointestinal bleeding (e.g., hematemesis, melena), and nausea/vomiting*

[‖]*Includes dizziness/syncope, headache, motor impairment (e.g., dystonia, movement disorders, muscle weakness), sensory impairment (e.g., balance/coordination disorders, paresthesia, visual disturbance), and mood disturbance (e.g., anxiety, insomnia, irritability)*

[¶]*Number needed to harm calculated as 10,000 multiplied by the reciprocal of the ED visit rate*

chemotherapeutic agents,[22] and drug-drug interactions potentiated by antibiotics may be attributed solely to the higher risk non-antibiotic agent. For example, overanticoagulation from interaction of sulfamethoxazole/trimethoprim and warfarin may be attributed only to warfarin in the ED setting.

Patient expectations for antibiotics, particularly expectations of young adults, might be tempered with specific information on antibiotic AEs. In a focus group evaluating knowledge and attitudes towards antibiotic AEs, most younger adults (age range, 23–53) reported that AEs were "not a significant issue" but also reported never having discussed the potential for AEs with their provider.[30] When provided information about AEs, however, messages about AEs were found to resonate with younger parents, particularly mothers of young children.[30] If specific data about acute harms from antibiotics can modify antibiotic safety assumptions of younger patients, targeting educational campaigns to these patients, who are more likely than older adults to be treated in the ED for antibiotic AEs and less likely to develop complications from infections,[31,32] may be an efficient strategy to improve antibiotic prescribing and reduce AEs.

ED visits for antibiotic AEs were disproportionately made by women (71.8%); however, this finding is consistent with higher ED utilization in general by women[33] and higher ED utilization by women for other types of adverse drug events,[22] so it is uncertain if targeting antibiotic safety messages to women would be an effective approach to reducing antibiotic AEs.[34–37]

Estimates of the number needed to harm (NNH) for individual antibiotics by patient age can also inform clinician decision-making when selecting among agents with similar activity. Among young adults, for example, the NNH for ED visits for AEs from oral antibiotics ranged more than 12-fold, from an estimated 1 in 200 moxifloxacin prescriptions to 1 in 2541 azithromycin prescriptions. Although the overall rates of ED visits for AEs from oral antibiotics were lower for older adults, the range in rates was greater, with more than 15-fold difference in rates between moxifloxacin and azithromycin.[38,39]

Efforts to improve antibiotic prescribing such as the Centers for Disease Control and Prevention's *Be Antibiotics Aware: Smart Use, Best Care* educational program seek to bridge the communication and education gap with patients and clinicians.[3] Engaging patients with data on rates of acute harms can help reinforce that there are downsides of antibiotic prescription, particularly for patients who may be unaware of or not understand the distinction between a viral and bacterial illness. However, for all patients, education on antibiotic use should include communicating the side effects and frequency of potential harms from antibiotic use.[40] Providing clinicians with information on acute harms from antibiotics is also important, as clinicians are more likely to prescribe appropriately if they understand that the antibiotics can cause harm.[41]

Public health surveillance data have limitations. First, these data likely underestimate the total burden of antibiotic AEs because such events often can be managed outside the ED setting. ED-based surveillance is not the best method to detect antibiotic AEs with subacute onset, such as fluoroquinolone-associated disability syndromes, medication interactions, or indirect and long-term harms such as those resulting from antibiotic resistance. Second, adverse events were identified according to the data available at the time of the ED visit. Thus, *Clostridium difficile* infections were rarely identified since this diagnosis is not typically confirmed during the course of the ED visit. Third, because medical history and prior treatment information is limited in the ED medical record, the contribution of inappropriate prescribing (e.g., guideline-discordant prescription of antibiotics for acute bronchitis) could not be directly assessed. Fourth, specific types of reactions to specific antibiotics (e.g., admissions for moderate-to-severe allergic reactions to moxifloxacin) were not frequent enough to calculate reliable estimates. Fifth, these national data could not be stratified at the regional or state level, owing to surveillance system sampling design. Sixth, rate calculations were based on QuintilesIMS dispensed prescription data obtained from retail and long-term care pharmacies only and did not include mail order prescriptions; however, mail order was not likely a major source of systemically administered antibiotic prescriptions.

CONCLUSION

Antibiotic AEs are a common cause of ED visits by adults for adverse drug events and represent an important safety issue. Quantification of acute harms associated with taking specific antibiotics for specific patient populations, such as younger adults, can provide additional information to help clinicians weigh the risks versus benefits when making the decision to prescribe or not prescribe antibiotics. Quantification of AE rates is also important for facilitating clinician communication about the risks and benefits with patients and may modify patient preferences and expectations for antibiotics as well. Efforts to improve antibiotic prescribing are central to patient safety, to both avoid unnecessary adverse events and optimize treatment of infections.

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Author Contributions *The authors thank Dr. Nina Weidle from Eagle Medical Services, LLC (contractor to CDC), Ms. Katie Rose, Ms. Sandra Goring, Ms. Arati Baral, and Mr. Alex Tocitu, from Northrop Grumman (contractor to CDC), for assistance with data coding and programming. The authors also thank Mr. Tom Schroeder, Ms. Elenore Sonski, Mr. Herman Burney, and data abstractors from the US Consumer Product Safety Commission, for their assistance with data acquisition.*

Funding *This study was funded by the Federal government of the USA.*

Compliance with Ethical Standards:

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

Disclaimer: *Federal government employees had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. However, the findings in and conclusions of this study are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.*

Prior Presentations: *None.*

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