Antiviral and Antibiotic Prescribing for Influenza in Primary Care

Jeffrey A. Linder, MD, MPH^{1,2}, Harry Reyes Nieva¹, and William A. Blumentals, PhD³

¹Division of General Medicine and Primary Care, Brigham and Women's Hospital, Boston, MA, USA; ²Harvard Medical School (JAL), Boston, MA, USA; ³Roche Pharmaceuticals (WAB), Nutley, NJ, USA.

BACKGROUND: Anti-influenza antiviral medications reduce influenza-related morbidity, but may often be used inappropriately.

OBJECTIVE: To measure the rate of antiviral and antibiotic prescribing, the appropriateness of antiviral prescribing, and evaluate independent predictors of antiviral and antibiotic prescribing for influenza in primary care.

DESIGN AND PATIENTS: Retrospective analysis of 958 visits of clinician-diagnosed influenza in 21 primary care clinics in eastern Massachusetts from 1999 to 2007. We considered antiviral prescribing appropriate if patients had symptoms for 2 or fewer days, had fever, and any 2 of headache, sore throat, cough, or myalgias.

MEASUREMENTS AND MAIN RESULTS: Clinicians prescribed antivirals in 557 (58%) visits and antibiotics in 104 visits (11%). Of antiviral prescriptions, 38% were not appropriate, most commonly because of symptoms for more than 2 days (24% of antiviral prescriptions). In multivariate modeling, selected independent predictors of antiviral prescribing were symptom duration of 2 or fewer days (odds ratio [OR], 12.4; 95% confidence interval [CI], 8.3 to 18.6), year (OR, 1.4 for each successive influenza season; 95% CI, 1.3 to 1.7), patient age (OR, 1.3 per decade; 95% CI, 1.2 to 1.5), and, compared to having no influenza testing, having a negative influenza test (OR, 5.5; 95% CI, 3.4 to 9.1) or a positive influenza test (OR, 11.4; 95% CI, 6.7 to 19.3). Independent predictors of antibiotic prescribing included otoscopic abnormalities (OR, 3.3; 95% CI, 1.8 to 6.0), abnormal lung examination (OR, 4.0; 95% CI, 2.1 to 6.2), and having a chest x-ray performed (OR, 2.2; 95% CI, 1.3 to 3.8).

CONCLUSIONS: Primary care clinicians are much more likely to prescribe antivirals to patients with symptoms for 2 or fewer days, but also commonly prescribe antivirals inappropriately.

KEY WORDS: influenza, human; antiviral agents; antibacterial agents; drug utilization.

J Gen Intern Med 24(4):504–10

DOI: 10.1007/s11606-009-0933-9

© Society of General Internal Medicine 2009

INTRODUCTION

Influenza is common and results in annual increases in hospitalization rates and death.^{1,2} Anti-influenza, antiviral medications reduce symptoms, reduce complications requiring antibiotics, may decrease hospitalizations and mortality, and are cost-effective.^{3–9} Despite the potential benefits, antivirals are challenging to use and are infrequently prescribed to patients diagnosed with influenza.¹⁰ The major barrier to the appropriate use of antivirals is the requirement that they be started within 2 days of symptom onset. Antibiotics are generally not indicated for patients with uncomplicated influenza.¹

We previously conducted a small, retrospective analysis of influenza visits.¹¹ Antiviral prescribing was associated with clinical factors, such as a shorter symptom duration and higher temperature, as well as non-clinical factors, such as race and ethnicity. We found that 30% of antiviral prescriptions were inappropriate. Because of the small sample size, we were unable to use multivariate modeling to evaluate independent predictors of antiviral and antibiotic prescribing. Other studies of influenza prescribing that are based solely on administrative data lack clinical detail with which to validate a claims diagnosis of influenza or assess the appropriateness of antiviral prescribing.^{12–15}

To assess the appropriateness of antiviral prescribing and evaluate independent predictors of antiviral and antibiotic prescribing in primary care, we conducted a larger, retrospective analysis of influenza visits to primary care clinics. Identification of independent predictors of antiviral and antibiotic prescribing could identify clinical factors that are important to clinicians in diagnosing patients with influenza as well as non-clinical factors that represent sociodemographic disparities. Knowledge of independent clinical and non-clinical factors could allow the design and implementation of patient, clinician, or system-oriented interventions to improve the prescribing of antivirals or antibiotics in ambulatory care. We focused on visits in which patients were diagnosed clinically with influenza during the influenza season to examine actual practice patterns and assess the internal consistency of clinician decision-making.

METHODS

Setting

The Partners Primary Care Practice-Based Research Network (PBRN) includes 21 primary care practices affiliated with Brigham and Women's Hospital and Massachusetts General Hospital. These practices include community health centers, community-based clinics, and hospital-based clinics and have

Received July 23, 2008

Revised December 2, 2008

Accepted January 27, 2009

Published online February 19, 2009

314 primary care clinicians. In 2005, these clinics provided primary care for about 250,000 adults and children and had approximately 720,000 patient visits.

Data Sources

Partners HealthCare maintains the Research Patient Data Repository (RPDR), which pools inpatient and outpatient encounter data from Partners HealthCare sites.¹⁶ The RPDR identifies claim diagnoses by ICD-9 codes and includes information about visit dates, site of care, visit notes, and patient demographics based on registration information. The RPDR also includes information about testing performed and medications prescribed.

Inclusion and Exclusion Criteria

The Partners Healthcare Institutional Review Board approved the study protocol. We identified potential influenza visits to Partners Primary Care PBRN Clinics using the RPDR to find visits with an ICD-9-CM code of 487 that occurred during the influenza seasons between October 1, 1999 and May 31, 2007. In addition, we identified primary care visits associated with a same-day electronic antiviral prescription of one of the 4 approved anti-influenza, anti-viral medications: amantadine, rimantadine, oseltamivir, and zanamivir. We began the study during the 1999–2000 influenza season because the neuraminidase inhibitors, oseltamivir and zanamivir, and 3 of the latest-generation rapid influenza tests were introduced just prior to the 1999–2000 influenza season.^{17,18} We excluded visits to non-primary care clinics (e.g., emergency department visits), follow-up visits, and visits that did not occur during the influenza seasons (from October 1 to May 31 of the following calendar year).

Because we wanted to examine the internal consistency of clinician decision-making for acute influenza during influenza season, we included only visits at which the treating clinician specifically diagnosed the patient with influenza (usually by writing that the patient had “influenza” or an “influenza-like illness”). We classified excluded visits into those at which the influenza vaccine was discussed or given, the clinician diagnosed the patient with some other respiratory diagnosis for which influenza could be in the differential diagnosis, or the clinician diagnosed the patient with some other, non-respiratory-related diagnosis. For visits identified through electronic antiviral prescribing, we further classified excluded visits into those at which antivirals were prescribed for influenza prophylaxis or as treatment for multiple sclerosis or Parkinson’s disease.

Data Analysis

For visits at which the treating clinician diagnosed the patient with acute influenza, we abstracted sociodemographic information, information about symptoms, physical exam findings, testing performed, test results, and medications prescribed. We abstracted information on up to 4 medications, giving preference to prescription medications — especially antiviral medications and antibiotics — if more than 4 were mentioned.

We used positive predictive value as the measure of accuracy for a claims diagnosis of acute influenza.¹⁹ In calculating positive predictive value, because our system identified emergency department visits and we were interested

only in visits to primary care clinics, we limited the denominator to visits made to primary care clinics. We examined adamantane prescribing over time in light of the Centers for Disease Control and Prevention (CDC) recommendation in the middle of the 2005–2006 influenza season not to use adamantanes because of high levels of influenza A resistance.^{1,20}

We considered antiviral prescribing appropriate if patients had symptoms for 2 or fewer days; had fever (either patient reported or a measured temperature greater than 38.0°C); and had any 2 of headache, sore throat, cough, or myalgias. Such a definition had a positive predictive value of 57–77% in trials of neuraminidase inhibitors during the influenza season when influenza is known to be circulating.^{21–24} We also determined whether patients who were not prescribed an antiviral met appropriateness criteria for antiviral prescribing. Influenza test results were not considered as part of the appropriateness criteria.

There may have been differences between visits identified using claims diagnoses and electronic prescribing; we repeated the analysis, limiting it only to visits identified with a claims diagnosis of influenza. In addition, we identified very few visits from the 2000–2001 influenza season. The 2000–2001 influenza season was mild in the United States and was only 1 of 2 seasons in the past 13 years which influenza A(H3N2) did not predominate.²⁵ We verified that our data acquisition method was consistent over time and repeated analyses without the 1999–2000 and 2000–2001 seasons.

Statistical Analysis

We used standard descriptive statistics. We used Fisher’s exact test to compare categorical variables, Student’s t-test for normally distributed continuous variables, and the Wilcoxon rank-sum test for non-normally distributed continuous variables (e.g., symptom duration). We used the chi-squared test for trend to evaluate antiviral and antibiotic prescribing over time.

To evaluate independent predictors of antiviral and antibiotic prescribing, we used multiple logistic regression modeling. For antiviral prescribing, we excluded pulse and blood pressure because of missing data. We modeled age and influenza season as linear predictors. For most categorical variables, we used the same categories as used for bivariate testing. We dichotomized symptom duration into those who had symptoms for 2 or fewer days and those who had symptoms for more than 2 days or had a missing value. We considered fever present if either the patient complained of fever or there was a measured temperature of greater than 38.0°C. For the antibiotic prescribing model, because antibiotics were prescribed infrequently, we evaluated a limited set of independent predictors that were associated with antibiotic prescribing on bivariate testing ($p < 0.05$).

All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA). P-values < 0.05 were considered significant.

RESULTS

Sample Characteristics

Between October 1, 1999 and May 31, 2007, there were 8161 visits with a claims diagnosis of influenza (Fig. 1). After applying the exclusion criteria, there were 689 primary care

Figure 1. Visit flow. * ED is emergency department. † MS is multiple sclerosis. ‡ Most common primary diagnoses were pharyngitis (23%), asthma (6%), fever (4%), bronchitis (3%), otitis media (3%), and non-specific upper respiratory infection (2%). § Most common primary diagnoses were non-specific upper respiratory infection (25%), fever (12%), bronchitis (11%), pharyngitis (10%), and asthma (7%). ** Most common other diagnoses were hypertension (10%), musculoskeletal diagnoses (9%), general medical examination (7%), hyperlipidemia (3%), obesity (1%), and diabetes (1%). †† Most common other diagnoses were musculoskeletal diagnoses (41%), hypertension (15%), general medical examination (7%), hyperlipidemia (6%), and diabetes (4%). †† After excluding the 1995 emergency department visits, a primary care claims diagnosis of influenza had a positive predictive value of 11% (689 visits with a clinical diagnosis of influenza divided by 6166 primary care visits).

visits at which the treating clinician diagnosed the patient with influenza. After excluding the 1995 emergency department visits, a claims diagnosis of influenza had a positive predictive value of 11% (689 visits with a clinical diagnosis of influenza divided by 6166 primary care visits) for identifying clinician-diagnosed acute influenza visits in primary care.

Between October 1, 1999 and May 31, 2007, there were 1127 visits associated with an electronic antiviral prescription for an anti-influenza, antiviral medication (Fig. 1). After applying the exclusion criteria, there were 447 antiviral prescriptions associated with a primary care visit at which the treating clinician diagnosed the patient with influenza. There were 178 common visits identified both through claims diagnoses and electronic antiviral prescribing, leaving a final sample size of 958 visits.

Patients in the sample of 958 acute primary care influenza visits had a mean age of 40, were 62% women, and 59% had private insurance (Table 1). The race and ethnicity of the sample was 63% White, 19% Latino, 8% Black, and 11% other race and ethnicity. The 958 acute influenza visits were made to 284 different clinicians (median visits to each clinician, 2; interquartile range, 1 to 4) in 21 different clinics (median visits to each clinic, 31; interquartile range, 15 to 46). The 21 clinics included 5 community health centers, 9 hospital-based clinics, and 7 community-based clinics.

Antiviral Prescribing

Clinicians prescribed antivirals to 557 (58%) patients (Fig. 1 and Table 1). In bivariate testing, compared to patients who did

not receive antivirals, patients who received antivirals were older, had symptoms for fewer days, were more likely to be White, have Medicare insurance, be seen at a hospital-based clinic, have myalgias, have received the influenza vaccine, have an influenza test done, and have a positive influenza test. Patients who received antivirals were less likely to be ill-appearing, have nasal symptoms, otoscopic abnormalities, lung abnormalities other than wheezing, or be pregnant.

Clinicians ordered an influenza test for 54% (521/958) of patients. Clinicians prescribed antivirals to 79% (412/521) of patients for whom they ordered an influenza test and 33% (144/437) of patients for whom they did not order an influenza test ($p < 0.0001$). Fifty percent (262/521) of the influenza tests were positive. Clinicians prescribed antivirals to 84% (219/262) of patients with a positive influenza test and to 75% (194/259) of patients with a negative influenza test ($p = 0.01$).

Antiviral prescribing became more common over time (Fig. 2). In restricting the bivariate analysis to visits identified with an ICD-9 code of influenza ($n = 689$), the only differences were that pregnancy and influenza vaccine use became non-significant.

We examined adamantane prescribing to see if the CDC recommendation in the middle of the 2005–2006 influenza season to not use adamantanes had an effect. There were 6 prescriptions (4% of antiviral prescribing) of amantadine or rimantadine in the 2005–2006 influenza season and 3 (6%) in the 2006–2007 influenza season. In all other influenza seasons — with the exception of the 2000–2001 season when

Table 1. Influenza Visit Characteristics and Association with Antiviral and Antibiotic Prescribing

Characteristic	Sample n=958*	Antiviral prescribing n=557		Antibiotic prescribing n=104	
			P Value		P Value
Age, years, mean (SD)	40 (17)	42 (15)	<0.0001	42 (19)	0.12
Symptom duration, mean days (SD)	2.9 (2.4)	2.1 (1.6)	<0.0001	3.8 (3.6)	0.01
Temperature, mean °F (SD)	100.9 (1.8)	101.0 (1.6)	0.05	100.9 (1.6)	0.80
Pulse, mean (SD)	93 (18)	94 (18)	0.36	92 (16)	0.71
Systolic blood pressure, mean (SD)	119 (16)	119 (16)	0.43	120 (15)	0.67
Diastolic blood pressure, mean (SD)	74 (10)	74 (10)	0.49	73 (9)	0.34
Gender, n (%)			0.30		0.24
Women	594 (62)	353 (63)		70 (67)	
Men	364 (38)	204 (37)		34 (33)	
Race and ethnicity, n (%)			<0.0001		0.55
White	599 (63)	400 (72)		70 (67)	
Latino	184 (19)	59 (11)		19 (18)	
Black	74 (8)	40 (7)		8 (8)	
Other	101 (11)	58 (10)		7 (7)	
Insurance, n (%)			<0.0001		0.31
Private	569 (59)	354 (64)		57 (55)	
Medicare	57 (6)	43 (8)		10 (10)	
Medicaid/Free care [†]	188 (20)	71 (13)		23 (22)	
Missing, self-pay, or other [‡]	144 (15)	89 (16)		14 (13)	
Clinic type, n (%)			0.03		0.74
Community health center	446 (47)	249 (45)		51 (49)	
Community-based clinic	194 (20)	104 (19)		22 (21)	
Hospital-based clinic	318 (33)	204 (37)		31 (30)	
Fever, n (%)	852 (89)	502 (90)	0.17	96 (92)	0.25
Ill-appearing, n (%)	361 (38)	178 (32)	<0.0001	42 (40)	0.55
Sore throat, n (%)	441 (46)	253 (45)	0.65	35 (34)	0.0073
Headache, n (%)	417 (44)	254 (46)	0.13	29 (28)	0.0007
Nasal symptoms, n (%)	426 (45)	221 (40)	0.0004	46 (44)	0.96
Cough, n (%)	796 (83)	456 (82)	0.23	91 (88)	0.20
Myalgias, n (%)	699 (73)	437 (78)	<0.0001	72 (69)	0.36
Lymphadenopathy, n (%)	163 (17)	98 (18)	0.57	24 (23)	0.08
Otoscopic abnormality*, n (%)	86 (9)	34 (6)	0.0002	18 (17)	0.0016
Wheezing, n (%)	64 (7)	36 (6)	0.75	14 (13)	0.0034
Other lung abnormality, n (%)	102 (11)	44 (8)	0.0012	30 (29)	<0.0001
Pregnancy, n (%)	6 (<1)	1 (<1)	0.04	0 (0)	0.39
Influenza vaccine, n (%)	60 (6)	43 (8)	0.03	7 (7)	0.83
Influenza test, n (%)	521 (54)	412 (74)	<0.0001	50 (48)	0.17
Positive influenza test, n (%)	262 (50)	219 (53)	0.01	33 (66)	0.02
Blood test, any type, n (%)	87 (9)	42 (8)	0.05	12 (12)	0.36
Chest x-ray, n (%)	133 (14)	82 (15)	0.38	31 (30)	<0.0001
Chest x-ray abnormal, n (%)	14 (11)	7 (9)	0.34	6 (19)	0.07

*Except for symptom duration (n=916), temperature (n=917), pulse (n=596), systolic blood pressure (n=724), diastolic blood pressure (n=724), positive influenza test (n=412 for antiviral prescribing and n=50 for antibiotic prescribing), and chest x-ray abnormal (n=82 for antiviral prescribing and n=31 for antibiotic prescribing).

[†]Free care was the Massachusetts Division of Healthcare Finance and Policy Uncompensated Care Pool for low-income uninsured or underinsured residents.

[‡]Missing, 126; self-pay, 10; and other insurance types, 8.

*Otoscopic abnormalities included abnormalities of the external auditory canal or the tympanic membrane.

there was no antiviral prescribing — amantadine and rimantadine accounted for more than 52% of antiviral prescribing.

In multivariate modeling, independent positive predictors of antiviral prescribing were year (successive influenza seasons), increasing patient age, symptom duration of 2 or fewer days, missing, self-pay, or other insurance, and, having either a negative or a positive influenza test compared to patients who had no testing (Table 2). Independent negative predictors of antiviral prescribing were Latino race and ethnicity, cough, otoscopic abnormality, and having any blood test performed. In limiting the analysis to visits identified only with ICD-9 diagnoses (n=689), missing, self-pay, or other insurance, Latino race and ethnicity, and cough became non-significant, but the point estimates were generally the same as the primary analysis.

Appropriateness of Antiviral Prescribing

Of the 557 patients who received an antiviral, 62% met criteria for appropriateness and 38% of prescriptions were inappropriate (Table 3). The most common reason for inappropriate prescribing was that patients did not have symptoms for fewer than 2 days (24% of all antiviral prescriptions). Of the 135 patients who received antivirals and did not have symptoms for fewer than 2 days, 18 (13%) had no documentation of symptom duration. Of the remaining 117 (87%), the mean duration of symptoms was 4 days and the median was 3 days. Twenty-five patients (21%) had symptoms for 5 days or longer and 5 (4%) patients had symptoms for 10 days or longer. Of patients who did not receive antivirals, 22% met criteria for appropriate antiviral use.

Figure 2. Antiviral and antibiotic prescribing by season * P for trend over time, <0.0001 for antivirals and <0.02 for antibiotics. Excluding 1999–2000 and 2000–2001, P for trend over time, <0.0001 for antivirals and 0.14 for antibiotics. The neuraminidase inhibitors, oseltamivir and zanamivir, as well as 3 of the latest generation rapid influenza tests were introduced prior to the 1999–2000 influenza season.

Antibiotic Prescribing

Clinicians prescribed antibiotics to 104 (11%) patients (Table 1). Compared to patients who did not receive antibiotics, patients who received antibiotics had symptoms for longer, were more likely to have an otoscopic abnormality, a lung abnormality, a positive influenza test, and have a chest x-ray performed, but were less likely to have sore throat or headache. Clinicians prescribed antibiotics to 43% (6/14) of patients with a positive chest x-ray and to 21% (25/119) of those with a negative chest x-ray ($p=0.07$).

Antibiotic prescribing may have become less common over time (from 1999–2000 to 2006–2007, $P<0.02$; excluding 1999–2000 and 2000–2001, $P=0.14$; Fig. 2). Clinicians prescribed antivirals to 49% (51/104) of patients who received antibiotics and antibiotics to 9% (51/557) of patients who received antivirals ($p=.05$). There were no differences when restricting

Table 2. Independent Predictors of Antiviral Prescribing* (n=958)

Predictor	OR (95% CI)
Year, each successive influenza season [†]	1.4 (1.3 to 1.7)
Age, each decade	1.3 (1.2 to 1.5)
Symptom duration, less than 2 days	12.4 (8.3 to 18.6)
Missing, self-pay, or other insurance, versus private	1.8 (1.1 to 3.2)
Latino race and ethnicity, versus whites	0.5 (0.3 to 0.8)
Cough	0.5 (0.3 to 0.9)
Otoscope abnormality	0.5 (0.2 to 0.9)
Any blood test	0.5 (0.3 to 0.9)
Negative influenza test, versus no influenza test	5.5 (3.4 to 9.1)
Positive influenza test, versus no influenza test	11.4 (6.7 to 19.3)

*Adjusted for year (successive influenza seasons), patient age, symptom duration, gender, race and ethnicity, insurance, clinic type, fever (measured or patient reported), ill-appearance, sore throat, headache, nasal symptoms, cough, myalgias, lymphadenopathy, otoscopic abnormality, wheezing, other lung abnormality, influenza vaccination, chest x-ray performed, blood testing, and influenza testing. The results were unchanged omitting patient-reported fever, using only measured temperature $>38.0^{\circ}\text{C}$.

[†]Omitting the 1999–2000 and 2000–2001 seasons, the only substantive change to the results was that the odds ratio for season decreased to 1.2 and retained statistical significance.

Table 3. Appropriateness of Antiviral Prescribing (n=958)

Characteristic	Received Antiviral (n=557)	Did Not Receive Antiviral (n=401)	P value
Symptom duration ≤ 2 days, n (%)	422 (76)	104 (26)	<0.0001
Fever, n (%)	508 (91)	354 (88)	0.14
Patient reported, n (%)	502 (90)	350 (87)	0.17
Measured $> 38.0^{\circ}\text{C}$, n (%)	352 (63)	218 (54)	0.006
Two influenza symptoms, n (%)	477 (86)	320 (80)	0.02
Headache, n (%)	254 (46)	163 (41)	0.13
Sore throat, n (%)	253 (45)	188 (47)	0.65
Cough, n (%)	456 (82)	340 (85)	0.23
Myalgias, n (%)	437 (78)	262 (65)	<0.0001
Appropriate, n (%)	344 (62)	87 (22)	<0.0001

the analysis to influenza visits identified only with ICD-9 diagnosis (n=689).

In multivariate modeling, otoscopic abnormalities, lung abnormalities, and having a chest x-ray performed were independent predictors of antibiotic prescribing (Table 4). Headache was an independent negative predictor of antibiotic prescribing. In restricting the analysis to visits identified only using a claims diagnosis of influenza (n=689), the variable for headache became non-significant.

DISCUSSION

In a retrospective analysis of acute influenza visits to primary care clinics, we found that clinicians prescribed antivirals to 58% of patients they diagnosed with influenza. This rate increased significantly over time. In our previous study, the antiviral prescribing rate was 31%.¹¹ This previous study was based on a small set of clinics and fewer visits. More importantly, our prior study was based on data from the 1999–2000 to 2003–2004 influenza seasons. In the present analysis, the antiviral prescribing rate increased from just over 20% in the 2001–2002 and 2002–2003 influenza seasons to over 50% in the 2003–2004 influenza seasons. In multivariate modeling, there was a 20% to 40% increase in antiviral prescribing from season to season. During this time, in accordance with the prescribing recommendations of the CDC, clinicians nearly stopped prescribing adamantanes.²⁰

Table 4. Independent Predictors of Antibiotic Prescribing (n=958)*

Predictor	OR (95% CI)
Headache	0.5 (0.3 to 0.8)
Otoscope abnormality	3.3 (1.8 to 6.2)
Lung abnormality	3.3 (1.9 to 5.6)
Chest x-ray	2.4 (1.4 to 4.1)

*Adjusted for influenza season, age, sex, symptom duration, sore throat, headache, otoscopic abnormality, wheezing, other lung abnormality, positive influenza test, and chest x-ray performance. Omitting the 1999–2000 and 2000–2001 seasons, there were no substantive changes.

As before, antiviral prescribing was associated with non-clinical factors such as insurance and race/ethnicity. Antiviral prescribing was positively associated with clinical factors such as age and negatively associated with clinical factors such as cough and otoscopic abnormalities. The strongest independent clinical predictor of antiviral prescribing — in accordance with prescribing guidelines for antivirals — was symptom duration for fewer than 2 days. Seemingly paradoxically, symptom duration was also the factor most strongly related to inappropriate antiviral prescribing: 24% of patients who received antivirals had symptoms for more than 2 days. Overall, 38% of prescriptions were inappropriate, and, as before, we found that about a quarter of patients who were not prescribed antivirals met appropriateness criteria.

Influenza testing was a strong independent predictor of antiviral prescribing. Clinicians prescribed antivirals to 84% of patients who had a positive influenza test and to 75% of patients who had a negative test raising the question of why most testing was performed.

We found good news in regards to antibiotic prescribing. In contrast to patients hospitalized with influenza,^{9,26} in primary care clinics antibiotic prescribing was infrequent and may have even decreased over time. In addition, the independent predictors of antibiotic prescribing suggest that clinicians tended to restrict antibiotic prescribing to patients who they suspected may have had otitis media or pneumonia. Based on these results, interventions to improve antibiotic prescribing for patients with influenza should not be a high priority.

On the other hand, given the high rate of inappropriate antiviral prescribing, interventions seem warranted. The greatest challenge in the appropriate prescribing of antivirals is that they be prescribed within 2 days. To reduce symptoms and potentially complications, systems should be in place to make it easy for patients to access care when it is likely they have influenza, without overwhelming clinics with patients who have non-specific upper respiratory tract infections.

This analysis has several limitations that should be considered. First, as with our prior analysis, it was difficult to identify influenza visits. A claims diagnosis of influenza had a positive predictive value of only 11% even after excluding emergency department visits from the denominator. Influenza cases included in this study made up few visits to the study clinics, lower than the rate suggested from CDC data,^{10,25,27} which highlights that we examined a specifically defined group of visits. Second, we used a hybrid method — using both claims diagnoses and electronic antiviral prescribing — of identifying influenza visits. However, there was no substantive difference in results when we limited the analysis to visits identified using only claims data. Third, our review was dependent on clinician documentation. The “gold standard” diagnosis was one in which the treating clinician documented a diagnosis of influenza in the visit note. We used clinicians’ own diagnoses as representative of actual practice, although this almost certainly included visits at which the patient did not actually have influenza and excluded visits in which the patient did have influenza. This allowed us to assess clinician documentation, the internal consistency of clinical decision-making, and appropriateness of antiviral use for visits with a clinical diagnosis of influenza. Finally, our definition of appropriateness allowed for patient-reported fever — as opposed to just

measured fever — and did not take into account the actual prevalence of influenza at the time of the visit. As such, it was a forgiving definition.

CONCLUSION

Antiviral medications have the potential to reduce symptoms and prevent complications. In this retrospective analysis, we found that clinicians increasingly prescribed antivirals to patients they clinically diagnosed with influenza. Clinicians prescribed antibiotics infrequently and restricted prescribing to patients who had findings that could be considered consistent with pneumonia or otitis media. To use antivirals effectively, clinicians, health system leaders, and researchers should consider how to deliver antivirals most accurately and efficiently to patients likely to have influenza.

Acknowledgements: This work was supported by Roche.

Prior Presentations: Previously presented in part at the Society of General Internal Medicine, 31st Annual Meeting, Pittsburgh, Pennsylvania, April 11, 2008 and at the American Academy of Family Practice Scientific Assembly, San Diego, California, September 18–20, 2008.

Conflict of Interest Statement: Dr. Linder is supported by a Career Development Award (K08 HS014563) from the Agency for Healthcare Research and Quality and has a research grant from Pfizer to study ambulatory adverse drug events. Dr. Blumentals is an employee of Roche.

Corresponding Author: Jeffrey A. Linder, MD, MPH; Division of General Medicine and Primary Care, Brigham and Women’s Hospital, 1620 Tremont Street, BC-3-2X, Boston, MA 02120, USA (e-mail: jlinder@partners.org).

REFERENCES

- Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007. *MMWR*. 2007;56(RR-6):1–54.
- Glezen WP. Prevention and treatment of seasonal influenza. *New Engl J Med*. 2008;359(24):2579–2585.
- Lalezari J, Campion K, Keene O, Silagy C. Zanamivir for the treatment of influenza A and B infection in high-risk patients: a pooled analysis of randomized controlled trials. *Arch Intern Med*. 2001;161(2):212–217.
- Libow LS, Neufeld RR, Olson E, Breuer B, Starer P. Sequential outbreak of influenza A and B in a nursing home: efficacy of vaccine and amantadine. *J Am Geriatr Soc*. 1996;44(10):1153–1157.
- Bowles SK, Lee W, Simor AE, et al. Use of oseltamivir during influenza outbreaks in Ontario nursing homes, 1999–2000. *J Am Geriatr Soc*. 2002;50(4):608–616.
- Rothberg MB, Bellantonio S, Rose DN. Management of influenza in adults older than 65 years of age: cost-effectiveness of rapid testing and antiviral therapy. *Ann Intern Med*. 2003;139:321–329.
- Rothberg MB, He S, Rose DN. Management of influenza symptoms in healthy adults: cost-effectiveness of rapid testing and antiviral therapy. *J Gen Intern Med*. 2003;18:808–815.
- Barr CE, Schulman K, Iacuzio D, Bradley JS. Effect of oseltamivir on the risk of pneumonia and use of health care services in children with clinically diagnosed influenza. *Curr Med Res Opin*. 2007;23(3):523–531.
- McGeer A, Green KA, Plevneshi A, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis*. 2007;45(12):1568–1575.
- Linder JA, Bates DW, Platt R. Antivirals and antibiotics for influenza in the United States, 1995–2002. *Pharmacoepidemiol Drug Saf*. 2005;14(8):531–536.

11. **Linder JA, Chan JC, Bates DW.** Appropriateness of antiviral prescribing for influenza in primary care: a retrospective analysis. *J Clin Pharm Ther.* 2006;31(3):245–252.
12. **Cole JA, Loughlin JE, Ajene AN, Rosenberg DM, Cook SE, Walker AM.** The effect of zanamivir treatment on influenza complications: a retrospective cohort study. *Clin Ther.* 2002;24(11):1824–1839.
13. **Gums JG, Pelletier EM, Blumentals WA.** Oseltamivir and influenza-related complications, hospitalization and healthcare expenditure in healthy adults and children. *Expert Opin Pharmacother.* 2008;9(2):151–161.
14. **Blumentals WA, Schulman KL.** Impact of oseltamivir on the incidence of secondary complications of influenza in adolescent and adult patients: results from a retrospective population-based study. *Curr Med Res Opin.* 2007;23(12):2961–2970.
15. **Cox F, Khan ZM, Schweinle JE, Okamoto L, McLaughlin T.** Cost associated with the treatment of influenza in a managed care setting. *MedGenMed.* 2000;2(4):E34.
16. **Murphy SN, Chueh HC.** A security architecture for query tools used to access large biomedical databases. *AMIA Annu Symp Proc.* 2002;552–556.
17. Two neuraminidase inhibitors for treatment of influenza. *Med Lett Drugs Ther.* 1999;41(1063):91–93.
18. Rapid diagnostic tests for influenza. *Med Lett Drugs Ther.* 1999;41(1068):121–122.
19. **Linder JA, Bates DW, Williams DH, Connolly MA, Middleton B.** Acute infections in primary care: accuracy of electronic diagnoses and electronic antibiotic prescribing. *J Am Med Inform Assoc.* 2006;13(1):61–66.
20. Centers for Disease Control and Prevention. High levels of adamantane resistance among influenza A (H3N2) viruses and interim guidelines for use of antiviral agents — United States, 2005–2006 influenza season. *MMWR.* 2006;55(2):44–46.
21. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. *Lancet.* 1998;352(9144):1877–1881.
22. **Monto AS, Fleming DM, Henry D, et al.** Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. *J Infect Dis.* 1999;180(2):254–261.
23. **Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J.** Clinical signs and symptoms predicting influenza infection. *Arch Intern Med.* 2000;160(21):3243–3247.
24. **Zambon M, Hays J, Webster A, Newman R, Keene O.** Diagnosis of influenza in the community: relationship of clinical diagnosis to confirmed virological, serologic, or molecular detection of influenza. *Arch Intern Med.* 2001;161(17):2116–2122.
25. Centers for Disease Control and Prevention. Flu Activity & Surveillance. Available at: <http://www.cdc.gov/flu/weekly/fluactivity.htm>. Accessed January 12, 2009.
26. **Falsey AR, Murata Y, Walsh EE.** Impact of rapid diagnosis on management of adults hospitalized with influenza. *Arch Intern Med.* 2007;167(4):354–360.
27. **Linder JA.** Improving care for acute respiratory infections: better systems, not better microbiology. *Clin Infect Dis.* 2007;45(9):1189–1191.