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Respiratory Fluoroquinolone Use and Influenza

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Abstract

We show that respiratory fluoroquinolone use is extremely seasonal and that fluoroquinolone use is strongly associated with influenza. In our time series model, instantaneous influenza activity was a significant predictor of use ($P < .0001$). Also, we estimated that reducing influenza activity by 20% would reduce prescriptions by 8%.

Background

There are national initiatives to decrease inappropriate antimicrobial use for respiratory infections,¹ and prescribing for acute respiratory tract infections has decreased.^{2,3} However, prescriptions for fluoroquinolone have increased substantially.^{2,4} Fluoroquinolones are commonly used to treat respiratory infections in adults but are rarely used to treat children. Thus, analyzing the seasonal pattern of respiratory fluoroquinolone use during the influenza season may indicate the burden of prescribing associated with influenza seasons, specifically among adult populations. Using time series models, we relate the seasonal fluoroquinolone usage patterns to the timing of the influenza seasons. We also estimate the proportion of use that is associated with influenza activity.

Methods

We extracted zip code-level data on monthly sales of levofloxacin, moxifloxacin, and gatifloxacin from 2000 to 2007 from IMS Health's Xponent database. The Xponent database captures more than 70% of all prescriptions filled in the United States and uses a patented projection methodology to represent 100% coverage of all prescription activity. Prescription data were derived from transaction records at retail pharmacies and were aggregated to the national and census region levels. To measure the monthly influenza activity in the United States, we extracted the weekly percentage of visits for influenza-like illness from the US outpatient influenza-like illness surveillance network from 2000 to 2007.⁵ For the summer weeks with missing influenza surveillance data, we used a mean imputation method.⁶ Finally, by averaging the weekly percentages, we obtained an aggregate monthly series reflecting influenza-like activity levels, one based on the same time periods as our monthly

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outpatient respiratory fluoroquinolone use series. We compiled series at both the national and the census region levels.

To investigate the association of influenza with fluoroquinolone use, we computed a cross-correlation function (CCF) between influenza activity and fluoroquinolone use. This CCF allows us to compare one time series (influenza) to another time series (antibiotics) in order to explore the temporal relationship between the 2 series.

Cross correlations between time series can be spurious due to the effects of common temporal patterns. For example, influenza and antibiotics may appear to be correlated simply because they both follow seasonal cycles, tending to peak during winter months. To establish that the association between the 2 series is not merely a result of the nature of their temporal progressions, we used a prewhitening process.⁷ This process removes the temporal patterns from either (or both) of the series by applying a common filter. This filter is constructed by fitting an autoregressive model to one of the series that reduces the residuals to white noise. The filter is then applied to the remaining series. In principle, any correlation that persists after applying the filter results from the factors above and beyond shared temporal behaviors.

To further examine the relationship between influenza and fluoroquinolone use, we constructed a seasonal time series regression model. In this model, antibiotic use serves as the response series, and concurrent influenza activity serves as the explanatory series. Autoregressive, seasonal autoregressive, and seasonal moving-average components were included to account for the temporal progression of the series.

In addition, to determine whether there is significantly more antibiotic use around the worst influenza month (January 2004), we performed an outlier analysis. We excluded the influenza series from the time series model and fitted the resulting seasonal autoregressive moving-average (SARIMA) model to the antibiotics series alone. Using this fitted SARIMA model, we then determined whether an additive outlier is present around the worst influenza month. For example, if seasonal antibiotic use was associated with influenza activity, then we would observe an additive outlier in the model residual around January 2004 (ie, there should be an excess use of antibiotics associated with this month representing the peak of the worst influenza season during our study period).

To determine the extent to which reducing influenza-like activity might reduce antibiotic use, we fitted a simple linear regression model with antibiotic use during the peak influenza month for each season as the response variable and influenza-like illness during the peak influenza month as the explanatory variable. SAS, version 9.2 (SAS Institute), and R, version 2.7.1 (R Foundation for Statistical Computing), were used for all statistical analyses.

Results

The time series regression model is summarized in Table 1 (model 1). In this model, antibiotic use serves as the response series, and concurrent influenza activity serves as the explanatory series. The model contains autoregressive terms of orders 1 and 2 (ar_1 , ar_2) to account for the association between the current series behavior and recent behavior. Seasonal autoregressive and seasonal moving average components of order 1 (sar_1 , sma_1) are included to describe the yearly periodicity in the series. A first-order difference is incorporated to accommodate the initial trend in the antibiotic series. These components were identified by inspecting autocorrelation functions (ACF) and partial autocorrelation functions (PACF) for the errors from an ordinary linear regression model fit to the response and explanatory series. The final fitted model showed no evidence of lack of fit, based on an

inspection of the ACF and the PACF of the residuals as well as a Durbin-Watson test for residual autocorrelation ($P = .7968$).

In this model, concurrent influenza activity significantly improves the prediction of antibiotic use ($P < .0001$). The importance of influenza activity in characterizing antibiotic use is pronounced: when the influenza series is dropped from the model, the estimated residual variance increased by roughly 70%. The fitted antibiotic series based on the model is displayed in Figure 1. Note that the model provides highly accurate predicted values of antibiotic use during the period under study.

Figure 2 shows the CCF between the prewhitened influenza-like illness series and antibiotics series. We observed a very significant peak at 0 months, indicating that antibiotics use increases concurrently with influenza activity. We obtained similar results across all 9 census regions, with a statistically significant 0-month lag cross correlation for all of the regions.

The SARIMA model fitted to the antibiotic series is summarized in Table 1 (model 2). In our outlier analysis based on this model, we detected an additive outlier in the antibiotic series at January 2004, corresponding to the worst influenza month during the study period. This further supports our conclusion that there is a contemporaneous relationship between seasonal influenza activity and antibiotic use. Specifically, antibiotic use increases during the same month that influenza activity increases.

Using our simple linear regression model, during the peak influenza month, we would expect an overall 8% reduction (corresponding to roughly 141,000 prescriptions) of respiratory fluoroquinolone use if influenza decreases by 20% during this month. Specifically, reductions for moxifloxacin would be 7% (24,000); for gatifloxacin, 12% (25,000); and for levofloxacin, 7.5% (92,000).

Discussion

Our results show that outpatient use of respiratory fluoroquinolone is seasonal and that it is strongly associated with influenza activity. Influenza can certainly increase the likelihood of acquiring secondary bacterial illnesses; however, a relatively small proportion of individuals develop a bacterial infection following a case of influenza.^{8,9} Because antimicrobial therapy cannot treat viral infections and the antimicrobials are not efficacious in preventing bacterial superinfections, a significant proportion of the increase of antimicrobial usage during influenza season is probably unnecessary and probably contributes to antimicrobial resistance.⁸

Although previous studies have shown that antibiotic use is seasonal and that this seasonality is, at least in part, generated by influenza,^{9–13} this article adds to these efforts in 3 respects. First, our study is focused on the United States, and most previous investigations concentrate on other countries. Second, previous studies, for the most part, either are descriptive^{11,12} or use basic inferential methods^{9,13–15} that do not fully exploit the benefits of using a time series modeling framework. We uncovered one study using time series methods that focused on the relationship between respiratory tract infections and antibiotic prescribing, but it focused on quarterly data and did not investigate the specific relationship between influenza activity and antimicrobial prescribing.¹⁶ In contrast to most of these studies, we use the appropriate statistical techniques for making statistical inferences from autocorrelated data. For example, our analysis controls for spurious causes of seasonality. Furthermore, our modeling framework takes into account not only the timing of the 2 series but also the relational intensity between the 2 series: we show that increases and decreases in influenza activity correspond to concurrent increases or decreases in fluoroquinolone use.

Note that studies that do not use the appropriate techniques for the analysis of autocorrelated data can yield misleading results. Finally, our approach allows us to provide an estimate of the potential to reduce inappropriate fluoroquinolone use by reducing the inappropriate practice of prescribing to people with influenza.

The observed association between antibiotic use and influenza suggests specific strategies for reducing seasonal variations in antibiotic use. A recent ecological study in Canada showed that in the Canadian province of Ontario, offering vaccines to the entire population was associated with reduced antibiotic prescriptions.¹⁷ A second strategy to reduce antibiotic use could focus on increasing diagnostic certainty by increasing the availability of rapid testing for influenza¹⁸ and improving local influenza surveillance data. If physicians know that influenza is circulating in their communities, they may be more likely to withhold antimicrobial therapy from patients with influenza-like symptoms. Unfortunately, in the United States, the only universally available local influenza activity surveillance data is at the state level, and it is often 1–2 weeks old when it becomes available. Thus, expanding point-of-care testing, perhaps using newer diagnostic technologies for influenza along with improving local surveillance data, may lead to reduced use of respiratory antibiotics.

Our study has several limitations. First, our study is ecological. Second, our analysis uses influenza-like activity as a proxy for influenza activity. Influenza-like illness data can include other viral-like illnesses—respiratory syncytial virus (RSV), for example. However, we applied the same analysis to an RSV time series extracted from the Nationwide Inpatient Sample¹⁹ and did not find a similar relationship between RSV and the fluoroquinolone series (data not shown). Thus, influenza seems to be the virus driving the seasonal pattern we describe.

Our results also indicate the degree to which fluoroquinolone prescribing could be reduced if influenza activity could be decreased or if inappropriate prescribing during the influenza season could be discouraged. Our analysis focuses on only the peak month. Because influenza seasons often last longer, we would expect to find a greater reduction in overall respiratory fluoroquinolone use before and after the peak influenza month. We find that a 20% reduction in influenza-like activity would correlate with a 7.5% reduction in levofloxacin use during the peak month. Future studies should investigate the association of influenza activity with the use of other antimicrobials used to treat respiratory infections (we predict similar findings). These additional studies may help design or refine existing antimicrobial stewardship efforts.

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References

1. Centers for Disease Control and Prevention. [Accessed February 4, 2010] Get smart: know when antibiotics work. <http://www.cdc.gov/getsmart/campaign-materials/about-campaign.html>
2. Grijalva CG, Nuorti JP, Griffin MR. Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. *JAMA*. 2009; 302:758–766. [PubMed: 19690308]
3. Vanderweil SG, Pelletier AJ, Hamedani AG, Gonzales R, Metlay JP, Camargo CA Jr. Declining antibiotic prescriptions for upper respiratory infections, 1993–2004. *Acad Emerg Med*. 2007; 14:366–369. [PubMed: 17296803]

4. Linder JA, Huang ES, Steinman MA, Gonzales R, Stafford RS. Fluoroquinolone prescribing in the United States: 1995 to 2002. *Am J Med.* 2005; 118:259–268. [PubMed: 15745724]
5. Centers for Disease Control and Prevention. [Accessed January 27, 2010] Seasonal influenza (flu). <http://www.cdc.gov/flu/>
6. Little, RJA.; Rubin, DB. Statistical analysis with missing data. 2nd ed. Hoboken, NJ: Wiley; 2002. p. 20
7. Cryer, JD.; Chan, KS. Time series analysis with applications in R. 2nd ed. New York: Springer; 2008. p. 265–273.
8. Low D. Reducing antibiotic use in influenza: challenges and rewards. *Clin Microbiol Infect.* 2008; 14:298–306. [PubMed: 18093237]
9. Meier CR, Napalkov PN, Wegmuller Y, Jefferson T, Jick H. Population-based study on incidence, risk factors, clinical complications and drug utilisation associated with influenza in the United Kingdom. *Eur J Clin Microbiol Infect Dis.* 2000; 19:834–842. [PubMed: 11152308]
10. Neuzil KM, Mellen BG, Wright PF, Mitchel EF Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med.* 2000; 342:225–231. [PubMed: 10648763]
11. Abella S, Chapmana S, Nadina L, Warren R. Seasonal variation in fluoroquinolone prescribing. *J Antimicrob Chemother.* 1999; 43:315–316. [PubMed: 11252345]
12. Ganestam F, Lundborg CS, Grabowska K, Cars O, Linde A. Weekly antibiotic prescribing and influenza activity in Sweden: a study throughout five influenza seasons. *Scand J Infect Dis.* 2003; 35:836–842. [PubMed: 14723359]
13. Elseviers MM, Ferech M, Vander Stichele RH, Goossens H. the ESAC Project Group. Antibiotic use in ambulatory care in Europe (ESAC data 1997–2002): trends, regional differences and seasonal fluctuations. *Pharmacoepidemiol Drug Safety.* 2007; 16:115–123.
14. Assink MD, Kiewiet JP, Rozenbaum MH, et al. Excess drug prescriptions during influenza and RSV seasons in the Netherlands: potential implications for extended influenza vaccination. *Vaccine.* 2009; 27:1119–1126. [PubMed: 19071185]
15. Glass SK, Pearl DL, McEwen SA, Finley R. A province-level risk factor analysis of fluoroquinolone consumption patterns in Canada (2000–06). *J Antimicrob Chemother.* 2010; 65:2019–2027. [PubMed: 20576640]
16. Fleming DM, Ross AM, Cross KW, Kendall H. The reducing incidence of respiratory tract infection and its relation to antibiotic prescribing. *Br J Gen Pract.* 2003; 53:778–783. [PubMed: 14601353]
17. Kwong JC, Maaten S, Upshur RE, Patrick DM, Marra F. The effect of universal influenza immunization on antibiotic prescriptions: an ecological study. *Clin Infect Dis.* 2009; 49:750–756. [PubMed: 19624280]
18. Falsey AR, Murata Y, Walsh EE. Impact of rapid diagnosis on management of adults hospitalized with influenza. *Arch Intern Med.* 2007; 167:354–360. [PubMed: 17242309]
19. Agency for Healthcare Research and Quality. [Accessed February 17, 2009] Overview of the Nationwide Inpatient Sample (NIS). <http://www.hcup-us.ahrq.gov/nisoverview.jsp>

Figure 1. Observed and fitted antibiotics series from 2000 to 2007. The solid line represents the actually observed antibiotics series; the dashed line represents the fitted antibiotics series from the time series regression model that uses influenza-like illness as an explanatory series.

Figure 2.

Cross-correlation function (CCF) of the prewhitened influenza-like illness series and antibiotics series. For a particular lag m , the plot features the correlation between the influenza-like illness series at time t and the antibiotic series at time $t + m$. Any cross-correlation outside the 2 dashed lines is significantly different from 0 at the .05 level. The highest cross-correlation at lag 0 indicates that the increase of influenza-like illness is associated with a simultaneous increase of antibiotic use.

Table 1

Summary of 2 Time Series Models for the Antibiotics Series

	Model 1			Model 2		
	Estimate	SE	P	Estimate	SE	P
ar1	-.3842	.1085	.0004*	-.3727	.1063	.0005*
ar2	-.2075	.1078	.0542	-.2075	.1055	.0492*
sar1	.9494	.0448	<.0001*	.9887	.0213	<.0001*
sma1	-.5079	.1940	.0088*	-.7641	.2068	.0002*
flu	104,104.06	12,092.53	<.0001*			

Note Model 1 is a time series regression model with antibiotic use as the response series and influenza activity as the explanatory series; model 2 is the seasonal autoregressive moving-average (SARIMA) model for the antibiotic use series. Both models include a first-order difference in addition to the indicated components. ar1, first-order autoregressive component; ar2, second-order autoregressive component; sar1, seasonal autoregressive component of order 1; sma1, seasonal moving average component of order 1; flu, explanatory series (ie, concurrent influenza activity).

* Significant at .05 level.