



Appropriateness of outpatient antibiotic prescribing among privately insured US patients: ICD-10-CM based cross sectional study

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ABSTRACT

OBJECTIVE

To assess the appropriateness of outpatient antibiotic prescribing for privately insured children and non-elderly adults in the US using a comprehensive classification scheme of diagnosis codes in ICD-10-CM (international classification of diseases-clinical modification, 10th revision), which replaced ICD-9-CM in the US on 1 October 2015.

DESIGN

Cross sectional study.

SETTING

MarketScan Commercial Claims and Encounters database, 2016.

PARTICIPANTS

19.2 million enrollees aged 0-64 years.

MAIN OUTCOME MEASURES

A classification scheme was developed that determined whether each of the 91 738 ICD-10-CM diagnosis codes “always,” “sometimes,” or “never” justified antibiotics. For each antibiotic prescription fill, this scheme was used to classify all diagnosis codes in claims during a look back period that began three days before antibiotic prescription fills and ended on the day fills occurred. The main outcome was the proportion of fills in each of four mutually exclusive categories: “appropriate” (associated with at least one “always” code during the look back period, “potentially appropriate” (associated with at least one “sometimes” but no “always” codes), “inappropriate” (associated only with “never” codes), and “not associated with a recent diagnosis code” (no codes during the look back period).

RESULTS

The cohort (n=19 203 264) comprised 14 571 944 (75.9%) adult and 9 935 791 (51.7%) female enrollees. Among 15 455 834 outpatient antibiotic prescription fills by the cohort, the most common antibiotics were azithromycin (2 931 242, 19.0%), amoxicillin (2 818 939, 18.2%), and amoxicillin-clavulanate (1 784 921, 11.6%). Among these 15 455 834 fills, 1 973 873 (12.8%) were appropriate, 5 487 003 (35.5%) were potentially appropriate, 3 592 183 (23.2%) were inappropriate, and 4 402 775 (28.5%) were not associated with a recent diagnosis code. Among the 3 592 183 inappropriate fills, 2 541 125 (70.7%) were written in office based settings, 222 804 (6.2%) in urgent care centers, and 168 396 (4.7%) in emergency departments. In 2016, 2 697 918 (14.1%) of the 19 203 264 enrollees filled at least one inappropriate antibiotic prescription, including 490 475 out of 4 631 320 children (10.6%) and 2 207 173 out of 14 571 944 adults (15.2%).

CONCLUSIONS

Among all outpatient antibiotic prescription fills by 19 203 264 privately insured US children and non-elderly adults in 2016, 23.2% were inappropriate, 35.5% were potentially appropriate, and 28.5% were not associated with a recent diagnosis code. Approximately 1 in 7 enrollees filled at least one inappropriate antibiotic prescription in 2016. The classification scheme could facilitate future efforts to comprehensively measure outpatient antibiotic appropriateness in the US, and it could be adapted for use in other countries that use ICD-10 codes.

Introduction

Inappropriate antibiotic prescribing to outpatients promotes the development of antibiotic resistance, which is one of the greatest threats to public health worldwide.¹ Over the past three decades, many countries have invested substantial resources in education, quality improvement, and antibiotic stewardship initiatives.²⁻⁵ Despite these initiatives, studies suggest that a large proportion of outpatient antibiotic prescriptions could still be unnecessary.^{6,7}

Although antibiotics are prescribed for a wide variety of conditions, studies assessing the appropriateness of outpatient antibiotic prescribing have mostly focused on specific conditions, such as acute respiratory tract infections.^{8,9} Furthermore, studies of outpatient antibiotic appropriateness in the US have been limited to pre-2015 data owing to reliance on diagnosis codes in ICD-9-CM (international classification of diseases-clinical modification, ninth revision).⁸⁻¹⁰ ICD-9-CM was replaced by ICD-10-CM in the US on 1 October

WHAT IS ALREADY KNOWN ON THIS TOPIC

Previous studies have used ICD-9-CM diagnosis codes and pre-2015 data to show widespread inappropriate prescribing of antibiotics to outpatients in the US

No study has examined outpatient antibiotic appropriateness using a comprehensive classification scheme of diagnosis codes contained in ICD-10-CM, which replaced ICD-9-CM in the US on 1 October 2015

WHAT THIS STUDY ADDS

This study used a comprehensive classification scheme of all 91 738 ICD-10-CM diagnosis codes and insurance claims data from 19.2 million privately insured US children and non-elderly adults in 2016

12.8% of outpatient antibiotic prescription fills were appropriate, 35.5% were potentially appropriate, 23.2% were inappropriate, and 28.5% were not associated with a recent diagnosis code

The classification scheme could facilitate future efforts to comprehensively measure outpatient antibiotic appropriateness in the US, and could also be adapted for use in other countries that use ICD-10 codes

2015; therefore future studies of outpatient antibiotic appropriateness in the US would be greatly facilitated by the development of a comprehensive ICD-10-CM based classification scheme. Such a scheme could be adapted for use in countries outside the US, many of which have been using a modified version of ICD-10 for decades.

We developed a novel classification scheme determining whether each of the 91 738 diagnosis codes in the 2016 version of ICD-10-CM justified the use of antibiotics. Using this classification scheme and a 2016 national US claims database, we assessed the appropriateness of all outpatient antibiotic prescriptions among a large cohort of US children and non-elderly adults with private employer sponsored insurance coverage. In 2016, about 152 million of the 320 million Americans had such coverage.¹¹

Methods

Data source and study cohort

We conducted a cross sectional analysis of data from the 2016 Truven MarketScan Commercial Claims and Encounters database, which contains claims for people aged 0-64 years who receive private health insurance from their employers.¹² Elderly people aged 65 years and older are not included in this database. Compared with all non-elderly people with employer sponsored insurance in the US, MarketScan enrollees have a similar age and sex distribution but are more likely to live in the South.¹³ The MarketScan Inpatient Services, Outpatient Services, and Facility Header databases include claims for medical visits from a variety of settings, including primary care offices, specialist offices, hospital outpatient departments, urgent care centers, retail clinics, ambulatory surgery centers, emergency departments, home visits, community hospitals, and academic hospitals. The MarketScan pharmacy database includes claims for outpatient prescription fills at retail and mail order pharmacies, but it does not capture antibiotic utilization in the inpatient setting.

We limited the cohort to children aged 0-17 years and adults aged 18-64 years who had pharmacy benefit coverage and were continuously insured for all 12 months in 2016 (or continuously insured since birth, as applicable).

Definition of antibiotics and identification of antibiotic prescription fills

We defined antibiotics as the 39 oral antibiotics assessed in the 2016 “antibiotic utilization” measure in the Healthcare Effectiveness Data and Information Set (HEDIS), a collection of quality measures reported by more than 90% of US health insurance plans (see appendix 1 for the list of antibiotics).¹⁴ These 39 oral antibiotics include agents against bacteria and protozoa but not against fungi, helminths, viruses, or malaria. To identify prescription fills for these antibiotics in the MarketScan pharmacy database, we used a list of 7177 national drug codes published on the website of the National Committee for Quality Assurance, which sponsors the HEDIS measures.¹⁴

ICD-10-CM diagnosis code classification scheme

Following the approach used in previous studies,^{6 7 15-17} we classified each of the 91 738 diagnosis codes in the 2016 version of ICD-10-CM as “always” if the associated condition is almost always an indication for antibiotics (eg, pneumonia or urinary tract infection), “sometimes” if the condition is a potential indication for antibiotics (eg, acute sinusitis or acute otitis media), and “never” if the condition is almost never an indication for antibiotics (eg, acute upper respiratory tract infection, acute bronchitis, or non-infectious conditions). We did not adapt previous ICD-9-CM based classification schemes to ICD-10-CM owing to the differences between these coding systems. Additionally, we aimed to develop a scheme that could be applied to any administrative dataset. Therefore, we created a new scheme in which we classified each ICD-10-CM diagnosis code one by one. The primary author (KC) initially decided on the classifications, which the other authors (JAL and MAF) reviewed; disagreements were resolved by discussion until consensus was achieved. The authors included one general pediatrician and two general internists with expertise in the measurement of antibiotic overuse and medication use in administrative data.^{3 6 18 19}

In developing the scheme, we erred on the side of assuming appropriate antibiotic use. For example, we classified several codes as “always” even though antibiotics might not always be required (eg, pneumonia is often viral). As another example, we classified several diagnosis codes as “sometimes” even when oral antibiotics are rarely necessary (eg, infective otitis externa), or even when the diagnosis code typically implies a viral illness (eg, infectious colitis and gastroenteritis). As a final example, we classified some non-specific diagnosis codes as “sometimes” when they might be used to denote complications requiring antibiotics (eg, superficial thrombophlebitis, a diagnosis code that could be used for thrombophlebitis complicated by cellulitis).

Appendix 2 includes additional details about the classification scheme. For illustrative purposes, box 1 presents the classification scheme for diseases of the respiratory system (ICD-10-CM codes J00-J99), which are among the most common indications for outpatient antibiotic prescriptions.⁶ Appendix 3 includes a table summarizing the scheme by diagnosis code category. We also developed a similar classification scheme (although not used in the current study) of all 17 553 diagnosis codes in the final 2015 version of ICD-9-CM to facilitate analyses using older datasets, as well as a classification scheme of all 94 249 codes in the 2017 version of ICD-10-CM. Appendix 4 discusses the comparability of the 2015 ICD-9-CM and 2016 ICD-10-CM scheme. For each version of the scheme, a full list of classification decisions is included online.

Claims based measure of outpatient antibiotic appropriateness

Because prescription drug claims do not report the indication for prescriptions, claims based studies

Box 1 ICD-10-CM respiratory system diagnosis codes (J00-J99) classified as always, sometimes, and never indications for oral antibiotics*
Always

- Streptococcal pharyngitis and tonsillitis; bacterial pneumonia; pneumonia, unspecified organism; pharyngeal abscess (peritonsillar, retropharyngeal, and parapharyngeal); abscess of lung and mediastinum; pyothorax; infection of tracheostomy stoma; ventilator associated pneumonia; mediastinitis

Sometimes

- Acute and chronic sinusitis; acute and chronic pharyngitis; acute and chronic tracheitis; acute and chronic tonsillitis; supraglottitis; acute epiglottitis; influenza with pneumonia, respiratory manifestations, or otitis media; unspecified acute lower respiratory tract infection; chronic adenoiditis; chronic bronchitis; emphysema; other chronic obstructive pulmonary disease; bronchiectasis; pleural effusion; other and unspecified tracheostomy complication; accidental laceration or puncture of respiratory organ during procedure

Never

- Acute and chronic nasopharyngitis; acute and chronic rhinitis; acute and chronic laryngitis; acute and chronic laryngotracheitis; acute and chronic laryngopharyngitis; croup; acute upper respiratory tract infection; influenza without pneumonia; viral pneumonia; acute and unspecified bronchitis; acute bronchiolitis; allergic rhinitis; asthma; pneumoconiosis; hypersensitivity pneumonitis; respiratory conditions due to inhalation of chemicals; pneumonitis due to solids and liquids; respiratory conditions due to radiation; acute respiratory distress syndrome; pulmonary edema and pulmonary eosinophilia; other interstitial pulmonary diseases (eg, pulmonary fibrosis); malignant pleural effusion, pleural plaque, and other pleural conditions (eg, chylous effusion); other pleural conditions (eg, chylous effusion); tracheostomy complications other than infection or "other and unspecified" complications; intraoperative and postprocedural respiratory complications other than ventilator associated pneumonia; respiratory failure; other and unspecified respiratory disorders other than mediastinitis (eg, bronchospasm)

*Classification scheme for respiratory conditions is presented for illustration. See supplement for full scheme.

†Unspecified bronchitis diagnosis code is often used to denote acute rather than chronic bronchitis.²⁹

typically infer indication by examining diagnosis codes on claims occurring in close temporal proximity to prescription fills.^{7 18 20} Following this approach, we used our scheme to classify diagnosis codes on all inpatient, outpatient, and facility claims during a look back period that began three days before antibiotic prescription fills and ended on the day fills occurred (eg, for fills on 4 May 2016, we examined claims from 1 May 2016 to 4 May 2016). We assigned fills into one of four mutually exclusive categories (fig 1): "appropriate" if associated with at least one "always" diagnosis code during the look back period, "potentially appropriate" if associated with at least one "sometimes" code but no "always" codes, "inappropriate" if associated with only "never" codes, and "not associated with a recent diagnosis code" if there were no diagnosis codes during the look back period (ie, either there were no claims during this period, or the only claims that occurred

during this period lacked diagnosis codes). In other words, appropriate antibiotic fills were associated with at least one recent diagnosis code that almost always justifies antibiotics, potentially appropriate fills were associated with at least one recent diagnosis code that sometimes justifies antibiotics but no codes that almost always justify antibiotics, and inappropriate fills were only associated with recent diagnosis codes that almost never justify antibiotics.

Study outcomes

The main outcome was the proportion of antibiotic prescription fills in each mutually exclusive appropriateness category. To generate population level prevalence estimates, we also calculated the proportion of enrollees who filled at least one prescription in each category in 2016. These proportions were not mutually exclusive (eg, an enrollee could fill one appropriate

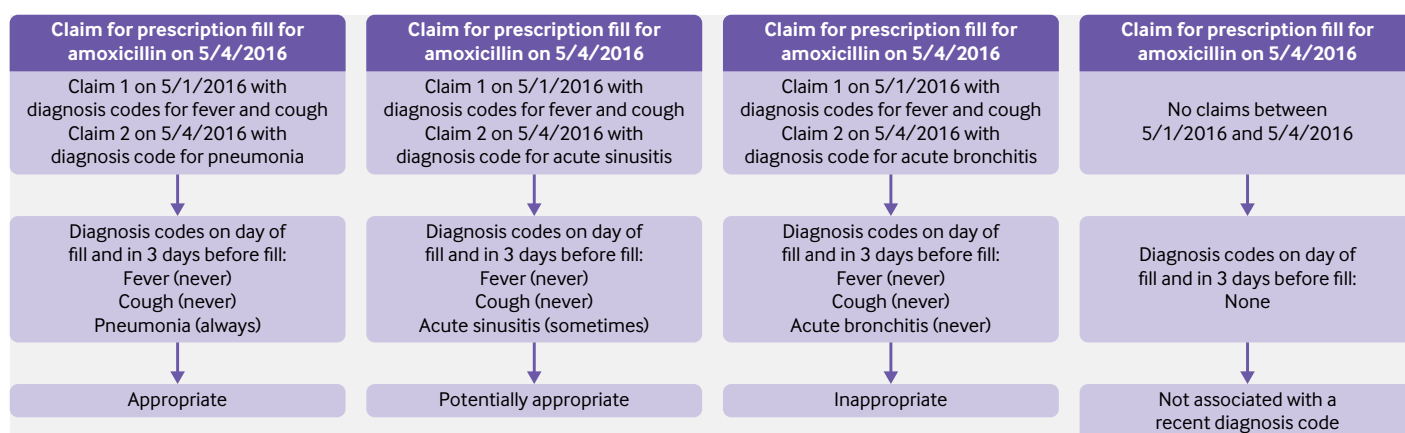


Fig 1 | Claims based measure of outpatient antibiotic appropriateness. (First column) At least one "always" code is present on a claim on the day of the fill or during the three days before the fill; (second column) at least one "sometimes" code and no "always" codes are present during the look back period; (third column) only "never" codes are present during the look back period; (fourth column) no claims and therefore no diagnosis codes are present during the look back period

prescription as well as one inappropriate prescription in 2016).

For each category, we determined the three most commonly prescribed antibiotics and the percentage of fills that were refills of a previous antibiotic prescription (based on the MarketScan variable REFILL, which equals 1 or more for true refills and 0 in all other cases, including new prescriptions for a previously filled antibiotic). Using a modified version of the Clinical Classifications Software ICD-10-CM diagnosis code grouping algorithm published by the US Agency for Healthcare Research and Quality,²¹ we identified the three most frequent diagnoses associated with appropriate, potentially appropriate, and inappropriate fills during the look back period (see appendix 5 for details). For these three categories of fills, we also identified the healthcare setting in which prescriptions were most likely written based on the types of claims present during the look back period (see appendix 6 for details).

Statistical analysis

We used SAS 9.4 (Cary, NC) to calculate descriptive statistics for the overall cohort and for each age subgroup (children versus adults). We did not conduct formal significance testing, as many clinically insignificant differences may have been statistically significant given the large size of the study cohort.

Sensitivity analyses

In sensitivity analyses, we examined the degree to which the proportion of fills assigned to each category changed when we examined diagnosis codes occurring on the day of fills and in the seven days before fills, instead of three days; excluded refills; excluded fills occurring between 1 January 2016 and 3 January 2016 (since we were unable to examine all claims in the look back period for some of these fills); and excluded fills

in which we assigned the setting to an inpatient visit or outpatient surgery (since diagnosis codes alone may not be sufficient to assess outpatient antibiotic appropriateness in these settings).

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Study population

Our database included 27 895 445 enrollees; we excluded 7 409 175 who were not continuously insured in 2016 and 1 283 006 who did not have pharmacy benefit coverage, leaving 19 203 264 enrollees in the study cohort. This cohort included 14 571 944 adults (75.9%) and 4 631 320 children (24.1%) (table 1). Among the 19 203 264 enrollees in the cohort, 9 935 791 (51.7%) were women, 2 273 862 (11.8%) lived in a rural area, and 3 100 589 (16.2%) were from the Northeast region, compared with 3 905 622 (20.3%) from the Midwest, 8 790 740 (45.8%) from the South, 3 326 768 (17.3%) from the West, and 79 545 (0.4%) from an unknown region.

Antibiotic fills and users

In 2016, patients in the cohort filled 15 455 834 outpatient antibiotic prescriptions, a rate of 805 prescriptions per 1000 enrollees. The most commonly filled antibiotics were azithromycin (2 931 242, 19.0%), amoxicillin (2 818 939, 18.2%), and amoxicillin-clavulanate (1 784 921, 11.6%). Among the 15 455 834 antibiotic prescription fills,

Table 1 | Demographic characteristics of cohort and of antibiotic users, MarketScan 2016. Values are numbers (percentages)

Characteristics	All enrollees in cohort			Enrollees filling ≥1 antibiotic prescription		
	Overall (n=19 203 264 enrollees)	Adults (n=14 571 944 enrollees)	Children (n=4 631 320 enrollees)	Overall (n=7 625 438 enrollees)	Adults (n=5 801 861 enrollees)	Children (n=1 823 577 enrollees)
Female	9 935 791 (51.7)	7 669 271 (52.6)	2 266 520 (48.9)	4 501 499 (59.0)	3 585 458 (61.8)	916 041 (50.2)
Age (years):						
0-4	1 229 293 (6.4)	N/A	1 229 293 (26.5)	582 525 (7.6)	N/A	582 525 (31.9)
5-12	2 052 971 (10.7)	N/A	2 052 971 (44.3)	760 659 (10.0)	N/A	760 659 (41.7)
13-17	1 349 056 (7.0)	N/A	1 349 056 (29.1)	480 393 (6.3)	N/A	480 393 (26.3)
18-34	4 930 434 (25.7)	4 930 434 (33.8)	N/A	1 809 888 (23.7)	1 809 888 (31.2)	N/A
35-50	4 704 587 (24.5)	4 704 587 (32.3)	N/A	1 886 258 (24.7)	1 886 258 (32.5)	N/A
51-64	4 936 923 (25.7)	4 936 923 (33.9)	N/A	2 105 715 (27.6)	2 105 715 (36.3)	N/A
Region:						
Northeast	3 100 589 (16.2)	2 375 299 (16.3)	725 290 (15.7)	1 118 269 (15.6)	906 257 (15.6)	282 012 (15.5)
Midwest	3 905 622 (20.3)	2 924 353 (20.1)	981 269 (21.2)	1 483 197 (19.5)	1 105 313 (19.1)	377 884 (20.7)
South	8 790 740 (45.8)	6 750 678 (46.3)	2 040 062 (44.1)	3 856 172 (50.6)	2 960 476 (51.0)	895 696 (49.1)
West	3 326 768 (17.3)	2 466 361 (16.9)	860 407 (18.6)	1 068 687 (14.0)	809 066 (13.9)	259 621 (14.2)
Unknown	79 545 (0.4)	55 253 (0.4)	24 292 (0.5)	29 113 (0.4)	20 749 (0.4)	8364 (0.5)
Urban or rural:						
Urban	16 861 099 (87.8)	12 765 740 (87.6)	4 095 359 (88.4)	6 593 228 (86.5)	5 011 642 (86.4)	1 581 586 (86.7)
Rural	2 273 862 (11.8)	1 759 314 (12.1)	514 548 (11.1)	1 007 328 (13.2)	772 569 (13.3)	234 759 (12.9)
Unknown	68 303 (0.4)	46 890 (0.3)	21 413 (0.5)	24 882 (0.3)	17 650 (0.3)	7232 (0.4)

N/A=not applicable.

Table 2 | Proportion of antibiotic prescription fills in each appropriateness category, and proportion of cohort filling at least one prescription in each category, MarketScan 2016

Categories	Proportion of fills in each category (%)*			Proportion of cohort filling ≥1 antibiotic prescription in each category in 2016 (%)†		
	Overall (n=15 455 834 fills)	Adults (n=11 780 881 fills)	Children (n=3 674 953 fills)	Overall (n=19 203 264 enrollees)	Adults (n=14 571 944 enrollees)	Children (n=4 631 320 enrollees)
Appropriate	1 973 873 (12.8)	1 347 569 (11.4)	626 304 (17.0)	1 446 673 (7.5)	973 292 (6.7)	473 381 (10.2)
Potentially appropriate	5 487 003 (35.5)	3 696 473 (31.4)	1 790 530 (48.7)	3 750 225 (19.5)	2 610 416 (17.9)	1 139 839 (24.6)
Inappropriate	3 592 183 (23.2)	2 965 194 (25.2)	626 989 (17.1)	2 697 918 (14.1)	2 207 173 (15.2)	490 745 (10.6)
Not associated with recent diagnosis code	4 402 775 (28.5)	3 771 645 (32.0)	631 130 (17.2)	2 756 082 (14.4)	2 360 472 (16.2)	395 610 (8.5)

*Proportions are mutually exclusive.

†Proportions are not mutually exclusive.

917 140 (5.9%) were refills of previous antibiotic prescriptions.

Antibiotics were filled by 7 625 438 enrollees (39.7% of the cohort); table 1 displays the demographic characteristics. Among these 7 625 438 antibiotic users, 3 995 690 (52.4%) filled one antibiotic prescription in 2016, 1 815 305 (23.8%) filled two, 852 979 (11.2%) filled three, and 961 464 (12.6%) filled four or more. Antibiotic users filled a mean of 2.0 antibiotic prescriptions in 2016.

Proportion of antibiotic prescription fills in each appropriateness category

Among all 15 455 834 fills, 1 973 873 (12.8%) were appropriate, 5 487 003 (35.5%) were potentially appropriate, 3 592 183 (23.2%) were inappropriate, and 4 402 775 (28.5%) were not associated with a recent diagnosis code (table 2). Among the 4 402 775 fills not associated with a recent diagnosis code,

4 392 068 (99.8%) were not associated with any claims during the look back period, whereas 10 707 (0.2%) were associated only with claims that lacked diagnosis codes.

In subgroup analyses by age, 3 696 473 (31.4%) of the 11 780 881 antibiotic prescription fills among adults were potentially appropriate, compared with 1 790 530 (48.7%) of the 3 674 953 fills among children. Additionally, 2 965 194 (25.2%) of the 11 780 881 fills among adults were inappropriate, compared with 626 989 (17.1%) of the 3 674 953 fills among children.

Population level prevalence estimates

In 2016, 1 446 673 (7.5%) of the 19 203 264 enrollees filled at least one appropriate antibiotic prescription, 3 750 225 (19.5%) filled at least one potentially appropriate prescription, 2 697 918 (14.1%) filled at least one inappropriate prescription, and 2 756 082

Table 3 | Characteristics of antibiotic prescription fills in each category, MarketScan 2016. Values are numbers (percentages)

Variables	Appropriate (n=1 973 873 fills)	Potentially appropriate (n=5 487 003 fills)	Inappropriate (n=3 592 183 fills)	Not associated with recent diagnosis code (n=4 402 775 fills)
Most frequent antibiotics	Amoxicillin (366 029 (18.5)), ciprofloxacin (285 971 (14.5)), nitrofurantoin (209 279 (10.6))	Amoxicillin (1 084 112 (19.8)), amoxicillin-clavulanate (1 038 934 (18.9)), azithromycin (970 750 (17.7))	Azithromycin (1 047 819 (29.2)), amoxicillin (408 059 (11.4)), amoxicillin-clavulanate (296 092 (8.2))	Amoxicillin (960 739 (21.8)), azithromycin (713 479 (16.2)), doxycycline (445 932 (10.1))
Refills of past prescriptions	12 807 (0.6)	38 146 (0.7)	118 845 (3.3)	747 341 (16.9)
Most frequent associated diagnoses*	Urinary tract infection (783 860 (39.7)), streptococcal pharyngitis/tonsillitis (594 069 (30.0)), bacterial pneumonia (241 254 (12.2))	Acute sinusitis (1 880 398 (34.3)), acute suppurative otitis media (1 030 481 (18.8)), acute pharyngitis (910 365 (16.6))	Acute bronchitis (667 245 (18.6)), acute upper respiratory tract infection (568 511 (15.8)), respiratory symptoms† (524 192 (14.6))	N/A
Prescriptions written in each setting‡:				
Office	1 331 154 (67.4)	4 385 257 (79.9)	2 541 125 (70.7)	N/A
Urgent care center	160 479 (8.1)	483 521 (8.8)	222 804 (6.2)	N/A
Emergency department	220 591 (11.2)	275 652 (5.0)	168 396 (4.7)	N/A
Inpatient	112 720 (5.7)	49 781 (0.9)	63 301 (1.8)	N/A
Outpatient surgery	14 036 (0.7)	51 506 (0.9)	115 688 (3.2)	N/A
Hospital outpatient	23 353 (1.2)	60 561 (1.1)	54 161 (1.5)	N/A
Home visit	3795 (0.2)	6566 (0.1)	26 035 (0.7)	N/A
Retail clinic	5024 (0.3)	9424 (0.2)	1730 (0.1)	N/A
Multiple¶	53 954 (2.7)	126 215 (2.3)	107 876 (3.0)	N/A
Unknown¶	48 767 (2.5)	38 520 (0.7)	291 067 (8.1)	N/A

N/A=not applicable.

*Three most frequently associated diagnoses on day of fills or in three days before fills. Numbers in parentheses refer to percentage of fills in category associated with diagnosis during this look back period. Diagnoses are not mutually exclusive; for example, a patient could have diagnosis codes corresponding to both acute bronchitis and respiratory symptoms such as cough in the look back period. See Appendix 5 for details.

†Acute pharyngitis not specifically specified as streptococcal.

‡Includes symptoms such as cough, shortness of breath, and wheezing.

§Percentage of antibiotic fills in category attributed to each setting. See Appendix 6 for details.

¶"Multiple" includes fills associated with multiple claim types during the look back period, whereas "unknown" includes fills associated with claims for encounters that are unlikely to be the source of antibiotic prescriptions, such as laboratory visits. See Appendix 6 for details.

(14.4%) filled at least one prescription that was not associated with a recent diagnosis code (table 2).

In subgroup analyses by age, 2 610 416 (17.9%) of the 14 571 944 adults in the cohort filled at least one potentially appropriate prescription during 2016, compared with 1 139 839 (24.6%) of the 4 631 320 children in the cohort. Additionally, 2 207 173 (15.2%) of the 14 571 944 adults filled at least one inappropriate prescription during 2016, compared with 490 745 (10.6%) of the 4 631 320 children.

Characteristics of antibiotic prescription fills in each category

Among the 1 973 873 appropriate fills, the three most frequently associated diagnoses were urinary tract infections, streptococcal pharyngitis/tonsillitis, and bacterial pneumonia (table 3). Among the 5 487 003 potentially appropriate fills, the three most frequently associated diagnoses were acute sinusitis, acute suppurative otitis media, and acute pharyngitis. Among the 3 592 183 inappropriate fills, the three most frequently associated diagnoses were acute bronchitis, acute upper respiratory tract infection, and respiratory symptoms such as cough.

Among the 11 053 059 antibiotic fills classified as either appropriate, potentially appropriate, or inappropriate, 8 257 536 (74.7%) were prescribed in office based settings, 866 804 (7.8%) were prescribed in urgent care centers, and 664 639 (6.0%) were prescribed in emergency departments. Among the 3 592 183 inappropriate fills, 2 541 125 (70.7%) were prescribed in office based settings, 222 804 (6.2%) in urgent care centers, and 168 396 (4.7%) in emergency departments.

Among the 4 402 775 antibiotic prescription fills that were not associated with a recent diagnosis code, 747 342 (16.9%) were refills of previous antibiotic prescriptions (table 3). Among these 747 342 refills, the most common antibiotics were doxycycline (218 668, 29.3%), minocycline (139 524, 18.7%), and sulfamethoxazole-trimethoprim (74 899, 10.0%).

Sensitivity analyses

Results did not change substantially when we used a longer look back period, excluded refills, excluded fills occurring between 1 January 2016 and 3 January 2016, or excluded fills in which the setting was assigned to inpatient visits or outpatient surgeries (see appendices 7-10).

Discussion

We developed a comprehensive classification scheme determining whether each of the 91 738 ICD-10-CM diagnosis codes justified the use of antibiotics. Using this scheme, we assessed outpatient antibiotic appropriateness for a cohort of 19.2 million US children and non-elderly adults with private employer sponsored insurance coverage in 2016—a cohort that accounted for about one eighth of those with such coverage in the US. Among all outpatient antibiotic prescription fills by the cohort, 12.8% were

appropriate, 35.5% were potentially appropriate, 23.2% were inappropriate, and 28.5% were not associated with a recent diagnosis code.

We classified 23.2% of outpatient antibiotic prescription fills as inappropriate because they were only associated with diagnoses that almost never justify antibiotics (eg, acute upper respiratory tract infections and acute bronchitis). Owing to the high rate of antibiotic prescribing at the population level in our study (805 per 1000 enrollees), a large proportion of enrollees in the cohort received inappropriate antibiotic prescriptions during the year. Specifically, 14.1% of enrollees filled at least one inappropriate antibiotic prescription in 2016, including 15.2% of adults and 10.6% of children.

By themselves, these findings would show the widespread nature of inappropriate outpatient antibiotic prescribing at the level of both prescription fill and population. However, two other findings in our study suggest that the true scope of inappropriate prescribing is even greater. First, among the 35.5% of fills classified as potentially appropriate, many could have been inappropriate. For example, 34.3% and 16.6% of fills in this category were associated with diagnoses of sinusitis and pharyngitis, respectively, and previous literature has shown that both these conditions have high rates of non-guideline adherent antibiotic prescribing.^{9 22}

Second, among the 28.5% of fills that were not associated with a recent diagnosis code in claims, many might also have been inappropriate. Some of these fills could represent non-visit based prescribing in which prescriptions were written without patients having been examined (eg, prescriptions sent to a pharmacy after telephone or online consultation).^{23 24} Additionally, some could represent antibiotic prescriptions from healthcare visits that were not observed in our medical claims database (eg, retail clinic and urgent care visits paid out of pocket, or dental visits, settings in which inappropriate antibiotic prescribing often occurs).^{15 25 26} Finally, among fills that were not associated with a recent diagnosis code, one sixth were refills. Although some of these refills could have been for conditions requiring a prolonged course of antibiotics (eg, many were for doxycycline and minocycline, which are commonly prescribed for the long term treatment of acne),²⁷ others may represent inappropriate refills of previous prescriptions. Collectively, fills that were potentially appropriate or not associated with a recent diagnosis code represented 64.0% of all fills, highlighting the importance of conducting future studies to assess their appropriateness using data sources with detailed clinical information, such as medical charts.

In our study, inappropriate outpatient antibiotic prescription fills were more prevalent among adults (25.2% of fills) than among children (17.1% of fills). This finding is potentially consistent with previous studies suggesting that antibiotic prescriptions for adults are more likely to be unnecessary compared with antibiotic prescriptions for children.⁶

Importantly, however, the proportion of fills classified as potentially appropriate was higher among children. Robust methods to assess these fills must be developed to examine age based differences in overall appropriateness of antibiotics in outpatients.

Comparison to past studies

This study assessed the appropriateness of outpatient antibiotic prescribing for all conditions using a comprehensive, ICD-10-CM based classification scheme. Our finding that 23.2% of outpatient antibiotic prescription fills were inappropriate seems to be lower than estimates from previous studies, but direct comparisons are challenging owing to key differences in methodology, data, and populations. For example, using nationally representative visit level data from US offices and emergency departments and a classification scheme based on ICD-9-CM diagnosis codes, Fleming-Dutra et al estimated that 30% of outpatient antibiotic prescriptions in 2010 and 2011 were inappropriate.⁶ To obtain this estimate, the authors considered all prescribing for conditions that never justify antibiotics to be inappropriate, and additionally they estimated the rate of inappropriate prescribing for conditions that sometimes justify antibiotics based on rates of bacterial prevalence or the lowest rate of prescribing among US census regions.⁶ In contrast, we only considered antibiotic prescription fills to be inappropriate if they were prescribed for conditions that never justify antibiotics. Furthermore, our study captured prescribing in a broader variety of healthcare settings than offices and emergency departments, although it did not capture prescribing in populations other than those who are privately insured.

As another example, Olesen et al adapted the ICD-9-CM classification scheme of Fleming-Dutra et al to US Medicare claims and found that 40% of outpatient antibiotic prescriptions filled by elderly Americans between 2011 and 2014 were inappropriate.⁷ In contrast, we used an ICD-10-CM based classification scheme that was not adapted from that of Fleming-Dutra et al, focused on a younger population, and used more recent data.

Limitations of this study

First, similar to previous studies of outpatient antibiotic prescribing, we relied on diagnosis codes assigned by clinicians.^{6 8 9 10 18 20 26} In some cases, however, clinicians may fail to code the condition for which antibiotics are prescribed,²⁸ whereas in other cases, clinicians may err on the side of up-coding when prescribing antibiotics (eg, coding pneumonia rather than bronchitis for a patient with ambiguous respiratory symptoms). Chart reviews will likely be necessary to ascertain the magnitude and direction of any misclassification bias due to inaccurate or incomplete coding.

Second, similar to previous studies of outpatient antibiotic appropriateness, we used a classification scheme that was developed on the basis of consensus.⁶⁷ We acknowledge that other authors may have made

different classification decisions, and we have provided a full list of our decisions to facilitate efforts to assess and validate our scheme.

Third, our database did not capture antibiotic prescription fills or visits paid entirely out of pocket, and additionally it did not contain information on prescriber specialty. Fourth, we assessed outpatient antibiotic appropriateness solely based on indication and not the choice of agent or duration of therapy, which are also important dimensions of appropriate prescribing.²⁸ Finally, findings may not generalize to publicly insured US patients covered by Medicaid or Medicare or to all privately insured people in the US.

Conclusion and policy implications

This study provides the most recent and comprehensive estimates of outpatient antibiotic appropriateness in the US privately insured population to date. Our results show the scale of inappropriate antibiotic prescribing at both the prescription and population levels. Furthermore, our results highlight the importance of conducting future studies to assess the 64.0% of outpatient antibiotic prescription fills that are either only potentially appropriate or not associated with a recent diagnosis code.

This study also provides a methodological framework for assessing outpatient antibiotic appropriateness using ICD-10-CM diagnosis codes. Our classification scheme could be applied to any dataset that uses ICD-10-CM, including claims data, visit level data, and electronic health record data. Furthermore, our scheme could be adapted to the country specific versions of ICD-10 that are currently being utilized across the world. As such, our scheme could be a valuable tool for policymakers and researchers interested in measuring and improving the appropriateness of outpatient antibiotic prescribing.

Contributors: KC, MAF, and JAL conceived and designed the study. KC acquired the data. KC, MAF, and JAL analyzed and interpreted the data. KC drafted the manuscript. KC, MAF, and JAL critically revised the manuscript for important intellectual content. KC was responsible for the statistical analysis. JAL supervised the study. KC is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Owing to the use of deidentified data, the institutional review board of the University of Michigan Medical School exempted this study from human subjects review.

Data sharing: Programming code is available from the corresponding author at chuak@med.umich.edu. The data used in this study are proprietary and cannot be shared.

Transparency: The lead author (KC) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted;

and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supplementary material: Appendices 1-10

Supplementary material: Spreadsheet showing ICD-9-CM and ICD-10-CM antibiotic appropriateness classification schemes