ORIGINAL RESEARCH

Treatment with Oseltamivir in Children Hospitalized with Community-Acquired, Laboratory-Confirmed Influenza: Review of Five Seasons and Evaluation of an Electronic Reminder

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BACKGROUND: When initiated within 48 hours of the onset of symptoms, oseltamivir has been shown to reduce severity and length of influenza illness. Few studies have evaluated the use of oseltamivir in patients hospitalized with influenza.
OBJECTIVE: To describe the prescribing practices for oseltamivir in children hospitalized with influenza and to evaluate a mechanism to improve the rate of appropriate prescription.
DESIGN, SETTING, PATIENTS: Retrospective cohort study of 929 patients aged 21 years or younger hospitalized with community-acquired laboratory-confirmed influenza (CA-LCI) during 5 consecutive seasons (2000-2005). We examined oseltamivir eligibility, which included patients 1 year of age or older with an influenza test result available within 48 hours of symptom onset. During the 2005-2006 season, an observational trial of an electronic reminder was conducted to improve the frequency of oseltamivir prescription.
MEASUREMENTS: Oseltamivir prescription.
RESULTS: Of 305 patients (32.8%) eligible for treatment with oseltamivir, 49 (16.1% of those eligible) were prescribed oseltamivir during hospitalization. Prescription rates for indications consistent with the US Food and Drug Administration (FDA) approval ("on label") increased from 0% to 37.2% over 5 seasons ($P < 0.0001$). Prescriptions outside this recommendation ("off label") also increased over 5 seasons ($P < 0.0001$). Twenty-nine (5%) of 624 patients were treated with oseltamivir off label; 11 were less than 1 year of age. Initiation of a reminder had no impact on prescription ($P > 0.05$).
CONCLUSIONS: Oseltamivir was used infrequently for children hospitalized with influenza. In addition, use inconsistent with the FDA label of oseltamivir occurs. Mechanisms are needed to improve appropriate prescription of oseltamivir. ***Journal of Hospital Medicine* 2009;4:171–178.** © *2009 Society of Hospital Medicine.*

KEYWORDS: children, influenza, oseltamivir.

Influenza is a common cause of acute respiratory illness in children, resulting in hospitalization of both healthy and chronically ill children due to influenza-related complications.[1,2] Currently, amantadine, rimantadine, oseltamivir, and zanamivir are approved for use in children to treat influenza. In early 2006, more than 90% of influenza isolates tested in the US were found to be resistant to the adamantanes, suggesting that these medications might be of limited benefit during future influenza seasons.[3] To date, most isolates of influenza remain susceptible to neuraminidase inhibitors, zanamivir and oseltamivir. Zanamivir has not been used extensively in pediatrics because it is delivered

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by aerosolization, and is only approved by the US Food and Drug Administration (FDA) for children ≥7 years of age. Oseltamivir is administered orally and is FDA-approved for use in children ≥1 year of age within 48 hours of onset of symptoms of influenza virus infection.

Studies performed in outpatient settings have shown that oseltamivir can lessen the severity and reduce the length of influenza illness by 36 hours when therapy is initiated within 2 days of the onset of symptoms.[4] Treatment also reduced the frequency of new diagnoses of otitis media and decreased physician-prescribed antibiotics.[4]

To date, there are limited data evaluating the use of oseltamivir in either adult or pediatric patients hospitalized with influenza. We sought to describe the use of antiviral medications among children hospitalized with community-acquired laboratory-confirmed influenza (CA-LCI) and to evaluate the effect of a computer-based electronic reminder to increase the rate of on-label use of oseltamivir among hospitalized children.

PATIENTS AND METHODS

We performed a retrospective cohort study of patients ≤21 years of age who were hospitalized with CA-LCI during 5 consecutive seasons from July 2000 through June 2005 (seasons 1-5) at the Children's Hospital of Philadelphia (CHOP). CHOP is a 418-bed tertiary care hospital with about 24,000 hospital admissions each year. Viral diagnostic studies are performed routinely on children hospitalized with acute respiratory symptoms of unknown etiology, which aids in assigning patients to cohorts. Patients who had laboratory confirmation of influenza performed at an outside institution were excluded from this analysis.

From June 2005 through May 2006 (season 6), an observational trial of an electronic clinical decision reminder was performed to assess a mechanism to increase the proportion of eligible children treated with oseltamivir. Patients were included in this analysis if they were ≤21 years of age and had a diagnostic specimen for influenza obtained less than 72 hours after admission. The CHOP Institutional Review Board approved this study with a waiver of informed consent.

Viral Diagnostic Testing

During the winter months from seasons 1-5, nasopharyngeal aspirate specimens were initially tested using immunochromatographic membrane assays (IA) for respiratory syncytial virus (RSV) (NOW RSV; Binax, Inc., Scarborough, ME) and, if negative, for influenza virus types A and B (NOW Flu A, NOW Flu B; Binax). If negative, specimens were tested by direct fluorescent antibody (DFA) testing for multiple respiratory viruses, including influenza A and B. During the winter season, IA testing was performed multiple times each day, and DFA was performed once or twice daily with an 8 to 24 hour turnaround time after a specimen was obtained. For season 6, the testing algorithm was revised: a panel of real-time polymerase chain reaction (PCR) assays were performed to detect nucleic acids from multiple respiratory viruses, including influenza virus types A and B, on specimens that tested negative for influenza and RSV by IA. PCR testing was performed multiple times each day, and specimen results were available within 24 hours of specimen submission. Comprehensive viral tube cultures were performed on specimens that were negative by IA and DFA (seasons 1-5) or respiratory virus PCR panel (season 6).

Study Definitions

Patients were considered to have CA-LCI if the first diagnostic specimen positive for influenza was obtained less than 72 hours after hospital admission. Prescriptions for oseltamivir that were consistent with the FDA recommendations were considered to be "on-label" prescriptions. Prescriptions for oseltamivir given to patients who did not meet these FDA criteria were considered "off-label" prescriptions.[5] Patients were considered "oseltamivir-eligible" if they were met the criteria for FDA approval for treatment with oseltamivir: at least 1 year of age with influenza symptoms of less than 48 hours duration. Patients who either by age and/or symptom duration were inconsistent with FDA labeling criteria for oseltamivir were deemed "oseltamivir-ineligible." This included those patients for whom influenza test results were received by the clinician more than 48 hours after symptom onset. Patients who were positive for influenza only by viral culture were considered oseltamivir-ineligible since the time needed to culture influenza virus was >48 hours. Because of the abrupt onset of influenza symptoms, the "duration of influenza symptoms" was defined by chart review of the emergency room or admission note. A hierarchy of symptoms was used to define the initial onset of influenza-related

symptoms and include the following: (1) For all patients with a history of fever, onset of influenza was defined as the onset of fever as recorded in the first physician note. (2) For patients without a history of fever, the onset of respiratory symptoms was recorded as the onset of influenza. (3) For patients without a history of fever but in whom multiple respiratory symptoms were noted, the onset of symptoms was assigned as the beginning of the increased work of breathing.

Because influenza IA were performed at least 4 times a day during the influenza season, the "date of result to clinician" was determined to be the same date as specimen collection for patients who had a positive influenza IA. Patients were identified as having a positive influenza result to the clinician 1 day after specimen collection if the test was positive by DFA or PCR. A "neurologic adverse event" was defined as the occurrence of a seizure after initiation of oseltamivir therapy. A "neuropsychiatric adverse event" was defined as any significant new neuropsychiatric symptom (psychosis, encephalopathy) recorded after the initiation of oseltamivir therapy. We defined a "dermatologic adverse event" as the report of any skin findings recorded after the initiation of oseltamivir therapy.

Chronic medical conditions

Information from detailed chart review was used to identify children with Advisory Committee on Immunization Practices (ACIP) high-risk medical conditions as previously described by our group (asthma, chronic pulmonary disease, cardiac disease, immunosuppression, hemoglobinopathies, chronic renal dysfunction, diabetes mellitus, inborn errors of metabolism, long-term salicylate therapy, pregnancy, and neurological and neuromuscular disease [NNMD]).[6]

Electronic Reminder

During season 6, a computer-based electronic reminder was designed. The reminder stated "Consider OSELTAMIVIR if Age >1 year AND symptoms <48 hours. May shorten illness by 36 hours. Page ID approval for more info." The reminder was embedded within the influenza results for all positive determinations, so a clinician would see the reminder when viewing positive laboratory results (Meditech, Westwood, MA).

At the initiation of season 6, we determined prescription rates of oseltamivir in patients with CA-LCI to measure the baseline rate of oseltamivir prescription. The electronic reminder was initiated during week 11 of influenza activity at our institution and continued through the end of the influenza season.

Data Collection

Two sources of antiviral prescription data were used. Inpatient prescription of antiviral medications was extracted from billing records and chart review; a 10% audit of the medication administration records showed that the billing records correctly identified oseltamivir prescription status in all cases reviewed. Patients with incomplete pharmacy data were removed from the analysis of prescription practices (n = 8). During all seasons studied, the infectious diseases pharmacist (T.A.M.) and an infectious diseases physician (T.E.Z.) reviewed requests for inpatient prescriptions for antiviral medications.

For season 6, daily review of infection control records was performed to conduct surveillance for children hospitalized with CA-LCI. To determine symptom duration and use of antiviral medications, inpatient medical charts were reviewed at the time of initial identification and then daily thereafter.

Statistical Analysis

Dichotomous variables were created for prescription of oseltamivir, age $\geq$1 year and symptom duration of <48 hours at time of clinician receipt of influenza results. Descriptive analyses included calculating the frequencies for categorical variables. Categorical variables were compared using Fisher's exact test. The Cochrane-Armitage test was employed to test for a trend in the prescription of oseltamivir by season. A 2-tailed P value of <0.05 was considered significant for all statistical tests. All statistical calculations were performed using standard programs in SAS 9.1 (SAS Institute, Cary, NC), STATA 8.2 (Stata Corp., College Station, TX), and Excel (Microsoft, Redmond, WA).

Prior to the start of season 6, we determined that if the rate of oseltamivir prescription was 40% before initiation of the reminder, we would need 20 eligible patients to detect a difference of 40% or greater in subsequent prescription rates (with 80% power and an alpha of 0.05). Once this

enrollment goal was met, an electronic reminder of the eligibility for oseltamivir was initiated.

RESULTS

Use of Antiviral Medications in Children Hospitalized with Influenza, 2000-2005

From July 2000 to June 2005, 1,058 patients were admitted with laboratory confirmed influenza; 8 were excluded because confirmatory testing was done at an outside institution, 24 were repeat hospitalizations, 89 nosocomial cases, and 8 cases were in patients >21 years. Thus, 929 patients had CA-LCI and were eligible for inclusion in this study. Most children were infected with influenza A and were ≥1 year of age (Table 1). During this study period, only 9.3% of study subjects were treated with antiviral medications, most of whom (91%) received oseltamivir. Eight patients received amantadine over all seasons studied.

Overall, one-third of patients (305/929; 33%) were eligible for treatment with oseltamivir. Among patients ≥1 year of age, approximately one-half (305/587; 52%) were oseltamivir-eligible. The additional 282 patients ≥1 year were ineligible because test results were returned to the clinician >48 hours after hospital admission. Only 49 (16.1%) of oseltamivir-eligible patients were prescribed oseltamivir during hospitalization (Figure 1). The rate of prescription of oseltamivir increased over all seasons from 0% in 2000-2001 to 20% in 2004-2005. On-label prescription rates increased from 0% in 2000-2001 to 37.2% in 2004-2005 ($P < 0.0001$; Figure 2).

"Off-Label" Oseltamivir Prescription

Oseltamivir was prescribed to 29 of the 624 patients who were determined to be oseltamivir-ineligible. The rate of off-label use increased over the seasons from 2000 to 2005 from 0% to 8.8% ($P < 0.0001$; Figure 1). Ineligible patients who received oseltamivir were ≤1 year of age (n = 11), had test results returned to the clinician ≥48 hours after hospital admission (n = 18), or both (n = 4). Most off-label prescriptions occurred in patients who had chronic medical conditions (21/29; 72%), including cardiac disease (n = 9), asthma (n = 6), or prematurity (n = 5). Four of 11 patients ≤1 year of age who were treated with oseltamivir had influenza-related respiratory failure. The oseltamivir dose for all patients ≤1 year of age was 2 mg/kg twice a day, all of whom survived to discharge.

TABLE 1
Characteristics of Patients Hospitalized with CA-LCI and Oseltamivir Eligibility During Five Influenza Seasons, 2000-2001 to 2004-2005

Characteristics	Patients Hospitalized with CA-LCI (n = 929)*	Eligible to Receive Oseltamivir (n = 305)*
Age (years)		
<1	342 (37)	0
≥1	587 (63)	305 (100)
Season		
2000-2001	107 (11.5)	32 (10)
2001-2002	252 (27)	78 (26)
2002-2003	135 (14.5)	31 (10)
2003-2004	243 (26)	86 (28)
2004-2005	192 (21)	78 (26)
Influenza type		
A	692 (75)	
B	237 (25)	

* Values are number of patients (%).

Evaluation of a Computer-Based Electronic Reminder Designed to Enhance the On-Label Prescription of Oseltamivir

During season 6, an electronic reminder about the labeled use of oseltamivir was evaluated to determine its ability to increase the rate of prescription of oseltamivir among eligible children hospitalized with CA-LCI. During season 6, most patients (226/311; 73%) were ≥1 year of age. A total of 84 patients were determined to be oseltamivir-eligible (age ≥1 year and test results back to the clinician within 48 hours of symptom onset).

During the initial 10 weeks of local influenza activity, 20 oseltamivir-eligible patients were admitted to our institution, and 8 received oseltamivir (40% prescription rate) (Table 2). In addition, 2 of 54 (3.7%) oseltamivir-ineligible patients were also treated. The computer-based electronic reminder was initiated in week 11 of the influenza season. After initiation of the reminder, 237 additional children with CA-LCI were hospitalized, of whom 64 (27%) were determined to be oseltamivir-eligible. The rate of on-label prescription of oseltamivir was similar to that observed prior to initiation of the reminder: 16 of 64 patients eligible for antiviral therapy received oseltamivir (25% prescription rate) (Figure 3). An additional 8 patients were prescribed oseltamivir off-label. The rate of oseltamivir prescription did not change

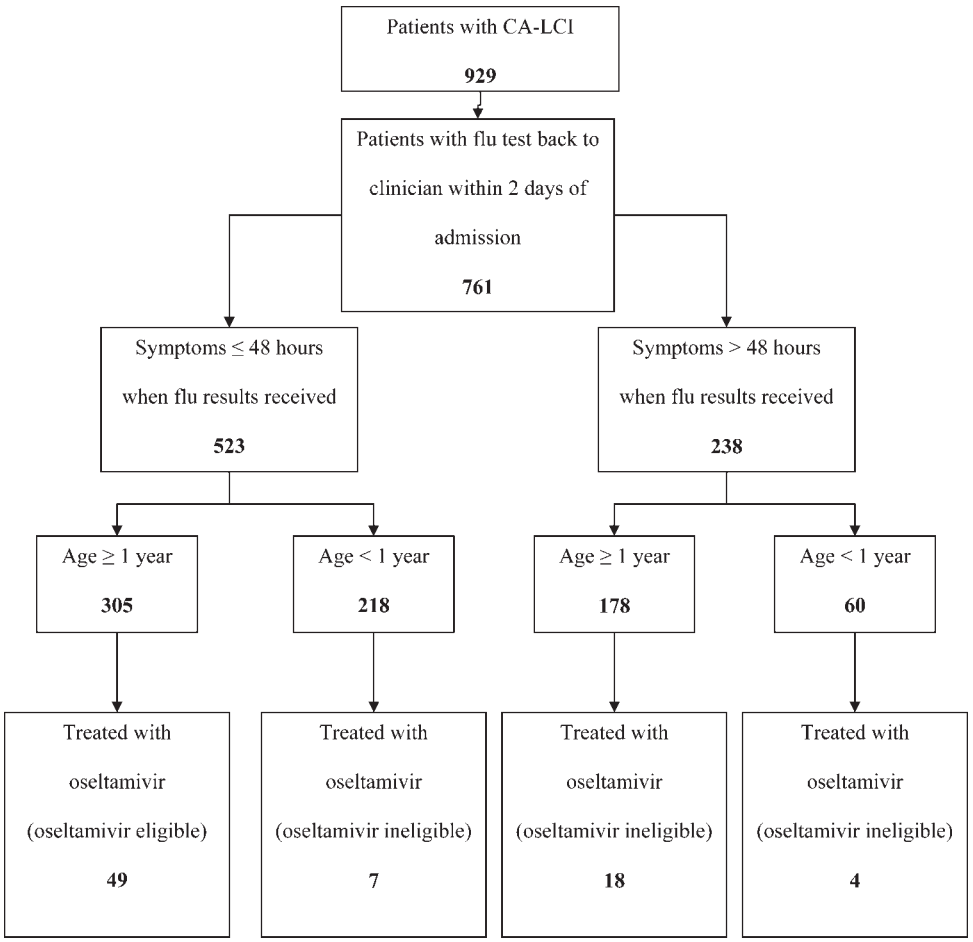

FIGURE 1. Study subjects: duration of symptoms, age, and treatment status.

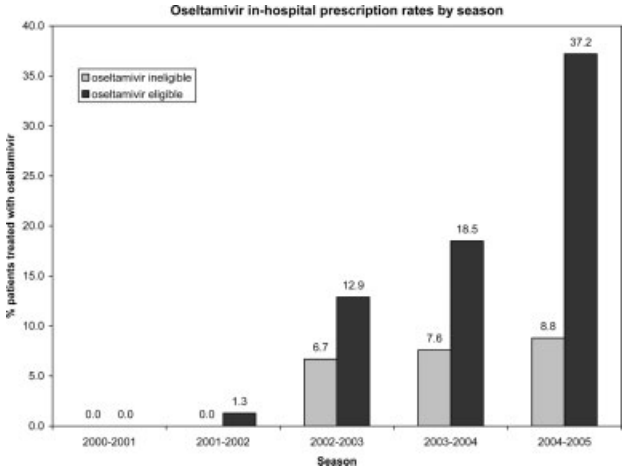

FIGURE 2. Oseltamivir prescription rates among hospitalized children, 2000-2005. Percent of eligible or ineligible patients treated with oseltamivir. A significant trend over time of oseltamivir use was found for both eligible and ineligible patients, by nonparametric (NP) trend test ($P < 0.0001$).

TABLE 2
Oseltamivir Eligibility and Use Among Patients Hospitalized with CA-LCI During the Intervention Season, 2005-2006

	Oseltamivir Use		
Prompt Active?	**Yes***	**No†**	**Total†**
No			
Eligible	8 (40)	12	20
Ineligible	2 (3.7)	52	54
Yes			
Eligible	16 (25)	48	64
Ineligible	8 (4.6)	165	173
Total	34	277	311

NOTE: No significant difference found in prescription of oseltamivir for those eligible and ineligible before and after the prompt was active, by Fisher's exact tests ($P > 0.5$).

*Values are number of patients (%).

†Values are number of patients.

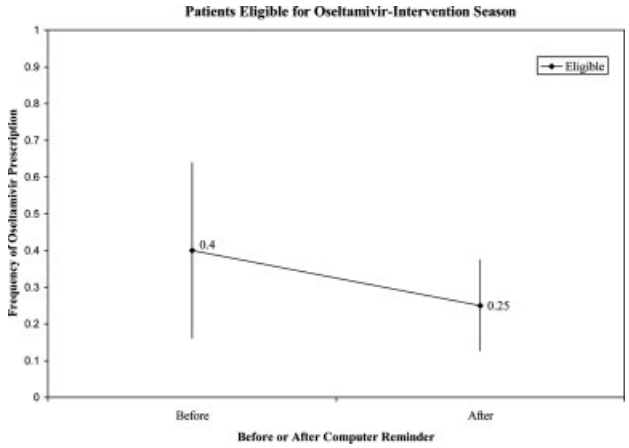

FIGURE 3. Proportion of eligible patients who were treated with oseltamivir during the intervention season (2005-2006). Two proportions represent proportions before and after activation of electronic prompt. No significant difference found in prescription of oseltamivir for those eligible before and after the prompt was active, by Fisher's exact tests ($P > 0.5$).

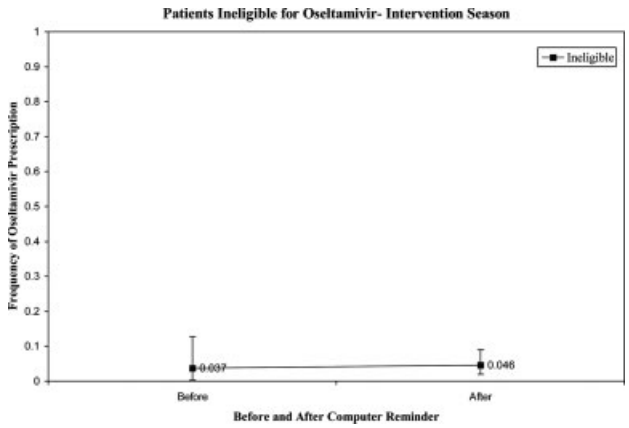

FIGURE 4. Proportion of ineligible patients who were treated with oseltamivir during the intervention season (2005-2006). Two proportions represent proportions before and after activation of electronic prompt. No significant difference found in prescription of oseltamivir for those ineligible before and after the prompt was active, by Fisher's exact tests ($P > 0.5$).

significantly for either oseltamivir-eligible (40-25%) or oseltamivir-ineligible (3.7-4.6%) (Figure 4).

Dermatologic, Neurologic, and Neuropsychiatric Adverse Events

We reviewed the medical records of all patients treated with oseltamivir during the 6 study seasons to identify dermatologic, neurologic, and neuropsychiatric adverse outcomes that developed after the initiation of oseltamivir therapy. No new-onset seizures, neuropsychiatric, or dermatologic reactions were identified among the children treated with oseltamivir.

DISCUSSION AND CONCLUSION

In this report, we describe the use of oseltamivir over 6 seasons in a cohort of children hospitalized with CA-LCI at 1 tertiary care pediatric hospital and examine the impact of a mechanism designed to increase prescription among those eligible for oseltamivir. We found that only one-third of patients hospitalized at our institution were eligible for oseltamivir treatment based on FDA-approved indications. Of the eligible patients, few were prescribed oseltamivir during their hospitalization. During the sixth season, we employed a computer reminder system for oseltamivir prescription, which had no appreciable effect upon prescription rates. Despite the lack of effect of the electronic reminder system, we observed an increase of on-label oseltamivir prescriptions over the entire study period. Finally, we identified 11 patients <1 year of age (3%) who were treated with oseltamivir. There were no adverse events identified in this group.

Although previous studies have addressed prescription rates of oseltamivir in children with influenza, few, if any, have looked at how these prescriptions correspond with FDA label criteria. In our cohort, only one-third of hospitalized children were eligible for treatment with oseltamivir based upon their age and symptom duration at the time the results of rapid laboratory testing became available. Of those patients in our cohort eligible for oseltamivir, few were treated. The prescription of oseltamivir in seasons falls within the ranges found by Schrag et al.[7] in their multistate review of pediatric influenza hospitalizations in 2003-2004. They noted that use of antiviral medications varied by location of surveillance ranging from 3% in Connecticut to 34% in Colorado, indicating significant regional differences in prescription practices.[7] Potential causes of low rates of appropriate use of oseltamivir include the observation that many physicians remain unaware of the potential severity of influenza infection in children.[8] Additionally, physicians may differ on how to define the onset of influenza infection in children. A recent study published by Ohmit and Monto[9] indicated that a fever and cough predicted

83% of children 5 to 12 years old who were determined to be influenza-positive. Finally, many physicians who do not prescribe antiviral therapy may believe that their patients present too late for appropriate initiation of therapy.[10]

We identified 29 patients who received oseltamivir although they did not meet the FDA label criteria, of whom 72% had a chronic underlying condition. Moore et al.[11] in their surveillance of influenza admissions in Canada found a similar trend. They described 26 of 29 (90%) hospitalized patients receiving antiinfluenza drugs had an underlying disease, and of those without a chronic condition, all had severe influenza-related complications such as encephalopathy.[11]

Implementation of a computerized reminder to improve use of oseltamivir had no statistically significant effect on prescribing practice. Our sample size calculation was based on detecting a 40% difference in prescription rates, which limited our power to detect a smaller difference in prescription rates. A systematic review by Garg et al.[12] identified barriers to the success of computer-based decision support systems (CDS), which included failure of practitioners to use the system, poor integration of the system to the physician's workflow, and disagreement with what was recommended. Future enhancements to our inpatient electronic hospital record may allow for more targeted and robust CDS interventions.

We observed an increase in on-label prescription rates of oseltamivir over the entire study period. We hypothesize that increased use of oseltamivir might be associated with growing concerns of pandemic influenza and attention to fatal influenza in children,[13] as evidenced by the recent addition of influenza-associated deaths in children to the list of nationally notifiable conditions in 2004.[14]

There has been considerable focus upon potential adverse events associated with treatment with oseltamivir in children. Reports have emerged, primarily from Japan, of neuropsychiatric and dermatologic adverse events of oseltamivir treatment.[15] In the fall of 2006, the FDA added a precaution to the labeling of oseltamivir due to these neuropsychiatric events.[16] In our treated cohort, no neurologic, neuropsychiatric, or dermatologic adverse events were identified. However, this finding is not surprising given the rarity of these adverse events and the limited number of children treated with oseltamivir in this study.

The strengths of this current study include a large cohort of laboratory-confirmed influenza in hospitalized children over multiple influenza seasons. In addition, this is the first study of which we are aware that has assessed the number of children eligible for oseltamivir but not treated. The limitations of this study include misclassification bias related to the retrospective study design. Because of this design, onset of influenza symptoms was collected through chart review, and the time of receipt of influenza results from virology was based upon known laboratory turnover time, rather than actual knowledge of time of physician awareness of the result. To address this issue we used a conservative estimate of the time of receipt of influenza test results. In addition, the retrospective design prevented us from assessing the clinical decision-making process, which led some patients to be treated with oseltamivir and others not. Our evaluation of the electronic reminder was designed to show a large change in prescription practices (ie, 40%), so it had insufficient power to detect a smaller impact. Finally, ascertainment bias may have limited our ability to identify adverse effects.

This study demonstrates that oseltamivir is prescribed infrequently among hospitalized children. Future studies are needed to determine whether appropriate use of oseltamivir improves outcomes among hospitalized children. Additional study of the safety and efficacy of oseltamivir in children aged <1 year is also needed given the large burden of disease in this age group.

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