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Emergency Department Visits for Antibiotic-Associated Adverse Events

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(See the editorial commentary by Linder on pages 744–6)

Background. Drug-related adverse events are an underappreciated consequence of antibiotic use, and the national magnitude and scope of these events have not been studied. Our objective was to estimate and compare the numbers and rates of emergency department (ED) visits for drug-related adverse events associated with systemic antibiotics in the United States by drug class, individual drug, and event type.

Methods. We analyzed drug-related adverse events from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (2004–2006) and outpatient prescriptions from national sample surveys of ambulatory care practices, the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey (2004–2005).

Results. On the basis of 6614 cases, an estimated 142,505 visits (95% confidence interval [CI], 116,506–168,504 visits) annually were made to US EDs for drug-related adverse events attributable to systemic antibiotics. Antibiotics were implicated in 19.3% of all ED visits for drug-related adverse events. Most ED visits for antibiotic-associated adverse events were for allergic reactions (78.7% of visits; 95% CI, 75.3%–82.1% of visits). One-half of the estimated ED visits were attributable to penicillins (36.9% of visits; 95% CI, 34.7%–39.2% of visits) and cephalosporins (12.2%; 95% CI, 10.9%–13.5%). Among commonly prescribed antibiotics, sulfonamides and clindamycin were associated with the highest rate of ED visits (18.9 ED visits per 10,000 outpatient prescription visits [95% CI, 13.1–24.7 ED visits per 10,000 outpatient prescription visits] and 18.5 ED visits per 10,000 outpatient prescription visits [95% CI, 12.1–25.0 ED visits per 10,000 outpatient prescription visits], respectively). Compared with all other antibiotic classes, sulfonamides were associated with a significantly higher rate of moderate-to-severe allergic reactions (4.3% [95% CI, 2.9%–5.8%] vs. 1.9 % [95% CI, 1.5%–2.3%]), and sulfonamides and fluoroquinolones were associated with a significantly higher rate of neurologic or psychiatric disturbances (1.4% [95% CI, 1.0%–1.7%] vs. 0.5% [95% CI, 0.4%–0.6%]).

Conclusions. Antibiotic-associated adverse events lead to many ED visits, and allergic reactions are the most common events. Minimizing unnecessary antibiotic use by even a small percentage could significantly reduce the immediate and direct risks of drug-related adverse events in individual patients.

Antibiotics are among the most frequently used medications in the United States. Annually, antibiotics are prescribed to an estimated 16% of patients during ambulatory care visits [1], and pharmaceutical manufacturers spend >$1 billion promoting antibiotics [2]. Antibiotic resistance resulting from excessive and injudicious use of antibiotics is perceived to be a serious threat to public health [3–5]. Consequently, efforts to promote judicious antibiotic use have focused largely on the long-term societal impact of antibiotic resistance [5–7]. The more immediate risks of antibiotic use in the community—namely, adverse effects—are generally considered to be infrequent and mild. National campaigns and communication strategies aimed at reducing inappropriate antibiotic use have not traditionally incorporated messages that address these more direct and short-term risks of antibiotic use [8, 9]. To better characterize the scope and burden of serious antibiotic-associated adverse events, we used nationally representative surveillance data from the United States to

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describe the frequency, rate, and nature of emergency department (ED) visits for adverse events caused by systemic antibiotics.

METHODS

National estimates of the number of ED visits for drug-related adverse events were based on data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, a national stratified probability sample of 63 hospitals with a minimum of 6 beds and a 24-h ED in the United States and its territories [10–12]. The NEISS-CADES project, which has been described in detail elsewhere, is a joint effort of the Centers for Disease Control and Prevention, the US Consumer Product Safety Commission, and the US Food and Drug Administration [11, 12]. In brief, trained coders located at each participating hospital review clinical records of every ED visit to identify physician-diagnosed drug-related adverse events, to report up to 2 medications implicated in each adverse event, and to record narrative descriptions of the incident. We defined a drug-related adverse event as an incident ED visit by a patient from 1 January 2004 through 31 December 2006 for a condition that the treating physician explicitly attributed to the use of an antibiotic or for an antibiotic-specific adverse effect. Topical antibiotics (i.e., dermatologic, ophthalmic, otic, or vaginal formulations) were excluded. Adverse events were categorized as adverse effects (defined as undesirable pharmacologic or idiosyncratic effects, such as diarrhea, dizziness, and headache, while a patient was receiving therapy at recommended doses), allergic reactions (defined as immunologically mediated effects, such as rash and anaphylaxis), unintentional overdoses (defined as toxic effects associated with excess dose, such as effects attributable to unintentionally ingesting more than the prescribed dose), unintentional exposures (defined as unintentional ingestion of a medication, such as a child finding and ingesting an antibiotic), and other effects (defined as adverse events not attributable to allergic reactions, adverse effects, or unintentional overdoses, such as injection site reactions and choking). On the basis of the diagnoses and symptoms provided for each case and with use of methods described elsewhere [12], the manifestations associated with each adverse event were categorized into various conditions. For simplification of presentation, adverse event conditions were assigned in mutually exclusive and hierarchical fashion.

National estimates of the number of outpatient prescription visits (i.e., ambulatory care visits during which an antibiotic was prescribed) were based on the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) [13–16]. The NAMCS and NHAMCS are national sample surveys that provide information about the provision and use of ambulatory medical care services, including physician office, hospital outpatient department, and ED visits, in the United States and have been used previously for estimates of the frequency of antibiotic prescribing [17–20]. We used public-use data from the period 2004–2005 (the most recent years available) to identify ambulatory care visits at which treatment with a systemic antibiotic was either started or continued by using a combination of the 4-digit National Drug Code Directory class, brand name, generic name (for single-ingredient drug products), and individual active ingredients (for multi-ingredient drug products). We estimated the number of outpatient prescription visits from NAMCS and NHAMCS for all systemic antibiotics that were implicated in an ED visit for a drug-related adverse event in the NEISS-CADES project from 2004 through 2006.

Each NEISS-CADES, NAMCS, and NHAMCS visit was assigned a sample weight on the basis of the inverse probability of selection, adjusted for nonresponse, population changes, and in NAMCS and NHAMCS, weight smoothing (i.e., adjustments for extremes in final weights of visits) [10, 21, 22]. We calculated national estimates of the frequency of ED and prescription visits and corresponding 95% CIs using the Surveymeans procedure in SAS, version 9.1 (SAS), to account for the sample weights and complex sample designs. We divided frequency estimates and 95% CIs by 3 for the period 2004–2006 (NEISS-CADES) and by 2 for the period 2004–2005 (NAMCS, NHAMCS), to obtain annual estimated frequencies. Estimates based on small numbers of cases (<20 cases for NEISS-CADES and <30 cases for NAMCS and NHAMCS) or with a coefficient of variation >30% were considered to be statistically unstable and are not presented here.

We calculated rates by dividing the estimated number of ED visits for drug-related adverse events (from NEISS-CADES) by the estimated number of outpatient visits at which that antibiotic or antibiotic class was prescribed (from NAMCS and NHAMCS). The 95% CI for each rate incorporated variance estimates for both numerator and denominator components of the corresponding rate estimate [23]. Because these components were calculated from separate surveillance systems, they were treated as independent and as having zero covariance [23].

RESULTS

On the basis of 6614 cases, an estimated 142,505 ED visits (95% CI, 116,506-168,504 visits) annually occurred because of antibiotic-associated adverse events from 2004 through 2006 (table 1). Systemic antibiotics were implicated in 19.3% of all ED visits for drug-related adverse events. Persons aged 15–44 years accounted for an estimated 41.2% of ED visits. Infants (age, <1 year) accounted for only an estimated 6.3% of ED visits; however, after accounting for prescription frequency, the estimated rate of ED visits for adverse events attributable to an-

Table 1. Number of cases and national estimates of emergency department (ED) visits for adverse events associated with systemic antibiotics, by patient and case characteristics—United States, 2004–2006.

Characteristic	ED visits for adverse events		
	No. of cases	Estimated annual no. of visits	Estimated annual visits, % (95% CI)
Age, years			
<1	545	8982	6.3 (5.3–7.3)
1–4	976	16,462	11.5 (10.1–13.0)
5–14	656	11,559	8.1 (7.1–9.1)
15–44	2577	58,711	41.2 (38.7–43.7)
45–64	1143	27,607	19.4 (18.0–20.7)
65–79	507	13,546	9.5 (8.4–10.6)
⩾80	210	5638	4.0 (3.3–4.7)
Sex			
Female	4263	95,444	67.0 (65.3–68.7)
Male	2351	47,061	33.0 (31.3–34.7)
Mechanism of adverse event[a]			
Adverse effect	1193	27,298	19.2 (15.8–22.6)
Allergic reaction	5265	112,116	78.7 (75.3–82.1)
Unintentional overdose	72	1321	0.9 (0.7–1.2)
Unintentional exposure	32	540	0.4 (0.2–0.6)
Other	52	1231	0.9 (0.7–1.6)
Disposition			
Admitted, observed, or transferred	372	8738	6.1 (4.6–7.7)
Treated and released or left against medical advice	6242	133,767	93.9 (92.3–95.4)
No. of implicated medications			
1	5784	125,882	88.3 (86.5–90.1)
⩾2	830	16,623	11.7 (9.9–13.5)
No. of concurrent medications			
None listed	4024	86,904	61.0 (55.0–67.0)
1–3	1907	38,628	27.1 (23.0–31.2)
4–6	477	11,554	8.1 (6.4–9.8)
⩾7	206	5419	3.8 (2.8–4.8)
Total	6614	142,505	100

NOTE. Estimates are based on the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (2004–2006).

[a] Adverse effects refer to undesirable pharmacologic or idiosyncratic effects that occur while the patient is receiving therapy at recommended doses (e.g., diarrhea, dizziness, and headache); allergic reactions refer to immunologically mediated effects (e.g., rash and anaphylaxis); unintentional overdoses refer to toxic effects linked to excess dose (e.g., because of unintentionally ingesting more than the prescribed dose); unintentional exposures (e.g., unintentional ingestion of a medication, such as a child finding and ingesting an antibiotic); and other effects refer to adverse events not associated with allergic reactions, adverse effects, or unintentional overdoses (e.g., injection site reactions and choking).

tibiotics was highest in this age group (15.9 ED visits per 10,000 outpatient prescription visits; 95% CI, 10.6–21.1 ED visits per 10,000 outpatient prescription visits). More than two-thirds of estimated ED visits for antibiotic-associated adverse events were by female patients, and the estimated rate of ED visits was significantly higher among female patients than among male patients (12.5 ED visits per 10,000 outpatient prescription visits [95% CI, 9.9–15.1 ED visits per 10,000 outpatient prescription visits] vs. 7.9 ED visits per 10,000 outpatient prescription visits [95% CI, 6.3–9.5 ED visits per 10,000 outpatient prescription visits]). An estimated 78.7% of drug-related adverse events were attributed to allergic reactions; 6.1% of drug-related adverse events led to hospitalization.

Together, penicillins and cephalosporins were implicated in one-half of the estimated ED visits for antibiotic-associated adverse events (36.9% and 12.2% of visits, respectively) (table 2). Among antibiotics commonly used in the community, the estimated rates of ED visits for drug-related adverse events were

Table 2. Number of cases and national estimates of emergency department (ED) visits for adverse events associated with systemic antibiotics, by drug—United States, 2004–2006.

Drugs class, drug	ED visits for adverse events		Estimated annual outpatient prescription visits, no. in thousands (%)	Estimated annual no. of ED visits per 10,000 outpatient prescription visits (95% CI)
	No. of cases	Estimated annual no. of visits (%)		
Penicillins				
All	2604	52,654 (36.9)	40,653 (29.8)	13.0 (10.3–15.6)
Amoxicillin and penicillin[a]	2130	42,340 (29.7)	27,276 (20.0)	15.5 (12.3–18.7)
Amoxicillin-clavulanate	429	9409 (6.6)	12,002 (8.8)	7.8 (5.5–10.2)
Cephalosporins				
All	801	17,376 (12.2)	28,406 (20.8)	6.1 (4.5–7.7)
Cephalexin	434	9935 (7.0)	12,988 (9.5)	7.6 (5.5–9.8)
Cefdinir	164	2506 (1.8)	4226 (3.1)	5.9 (3.3–8.6)
Ceftriaxone	55[b]	1085 (0.8)	5483 (4.0)	2.0 (1.1–2.9)
Cefuroxime	48[b]	1276 (0.9)	1072 (0.8)	11.9 (4.9–18.9)
Cefprozil	44	1184 (0.8)	1832 (1.3)	6.5 (3.0–10.0)
Fluoroquinolones				
All	791	19,279 (13.5)	20,913 (15.3)	9.2 (7.0–11.5)
Levofloxacin	337	8342 (5.9)	9425 (6.9)	8.9 (6.2–11.5)
Ciprofloxacin	219	4970 (3.5)	7709 (5.7)	6.4 (4.5–8.4)
Moxifloxacin	182	4665 (3.3)	2253 (1.7)	20.7 (11.9–29.5)
Gatifloxacin	38	875 (0.6)	1351 (1.0)	6.5 (2.8–10.2)
Sulfonamides and trimethoprim[c]				
All	756	16,865 (11.8)	8629 (6.5)	18.9 (13.1–24.7)
Sulfamethoxazole-trimethoprim	718	16,068 (11.3)	8577 (6.3)	18.7 (12.9–24.6)
Macrolides and ketolides				
All	602	13,704 (9.6)	26,574 (19.6)	5.1 (3.8–6.4)
Azithromycin	371	8491 (6.0)	18,822 (13.8)	4.5 (3.2–5.8)
Erythromycin	100[b]	2545 (1.8)	2540 (1.9)	10.0 (5.4–14.6)
Clarithromycin	102[b]	2025 (1.4)	5109 (3.7)	4.0 (2.2–5.7)
Lincosamides (clindamycin)	204	4419 (3.1)	2385 (1.8)	18.5 (12.1–25.0)
Tetracyclines				
All	187	4488 (3.1)	8550 (6.3)	5.2 (3.7–6.8)
Doxycycline	131	3209 (2.3)	5543 (4.1)	5.8 (3.9–7.7)
Metronidazole	125	2620 (1.8)	3456 (2.5)	7.6 (5.1–10.1)
Nitrofurans (nitrofurantoin)	96	2226 (1.6)	2306 (1.7)	9.7 (5.8–13.5)
Vancomycin and linezolid				
All	52	1166 (0.8)	484 (0.4)	24.1 (10.9–37.3)
Vancomycin	45	963 (0.7)	444 (0.3)	21.7 (8.9–34.4)
Unspecified and other antibiotics[d]	214	4362 (3.1)	2972 (2.2)	14.7 (9.6–19.8)
Two antibiotics from different drug classes[e]	182	3345 (2.3)	8595	…

NOTE. Estimates of the number of adverse events are based on the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (2004–2006). Estimates of the number of outpatient prescription visits are based on the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey (2004–2005). Individual drugs are shown in the table only if they were implicated in ⩾0.5% of estimated emergency department visits for antibiotic-associated adverse events. For example, cefaclor was counted under cephalosporins but was implicated in only 18 patients (estimated percentage of ED visits, 0.4%) and, therefore, is not shown.

[a] Penicillin includes penicillin V and penicillin G salts.

[b] Because each case was individually weighted, categories with a similar number of cases may not reflect identical national estimates.

[c] Sulfonamides include sulfamethoxazole-trimethoprim, sulfisoxazole, and sulfisoxazole-erythromycin.

[d] For ED visits for adverse events, "other" antibiotics include imipenem-cilastatin (3 cases), ertapenem (1 case), gentamicin (3 cases), tobramycin (1 case), and daptomycin (1 case). For outpatient prescription visits, "other" antibiotics include carbapenems, aminoglycosides (excluding neomycin sulfate), and daptomycin.

[e] Outpatient prescription visits when >1 antibiotic from different drug classes were mentioned were included in the count for each antibiotic class.

highest for sulfonamides (18.9 ED visits per 10,000 outpatient prescription visits) and clindamycin (18.5 ED visits per 10,000 outpatient prescription visits). Within most antibiotic classes, the rates of ED visits for adverse events attributable to individual drugs were similar. However, the rate of ED visits for adverse events attributable to amoxicillin or penicillin was significantly higher than that for adverse events attributable to amoxicillin-clavulanate (15.5 ED visits per 10,000 outpatient prescription visits [95% CI, 12.3–18.7 ED visits per 10,000 outpatient prescription visits] vs. 7.8 ED visits per 10,000 outpatient prescription visits [95% CI, 5.5–10.2 ED visits per 10,000 outpatient prescription visits]), and the rate of ED visits for adverse events attributable to moxifloxacin was significantly higher than that for adverse events attributable to any other fluoroquinolone (table 2). Overall, the rate of ED visits for antibiotic-associated adverse events was 10.5 ED visits per 10,000 outpatient prescription visits (95% CI, 8.3–12.6 ED visits per 10,000 outpatient prescription visits).

Among ED visits for adverse events attributed only to 1 antibiotic or 2 antibiotics from the same class, the most common drug-related adverse event conditions were allergic reactions (table 3). Sulfonamides were associated with a significantly higher rate of moderate-to-severe allergic reactions, compared with all other antibiotic classes combined (4.3% [95% CI, 2.9%–5.8%] vs. 1.9% [95% CI, 1.5%–2.3%]). The rate of mild allergic reactions was significantly higher with penicillins, sulfonamides, and clindamycin than with all other antibiotic classes combined (7.8% [95% CI, 6.2%–9.3%] vs. 2.8% [95% CI, 2.2%–3.4%]). The rate of gastrointestinal disturbances was highest with clindamycin (3.0%; 95% CI, 1.5%–4.6%), but this rate was not significantly different from the rate with all other antibiotic classes. Sulfonamides and fluoroquinolones were associated with significantly higher rates of neurologic or psychiatric effects than were all other antibiotic classes combined (1.4% [95% CI, 1.0%–1.7%] vs. 0.5% [95% CI, 0.4%–0.6%]). Sulfonamides and fluoroquinolones were also associated with the highest rates of hospitalization (1.0% [95% CI, 0.5%–1.6%] and 0.9% [95% CI, 0.5%–1.2%]), but rates of hospitalization were not significantly different among classes.

DISCUSSION

This investigation was the first that we are aware of to use timely, nationally representative surveillance data to estimate and compare the numbers and rates of adverse events attributable to systemic antibiotics by drug class, individual drug, and event type. We estimated that adverse events attributable to antibiotics caused >142,000 ED visits per year, and nearly four-fifths of these events were allergic reactions. The overall rate of ED visits for antibiotic-associated adverse events (10.5 ED visits per 10,000 outpatient prescription visits) was higher than expected. The rate of ED visits for antibiotic-associated adverse events is one-half of the rate of ED visits for adverse events attributable to "high-risk" medications, such as warfarin, insulin, and digoxin (20.6 ED visits per 10,000 outpatient prescription visits); however, the rate of ED visits for antibiotic-associated adverse events is 3 times higher than that for adverse events attributable to some anticoagulant and antiplatelet agents (e.g., aspirin and clopidogrel), oral hypoglycemics (e.g., metformin), and some narrow therapeutic index agents (e.g., phenytoin and lithium; rate for all of these drug classes combined, 3.3 ED visits per 10,000 outpatient prescription visits) [24].

Previous studies using NAMCS, NHAMCS, and NEISS-CADES data have estimated that antibiotics cause ~19% of ambulatory care visits [25] and 18% of ED visits [12] for drug-related adverse events. However, these studies did not provide detailed comparisons among antibiotic classes and drugs, account for antibiotic prescribing frequency, or describe the nature of antibiotic-associated adverse events. More-detailed studies of antibiotic-associated adverse events have been largely limited to studies involving hospitalized patients, spontaneous reports of adverse drug reactions attributable to a single antibiotic or antibiotic class, or studies of specific adverse events [26–30].

We found that nearly 80% of ED visits for antibiotic-associated adverse events among patients receiving ambulatory care were the result of allergic reactions. This finding is in contrast to those for other medication classes that cause many ED visits for drug-related adverse events (e.g., anticoagulants, antidiabetics, and anticonvulsants), which primarily result from medication errors and overdoses [12, 24]. Although medication errors and overdoses can be prevented by improving administration and monitoring, most allergic reactions can only be prevented by avoiding exposure to a drug. We could not assess the appropriateness of antibiotic prescribing from these data; however, more than one-half of the estimated 100 million antibiotic prescriptions written in the community each year for respiratory tract infections may be unnecessary [17, 18, 31]. Although the risk of an ED visit for an antibiotic-associated adverse event is small for an individual patient, when antibiotics are commonly prescribed for indications for which they have no benefit, the burden of preventable adverse events in the population is great. Thus, efforts to mitigate the burden of untoward effects of antibiotics should focus on minimizing excessive use of antibiotics, because decreasing inappropriate antibiotic use by even a small percentage could substantially reduce the number of patients who experience antibiotic-associated adverse events.

Previous studies have found that, when both infectious diseases specialists and general physicians prescribe broad-spectrum antibiotics, such as fluoroquinolones, they often cite perceived advantages of these agents in terms of their safety profiles

Table 3. Number of cases and national estimates of the rate of emergency department (ED) visits for adverse events associated with a single systemic antibiotic class, by adverse event condition—United States, 2004–2006.

	Adverse event condition									
	Moderate-to-severe allergic reaction[b]		Neurologic and/or psychiatric		Gastrointestinal		Mild allergic reaction[c]		Other or unspecified effect	
Drug class[a]	No. of cases	Estimated no. of ED visits per 10,000 OPV (95% CI)	No. of cases	Estimated no. of ED visits per 10,000 OPV (95% CI)	No. of cases	Estimated no. of ED visits per 10,000 OPV (95% CI)	No. of cases	Estimated no. of ED visits per 10,000 OPV (95% CI)	No. of cases	Estimated no. of ED visits per 10,000 OPV (95% CI)
Penicillins	420	2.2 (1.7–2.7)	66	0.4 (0.3–0.6)	212	1.1 (0.6–1.6)	1528	7.6 (6.0–9.1)	175	0.7 (0.4–0.9)
Cephalosporins	184	1.3 (0.9–1.7)	39	0.3 (0.2–0.5)	88	0.7 (0.3–1.0)	357	2.8 (2.0–3.5)	58	0.4 (0.2–0.6)
Fluoroquinolones	212	2.4 (1.8–3.1)	100	1.2 (0.9–1.6)	83	1.1 (0.6–1.5)	228	2.8 (1.9–3.7)	75	0.7 (0.4–0.9)
Sulfonamides and trimethoprim	163	4.3 (2.9–5.8)	55	1.7 (0.9–2.4)	61	2.0 (0.8–3.1)	355	8.3 (5.8–10.7)	57	1.2 (0.6–1.9)
Macrolides and ketolides	120	1.1 (0.7–1.4)	39	0.3 (0.2–0.4)	111	1.0 (0.6–1.4)	190	1.7 (1.2–2.2)	59	0.4 (0.3–0.6)
Lincosamides (clindamycin)	32	2.8 (1.3–4.2)	11	…	34	3.0 (1.5–4.6)	80	8.4 (5.1–11.7)	18	…
Tetracyclines	38	1.2 (0.6–1.8)	11	…	28	0.7 (0.4–1.0)	66	2.0 (1.3–2.6)	22	0.4 (0.2–0.6)
All other antibiotic classes[d]	80	1.9 (1.2–2.7)	52	1.4 (0.8–1.9)	66	1.7 (0.9–2.4)	171	4.0 (2.9–5.1)	58	1.2 (0.6–0.8)

NOTE. Estimates of the number of adverse events are based on the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (2004–2006). Estimates of the number of outpatient prescription visits (OPV) are based on the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey (2004–2005). Adverse events were categorized into 1 condition. Adverse event conditions are mutually exclusive and were assigned hierarchically (left to right). For example, a case in which a patient experienced both a severe allergic reaction and gastrointestinal effects would be categorized as a moderate-to-severe allergic reaction.

[a] Only cases in which drugs from a single systemic antibiotic class were implicated in the adverse event are included (5802 cases). Estimates with coefficient of variation >30% or based on <20 cases were not calculated.

[b] Includes anaphylaxis, angioedema, erythema multiforme, exfoliative dermatitis, facial-pharyngeal-genital edema, hypersensitivity vasculitis, red man syndrome, respiratory distress or arrest, serum sickness, and Stevens-Johnson syndrome.

[c] Includes dermatitis, drug eruption, erythema, flushing, localized edema, pruritus, rash, rash morbilliform, and urticaria.

[d] Includes metronidazole, nitrofurans, vancomycin, linezolid, unspecified, and other antibiotic classes.

[32, 33]. Although the rate of ED visits for adverse events attributable to fluoroquinolones was lower than the rates of ED visits for adverse events attributable to sulfonamides and clindamycin, it was higher than the rates of ED visits for adverse events attributable to cephalosporins, macrolides, and tetracyclines. In addition, fluoroquinolones were associated with the second highest rates of neurologic or psychiatric effects and hospitalization. The significantly higher rate of adverse events attributable to moxifloxacin, compared with fluoroquinolones, is similar to findings from clinical trials and studies based on spontaneous reporting [28, 34] and is contrary to the perception that "newer" antibiotics have superior adverse effect profiles [32, 33].

Adverse event data cannot be used in isolation to dictate the decision as to whether to prescribe antibiotics or to determine optimal antibiotic selection for individual patients. However, these national surveillance data can be used by clinicians to help assess the validity of their perceptions of the safety profile of various antibiotics and antibiotic classes. These population-based findings are also important, because adverse event data from spontaneous reports cannot provide population rates, and safety data from clinical trials largely reflect adverse events among a small number of highly selected persons relative to those eventually exposed to antibiotics in the community [35].

The infectious diseases and public health communities have long argued for judicious antibiotic use by physicians because of the lack of effectiveness for treating certain conditions (e.g., upper respiratory tract infection caused by a virus) and the threat of antibiotic resistance [5–9]. Nevertheless, unnecessary prescribing of antibiotics in the community remains common [18, 19, 36–38]. In qualitative studies of antibiotic prescribing practices, physicians reported difficulty with communicating information on antibiotic effectiveness and resistance and expressed concerns about the time required for such explanations [39, 40]. Physicians often perceived antibiotic resistance as a societal problem, identified the interests of their individual patients as being more important, and prescribed antibiotics to patients who they believed expected to receive antibiotics [32, 33, 39–41]. National data quantifying the risks of clinically relevant antibiotic-associated adverse events (i.e., those resulting in ED visits) can support a simpler argument for using antibiotics judiciously and one that directly addresses the individual patient and the physician's primary responsibility, primum non nocere, first do no harm.

National antibiotic-associated adverse event data can also be used by campaigns targeted at changing patient expectations of antibiotic therapy. In studies that assessed patients' perceptions of the harmful consequences of antibiotic use, the association between antibiotics and adverse effects (e.g., rash) was almost always mentioned, but the association between antibiotics and resistance was rarely mentioned [39]. Similar research has demonstrated that patients frequently do not understand that antibiotics are ineffective against viral infections [42]. Thus, communicating the risk of serious antibiotic-associated adverse events to patients can add to their existing perceptions of risks of antibiotic therapy and may reduce the amount of requests for antibiotic therapy more than by trying to convey information on antibiotic effectiveness or resistance alone [32, 33, 39, 40]. Because one-quarter of all estimated ED visits for antibiotic-associated adverse events (~37,000 visits) were by children aged <15 years and the highest rate of ED visits was among infants, this message could be targeted at parents of pediatric patients, in particular.

Antibiotic use guidelines are beginning to recognize that the risk of adverse effects in individual patients can outweigh the benefits of antibiotics for certain prophylactic indications. Recently, infective endocarditis prophylaxis guidelines were revised, at least in part, on the basis of the assessment that the risk of antibiotic-associated adverse events exceeds the benefits of prophylactic use for many patients [43, 44]. Future antibiotic use guidelines should incorporate the best available evidence on risk of antibiotic-associated adverse events in individual patients in ways that can be integrated in clinical practice [32, 35, 40].

This investigation focused on drug-related adverse events diagnosed in EDs, and thus, the numbers and rates do not reflect all antibiotic-associated adverse events. Although our data describe clinically relevant drug-related adverse events that warranted medical attention and contributed to health care resource use, we could not account for unreported events and events identified in other health care settings, such as physicians' offices. Because case identification in the NEISS-CADES project relies on the presence of a physician-diagnosed drug-related adverse event in the ED, rare and less well-recognized events and events with subacute onset are less likely to be captured. We limited our analysis of drug-related adverse event conditions and outcomes (table 3) to cases in which only drugs from a single antibiotic class were implicated in the adverse event, to describe only the events that were attributed to antibiotics and not to other types of drugs. In doing so, we may have neglected to describe certain adverse events, such as those resulting from drug-drug interactions (e.g., hemorrhage in a patient receiving warfarin and a fluoroquinolone) [45]. Physicians may also be more likely to recognize certain adverse event conditions associated with a particular antibiotic class than those associated with other classes (e.g., they are more likely to identify allergic reactions associated with β-lactam antibiotics than allergic reactions associated with fluoroquinolones), thus influencing the spectrum of adverse events described in association with each antibiotic class. Similar to most previous studies on antibiotic prescribing [17–20], we used NAMCS and NHAMCS for estimates of the frequency of out-

patient antibiotic prescribing. Our estimates of the frequency of outpatient antibiotic prescribing are similar to those previously reported using NAMCS and NHAMCS [1, 20]. However, different prescription databases may have yielded different estimates of the frequency of outpatient antibiotic prescribing [46], and the frequency of outpatient antibiotic prescribing, when based on NAMCS and NHAMCS, is likely to be underestimated, because these databases exclude telephone and e-mail contacts, antibiotics prescribed in nursing homes or ambulatory surgery centers, and antibiotic courses initiated during hospitalization or provided at hospital discharge.

Antibiotic-associated adverse events lead to many ED visits, and allergic reactions are the most common events. Communicating the risks of antibiotic-associated adverse events can become an important strategy in efforts to promote judicious antibiotic use. Avoiding unnecessary antibiotic use reduces not only the public health threat of antibiotic resistance but also the risk of drug-related adverse events in individual patients.

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