MAJOR ARTICLE

Antiviral Therapy and Outcomes of Influenza Requiring Hospitalization in Ontario, Canada

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Background. We conducted a prospective cohort study to assess the impact of antiviral therapy on outcomes of patients hospitalized with influenza in southern Ontario, Canada.

Methods. Patients admitted to Toronto Invasive Bacterial Diseases Network hospitals with laboratory-confirmed influenza from 1 January 2005 through 31 May 2006 were enrolled in the study. Demographic and medical data were collected by patient and physician interview and chart review. The main outcome evaluated was death within 15 days after symptom onset.

Results. Data were available for 512 of 541 eligible patients. There were 185 children (<15 years of age), none of whom died and none of whom were treated with antiviral drugs. The median age of the 327 adults was 77 years (range, 15–98 years), 166 (51%) were male, 245 (75%) had a chronic underlying illness, and 216 (71%) had been vaccinated against influenza. Of the 327 adult patients, 184 (59%) presented to the emergency department within 48 h after symptom onset, 52 (16%) required intensive care unit admission, and 27 (8.3%) died within 15 days after symptom onset. Most patients (292 patients; 89%) received antibacterial therapy; 106 (32%) were prescribed antiviral drugs. Treatment with antiviral drugs active against influenza was associated with a significant reduction in mortality (odds ratio, 0.21; 95% confidence interval, 0.06–0.80; $P = .03$). There was no apparent impact of antiviral therapy on length of stay in survivors.

Conclusions. There is a significant burden of illness attributable to influenza in this highly vaccinated population. Treatment with antiviral drugs was associated with a significant reduction in mortality.

Despite widespread use of effective vaccines, influenza remains a common cause of morbidity and mortality, particularly among older adults [1–3]. Early therapy with neuraminidase inhibitors has been shown to reduce the severity and duration of symptoms and the risk of complications associated with influenza [4–8]. However, the randomized, controlled trials demonstrating these effects involved relatively young, healthy adult outpatients treated within 48 h after the onset of symptoms [4–8]. The extent to which therapy with neuraminidase inhibitors may benefit patients with severe and/or complicated influenza is unknown. To assess whether antiviral therapy was associated with reduced mortality and/or reduced length of stay in patients requiring hospitalization for influenza-associated illness, we undertook surveillance for laboratory-confirmed influenza requiring hospitalization in south-central Ontario, Canada.

METHODS

The Toronto Invasive Bacterial Diseases Network is a collaborative network of microbiology laboratories, infection-control practitioners, and public health departments that performs population-based surveillance for infectious diseases in south-central Ontario [9–12]. During the 2004–2005 and 2005–2006 influenza seasons, hospitals from this network were asked to participate in surveillance for laboratory-confirmed influenza illness requiring hospitalization.

Participating hospitals reported to the study office information regarding all specimens in which influenza virus was identified by culture, direct fluorescent antigen detection, or EIA. Routine laboratory protocols

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for specimen processing were not altered for the study. Of the 19 laboratories that served the 21 participating hospitals, 2 academic centers performed direct fluorescent antigen detection and culture of all specimens, and 10 laboratories submitted all specimens to the Ontario Central Public Health Laboratory for culture (7 performed no rapid testing, 2 tested all specimens by EIA (Directigen FluA+B; Becton Dickinson), and 1 performed EIA (Directigen FluA+B) testing if a physician requested it). The 7 remaining laboratories submitted specimens for culture to the Public Health Laboratory only if an EIA had negative results or was not done. Two laboratories (both using Directigen FluA+B) tested all specimens by EIA, and 5 performed EIA only on physician request (3 using Directigen FluA+B, 1 using Directigen FluA, and 1 using BinaxNOW Influenza A & B [Binax]).

Eligible patients were those with influenza virus identified by EIA, direct fluorescent antigen detection, and/or culture who required hospitalization for the illness associated with the positive test result. Study staff screened results to identify eligible cases, approached patients or their substitute decision makers for consent, and collected demographic and medical data, including Charlson comorbidity index data [13], by patient and physician interview and chart review. The surveillance and this study were approved by the ethics review boards of all participating hospitals.

Clinical diagnoses (e.g., pneumonia) and chronic underlying illnesses that would qualify patients for receipt of influenza vaccine [14] were recorded in accordance with attending physician notes. Patients who were improving at hospital discharge, were discharged before hospital day 30, and were not readmitted to the same hospital were assumed to have survived. The primary outcome was mortality within 15 days after symptom onset, excluding patients who were receiving palliative care. To assess the validity of this outcome as the primary outcome, the charts and death certificates of all patients who died were reviewed to assess the contribution of influenza to death.

Data were entered and analyzed in SAS, version 9.1 for PC (SAS Institute). Differences in group proportions were assessed by the χ^2 test or Fisher's exact test. Differences in medians were assessed by the Wilcoxon rank-sum test.

Antiviral therapy was defined as an intended course of therapy with an antiviral drug active against the influenza virus isolate that was interrupted by death or inability to tolerate medication. Patients who initiated therapy with an effective antiviral as outpatients but who received <4 doses and whose therapy was not continued when they were hospitalized were excluded from the analysis. Patients prescribed amantadine were included in the arm that did not receive therapy, because influenza B virus isolates are intrinsically resistant to amantadine, and because >90% of Canadian influenza A virus isolates identified during the study period were A(H3N2), >90% of which were resistant to amantadine [14, 15]. Logistic regression models were used to adjust the estimated effect of antiviral therapy on 15-day mortality for covariates that might be potential confounders or effect modifiers, based both on relationships within the cohort and data from other publications. The covariates considered were age, residence in a nursing home, Charlson comorbidity index, time from onset of symptoms to hospital admission, requirement for intensive care unit admission, season, influenza subtype, prior influenza vaccination, type of positive test result (direct antigen vs. culture), and whether the hospital was a teaching hospital. Generalized linear models were used to evaluate the impact of antiviral therapy on length of stay for survivors using log-transformed length of stay and the same variable selection method used for the logistic regression models of mortality.

RESULTS

From 1 January 2005 through 31 May 2006, the 21 participating acute-care hospital sites identified 541 eligible patients—362 from 1 January through 11 May 2005 (the 2005 season) and 179 from 26 December 2005 through 24 May 2006 (the 2006 season). The median rate of disease was 1.0 case per 1000 hospital admissions during the 2004–2005 season and 0.44 cases per 1000 admissions during the 2005–2006 season, with per hospital rates ranging from 0 to 3.6 cases per 1000 admissions during the 2004–2005 season and from 0 to 1.2 cases per 1000 admissions during the 2005–2006 season.

Detailed clinical data are available for 512 (95%) of the patients. Of these, 185 (36%) were children (<15 years of age). A minority of children (36 children; 19%) had underlying illnesses; the most frequent underlying illness was asthma (found in 25 children). Eighty-three (45%) of the children were <1 year of age. The median hospital length of stay was 2 days (range, 1–33 days). Two children (1%) required admission to the intensive care unit. None of the children died, and none received specific antiviral therapy; therefore, children were excluded from further analysis.

The median age of the 327 adult patients was 77 years (range, 15– 99 years) (table 1). Of the 303 patients for whom data were available, 216 (71%) had been vaccinated. Vaccinated individuals included 6 (18%) of 33 previously healthy patients aged 18–64 years, 24 (56%) of 43 patients aged 18–64 years with chronic underlying illness, and 186 (82%) of 227 patients aged ⩾65 years.

Coded discharge diagnoses included influenza for 187 (57%) of the patients. In cases for which influenza was not coded at discharge, the most responsible diagnosis was pneumonia of unspecified cause in 71 patients (22%), another respiratory tract infection (most commonly, bronchitis or upper respiratory tract infection) in 36 patients (11%), another cardiorespiratory diagnosis (most commonly, exacerbation of chronic obstructive

Table 1. Characteristics of adult patients with laboratory-confirmed influenza requiring hospitalization who either were or were not prescribed antiviral therapy at admission, Toronto Invasive Bacterial Diseases Network surveillance, 2005–2006.

Variable	All patients (n = 327)	Patients who were not prescribed active anti-influenza therapy[a,b] (n = 219)	Patients who were prescribed oseltamivir[a] (n = 103)	OR (95% CI)	P
Age, median years (range)	77.2 (16–99)	75.4 (15–99)	78.9 (17–98)	NA	.05
Male sex	166 (51)	106 (48)	57 (55)	1.3 (.83–2.1)	.28
Underlying chronic illness[c]					
Any	245 (75)	167 (76)	76 (74)	0.90 (0.52–2.1)	.78
Cardiac disease	137 (42)	90 (41)	44 (44)	1.6 (0.67–1.7)	.81
Pulmonary disease (including asthma)	112 (34)	83 (38)	28 (27)	0.61 (0.37–1.0)	.06
Diabetes mellitus	94 (28)	66 (30)	28 (27)	0.89 (0.52–1.5)	.69
Cancer	34 (10)	17 (7.8)	17 (17)	2.3 (1.1–4.5)	.02
Renal disease	30 (9.2)	20 (9.1)	10 (10)	1.1 (0.48–2.4)	.84
Current smoker	34 (10)	26 (12)	8 (7.8)	0.63 (0.27–1.4)	.33
Received influenza vaccination[d]	216/303 (71)	134/199 (67)	77/99 (78)	1.7 (0.97–3.0)	.08
Nursing home resident	66 (20)	35 (16)	28 (27)	2.0 (1.2–3.6)	.02
Influenza A virus infection	265 (81)	168 (77)	93 (90)	2.8 (1.4–5.9)	.004
Test(s) yielding influenza[e]					
Antigen test and culture	118 (36)	61 (28)	55 (53)	NA	<.001
Antigen test only; culture negative	1 (0.3)	…	1 (1)	NA	
Antigen test only; culture not done	60 (18)	25 (11)	35 (34)	NA	
Culture only; antigen test negative	47 (14)	40 (18)	6 (6)	NA	
Culture only; antigen test not done	101 (31)	93 (42)	6 (6)	NA	
Time from symptom onset to ED registration, median h (IQR)	37 (23–63)	41.5 (24–72)	37 (12–54)	NA	.003

NOTE. Data are no. (%) of patients, unless otherwise indicated. ED, emergency department; IQR, interquartile range; NA, not applicable.

[a] One patient who received palliative care only and 4 patients who received 1 or 2 doses of an antiviral (oseltamivir) prior to hospital admission but who did not continue to receive therapy were excluded. Rimantadine is not licensed in Canada. Zanamivir was not prescribed for any patient.

[b] Includes patients treated with amantadine (see Methods).

[c] Conditions included are those that would qualify patients for influenza vaccination [14]. Patients may have had illnesses related to >1 organ system. All patients with underlying illness had at least 1 of the chronic illnesses listed, with the exception of 1 patient with HIV infection and 1 patient who had received a liver transplant. The most common underlying cardiac illness was coronary artery disease (88 patients); the most common underlying pulmonary diseases were chronic obstructive pulmonary disease (59 patients) and asthma (59 patients); the most common underlying cancers were lung, breast, and colon cancer (3 patients each).

[d] Received influenza vaccination in the fall prior to the episode of infection. Denominators are different, because data regarding prior influenza vaccination were not available for all patients.

[e] Participating hospitals had different algorithms for processing specimens submitted for influenza testing (see Methods).

pulmonary disease) in 20 patients (6%); and another diagnosis (most commonly, urinary tract infection) in 13 patients (4%).

The specimen used to obtain a diagnosis of influenza was a nasopharyngeal swab in 315 patients (96%), bronchoalveolar lavage fluid in 9 (3%), and throat or nasal swab in 3 (1%). One hundred seventy-nine specimens (55%) had positive direct antigen test results (table 1). One-half of the specimens that yielded influenza virus (165 specimens; 50%) were received in the laboratory on the day of emergency department registration or admission (day 0), 101 (31%) were received on day 1, 37 (11%) were received on day 2, 21 (6.5%) were received on day 3 or 4, and 3 (0.9%) were received on day 5 or 6 of hospitalization.

Three hundred fourteen (96%) of the patients were able to estimate the time of onset of symptoms compatible with influenza. Of these, 81 (26%) presented to the emergency department within 24 h, 184 (59%) presented within 48 h, 247 (79%) presented within 72 h, and 278 (89%) presented within 96 h after symptom onset. One hundred thirty-seven patients (42%) had seen a physician prior to the emergency department visit that resulted in their admission to the hospital. Of these, 75 (55%) had been prescribed an antibiotic, and 10 (8.0%) had been prescribed an antiviral drug.

Blood cultures were obtained at hospital admission for 272 cases (83%), sputum cultures were obtained for 83 cases (25%), and cultures of bronchoscopy specimens were obtained for 18 cases (5.5%). Thirteen patients (4.0%) had definite or possible respiratory copathogens identified, and an additional 17 patients (5.1%) had clinical symptoms or a culture result suggestive of infection at another site (table 2).

Table 2. Therapy and outcomes of laboratory-confirmed influenza requiring hospitalization in adults, Toronto Invasive Bacterial Diseases Network surveillance, 2005–2006.

Variable	All patients (n = 327)	Patients who were not prescribed active anti-influenza therapy[a,b] (n = 219)	Patients who were prescribed oseltamivir[a] (n = 103)	OR (95% CI)	P
Antibacterial treatment at admission					
None	35 (11)	20 (10)	13 (13)	NA	.37
Respiratory fluoroquinolone alone	155 (47)	107 (49)	47 (46)	NA	
Respiratory fluoroquinolone plus other	56 (17)	36 (17)	19 (18)	NA	
Cephalosporin or penicillin alone	23 (7.0)	18 (7.7)	6 (5.8)	NA	
Cephalosporin plus macrolide	28 (8.6)	22 (10)	5 (4.9)	NA	
Other antibiotic regimen	30 (9.2)	16 (7.3)	13 (13)	NA	
ICU admission	52 (16)	36 (16)	16 (14)	0.93 (0.46–1.8)	.84
Length of ICU stay, median days (range)[c]	5 (1–22)	5 (1–15)	8 (2–22)	NA	.09
Laboratory evidence of coinfection[d]	30 (9.2)	20 (9.1)	10 (9.7)	1.1 (0.43–2.5)	.88
Extra-pulmonary complications[e]	45 (14)	30 (14)	15 (15)	1.1 (0.51–2.1)	.83
Length of hospital stay, median days (range)	6 (1–103)	6 (1–103)	7.5 (1–63)	NA	.07
15-day mortality	27 (8.3)	22 (10)	4 (3.9)	0.36 (0.12–1.1)	.08

NOTE. Data are no. (%) of patients, unless otherwise indicated. ICU, intensive care unit.

[a] One patient who received palliative care only and 4 patients who received 1 or 2 doses of an antiviral (oseltamivir) prior to hospital admission but who did not continue to receive therapy were excluded. Rimantadine is not licensed in Canada. Zanamivir was not prescribed for any patient.

[b] Includes patients treated with amantadine (see Methods).

[c] For patients admitted to the ICU only.

[d] Thirteen patients had respiratory copathogens: 6 had *Staphylococcus aureus* (1 with positive blood, sputum, and bronchoalveolar lavage cultures and 5 with positive respiratory [bronchoalveolar lavage and/or sputum] cultures); 3 had *Haemophilus influenzae* obtained from respiratory cultures; 3 had *Streptococcus pneumoniae* obtained from respiratory cultures; and 1 had *Escherichia coli* obtained from blood and sputum cultures. Fifteen patients had asymptomatic bacteriuria, and 2 patients had symptomatic urinary tract infection.

[e] A total of 45 patients experienced 48 extrapulmonary complications: 13 myocardial infarctions; 8 acute arrhythmias (6 atrial fibrillation, 1 ventricular tachycardia, and 1 supraventricular tachycardia); 6 episodes of acute renal failure; 5 acute strokes; 2 episodes each of hip fracture, *Clostridium difficile*–associated diarrhea, acute coronary syndrome, gout, and seizures; and 1 episode each of diabetic ketoacidosis, exacerbation of multiple sclerosis, adrenal crisis, bone marrow suppression, and gastrointestinal bleeding.

At hospital admission, 290 (89%) of 327 patients were treated with antibacterial agents, and 106 (32%) were prescribed antiviral drugs (table 2). Three patients received amantadine (all of whom were infected with influenza A), and 103 patients were prescribed oseltamivir. All patients who were prescribed oseltamivir were prescribed 75 mg twice daily for 5 days or an equivalent dose after adjustment for renal failure. Of the 100 patients for whom data were available, 5 (6%) were treated within 24 h after symptom onset, 19 (19%) were treated within 36 h, 29 (29%) were treated within 48 h, 51 (51%) were treated within 72 h, and 72 (72%) were treated within 96 h. Among adults, oseltamivir was prescribed more often to patients who were older, had influenza A virus infection, were nursing home residents, had a shorter time from onset of symptoms to hospital admission, and had a positive direct antigen test result (table 1).

Twenty-seven patients (8.2%) died within 15 days after symptom onset, either during the initial hospitalization (26 patients) or during a subsequent hospitalization (1 patient). One of these patients received palliative care only; therefore, 26 deaths are included in the primary analysis of the impact of antiviral therapy on mortality (figure 1). To assess the validity of this primary outcome, we compared it with an assessment of whether death was attributable to influenza. The primary cause of death was listed as influenza for 5 of 26 patients, as pneumonia or other respiratory tract infection for 11, as myocardial infarction for 3, and as viral pericarditis, congestive heart failure, exacerbation of chronic obstructive pulmonary disease, newly diagnosed lung cancer with acute renal failure, sudden unexplained cardiac arrest, multiorgan failure, and small bowel obstruction in 1 patient each. Twenty-three of these deaths were judged to be attributable to influenza by the original study staff and by 2 repeat reviewers (A.M. and K.A.G.). The remaining 3 deaths were judged to be related to influenza by 2 of 3 reviewers (a different reviewer disagreed in each case).

The associations between death, antiviral therapy, and potential confounders and effect modifiers are shown in tables 2–4. In the final multivariable model, oseltamivir therapy was associated with a clinically and statistically decreased risk of death (OR, 0.21; 95% CI, 0.06–.80; $P = .02$). No interaction terms were identified as significant. There was no clinically significant change in the estimate of the impact of oseltamivir

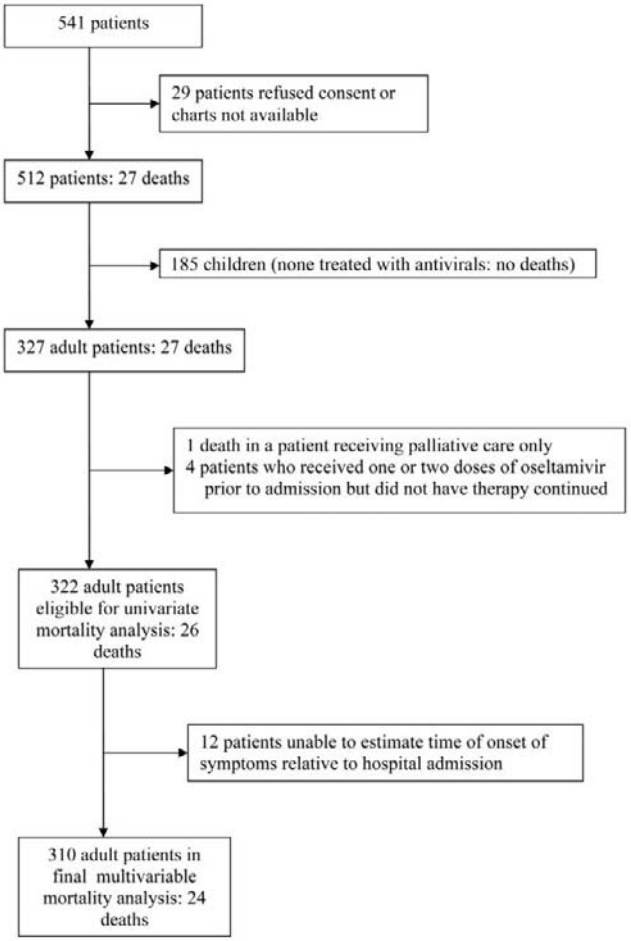

Figure 1. Flow chart of patients enrolled and included in the analysis of the impact of antiviral therapy on mortality.

therapy on death in exploratory analyses. In analyses considering only adults aged ⩾65 years, the OR for mortality associated with oseltamivir therapy was 0.24 (95% CI, 0.06–0.92); considering only influenza A virus infections, the OR was 0.13 (95% CI, 0.03–0.63); considering only oseltamivir therapy initiated >48 h after symptom onset, the OR was 0.24 (95% CI, 0.05–1.14); excluding deaths that occurred within 48 h after admission to the emergency department, the OR was 0.41 (95% CI, 0.10–1.7); including only deaths assessed by all reviewers as due to influenza, the OR was 0.24 (95% CI, 0.06–0.85); and considering deaths that occurred within 30 days after symptom onset, the OR was 0.41 (95% CI, 0.14–1.2).

Among survivors, the median length of stay was 6 days (range, 0–103 days) for patients who did not receive oseltamivir and 8 days (range, 1–63 days) for those who did ($P = .07$). In adjusted analysis, oseltamivir therapy was not associated with length of stay ($P = .35$). Older age ($P < .001$), intensive care unit admission ($P < .001$), and increasing Charlson comorbidity score ($P = .003$) were associated with increased length of stay.

DISCUSSION

In this prospectively identified cohort of patients with laboratory-confirmed influenza requiring hospital admission, treatment of adults with oseltamivir was associated with a clinically significant reduction in 15-day mortality. These data are congruent with evidence from randomized controlled trials indicating that therapy with neuraminidase inhibitors reduces symptom duration, complications, and hospitalization for influenza among adult outpatients [5, 7, 8], with cohort data identifying that oseltamivir therapy reduces the risk of death among ill nursing home residents during influenza outbreaks [16], with an analysis of administrative databases identifying a reduction in the rate of hospitalization among outpatients with influenza-like illness treated with oseltamivir [17], and with trends to improved outcomes reported in a randomized, controlled trial of zanamivir plus rimantadine versus rimantadine alone [18]. In contrast with Lee et al. [19], we did not identify an association between oseltamivir therapy and reduced length of stay; however, our power to do so was limited. In addition, if oseltamivir treatment prevents some severely ill persons from dying, examining the length of stay in survivors, as we did, may underestimate the impact of treatment.

One important difference between our study and others is that the patients in our cohort appeared to benefit from antiviral therapy initiated >48 h after symptom onset. This does not contradict data demonstrating that, in healthy adults, antiviral therapy must be started sooner than 48 h after symptom onset to be of benefit [20, 21]. In otherwise healthy adults, influenza virus is cleared promptly by the immune response. Viral load begins to decrease 24–48 h after symptom onset, and late antiviral therapy is unhelpful [22]. However, patients with severe immunocompromise may not control viral replication for many days [23, 24], and little is known about the time course of viral load in older patients at risk of influenza complications. In our cohort, all treated patients were shedding virus immediately prior to treatment (88% had a positive direct antigen test result), so that specific antiviral therapy might have been expected to be of benefit. Although we did not detect an effect of earlier therapy relative to later therapy, the power of this study to detect such an effect was very limited, and our results should not be interpreted to mean that timing of therapy is not important.

The proportion of patients in this cohort who had been vaccinated against influenza was substantial but is lower than vaccination rates among the general population of Ontario [25]. Other research clearly demonstrates that influenza vaccination is effective in preventing influenza and cost-saving to the health care system [26–29]. However, these data demonstrate that life-threatening influenza may still occur in highly vaccinated populations in years when the vaccine is well matched to the infecting strains [30, 31].

Table 3. Demographic and clinical characteristics of adult patients requiring hospital admission for laboratory-confirmed influenza.

Variable	Patients who survived (n = 296)	Patients who died (n = 26)	OR (95% CI)	P
Age, median years (range)	76 (15–99)	78 (17–98)	NA	.16
Charlson comorbidity score, median score (range)	1 (0–10)	2 (0–8)	NA	.35
Time from symptom onset to hospital admission, median h (IQR)	39 (23–66)	25 (23–81)	NA	.02
Influenza occurring during the 2005–2006 season	72 (24)	3 (12)	0.41 (0.12–1.4)	.22
Nursing home resident	51 (17)	11 (42)	3.5 (1.6–8.1)	.007
Influenza A virus infection	238 (80)	23 (88)	1.9 (0.54–6.4)	.44
Positive direct antigen test result	161 (54)	16 (62)	1.3 (0.55–3.4)	.62
Previously vaccinated against influenza[a]	196/278 (71)	19/24 (79)	1.6 (0.59–4.4)	.48
Required ICU admission	39 (13)	13 (50)	6.6 (2.8–15)	<.001
Treated with antibacterials at hospital admission				
Any	265 (90)	24 (92)	1.4 (0.32–13)	1.0
IDSA recommended regimen for CAP	214 (72)	22 (85)	2.1 (0.69–8.7)	.26
Treated with oseltamivir[b]	99 (33)	4 (15)	.36 (0.12–1.1)	.08

NOTE. Data are no. (%) of patients, unless otherwise indicated. Survival is defined as survival until the fifteenth day after the onset of symptoms of influenza. Twelve patients included in this table (10 patients who survived and 2 patients who died) are not included in the final multivariable model, because data for time from symptom onset to hospital admission were not available for these patients. Exclusion of these patients does not change the results of multivariable analysis (data not shown). CAP, community-acquired pneumonia; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; IQR, interquartile range.

[a] Data on influenza vaccination are available for 302 patients only.

[b] All specific anti-influenza therapy was with oseltamivir (see table 1).

It is evident from the variability in rates of disease in different hospitals and from the fact that the number of patients who received a diagnosis of laboratory-confirmed influenza in this cohort was much smaller than the expected number of hospital admissions attributable to influenza in a population this size [32] that influenza testing was not often considered by clinicians. This lack of clinician diagnosis of influenza has been observed in other populations. In a recent cohort, 53% of diagnostic tests for influenza performed at hospital admission were ordered for infection-control screening rather than by clinicians [33]. In a population-based surveillance study involving children, only 28% of inpatients who had a test result positive for influenza had a clinician diagnosis of influenza [34]. Therefore, increasing the frequency with which testing for influenza is performed during the influenza season will result in the identification of many more patients with illness attributable to influenza.

EIAs are the most readily available diagnostic tests for influenza. Their use has 2 potential drawbacks. Clinicians may be misled by the significant rate of false-positive results associated with some tests [35]. In addition, these tests are, at best, 70% sensitive, compared with culture, and will fail to diagnose many cases of influenza. One alternative approach would be to consider empirical treatment of respiratory illness during influenza season. Because neuraminidase inhibitors are influenza specific, treatment of patients who do not have influenza does not create selective pressure for drug resistance. However, treatment of patients without influenza is a waste of resources, and clinicians are unlikely to adopt empirical therapy in the absence of algorithms with reasonable positive predictive values for influenza. Such algorithms exist for healthy, young adults, but they do not exist for patients requiring hospitalization [36, 37]. Another approach would be to use PCR for the diagnosis of influenza. This would greatly increase the sensitivity of detection of influenza [35]. However, cases detected by PCR and not by direct antigen testing may be systematically different from those identified by direct antigen testing, and our conclusions about the impact of therapy may not apply.

One-half of the patients who were admitted to the hospital with laboratory-confirmed influenza had seen a physician before the emergency department visit that resulted in their hospitalization, and almost one-half of these were prescribed an antibiotic. Other studies have also demonstrated that many patients with influenza who see a physician are treated with antibiotics [34]. Presumably, physicians prescribe antibiotics to at-risk outpatients with upper respiratory illness, because they perceive that treating possible bacterial complications will most effectively reduce the risk of progression to severe disease. Our data suggest that, in some circumstances, influenza itself may progress to require hospitalization. Further work is needed to understand whether or when antiviral therapy should be selected over antibacterial therapy in these circumstances.

There are a number of limitations to our study. It is a natural limitation of observational studies that undetected confounding may be present even in multivariable analyses. For instance, if oseltamivir therapy was itself associated with unmeasured overall increases in quality of care, this increased quality may have been the true effect resulting in reduced mortality. We did not

Table 4. Multivariable analysis of the impact of antiviral therapy on mortality associated with laboratory-confirmed influenza requiring hospitalization, Toronto Invasive Bacterial Diseases Network surveillance, 2005–2006.

Variable	OR (95% CI)	*P*
Oseltamivir therapy	0.21 (0.06–0.80)	.02
Intensive care unit admission	10.5 (3.9–27)	<.001
Charlson comorbidity score (per point)	1.3 (1.0–1.6)	.03
Time from onset of symptoms to emergency department presentation (per 24-h period)	0.51 (0.31–0.87)	.01

NOTE. ORs <1 indicate that the variable is associated with reduced mortality. Variables that were considered in multivariable analysis are listed in the final paragraph of Methods.

ask clinicians to justify their decisions about treatment, so we cannot explore the reasons behind these choices. The sample size was insufficient to compare treatment effects in different subgroups, and our power to identify an effect of time of first treatment relative to symptoms was low. No children in our cohort were treated with antiviral therapy; thus, it was not possible to assess treatment impact in children. Our sample size was not large enough to ask whether treatment effect might differ between influenza A and B virus infections [38–40] or between infections due to different types of influenza A virus. As with all studies of influenza, our conclusions only apply to the strains circulating during the years of our study. Finally, because the proportion of patients admitted to the hospital with respiratory illness who had testing performed for influenza was low, these results may not apply to all patients who require hospitalization for influenza.

The neuraminidase class of antiviral drugs were initially assessed for their ability to reduce symptom severity and duration in healthy adults. This analysis contributes to the accumulating evidence that, in addition to reducing influenza complications in otherwise healthy adults [4, 5], neuraminidase inhibitors have a role in the treatment of more-seriously ill patients.

TORONTO INVASIVE BACTERIAL DISEASES NETWORK

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