Seasonality and Temporal Correlation between Community Antibiotic Use and Resistance in the United States

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Background. Therapeutic antibiotic use in humans is a significant driver of antibiotic resistance. The seasonal effect of antibiotic use on antibiotic resistance has been poorly quantified because of lack of large-scale, spatially disaggregated time-series data on antibiotic use and resistance.

Methods. We used time-series analysis (Box–Jenkins) on US antibiotic usage from IMS Health and on antibiotic resistance from The Surveillance Network from 1999–2007 to estimate the effect of aminopenicillin, fluoroquinolone, trimethoprim/sulfamethoxazole, and tetracycline usage on resistance of Escherichia coli to drugs within these classes. We also quantified the effect of fluoroquinolone and macrolide/lincosamide usage on resistance of methicillin-resistant Staphylococcus aureus (MRSA) to ciprofloxacin and clindamycin (which has a similar mode of action to macrolides), respectively.

Results. Prevalence of resistant Escherichia coli was significantly correlated with lagged (by 1 month) antibiotic prescriptions for aminopenicillins (0.22, \(P = .03\)) and fluoroquinolones (0.24, \(P = .02\)), which are highly prescribed, but was uncorrelated to antibiotic classes with lower prescription levels. Fluoroquinolone prescriptions were also significantly correlated with a 1-month lag with the prevalence of ciprofloxacin-resistant MRSA (0.23, \(P = .03\)).

Conclusions. Large-scale usage of antibiotics can generate seasonal patterns of resistance that fluctuate on a short time scale with changes in antibiotic retail sales, suggesting that use of antibiotics in the winter could have a significant effect on resistance. In addition, the strong correlation between community use of antibiotics and resistance isolated in the hospital indicates that restrictions imposed at the hospital level are unlikely to be effective unless coordinated with campaigns to reduce unnecessary antibiotic use at the community level.

INTRODUCTION

Antibiotic resistance poses high costs for society, including significant excess morbidity and mortality [1], increased risk of transplants and other surgical procedures dependent on antibiotic effectiveness [2], and expensive new antibiotics to treat resistant pathogens [3].

Consumption of antibiotics for therapy is generally recognized as the primary driver of resistance patterns [4–6]. Thus, understanding how changes in consumption rates affect antibiotic susceptibility, and at what time scale, is important for developing policies to manage drug resistance.

Although the relationship between human antibiotic use and resistance is complicated by multiple environmental and societal forces [2], some studies have found evidence of significant temporal relationships between antibiotic use and resistance [7–11]. Within the hospital, antibiotic susceptibility rates were highly correlated with prescribing patterns with a lag of only 1 to 3 months [7,8,11]. Similar findings have also been seen at the community level [9,10]. In addition, studies have noted strong interactions between antibiotic prescriptions in the community and resistance...
profiles of hospital isolates [12–14]. The rapidity with which resistance in certain organisms has been shown to respond to changes in antibiotic use, as well as the interaction between community antibiotic use and resistance in both the community and the hospital, suggests that strong seasonal variation in outpatient antibiotic use due to seasonal increases in respiratory diseases, such as influenza [15], may be associated with seasonal changes in drug resistance levels.

In this study, we investigated the seasonal relationship between antibiotic prescriptions and resistance for the United States from 1999 to 2007. Previous studies have observed that certain antibiotic prescriptions (particularly fluoroquinolones) are highly seasonal [6, 15], and similarly bacterial resistance for some pathogens (such as Neisseria gonorrhoea and Streptococcus pneumonia) is also highly seasonal [16, 17]. We investigated seasonal trends in prescription levels of multiple drugs and resistance of 2 bacteria, Escherichia coli (E. coli) and Staphylococcus aureus, which can asymmetrically colonize the flora of healthy individuals and can serve as reservoirs for resistance genes, as well as indicators of antibiotic exposure [9, 18].

METHODS

Antibiotic retail sales data were obtained from IMS Health’s Xponent database, which contains data on dispensed drug prescriptions collected from retail pharmacies (chain, mass merchandisers, independents, and food stores) in the United States [19] and has been previously used to assess the effect of antibiotic use on resistance [14]. The database covers more than 70% of all prescriptions filled in the United States, and records are then weighted to project 100% of total prescriptions dispensed [15]. We investigated the total number of retail prescription sales between 1999 and 2007 by month for 5 antibiotic classes that, together, account for approximately 70% of yearly antibiotic prescriptions and exhibit differing levels of usage: (1) aminopenicillins, β-lactam antibiotics that inhibit bacterial cell wall synthesis; (2) quinolones, which interfere with bacterial DNA replication; (3) macrolides/lincosamides, which target the process of translation and inhibit protein synthesis within bacterial cells; (4) trimethoprim/sulfamethoxazoles, combination antibiotics which inhibit bacterial folate synthesis; and (5) tetracyclines, which inhibit translation and protein synthesis (see Supplementary Table 1 for drugs included in each class).

Resistance data for the same period were obtained from The Surveillance Network (TSN) Database-USA (Focus Diagnostics, Herndon, VA). TSN is an electronic repository of susceptibility test results collected from more than 300 geographically dispersed laboratories in the United States [20]; it has been used extensively by previous studies to characterize trends in antimicrobial resistance [21–24]. Participating laboratories are geographically dispersed throughout the 9 US Census Bureau regions [23] and are selected to be representative of hospital bed size and patient population [22, 23]. Bacterial isolates from inpatients and outpatients were tested on site for susceptibility to a range of antimicrobials, then classified as susceptible, intermediate, or resistant using interpretive standards established by the Clinical and Laboratory Standards Institute (CLSI). The small number of isolates classified as intermediate (<0.01%) were grouped with the susceptible isolates. Data from TSN encompassed approximately 2.5 million tests of E. coli isolates for resistance to ampicillin and trimethoprim/sulfamethoxazole each, or approximately 23 000 tests each per month. Tests for E. coli resistance to ciprofloxacin numbered approximately 2.2 million, and there were approximately 700 000 tests of E. coli tetracycline resistance. Isolate tests for methicillin-resistant S. aureus (MRSA) numbered approximately 1.4 million and approximately 800 000 for resistance to clindamycin and ciprofloxacin, respectively.

Seasonal time trends for antibiotic sales and resistance data were analyzed using a seasonal-trend decomposition procedure based on LOESS (STL), which robustly detects both trends and seasonal variation [25]. STL employs a sequence of smoothing fits on localized subsets of data to generate a seasonal component, a trend component, which represents the long-term secular pattern in data over the years, and a remainder, which accounts for the residual variation. We ran our analysis over the entire range of data, such that the seasonal component is an annually repeating pattern of the mean fitted seasonal change (either a relative increase or decrease) for each month.

In correlating 2 time series, it is necessary to remove trend and seasonal components from each series to avoid false correlations. For example, a strong positive correlation between imported oranges and ischemic heart disease deaths in the United Kingdom disappears once that data are corrected for seasonal and time trends [26]. Avoiding spurious correlations of this type is more likely when the short-term fluctuations in 1 series (or the residuals after removing the trend and seasonal component) are consistently correlated with short-term fluctuations in the other. This type of cross-correlational analysis is common in epidemiological studies [26, 27].

We applied the Box–Jenkins approach to fit time-series data to autoregressive moving average (ARIMA) statistical models, thereby transforming the data into a series of independent, identically distributed random variables [8, 28, 29]. Because the data were seasonal, we used the seasonal ARIMA (SARIMA) extension, which includes seasonal autoregressive and moving average terms as well as a seasonal differencing operator [30, 31], to fit prescription and resistance monthly time series. After differencing each time series to render it stationary, as measured by the Dickey–Fuller unit root test [32], we constructed separate models for each prescription and
resistance time series, then diagnosed them for acceptability using the Akaike information criterion (AIC) and Box–Ljung white noise test for residuals. The residuals from these models were then cross-correlated to examine the association between each pathogen–drug combination.

Cross-correlation analysis of the effect of antibiotic use on *E. coli* resistance was done for (1) aminopenicillin prescriptions and the percentage of isolates resistant to ampicillin, (2) fluoroquinolone prescriptions and the percentage of isolates resistant to ciprofloxacin, (3) trimethoprim/sulfamethoxazole prescriptions and the percentage of isolates resistant to trimethoprim/sulfamethoxazole, and (4) tetracycline prescriptions and the percentage of isolates resistant to tetracycline. The prescription data for each antibiotic were cross-correlated separately with resistance data for isolates from inpatients, outpatients, and both combined. All data were monthly.

No seasonal variation has been noted for *S. aureus* carriage [33]; however, recent reports have suggested that MRSA infections have a seasonal pattern [34]. Because healthcare-associated MRSA isolates are generally resistant to multiple drugs [18], we hypothesized that seasonal changes in antibiotic consumption could be correlated with changes in MRSA resistance profiles. Isolates that were resistant to oxacillin, a proxy for all β-lactam antibiotics, were considered MRSA and included in the analysis. The percentage of MRSA isolates that were resistant to other drugs was then calculated. Only 2 drugs, ciprofloxacin and clindamycin, fluctuated seasonally (Supplementary Figure 1) and were included in further analysis. Monthly resistance data for these drugs were cross-correlated with fluoroquinolone prescriptions and lincosamide/macrolide prescriptions. We combined lincosamide and macrolide prescriptions because of the similarity in their mode of action [35] and because MRSA isolates were not tested specifically for macrolide resistance. Furthermore, macrolide usage has been shown to induce clindamycin resistance, and cross-resistance to both antibiotics (the MLSβ phenotype) often occurs [35, 36]. Cross-correlation analyses were performed using Stata (StataCorp, Stata Statistical Software, release 10; College Station, TX), and STL analysis was done in [R] (R Foundation for Statistical Computing, version 2.13, Vienna).

**RESULTS**

Strength of seasonality in the prescription data (ie, the difference between yearly low and high prescriptions) was observed to be correlated with the mean number of prescriptions in each antibiotic class (Figure 1). This was also observed in the *E. coli* resistance data (Supplementary Figure 2). Seasonal patterns, excluding trends, in *E. coli* resistance and prescription data were calculated using a seasonal decomposition method. Strong similarity in the seasonal signals of aminopenicillin prescriptions and ampicillin-resistant *E. coli* isolates, as well as fluoroquinolone prescriptions and ciprofloxacin-resistant *E. coli* isolates, was observed (Figure 2). Similar winter-peak seasonal patterns were also observed for inpatient and outpatient isolates separately (Supplementary Figures 3 and 4). Antibiotic classes with a lower number of prescriptions—trimethoprim/sulfamethoxazole and tetracycline—were also generally seasonal with a winter peak. However, their seasonality, and that of the corresponding *E. coli* resistance time series, was less pronounced and not as smooth for all isolates combined (Figure 3) as well as for the inpatient and outpatient isolates separately (Supplementary Figures 5 and 6).

The same seasonal decomposition analysis was performed for the MRSA isolates, with comparable results. Both fluoroquinolone prescriptions and the percentage of MRSA isolates that were resistant to ciprofloxacin peaked in the winter. Similarly, a winter peak was observed for both the percentage of MRSA isolates resistant to clindamycin and macrolide/lincosamide prescriptions (Figure 4). Results for inpatient and outpatient isolates separately were nearly identical (Supplementary Figures 7 and 8).

Differencing the prescription and resistance time series succeeded in rendering them stationary (Dickey–Fuller unit root test, MacKinnon approximate *P* value <.05 in all cases). We then constructed seasonal ARIMA models for each time series (all models were diagnosed as acceptable based on the AIC and Box–Ljung test for white noise of residuals; Supplementary
Figure 2. Seasonal pattern of high-usage antibiotic prescriptions and *Escherichia coli* (*E. coli*) resistance, showing 1-month lag. A, Mean monthly seasonal variation for aminopenicillin prescriptions and *E. coli* resistance to ampicillin calculated by seasonal-trend decomposition procedure based on LOESS (STL) method. B, Mean monthly seasonal variation for fluoroquinolone prescriptions and *E. coli* resistance to ciprofloxacin calculated by STL method. Prescription data source: IMS Health, Xponent, 1999–2007. Resistance data source: The Surveillance Network Database-USA (Focus Diagnostics, Herndon, VA). Abbreviation: *E. coli*, *Escherichia coli*.

Figure 3. Seasonal pattern of low-usage antibiotic prescriptions and *Escherichia coli* (*E. coli*) resistance. A, Mean monthly seasonal variation for trimethoprim/sulfamethoxazole prescriptions and *E. coli* resistance to trimethoprim/sulfamethoxazole calculated by seasonal-trend decomposition procedure based on LOESS (STL) method. B, Mean monthly seasonal variation for tetracycline prescriptions and *E. coli* resistance to tetracycline calculated by STL method. Though these time series also seem synchronized in seasonality, seasonal autoregressive moving average analysis shows that the relationship is only correlative. Prescription data source: IMS Health, Xponent, 1999–2007. Resistance data source: The Surveillance Network Database-USA (Focus Diagnostics, Herndon, VA). Abbreviations: *E. coli*, *Escherichia coli*; TMP/Sultra, trimethoprim/sulfamethoxazole.
Tables 2 and 3), and we cross-correlated ARIMA residuals for each prescription time series with its concomitant resistance series. We found positive and significant (P values at or below the 10% level) cross-correlation coefficients for antibiotics with higher prescription levels—aminopenicillins, fluoroquinolones, and macrolides/lincosamides. However, cross-correlations for antibiotic classes with lower prescription levels (<2 million average monthly prescriptions) were nonsignificant.

For aminopenicillin prescriptions and ampicillin-resistant E. coli, cross-correlation peaked at a 1-month lag with a coefficient of 0.20 (P = .06) for inpatient isolates, 0.17 (P = .09) for outpatient isolates, and 0.22 (P = .03) for all isolates combined. Fluoroquinolone prescriptions and ciprofloxacin-resistant E. coli had similar results; correlation coefficients, which also peaked at a 1-month lag, were 0.24 (P = .02), 0.17 (P = .1), and 0.24 (P = .02) for inpatient, outpatient and all isolates combined, respectively (see Table 1 for the peak correlation coefficients).

Macrolide/lincosamide prescriptions, which were extremely seasonal, were significantly correlated with clindamycin-resistant MRSA. These correlations also peaked at a 1-month lag and were the highest of any pathogen-drug combination investigated, with coefficients of 0.42 (P < .001), 0.32 (P = .002), and 0.43 (P < .001) for inpatient, outpatient, and all isolates combined, respectively. Peak correlations between fluoroquinolone prescriptions and ciprofloxacin-resistant MRSA occurred at 1-month lag with coefficients of 0.24 (P = .02) for inpatient isolates, 0.16 (P = .12) for outpatient isolates, and 0.23 (P = .03) for all isolates combined.

**DISCUSSION**

In this study, we demonstrated temporal correlation between some combinations of antibiotic prescriptions and drug resistance levels in E. coli and S. aureus. Even though we observed seasonal patterns in both prescriptions and resistance for all classes of antibiotics, these associations do not imply a causal relationship, since time-series data are autocorrelated and extrinsic factors could be causing similar seasonal variations in both prescription and resistance time series.

By using time-series analysis, we could account for autocorrelation as well as factors that might cause spurious correlation. Based on this analysis, we found strong associations between some antibiotic prescriptions and resistance. For aminopenicillins, fluoroquinolones and macrolides/lincosamides, which account for more than 50% of yearly antibiotic sales, cross-correlation coefficients between residuals of SARIMA models were positive and significant at the 10% level with a 1-month lag for nearly all cases analyzed. These results were generally consistent whether we analyzed isolates from inpatients, outpatients, or all patients. Only outpatient MRSA isolates did not show a significant cross-correlation with fluoroquinolone.

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prescriptions at the 10% level. Thus, even with autocorrelation accounted for and trend and seasonal components removed by the SARIMA model, we found a statistical association between prescription levels and resistance. However, an association was not found for all prescription-resistance pairs. Although the seasonal pattern of prescriptions and E. coli resistance for both trimethoprim/sulfamethoxazole and tetracycline are highly synchronized, we found that the cross-correlation coefficients were not statistically significant. Thus, despite their similar winter-peaking seasonal patterns, we found no association between short-term changes in trimethoprim/sulfamethoxazole and tetracycline prescriptions and E. coli resistance.

Our results suggest that seasonal changes in antibiotic use are significantly associated with short-term changes in resistance. Since resistance lags the increase in prescriptions, an exogenous seasonal driver must underlie the pervasive seasonal trend seen in prescription rates across different drug types. One suggestion is that influenza and other respiratory infections, which rise and fall in near unison with antibiotic prescriptions, result in more prescriptions during the cold months [15, 37]. Though some bacterial infections also increase in the winter, a large fraction of antibiotic prescriptions in the winter are estimated to be inappropriate [38]. The close relationship between respiratory infections and antibiotic prescriptions suggests that reducing the incidence of influenza through vaccination efforts could help decrease overprescription of some highly prescribed antibiotic classes and reduce the annual increase in antibiotic-resistant infections. The linkage between seasonality and antibiotic use has been seen in European countries as well [6, 39], with increased overall use (much of which is presumably also inappropriate) being associated with stronger seasonality.

Our finding that only antibiotics with higher prescription levels had significant correlation coefficients suggests that the scale of antibiotic usage as a whole is important in structuring the dynamics of resistance. The data presented link prescriptions filled at pharmacies with resistant isolates observed in patients in the hospital and in outpatient clinics. The strong associations seen in certain drug-pathogen combinations, which were generally consistent regardless of isolate location, suggest that antibiotic use in the community has significant consequences for resistance in the hospital—an idea that complements previous studies showing relationships between antibiotic use in the community and resistance in the hospital [12–14]. Though this is not surprising, considering that approximately 260 million antibiotic prescriptions are filled each year, it suggests that individual hospitals’ efforts to restrict antibiotic usage are unlikely to have a large effect on certain pathogens unless coordinated with campaigns at the community level.

This study has several limitations. First, because of data limitations, we used aggregate prescription numbers rather than

### Table 1. Peak Cross-Correlation Coefficients Between Drug-Resistant Isolates and Antibiotic Prescriptions, 1999–2007

<table>
<thead>
<tr>
<th>Drug-Resistant Isolates</th>
<th>Prescriptions</th>
<th>Isolate Location</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Inpatients</td>
</tr>
<tr>
<td><strong>Escherichia coli</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Aminopenicillins</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-month lag</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Fluoroquinolones</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-month lag</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>Trimethoprim/sulfamethoxazoles</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-month lag</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Tetracyclines</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-month lag</td>
</tr>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
<td>Ciprofloxacin</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-month lag</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>Macrolides/lincosamides</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-month lag</td>
</tr>
</tbody>
</table>

defined daily dose (DDD), a standardized measure of antibiotic consumption. While this would have been useful for comparison with other studies, it is not known what measure of antibiotic use is most closely associated with selection for resistance, and thus no systematic bias was introduced by the use of sales data rather than DDDs. Second, we did not explicitly control for variations in age, geographical area, immune status, or other factors across the county, and these may have affected seasonal patterns of use and drug resistance. Third, we have correlated antibiotic consumption in the community with isolates from both inpatients and outpatients. Though this does not account for antibiotic usage in the hospital, usage in the hospital also fluctuates seasonally [40], and the results were generally consistent across location despite lower numbers of isolates, and thus less statistical power, in the inpatient and outpatient areas compared to the total. In addition, the overall number of prescriptions in the community is more than 6 times the total number of estimated hospitalizations. Thus, we believe that our results are a good indicator of the ecological effect of antibiotic usage on the whole community. Our methods are also in accord with other studies using IMS data to estimate the impact on resistance at the population level [14]. It should be noted, though, that this type of ecological analysis assumes that indirect exposure (eg. transmission from a child using antibiotics to the mother) plays a large role.

Third, we did not explicitly control for variations in age, geographical area, immune status, or other factors across the country that may have affected seasonal patterns of use and drug resistance. Fourth, although TSN is national in scope, it does not represent a fully stratified random sample of hospitals in the United States by type and region. Lastly, changes in surveillance, CLSI criteria, or bias in the types of infections cultured over time (such as more severe or unusual infections) could alter the results.

This is the first study to use time-series analyses to investigate seasonality and causal correlations between antibiotic prescriptions and resistance on a nationwide scale in the United States. Although all prescription and resistance time series exhibited winter-peaking seasonality, cross-correlation analysis found that only antibiotic prescriptions dispensed in large quantities were associated with short-term fluctuations in resistance patterns. Further studies are needed to confirm whether these relationships hold for other combinations of antibiotics and resistant bacteria, and to investigate how these results vary over heterogeneous US subpopulations. However, overall, this nationwide study suggests that policies and public campaigns to lower antibiotic use could be important and effective measures in the effort to maintain the effectiveness of existing drugs and control the global threat of antibiotic resistance.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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