ORIGINAL INVESTIGATION

Impact of Oseltamivir Treatment on Influenza-Related Lower Respiratory Tract Complications and Hospitalizations

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Background: Influenza causes lower respiratory tract complications (LRTCs), particularly bronchitis and pneumonia, in both otherwise healthy adults and those with underlying conditions. The aim of this study was to assess the effect of oseltamivir treatment on the incidence of LRTCs leading to antibiotic treatment and hospitalizations following influenza illness.

Methods: We analyzed prospectively collected data on LRTCs and antibiotic use from 3564 subjects (age range, 13-97 years) with influenzalike illness enrolled in 10 placebo-controlled, double-blind trials of oseltamivir treatment.

Results: In adults and adolescents with a proven influenza illness, oseltamivir treatment reduced overall antibiotic use for any reason by 26.7% (14.0% vs 19.1% with placebo; $P<.001$) and the incidence of influenza-related LRTCs resulting in antibiotic therapy by 55% (4.6% vs 10.3% with placebo; $P<.001$). In those subjects considered at increased risk of complications, 74 (18.5%) of 401 placebo recipients developed an LRTC leading to antibiotic use compared with 45 (12.2%) of 368 oseltamivir recipients (34.0% reduction; $P=.02$). Hospitalization for any cause occurred in 18 (1.7%) of 1063 placebo recipients compared with 9 (0.7%) of 1350 oseltamivir-treated patients (59% reduction; $P=.02$). In contrast, among subjects with an influenzalike illness but without a confirmed influenza infection, the incidence of LRTCs (6.7% vs 5.3%), overall antibiotic use (19.7% vs 19.3%), or hospitalizations (1.7% vs 1.9%) was similar between placebo and oseltamivir recipients, respectively.

Conclusion: Oseltamivir treatment of influenza illness reduces LRTCs, antibiotic use, and hospitalization in both healthy and "at-risk" adults.

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INFLUENZA-RELATED lower respiratory tract complications (LRTCs) including acute bronchitis, pneumonia, and exacerbations of underlying airways disease frequently lead to antibiotic use and hospitalizations. Severe influenza outbreaks have been associated with the hospitalization of up to 300 000 patients and 50 000 deaths in the United States alone.[1,2] The annual influenza-associated underlying respiratory and circulatory deaths are estimated to be 36 155 in recent years.[1] Those at increased risk of LRTCs include elderly persons (age ≥65 years) and individuals with underlying chronic respiratory or cardiovascular problems.[3] Although the incidence of complications is lower in otherwise healthy adults, influenza has a major impact and contributes significantly to the use of antibiotics within communities.[4,5] Even though preseason influenza immunization can reduce hospitalizations and mortality in the elderly and "at-risk" populations, it is uncertain whether early antiviral treatment of influenza illness can reduce LRTCs and their associated sequelae.[6] An analysis of the studies conducted with inhaled zanamivir found reductions in LRTCs associated with antibiotic use but no apparent effect on hospitalizations.[5]

Oseltamivir carboxylate is a potent and selective inhibitor of both influenza A and influenza B neuraminidases,[7] and the oral prodrug oseltamivir is effective for the treatment of influenza in ambulatory adults when given within 2 days after symptom onset.[8,9] The large database of phase 3 studies offered the opportunity to evaluate the impact of oseltamivir treatment on the incidence of LRTCs leading to antibiotic use and the risk of hospitalization among influenza-infected adults and adolescents, including elderly persons and patients with underlying conditions at higher risk of complications. For comparison, the effect of oseltamivir on complications of influenza-like illness not due to influenza virus infection was also determined.

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Table 1. Summary of Randomized, Double-blind, Placebo-Controlled Trials of Oseltamivir Therapy in Adults and Adolescents

Study No.	Population (Age, y)	Region or Country	No. Enrolled	No. Randomized	Season	Predominant Influenza Virus	% of Patients Infected	Patients With Antibiotics at Study Start, No. (%)	Reference
WV15670	Adult (18-68)	NH	482	477	Dec 1997-Mar 1998	A-H3N2	67.0	13 (2.7)	9
WV15671	Adult (18-64)	USA	418	418	Dec 1997-Mar 1998	A-H3N2	60.4	11 (2.6)	8
WV15730	Adult (18-65)	SH	60	58	Jul-Sep 1998	A-H3N2	65.5	1 (1.7)	10
WV15707	Elderly (≥65)	SH	27	26	Jul-Sep 1998	A-H3N2	46.2	0	*
M76001	Adult (≥13-80)	USA	1459	1447	Dec 1998-Feb 1999	A	73.5	48 (3.3)	11
WV15812	Adults with COAD (≥13)	USA and NH	304	402	Jan-Mar 1996	A-H3N2	66.6	10 (2.5)	12
WV15872	Adults with COAD (≥13)	SH	100		Jun-Sep 1999		50.0		12
WV15819	Elderly (≥65)	USA and NH	172	736	Jan-Mar 1999	A	71.6	12 (1.6)	12
WV15876	Elderly (≥65)	SH	99		May-Sep 1999		46.5		12
WV15978	Elderly (≥65)	USA and NH	470		Nov 1999-Feb 2000		66.2		12

Abbreviations: COAD, chronic obstructive airways disease; NH, northern hemisphere; SH, southern hemisphere.
*Data on file, Hoffmann-LaRoche, Inc, Nutley, NJ.

METHODS

STUDY DESIGN

The oseltamivir database includes 10 double-blind, placebo-controlled, multicenter phase 3 trials investigating the safety and efficacy of oseltamivir use in adults and adolescents during the northern and southern hemisphere influenza seasons, from 1997 to 2000. **Table 1** displays the trial profiles and shows the proportions of subjects enrolled.[8-12] The enrolled patients included otherwise healthy unimmunized adults and adolescents (age 13-64 years) and a substantial number of at-risk patients, defined as immunized or unimmunized community-living elderly persons 65 years or older and adults and adolescents with chronic obstructive airways disease, asthma, and/or cardiac disease of sufficient severity to require regular outpatient medical care. Patients with New York Heart Association class IV and American Thoracic Society stage III status were excluded from participation. All studies were conducted in compliance with the Declaration of Helsinki (and subsequent amendments), and written informed consent was obtained from patients (and parent or guardian for adolescents under the legal age of consent) prior to inclusion into each study.

PATIENTS AND DRUG ADMINISTRATION

All patients were enrolled during periods when influenza virus was documented to be circulating in their communities. Patients were eligible if they presented within 36 hours of first symptom onset and met a standard case definition including fever (temperature ≥37.8°C in adults and adolescents aged <65 years; ≥37.5°C in adults aged ≥65 years) plus at least 1 respiratory symptom (cough, sore throat, or coryza) and 1 constitutional symptom (headache, myalgia, chills/sweats, or fatigue). Patients were randomized to receive oseltamivir (75 mg twice daily) or placebo, for 5 days. The results from the 150-mg dose arms from 2 studies[8,9] of otherwise healthy adults are not included in the current analysis. Randomization was computer-generated by a central randomization facility, which had sole access to the code. Each center provided its own medication in individually numbered packs, according to the instructions of the randomization center. When appropriate, randomization was stratified according to the presence and disease status of any comorbid conditions (eg, chronic obstructive pulmonary disease or cardiac disease) and influenza immunization status within the season of study. Patients self-administered the medication and were asked to record the date and time of each dose on their diary card. Monitoring of diary card entries found that approximately 90% of enrolled patients were fully compliant.

As described previously,[8,9] influenza infection was confirmed by virus isolation from combined nose and throat swabs or by 4-fold or greater rises in hemagglutination-inhibition antibody titers to the circulating strain. The virologic studies were performed by independent, certified laboratories during the course of the individual trials and were completed prior to unblinding of the results.

CLINICAL MONITORING

Patients were evaluated in person at baseline, mid-therapy (day 2, 3, or 4), immediately after treatment (day 5 or 6), and at day 28. They also measured oral temperatures and completed a symptom diary twice daily for the duration of the study or until all symptoms (cough, nasal obstruction, sore throat, fatigue, headache, myalgia, and/or feverishness) were reported alleviated (score, 0 [absent] or 1 [mild]) for at least 24 hours. Five selected complications involving the upper (sinusitis or otitis media) and lower (bronchitis, lower respiratory tract infection, or pneumonia) respiratory tract were prospectively recorded on case report forms, as was the use of antibiotics for any indication. The diagnosis of complications and the need for antibiotics were determined by individual treating physicians using their clinical judgment; no microbiological or radiologic tests were required. Hospitalizations and other complications or adverse events were collected on the case record forms.

OUTCOMES AND DATA ANALYSIS

The primary end point in this analysis was the occurrence of LRTCs requiring antibiotic intervention (prospectively defined as bronchitis, lower respiratory tract infection, or pneumonia) following influenza illness that started at least 48 hours after the start of study treatment and before day 28. Other outcomes examined included hospitalizations, upper respiratory tract complications (URTCs), and overall antibiotic use. An individual subject could have reported more than 1 URTC or LRTC. The Fisher 2-tailed exact test was used to compare frequencies and relative risk for the comparison of antibiotic use.

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Table 2. Demographic and Clinical Characteristics of Individuals With Laboratory-Proven Influenza Illness or Influenzalike Illness Not Due to Influenza Virus Infection*

Characteristic	Influenza Infected†		Not Infected	
	Placebo bid (n = 1063)	Oseltamivir, 75 mg bid (n = 1350)	Placebo bid (n = 478)	Oseltamivir, 75 mg bid (n = 673)
Age, median (range), y	44.5 (13-97)	40.0 (13-96)	42.0 (13-95)	42.0 (13-91)
Male	516 (49)	618 (46)	188 (39)	286 (42)
Influenza type				
Influenza A	945 (89)	1168 (87)		
Influenza B	112 (11)	172 (13)		
Unknown	6 (<1)	9 (<1)		
Not infected	0	1 (<1)		
Duration of illness before study start, median (range), h	25.0 (0.0-58.8)	24.7 (0.3-60.0)	24.7 (0.2-51.6)	24.5 (0.0-229.3)
At-risk individuals‡	401 (38)	368 (27)	200 (42)	237 (35)
Elderly ≥65 y	294 (28)	285 (21)	146 (31)	191 (28)
Chronic respiratory and/or cardiac disease	157 (15)	137 (10)	84 (18)	90 (13)
Current vaccination	188 (18)	206 (15)	128 (27)	151 (22)

Abbreviation: bid, twice daily.
*Data are given as number (percentage) unless otherwise specified.
†One patient was erroneously included in the influenza-infected population when not influenza infected.
‡Some subjects fulfill both criteria of being elderly and having chronic respiratory and/or cardiac conditions.

RESULTS

PATIENT CHARACTERISTICS

The 10 studies enrolled 3591 adults and adolescents (subsequently, 1541 individuals were randomized to placebo and 2023 randomized to oseltamivir, 75 mg twice daily), who comprised the intent-to-treat population (Table 1). Among placebo recipients 74 (4.8%) subjects withdrew early, 28 (1.8%) for adverse events. Among oseltamivir recipients, 113 (5.9%) withdrew prematurely, 35 (1.8%) for adverse events. These subjects were included in the analyses up to the date of withdrawal. Of the enrolled subjects, 68% had laboratory-confirmed influenza (12% influenza B and 88% influenza A, predominantly influenza A H3N2), and 32% had an influenza-like illness but no evidence of influenza virus infection. The demographic and clinical characteristics of the influenza-positive and influenza-negative populations and the oseltamivir and placebo subgroups were comparable (**Table 2**). Among infected persons, the proportion of at-risk individuals tended to be higher in the placebo group (38% vs 27%; $P<.001$). A small proportion of subjects were taking antibiotics at the time of enrollment (Table 1); these individuals were included in the analysis of complications and hospitalizations.

LRTCs LEADING TO ANTIBIOTIC USE

The overall incidence of LRTCs leading to antibiotic use was higher (10.3%) among influenza-infected placebo recipients compared with those without influenza (6.7%; $P=.03$) (**Table 3**). The proportions of individuals with clinically diagnosed pneumonia (1.8% vs 1.9%) was similar in the 2 groups, but the incidence of bronchitis in the influenza-infected population (8.2%) was almost double that observed in the noninfected population (4.4%; $P=.007$).

As shown in Table 3, among influenza-infected persons, oseltamivir use reduced the incidence of LRTCs leading to antibiotic intervention by 55% compared with placebo (4.6% vs 10.3%; $P<.001$). In contrast, there was no difference in the incidence of LRTCs between oseltamivir (5.3%) and placebo (6.7%) recipients without influenza. Most of these events occurred within the first 10 days after enrollment (**Figure 1**). The frequency of LRTCs and the reductions found with oseltamivir were similar in both influenza A– and B–infected subjects (Table 3). Following influenza A illness, LRTCs were observed in 10.5% of placebo- and 4.7% of oseltamivir-treated patients. Similarly, in influenza B–infected subjects, the incidence of LRTCs in placebo and oseltamivir recipients was 8.9% and 4.1%, respectively. No important effect of timing of therapy was observed, since the risk of a specified LRTC leading to antibiotic use was reduced by 54% (95% confidence interval [CI], 35%-84%) among oseltamivir recipients treated within 24 hours of symptom onset and by 44% (95% CI, 30%-65%) among those treated in 24 hours or more compared with placebo.

Among placebo recipients with influenza infection, the incidence of complications was, as expected, significantly higher in the at-risk patients (18.5%) compared with otherwise healthy adults (5.3%; $P<.001$). Compared with placebo, oseltamivir treatment reduced the incidence of LRTCs associated with antibiotic use by 34% (95% CI, 19.6%-47.9%) in at-risk subjects (18.5% vs 12.2%; $P=.02$) and by 67% (95% CI, 34.6%-99.9%) in the healthy adult population (5.3% vs 1.7%; $P<.001$).

OTHER RESPIRATORY EVENTS AND ANTIBIOTIC USE

Oseltamivir use reduced the overall incidence of respiratory events following influenza infection by 28% compared with placebo (11.9% vs 16.9%; $P=.001$). How-

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Table 3. Lower Respiratory Tract Complications (LRTCs) Leading to Antibiotic Use in Influenza-Infected and Uninfected Subjects With Influenzalike Illness

	Confirmed Influenza Illness						Influenza Uninfected			
	Overall		Otherwise Healthy (Age 13-65 y)		At Risk		Otherwise Healthy (Age 13-65 y)		At Risk	
LRTCs Leading to Antibiotic Use	Placebo (n = 1063)	Oseltamivir (n = 1350)	Placebo (n = 662)	Oseltamivir (n = 982)	Placebo (n = 401)	Oseltamivir (n = 368)	Placebo (n = 278)	Oseltamivir (n = 436)	Placebo (n = 200)	Oseltamivir (n = 237)
All LRTCs, No. (%)	109 (10.3)	62 (4.6)*	35 (5.3)	17 (1.7)*	74 (18.5)†	45 (12.2)‡	11 (4.0)	12 (2.8)	21 (10.5)	24 (10.1)
Bronchitis, No. (%)	87 (8.2)	53 (3.9)	25 (3.8)	15 (1.5)	62 (15.5)	38 (10.3)	8 (2.9)	11 (2.5)	13 (6.5)	19 (8.0)
Unspecified LRTCs, No. (%)	4 (0.4)	1 (0.1)	1 (0.2)	0	3 (0.7)	1 (0.3)	0	0	2 (1.0)	2 (0.8)
Pneumonia, No. (%)	19 (1.8)	9 (0.7)	9 (1.4)	2 (0.2)	10 (2.5)	7 (1.9)	3 (1.1)	1 (0.2)	6 (3.0)	3 (1.3)
Influenza A, No./total infected (%)	99/945 (10.5)	55/1168 (4.7)	31/579 (5.4)	15/840 (2.0)	68/366 (18.6)	40/328 (12.2)				
Influenza B, No./total infected (%)	10/112 (8.9)	7/172 (4.1)	4/77 (5.2)	2/133 (1.5)	6/35 (17.1)	5/39 (12.8)				

*Comparison of oseltamivir vs placebo, $P<.001$.
†Comparison of at-risk placebo vs otherwise healthy placebo, $P<.001$.
‡Comparison of oseltamivir vs placebo, $P=.02$.

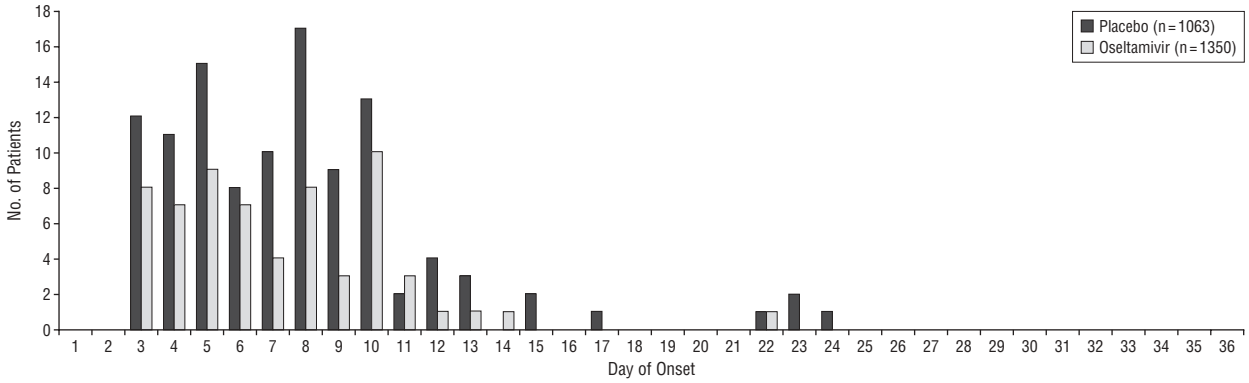

Figure 1. Day of onset of antibiotic therapy for lower respiratory tract complications in oseltamivir (75 mg twice daily) and placebo recipients with influenza infection. The analysis included prospectively specified complications (bronchitis, lower respiratory tract illness, and pneumonia) and was restricted to days 3 through 28 after enrollment. A patient is counted each time an antibiotic is taken for a new complication. Only the first of multiple antibiotics taken for a given complication is counted.

ever, no differences were observed in physician-diagnosed URTCs leading to antibiotic use (most commonly sinusitis) between oseltamivir (6.8%) and placebo (5.9%). Overall, 19.1% of the influenza-infected placebo recipients compared with 14.0% of oseltamivir recipients (26.7% reduction; $P<.001$) took an antibiotic for any reason. In contrast, for those without influenza infection, oseltamivir did not reduce the incidence of respiratory complications compared with placebo (12.5% vs 13.6%; $P=.64$) or of overall antibiotic use (19.3% vs 19.7%).

HOSPITALIZATIONS

Among placebo recipients with a documented influenza illness, the percentage hospitalized for any reason was small but was 4-fold higher (3.2% [13/401]) in the at-risk population compared with the otherwise healthy group (0.8% [5/662]) (**Table 4**). The overall percentage of patients hospitalized for any cause was 1.7% (18/1063) in the placebo group compared with 0.7% (9/1350) in the oseltamivir group (59% reduction; $P=.02$). The reduction in overall hospitalizations in the oseltamivir-treated, influenza-infected at-risk patients was 50% compared with placebo recipients (1.6% vs 3.2%; $P=.17$). Most hospitalizations occurred within 10 days of study enrollment, although later hospitalizations were noted (**Figure 2**). In contrast, no beneficial effect on hospitalizations was seen in those without influenza infection (Table 4).

The percentage of infected individuals hospitalized for conditions probably or possibly related to influenza (venous thrombosis, cerebrovascular disease, cardiac disorders, exacerbation of comorbid conditions, and respiratory diseases) was lower in oseltamivir recipients (0.4%) than in those receiving placebo (1.1%) (Table 4). Hospitalizations due to respiratory disease were 50% lower among oseltamivir recipients (0.3%) compared with placebo recipients (0.6%). Two patients who took placebo were admitted to the intensive care unit and required ven-

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Table 4. Number of Hospitalizations in Influenza-Infected and Uninfected Subjects With Influenzalike Illness (ILI)

	Confirmed Influenza Illness						Influenza Uninfected			
	Overall		Otherwise Healthy (Age 13-65 y)		At Risk		Otherwise Healthy (Age 13-65 y)		At Risk	
Hospitalizations	Placebo (n = 1063)	Oseltamivir (n = 1350)	Placebo (n = 662)	Oseltamivir (n = 982)	Placebo (n = 401)	Oseltamivir (n = 368)	Placebo (n = 278)	Oseltamivir (n = 436)	Placebo (n = 200)	Oseltamivir (n = 237)
Possibly related to ILI, No. (%)	12 (1.1)	6 (0.4)*	3 (0.5)	1 (0.1)	9 (2.2)	5 (1.4)	0	3 (0.7)	6 (3.0)	4 (1.7)
All causes of hospitalizaitons, No. (%)	18 (1.7)	9 (0.7)†	5 (0.8)	3 (0.3)	13 (3.2)	6 (1.6)‡	2 (0.7)	7 (1.6)	6 (3.0)	6 (3.0)

*Comparison of oseltamivir vs placebo, $P = 14$.
†Comparison of oseltamivir vs placebo, $P = .02$.
‡Comparison of oseltamivir vs placebo, $P = .17$.

tilation. One patient who was not influenza infected died of her illness.

COMMENT

Our analysis found that early treatment of influenza illness with the neuraminidase inhibitor oseltamivir significantly reduced influenza-related LRTCs, associated antibiotic use, and the risk of hospitalization. This effect was observed in both at-risk subjects and otherwise healthy individuals. Most hospitalizations occurred in the at-risk population, and in this group oseltamivir use was associated with a 50% reduction in hospitalization rate. Oseltamivir use did not affect the incidence of respiratory complications or antibiotic use in patients without proven influenza infection, which indicated that the benefit observed was specifically related to its antiviral effects. The magnitude of the reduction in LRTCs was similar in both influenza A– and B–infected subjects, which is consistent with the antiviral spectrum of oseltamivir.

Our data complement those previously reported in which inhaled zanamivir was shown to reduce the incidence of LRTCs by 40% in mainly healthy subjects with acute influenza.[5] However, in this earlier report, only 12% of the analyzed population was considered at risk for influenza complications and a reduction in hospitalizations was not observed, possibly in part because of the low frequency of hospitalizations (0.4% overall). The present study extends these observations to a larger population of subjects considered to be at increased risk for complications and provides the first prospective evidence that antiviral and specifically neuraminidase inhibitor treatment reduces influenza-related hospitalizations. Of note, a recent retrospective analysis of the open-label, compassionate use of oseltamivir in nursing home residents found that early treatment (within 2 days of symptom onset) appeared to reduce the likelihood of complications, antibiotic use, and hospitalizations compared with delayed therapy or no treatment.[13]

Lower respiratory tract complications were the most common complications observed in both healthy adults and the at-risk population receiving placebo, contributing to 65% and 91%, respectively, of all prospectively recorded events following influenza illness. These events occurred with comparable frequency following influenza A and B virus infections. Among these complications, acute bronchitis was the most common event in both healthy adults (71%) and the at-risk population (84%). This is consistent with prior studies that have found that acute bronchitis was a leading complication of influenza.[14,15] Such findings support the conclusion that bronchitis is a part of influenza illness. This is also supported by the additional observation that bronchitis was more frequent among influenza-infected persons compared with those without influenza. This is of major importance, since acute bronchitis is a leading cause of antibiotic overuse in clinical practice.[16] Therefore, awareness that acute bronchitis is a frequent event following influenza illness and that oseltamivir treatment can prevent this complication may enable reductions in excess antibiotic use when influenza is circulating in the community.

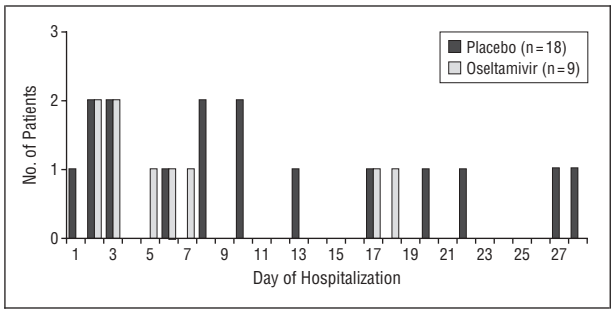

Figure 2. Day of hospitalization among placebo- or oseltamivir (75 mg twice daily)-treated adults with influenza infection. Date of hospitalization was missing for 1 oseltamivir and 2 placebo recipients. One oseltamivir-treated patient had 2 hospitalizations over different dates and is included twice in the figure.

All of the studies included in this analysis were double-blind, placebo-controlled, randomized trials that used prospective diagnosis of specified URTCs and LRTCs. One limitation of these studies was the lack of standardized clinical guidelines across participating centers for diagnosing complications. Thus, it is unclear how often viral infection alone or bacterial superinfection resulted in antibiotic use. Nonspecificity in diagnosis may explain in part the failure in these studies to observe a reduction in URTCs, specifically sinusitis, in contrast to the 44% reduction with oseltamivir treatment in new otitis media diagnoses found in children.[17] However, because the current studies relied on the clinical discre-

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tion of the many participating physicians with regard to use of antibiotics and need for hospitalization, the results are reflective of current patterns of practice in the participating countries.

As expected, the incidence of LRTCs and hospitalizations was higher among the at-risk subjects than among the otherwise healthy adults and adolescent population.[6] The effectiveness of oseltamivir in reducing the incidence of LRTCs among the at-risk population (34%) was lower than that observed in the otherwise healthy population (67%). This may be due to the more complex pathological condition in at-risk individuals. This further supports the importance of prevention of influenza with annual vaccination in target populations. Nevertheless, the reduction in complications among these at-risk individuals is a substantial benefit and supports the use of antiviral treatment to prevent serious sequelae of influenza in those developing illness despite vaccination or in case of emergence of drifted strain not covered by the vaccine.

In our at-risk population we observed a hospitalization rate of 3.2% following influenza illness compared with 0.8% in otherwise healthy subjects. Others have reported higher hospitalization rates among at-risk populations, but our protocols excluded those with unstable or poorly controlled comorbid diseases.[6,18] The data in this study are therefore more representative of the healthy older persons living in the community and individuals with stable chronic disorders. Although some subjects were hospitalized for coincidental conditions (eg, acute appendicitis or hernia repair), many were hospitalized for reasons that are known to be associated with influenza, including exacerbation of underlying conditions and coagulation disorders.[6,18,19] Among the influenza-infected at-risk population, the 39% overall reduction in hospitalizations due to influenza-related illness in the oseltamivir group was proportionate to the observed 34% reduction in LRTCs.

We have observed that acute bronchitis is the most frequent respiratory complication following influenza illness and that approximately 1 in 5 of at-risk subjects with confirmed influenza illness experienced an LRTC. Early oseltamivir treatment significantly reduced the rate of these complications, including associated antibiotic use, and also reduced the numbers of hospitalizations following influenza. These important clinical benefits were observed both in otherwise healthy adults and at-risk subjects.

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