



US Emergency Department Visits for Adverse Drug Events From Antibiotics in Children, 2011–2015

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Background. Antibiotics are among the most commonly prescribed medications for children; however, at least one-third of pediatric antibiotic prescriptions are unnecessary. National data on short-term antibiotic-related harms could inform efforts to reduce overprescribing and to supplement interventions that focus on the long-term benefits of reducing antibiotic resistance.

Methods. Frequencies and rates of emergency department (ED) visits for antibiotic adverse drug events (ADEs) in children were estimated using adverse event data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project and retail pharmacy dispensing data from QuintilesIMS (2011–2015).

Results. On the basis of 6542 surveillance cases, an estimated 69 464 ED visits (95% confidence interval, 53 488–85 441) were made annually for antibiotic ADEs among children aged ≤ 19 years from 2011 to 2015, which accounts for 46.2% of ED visits for ADEs that results from systemic medication. Two-fifths (40.7%) of ED visits for antibiotic ADEs involved a child aged ≤ 2 years, and 86.1% involved an allergic reaction. Amoxicillin was the most commonly implicated antibiotic among children aged ≤ 9 years. When we accounted for dispensed prescriptions, the rates of ED visits for antibiotic ADEs declined with increasing age for all antibiotics except sulfamethoxazole-trimethoprim. Amoxicillin had the highest rate of ED visits for antibiotic ADEs among children aged ≤ 2 years, whereas sulfamethoxazole-trimethoprim resulted in the highest rate among children aged 10 to 19 years (29.9 and 24.2 ED visits per 10 000 dispensed prescriptions, respectively).

Conclusions. Antibiotic ADEs lead to many ED visits, particularly among young children. Communicating the risks of antibiotic ADEs could help reduce unnecessary prescribing. Prevention efforts could target pediatric patients who are at the greatest risk of harm.

Keywords. adverse drug event; antibiotic resistance; antibiotics; allergic reaction; medication safety.

Antibiotics are among the most commonly prescribed medications for children in the United States [1]. In 2011, 889 antibiotic prescriptions were dispensed from retail pharmacies for every 1000 children aged ≤ 19 years, which accounts for nearly 74 million prescriptions [2]. Antibiotic use drives the development of antibiotic resistance, which is considered a major public health threat worldwide [3]. Antibiotic use also carries the risk of harming individual patients. Antibiotic-related harms (which range from mild gastrointestinal disturbance to life-threatening anaphylactic reaction) are a common cause of outpatient clinic visits and are the leading cause of emergency department (ED) visits for adverse drug events (ADEs) among children in the United States [4–6].

Recent efforts to reduce antibiotic resistance have focused largely on reducing inappropriate prescribing [7–9], and national clinical guidelines have been updated accordingly

[10–12]. Although clinicians generally concur and are familiar with guideline recommendations [13], national data from 2010–2011 indicate that at least 29% of outpatient pediatric antibiotic prescriptions were unnecessary, and more were likely inappropriate in antibiotic selection, dosing, or duration of therapy [14]. Continued inappropriate prescribing has been attributed to factors such as perceived parent/caregiver expectation for antibiotics and concern for parent/patient satisfaction [13, 15, 16]. Long-term societal risks of antibiotic resistance in the community are also not prioritized in clinicians' prescribing decisions or in parent/patient considerations about treatment [13, 17–19]. Data on the short-term individual risks of antibiotic ADEs could help clinicians, as well as parents/caregivers, weigh the risks and benefits of antibiotic treatment [20, 21].

We used nationally representative public health surveillance data to identify (1) the antibiotics that result in the highest frequencies and rates of ED visits for ADEs and (2) the pediatric patients at the highest risk to help inform and target prevention efforts.

METHODS

Data Sources

National estimates of ED visits for antibiotic ADEs were based on data from the National Electronic Injury Surveillance

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System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, a joint collaboration of the Centers for Disease Control and Prevention (CDC), the US Consumer Product Safety Commission, and the US Food and Drug Administration. NEISS-CADES is based on a nationally representative and stratified probability sample of hospitals in the United States and its territories with at least 6 beds and a 24-hour ED (4 hospital-size strata and 1 pediatric-hospital stratum). From 2011 to 2015, the number of hospitals participating in NEISS-CADES ranged from 55 to 62 depending on the year.

As described previously, trained data abstractors at the participating hospitals review all ED medical records to identify clinician-diagnosed ADEs and up to 2 medications implicated in each ADE [22, 23]. Abstractors then record patient demographics, clinical diagnoses, and narrative descriptions of the event, including precipitating circumstances (eg, medication errors), clinical manifestations, treatments administered, and ED disposition. Narrative descriptions are then coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 9.1.

National estimates of oral antibiotic prescriptions dispensed from outpatient retail pharmacies were based on data from the QuintilesIMS National Prescription Audit (NPA). The NPA includes new and refilled prescriptions from nearly 48 000 nonfederal retail pharmacies across the United States, which represents approximately 80% of retail prescription activity from pharmacies and food/mass merchandise stores. QuintilesIMS projects national estimates using proprietary methods.

Definitions

Cases included ED visits from 2011 to 2015 that the treating clinician attributed to the use of a systemic antibiotic by a child aged ≤ 19 years. Systemic antibiotics, hereafter just “antibiotics,” included oral and injectable formulations and excluded topical, ophthalmic, and otic formulations. ED visits for ADEs that involved any other systemic medication were used for comparison. ADEs were classified as allergic reactions (immunologically mediated effects, including severe hypersensitivity reactions such as Stevens-Johnson syndrome), adverse effects (undesirable pharmacologic or idiosyncratic effects at recommended doses), effects of excess dose, or other effects (eg, injection-site reactions, choking). Adverse-event manifestations were categorized in a mutually exclusive and hierarchical manner on the basis of severity (eg, a case that involved angioedema and mild nausea would be classified as a moderate-to-severe allergic reaction on the basis of the angioedema). Hospitalizations included inpatient admissions, observation admissions, and transfers to another facility. Cases in which a child aged ≤ 10 years accessed medication without caregiver oversight were excluded from the analysis. Cases of therapeutic drug failure, nonadherence, substance use disorder, intentional self-harm, occupational

exposure, and ADEs that resulted from treatment received in the ED were not included. Deaths that occurred in or en route to the ED also were not included.

Statistical Analysis

Cases collected from the NEISS-CADES hospital EDs are weighted to calculate national estimates. Weights are assigned to each case on the basis of the inverse probability of selection, adjusted for nonresponse and poststratified to adjust for changes in the number of annual hospital ED visits [24]. National estimates of ED visits and corresponding 95% confidence intervals (CIs) were calculated using the SURVEYMEANS procedure in SAS 9.3 (SAS Institute, Cary, North Carolina) to account for sample weights and sample design. National estimates were annualized by dividing total estimates for the 5-year period by 5. Estimates based on <20 cases or total estimates of <1200 were considered statistically unstable and are not shown. Estimates with a coefficient of variation of $>30\%$ might be statistically unstable and are noted. Population-based rates were calculated by dividing the ED visit estimate for each age group (from NEISS-CADES) by the corresponding bridged-race population estimates from the US Census Bureau [25]. Population estimates were considered free of sampling error.

Estimated numbers of dispensed retail prescriptions for oral antibiotics (from the QuintilesIMS NPA) were used to calculate the rates of ED visits for ADEs that resulted from an oral antibiotic relative to outpatient antibiotic use and the number needed to harm (NNH). Rates were estimated also for specific drug products and patient age groups. Accompanying 95% CIs for rate estimates were calculated and incorporated the variance of the numerator estimates of ED visits; because of the large sample size (approximately 3.5 billion dispensed prescriptions annually), the variance of QuintilesIMS estimates was considered to be negligible.

RESULTS

On the basis of 6542 surveillance cases, an estimated 69 464 ED visits (95% CI, 53 488–85 441) were made annually in the United States for antibiotic ADEs among children aged ≤ 19 years from 2011 to 2015 (Table 1). ED visits for antibiotic ADEs accounted for 46.2% (95% CI, 43.2%–49.1%) of all ED visits for ADEs from a systemic medication in this age group. Among children aged ≤ 2 years, antibiotics were implicated in nearly two-thirds (63.9% [95% CI, 60.0%–67.8%]) of the ED visits for ADEs from a systemic medication, whereas among children aged 10 to 19 years, an antibiotic was implicated in one-third (32.4% [95% CI, 29.7%–35.2%]) of the ED visits for ADEs. Just over one-half (53.7%) of ED visits for antibiotic ADEs involved girls, and 3.0% of the ED visits for antibiotic ADEs resulted in hospitalization.

Compared with ED visits for ADEs from another systemic medication, ED visits attributed to antibiotic ADEs more

Table 1. ED Visits for a ADEs From Medications in Children ≤19 Years Old—United States, 2011–2015^a

Patient or Case Characteristic	ED Visits for a ADEs That Involved an Antibiotic			ED Visits for a ADEs That Involved Another Medication ^b		
	No. of Cases	Annual National Estimate		No. of Cases	Annual National Estimate	
		No.	% (95% CI)		No.	% (95% CI)
Age						
<1–2 years	2870	28 240	40.7 (38.5–42.8)	1637	15 959	19.7 (16.1–23.3)
3–4 years	743	7118	10.2 (8.9–11.6)	889	7101	8.8 (7.8–9.7)
5–9 years	1187	12 356	17.8 (16.0–19.5)	1535	12 662	15.6 (14.0–17.2)
10–19 years	1742	21 751	31.3 (29.2–33.4)	4476	45 329	55.9 (51.6–60.3)
Sex						
Female	3411	37 292	53.7 (52.0–55.4)	4303	42 139	52.0 (50.2–53.8)
Male	3131	32 172	46.3 (44.6–48.0)	4234	38 911	48.0 (46.2–49.8)
Type of ADEs						
Allergic reaction	5763	59 776	86.1 (82.3–89.8)	1769	20 797	25.7 (22.8–28.5)
Adverse effect	693	8798	12.7 (9.0–16.4)	3176	23 269	28.7 (24.1–33.3)
Effect of excess dose	37	373	0.5 (0.3–0.8)	1793	17 510	21.6 (19.2–24.0)
Other effect ^c	49	517	0.7 (0.4–1.1)	1799	19 473	24.0 (20.0–28.0)
Documented medication error ^d						
Yes	63	651	0.9 (0.5–1.3)	1434	13 896	17.1 (14.4–19.9)
No	6479	68 813	99.1 (98.7–99.5)	7103	67 154	82.9 (80.1–85.6)
No. of implicated medications						
1	6156	65 526	94.3 (93.3–95.3)	7393	72 609	89.6 (87.9–91.3)
≥2	386	3938	5.7 (4.7–6.7)	1144	8440	10.4 (8.7–12.1)
Disposition ^e						
Admitted, transferred, or held for observation	265	2056	3.0 (2.1–3.8)	1728	8466	10.4 (6.1–14.8)
Treated/released or left against medical advice	6277	67 408	97.0 (96.2–97.9)	6808	72 580	89.5 (85.2–93.9)
Total	6542	69 464	100.0	8537	81 050	100.0

Abbreviations: ADE, adverse drug event; CI, confidence interval; ED, emergency department.

^aEstimates of ED visits for ADEs are based on the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (2011–2015). Data exclude cases of unsupervised ingestion in which children aged ≤10 years accessed the medication without caregiver oversight.

^bIncludes prescription and over-the-counter medications, dietary supplements, homeopathic products, and vaccines that were administered by the oral, sublingual, injectable, rectal, or transdermal route.

^cExamples of other effects include injection-site reaction, choking, and vaccination reaction.

^d"Errors" refer to errors in drug prescribing, dispensing, or administration, including administration of another individual's prescription medication or accidental needle stick in children aged >10 years.

^eThis information for 1 case attributed to another medication was missing.

commonly involved children aged ≤2 years (40.7% [95% CI, 38.5%–42.8%] vs 19.7% [95% CI, 16.1%–23.3%], respectively) and more commonly involved an allergic reaction (86.1% [95% CI, 82.3%–89.8%] vs 25.7% [95% CI, 22.8%–28.5%], respectively). When we accounted for population, ED visits for antibiotic ADEs were found to disproportionately involve young children. The population rate of ED visits for antibiotic ADEs was 4 times higher for children aged ≤2 years than for children aged 10 to 19 years (23.8 [95% CI, 17.8–29.8] vs 5.2 [95% CI, 4.0–6.4] ED visits per 10 000 population, respectively).

In an estimated 95.9% (95% CI, 95.0%–96.7%) of the pediatric ED visits for antibiotic ADEs, a single class of oral antibiotics was implicated; few visits (2.2%) involved 2 antibiotics from different classes (Table 2). Only 1.9% of the ED visits for antibiotic ADEs were attributed to only an injectable antibiotic. Oral penicillins alone were implicated in an estimated 38 680 (95% CI, 30 311–47 048) ED visits annually, which accounted for 55.7% of the ED visits for antibiotic ADEs. The next most frequently implicated classes were oral cephalosporins (11.9%) and sulfonamides (11.1%) alone. Overall, oral sulfonamides

and clindamycin resulted in the highest rates of ED visits for antibiotic ADEs after we accounted for estimates of prescriptions from retail pharmacies (18.0 and 16.6 ED visits per 10 000 dispensed prescriptions, respectively).

Mild allergic reaction (eg, rash, pruritus) was the most common manifestation of antibiotic ADEs and ranged from half of the visits that involved an oral quinolone alone (51.4% [95% CI, 36.1%–66.7%]) to four-fifths of the visits that involved a penicillin (81.0% [95% CI, 77.0%–84.9%]) or sulfonamide (80.9% [95% CI, 76.7%–85.1%]) alone (Supplementary Table 1). A moderate-to-severe allergic reaction (eg, anaphylaxis, angioedema) was documented in 30.0% (95% CI, 16.9%–43.1%) of the ED visits for ADEs from an oral quinolone alone and 19.8% (95% CI, 11.2%–28.3%) of the visits that resulted from a tetracycline alone. The NNH for ED visits that involved a mild allergic reaction was lowest for the oral sulfonamides and clindamycin (1 in 688 and 1 in 856 dispensed prescriptions, respectively). The NNH for ED visits that involved a moderate-to-severe allergic reaction was lowest for the oral quinolones (1 in 2525 dispensed prescriptions).

Table 2. ED Visits for ADEs From an Antibiotic in Children ≤19 Years Old According to Drug Class—United States, 2011–2015^a

Antibiotic Drug Class	ED Visits for Antibiotic ADEs			Rate per 10 000 Dispensed Prescriptions (95% CI) ^b
	No. of Cases	No.	% (95% CI)	
Oral antibiotics ^c	6406	68 118	98.1 (97.4–98.7)	NA
Penicillins ^d	3904	38 680	55.7 (53.3–58.1)	12.1 (9.5–14.8)
Cephalosporins	733	8260	11.9 (10.2–13.6)	6.8 (4.6–9.0)
Sulfonamides	623	7707	11.1 (9.0–13.2)	18.0 (13.3–22.7)
Macrolides	378	5249	7.6 (6.4–8.7)	3.9 (2.8–5.0)
Lincomycins (clindamycin)	186	1820	2.6 (2.2–3.1)	16.6 (12.2–21.1)
Tetracyclines	136	1524	2.2 (1.6–2.8)	3.9 (2.3–5.4)
Quinolones	67	971	1.4 (0.9–1.9)	13.2 (8.0–18.4)
Other or unspecified antibiotics	220	2390	3.4 (2.7–4.2)	NA
2 antibiotics from different classes	159	1518	2.2 (1.7–2.7)	NA
Injectable antibiotics ^e	136	1346	1.9 (1.3–2.6)	NA
Total	6542	69 464	100.0	NA

Abbreviations: ADE, adverse drug event; CI, confidence interval; ED, emergency department; NA, not applicable.

^aEstimates of ED visits for ADEs are based on the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (2011–2015); estimates of dispensed oral prescriptions from retail pharmacies are based on the National Prescription Audit from QuintilesIMS (2011–2015). Data for specific drug classes represent only those for ED visits in which an antibiotic from that single drug class was implicated. Data exclude cases of unsupervised ingestion in which children aged ≤10 years accessed the medication without caregiver oversight.

^bRate estimates were calculated only for ED visits attributed to a single specified class of oral antibiotics. Rates were not calculated for ED visits attributed to an injectable antibiotic because the QuintilesIMS data on numbers of dispensed outpatient retail prescriptions do not estimate the use of injectable antibiotics (which are often administered in a clinical setting) reliably.

^cIncludes 7 cases in which an oral antibiotic and an injectable antibiotic from the same drug class were both implicated.

^dIncludes penicillins used in combination with a β -lactamase inhibitor (eg, amoxicillin in combination with clavulanate).

^eIncludes injectable cephalosporins (55 cases), penicillins (52 cases), other antibiotics (25 cases), and 2 injectable antibiotics from different classes (4 cases).

Without accounting for prescribing frequency, the oral antibiotics most commonly implicated in ED visits for ADEs were similar across age groups, but the relative frequencies varied according to age (Table 3). Amoxicillin was the most commonly implicated drug product in ED visits for antibiotic ADEs among children aged ≤9 years; however, the proportion of visits attributed to amoxicillin ADEs declined with increasing age (≤2 years, 67.6%; 3–4 years, 54.5%; 5–9 years, 44.7%). The number of oral antibiotic products implicated in ED visits for antibiotic ADEs was higher among older children than among younger children. For children ≤2 years old, the 3 most commonly implicated antibiotics combined were implicated in 83.2% (95% CI, 80.9%–85.5%) of the ED visits for antibiotic ADEs (amoxicillin, 67.6%; amoxicillin/clavulanate, 8.5%; cefdinir, 7.6%), whereas for children aged 10 to 19 years, the 3 most commonly implicated antibiotics combined were implicated in 55.0% (95% CI, 50.5%–59.6%) of the ED visits for ADEs (sulfamethoxazole-trimethoprim, 24.3%; amoxicillin, 20.8%; and azithromycin, 10.5%).

After we accounted for prescribing frequency, we found that the estimated rates of ED visits for antibiotic ADEs per 10 000 dispensed retail prescriptions declined with age for all oral antibiotics except sulfamethoxazole-trimethoprim (Figure 1). Amoxicillin resulted in the highest rate of ED visits for antibiotic ADEs among children aged ≤2 years (29.9 ED visits per 10 000 dispensed prescriptions); the rate of ED visits for amoxicillin ADEs declined to 10.4 ED visits per 10 000 dispensed prescriptions among children aged 3 to 4 years and further to 6.8 ED visits per 10 000 dispensed prescriptions among children

aged 10 to 19 years. Sulfamethoxazole-trimethoprim (24.2 ED visits per 10 000 dispensed prescriptions) and clindamycin (19.6 [95% CI, 14.1–25.2] ED visits per 10 000 dispensed prescriptions) resulted in the highest rates of ED visits for antibiotic ADEs among the oldest children (aged 10–19 years).

DISCUSSION

Antibiotic ADEs lead to nearly 70 000 estimated ED visits among children each year in the United States and should be a key area of focus for outpatient pediatric medication safety efforts. Antibiotics are implicated in nearly half of all ED visits for ADEs attributed to a systemic medication among children of all ages and are implicated in nearly two-thirds of ED visits for all ADEs among the youngest children (aged ≤2 years). Including age and drug-specific adverse-event data in efforts to improve prescribing could help clinicians and parents/caregivers weigh the risks of antibiotic treatment and reduce unnecessary prescribing.

High numbers of ED visits for antibiotic ADEs among younger children can be explained partially by the higher number of prescriptions of antibiotics given for younger children. Two-fifths (41%) of the estimated ED visits for a pediatric antibiotic ADEs involved a child aged ≤2 years, and the population rate of ED visits for antibiotic ADEs is 4 times higher among children aged ≤2 years than among those aged 10 to 19 years (23.8 vs 5.2 ED visits per 10 000 children, respectively). The antibiotic-prescribing rate has been reported to be nearly 2 times higher among children aged ≤2 years than among those aged 10

Table 3. ED Visits for ADEs From the Most Commonly Implicated Oral Antibiotics in Children ≤19 Years Old According to Patient Age—United States, 2011–2015^a

Most Commonly Implicated Antibiotic Drug Products for Each Age Group (Annual Estimate)	ED Visits for Antibiotic ADEs			NNH ^b
	Annual National Estimate			
	No. of Cases	No.	% (95% CI)	
Patients aged <1–2 years (27 871)				
Amoxicillin	1977	18 835	67.6 (63.6–71.5)	334
Amoxicillin-clavulanate	275	2357	8.5 (6.8–10.1)	723
Cefdinir	228	2117	7.6 (5.3–9.9)	851
Azithromycin	102	1418	5.1 (3.9–6.3)	1458
Cephalexin	74	1000	3.6 (2.2–5.0)	566
Sulfamethoxazole-trimethoprim	87	821 ^c	2.9 (1.4–4.5)	836 ^c
Patients aged 3–4 years (7067)				
Amoxicillin	430	3852	54.5 (49.5–59.5)	958
Amoxicillin-clavulanate	71	707	10.0 (6.2–13.8)	1474
Cefdinir	63	562	7.9 (4.5–11.3)	1873
Azithromycin	44	544	7.7 (5.1–10.3)	3126
Sulfamethoxazole-trimethoprim	46	486	6.9 (3.9–9.8)	1039
Cephalexin	29	264	3.7 (2.1–5.4)	1870
Patients aged 5–9 years (11 931)				
Amoxicillin	566	5330	44.7 (39.9–49.5)	1331
Sulfamethoxazole-trimethoprim	155	1768	14.8 (10.6–19.1)	539
Azithromycin	94	1024	8.6 (6.1–11.0)	3364
Amoxicillin-clavulanate	82	876	7.3 (5.1–9.6)	2075
Cefdinir	83	793	6.6 (4.3–9.0)	2033
Cephalexin	59	624	5.2 (3.5–7.0)	1929
Penicillin	26	371	3.1 (1.6–4.6)	707
Clindamycin	35	335	2.8 (1.4–4.2)	646
Patients aged 10–19 years (21 249)				
Sulfamethoxazole-trimethoprim	384	5167	24.3 (20.3–28.4)	413
Amoxicillin	366	4414	20.8 (18.3–23.3)	1469
Azithromycin	153	2225	10.5 (8.0–13.0)	2529
Cephalexin	127	1711	8.1 (5.9–10.2)	1326
Amoxicillin-clavulanate	112	1419	6.7 (5.3–8.1)	1720
Clindamycin	126	1304	6.1 (4.9–7.4)	509
Doxycycline	78	845	4.0 (2.5–5.4)	2344
Ciprofloxacin	52	773	3.6 (2.2–5.1)	700
Minocycline	58	686	3.2 (2.1–4.3)	2628
Penicillin	48	655	3.1 (2.1–4.1)	1114
Cefdinir	55	601	2.8 (1.4–4.2)	2017
Metronidazole	40	458	2.2 (1.2–3.1)	1082

Abbreviations: ADE, adverse drug event; CI, confidence interval; ED, emergency department; NNH, number needed to harm.

^aEstimates of ED visits for ADEs are based on the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (2011–2015); estimates of dispensed oral prescriptions from retail pharmacies are based on the National Prescription Audit from QuintilesIMS (2011–2015). Drug products are not mutually exclusive; for some ED visits, more than 1 drug product was implicated in the ADEs. Drug products are shown if they were implicated in ≥2% of the estimated ED visits for antibiotic ADEs within each age group. Data exclude cases of unsupervised ingestion in which children aged ≤10 years accessed the medication without caregiver oversight.

^bThe NNH was calculated as the reciprocal of the estimated number of ED visits divided by the number of dispensed prescriptions.

^cThe coefficient of variation is >30%.

to 19 years (1287 vs 691 antibiotic prescriptions per 1000 children, respectively) [2]; however, 2-fold higher prescribing rates alone cannot account for a >4-fold higher population rate of ED visits for antibiotic ADEs among the youngest children.

After we accounted for prescribing frequency, we found that the risk of an ED visit for antibiotic ADEs was higher for young children than for older children for all antibiotics except sulfamethoxazole-trimethoprim. For example, the rate of ED visits for amoxicillin ADEs was 4 times higher for the youngest children

(aged ≤2 years) than for the oldest children (aged 10–19 years) (29.9 vs 6.8 ED visits per 10 000 dispensed prescriptions, respectively). Several factors likely contribute to the increased risk of ED visits for antibiotic ADEs in young children. Most (86%) ED visits for antibiotic ADEs involved an allergic reaction, and young children might be more susceptible to antibiotic allergy than older children [26]. Also, allergic reactions or other adverse effects after antibiotic exposure at a young age are typically documented so that future reactions can be avoided [27]. Last,

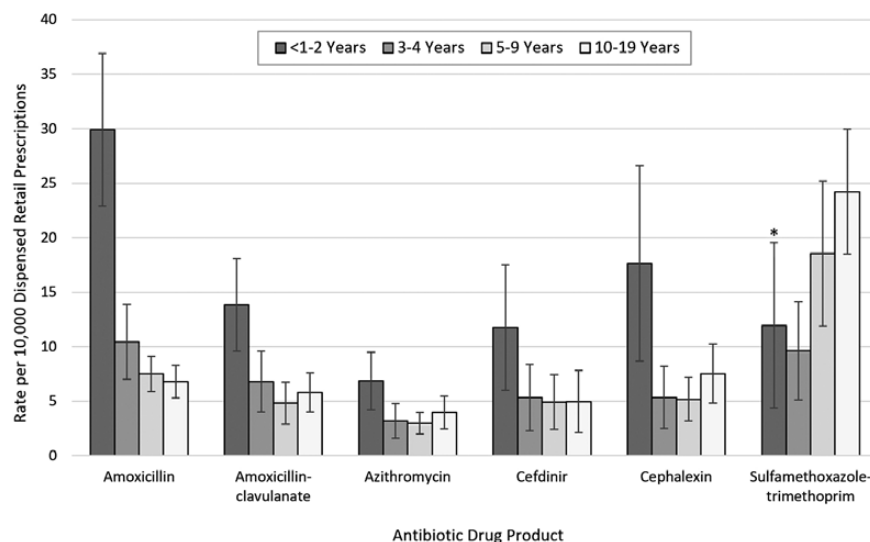


Figure 1. Rates of emergency department (ED) visits for adverse drug events (ADEs) that resulted from the most commonly implicated oral antibiotics in children ≤ 19 years old according to patient age—United States, 2011–2015. Estimates of ED visits for ADEs are based on the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (2011–2015); estimates of dispensed oral prescriptions from retail pharmacies are based on the National Prescription Audit from QuintilesIMS (2011–2015). Drug products are not mutually exclusive; for some ED visits, >1 antibiotic was implicated in the ADEs. Data exclude cases of unsupervised ingestion in which children aged ≤ 10 years accessed the medication without caregiver oversight. *, the coefficient of variation is $>30\%$.

parents/caregivers might have a lower threshold for seeking emergency care for young children because they might perceive young children to be more vulnerable [26].

Pediatric antibiotic prescribing has declined in recent years after efforts to reduce unnecessary antibiotic use, but room exists for continued improvement [28–30]. An estimated 29% of outpatient antibiotic prescriptions for children in 2010–2011 were deemed unnecessary (ie, prescribed for a condition, such as viral infection, for which national guidelines recommend against antibiotic use) [14]. Although many antibiotic prescriptions are appropriate and not all antibiotic ADEs can be avoided, minimizing unnecessary antibiotic prescribing can reduce the burden of acute antibiotic-related harms and help preserve antibiotic efficacy [20].

The availability of detailed nationally representative data on antibiotic ADEs risks and the patient populations at the highest risk (young children) might help clinicians continue to reduce unnecessary prescribing. Efforts to reduce inappropriate prescribing have focused historically on the long-term benefits of limiting antibiotic resistance rather than the short-term risks of adverse events. However, focusing solely on limiting antibiotic resistance might not be sufficient for changing prescribing behavior, because inappropriate prescribing and subsequent antimicrobial resistance are often perceived as external problems caused by other prescribers [17]. Instead, efforts to reduce inappropriate prescribing could place more focus on immediate risks to individual patients. In 1 recent study, 78% of parents did not recall any discussion of possible antibiotic harms during their child's last doctor visit for an

acute respiratory infection [19]. For example, the finding that each year, nearly 1 in 400 children aged ≤ 2 years are brought to an ED for antibiotic ADEs might help remind clinicians that antibiotic ADEs are near-term events that can be clinically significant and consequential for their pediatric patients.

Incorporating up-to-date national data on harms into initiatives to improve antimicrobial prescribing, such as CDC's "Be Antibiotics Aware: Smart Use, Best Care" educational program and the American Board of Internal Medicine Foundation's "Choosing Wisely" series of recommendations by health-care professional societies, might enhance the effectiveness of these initiatives [7, 8]. In addition, providing support for clinical decisions is a recommendation in CDC's "Core Elements of Outpatient Antimicrobial Stewardship" [9]; incorporating patient-specific information about the risks of antibiotic ADEs (eg, NNH according to age, drug, and sex) in clinical decision-support systems might help reinforce the potential for acute antibiotic harms when prescribing decisions are being made.

Similarly, communicating information on antibiotic ADEs risks to parents/caregivers might help lessen the demand for or expectation of antibiotics. Parents/caregivers often overestimate the benefits of antibiotics, which can lead to their demand for or expectation of antibiotic treatment [19, 31]. Clinicians might perceive parent/caregiver expectations and, coupled with a concern for parent/patient satisfaction, might overprescribe antibiotics [13, 15, 16]. However, in a recent study, few mothers of young children were familiar with severe antibiotic-associated ADEs, and nearly all of them would have liked to receive this

information when antibiotics were prescribed [21]. Engaging parents/caregivers in informed decision making by discussing risks and benefits of antibiotic treatment and suggesting specific symptom-relief strategies might help to reduce parent/caregiver demands and overprescribing by clinicians [9, 32, 33]. National estimates of the NNH (1 ED visit by a child aged ≤ 2 years for amoxicillin ADEs for every 330 prescriptions) could be used in these discussions and incorporated into educational materials, such as those available through the CDC's "Be Antibiotics Aware: Smart Use, Best Care" program [8].

These public health surveillance data have limitations. First, the burden of ADEs from outpatient antibiotic use is likely underestimated, because only ADEs that resulted in an ED visit were included; antibiotic ADEs treated in other settings (eg, urgent care, physician's office), ADEs for which no treatment was sought, and ADEs that resulted in death were not included. An analysis of national surveillance data from 1995–2005 found that there were approximately twice as many estimated outpatient clinic visits than ED visits for antibiotic ADEs among children [4]. A more recent cohort study found that 3% to 4% of children prescribed an antibiotic had a clinician-documented adverse event and 25% to 36% of children experienced a parent-reported adverse event [34]. Second, ADEs that are less likely to be diagnosed in the ED setting (eg, *Clostridium difficile* infection) are not reliably included. Nonetheless, the ED setting is well suited to identify well-recognized ADEs with acute onset, including those that result in serious harm. Third, it was not possible to assess which antibiotic prescriptions were appropriate because information on the indication and prescribed dose and duration was not available. However, it has been estimated that 29% of pediatric antibiotic prescriptions are unnecessary, which suggests that a substantial number of these ED visits could have been avoided [14]. Fourth, diagnoses were made in an emergency setting in which patient management and symptom relief are the priority. Some rashes attributed to antibiotic allergic reaction might have been caused by a viral exanthem, which is common in young children but can be misdiagnosed as an allergic reaction [35]. In addition, some adverse-event manifestations categorized as allergic might not have proven to be immunomediated after further investigation [36]. Documentation of true drug allergies is important for preventing repeat occurrences; however, overestimation of antibiotic allergies can lead to suboptimal prescribing (eg, overuse of broad-spectrum agents) [27, 35, 37]. Last, only outpatient retail pharmacy data from QuintilesIMS were included in the analysis. Although less common, antibiotics can be obtained from other settings (eg, mail-order, federal, or specialty pharmacies) that were not included in this analysis.

CONCLUSION

Antibiotic ADEs lead to nearly 70 000 estimated pediatric ED visits each year in the United States. Minimizing antibiotic

overprescribing is important for reducing acute and clinically significant harms to individual patients and for reducing the societal risk of antibiotic resistance. Quantifying the risks of antibiotic ADEs can provide additional information to help clinicians and parents/caregivers weigh the risks and benefits of antibiotic treatment. Prevention efforts could target pediatric patients with the highest frequencies and rates of ED visits for antibiotic ADEs.

Supplementary Data

Supplementary materials are available at *Journal of the Pediatric Infectious Diseases Society* online.

Notes

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References

- Chai G, Governale L, McMahon AW, et al. Trends of outpatient prescription drug utilization in US children, 2002–2010. *Pediatrics* **2012**; 130:23–31.
- Hicks LA, Bartoces MG, Roberts RM, et al. US outpatient antibiotic prescribing variation according to geography, patient population, and provider specialty in 2011. *Clin Infect Dis* **2015**; 60:1308–16.
- Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. Available at: <https://www.cdc.gov/drugresistance/threat-report-2013/>. Accessed July 17, 2018.
- Bourgeois FT, Mandl KD, Valim C, Shannon MW. Pediatric adverse drug events in the outpatient setting: an 11-year national analysis. *Pediatrics* **2009**; 124:e744–50.
- Shehab N, Lovegrove MC, Geller AI, et al. US emergency department visits for outpatient adverse drug events, 2013–2014. *JAMA* **2016**; 316:2115–25.
- Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis* **2008**; 47:735–43.
- American Board of Internal Medicine Foundation. Antibiotics for ear infections in children: when you need them—and when you don't. Available at: <http://www.choosingwisely.org/patient-resources/antibiotics/>. Accessed July 17, 2018.
- Centers for Disease Control and Prevention. Antibiotic prescribing and use in doctor's offices. Available at: <https://www.cdc.gov/getsmart/community/index.html>. Accessed July 17, 2018.
- Sanchez GV, Fleming-Dutra KE, Roberts RM, Hicks LA. Core elements of outpatient antibiotic stewardship. *MMWR Recomm Rep* **2016**; 65:1–12.
- Fashner J, Ericson K, Werner S. Treatment of the common cold in children and adults. *Am Fam Physician* **2012**; 86:153–9.
- Hersh AL, Jackson MA, Hicks LA; American Academy of Pediatrics, Committee on Infectious Diseases. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. *Pediatrics* **2013**; 132:1146–54.
- Wald ER, Applegate KE, Bordley C, et al; American Academy of Pediatrics. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. *Pediatrics* **2013**; 132:e262–80.

13. Sanchez GV, Roberts RM, Albert AP, et al. Effects of knowledge, attitudes, and practices of primary care providers on antibiotic selection, United States. *Emerg Infect Dis* **2014**; 20:2041–7.
14. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. *JAMA* **2016**; 315:1864–73.
15. Dempsey PP, Businger AC, Whaley LE, et al. Primary care clinicians' perceptions about antibiotic prescribing for acute bronchitis: a qualitative study. *BMC Fam Pract* **2014**; 15:194.
16. Mangione-Smith R, McGlynn EA, Elliott MN, et al. The relationship between perceived parental expectations and pediatrician antimicrobial prescribing behavior. *Pediatrics* **1999**; 103:711–8.
17. McCullough AR, Rathbone J, Parekh S, et al. Not in my backyard: a systematic review of clinicians' knowledge and beliefs about antibiotic resistance. *J Antimicrob Chemother* **2015**; 70:2465–73.
18. Metlay JP, Shea JA, Crossette LB, Asch DA. Tensions in antibiotic prescribing: pitting social concerns against the interests of individual patients. *J Gen Intern Med* **2002**; 17:87–94.
19. Coxeter PD, Mar CD, Hoffmann TC. Parents' expectations and experiences of antibiotics for acute respiratory infections in primary care. *Ann Fam Med* **2017**; 15:149–54.
20. Linder JA. Editorial commentary: antibiotics for treatment of acute respiratory tract infections: decreasing benefit, increasing risk, and the irrelevance of antimicrobial resistance. *Clin Infect Dis* **2008**; 47:744–6.
21. Roberts RM, Albert AP, Johnson DD, Hicks LA. Can improving knowledge of antibiotic-associated adverse drug events reduce parent and patient demand for antibiotics? *Health Serv Res Manag Epidemiol* **2015**; 2:2333392814568345.
22. Budnitz DS, Pollock DA, Weidenbach KN, et al. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA* **2006**; 296:1858–66.
23. Jhung MA, Budnitz DS, Mendelsohn AB, et al. Evaluation and overview of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES). *Med Care* **2007**; 45:S96–102.
24. Schroeder T, Ault K. The NEISS sample (design and implementation) 1997 to present. Available at: https://www.cpsc.gov/s3fs-public/pdfs/blk_media_2001d011-6b6.pdf. Accessed July 17, 2018.
25. Centers for Disease Control and Prevention. Bridged-race population estimates: 1990–2015. Available at: <https://wonder.cdc.gov/bridged-race-population.html>. Accessed July 17, 2018.
26. Marrs T, Fox AT, Lack G, du Toit G. The diagnosis and management of antibiotic allergy in children: systematic review to inform a contemporary approach. *Arch Dis Child* **2015**; 100:583–8.
27. Langley J, Halperin S. Allergy to antibiotics in children: perception versus reality. *Can J Infect Dis* **2002**; 13:160–3.
28. Centers for Disease Control and Prevention. Office-related antibiotic prescribing for persons aged ≤14 years—United States, 1993–1994 to 2007–2008. *MMWR Morb Mortal Wkly Rep* **2011**; 60:1153–6.
29. Vaz LE, Kleinman KP, Raebel MA, et al. Recent trends in outpatient antibiotic use in children. *Pediatrics* **2014**; 133:375–85.
30. Centers for Disease Control and Prevention. Antibiotic prescribing and use in doctor's offices: measuring outpatient antibiotic prescribing. Available at: <https://www.cdc.gov/antibiotic-use/community/programs-measurement/measuring-antibiotic-prescribing.html>. Accessed July 17, 2018.
31. Vaz LE, Kleinman KP, Lakoma MD, et al. Prevalence of parental misconceptions about antibiotic use. *Pediatrics* **2015**; 136:221–31.
32. Mangione-Smith R, Zhou C, Robinson JD, et al. Communication practices and antibiotic use for acute respiratory tract infections in children. *Ann Fam Med* **2015**; 13:221–7.
33. Butler CC, Simpson SA, Dunstan F, et al. Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. *BMJ* **2012**; 344:d8173.
34. Gerber JS, Ross RK, Bryan M, et al. Association of broad- vs narrow-spectrum antibiotics with treatment failure, adverse events, and quality of life in children with acute respiratory tract infections. *JAMA* **2017**; 318:2325–36.
35. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* **2010**; 105:259–73.
36. Vyles D, Adams J, Chiu A, et al. Allergy testing in children with low-risk penicillin allergy symptoms. *Pediatrics* **2017**; 140.
37. Esposito S, Castellazzi L, Tagliabue C, Principi N. Allergy to antibiotics in children: an overestimated problem. *Int J Antimicrob Agents* **2016**; 48:361–6.

Supplementary Table. ED Visits for an ADE From an Oral Antibiotic in Children ≤19 Years Old According to Drug Class and Adverse Event Manifestation--United States, 2011-2015^a

Adverse Event Manifestation ^b	ED Visits for an Antibiotic ADE			
	No. of Cases	Annual National Estimate		
		No.	% (95% CI)	NNH ^c
Penicillins				
Moderate-to-Severe Allergic Reaction	457	3,678	9.5 (7.2 - 11.8)	8,658
Mild Allergic Reaction	3,173	31,497	81.4 (77.4 - 85.5)	1,011
Gastrointestinal Disturbance	220	2,879	7.4 (4.5 - 10.4)	11,063
Other or Unspecified Effect	54	625	1.6 (1.1 - 2.2)	50,928
Cephalosporins				
Moderate-to-Severe Allergic Reaction	134	1,295	15.7 (11.0 - 20.4)	9,368
Mild Allergic Reaction	475	5,549	67.2 (59.3 - 75.0)	2,186
Gastrointestinal Disturbance	106	1,176 ^d	14.2 (8.4 - 20.1)	10,313
Sulfonamides				
Moderate-to-Severe Allergic Reaction	92	979	12.7 (9.0 - 16.4)	4,381
Mild Allergic Reaction	501	6,233	80.9 (76.7 - 85.1)	688
Gastrointestinal Disturbance	25	399	5.2 (3.2 - 7.2)	10,741
Macrolides				
Moderate-to-Severe Allergic Reaction	64	730	13.9 (9.2 - 18.6)	18,372
Mild Allergic Reaction	246	3,462	66.0 (59.2 - 72.7)	3,874
Gastrointestinal Disturbance	59	952 ^d	18.1 (10.6 - 25.7)	14,091
Lincomycins (clindamycin)				
Moderate-to-Severe Allergic Reaction	26	273	15.0 (6.8 - 23.2)	4,016
Mild Allergic Reaction	136	1,279	70.3 (59.8 - 80.7)	856
Tetracyclines				
Moderate-to-Severe Allergic Reaction	24	297	19.5 (11.0 - 28.0)	13,167
Mild Allergic Reaction	60	807	52.9 (41.8 - 64.1)	4,852
Gastrointestinal Disturbance	34	261 ^d	17.1 (6.5 - 27.7) ^d	15,027
Quinolones				
Moderate-to-Severe Allergic Reaction	20	291	30.0 (16.9 - 43.1)	2,525
Mild Allergic Reaction	33	499	51.4 (36.1 - 66.7)	1,474

Abbreviations: ADE, adverse drug event; CI, confidence interval; ED, emergency department; NNH, number needed to harm.

^aEstimates of ED visits for an ADE are based on the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (2011–2015); estimates of dispensed oral prescriptions from retail pharmacies are based on the National Prescription Audit from QuintilesIMS (2011–2015). Data represent only ED visits in which a single oral drug class was implicated. Data exclude cases of unsupervised ingestion in which children aged ≤10 years accessed medication without caregiver oversight.

^bAdverse event manifestations were categorized in a mutually exclusive and hierarchical manner based on severity for each drug class. For example, a case involving angioedema and mild nausea would be classified as a moderate-to-severe allergic reaction. Allergic reactions include immunologically-mediated effects, including severe hypersensitivity reactions. Adverse event manifestations with estimates based on <20 cases or with total (5-year) estimates <1,200 are not shown since they are considered statistically unstable.

^c NNH calculated as the reciprocal of the estimated number of ED visits divided by the number of dispensed prescriptions.

^dThe coefficient of variation is >30%.