Trends and Seasonal Variation in Outpatient Antibiotic Prescription Rates in the United States, 2006 to 2010

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Antibiotic-resistant bacteria are an increasing threat to the effectiveness of antibiotics. The majority of antibiotics are prescribed in primary care settings for upper respiratory tract infections. The purpose of this study was to describe seasonal trends in outpatient antibiotic prescriptions (Rx) in the United States over a 5-year period. This study was a retrospective, cross-sectional observation of systemic antibiotic prescriptions in the outpatient setting from 2006 to 2010. Winter months were defined as the first and fourth quarters of the calendar year. Antibiotic prescribing rates were calculated (prescriptions/1,000 population) using annual U.S. Census Bureau population data. Over 1.34 billion antibiotic prescriptions were dispensed over the 5-year period. The antibiotic prescription (Rx) rate decreased from 892 Rx/1,000 population in 2006 to 867 Rx/1,000 population in 2010. Penicillins and macrolides were the primary antibiotic classes prescribed, but penicillin prescribing decreased while macrolide prescribing increased over the study period. Overall, antibiotic prescriptions were 24.5% higher in winter months than in the summer, with the largest difference (28.8%) in 2008 and the smallest (20.4%) in 2010. This seasonality was consistently drug class dependent, driven by 75% and 100% increases in penicillin and macrolide prescriptions, respectively, in the winter months. The mean outpatient antibiotic prescription rate decreased in the United States from 2006 to 2010. More antibiotic prescribing, predominantly driven by the macrolide and penicillin classes, in the outpatient setting was observed in the winter months. Understanding annual variability in antibiotic use can assist with designing interventions to improve the judicious use of antibiotics.

A ntiibiotic-resistant bacteria continue to be a threat to the effectiveness of antibiotics and pose a significant challenge for clinicians treating patients with bacterial infections. Infections caused by resistant organisms limit provider treatment options, and with the lack of availability and development of new antibiotics, there has been little improvement in the armamentarium (1, 2). The overuse and volume of antibiotic prescribing in communities has been found to correlate to the incidence of bacterial resistance (3–5). Therefore, to reduce the number of infections caused by resistant bacteria, inappropriate antibiotic prescribing must decrease (3–8).

The majority of antibiotics in the United States are prescribed in primary care settings for the treatment of upper respiratory tract infections (URIs), for which antibiotic therapy is rarely indicated (9–14). Additionally, most antibiotics are prescribed in the winter (the first and fourth quarters of the calendar year), when bacterial and, especially, viral illnesses such as rhinosinusitis and influenza are common (15–17). Although recent data have shown an improvement in the prescribing patterns for URIs in children (9), these visits still accounted for over half of all antibiotic prescriptions (Rx) for children in outpatient settings.

Overall antibiotic expenditures in the United States reached $10.7 billion in 2009 (18). Antibiotic use in the United States has been reported to be higher than that in most other industrialized countries after adjusting for population (19). Despite this large volume of use, surprisingly little is known about patterns of use. Since greater than 60% of all antibiotic expenditures are in the outpatient setting (18) and a significant percentage of prescribing is inappropriate (9, 14, 20, 21), it is important to identify when and where to target interventions to reduce use in ambulatory care. The purpose of this study was to describe trends and seasonal variations in dispensed outpatient antibiotic prescriptions in the United States over a 5-year period to identify opportunities for public health intervention where seasonal peaks may represent increases in inappropriate use.

MATERIALS AND METHODS

This study was a retrospective analysis of a national database (IMS Health Xponent) of outpatient antibiotic prescriptions in the United States from 2006 to 2010. Oral and injectable systemic antibiotic prescriptions dispensed from retail community pharmacies, mail service pharmacies, and medical clinics were included in the analysis. The United States division of IMS Health captures greater than 70% of all prescription medication use, a capture rate comparable to that of the U.S. Census. These data are then extrapolated using a patented methodology to a statistically valid projection of prescription use to reflect 99% of the U.S. population (22). Variables in the data set include the name of the antibiotic and the month prescribed.

With the exception of antimycobacterial agents, all systemic antibacterials were included. Antibiotic class was defined according to guidelines of the American Hospital Formulary Service (AHFS). Sulfamethoxazole–trimethoprim and their individual components (not in combination) are grouped into the sulfonamide class. Ketolides (e.g., telithromycin) and azalides (e.g., azithromycin) are included with the macrolide class. Cephamycins are grouped with the cephalosporins. Urinary anti-infectives in-
results, the overall number of prescriptions and the prescription rate per 1,000 population by calendar year.

By rate, percentage, and overall number of prescriptions, the most commonly prescribed antibiotic classes were penicillins, macrolides, cephaplospirins, and quinolones. Table 2 illustrates the percentages of total antibiotic consumption and antibiotic prescription rates by class and year. From 2006 to 2010, significant decreases were observed for penicillins (8.8% decrease), cephaplospirins (10.3% decrease), and other (26.3% decrease), while outpatient prescriptions for tetracyclines (7.8% increase) and sulfonamides (17.3% increase) increased significantly. Although the 6.1% increase in the macrolide prescription rate would not have been statistically significant from a random sample, this trend in the macrolide class remains clinically significant due to the completeness of the data set.

An average of 24.5% (range, 20.4% to 28.8%) more antibiotic prescriptions were dispensed in the winter months than in the summer. Seasonality was consistently drug class dependent over the 5-year period, driven by 75% more penicillin and 100% more macrolide prescriptions in the winter months ($P < 0.0001$ for seasonality; Fig. 1). The cephaplosporin and quinolone classes also demonstrated a significant increase in the winter months ($P < 0.0001$ for seasonality), but this variability was less dramatic that of the penicillins and macrolides. The sulfonamide, tetracycline, aminoglycosides, anthelmintics, chloramphenicol, and miscellaneous beta-lactams.

Results

Over 1.34 billion antibiotic prescriptions were dispensed over the 5-year period. The annual number of antibiotic prescriptions remained consistent. However, the overall prescribing rate (prescriptions per 1,000 persons) decreased by 2.8% between 2006 and 2010. The rate decreased annually, with the exception of 2009, where a 0.4% increase was observed relative to 2008. Table 1 describes the overall number of prescriptions and the prescription rate per 1,000 population by calendar year.

Annual rates and percentages of outpatient antibiotic consumption by class, 2006 to 2010

TABLE 1 Numbers and rates of outpatient antibiotic prescriptions, 2006 to 2010

<table>
<thead>
<tr>
<th>Yr</th>
<th>No. of Rx (millions)</th>
<th>Rx rate (no. of Rx/1,000 population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>266.26</td>
<td>892.21</td>
</tr>
<tr>
<td>2007</td>
<td>268.78</td>
<td>891.79</td>
</tr>
<tr>
<td>2008</td>
<td>269.07</td>
<td>884.57</td>
</tr>
<tr>
<td>2009</td>
<td>272.31</td>
<td>887.98</td>
</tr>
<tr>
<td>2010</td>
<td>268.13</td>
<td>867.58</td>
</tr>
</tbody>
</table>

Other miscellaneous drugs of the antibacterial AHFS classes include the glycopeptide, lincomycin, oxazolidinone, aminocyclitol, streptogramin, polymyxin, cyclic lipopeptide, and bacitracin classes. The “other” category includes aminoglycosides, anthelmintics, chloramphenicol, and miscellaneous beta-lactams.

Winter months were defined as the first (January, February, and March) and fourth (October, November, and December) quarters of the calendar year. Monthly variations of antibiotic use were annualized. Antibiotic rates are presented per 1,000 population as defined by midyear estimates reported by the U.S. Census Bureau. Analyses were performed with SAS Version 9.3 (SAS Inc., Cary, NC). To assess annual trends in the overall number and rate of prescriptions dispensed during the study period, simple linear regression was applied. Multiple regression analysis was performed to test for seasonality, with month and year as dummy variables (explanatory variables). The month variable was categorized into season (winter and summer) as defined above to adjust for monthly variability in prescribing. The year variable was categorized into sequential time points (e.g., $1 = 2006$, $5 = 2010$). For regression analyses, the overall number or rate of prescriptions was the response variable. A $P$ value $\leq 0.05$ was considered statistically significant. $P$ values were computed as if these census-level measurements were statistical estimates based on a small random sample, to conform to other $P$ value interpretations in the literature and for comparison, but, in fact, all differences and trends represent census-measured and not small-sample-estimated changes.

RESULTS

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TABLE 2 Annual rates and percentages of outpatient antibiotic consumption by class, 2006 to 2010

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>No. (%) of Rx/1,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2006</td>
</tr>
<tr>
<td>Cephaplosporin</td>
<td>131.41 (15.2)</td>
</tr>
<tr>
<td>Macrolide</td>
<td>176.01 (20.4)</td>
</tr>
<tr>
<td>Misc. antibacterial$^b$</td>
<td>24.55 (2.8)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>293.10 (33.9)</td>
</tr>
<tr>
<td>Quinolone</td>
<td>119.02 (13.8)</td>
</tr>
<tr>
<td>Sulfonamide</td>
<td>56.32 (6.5)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>62.37 (7.2)</td>
</tr>
<tr>
<td>Urinary anti-infective</td>
<td>28.25 (0.1)</td>
</tr>
<tr>
<td>Other$^c$</td>
<td>0.80 (0.08)</td>
</tr>
</tbody>
</table>

$^a$ $P$ values reported in the table are from the linear regression analysis.

$^b$ Misc. antibacterial = miscellaneous aminocyclitols, bacitracins, cyclic lipopeptides, glycopeptides, lincomycins, oxazolidinones, polymyxins, and streptogramins.

$^c$ Other = aminoglycosides, anthelmintics, chloramphenicol, and miscellaneous beta-lactams.
urinary anti-infective, and miscellaneous antibacterial classes demonstrated little seasonality.

**DISCUSSION**

We observed a modest decrease in the overall prescription rate during the study period; while prescribing of penicillins and cephalosporins decreased, macrolide prescribing increased. Prescribing of antibiotics is a complex process and is driven by physician attitudes, patient signs and symptoms, and time pressure (23). The Center for Disease Control and Prevention’s (CDC’s) Get Smart: Know When Antibiotics Work program is designed to address inappropriate prescribing in response to such pressures. Of note, an increase in antibiotic prescribing in 2009 may be explained by the H1N1 influenza pandemic. Additional years of data will determine if antibiotic consumption continues to decrease.

Prescribing of most antibiotic classes decreased over the study period. Prescribing rates are likely declining due to patient education, changes in provider behavior, decreases in outpatient visits for acute respiratory infections, and increases in vaccine administration rates (9, 24, 25). However, it is intriguing that an increase in the macrolide class was observed with consistent, dramatic increases in the winter months. Inappropriate prescribing of macrolides for infections predominately of viral origin has been previously reported (13, 21), and it is likely that the fluctuations in the macrolide class in our results represent similar inappropriate indications. Increasingly judicious prescribing of this class is important because outpatient prescriptions for macrolides, the majority for azithromycin, have been associated with bacterial resistance (5). Azithromycin is conveniently packaged and is primarily indicated because outpatient prescriptions for macrolides, the majority for azithromycin, have been associated with bacterial resistance (5). Azithromycin is conveniently packaged and is primarily indicated for short durations of administration once daily (26). These factors may be contributing to inappropriate prescribing of this drug.

Seasonal variation in the prescribing of antibiotics has been reported in Europe (16, 27), Canada (28), and Israel (29) and, recently, in the United States (15). In the European and Canadian studies, the increase in antibiotic use in the winter months ranged from 21% to 42% (16, 27–29), in similarity to the results found here. Achermann et al. and Sun et al. also found that the seasonality of antibiotics was driven by increases in the prescribing of penicillins and macrolides (15, 27). Dramatic seasonality of antibiotic use is likely related to the increase in the incidence of respiratory tract infections in the first and fourth quarters of the calendar year. According to influenza surveillance conducted by the CDC, peaks in outpatient visits for influenza-like illness parallel trends in the prescription of macrolides and penicillins observed here (30). In Israel, monthly increases in antibiotics prescribed to Jewish children less than 5 years of age in the winter have been associated with an increase in the numbers of penicillin-resistant pneumococcal strains (29). Educational efforts to reduce inappropriate antibiotic use may have the most impact if initiated during or just before the peak prescribing period. The CDC and the World Health Organization (WHO) work year-round to educate the public and providers about using antibiotics appropriately (31, 32). An annual week to highlight the importance of appropriate antibiotic use is observed in Australia, Canada, Europe, and the United States in November (33). These and other efforts (e.g., guidelines) may be impacting inappropriate antibiotic prescribing.

Our results from a robust data source representing national outpatient drug use corroborate other reports demonstrating decreasing outpatient antibiotic prescribing rates using survey data (9, 21). In attempts to estimate the use of a class of drugs that, as we have demonstrated, exhibits significant seasonality, quarterly prescribing data may not truly reflect use. In addition, our data reflected actual prescriptions dispensed to outpatients and not medical claims or purchase data.

Our data did not include any information on patient encounters with providers, including diagnosis. Therefore, we could not directly determine appropriateness of use. In addition, a dispensed prescription does not necessarily reflect actual consumption or patient adherence. However, it more accurately reflects antibiotic use than written prescriptions, because 22% of prescribed medications are never dispensed (34). We used a single data source that presents a de facto (99%) census of the United States, including all age groups, geographic regions, insurers, etc. Further analyses will evaluate variation in prescribing rates over time for specific antibiotic classes and within specific subgroups.

**Conclusion.** Over the 5-year study period, antibiotic prescription rates were lowest in 2010. Penicillins were the most commonly prescribed class of antibiotics, but an increase in macrolide prescribing during this time was observed. Seasonality is a robust, reoccurring phenomenon, and the macrolide and penicillin classes drive antibiotic use in the community during the winter months. Understanding how antibiotic prescribing varies throughout the year will be useful for designing an optimal intervention strategy to reduce inappropriate antibiotic use.

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The statements, findings, conclusion, views, and opinions contained and expressed here are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

K.J.S., L.A.H., R.M.R., and T.H.T. declare that we have no conflicts of interest. R.J.H. is an employee of IMS Health.

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**REFERENCES**


