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MAJOR ARTICLE

Non-Visit-Based and Non-Infection-Related Antibiotic Use in the US: A Cohort Study of Privately Insured Patients During 2016–2018

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Background. Ambulatory antibiotic prescriptions without a clinic visit or without documentation of infection could represent overuse and contribute to adverse outcomes. We aim to describe US ambulatory antibiotic prescribing, including those without an associated visit or infection diagnosis.

Methods. We conducted an observational cohort study using data of all patients receiving antibacterial, antibiotic prescriptions from 04/01/2016 to 06/30/2018 in a large US private health insurance plan. We identified outpatient antibiotic prescriptions as (1) associated with a clinician visit and an infection-related diagnosis; (2) associated with a clinician visit but no infection-related diagnosis; or (3) not associated with an in-person clinician visit in the 7 days before the prescription (non-visit-based). We then assessed whether non-visit-based antibiotic prescriptions (NVBAPs) differed from visit-based antibiotics by patient, clinician, or antibiotic characteristics using multivariable models.

Results. The cohort included 8.6M enrollees who filled 22.3M antibiotic prescriptions. NVBAP accounted for 31% (6.9M) of fills, and non-infection-related prescribing accounted for 22% (4.9M). NVBAP rates were lower for children than for adults (0–17 years old, 16%; 18–64 years old, 33%; >65 years old, 34%). Among most commonly prescribed antibiotic classes, NVBAP was highest for penicillins (36%) and lowest for cephalosporins (25%) and macrolides (25%). Specialist physicians had the highest rate of NVBAP (38%), followed by internists (28%), family medicine (20%), and pediatricians (10%). In multivariable models, NVBAP was associated with increasing age, and NVBAP was less likely for patients in the South, those with more baseline clinical visits, or those with chronic lung disease.

Conclusions. Over half of ambulatory antibiotic use was either non-visit-based or non-infection-related. Particularly given health care changes due to the coronavirus disease 2019 pandemic, efforts to improve antibiotic prescribing must account for non-visit-based and non-infection-related prescribing.

Keywords. antibiotic prescribing; quality of prescribing; virtual care.

Antibiotic use is one of the most common outpatient medical interventions, with >259 million outpatient antibiotic prescriptions dispensed in the United States in 2018 [1]. Clinicians prescribe antibiotics at 13% of all ambulatory visits [2].

Overuse of antibiotics, however, increases the risk of antibiotic resistance and adverse effects. According to the 2019 Centers for Disease Control and Prevention (CDC) report "Antibiotic Resistance Threats," ~2.8 million antibiotic-resistant illnesses and 35 000 deaths occur each year in the United States [3]. Moreover, every 1000 outpatient antibiotic prescriptions result in 1 emergency department visit for an antibiotic-associated adverse drug event [4].

Up to 50% of prescribed antibiotics may be unnecessary [2, 5], meaning that patients do not even realize a clinical benefit in return for taking on the risk of adverse events. Antibiotic stewardship programs aim to measure and optimize antibiotic use to reduce the burden of antibiotic resistance and adverse effects. Such attempts at antibiotic stewardship have included interventions directed at prescribers, patients, and the public.

Most efforts to improve antibiotic prescribing address prescribing during a clinician visit with an infection-related diagnosis. For example, the Healthcare Effectiveness Data and Information Set (HEDIS) measures focus on avoiding antibiotic prescribing during the treatment of infections that are unlikely to be bacterial [6]. However, studies evaluating overall outpatient antibiotic use have recognized that many antibiotic prescriptions occur without a clinical encounter [7, 8]. Assessing the appropriateness of such prescriptions and designing interventions to improve quality and safety are

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challenging without an associated clinician visit. In a recent evaluation of 10 years of outpatient antibiotic prescriptions filled by Medicaid beneficiaries, we identified 28% that were not associated with a clinician encounter and an additional 17% associated with an encounter that lacked evidence of an infection-related diagnosis [9]. Given that patient-level Medicaid data are only available with a delay of several years, that Medicaid beneficiaries may differ in important respects from other populations, and the lack of clinician information in the Medicaid claims data, we sought to assess antibiotic prescribing using a contemporary, commercially insured cohort that included prescriber information. In addition, the health care changes from the coronavirus disease 2019 (COVID-19) pandemic—including increased non-visit-based care—have made measuring ambulatory antibiotic prescribing and assessment of care delivery without face-to-face encounters even more important [10–14].

METHODS

Data Sources

This study was a cross-sectional analysis of antibiotic prescribing among privately insured US patients from April 1, 2016, through June 30, 2018, using Optum's de-identified Clinformatics Data Mart Database commercial health insurance claims data. This data source includes deidentified administrative claims data for 12–14 million privately insured patients, representing multiple regions and types of health insurance from the overall US population [15]. The data include complete information on paid claims for all patients actively enrolled in a commercial health insurance plan. This includes all filled outpatient prescriptions, all inpatient and outpatient services along with accompanying diagnosis and procedure codes, and demographic information such as age and sex. We used data starting October 1, 2015, to correspond to the introduction of the International Classification of Diseases, version 10 (ICD-10), system. The institutional Review Board of Brigham and Women's Hospital approved the study.

Cohort Identification

We identified all claims for absorbable, oral antibiotic prescriptions filled in the outpatient setting from April 1, 2016, to June 30, 2018. Patients could contribute multiple prescriptions to the study cohort. We identified filled claims for all antibiotics on a predefined list (Supplementary Table 1) and required the patient filling the prescription to have at least 180 days of continuous prior insurance coverage to ensure that we adequately captured all baseline information such as comorbidities and prior medication use. We excluded several groups of antibiotics such as methenamine (used for urinary tract infection prophylaxis), nonoral antibiotics, and nonabsorbable oral antibiotics (eg, vancomycin).

Non-Infection-Related and Non-Visit-Based Antibiotic Prescriptions

For each prescription, we used the individual patient identifier to link to the claims for outpatient visits (including emergency department), inpatient visits, and all other services. We examined claims for the 7 days before the antibiotic filling (including the day of filling). The 7-day window was selected based on prior analyses that used up to 5-day windows between visits and prescriptions [2, 7], with an extra 2 days to allow for delays in filling of antibiotics that may occur in real-world practice situations:

- *Clinician encounter:* We identified claims for visits with clinicians using Current Procedural Terminology-4 (CPT-4) codes or Healthcare Common Procedure Coding System (HCPCS) codes for all in-person assessments, including codes for clinicians' evaluations and management and for any service that specified a patient visit. We captured outpatient visits, emergency department visits, or hospitalizations.
- *Infection-related encounters:* We identified the ICD-10 codes associated with each medical claim. We reviewed all 94 249 ICD-10 codes and classified them as infection-related or not (Supplementary Table 2) [7]. Among the infection-related codes, we additionally flagged those codes for chronic infectious conditions such as chronic osteomyelitis (M86.3) or acne (L70.0).
- *Any encounter:* We lastly identified claims for medical service of any type, irrespective of either the setting of care provided or any association with a clinician visit or an infection-related diagnosis code.

Using these definitions, we classified each antibiotic fill based on its association with encounters in the 7-day window. We defined 3 mutually exclusive groups:

1. *Visit-based, infection-related:* antibiotic fills associated with both a clinician visit and an infection-related diagnosis code in the 7 days before antibiotic filling.
2. *Visit-based, non-infection-related:* antibiotic fills associated with a clinician visit, but not an infection-related ICD-10 code.
3. *Non-visit-based:* If no encounters or only encounters that did not include a clinician visit were identified during the 7-day window, then the prescription was classified as non-visit-based.

We identified 2 special categories of antibiotic prescribing that might be less likely to be associated with a clinician visit. For antibiotic prescriptions for durations of ≥21 days, we checked the patient's claims record for the 180 days before and after the prescription filling date. If the patient received ≥90 days supplied of that antibiotic in the time period assessed, then we flagged the relevant prescriptions as "chronic antibiotic therapy." We also identified antibiotics commonly used for dental prophylaxis (Supplementary Table 3) for which the filled prescriptions provided only a 1-day supply and flagged those prescriptions as "probable dental prophylaxis."

Statistical Analysis

We calculated the per-population antibiotic prescribing by region, expressed as the overall rates of antibiotic use per 1000 eligible enrollees, to provide context for the proportionate measure of non-visit-based antibiotic prescribing.

We examined descriptive statistics for baseline characteristics of patients included in the study cohort, as well as the prevalence of chronic diseases (as defined using validated claims-based algorithms), number of office visits and hospitalizations in the 180-day baseline period (excluding the 7-day window used to define study outcomes), and number of prescriptions filled in the baseline period. For each index prescription, details such as antibiotic class, duration of prescription, and prescribing clinician type were reported. Optum uses the information attached to an individual clinician's National Provider Identification (NPI) to link to variables describing the clinician credential (eg, physician, nurse practitioner/physician assistant) and clinician specialty. We identified a potential issue with antibiotics prescribed by dental clinicians: Those medications appear in the prescription claims files, but as most enrollees had separate dental coverage, we were unable to assess whether those prescriptions were associated with a preceding visit. We retained these prescriptions in the overall cohort to provide as complete as possible a measurement of antibiotic use.

We assessed whether the proportion of non-visit-based antibiotic prescriptions differed by patient demographic characteristics such as age, sex, and region, as well as by clinical characteristics such as the presence of chronic medical conditions or baseline volume of visits and medications. We further compared the rates of non-visit-based antibiotic prescriptions across antibiotic class and clinician characteristics. Given the massive sample size, we did not test for statistical significance and considered absolute differences of 5% across variable categories to be clinically significant.

To evaluate the relative associations of patient, prescriber, and medication characteristics with the rates of non-visit-based antibiotic prescribing, we developed logistic regression models to evaluate the predictors of non-visit-based vs visit-based antibiotic prescribing (which included both infection-related and non-infection-related visits). We included all available variables in the model. Age was included as a continuous variable so that the parameter estimate provides the change in odds of a prescription being non-visit-based with each year's increase in age. For all categorical variables, we assigned the most common category as the reference value. We included indicator variables for year to control for underlying changes in antibiotic use over time and indicator variables for month to control for seasonal variation in antibiotic prescribing [16]. The variables for clinician specialty included a substantial fraction with a value of "missing" or "other"; we retained those observations in the models. The extremely large cohort size led to essentially all of the odds ratios being statistically significant by traditional criteria, so we focused on prespecified differences of ≥5% across categories as clinically meaningful effects when interpreting the model results. All analyses for the study were performed using SAS, version 9.4 (SAS Institute).

Patient Consent

This study does not include factors necessitating patient consent.

RESULTS

Cohort Description

We initially identified 27.5 million antibiotic prescriptions filled during the study period. After excluding prescriptions issued to patients without adequate baseline enrollment in the health plan (4.6 million, 16%) and prescriptions for methenamine (61 000, 0.3%), nonoral antibiotics (0.4 million, 1.7%), and nonabsorbable antibiotics (0.1 million, 0.5%), our final cohort included 22.3 million filled antibiotic prescriptions. These prescriptions were dispensed to 8.6 million unique patients (Figure 1).

Most of the patients filling antibiotic prescriptions were adults (mean age, 46 ± 24; 85% age ≥18), and 58% were female (Table 1). By region, the South accounted for the most patients and the Northeast the fewest, consistent with the known distribution of patients covered by these insurance plans [15]. Among the 22.3 million prescriptions, penicillins were the most common antibiotic class, followed by macrolides and cephalosporins, with most prescriptions running for 5–20 days (87%). We identified 5% of the total filled prescriptions that were for chronic antibiotic therapy and another 1% that were for probable dental prophylaxis.

In our cohort, 73% of the antibiotic prescriptions were issued by physicians, 17% were dispensed by allied health care professionals such as nurse practitioners, physician assistants, or dental clinicians, and the credential of the clinician was other or unknown for 10%. Prescriptions were issued by a wide range of specialties; primary care specialties accounted for 47%, split among family practice, internal medicine, and pediatrics; 26% were prescribed by medical or surgical specialists, and 6% by dental clinicians. For 15% of the prescriptions, the prescriber fields did not have accompanying information about the clinician's credential or specialty. Another 6% of antibiotic prescriptions were issued by clinicians identified in the data as nurses, without information on the specialty in which they practiced.

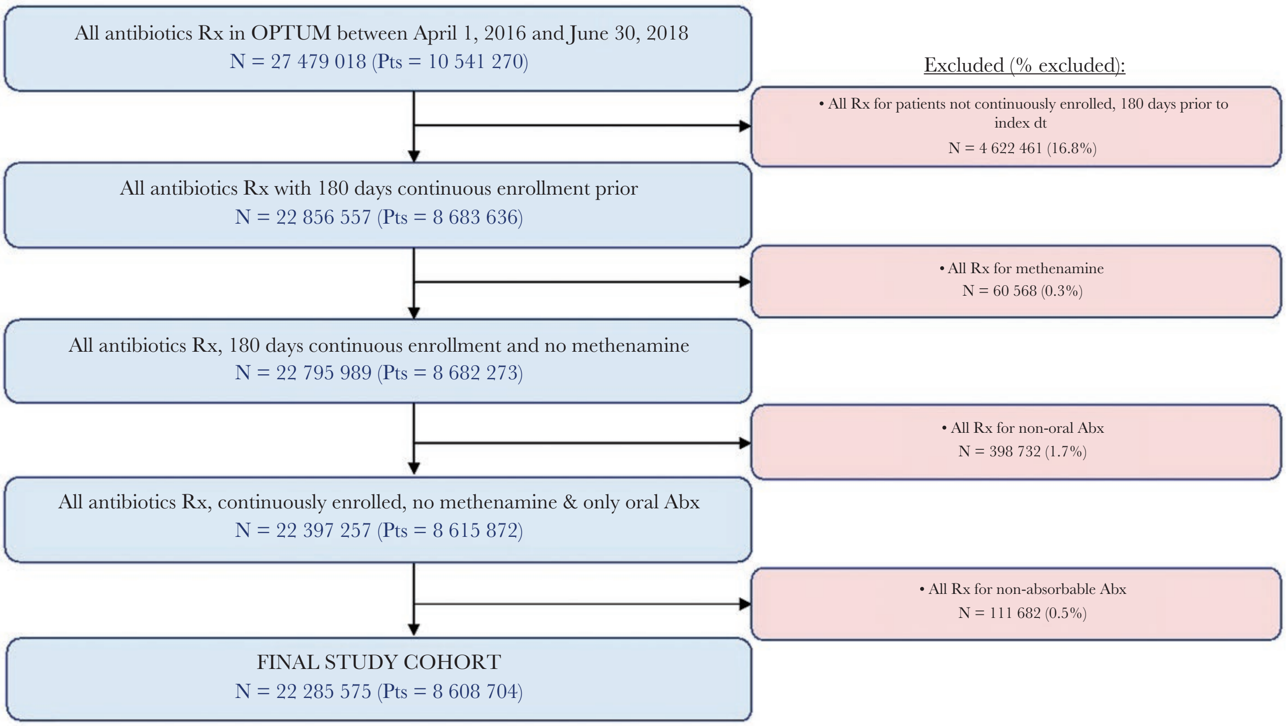

Figure 1. Cohort flowchart for cohort definition after application of all inclusion and exclusion criteria. Abbreviations: Abx, antibiotics; dt, date; Pts, patients; Rx, prescription.

Non-Visit-Based and Non-Infection-Related Antibiotics

Thirty-one percent (6.9M) of antibiotic fills were non-visit-based; another 22% (4.9M) were associated with a clinician visit that did not have an infection-related diagnosis; the remaining 47% (10.4M) of antibiotic fills were associated with a clinician visit and an infection-related diagnosis (Table 2). Compared with children, adults had over twice as high a proportion of antibiotic fills that were non-visit-based and also had higher rates of visit-based but non-infection-related antibiotic fills. There were no differences by gender. The rates of non-visit-based prescriptions were highest for penicillins (36%) and the group of classes combined as "other" (37%), were somewhat lower for sulfa drugs (30%), and were lowest for the remaining drug classes (25%–26%).

Patients in the South had lower rates of non-visit-based antibiotic prescriptions than patients in other regions, though per-population antibiotic prescribing in the South was higher than in other regions (Table 3). Overall national annual antibiotic prescribing in our cohort was ~800 prescriptions per 1000 patients. In terms of regional variability in non-visit-based antibiotic prescriptions, only the difference between the South and West regions reached the prespecified 5% threshold.

By clinician credential, non-visit-based antibiotic prescribing rates were lower for physicians (27%) compared with other allied health professionals (41%) or those whose credential was unknown (42%). When comparing across clinician specialties, the highest non-visit-based prescribing rate was among medical and surgical specialists (38%), followed by internists (28%) and family practitioners (20%). The lowest non-visit-based prescribing rates were reported among pediatricians (10%) and nurses (16%). For dental clinicians, 85% of antibiotic prescriptions were not associated with a clinician visit; however, this likely reflected the fact that we did not have claims records for dental visits, as previously described. These results are summarized graphically in Supplementary Figure 1.

Table 3 shows the per-population prescribing rates during the study period, separated by year. Prescribing rates in the South were >20% higher than in any other region, and prescribing rates in the West were the lowest in all 3 years studied. The per-population prescribing rate generally increased by 2%–5% per year in all 4 regions during the study period, with the exception of a 2% decrease in the Northeast region in 2018.

In multivariable modeling (Table 4), non-visit-based antibiotic use was strongly associated with increasing age, with the odds of non-visit-based antibiotic prescribing increasing by >1% for each year of age. Compared with the South, non-visit-based antibiotic use was similar in the Northeast and more common in the Midwest (by 8%) and West (by 14%).

Non-visit-based antibiotic use was less likely among enrollees who had more medical encounters in the baseline period, including office visits, emergency department visits, or hospitalizations. Enrollees with chronic lung disease were less likely to have non-visit-based prescriptions, and enrollees with cancer were more likely to receive non-visit-based prescriptions. All antibiotic classes except for clindamycin were less likely to be non-visit-based when compared with penicillin, which served

Table 1. Patient and Antibiotic Prescription Characteristics Included in Study Population

Patient Characteristics	No. (Total = 8 608 704)
Patient age at time of first antibiotic dispensing, mean (SD), y	46.3 (23.9)
Age groups, No. (%)	
0–5 y	501 000 (6)
6–12 y	467 939 (5)
13–17 y	368 412 (4)
18–65 y	4 991 304 (58)
>65 y	2 280 049 (27)
Gender	
Female	58
Male	42
Region	
Midwest	1 971 399 (23)
Northeast	859 702 (10)
South	4 031 326 (47)
West	1 725 019 (20)
Combined comorbidity score, mean (SD)	0.6 (1.6)
Prescription Characteristics	No. (Total = 22 285 575)
Patient age at time of antibiotic dispensing, mean (SD), y	49.8 (24.2)
Age groups, No. (%)	
0–5 y	1 244 705 (6)
6–12 y	970 027 (4)
13–17 y	812 196 (4)
18–65 y	11 937 211 (54)
>65 y	7 321 436 (33)
Antibiotic class, No. (%)	
Penicillins	6 670 586 (30)
Macrolides	4 031 195 (18)
Cephalosporins	3 261 810 (15)
Sulfa drugs	1 744 917 (8)
Fluoroquinolones	2 564 864 (12)
Tetracyclines	1 780 484 (8)
Other[a]	2 231 719 (10)
Duration of prescription, No. (%)	
>20 d	1 575 292 (7)
5–20 d	19 377 998 (87)
0–4 d	1 332 285 (6)
Chronic antibiotic prescriptions, No. (%)	1 128 530 (5)
Probable dental prophylaxis, No. (%)	190 257 (1)
Prescribing clinician credential, No. (%)	
Physician	16 299 747 (73)
Allied health provider[b]	3 800 902 (17)
Other/unknown	2 184 926 (10)
Prescribing clinician specialty, No. (%)	
Primary care	10 419 472 (47)
Family practice	5 817 659 (26)
Internal medicine	3 088 018 (14)
Pediatrics	1 513 795 (7)
Specialist	5 880 275 (26)
Dental clinician	1 257 095 (6)
Nurse	1 343 459 (6)
Other/unknown	3 385 274 (15)

[a]Most frequent "other": nitrofurantoin, metronidazole, clindamycin.
[b]"Allied health provider" includes nurse practitioners, physician assistants, and dental clinicians.

as the reference group. Nitrofurantoin was the only other antibiotic that did not have at least a 20% lower odds of non-visit-based prescribing relative to penicillin.

Prescriptions for long courses, chronic antibiotic therapy, and probable dental prophylaxis were all more likely to be non-visit-based. Prescriptions from pediatricians were 21% less likely to be non-visit-based than those from family practitioners (reference group), while prescriptions from internists were 46% more likely to be non-visit-based and those from medical or surgical specialists were more than twice as likely to be non-visit-based. Prescriptions filled in the first 4 months of the year were more likely to be associated with an in-person visit (ie, were less likely to be non-visit-based) compared with the reference month of July.

DISCUSSION

In this large, contemporary cohort of >20 million antibiotic prescriptions, 31% were not associated with an in-person visit, and another 22% did not include an infection-related diagnosis code. Our findings add to concerns about antibiotic overuse and the associated risks of adverse events and antibiotic resistance. Prescriptions issued and filled in the absence of an in-person visit or without documentation of an infection raise particular problems, as antibiotic stewardship interventions may not reach the prescribing clinician at the time when a decision is being made.

The overall antibiotic prescribing rates in our US study population were ~800 per 1000 patients, consistent with previous national studies [1] and higher than in most other comparable countries [17–22]. We observed differences by region in overall antibiotic prescribing rates, with patients in the South filling antibiotic prescriptions at a per-population rate 20%–30% higher than in any other region, consistent with prior findings [1]. The results of multivariable models controlling for other patient and clinician factors found that antibiotic prescriptions in the South were less likely to be non-visit-based compared with the Midwest and West.

The rates of non-visit-based antibiotic prescribing identified in this study population were similar to those from a recent evaluation of Medicaid patients using older data [9], as well as smaller prior studies [7, 8]. This new finding with more recent data confirms that non-visit-based antibiotic prescribing remains a problem in multiple populations and further shows that the phenomenon has not become less common in recent years. Our ability to include information about the prescribing clinicians in our analysis allowed us to develop models estimating the independent associations of patient, prescription, clinician, and regional factors with non-visit-based antibiotic use to identify under what circumstances it is more common.

Several patient characteristics were associated with non-visit-based prescribing, with a strong association between

Table 2. Non-Visit-Based, Non-Infection-Related, and Clinician Interaction/Infection-Related Antibiotic Prescriptions, by Patient and Prescription Characteristics

	Non-Visit-Based (No Claim or Clinician Interaction)	Non-Infection-Related (Clinician Interaction, No Infection)	Clinician Interaction, Infection	Total
	No. in Millions (Row %)			
Total	6.9 (31)	4.9 (22)	10.4 (48)	22.3 (100)
Age, y				
0–17	0.5 (16)	0.4 (15)	2.1 (69)	3.0
18–64	3.8 (33)	2.6 (22)	5.2 (45)	11.6
>65	2.6 (34)	1.9 (25)	3.1 (41)	7.7
Gender				
Female	4.2 (31)	3.0 (22)	6.5 (47)	13.6
Male	2.7 (31)	1.9 (23)	4.0 (46)	8.7
Antibiotic class				
Penicillins	2.4 (36)	1.0 (16)	3.2 (49)	6.7
Macrolides	1.0 (25)	1.4 (36)	1.6 (40)	4.0
Cephalosporins	0.8 (25)	0.7 (20)	1.8 (55)	3.3
Sulfa drugs	0.5 (30)	0.3 (20)	0.9 (50)	1.7
Quinolones	0.7 (26)	0.7 (26)	1.2 (48)	2.6
Other[a]	1.5 (37)	0.8 (20)	1.7 (43)	4.0
Duration of index antibiotic Rx				
Short duration (<4 d)	0.6 (45)	0.3 (25)	0.4 (30)	1.3
Medium duration (4–21 d)	5.3 (27)	4.4 (23)	9.7 (50)	19.3
Long duration (>21 d)	1.0 (62)	0.2 (15)	0.4 (23)	1.6
Region				
Midwest	1.6 (32)	1.0 (21)	2.4 (48)	5.0
Northeast	0.7 (31)	0.5 (23)	1.0 (45)	2.2
South	3.1 (29)	2.5 (23)	5.1 (48)	10.7
West	1.5 (34)	0.9 (21)	1.9 (44)	4.3
Unknown/other US	0.02 (40)	0.01 (20)	0.02 (40)	0.05
Clinician credential				
Physician	4.4 (27)	3.9 (24)	8.0 (49)	16.3
Allied provider	1.5 (41)	0.7 (19)	1.6 (41)	3.8
Other/unknown[b]	0.9 (42)	0.4 (17)	0.9 (40)	2.2
Clinician specialty				
Primary care	2.2 (21)	2.6 (25)	5.6 (54)	10.4
Family practice	1.2 (20)	1.5 (26)	3.1 (54)	5.8
Internal medicine	0.9 (28)	0.8 (27)	1.4 (45)	3.1
Pediatrics	0.1 (10)	0.2 (16)	1.1 (74)	1.5
Specialist	2.2 (38)	1.3 (21)	2.4 (41)	5.9
Dental clinician	1.1 (85)	0.2 (12)	0.04 (3)	1.3
Nurse[c]	0.2 (16)	0.3 (21)	0.8 (62)	1.3
Other/unknown[b]	1.2 (36)	0.6 (19)	1.5 (46)	3.4

[a]"Other" antibiotics include tetracycline, nitrofurantoin, metronidazole, clindamycin.

[b]The most common "other/unknown" clinician credentials and clinician specialties: unknown, missing, legal medicine specialist, chiropractor, certified acupuncturist, registered dietician, speech pathologist, etc.

[c]"Nurse" appeared in the clinician category field without additional information on specialty.

increasing age and the likelihood of non-visit-based antibiotic prescribing. It is perhaps reassuring that children, who might be more vulnerable to antibiotic side effects, were less likely to fill prescriptions without a clinician visit, although almost 1 out of 6 of the prescriptions for children were non-visit-based.

Non-visit-based antibiotic use was less common among patients with more baseline medical encounters even after controlling for other factors. Whether this reflects a predisposition by these patients to seek in-person medical care more readily cannot be determined from the claims data used for this study. Patients with chronic pulmonary disease were less likely to have non-visit-based antibiotic prescribing, perhaps corresponding to desire by either the patients or their treating clinicians to assess for infection more closely in-person.

The specialty of the prescribing clinician was strongly associated with non-visit-based antibiotic prescribing. Our finding that dental clinicians appeared to have extremely high rates of non-visit-based antibiotic use is likely an artifact of dental

Table 3. Antibiotic Prescribing Rates per 1000 Enrollees by Region

Region	Type of Visit Associated With Antibiotic Rx	Antibiotic Rx Rate (per 1000 Enrollees)		
		2016	2017	2018
Midwest	Non-visit-based	226	225	227
	Non-infection-related	145	148	151
	Clinician interaction, infection	322	345	352
	Total	692	718	730
Northeast	Non-visit-based	223	228	223
	Non-infection-related	165	171	166
	Clinician interaction, infection	319	329	327
	Total	707	728	716
South	Non-visit-based	262	258	263
	Non-infection-related	195	207	213
	Clinician interaction, infection	414	433	442
	Total	871	898	918
West	Non-visit-based	221	224	232
	Non-infection-related	132	142	151
	Clinician interaction, infection	277	294	310
	Total	629	661	693

claims being handled separately from medication claims. This data issue may also account for the finding that clindamycin was much more likely to be prescribed without a clinician visit given the frequent use of this agent for dental indications. The proportion of antibiotics prescribed by dental clinicians (6%) was lower than the 10% found in another recent analysis [23], which may further reflect that data on dental encounters and clinicians were not complete in these medical insurance claims files. While prescribing of antibiotics by dental clinicians is an important area for future study [24–26], these data concerns prevent us from drawing any conclusion about non-visit-based antibiotic prescribing in the dental care setting.

Compared with primary care specialties, medical and surgical subspecialists had higher non-visit-based prescribing rates, and when we developed models to control for other factors, specialists' antibiotic prescriptions were twice as likely to be non-visit-based compared with those written by family medicine physicians. Pediatricians had a much lower non-visit-based antibiotic prescribing rate, which was somewhat attenuated in the models including patient characteristics, but even after controlling for patient age, we estimated that pediatricians' antibiotic prescriptions were about 20% less likely to be non-visit-based. The higher rate of non-visit-based antibiotic prescribing by specialists is particularly concerning given the decrease in the use of primary care in the United States [27, 28].

These variations by region, patient, and clinician characteristics suggest that antibiotic stewardship programs seeking to reduce overuse may need to be customized to reflect patient populations and practice patterns in a given area. Analyses of both non-visit-based antibiotic prescribing and overall antibiotic use that include clinical data will be needed to identify the clinical decision points at which stewardship interventions could make a difference. Patients are increasingly connecting with their clinicians via patient portals or virtual visits [29–31]. The COVID-19 pandemic has caused profound shifts in care, including decreases in total visits, in-person visits [32, 33], and ambulatory antibiotic prescribing [11–13]. Designing antibiotic stewardship interventions customized to online and asynchronous interactions should be a priority [34].

There are several important limitations to consider when interpreting these analyses. While the use of claims data allowed us to evaluate a large and nationally representative sample, claims do not include information on clinical decision-making or other contextual elements [35], so we cannot evaluate whether specific patient or disease characteristics might have warranted prescribing an antibiotic without an in-person evaluation in a given situation. The models that we developed assess the association between the observed characteristics and non-visit-based prescribing, but we cannot assess whether such associations are causal, nor can we exclude residual confounding of these associations. While the possibility that non-visit-based antibiotic prescriptions would not be included in stewardship initiatives is a concern, these analyses do not provide insight into whether such prescriptions are associated with adverse events or outcomes for patients.

The data for this analysis came from a single health insurance provider, which may limit the generalizability of our findings. In particular, the claims data we used do not include information on race or ethnicity, so we were not able to explore any potential associations between these characteristics and non-visit-based antibiotic prescribing. Our findings provide some insights into prescribing without face-to-face encounters before the COVID-19 pandemic, but models of care have changed due to the pandemic and replication of our study in postpandemic data represents an important area for future research. We only captured interactions for which a bill was submitted. If clinicians communicated with patients by phone or electronically, that might not have been captured, although it is notable that such visits still would not include an in-person evaluation. In recent years, commercial urgent care clinics have become more common [36]; if a patient paid cash for a visit to an urgent care clinic and then filled a prescription for an antibiotic using their insurance, we might erroneously classify that visit as non-visit-based. These limitations highlight some of the challenges created by the extreme fragmentation that characterizes the US health care system [37–39].

Our secondary analysis of whether visits included service charges indicating an infectious condition is also limited by the use of claims data; if clinicians evaluate a patient for infection during a visit but do not include that in the billing diagnoses submitted

Table 4. Multivariable Logistic Regression Analysis Showing Association of Non-Visit-Based Antibiotics With Patient, Prescription, Clinician, and Regional Factors (see Supplementary Table 4 for Full Model; n = 22.2M Prescriptions)

Variables	Odds Ratio	99% CI
Patient characteristics		
Demographics & health care utilization variables		
Age, per year	1.014	1.014–1.014
Sex (female)	0.992	0.989–0.995
Percentage of patients with race = Black in state (using state on claim)	0.997	0.996–0.997
Percentage of patients with a high school degree or greater in state (using state on claim), vs < high school degree	0.992	0.992–0.993
No. of unique medications	1.043	1.042–1.043
No. of physician office visits	0.905	0.904–0.905
Occurrence of ED visit	0.867	0.865–0.868
Occurrence of hospitalization for any reason	0.996	0.994–0.997
No. of physicians associated with claims for patient	1.008	1.008–1.009
Medical comorbidities of categories of interest		
Chronic lung disease	0.862	0.858–0.866
Immunosuppression	1.053	1.044–1.062
Biologic immunosuppressive agents	0.921	0.909–0.934
Nonbiologic immunosuppressive agents	0.917	0.910–0.924
Cancer	1.118	1.112–1.123
Combined comorbidity score	0.969	0.968–0.970
Prescription characteristics		
Index antibiotic class		
Macrolides vs penicillins	0.776	0.773–0.779
Cephalosporins vs penicillins	0.725	0.722–0.729
Sulfa drugs vs penicillins	0.763	0.759–0.767
Quinolones vs penicillins	0.755	0.751–0.759
Clindamycin vs penicillins	1.341	1.330–1.352
Metronidazole vs penicillins	0.784	0.777–0.790
Nitrofurantoin vs penicillins	0.915	0.909–0.921
Other vs penicillins	0.771	0.767–0.776
Duration of antibiotic Rx		
Index Rx—long duration (>21 d; reference: short duration [<4 d])	1.190	1.178–1.203
Index Rx—medium duration (4–21 d; reference: short duration [<4 d])	0.608	0.604–0.611
Chronic antibiotic Rx	3.958	3.918–3.997
Probable dental prophylaxis	2.135	2.103–2.168
Prescribing clinician characteristics		
Prescribing clinician specialty		
Pediatrics vs family practice	0.788	0.782–0.795
Internal medicine vs family practice	1.462	1.457–1.467
Medical/surgical specialty vs family practice	2.174	2.167–2.180
Prescribing clinician type		
Allied health providers vs primary care	0.820	0.816–0.824
Dental clinician vs primary care	20.373	20.258–20.488
Other vs primary care	1.810	1.795–1.825
Missing vs primary care	2.563	2.554–2.571
Geographic variation		
Region		
Midwest vs South	1.083	1.079–1.087
Northeast vs South	0.991	0.986–0.995
Unknown/other US territories vs South	2.676	2.171–3.299
West vs South	1.142	1.137–1.146
Time variation (by calendar year)		
2017 vs 2016	0.983	0.980–0.986
2018 vs 2016	1.003	0.998–1.007
Seasonal variation (July is reference month)		
January vs July	0.866	0.859–0.872
February vs July	0.861	0.855–0.868
March vs July	0.899	0.892–0.905

Table 4. Continued

Variables	Odds Ratio	99% CI
April vs July	0.924	0.918–0.931
May vs July	0.941	0.935–0.947
June vs July	0.989	0.983–0.996
August vs July	1.015	1.008–1.022
September vs July	0.992	0.985–0.999
October vs July	0.945	0.939–0.952
November vs July	0.955	0.949–0.962
December vs July	0.954	0.947–0.960

Abbreviation: ED, emergency department.

to insurance, we would have no way to capture the information. Special cases such as antibiotics used chronically or those prescribed for probable dental prophylaxis may be appropriately prescribed without a visit, but we checked for these categories and they accounted for a small percentage of antibiotic prescribing.

CONCLUSIONS

Non-visit-based antibiotic prescribing occurs often in clinical practice, accounting for 31% of filled antibiotics in this recent national cohort, with an additional 22% of filled antibiotics lacking documentation of infection. The phenomenon of non-visit-based antibiotic prescribing is more common for adults, and its prevalence varies significantly based on clinician specialty and region. Efforts to improve the quality and safety of ambulatory antibiotic use should measure non-visit-based and non-infection-related antibiotic prescriptions to design interventions that can address the full range of antibiotic prescribing.

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