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ORIGINAL ARTICLE

Antibiotic dispensing following pediatric visits in the US emergency departments and outpatient settings from 2006 to 2016

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Abstract

This study measured rates and trends in antibiotic dispensing for emergency department (ED) and outpatient visits by age groups. This retrospective analysis used data from the National Institutes of Health Collaboratory Distributed Research Network. The analysis included children (aged > 3 months to <12 years) and adolescents (aged 12 to <19 years) with or without an antibiotic dispensed within 3 days following visits for infectious diagnoses occurring from 2006 to 2016, with no antibiotic fills 90 days prior. Diagnoses were classified as: 1) respiratory tract infections (RTIs) for which antibiotics are mostly indicated; 2) RTIs for which antibiotics are mostly not indicated; 3) respiratory conditions for which antibiotics are never indicated; 4) infectious conditions beyond RTIs regardless of antibiotic indication. The largest annual decrease in any dispensed antibiotics (5% per year) was seen in ED visits for not indicated RTIs and never indicated respiratory conditions (incidence rate ratio [IRR] 0.95, 95% confidence interval [CI] 0.95-0.96). In outpatient settings, a 2% per year decrease was seen for not indicated RTIs and never indicated respiratory conditions (IRR 0.98, 95% CI 0.98-0.98). Broad-spectrum antibiotics had a 1% per year increase in outpatient settings for mostly indicated RTIs (IRR 1.01, 95% CI 1.01-1.01). Compared with adolescents, broad-spectrum antibiotic dispensing rates and trends were consistently higher for children regardless of diagnosis or care setting. Using national claims data, this real-world analysis found uneven decreases in potentially inappropriate antibiotic dispensing, suggesting the need for antibiotic stewardship interventions to become more common in outpatient settings.

KEYWORDS

antibiotic dispensing, claims analysis, observational study, pediatric visits, respiratory infections

Abbreviations: CDC, Centers for Disease Control and Prevention; CDM, Common Data Model; CI, Confidence interval; DRN, Distributed Research Network; ED, Emergency department; ICD, International Classification of Diseases; IRR, Incidence rate ratio; NIH, National Institutes of Health; RTI, Respiratory tract infection.

1 | INTRODUCTION

Antibiotic stewardship is the effort to improve antibiotic use so that antibiotics are only used when needed and, when needed, the right antibiotic is used correctly.[1] Broad-spectrum antibiotics should only be used in cases where narrow-spectrum antibiotics are inappropriate since broad-spectrum antibiotics are more likely to contribute to antibiotic resistance. Two core strategies form the foundation of antibiotic stewardship interventions: prospective audit with feedback to the prescriber at the point of order entry, and formulary restriction requirements.[2] In the United States, a national effort to promote outpatient stewardship interventions was started in 2015 with the goal of reducing inappropriate antibiotic use in outpatient settings by 50% by 2020.[3] Although outpatient antibiotic stewardship interventions are a key component of the National Action Plan in the US regarding antibiotic use, it is unclear whether emergency department (ED) or outpatient settings require more focused intervention.

The trend in overall antibiotic prescribing among the US children has been declining in outpatient settings (ie, office visits and outpatient encounters) since the mid-1990s.[4-7] Despite the promising trend, a recent study that analyzed data from three regional health plans from 2000 through 2010 raised alarm that the downward trend in antibiotic use for children may be ending.[8] Although a new result from the same three regional health plans reported declines in antibiotic prescribing from 2010 to 2014,[9] it is not clear if that is the case in a much larger dataset of national health plans with more recent data.

Furthermore, antibiotic dispensing rates and trends by age groups (children vs adolescents) in EDs for the full spectrum of infectious diagnoses are not as well documented as in outpatient settings, although one study reported a decreasing trend among children from 2001 through 2010.[10] In a study that included data from both ED and outpatient settings, the authors pondered whether the limits of general messaging on antibiotic prescribing had been reached and if it was time to consider tailoring antibiotic stewardship interventions by setting, given the between-setting differences in patient mixes and commonly seen diagnoses.[8]

An updated analysis using data from the most recent decade available (2006 through 2016) from multiple national sources could provide clarity for outpatient antibiotic stewardship efforts. Such a study could also be informative, especially if it looks at dispensing patterns by age groups (children vs adolescents) over time and across the spectrum of diagnoses beyond respiratory tract infections (RTIs), such as urinary tract infections or skin and soft tissue infections. A number of prior studies were limited to RTIs,[4-6,11,12] and to our knowledge only three recent studies covered all infectious diagnostic conditions.[13-15] Diagnoses beyond RTIs were included in this study to address the possible concerns that clinicians may simply change their infectious diagnosis coding practices over time to justify antibiotic prescribing. Furthermore, it would be useful to examine if there are any age group-related differences in antibiotic dispensing by the two most commonly used encounter settings for children: EDs and outpatient settings.

Our objective was to measure rates and trends in overall and broad-spectrum antibiotic dispensing in EDs and outpatient care settings by age groups across the spectrum of infectious diagnostic conditions.[14] To achieve this, we leveraged information available via the National Institutes of Health (NIH) Collaboratory Distributed Research Network (DRN).[16,17] Outpatient care setting consists of physician-led clinics, outpatient hospital departments, urgent care centers, retail health clinics, and telehealth visits (although the common data model used by the DRN does not provide such separate breakdowns). Using national claims data, this real-world analysis found uneven decreases in potentially inappropriate antibiotic dispensing, suggesting the need for antibiotic stewardship interventions to become more common in outpatient settings.

2 | MATERIALS AND METHODS

2.1 | Data source and study design

The details regarding the use of NIH Collaboratory DRN for research have been documented previously.[16] Three data partners provided summarized population level data for this study (no patient-level or visit-level data were provided). The HealthCore Integrated Research Environment^{SM} (HIRE) provided access to data from 65 million commercially insured members in primarily 14 different states, of whom 25% were children.[18] The Aetna research database provided access to data from 40 million commercially insured members, of whom 25% were children.[19] The Harvard Pilgrim HealthCare Institute provided access to data from 3.7 million members of nonprofit health plans, of whom 28% were children.[20] A prior study compared HIRE enrollees to the US Census found that the HIRE database may underrepresent those who live in the Southern United States and overrepresent those who live in the Midwestern United States.[21] Enrollees in the Harvard Pilgrim HealthCare Institute data were limited to the Northeastern United Sates. Compared with the US Census, the Aetna research database population may overrepresent people living in some states (New York, Pennsylvania, Ohio, New Jersey, Maryland, Virginia, Florida, and Texas) and underrepresent people in other states (Massachusetts, Michigan, Wisconsin, Illinois, Minnesota, Iowa, Missouri, Tennessee, North Carolina, South Carolina, Alabama, Mississippi, Louisiana, New Mexico, California, and Oregon).

All three data partners participate in the Food and Drug Administration Sentinel project that has used the same data for hundreds of queries over the past 8 years.[22] Each data source contains member eligibility files and fully adjudicated inpatient and outpatient medical claims from facilities and medical professionals. Pharmacy claims are limited to outpatient dispensing. The NIH Collaboratory coordinating center created queries using publicly available Sentinel modular SAS programs designed to run against data in the Common Data Model (CDM) format[23]; aggregate results were returned for review, analysis, and reporting (no patient-level or visit-level data were provided). The CDM does not contain prescriber information such as clinician specialty. Differences in antibiotic dispensing by clinician specialty and treatment setting using the HIRE data were reported by a recent publication.[24]

This observational and retrospective study was conducted under the Research Exemption provisions of Privacy Rule 45 CFR 164.514(e) and was determined exempt by Investigational Review Board reviews at each data site as researchers did not access individual patient-level data. All data were obtained from administrative claims; no patients were directly contacted during the conduct of this study.

2.2 | Study population and infectious diagnosis categories

The analysis included children or adolescents younger than 19 years of age at the time of diagnosis. We identified antibiotic dispensing within 3 days following visits for specific infectious diagnoses (Table 1) in either ED or outpatient settings during 2006 through 2016. We excluded children with antibiotic dispensing 90 days before an infectious diagnosis since we wanted to capture a population with limited prior antibiotic exposure or recurrent antibiotic treatment, which could have influenced subsequent antibiotic prescribing decisions. To ensure data completeness 90 days preceding an infectious diagnosis, we excluded children or adolescents who lacked continuous medical and pharmacy insurance coverage for 3 months prior. Consequently, children aged 3 months or younger were excluded because they were most likely to lack a full 90 days continuous medical and pharmacy insurance history.

Based on adaptations from prior studies,[1,4,14] *International Classification of Diseases (ICD)*, Ninth/Tenth Revision, Clinical Modification codes were used to identify episodes and assign diagnosis categories. Following a prior study,[14] diagnoses were divided into four mutually exclusive classifications: (a) RTIs for which antibiotics are typically indicated (mostly indicated RTIs; eg, otitis media, sinusitis, pharyngitis, pneumonia); (b) RTIs for which antibiotics are mostly not indicated (mostly not indicated RTIs; eg, nasopharyngitis, bronchitis, viral pneumonia, influenza); (c) respiratory conditions for which antibiotics are definitely not indicated (never indicated respiratory conditions; eg, asthma, allergy, chronic sinusitis, chronic bronchitis); and (d) all other infectious conditions beyond RTIs regardless of antibiotic indication status (eg, skin/cutaneous/mucosal conditions, urinary tract infections, gastrointestinal infections, and miscellaneous infections; Table 1). We limited the query to four high-level diagnostic classifications to mirror a prior study[14] and account for limitation to ICD coding. For certain diagnoses, such as pharyngitis and pneumonia, ICD-9 or ICD-10 diagnosis codes do not adequately specify bacterial or viral etiology (ICD codes in insurance claim billing data could not be relied on to distinguish streptococcal pharyngitis from nonstreptococcal pharyngitis, or bacterial pneumonia from nonspecific pneumonia).Therefore, we classified these as conditions for which antibiotics are mostly indicated, similar to prior

TABLE 1 Diagnoses used to classify antibiotic dispensing from pharmacies following ED or outpatient pediatric visits

Condition Classification Based on Infectious Diagnosis	Description	Total Number of Visits With Diagnosis		
		ED	Outpatient	Total (column %)
RTIs for which antibiotics are mostly indicated	Sinusitis, pharyngitis, tonsillitis, otitis media, mastoiditis, streptococcal sore throat, peritonsillar abscess, nonspecific pneumonia	658 924	20 634 865	21 293 789 (29%)
RTIs for which antibiotics are mostly not indicated	Nasopharyngitis, laryngitis/tracheitis, unspecified upper respiratory infections, bronchitis (acute and not otherwise specified), bronchiolitis, viral pneumonia, influenza	524 528	11 431 505	11 956 033 (16%)
Respiratory conditions for which antibiotics are never indicated	Chronic sinusitis, chronic bronchitis, asthma, allergy, other respiratory conditions	518 220	8 067 417	8 585 637 (12%)
Other infectious diagnoses beyond RTIs regardless of antibiotic indication status	Urinary tract infections (eg, acute pyelonephritis, renal abscess, other pyelonephritis/pyelonephrosis, unspecified kidney infection, acute cystitis, unspecified cystitis), Skin/cutaneous/mucosal infections (eg, open wounds, burns, erysipelas, dermatophytosis/dermatomycosis, ear diseases other than otitis media and mastoiditis, folliculitis, infective myositis, mastitis, necrotizing fasciitis), Gastrointestinal infections (eg, intestinal infectious diseases, nausea/vomiting, diarrhea), Miscellaneous infections (eg, Lyme disease, cellulitis/abscess, tuberculosis, zoonotic diseases, diphtheria, pertussis, meningitis, sexually transmitted infections, parasitic diseases other than those of the skin and subcutaneous tissue or digestive tract)	2 912 696	28 537 883	31 450 579 (43%)
	Total (row %)	4 614 368 (6%)	68 671 670 (94%)	73 286 038 (100%)

Abbreviations: ED, emergency department; RTI, respiratory tract infection.

studies.[1,14,25] The "mostly indicated" category was included in this study to address possible concerns that clinicians may change their coding practices over time toward the mostly indicated category to justify antibiotic prescribing. Similar reasons led to the inclusion of the fourth category of other infectious conditions beyond RTIs.

As respiratory conditions provide the greater opportunity to reduce inappropriate antibiotic use,[26] the "mostly not indicated" and "never indicated" categories are the most relevant categories for outpatient antibiotic stewardship efforts. Since it will not be possible to discuss the rationale of each diagnosis placement in the two categories, we have limited our discussion to those that might be less apparent. Antibiotics are not recommended for acute or chronic bronchitis[27,28] and the relevance of a bronchitis diagnosis in children is itself uncertain.[29,30] The role of bacterial infection as a primary cause of chronic sinusitis is controversial.[31,32] Chronic sinusitis in children is probably a consequence of noninfectious conditions such as allergy, environmental pollutants, cystic fibrosis, or gastroesophageal reflux. As such, antibiotic therapy for chronic sinusitis in children is not recommended.

2.3 | Outcome measures and antibiotic classification

The denominator was the unique number of persons with visits for an infectious diagnosis (with or without antibiotic dispensing). The numerator was the total number of visits with infectious diagnoses resulting in any antibiotic dispensing. No person was counted more than once for the denominator although a person may have contributed multiple visits to the numerator. For visits with one of the four diagnosis classifications, the primary outcome was the number of visits per 1000 persons with a diagnosis for which any antibiotics were dispensed. A secondary outcome was the dispensing of broad-spectrum antibiotics, defined as the number of visits per 1000 persons with diagnosis in which broad-spectrum antibiotics were dispensed. Details on the list of oral systemic antibiotics we adopted in this study have already been documented in a prior study.[14] Antibiotics included were penicillins, sulfonamides, cephalosporins, macrolides, quinolones, lincomycin derivatives, tetracyclines, and carbapenems (excluding any topical formulations). Broad-spectrum antibiotics were defined as broad-spectrum penicillin (antipseudomonal penicillin and β-lactam/β-lactamase inhibitor combinations), second- to fourth-generation cephalosporins, macrolides, quinolones, lincomycin derivatives (clindamycin), and carbapenems. Following the age classification guidance from the Food and Drug Administration,[33] data were stratified according to age at diagnosis: infants (4 months to <2 years), preschool or school age (2-11 years), and adolescents (12-19 years). For the sake of brevity in reporting the results, we combined infants, preschool, and school age to create an age group of children (4 months – 11 years) to contrast with adolescents. Results were further stratified by sex (female vs male); year of diagnosis (2006-2016); winter season at time of diagnosis (November-March vs April-October); and encounter setting at time of diagnosis (ED vs outpatient).

2.4 | Statistical analysis

We used separate regression models for each of the four diagnosis classifications and two different encounter settings for a total of eight models for the primary outcome of any antibiotic dispensing. We also created eight analogous regression models for the secondary outcome of broad-spectrum antibiotic dispensing. We assessed temporal changes in antibiotic dispensing following a diagnosis across all years adjusting for age, sex, year of diagnosis, and winter season using Poisson regression with offsets. Poisson regression with population size denominator offsets (in our case, the log of number of persons with an infectious diagnosis) offered a natural way of analyzing aggregate data in the absence of person-level datasets. Year of diagnosis was entered into the regression models as a continuous variable while age group, sex, and winter season were entered in as binary variables. As exponentiation was applied to regression estimates and the confidence intervals (CI) for the aforementioned four variables, the estimates were interpreted as incidence rate ratios (IRR). All analyses were conducted using SAS Enterprise Guide 7.1 (SAS, Inc), and all tests were two-sided with a *P*-value of <.05 as the level of significance.

3 | RESULTS

A total of 73.3 million pediatric visits with infectious diagnoses were included in the analysis, of which 4.6 million (6%) occurred in EDs and 68.7 million (94%) in outpatient settings (Table 1). By the four diagnosis classifications, 21.3 million visits (29%) were for mostly indicated RTIs; 11.9 million visits (16%) were for mostly not indicated RTIs; 8.6 million visits (12%) were for never indicated respiratory conditions; and 31.5 million visits (43%) were for other infectious conditions beyond RTIs (Table 1).

3.1 | Population characteristics

For the outpatient setting, the study population was evenly divided between males and females for all diagnosis classifications except never indicated respiratory conditions. In contrast, the ED setting saw more visits for males in three of the four diagnosis classifications compared with females, while the sex distribution was equally divided for mostly indicated RTIs (Table 2). For both ED and outpatient encounters, children younger than 12 years accounted for a higher proportion of the study population across all four diagnosis classifications, compared with adolescents. The distribution of winter season and year at diagnosis was similar between ED and outpatient settings for all four diagnosis classifications.

3.2 | Overall antibiotic dispensing by setting

Pharmacy dispensing of any antibiotics decreased from 2006 to 2016 in all four classifications for diagnoses made in both settings

TABLE 2 Characteristics of children and adolescents with infectious diagnoses following ED or outpatient pediatric visits

	RTIs for Which Antibiotics are Mostly Indicated		RTIs for Which Antibiotics are Mostly Not Indicated		Respiratory Conditions for Which Antibiotics are Never Indicated		Other Infectious Diagnoses Beyond RTIs Regardless of Antibiotic Indication Status	
	ED n (%)	Outpatient n (%)	ED n (%)	Outpatient n (%)	ED n (%)	Outpatient n (%)	ED n (%)	Outpatient n (%)
Number of children/adolescents with diagnosis	305 011	5 528 211	246 133	3 854 809	229 869	2 604 637	1 276 381	7 236 988
Sex								
Female	151 108 (50)	2 793 671 (51)	111 029 (45)	1 904 359 (49)	98 636 (43)	1 208 316 (46)	581 700 (46)	3 642 768 (51)
Male	153 903 (50)	2 734 540 (49)	135 104 (55)	1 950 450 (51)	131 233 (57)	1 396 321 (54)	694 681 (54)	3 564 220 (49)
Age at diagnosis[a]								
Children (<12 y)	210 164 (67)	4 756 968 (66)	195 634 (77)	3 277 861 (71)	130 647 (54)	1 829 331 (59)	753 374 (56)	5 420 640 (57)
Adolescents (12-<19 y)	105 007 (33)	2 446 799 (34)	57 869 (23)	1 365 662 (29)	109 722 (46)	1 246 065 (41)	598 550 (44)	4 059 860 (43)
Total number of visits with diagnosis	658 924	20 634 865	524 528	11 431 505	518 220	8 067 417	2 912 696	28 537 883
Season of diagnosis[b]								
Winter (Nov-Mar)	236 588 (36)	7 963 060 (39)	222 262 (42)	4 936 513 (43)	151 486 (29)	2 278 241 (28)	772 280 (27)	8 148 915 (29)
Summer (Apr-Oct)	422 336 (64)	12 671 805 (61)	302 266 (58)	6 494 992 (57)	366 734 (71)	5 789 176 (72)	2 140 416 (73)	20 388 968 (71)
Year of diagnosis[b]								
2006	46 911 (7)	1 220 090 (6)	27 374 (5)	604 663 (5)	27 042 (5)	443 742 (6)	188 653 (6)	1 638 367 (6)
2007	64 352 (10)	1 762 662 (9)	43 356 (8)	922 140 (8)	38 952 (8)	606 691 (8)	244 610 (8)	2 199 361 (8)
2008	73 985 (11)	2 062 885 (10)	49 610 (9)	1 096 142 (10)	49 790 (10)	743 996 (9)	298 249 (10)	2 790 487 (10)
2009	81 310 (12)	2 246 614 (11)	80 088 (15)	1 493 751 (13)	56 956 (11)	784 357 (10)	314 103 (11)	2 888 457 (10)
2010	66 794 (10)	2 034 727 (10)	45 374 (9)	1 028 027 (9)	50 104 (10)	766 161 (9)	280 960 (10)	2 706 972 (9)
2011	63 531 (10)	2 012 404 (10)	46 362 (9)	1 055 779 (9)	46 902 (9)	728 774 (9)	262 631 (9)	2 613 604 (9)
2012	55 448 (8)	1 749 044 (8)	44 542 (8)	9547 93 (8)	44 798 (9)	688 124 (9)	249 645 (9)	2 447 055 (9)
2013	49 187 (7)	1 733 625 (8)	44 446 (8)	1 013 717 (9)	44 716 (9)	769 745 (10)	253 102 (9)	2 650 650 (9)
2014	53 829 (8)	1 900 773 (9)	52 380 (10)	1 113 312 (10)	54 234 (10)	848 648 (11)	271 738 (9)	2 839 913 (10)
2015	52 990 (8)	1 921 015 (9)	46 710 (9)	1 075 316 (9)	52 824 (10)	843 910 (10)	271 676 (9)	2 839 208 (10)
2016	50 587 (8)	1 991 026 (10)	44 286 (8)	1 073 865 (9)	51 902 (10)	843 269 (10)	277 329 (10)	2 923 809 (10)

[a]Sample sizes add up to more than total sample of children/adolescents since individuals could have more than one visit at different ages.
[b]Denominator is total number of visits with diagnosis.

(Table 3). The only exception was in outpatient settings for mostly indicated RTIs, which showed no relative change. The largest relative decreases in dispensed antibiotics were seen in pediatric visits from EDs for mostly not indicated RTIs (−43% from 303 fills in 2006 to 173 fills in 2016, both per 1000 persons with diagnosis), amounting to an annual decrease of 5% per year (IRR 0.95, 95% CI 0.95-0.96). Similarly, a large decrease in antibiotic dispensing was observed in pediatric visits from EDs for never indicated respiratory conditions (−40% from 195 fills in 2006 to 116 fills in 2016, both per 1000 persons with diagnosis), translating to a 5% per year annual decrease (IRR 0.95, 95% CI 0.95-0.96). The relative changes were more modest for pediatric visits from outpatient settings, where the largest change was a decrease of 16.9% (from 361 fills in 2006 to 300 fills in 2016, both per 1000 persons with diagnosis) for mostly not indicated RTIs, amounting to a 2% per year annual decrease (IRR 0.98, 95% CI 0.98-0.98). No changes were observed in pediatric visits from outpatient settings for mostly indicated RTIs and other infectious diagnosis beyond RTIs (Figure 1).

3.3 | Overall antibiotic dispensing by age groups

Children were slightly more likely to receive any antibiotics for mostly indicated RTIs if diagnosed in EDs (IRR 1.16, 95% CI 1.15-1.17) and outpatient settings (IRR 1.09, 95% CI 1.08-1.09), compared with adolescents. Similarly, children were more likely to receive antibiotics if diagnosed in EDs for never indicated respiratory conditions (IRR 1.14, 95% CI 1.11-1.16), whereas children were less likely to receive antibiotics if diagnosed in both settings for mostly not indicated RTIs (ED: IRR 0.68, 95% CI 0.67-0.70; outpatient: IRR 0.75, 95% CI 0.74-0.75) or for other infectious conditions beyond RTIs (ED: IRR 0.79, 95% CI 0.79-0.80; outpatient: IRR 0.85, 95%CI 0.84-0.85), compared with adolescents (Table 3; Figure S1 in Supplement).

3.4 | Broad-spectrum antibiotic dispensing by setting

Pharmacy dispensing of broad-spectrum antibiotics followed a different pattern. The relative change over the 11-year period showed an 8% increase in pediatric visits from EDs (from 329 fills in 2006 to 355 fills in 2016, both per 1000 persons with diagnosis) and a 9.6% increase (from 376 fills in 2006 to 412 fills in 2016, both per 1000 persons with diagnosis) in pediatric visits at outpatient settings for mostly indicated RTIs (Table 4). Broad-spectrum antibiotic dispensing for pediatric visits in EDs decreased by 34.6% (from 114 fills in 2006 to 75 fills in 2016, both per 1000 persons with diagnosis) for mostly not indicated RTIs and by 28.6% (from 81 fills in 2006 to 58 fills in 2016, both per 1000 persons with diagnosis) for never indicated respiratory conditions, both of which translated to a 3% per year annual decrease (IRR 0.97, 95% CI 0.96-0.97). Additionally, a 23% decrease (from 68 fills in 2006 to 52 fills in 2016, both per 1000 persons with diagnosis) in broad-spectrum antibiotic dispensing was observed for other infectious conditions beyond RTIs in pediatric visits at EDs, amounting to a 2% per year annual decrease (IRR 0.98, 95% CI 0.97-0.98). No change was observed in pediatric visits in outpatient settings for mostly not indicated RTIs, never indicated conditions, and other infectious diagnoses beyond RTIs.

3.5 | Broad-spectrum antibiotic dispensing by age groups

Children were more likely than adolescents to receive broad-spectrum antibiotics for mostly not indicated RTIs in ED (IRR 1.77, 95% CI 1.7 1-1.83) and outpatient settings (IRR 1.43, 95% 1.43-1.44). Similarly, children were more likely than adolescents to receive broad-spectrum antibiotics for never indicated respiratory conditions in ED (IRR 1.84, 95% CI 1.79-1.91) and outpatient settings (IRR 1.37, 95% 1.36-1.38). Lastly, children were more likely than adolescents to receive broad-spectrum antibiotics at both settings for mostly indicated RTIs, with the highest differential observed in outpatient settings for other infectious conditions beyond RTIs (IRR 2.07, 95% CI 2.06-2.08) in contrast to ED setting (IRR 1.70, 95% 1.67-1.72).

4 | DISCUSSION

Using national, geographically diverse claims data from a distributed research network, this real-world analysis of antibiotic dispensing patterns from 2006 through 2016 found that the overall antibiotic utilization rate for children with infectious diagnoses is decreasing. However, the rate of decrease varied depending on encounter setting (EDs or outpatient care settings), age at diagnosis (children younger than 12 years or adolescents), the antibiotic indication classification of the diagnosis (ie, whether antibiotics were mostly indicated, mostly not indicated, or never indicated), and the type of antibiotic (any antibiotics or broad-spectrum antibiotics). The largest relative decreases in antibiotic utilization were seen in EDs for any antibiotic dispensing, particularly for the classifications of mostly not indicated RTIs or never indicated respiratory conditions. More modest decreases were observed in outpatient settings for mostly not indicated RTIs or never indicated respiratory conditions.

A prior study concluded that overall and broad-spectrum antibiotic prescribing for RTIs among children was similar between ED and outpatient settings. However, the study was cross-sectional and did not explore possible differences across time.[25] In another study that looked at ED setting alone, antibiotic prescribing for children with RTIs declined from 2001 to 2010.[10] Our finding suggests that EDs continued to be correlated with greater decreasing rates in overall antibiotic dispensing than outpatient settings over the most recent decade (2006-2016). Additionally, EDs were associated with decreasing rates in broad-spectrum antibiotic dispensing in two of four infectious disease classifications studied, while outpatient encounters were associated with either flat or increasing rates for all four classifications studied. Although the reductions for each year may appear small—that is, a 5% decrease in EDs for mostly not indicated or never indicated respiratory conditions for

TABLE 3 Adjusted number of visits and incidence rate ratios in which any antibiotics were dispensed per 1000 persons with infectious diagnosis

	RTIs for Which Antibiotics are Mostly Indicated		RTIs for Which Antibiotics are Mostly Not Indicated		Respiratory Conditions for Which Antibiotics are Never Indicated		Other Infectious Diagnoses Beyond RTIs Regardless of Antibiotic Indication Status	
	ED Mean[a] (95% CI)	Outpatient Mean[a] (95% CI)	ED Mean[a] (95% CI)	Outpatient Mean[a] (95% CI)	ED Mean[a] (95% CI)	Outpatient Mean[a] (95% CI)	ED Mean[a] (95% CI)	Outpatient Mean[a] (95% CI)
2006[b]	575.4 (565.5-585.4)	615.0 (612.5-616.5)	303.4 (294.0-313.1)	361.0 (358.4-362.7)	194.5 (186.7-202.7)	269.0 (266.9-271.7)	194.1 (191.3-196.9)	167.0 (166.4-168.2)
2016[b]	510.5 (501.7-519.4)	614.0 (611.9-615.1)	172.5 (166.9-178.2)	300.0 (298.8-301.7)	116.3 (112.1-120.8)	243.0 (241.2-244.4)	152.8 (150.8-154.8)	157.0 (156.1-157.4)
All years[b]	538.7 (536-541.4)	598 (597.1-598.2)	233.5 (231.5-235.6)	333.1 (332.6-333.6)	154.7 (152.9-156.6)	264 (263.2-264.5)	177.2 (176.4-178.1)	160 (159.6-160.1)
Relative Change[c] (%)	-11.3%	0%	-43.1%	-16.9%	-40.2%	-9.7%	-21.3%	-6.0%
	ED IRR[d] (95% CI)	Outpatient IRR[d] (95% CI)	ED IRR[d] (95% CI)	Outpatient IRR[d] (95% CI)	ED IRR[d] (95% CI)	Outpatient IRR[d] (95% CI)	ED IRR[d] (95% CI)	Outpatient IRR[d] (95% CI)
Year[e] (per 1 y)	0.99* (0.99-0.99)	1.0 (1.0-1.0)	0.95* (0.95-0.96)	0.98* (0.98-0.98)	0.95* (0.95-0.96)	0.98* (0.98-0.98)	0.98* (0.98-0.98)	0.99 (0.99-1.0)
Children[f] (Ref = Adolescent)	1.16* (1.15-1.17)	1.09* (1.08-1.09)	0.68* (0.67-0.70)	0.75* (0.74-0.75)	1.14* (1.11-1.16)	1.0 (1.0-1.01)	0.79* (0.79-0.80)	0.85* (0.84-0.85)

Abbreviations: CI, confidence interval; ED, emergency department; IRR, incidence rate ratio; RTI, respiratory tract infections.

[a]Mean rates of antibiotic dispensing should not be summed across the four categories of infectious disease as a person may have multiple visits in a calendar year across categories.

[b]Antibiotic fills per 1000 children or adolescents with infectious diagnosis.

[c]Relative change percentage is calculated as (2016 rate − 2006 rate)/2006 rate.

[d]IRR estimates include adjustment for age sex, winter season of diagnosis, and year of diagnosis. IRR values <1 indicate decreased likelihood, whereas values >1 indicate increased likelihood of antibiotic dispensing.

[e]All years from 2006 to 2016 entered in model as continuous variable. IRR estimates include adjustment for sex, winter season of diagnosis, and age group (children/adolescents).

[f]Children ages 4 mo – 11 y; adolescent ages 12-19 y.

*$P < .001$.

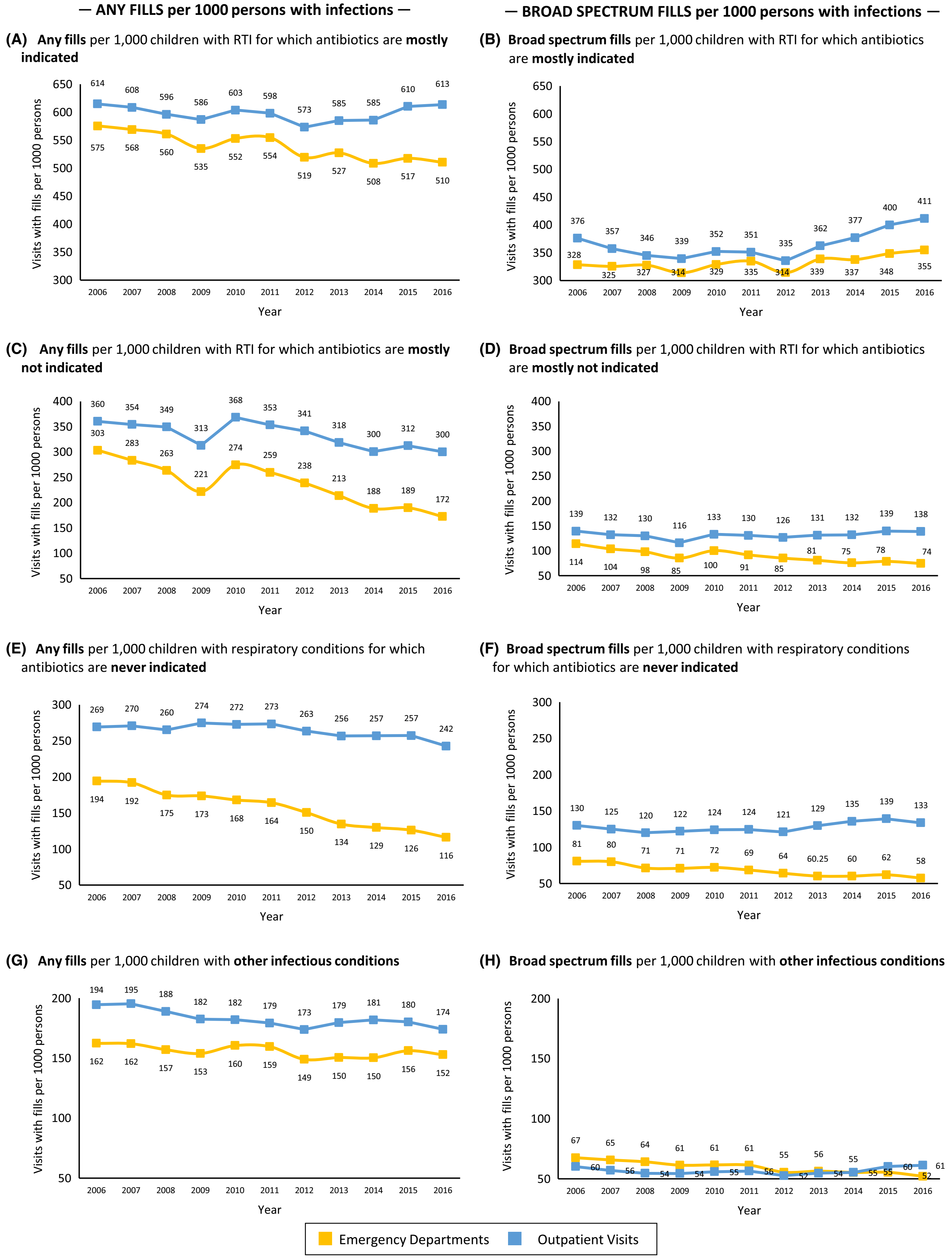

FIGURE 1 Rates for adjusted number of pediatric visits with antibiotic dispensing from pharmacies by encounter setting

TABLE 4 Adjusted number of visits and incidence rate ratios in which broad-spectrum antibiotics were dispensed per 1000 persons with infectious diagnosis

	RTIs for Which Antibiotics are Indicated		RTIs for Which Antibiotics are Mostly Not Indicated		Respiratory Conditions for Which Antibiotics are Never Indicated		Other Infectious Diagnoses Beyond RTIs Regardless of Antibiotic Indication Status	
	ED Mean[a] (95% CI)	Outpatient Mean[a] (95% CI)	ED Mean[a] (95% CI)	Outpatient Mean[a] (95% CI)	ED Mean[a] (95% CI)	Outpatient Mean[a] (95% CI)	ED Mean[a] (95% CI)	Outpatient Mean[a] (95% CI)
2006[‡]	328.7 (321.3-336.2)	376.0 (374.7-377.8)	114.2 (108.7-119.9)	139.0 (138.0-140.7)	80.7 (75.6-86.2)	130.0 (128.4-131.8)	67.5 (65.8-69.3)	60.0 (59.6-60.7)
2016[‡]	355.0 (347.7-362.4)	412.0 (410.6-413.2)	74.7 (71.3-78.2)	139.0 (137.7-139.7)	57.6 (54.5-60.8)	134.0 (132.6-135.0)	52.0 (50.8-53.3)	61.0 (60.9-61.7)
All years[‡]	332.1 (330-334.3)	364 (363.4-364.2)	89.2 (87.89-90.53)	132 (131.4-132)	67.6 (66.43-68.76)	128 (127.2-128.1)	59.4 (58.93-59.88)	57 (56.4-56.7)
Relative Change[b] (%)	8.0%	9.6%	-34.6%	0.0%	-28.6%	3.1%	-23.0%	1.7%
	ED IRR[c] (95% CI)	Outpatient IRR[c] (95% CI)	ED IRR[c] (95% CI)	Outpatient IRR[c] (95% CI)	ED IRR[c] (95% CI)	Outpatient IRR[c] (95% CI)	ED IRR[c] (95% CI)	Outpatient IRR[c] (95% CI)
Year[d] (per 1 y)	1.0 (1.0-1.01)	1.01* (1.01-1.01)	0.97* (0.96-0.97)	0.98* (0.98-0.98)	0.97* (0.96-0.97)	1.01 (1.0-1.01)	0.98* (0.97-0.98)	1.0 (1.0-1.1)
Children[e] (Ref = Adolescent)	1.71* (1.68-1.73)	1.50* (1.49-1.50)	1.77* (1.7 1-1.83)	1.43* (1.43-1.44)	1.84* (1.79-1.91)	1.37* (1.36-1.38)	1.70* (1.67-1.72)	2.07* (2.06-2.08)

Abbreviations: CI, confidence interval; ED, emergency department; IRR, incidence rate ratio; RTI, respiratory tract infections

[a]Mean rates of antibiotic dispensing should not be summed across the four categories of infectious disease as a person may have multiple visits in a calendar year across categories [‡]Antibiotic fill per 1000 children with infectious diagnosis.

[b]Relative change percentage is calculated as (2016 rate − 2006 rate)/2006 rate.

[c]IRR estimates include adjustment for age, sex, winter season of diagnosis, and year of diagnosis IRR values <1 indicate decreased likelihood, whereas values >1 increased likelihood of broad-spectrum antibiotic dispensing.

[d]All years from 2006 to 2016 entered in model as continuous variable. IRR estimates include adjustment for sex, winter season of diagnosis, and age group (children/adolescents).

[e]Children ages 4 mo – 11 y; adolescent ages 12-19 y.

*$P < .001$.

any antibiotic dispensing—the reduction becomes more meaningful when accumulated over the course of a decade. We speculate that the proximity to inpatient stewardship programs may be a reason for lower rates of antibiotic use and a greater downward trend of antibiotic use for mostly not indicated conditions in EDs vs outpatient settings.

Two findings were particularly reassuring regarding "diagnosis creep," where certain infectious diagnoses are selected specifically to justify higher levels of antibiotic prescribing.[34,35] The concern that clinicians may change their coding practices over time toward mostly indicated diagnoses to justify antibiotic prescribing is less likely as overall antibiotic dispensing for mostly indicated conditions remained flat. Similarly, the concern that clinicians may shift their coding practices over time toward diagnoses beyond RTIs is less likely as antibiotic dispensing was stable for this category of diagnoses. Our results highlight the key differences in antibiotic dispensing rates for children vs adolescents across settings, over time, and by the spectrum of infectious diagnosis, thereby making a novel contribution that could inform future stewardship interventions. A prior study reported that antibiotic prescribing was highest in children younger than 10 years, who received more than 40 million courses per year.[36] However, that study did not link prescriptions to indications, making it difficult to assess the level of prescribing by diagnosis. We found that although children received less overall antibiotic dispensing for mostly not indicated RTIs and other infectious diagnoses beyond RTIs compared with adolescents, they received a greater amount of broad-spectrum antibiotic dispensing for both classifications. In fact, children received a greater level of broad-spectrum antibiotics than adolescents in all four diagnosis classifications studied adjusted for year, sex, winter season, and encounter setting. This finding suggests that antibiotic stewardship strategies for children younger than 12 years should focus more on broad-spectrum than overall antibiotic dispensing. This is very important as a recent prospective study on children reported that broad-spectrum antibiotic dispensing was not associated with better outcomes for RTIs.[37] Although our findings of flat or increased rates for broad-spectrum antibiotics among children are aligned with past peer-reviewed publications,[8,36] they contrast with unadjusted findings from a report that indicated a 16% decrease.[38] That report did not limit the denominator to children with infectious diagnoses, which could have impacted the reported results. Nevertheless, the report raises concerns that some antibiotic dispensing among children may be unrelated to infectious diagnosis. Prior study results that reported antibiotic dispensing per 1000 persons (persons with or without infectious diagnoses combined in the denominator) will naturally differ from our study where the denominator is per 1000 persons with infectious diagnoses. As children without infectious diagnoses are less likely to receive antibiotics and less likely to count toward the numerator measure of antibiotic fills, study reports on antibiotic fills per 1000 person will report lower rates than our results.

Clinicians' perceptions of parental expectations[39-41] might explain the result that antibiotic dispensing for mostly indicated conditions went up for children compared with adolescents in both ED and outpatient settings. Clinicians may have felt that parents were more likely to expect antibiotic dispensing for children if the possible downside for not taking antibiotics when indicated for children is perceived to be higher than for adolescents. In contrast, such parental expectations may have been perceived to be less influential by clinicians when faced with prescribing decisions for mostly not indicated conditions (where children were less likely to receive antibiotic dispensing compared with adolescents). This is good news as exposure to antibiotics in childhood for potentially unnecessary indications could have downstream consequences during adult years (such as increased risk for obesity or autoimmune diseases such as asthma). The one exception is for never indicated conditions. Compared with adolescents, children were more likely to be dispensed antibiotics for never indicated conditions in the ED setting, which is concerning and deserves attention from ED clinicians. The unexpected result that children were less likely to be dispensed antibiotics for conditions beyond RTIs compared with adolescents should be explored in future studies with additional breakdown of this category into more granular classifications. Overall, our findings suggest the need to encourage antibiotic stewardship interventions to become common in outpatient settings beginning with stronger messaging, such as posting antibiotic prescription policies in patient examination rooms and waiting areas.[24,42] Contents for such messaging can be derived from the CDC Be Antibiotics Aware: Smart Use, Best Care educational effort.[43] Moreover, altering the order of predetermined menus in electronic health record programs,[44] providing physicians with monthly peer comparisons,[45] and prompting clinicians to enter free-text justifications for prescribing antibiotics incorporated into electronic health record reminders[46] will be helpful.

A strength of our study was that it measured antibiotic dispensing rather than prescribing, thus overcoming limitations of studies that only had access to written prescriptions.[4-6,10-12,44,47] Since not all prescriptions are dispensed, fills are one step closer to actual antibiotic consumption and a better measure of utilization. Another strength was the use of national data from two of the three largest US commercial health insurers, with the ability to link pharmacy dispensing to medical diagnoses. However, we were unable to confirm the accuracy of infectious diagnoses or clinical presentations—factors that influence the decision to prescribe antibiotics—as ICD diagnoses lack specificity to differentiate among all infectious diagnoses. In addition, we limited our analysis to four high-level classifications of diagnoses, which could have introduced more misclassification bias than a granular analysis that would have allowed many levels of infectious diagnosis classification (eg, breaking down other infectious conditions beyond RTIs into more categories). All data were from children insured by nonprofit or commercial health plans and the results may not be generalizable to those with other types of health insurance, such as Medicaid.

The decreases in antibiotic dispensing rates and trends observed counter previous research that suggested an end to the downward trend of antibiotic dispensing in children[8] and support a recent study that reported a continuing decreasing trend.[9] By examining antibiotics dispensed in addition to analyzing each encounter setting separately, our findings demonstrate that not only is the downward rate continuing, but also that the trend is more evident in some settings than others, suggesting the need to encourage antibiotic stewardship interventions to become common in outpatient settings (rather than the ED). More importantly, our analysis highlighted that the downward rate in overall antibiotic use does not extend to broad-spectrum agents, particularly for children under the age of 12—dispensing of broad-spectrum antibiotics increased across most of the infectious condition classifications in outpatient settings. This is concerning given efforts aimed to reduce the inappropriate use of broad-spectrum antibiotics. The finding of increased broad-spectrum dispensing indicates that selection of inappropriate agents by clinicians is as much of a challenge as the overuse of antibiotics in the first place. Antibiotic stewardship interventions need to focus on outpatient settings (rather than the ED), specifically on the use of broad-spectrum agents among children younger than 12, to meet the national goal of reducing inappropriate antibiotic use in outpatient settings.[26]

5 | CONCLUSIONS

This study provides evidence of a decrease of approximately 5% per year in overall antibiotic dispensing in two of four infectious disease classifications studied (mostly not indicated RTIs and never indicated respiratory conditions—the two classifications where a reduction is most needed) in ED settings, compared with approximately 2% decrease in outpatient settings. ED encounters were associated with decreasing rate of 2% to 4% per year in broad-spectrum antibiotic dispensing in the same two classifications, while outpatient encounters were associated with increasing rate of 1% per year. Antibiotic stewardship interventions need to focus on outpatient settings, specifically the use of broad-spectrum agents. Such efforts could be refined further by focusing on prescribing for children younger than 12 years. Future research should examine differences in the distribution of infectious diagnoses between ED and outpatient settings across age groups. Another area for future research is to analyze the contribution of individual antibiotic agents toward the observed differences in broad-spectrum antibiotic dispensing.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the NIH.

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AUTHOR CONTRIBUTIONS

Drs. Agiro, Haynes, and Brown conceptualized and designed the study, obtained funding, collected and assembled data, analyzed and interpreted data, reviewed, and revised the manuscript for important intellectual content. Dr Agiro drafted the initial manuscript. Dr Sridhar and Ms Gordon analyzed and interpreted data, reviewed and revised the manuscript for important intellectual content, and provided administrative (technical or material) support. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. None of the authors receive any compensation for their role in the study.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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