Inappropriate Antibiotic Prescribing in Managed Care Subjects With Influenza

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Objectives: To evaluate costs of inappropriate oral antibiotic prescribing in a managed care population with influenza.

Methods: This was a retrospective (January 1, 2005, through December 31, 2009) analysis of the US Impact National Benchmark Database. Patients with an influenza diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code 487.xx) and continuous health plan enrollment for ≥12 months before and 1 month after the index influenza diagnosis date were included. We identified patients with an antibiotic prescription claim within 3 days before or 3 days after the index influenza diagnosis date. Patients were classified as having received appropriate antibiotic treatment if a secondary respiratory infection was observed within the 2-week postindex period or if there was a previous comorbid diagnosis of diabetes, congestive heart failure, chronic obstructive pulmonary disease, asthma, acute myocardial infarction, or sickle cell anemia as identified by *ICD-9-CM* codes.

Results: We identified 270,057 subjects with influenza (mean age, 31.6 years). Antibiotics were prescribed in 58,477 (21.65%) patients. Among patients receiving antibiotics, 99% did not have a follow-up diagnosis for a respiratory bacterial infection and 79% had neither a secondary infection nor evidence of a comorbidity (ie, received inappropriate antibiotic treatment). Based on a conservative annual seasonal influenza rate of 10%, we estimated that inappropriate antibiotic prescribing for influenza costs the United States approximately $211 million annually.

Conclusions: Empiric antibiotics were inappropriately prescribed in a high percentage of influenza patients. This represents a significant financial burden to the US healthcare system and may contribute to increased antibiotic resistance.

(Am J Manag Care. 2011;17(9):601-608)

For author information and disclosures, see end of text.

Influenza is a highly contagious respiratory illness. In the United States, the seasonal influenza epidemic typically occurs in the late fall or early winter months and usually lasts through the spring.[1] Annually, approximately 10% to 20% of the US population develops influenza.[2] In the United States, influenza A (H3N2) and B viruses are the primary causes of the seasonal influenza epidemic. However, the 2009 influenza pandemic was the result of a new influenza A (H1N1) virus, which resulted in an estimated 12,500 deaths in the United States.[3] In the last 30 years the average annual number of influenza-related deaths with underlying respiratory and circulatory causes has been approximately 23,600, with the majority of deaths (89%) occurring in patients at least 65 years of age.[4] The high morbidity and mortality associated with influenza result in substantial productivity losses[5] and exert a significant direct and indirect economic burden on the US healthcare system.[6] Additionally, a recent study reported that from 2004 to 2008, influenza was the fastest growing disease state in terms of healthcare spending by employers.[7]

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While the mainstay of influenza prevention is immunization, several antiviral medications including oseltamivir, zanamivir, rimantadine, and amantadine are approved for influenza treatment and chemoprophylaxis. In addition to antivirals, empiric antibiotic use (defined as antibiotic use despite a lack of adequate evidence confirming the presence of infection) is a common treatment approach for influenza patients.[8-10] Guidelines on clinical management of pandemic influenza patients recommend antibiotic prescribing only among patients who (1) experience worsening of influenza symptoms (eg, increasing breathlessness or recrudescent fever) during the course of illness; (2) have severe preexisting illness or chronic obstructive pulmonary disease (COPD); or (3) have influenza-related pneumonia or are at a high risk of developing influenza-related complications or secondary infections (eg, respiratory disorders, heart disease, renal disease).[11] While these recommendations were made in the context of pandemic influenza, antibiotic use is generally not recommended among "seasonal" influenza patients with uncomplicated influenza either.[12]

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Despite current guidelines, unnecessary antibiotic use in influenza continues to be a problem, contributing to the ongoing public health problem of antibiotic drug resistance.[8-10] High rates of antibiotic use

Take-Away Points

Using retrospective analysis of the US Impact National Benchmark Database, we evaluated the costs of inappropriate oral antibiotic prescribing in a managed care population with influenza.

- Antibiotics were prescribed inappropriately in about 80% of subjects with influenza.
- The mean cost of an antibiotic prescription in those with influenza was $40.09.
- Extrapolated to the entire US population, the inappropriate prescribing of antibiotics for subjects with influenza costs more than $200 million.

among patients with respiratory tract infections including influenza have been documented in several previous studies.[8-10,13] Unnecessary prescription antibiotics also exert a significant cost burden on healthcare systems.[10,13] The use of empiric oral antibiotics among patients with influenza has not been evaluated retrospectively in a US pharmacy and medical claims database. Therefore, the objective of this study was to assess real-world empiric oral antibiotic prescribing and the associated cost of inappropriate prescribing in a large population of influenza patients enrolled in managed care health plans in the United States.

METHODS

Study Design and Data Source

In this longitudinal retrospective cohort study, we analyzed patient-linked administrative claims data from the United States Impact National Benchmark Database for the years 1997 to 2009. The database consists of administrative insurance claims from a national sample of more than 40 managed care health plans covering approximately 90 million lives and is representative of the US managed care population. Details on adjudicated medical (eg, inpatient, physician office, outpatient) claims, pharmacy claims, and associated costs along with information on health plan enrollment and demographic characteristics are included in the database. The age and sex distribution of health plan enrollees in the Impact National Benchmark Database is representative of national managed care enrollment.[14]

■ **Table 1.** List of Conditions Requiring Antibiotic Treatment in the Preindex Period

Diagnosis	*ICD-9-CM* Code
Streptococcal sore throat	034.0
Streptococcus, unspecified infection	041.00
Bacterial infection, unspecified	041.9
Unspecified otitis media	382.9
Other acute sinusitis	461.8
Acute sinusitis, unspecified	461.9
Acute tonsillitis	463
Acute pharyngitis	462
Chronic sinusitis, unspecified	473.9
Peritonsillar abscess	475
Pneumonia, organism unspecified	486
Periapical abscess without sinus	522.5
Cholecystitis, unspecified	575.1
Urinary tract infection, site not specified	599.0
Other cellulitis and abscess of trunk	682.2
Unspecified local infection of skin and subcutaneous tissue	686.90
Acne	706.10
Pneumonia adenovirus	480.0
Pneumonia respiratory syncytial virus	480.1
Pneumonia parainfluenza virus	480.2
Pneumonia SARS-associated corona virus	480.3
Pneumonia other virus	480.8
Unspecified viral pneumonia	480.9
Pneumonia organism unspecified	486

ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification;* SARS, severe acute respiratory syndrome.

Patient Selection

We initially selected patients with a diagnosis of influenza (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code 487.xx)[10,13] recorded in the medical claims file during the period January 1, 2005, to November 30, 2009. The date of the first influenza diagnosis claim during this period defined the study index date. Patients were required to have continuous health plan enrollment for at least 12 months before and 1 month after the index date. We excluded patients with a diagnosis for conditions requiring antibiotic treatment during the 12-month preindex period (Table 1). To comprehensively identify comorbidities, we looked back as far as data was available for each subject.

Outcome Measures

The primary outcome for this study was to assess the frequency of inappropriate oral antibiotic prescribing among influenza patients. We classified patients based on the presence (antibiotic users) or absence (antibiotic nonusers) of a prescription for an antibiotic medication (see eAppendix at **www.ajmc.com** for medication list) within the 3-day preindex to 3-day postindex period. Patients were further classified based on the presence or absence of a secondary bacterial respiratory infection (*ICD-9-CM* codes available upon request) within a 15-day period following the index date. They were also classified according to the presence or absence of at least 1 related comorbidity. Comorbidities of interest were diabetes, congestive heart failure (CHF), COPD, asthma, acute myocardial infarction (AMI), and sickle cell anemia (*ICD-9-CM* codes available upon request).

Among patients who received an antibiotic during the 3-day preindex to 3-day postindex period, prescribing of the antibiotic was classified as "appropriate" if these patients also had a diagnosis for a secondary bacterial respiratory infection during the ensuing 15 days or a comorbidity of interest during the preindex period. Accordingly, antibiotic prescribing was considered "inappropriate" in influenza patients who did not have a diagnosis for a secondary infection or evidence of comorbidity. Cost estimates were limited to reimbursements for prescriptions only; thus, costs attributable to other drugs or service categories were not considered. Costs were estimated separately for patients receiving appropriate and inappropriate antibiotic treatment (2009 dollars). Of note, this study also focused only on oral antibiotics in order to illustrate the clinical challenge physicians face in the absence of a definitive influenza diagnosis in the outpatient setting. Thus, the cost associated with inappropriate inpatient prescribing of antibiotics was beyond the scope of the current study.

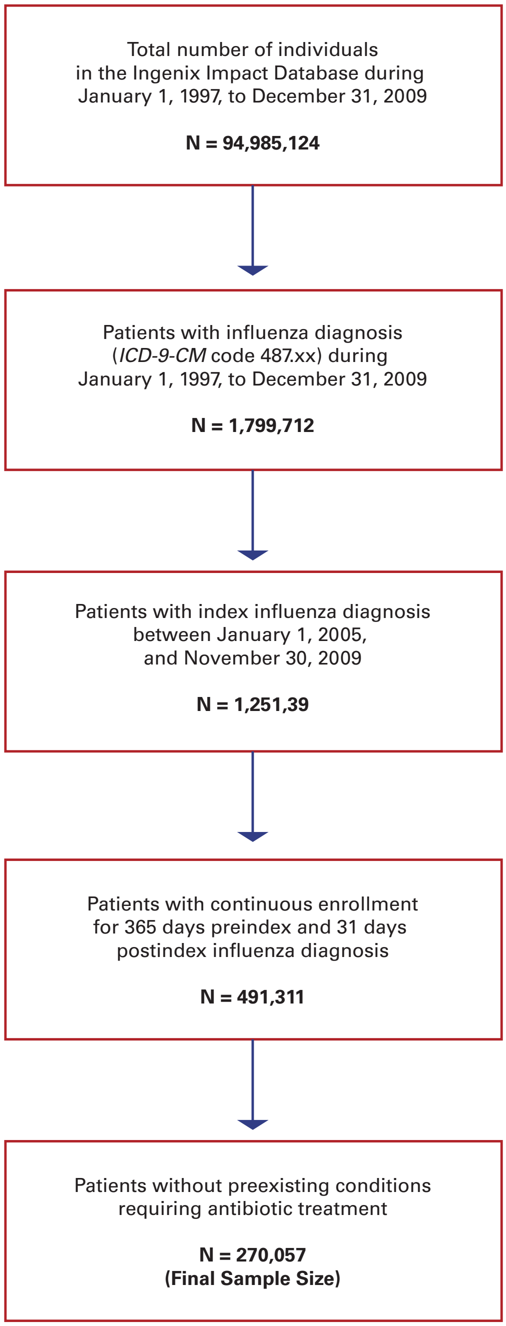
Background Patient Characteristics

Background patient characteristics considered for this study included patient demographics and baseline (ie, 12-month preindex) comorbidity burden. Patient demographic characteristics included age, sex, geographic region, payer type, and plan type. Baseline comorbidity burden was assessed using the Deyo adaptation of the Charlson Comorbidity Index, which includes 17 categories of conditions identified using *ICD-9-CM* codes, with corresponding weights that are aggregated into a composite comorbidity score.[15] We also assessed whether or not patients received an antiviral medication within 1 day of the preindex or 1 day of the postindex date.

Statistical Analyses

All statistical analyses were conducted using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina). All analyses were descriptive. Unadjusted, descriptive statistics were generated for all analysis variables, which included frequency distributions for categorical variables and mean values and standard deviations for continuous variables.

■ **Figure 1.** Attrition Chart for Influenza Sample Selection



ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification.*

RESULTS

Baseline Patient Characteristics

Figure 1 presents the sample attrition resulting from the study inclusion criteria. The final study cohort consisted of 270,057 influenza patients, with a mean (SD) age of 31.6 (18.9) years (Table 2). Approximately 52% of the

■ **Table 2.** Patient Baseline Demographic Characteristics

Characteristic	No. (%)
Sex	
Male	139,832 (51.78)
Female	130,225 (48.22)
Age, y, mean (SD)	31.63 (18.90)
Age category, y	
0-4	14,013 (5.19)
5-24	92,151 (34.12)
25-49	108,018 (40)
50-64	48,277 (17.88)
≥65	7598 (2.81)
Geographic region	
Midwest	43,674 (16.17)
Northeast	70,862 (26.24)
South	128,518 (47.59)
West	26,911 (9.96)
Other	92 (0.03)
Payer type	
Commercial	266,048 (98.52)
Medicaid	2431 (0.9)
Medicare	1578 (0.58)
Insurance type	
HMO	48,305 (17.89)
IND	2330 (0.86)
POS	153,390 (56.80)
PPO	65,357 (24.20)
Other	675 (0.25)
Comorbidity	
Congestive heart failure	2591 (0.95)
Chronic obstructive pulmonary disorder	7459 (2.76)
Asthma	28,160 (10.43)
Diabetes mellitus	16,188 (5.99)
Acute myocardial infarction	2002 (0.74)
Sickle cell anemia	206 (0.08)
Any comorbidity from above list	48,095 (17.81)
Deyo-Charlson Comorbidity Index score, mean (SD)	0.24 (0.76)
No. of patients receiving antibiotics in the 3-day preindex to 3-day postindex window	58,477 (21.65)
No. of patients receiving antiviral medications during the 1-day preindex to 1-day postindex window	112,610 (41.70)

HMO indicates health maintenance organization; IND, indemnity; POS, point of service; PPO, preferred provider organization.

selected patients were male and more than 47% resided in the South. Of the 5 comorbidities of interest, asthma was the most commonly observed (10.4% of patients), followed by diabetes (6.0%), COPD (2.8%), CHF (1.0%), AMI (0.7%), and sickle cell anemia (0.08%). Overall, 112,610 (41.7%) of patients received at least 1 antiviral medication.

Antibiotic Prescribing

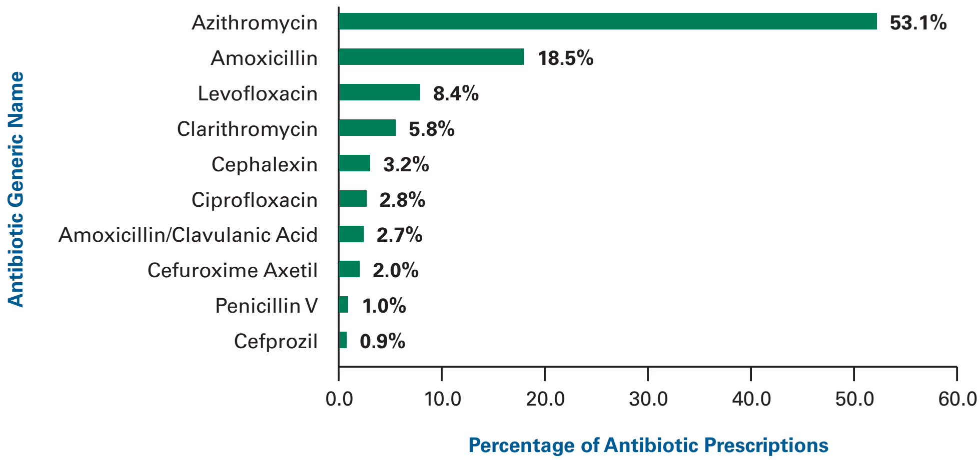
Overall, 58,477 (22%) influenza patients had evidence of antibiotic prescriptions (Table 2). Among patients receiving antibiotic medications, approximately 1% (n = 600) had a diagnosis for secondary bacterial respiratory infections during the follow-up period, and 20% (n = 11,379) had evidence of at

Table 3. Antibiotic Prescribing at the Index Influenza Event, by Secondary Infection and Comorbidity Status

	Antibiotic Users (n = 58,477)				Antibiotic Nonusers (n = 211,580)			
	With Secondary Infections		Without Secondary Infections		With Secondary Infections		Without Secondary Infections	
Comorbidity	No.	%	No.	%	No.	%	No.	%
Overall	600	100.00	57,877	100.00	868	100.00	210,712	100.00
Without a comorbidity	422	70.33	46,316	80.02	565	65.09	174,659	82.89
With a comorbidity	178	29.67	11,561	19.98	303	34.91	36,053	17.11
Individual comorbidity								
CHF	15	2.50	645	1.11	51	5.88	1850	0.88
COPD	37	6.17	2148	3.71	99	11.41	5175	2.46
Asthma	95	15.83	6287	10.86	126	14.52	21,652	10.28
Diabetes mellitus	77	12.83	4253	7.35	139	16.01	11,719	5.56
Acute myocardial infarction	16	2.67	524	0.91	22	2.53	1440	0.68
Sickle cell anemia	0	0	36	0.6	1	0.12	169	0.08

CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease.

Figure 2. Top 10 Most Commonly Prescribed Antibiotics Among Influenza Patients With Antibiotic Use Within 3 Days Preindex to 3 Days Postindex Diagnosis



least 1 relevant comorbidity during the preindex period (Table 3). Overall, 46,316 antibiotic users had neither a secondary infection during the ensuing 15-day period nor a relevant comorbidity, suggesting that approximately 79% of the antibiotic use was inappropriate. Among influenza patients not using antibiotics and with no evidence of a preindex comorbidity, only a small number (868 [0.3%; 565 without comorbidity and 303 with comorbidity]) had evidence of a secondary infection during the follow-up period.

Among influenza patients with a comorbid diagnosis, antibiotics were most commonly prescribed for those with COPD (29%), followed by diabetes and AMI (both 27%), CHF (26%), asthma (23%), and sickle cell anemia (17%).

Figure 2 presents data on the 10 most commonly prescribed antibiotics among antibiotic users. Among the 58,477 patients with a claim for an antibiotic, azithromycin was the most commonly prescribed antibiotic (approximately 53.1% of antibiotic users). Amoxicillin and levofloxacin were the next most commonly prescribed at 18.5% and 8.4%, respectively.

Costs Associated With Antibiotic Prescribing

The mean per patient cost (in the form of insurance reimbursements) for antibiotics prescribed to patients with no evidence of secondary infection or relevant comorbidity was \$40.09 (95% confidence interval [CI] \$39.98-\$40.37). Per patient cost associated with antibiotic prescriptions among patients with evidence of a comorbidity but no infection was \$44.14 (95% CI \$43.51-\$44.78). Similarly, per patient cost associated with antibiotic prescriptions among patients with evidence of a secondary infection and no comorbidity was $63.81 (95% CI $59.19-$68.43). For subjects with both a secondary infection and comorbidity, the per patient cost was $69.73 (95% CI $61.83-$77.64). Based on a conservatively estimated annual influenza rate of 10% of the US population (approximately 30.7 million persons) and our estimated inappropriate antibiotic treatment rate of 21.65% among influenza patients (Table 2), we extrapolate that approximately 6.6 million influenza patients per year receive antibiotic therapy. Assuming that 79% of these patients receive antibiotics inappropriately (Table 3) and that average per patient cost for antibiotic prescriptions is $40.09, we estimate that inappropriate antibiotic use in the United States costs $211 million annually.

DISCUSSION

To our knowledge this is the first retrospective, longitudinal claims database study to assess the rate and costs associated with empiric antibiotic prescribing among influenza patients enrolled in managed care health plans. In our study cohort we estimated that antibiotic use was inappropriate approximately 80% of the time. In contrast, only 868 (0.3%) influenza patients who did not receive antibiotic therapy developed a secondary infection. Inappropriate antibiotic prescribing was estimated to cost approximately $211 million annually. This value was based on a 10% annual incidence estimate; however, the range is 10% to 20%. A higher annual incidence would substantially increase this value. We also considered all antibiotic prescribing in patients with comorbidities to be appropriate; as there may be some instances where this prescribing is inappropriate, our estimates may be slightly conservative. Moreover, this commercial database underrepresents the elderly population (substantiated by a relatively low mean age), in whom the rate of influenza is higher. However, it is plausible that those in a managed care plan may be more frequently prescribed more expensive antibiotics than those without private insurance, which would increase the cost burden. In any event, inappropriate antibiotic prescribing contributes to the estimated $10.4 billion (2003 dollars) in direct costs associated with influenza.[6]

Overall, approximately 22% of the study cohort received antibiotic therapy for their index influenza event. Estimated rates of antibiotic use among influenza patients have ranged from 11% to 43% in other studies.[8,10,13,16,17] The current estimate falls slightly to the left of the midpoint of this range. Several factors, including differences in the study design, geographic region, service setting (eg, outpatient, physician office), and age representation (eg, adults vs children) may explain the variability observed in the rate of antibiotic prescribing across studies.

In addition to the high costs associated with empiric antibiotic prescribing in influenza, antibiotic use in patients without a bacterial infection likely contributes to the ongoing public health problem of antibiotic drug resistance. While several strategies have been suggested to lower the rate of empiric antibiotic prescribing, the primary strategy remains improving the influenza vaccination rate in order to reduce influenza transmission and subsequently the need for antibiotics.[9,18] A recent study assessing the impact of influenza immunization on antibiotic use reported that universal immunization is associated with a 64% decline in the rate of influenza-related respiratory antibiotic use.[9] Additionally, other studies suggest that rapid diagnostic testing for influenza can help increase the rate at which bacterial infections are ruled out and thereby lower the rate of empiric antibiotic use.[17,19,20]

A 2004 study assessing ambulatory prescribing of antibiotics for influenza in the United States from 1997 to 2001 concluded that the annual cost related to inappropriate antibiotic prescribing amounted to $18.5 million.[13] This estimate is much lower than that in the present analysis; however, there are several differences in the studies. The present study is based on paid claims, while the Ciesla et al study estimates were based on 2 surveys where antibiotic costs were derived by using average wholesale prices published in the *RED BOOK* and where regimens were not known but assumed, based on the *Physicians' Desk Reference*. Survey-based studies have inherent limitations, some of which are relevant to the previous study. Survey data may not have completely accounted for all antibiotic prescribing. The National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey (NHAMCS) used by Ciesla et al are not always completed by the attending physician. In fact NHAMCS is completed by hospital staff. Another important difference is that the Ciesla et al study was limited to subjects aged 5 to 49 years. The present analysis included all ages, with approximately 26% of the study population being either less than 5 years of age or more than 50 years of age. This could further account for some of the difference in the estimates, as empiric use of antibiotics is likely greater in these groups, particularly the group over age 65 years. It should also be considered that the Ciesla et al estimate is in 2003 dollars, while the results of this study are in 2009 dollars. Prescribing practices may also have changed, although all of the cost-driving antibiotics in this analysis were included in both analyses.

The estimate for the US population in this study is only a rough estimate based on data from a commercially insured population. While the database is representative of a US commercially insured population, it is not weighted to represent the overall US population. Furthermore, there may be a tendency to prescribe more costly brand name antibiotics in the commercially insured population. Thus, additional research using formal techniques is warranted to precisely estimate the national burden of inappropriate antibiotic prescribing.

Additional limitations to our study included the fact that although we used well-accepted *ICD-9-CM* codes in the selection of influenza patients, inaccuracy in coding by claims administrators may have led to underestimation or overestimation of the number of influenza cases in the database. The coding was not validated by investigating medical records. Second, the antibiotic cost estimates presented in our study were limited to reimbursements for prescriptions and represent the perspective of third-party payers (primarily commercial managed care health plans). Therefore, our cost estimates are conservative because they do not account for subsequent prescriptions and medical encounters for treatment of possible antibiotic side effects (eg, allergic reactions, gastrointestinal problems, infections). Only oral antibiotics were included in this analysis, which may have led to underestimation of overall costs. Third, our data were limited to managed care enrollees, which predominantly includes working adults and their dependents. Fourth, even though our classification of inappropriate and appropriate antibiotic use is based on published guidelines, we cannot account for pragmatic factors such as physician judgment or missing/unavailable data on patients' medical histories that may have led to antibiotic use. For example, our analysis could not account for influenza cases that were worsening. Under current guidelines, antibiotic prescribing for cases of influenza that are worsening is appropriate. We also cannot account for incorrect coding of comorbid conditions or secondary bacterial infections that may have led to misclassification of inappropriate and appropriate antibiotic use. Fifth, coding errors may have resulted in the inclusion of pandemic influenza in the June to November 2009 cohort. Finally, it is also possible that pharmacy claims were paid by health plans not represented in the Impact National Benchmark Database. Consequently, pharmacy claims for subjects with influenza may have been missed. Of note, however, the current study estimated a greater percentage of patients using antivirals compared with a previous study (42% vs 30%).[21]

Despite the above-mentioned limitations, our study provides previously unavailable information on the costs associated with empiric antibiotic prescribing among influenza patients enrolled in managed care health plans. Inappropriate prescribing of antibiotics among influenza patients continues to be a significant problem and exerts a substantial economic burden on the healthcare system. Given increasingly constrained healthcare budgets, it would seem imperative to curtail unnecessary expenditures on empiric antibiotic prescribing and possibly to divert funds to concerted efforts to improve rates of influenza vaccination. Our study findings may serve as a useful resource for policy makers and researchers in evaluating the cost-effectiveness of these efforts.

Acknowledgments

The authors thank Sudeep Karve, PhD, and Keith Davis, MA, of RTI Health Solutions, Research Triangle Park, NC, for their support in helping write this manuscript.

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Funding Source: Support for this manuscript was provided by GlaxoSmithKline to RTI Health Solutions.

Author Disclosures: Drs Misurski and Lipson report being employed by GlaxoSmithKline, which manufactures influenza vaccines. Dr Misurski reports receiving payment for involvement in the preparation of this manuscript and owning stock in the company. Dr Lipson also reports owning stock in the company. Dr Changolkar reports serving as a paid consultant for GlaxoSmithKline.

Authorship Information: Concept and design (DAM, DAL, AKC); acquisition of data (DAM, AKC); analysis and interpretation of data (DAM, DAL, AKC); drafting of the manuscript (DAM); critical revision of the manuscript for important intellectual content (DAM, DAL, AKC); statistical analysis (DAM, AKC); provision of study materials or patients (DAM); obtaining funding (DAM); administrative, technical, or logistic support (DAM); and supervision (DAM).

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eAppendix. List of Antibiotic and Antiviral Medications Considered for This Study

Antibiotic Medications	Antiviral Medications
Amoxicillin	Zanamivir
Amoxicillin/clavulanic acid	Oseltamivir
Ampicillin	Amantadine
Azithromycin	Rimantadine
Cefaclor	
Cefadroxil	
Cefixime	
Cefprozil	
Cefuroxime axetil	
Cephalexin	
Ciprofloxacin	
Ciprofloxacin/ciprofloxacin	
Clarithromycin	
Erythromycin	
Levofloxacin	
Loracarbef	
Ofloxacin	
Penicillin V	
Trimethoprim	