

Infections With Oseltamivir-Resistant Influenza A(H1N1) Virus in the United States

Nila J. Dharan, MD

Larisa V. Gubareva, PhD

John J. Meyer, MPH

Margaret Okomo-Adhiambo, PhD

Reginald C. McClinton, MPH

Steven A. Marshall, MS

Kirsten St. George, MAppSc, PhD

Scott Epperson, MPH

Lynnette Brammer, MPH

Alexander I. Klimov, PhD

Joseph S. Bresee, MD

Alicia M. Fry, MD, MPH

for the Oseltamivir-Resistance Working Group

IN JANUARY 2006, THE US CENTERS for Disease Control and Prevention (CDC) recommended against the use of adamantanes due to a significant increase in resistance among circulating influenza A(H3N2) viruses.¹ As a result, neuraminidase inhibitors (NAIs) became the only class of antiviral agents recommended for the treatment and prophylaxis of influenza virus infections in the United States.^{1,2} Since their introduction in 1999, the proportion of influenza viruses resistant to NAIs among circulating influenza viruses has been low, generally less than 1% of isolates tested worldwide.³⁻⁵

However, during the 2007-2008 influenza season, increased levels of resistance to oseltamivir, 1 of the 2 licensed NAIs, were detected for the first time in the United States and worldwide.^{4,6,7} In addition, early 2008-2009

See also related articles.

Context During the 2007-2008 influenza season, oseltamivir resistance among influenza A(H1N1) viruses increased significantly for the first time worldwide. Early surveillance data suggest that the prevalence of oseltamivir resistance among A(H1N1) viruses will most likely be higher during the 2008-2009 season.

Objectives To describe patients infected with oseltamivir-resistant influenza A(H1N1) virus and to determine whether there were any differences between these patients and patients infected with oseltamivir-susceptible A(H1N1) virus in demographic or epidemiological characteristics, clinical symptoms, severity of illness, or clinical outcomes.

Design, Setting, and Patients Influenza A(H1N1) viruses that were identified and submitted to the Centers for Disease Control and Prevention by US public health laboratories between September 30, 2007, and May 17, 2008, and between September 28, 2008, and February 19, 2009, were tested as part of ongoing surveillance. Oseltamivir resistance was determined by neuraminidase inhibition assay and pyrosequencing analysis. Information was collected using a standardized case form from patients with oseltamivir-resistant A(H1N1) infections and a comparison group of patients with oseltamivir-susceptible A(H1N1) infections during 2007-2008.

Main Outcome Measures Demographic and epidemiological information as well as clinical information, including symptoms, severity of illness, and clinical outcomes.

Results During the 2007-2008 season, influenza A(H1N1) accounted for an estimated 19% of circulating influenza viruses in the United States. Among 1155 influenza A(H1N1) viruses tested from 45 states, 142 (12.3%) from 24 states were resistant to oseltamivir. Data were available for 99 oseltamivir-resistant cases and 182 oseltamivir-susceptible cases from this period. Among resistant cases, median age was 19 years (range, 1 month to 62 years), 5 patients (5%) were hospitalized, and 4 patients (4%) died. None reported oseltamivir exposure before influenza diagnostic sample collection. No significant differences were found between cases of oseltamivir-resistant and oseltamivir-susceptible influenza in demographic characteristics, underlying medical illness, or clinical symptoms. Preliminary data from the 2008-2009 influenza season identified resistance to oseltamivir among 264 of 268 influenza A(H1N1) viruses (98.5%) tested.

Conclusions Oseltamivir-resistant A(H1N1) viruses circulated widely in the United States during the 2007-2008 influenza season, appeared to be unrelated to oseltamivir use, and appeared to cause illness similar to oseltamivir-susceptible A(H1N1) viruses. Circulation of oseltamivir-resistant A(H1N1) viruses will continue, with a higher prevalence of resistance, during the 2008-2009 season.

JAMA. 2009;301(10):(doi:10.1001/jama.2009.294)

www.jama.com

influenza season surveillance data suggest that oseltamivir resistance among influenza A(H1N1) viruses will most likely be higher during the upcoming season.⁸ Resistance to oseltamivir was identified in only 1 influenza A virus subtype, influenza A(H1N1), and all of the identified resistant viruses have had the same mutation known to con-

fer resistance, H274Y (N2 NA numbering) in the viral neuraminidase.⁶ Before the 2007-2008 influenza season,

Author Affiliations and a complete list of the Oseltamivir-Resistance Working Group appear at the end of this article.

Corresponding Author: Nila J. Dharan, MD, Influenza Division, Centers for Disease Control and Prevention, 1600 Clifton Rd, MS A-32, Atlanta, GA 30333 (nfd6@cdc.gov).

detection of oseltamivir-resistant viruses in humans had typically been reported only among persons treated with oseltamivir,⁹⁻¹³ and human-to-human transmission of an NAI-resistant virus had never been documented.^{14,15} In addition, clinical case reports and *in vitro* and animal studies suggested that the infectivity and replicative ability of NAI-resistant viruses were compromised.¹⁶⁻¹⁸ As a result, it was unknown whether resistant viruses would cause clinical illness similar to other influenza viruses.

In this study, we described patients infected with oseltamivir-resistant influenza A(H1N1) identified from influenza surveillance in the United States during the 2007-2008 influenza season and described risk factors for infection with oseltamivir-resistant viruses. In addition, we compared characteristics of patients with oseltamivir-resistant and oseltamivir-susceptible influenza A(H1N1) infection to determine whether there were any differences in demographic or epidemiological characteristics, clinical symptoms, severity of illness, or clinical outcomes.

METHODS

Each year, US public health laboratories submit a sample of influenza isolates to the CDC for virus stain and antiviral resistance surveillance. During the 2007-2008 influenza season (September 30, 2007-May 17, 2008), the US public health laboratories were asked to submit all A(H1N1) virus isolates, clinical specimens, or both, in addition to a sample of other virus types and subtypes. Early during the 2008-2009 season (September 28, 2008-February 19, 2009), the number of isolates sent to the CDC was standardized, the first 10 or 20 (depending on state population) isolates were sent to the CDC. After the early season aliquot was sent, each laboratory was asked to send a random sample of isolates selected each week (the number selected depended on state population).

Testing for NAI resistance was performed by the neuraminidase inhibi-

tion assay with chemiluminescent substrate as previously described.⁴ All oseltamivir-resistant viruses exhibited IC₅₀ values of more than 80 nM. IC₅₀ is a concentration of drug (oseltamivir carboxylate) needed to inhibit enzyme activity by 50%. The presence of the oseltamivir-resistance conferring mutation (H274Y) in the neuraminidase of virus isolates with elevated IC₅₀ values was determined by sequencing, pyrosequencing, or both, as previously described.^{4,19} Testing for adamantane resistance was performed by a pyrosequencing assay for detection of markers of adamantane resistance in the M2 gene as previously described.²⁰ When only an unsubtype clinical specimen (without a matching virus isolate) was provided for NAI-resistance testing, the viral RNA was isolated directly from the clinical specimen and used in both pyrosequencing assays targeting N1 and M2 genes.

Clinical specimens from patients from Wisconsin with A(H1N1) infections were tested by the Wisconsin State Laboratory of Hygiene (WSLH) by using the pyrosequencing assays for N1 NA and M2 mutations. Clinical specimens from patients from New York with A(H1N1) infections were tested at the Wadsworth Center, New York State Department of Health (NYSDOH), by the pyrosequencing assay for M2 mutations and by dideoxysequencing of the NA gene²¹; sequencing was performed in the Molecular Genetics Core facility. A subset of New York and Wisconsin specimens was also tested at the CDC.

Because a majority of A(H1N1) viruses but only a sample of reported A(H3N2) and B viruses were submitted to the CDC for antiviral resistance testing during the 2007-2008 influenza season, we estimated an adjusted overall proportion of influenza viruses resistant to oseltamivir in the United States. We assumed that the proportion of A(H1N1) and A(H3N2) viruses among subtyped influenza A viruses was equal to the proportion among those influenza A viruses that were not subtyped. The proportions of sub-

typed A viruses reported to the CDC by the US World Health Organization (WHO) Collaborating Laboratories and the National Respiratory and Enteric Virus Surveillance System⁷ that were A(H1N1) and A(H3N2) were applied to the number of reported influenza A viruses without subtype data to estimate the total number of viruses of each subtype. The adjusted proportion of overall oseltamivir resistance was estimated by the following equation (the percentage of oseltamivir resistance detected among A[H1N1] viruses by CDC, WSLH, and NYSDOH \times the total estimated number of A[H1N1] viruses)/(the total estimated number of A[H3N2] and A[H1N1] viruses and the total number of B viruses reported by the WHO and the National Respiratory and Enteric Virus Surveillance System).

As infections with oseltamivir-resistant A(H1N1) viruses were identified during the 2007-2008 season, each case-patient was contacted by telephone and information on demographic characteristics, medical history, whether the patient received the 2007-2008 influenza vaccine, influenza illness, and illness in household members was collected by using a standardized questionnaire. Race and ethnicity were collected for demographic characterization and were determined by the patients from options read to them by the interviewer. In addition, the health care professional for each patient was contacted by telephone and information was obtained regarding medications prescribed to the patient, temperature documented at the visit, and whether the patient had received the 2007-2008 influenza vaccine. Data on vaccination status were obtained from the patient interview. Data on prescribed antiviral medications and length of illness before seeking care were obtained from the patient's health care clinician interview when available. The clinician confirmed that an antiviral agent was taken for 93% of those patients who reported taking

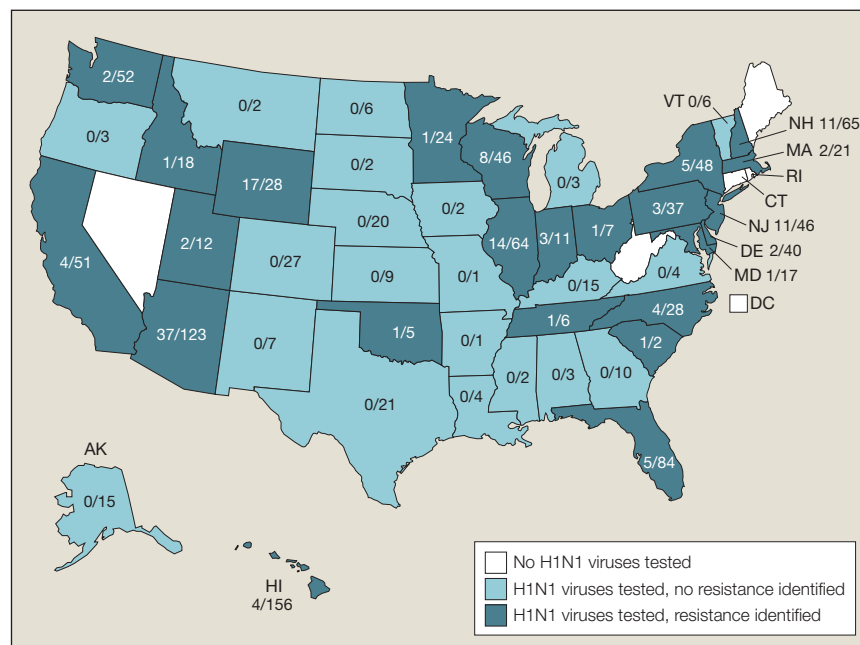
an antiviral agent for their influenza illness; 7% of clinicians were unable to be interviewed.

In states in which oseltamivir-resistant A(H1N1) cases had been identified, the state health department identified a comparison group of persons who had oseltamivir-susceptible A(H1N1) infections by randomly selecting from the list of oseltamivir-susceptible A(H1N1) viruses from each state's laboratory log. There were no matching criteria. Each state chose 1 to 4 comparison cases for each person infected with an oseltamivir-resistant A(H1N1) virus depending on the number of identified A(H1N1) viruses isolated within the state and state resources. The patients with oseltamivir-susceptible A(H1N1) infections were called and interviewed using the same standardized questionnaire as patients with oseltamivir-resistant A(H1N1) infections. Health care clinicians of patients with oseltamivir-susceptible A(H1N1) infections were not contacted.

To compare demographic and clinical characteristics between patients with oseltamivir-resistant and oseltamivir-susceptible A(H1N1) infections, we conducted univariate analyses by using 2-sided χ^2 and Fisher exact tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Because univariate analysis did not identify variables that significantly differed between the 2 groups, multivariable analysis was not performed. However, we did control for age and state. Underlying illness and symptoms vary between age groups and state surveillance and laboratory practices vary.

We determined an adjusted odds ratio for each variable, controlling for age group (0-4 years, 5-18 years, 19-50 years, or >50 years) and state as a clustered variable, with logistic regression analysis using generalized estimating equations. In the comparison of age groups, we only controlled for state. Two-sided $P \leq .05$ was considered statistically significant. Statistical analysis was conducted by using SAS version 9.1 (SAS Institute Inc, Cary, North

Figure 1. Distribution of Oseltamivir-Resistant Influenza A(H1N1) Viruses Identified in the United States, 2007-2008



The map illustrates the number of oseltamivir-resistant influenza A(H1N1) viruses that were identified as of September 5, 2008. An interactive eFigure is available at <http://www.jama.com>.

Carolina). We excluded 7 oseltamivir-resistant A(H1N1) cases from 1 state that was unable to interview a comparison group of oseltamivir-susceptible A(H1N1) cases.

We compared the proportion of A(H1N1) viruses tested for antiviral resistance that were resistant to oseltamivir during the 2007-2008 season and the proportion of total filled anti-infective prescriptions (including antibiotics, antifungals, antiparasitic, and antiviral drugs except for antiretroviral medications) that were prescriptions for oseltamivir during 2007.

The annual number of total filled anti-infective prescriptions and filled oseltamivir prescriptions from 2007 was supplied by BioSense.²² The prescription data were provided to BioSense by RelayHealth, a national electronic pharmacy claims management services provider that collects data from 20 000 to 30 000 pharmacies in the United States, Virgin Islands, Puerto Rico, and Guam.²³ We chose states that had more than

18 A(H1N1) viruses tested for antiviral resistance. We could detect 5% prevalence with a 10% error with 18 specimens. A correlation coefficient between the proportion of state A(H1N1) viruses from the 2007-2008 influenza season resistant to oseltamivir and the 2007 proportion of filled total anti-infective prescriptions that were for oseltamivir was calculated by using SAS version 9.1.

The investigation of oseltamivir-resistant influenza A(H1N1) cases during the 2007-2008 influenza season was deemed public health practice (surveillance, not human subjects research) and therefore did not require institutional review board review. Before we asked any state to contact A(H1N1) cases identified through routine surveillance, we submitted a summary of the current situation, reasons additional information needed to be collected, and the data forms and telephone scripts for determination of applicability of human subjects regulations. All

Table 1. Comparison of Demographic Features and Risk Groups Between Osetamivir-Resistant and Osetamivir-Susceptible Influenza A(H1N1) Cases, 2007-2008

Characteristics	No. (%) of Influenza A(H1N1) Cases		Adjusted OR (95% CI) ^b	P Value
	Osetamivir Resistant (n = 92) ^a	Osetamivir Susceptible (n = 182)		
Male sex	39 (42)	85 (47)	0.87 (0.48-1.58)	.64
Age group, y				
0-4	13 (14)	34 (19)	0.61 (0.24-1.57)	.30
5-18	25 (27)	50 (27)	0.80 (0.30-2.12)	.65
19-50	47 (51)	82 (45)	1 [Reference]	NA
>50	7 (8)	16 (9)	0.75 (0.21-2.62)	.65
Race/ethnicity				
White	67 (73)	122 (67)	1 [Reference]	NA
Black	6 (7)	9 (5)	1.39 (0.47-4.11)	.55
Hispanic/Latino	4 (4)	16 (9)	0.53 (0.22-1.31)	.17
Other ^c	15 (16)	35 (19)	0.88 (0.42-1.83)	.74
Any underlying medical conditions	22 (25)	40 (23)	1.17 (0.64-2.14)	.61
Cardiac	3 (3)	8 (4)	0.82 (0.17-3.88)	.80
Pulmonary	18 (20)	26 (14)	1.53 (0.78-3.03)	.22
Diabetes	0	6 (3)	NA	.18 ^d
Malignancy	2 (2)	5 (3)	0.77 (0.11-5.46)	.79
Neurologic	2 (2)	3 (2)	1.40 (0.21-9.16)	.72
Immunocompromising condition	4 (4)	8 (4)	1.04 (0.28-3.79)	.96
Received 2007-2008 influenza vaccine	27 (31)	45 (25)	0.71 (0.34-1.49)	.37
First sought care in an ED or hospital (vs clinic)	39 (42)	79 (43)	1.08 (0.54-2.17)	.82
Travel within ≤5 d before seeking care	9 (11)	11 (7)	1.60 (0.69-3.75)	.28

Abbreviations: CI, confidence interval; ED, emergency department; NA, not available; OR, odds ratio.

^aSeven cases excluded from 1 state for which a comparison group was not available.

^bAdjusted OR for age group and state.

^cOther includes Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, unknown, or multiracial.

^dUnadjusted for age group and state.

documents were submitted to the Influenza Division for approval and clearance and then to the National Center for Immunization and Respiratory Diseases (NCIRD) Human Subjects Contact. The final determination that this was public health practice (surveillance and not human subjects research) was made by the NCIRD Human Subjects Contact in consultation with the NCIRD Associate Director of Science. After the final determination that this was public health practice (surveillance), we asked the state influenza coordinators to collect additional information from the surveillance A(H1N1) cases by telephone interview. All A(H1N1) cases were contacted by telephone and gave oral consent before answering questions.

RESULTS

Resistance to oseltamivir was identified among 142 of 1155 US influenza

A(H1N1) viruses (12.3%) tested during the 2007-2008 influenza season. Of the 142 oseltamivir-resistant A(H1N1) viruses identified, 134 were identified at the CDC, 5 at the WSLH and 3 at the Wadsworth Center, NYSDOH. All oseltamivir-resistant A(H1N1) viruses were sensitive to zanamivir, the other licensed NAI, and the adamantanes.

Of the 45 states that submitted A(H1N1) viruses for antiviral resistance testing, oseltamivir-resistant viruses were identified in 24 states (53%) (FIGURE 1). Eighteen states (75%) collected data on patients with oseltamivir-resistant infections and 17 states (94%) collected data on a comparison group of patients with oseltamivir-susceptible A(H1N1) infections.

The proportion of influenza A(H1N1) among all influenza viruses identified in the United States, including type A and B, was greatest early in the season, between September 30,

2007, and February 2, 2008.^{24,25} For the entire 2007-2008 season, between September 30, 2007, and May 17, 2008, 39 827 influenza viruses were reported to the CDC, 2175 (5%) were reported as A(H1N1), 6115 (15%) were reported as A(H3N2), 19 973 (50%) were reported as type A, no subtype specified, and 11 564 (29%) were reported as type B. Applying our assumption to the unsubtyped A viruses, we estimated a total of 7415 A(H1N1) viruses (19%). Overall, 2% of all influenza viruses (A[H1N1], A[H3N2] and B) were resistant to oseltamivir.

Preliminary data from the early 2008-2009 influenza season demonstrate that oseltamivir resistance among A(H1N1) viruses continues to be detected. As of February 19, 2009, resistance to oseltamivir had been identified among 264 of 268 US influenza A(H1N1) viruses (98.5%) tested.²⁶

Among 142 oseltamivir-resistant A(H1N1) viruses identified, 99 patients (70%) were contacted and agreed to participate. Among the 99 cases, the median age was 19 years (range, 1 month to 62 years), 41 cases (41%) were male, and 70 cases (71%) were white. Twenty-four cases (24%) reported having 1 or more chronic underlying medical conditions. Thirty cases (30%) received the 2007-2008 influenza vaccine. None of the oseltamivir-resistant A(H1N1) cases reported taking oseltamivir before testing for influenza, and none of the cases had household contacts that took oseltamivir before the case's onset of illness. Of the 11 cases who reported travel in the 5 days before their onset of illness, 3 reported international travel (2 to Europe and 1 to the Bahamas and Central America).

A total of 47 oseltamivir-resistant cases (47%) received a prescription for an antiviral agent, all of whom reported taking the antiviral agent after a specimen was collected for influenza testing. Of these 47 cases, 44 (94%) received oseltamivir alone and 3 (6%) received both oseltamivir and rimantadine. Of the 47 patients who

took oseltamivir, 36 (77%) took the medication within 2 days after the onset of illness. Five cases were hospitalized; 3 of these recovered and 2 died.

Four patients with oseltamivir-resistant influenza A(H1N1) infection died. Two patients died on the way to the hospital or in the emergency department, 1 patient was 4 years old and previously healthy, and 1 patient was 4 years old with neurological problems. Both were thought to die from complications of their influenza infection. Two deaths were among hospitalized patients, 1 patient was a 1-year-old with multiple medical problems (admitted in respiratory failure and subsequently was deemed do not resuscitate) and 1 patient, hospitalized for a stem cell transplant, was 22 years old and diagnosed with influenza infection on the fifth day of hospitalization. Influenza vaccination status was available for 2 of the patients, both with underlying medical conditions; 1 had been vaccinated and 1 had not.

In our comparison of patients with oseltamivir-resistant and oseltamivir-susceptible influenza A(H1N1) infections, we excluded 7 cases from 1 state. As a result, we compared 92 cases of oseltamivir-resistant A(H1N1) infection with 182 cases of oseltamivir-susceptible A(H1N1) infection (TABLE 1). We found no significant differences in sex, age group, race/ethnicity, or underlying medical conditions. Also, there were no differences in whether cases received the 2007-2008 influenza vaccine, whether they had traveled in the 5 days before they sought care for their influenza illness, or whether they presented first for care to an emergency department or hospital vs a clinic. Of those patients who were prescribed antiviral agents, 47 of 47 oseltamivir-resistant cases (100%) received oseltamivir and 62 of 66 oseltamivir-susceptible cases (94%) reported receiving oseltamivir. One of the 66 oseltamivir-susceptible cases (2%) reported receiving zanamivir and 3 (5%) reported receiving adamantanes (2 received amantadine and 1 received rimantadine).

We found no significant difference in our comparison of the clinical symptoms and outcomes of untreated patients with oseltamivir-resistant and oseltamivir-susceptible influenza A(H1N1) infections, excluding patients who were treated with antiviral agents (TABLE 2). Patients with oseltamivir-susceptible A(H1N1) infections were statistically more likely to report myalgias or arthralgias and to be hospitalized. However, 1 of the

untreated patients with oseltamivir-resistant influenza A(H1N1) infection died on the way to the hospital and a second patient died in the emergency department before admission. If these 2 cases had been included as hospital admissions in the analysis, the difference would be no longer significant.

We found no correlation between the prevalence of oseltamivir resistance and the proportion of total filled anti-

Table 2. Comparison of Clinical Symptoms and Severity of Illness Between Untreated Oseltamivir-Resistant and Untreated Oseltamivir-Susceptible Influenza A(H1N1) Cases, 2007-2008

	Untreated Influenza A(H1N1) Cases		Adjusted OR (95% CI) ^b	P Value
	Oseltamivir Resistant (n = 49) ^a	Oseltamivir Susceptible (n = 97) ^a		
Clinical Variables, No. (%)				
Age group, y				
0-4	8 (16)	18 (19)	0.73 (0.22-2.38)	.60
5-18	7 (14)	27 (28)	0.45 (0.10-2.01)	.29
19-50	28 (57)	45 (46)	1 [Reference]	NA
>50	6 (12)	7 (7)	1.42 (0.40-5.01)	.58
Any underlying medical conditions	11 (23)	23 (25)	0.75 (0.31-1.80)	.52
Cardiac	2 (4)	3 (3)	1.11 (0.09-13.37)	.94
Pulmonary	9 (18)	14 (14)	1.08 (0.37-3.11)	.89
Diabetes	0	4 (4)	NA	.30 ^c
Malignancy	0	3 (3)	NA	.55 ^c
Neurologic	2 (4)	3 (3)	1.27 (0.21-7.79)	.80
Immunocompromising condition	0	5 (5)	NA	.17 ^c
Received 2007-2008 influenza vaccine	12 (27)	22 (23)	0.83 (0.39-1.77)	.62
Clinical illness				
Fever	43 (91)	93 (97)	0.44 (0.17-1.12)	.09
Cough	40 (82)	75 (79)	1.17 (0.45-3.05)	.75
Sore throat	25 (56)	53 (62)	0.72 (0.39-1.33)	.29
Chills	35 (76)	69 (77)	0.72 (0.33-1.56)	.40
Myalgias or arthralgias	30 (70)	68 (81)	0.38 (0.16-0.90)	.03
Difficulty breathing	21 (48)	43 (47)	0.97 (0.56-1.68)	.92
Severity of illness				
Took medications for fever	37 (93)	88 (93)	1.23 (0.27-5.57)	.79
Hospital admission	1 (2)	8 (8)	0.21 (0.07-0.62)	.005
Missed work or school	33 (77)	63 (74)	0.91 (0.38-2.22)	.84
Continuous Variables, Median (Range)				
Highest temperature, °C	39.4 (37.3-40.8)	39.4 (37.2-41.1)	NA	.89
Fever, d	3 (1-14)	4 (1-14)	NA	.44
Cough, d	12 (1-30)	7 (1-90)	NA	.51
Missed work or school, d	4 (1-10)	4 (1-30)	NA	.94
Activities limited, d	4 (1-7)	6 (1-30)	NA	.34
Hospitalized, d	2 (n = 1)	3 (1-7) (n=8)	NA	.45

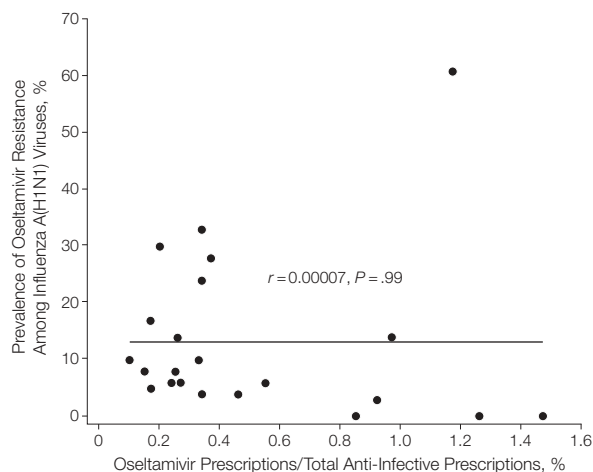
Abbreviations: CI, confidence interval; OR, odds ratio; NA, not available.

^aSeven cases excluded from 1 state for which a comparison group was not available. Cases treated with antiviral agents excluded.

^bAdjusted OR for age group and state.

^cUnadjusted for age group and state.

Figure 2. Correlation of Proportion of Total Filled Anti-infective Prescriptions That Were Prescriptions for Oseltamivir During 2007 and 2007-2008 State Prevalence of Oseltamivir-Resistant Influenza A(H1N1) Viruses in 22 States



Scatterplot of proportion of total filled anti-infective prescriptions that were prescriptions for oseltamivir during 2007 by 2007-2008 state prevalence of oseltamivir-resistant influenza A(H1N1) and the line of best fit (determined using least squares regression). Total anti-infective prescriptions include antibiotics, antifungals, antiparasitic, and antiviral medications except for antiretroviral drugs.

infective prescriptions that were prescriptions for oseltamivir during 2007 in 22 states ($r=0.00007$, $P=.99$) (FIGURE 2).

COMMENT

We report the first, to our knowledge, detailed description of persons infected with oseltamivir-resistant influenza A(H1N1) viruses identified during the 2007-2008 influenza season in the United States. Although oseltamivir-resistant A(H1N1) viruses circulated widely in the United States, during the 2007-2008 influenza season, the national adjusted overall proportion of oseltamivir-resistance among all influenza viruses was low (2%), and national recommendations for use of antiviral agents were not changed during 2007-2008.⁷ However, early surveillance data from 2008-2009 suggest that the prevalence of oseltamivir resistance among A(H1N1) viruses will most likely be higher (>90%) during the 2008-2009 season.^{8,26} The findings of this investigation informed interim guidelines released by the CDC on the use of antiviral agents for the 2008-2009 influenza season.²⁷

We did not find an association between use of oseltamivir and cases of illness due to infection with oseltamivir-resistant A(H1N1) viruses in the United States. Similar findings were reported to the WHO and by investigators in Norway.^{6,28-31} Before the 2007-2008 influenza season, resistance to oseltamivir had only been described in association with oseltamivir exposure.⁹⁻¹³ At the present time, it is unclear why oseltamivir-resistant influenza A(H1N1) viruses emerged during the 2007-2008 season and appear to continue circulating during the 2008-2009 season.

The prevalence of underlying medical conditions, the age distribution, and the clinical symptoms of patients with oseltamivir-resistant and oseltamivir-susceptible A(H1N1) infections were similar. Although oseltamivir-resistant cases reported fewer hospitalizations compared with oseltamivir-susceptible cases, 2 oseltamivir-resistant cases died on the way to the hospital and were not included as hospital admissions. Thus, it is likely that there were no significant clinical differences between patients with

oseltamivir-resistant and oseltamivir-susceptible A(H1N1) infections. A study²⁸ from 2007-2008 in Norway found similar results.

We identified 4 deaths among cases with oseltamivir-resistant influenza A(H1N1) infections. Three of these deaths were among patients with severe underlying medical conditions that put them at high risk for complications associated with influenza virus infection, similar conditions as the 1 previously reported death in a patient with oseltamivir-resistant A(H1N1) infection.³² We were not able to compare the risk of death between oseltamivir-resistant and oseltamivir-susceptible A(H1N1) cases because death from influenza A(H1N1) infection is a rare outcome and oseltamivir-resistant A(H1N1) cases were identified from all states, whereas oseltamivir-susceptible cases were identified from states in which resistant viruses were identified.

Before the 2007-2008 season, the level of resistance to oseltamivir among circulating influenza viruses was less than 1%.³⁻⁵ Transmission of 1 virus with the H274Y mutation, originally recovered from a patient treated with oseltamivir, was demonstrated in a ferret model,¹⁸ but transmission of oseltamivir-resistant viruses among humans had never been documented previously.^{14,15} Worldwide, from the last quarter of 2007 to March 31, 2008, 1182 of 7530 influenza A(H1N1) viruses (16%) tested and reported to the WHO were resistant to oseltamivir.⁶ It is unclear how oseltamivir-resistant A(H1N1) viruses became able to maintain the ability to circulate among humans as widely as oseltamivir-susceptible viruses. Mutations that confer resistance to NAI occur in or nearby the active site of the neuraminidase, an enzyme that plays an important role in the ability of the virus to infect host cells, and it was expected previously that NAI-resistant viruses would be less viable than sensitive ones.^{16,17} It is possible that the resistant viruses may have acquired other mutations that compensate for these changes to the neuraminidase.

dase and allow for continued efficient transmission of virus and continued pathogenicity. Further studies are needed to better understand the mechanisms of emergence of NAI-resistant mutants in influenza viruses.

Our study had the following limitations. The number of A(H1N1) cases identified from surveillance was small and the confidence intervals in our comparison analysis were large. We could not detect small or moderate differences (<50%) between oseltamivir-resistant and oseltamivir-susceptible cases for most categorical outcomes; however, we had sufficient power to detect a 1 day difference in continuous outcomes. Viral strain surveillance was passive; states received varying numbers of influenza specimens and submitted varying proportions of influenza viruses for oseltamivir-resistance testing at the CDC. Therefore, these results may not be representative of all A(H1N1) infections during the 2007-2008 season in the United States.

The emergence of oseltamivir resistance has highlighted the need for the development of new antiviral drugs and rapid diagnostic tests that determine viral subtype or resistance, as well as improved representativeness and timeliness of national influenza surveillance for antiviral resistance. Timely monitoring and weekly reporting of resistance during the 2008-2009 influenza season will be conducted to help inform policy for antiviral use in the United States and inform clinical antiviral treatment decision making.

Early surveillance data from the 2008-2009 influenza season has demonstrated that although influenza activity was still low, the majority of subtyped influenza A viruses were A(H1N1) and more than 90% of tested A(H1N1) viruses were resistant to oseltamivir and sensitive to zanamivir.^{8,26} As a result, the CDC released interim recommendations for the use of influenza antiviral medications.²⁷ The guidelines recommend that clinicians consider the results of patient testing and local influenza surveillance data on circulating types and subtypes of in-

fluenza viruses in deciding whether oseltamivir alone could be used. These guidelines provide options, including preferential use of zanamivir or a combination of oseltamivir and rimantadine, which might be more appropriate in treating patients who might have influenza caused by an oseltamivir-resistant virus.

Updated CDC influenza antiviral recommendations can be monitored at <http://www.cdc.gov/flu/professionals/antivirals>. Additional options for the treatment and prophylaxis of influenza virus infection are critically needed.

Published Online: March 2, 2009 (doi:10.1001/jama.2009.294).

Author Affiliations: Epidemic Intelligence Service, Office of Workforce and Career Development Assigned to Influenza Division (Dr Dharan), and Influenza Division (Drs Gubareva, Okomo-Adhiambo, Klimov, Bresee, and Fry and Ms Brammer and Mr Epperson), Centers for Disease Control and Prevention, Atlanta, Georgia; Arizona Department of Health Services, Phoenix (Mr Meyer); Wyoming Department of Health, Cheyenne (Mr McClinton); Wisconsin State Laboratory of Hygiene, Madison (Mr Marshall); and Wadsworth Center, New York State Department of Health, Albany (Dr St. George).

Author Contributions: Dr Dharan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Dharan, Epperson, Klimov, Bresee, Fry.

Acquisition of data: Dharan, Gubareva, Meyer, Okomo-Adhiambo, McClinton, Marshall, St. George, Epperson, Fry.

Analysis and interpretation of data: Dharan, Gubareva, St. George, Epperson, Brammer, Klimov, Fry.

Drafting of the manuscript: Dharan, Epperson, Bresee, Fry.

Critical revision of the manuscript for important intellectual content: Dharan, Gubareva, Meyer, Okomo-Adhiambo, McClinton, Marshall, St. George, Epperson, Brammer, Klimov, Bresee, Fry.

Statistical analysis: Dharan, Epperson, Fry.

Obtained funding: Klimov, Bresee.

Administrative, technical, or material support: Dharan, Gubareva, McClinton, St. George, Epperson, Bresee.

Study supervision: St. George, Klimov, Fry.

Financial Disclosures: None reported.

Funding/Support: No additional funds were required for enhanced surveillance.

Role of the Sponsor: Members of the Epidemiology and Prevention Branch of the Influenza Division of the Centers for Disease Control and Prevention are responsible for the design and conduct of the study, for the collection, management, analysis, and interpretation of the data, and for the preparation, review, and approval of the manuscript.

Osetamivir-Resistance Working Group Members: Farhad Ahmed, MBBS, MPH, Kumar Nalluswami, MD, MPH, Pennsylvania Department of Health, Harrisburg; Susan D. Bascom, BSN, Communicable Disease Surveillance Section, New Hampshire Department of Health and Human Services, Concord; Vjollca Berisha, MD, MPH, Office of Epidemiology, Maricopa County Department of Public Health, Phoenix, Arizona; Rachele B. Boulton, MSPH, Utah Depart-

ment of Health, Salt Lake City; Joyce Cohen, MPH, Edward Corkren, MPH, Molly Crockett, MPH, Massachusetts Department of Public Health, Boston; Christine Dao, Varough M. Deyde, MSc, PhD, Henrietta Hall, Monica Patton, Tiffany G. Sheu, Teresa R. Wallis (Influenza Division), Craig Hales, MD, MPH (National Center for Public Health Informatics), Rebecca Sunenshine, MD (Coordinating Office for Terrorism and Emergency Response), Centers for Disease Control and Prevention, Atlanta, Georgia; Laura M. Erhart, MPH, Ken Komatsu, MPH (state epidemiologist), Rebecca Sunenshine, MD, Arizona Department of Health Services, Phoenix; Kate Goodin, MPH, Florida Department of Health, Tallahassee; Matt Hanson, MD, DTM&H (Epidemic Intelligence Service Officer), Jenny Koepsell, MS, Krista Rietberg, MPH, Communicable Disease Epidemiology and Immunization Section, Public Health—Seattle & King County, Washington; Thomas Haupt, MS, Wisconsin Division of Public Health, Madison; Jennifer M. Laplante, Lisa Mingle, PhD (Laboratory of Viral Diseases), Wadsworth Center, New York State Department of Health, Albany; Purisima Linchangco, MPH, Vaccine Preventable Disease Unit, Cook County Department of Public Health, Chicago, Illinois; Janice Louie, MD, MPH, Anthony Moore, California Department of Public Health, Viral and Rickettsial Disease Laboratory, Richmond; Lisa McHugh, MPH, New Jersey Department of Health and Senior Services, Trenton; Zach Moore, MD, MPH, North Carolina Department of Health and Human Services, Raleigh; Rene Najera, MT, MPH, Division of Communicable Disease Surveillance, Office of Epidemiology and Disease Control Programs, Maryland Department of Health and Mental Hygiene, Baltimore; Sarah Park, MD, Ranjani Rajan, MPH, Hawaii State Department of Health, Honolulu; Cara J. Person, MPH, Kimberly Yousey-Hindes, MPH, CDC/CSTE Applied Epidemiology Fellow, New York State Department of Health, Albany; Rene J. Powell, MPH (epidemiologist), Oklahoma State Department of Health, Acute Disease Service, Communicable Disease Division, Oklahoma City; Erik Reisdorf, BS, CLS M (NCA), Communicable Disease Division, Peter A. Shult, PhD, Tam T. Van, PhD (Emerging Infectious Disease Research Fellow), Wisconsin State Laboratory of Hygiene, Madison; Shawn M. Richards, Indiana State Department of Health, Indianapolis; Alicia Siston, PhD, MPH, MS, Chicago Department of Public Health, Chicago, Illinois; Alaina Stoute, MPH, New York City Department of Health and Mental Hygiene, New York City, New York; Clayton Van Houten Jr, MS, Wyoming Department of Health, Cheyenne. The members of the Oseltamivir-Resistance Working Group helped with the acquisition of data but did not receive any extra compensation for their contribution.

Disclaimer: The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Previous Presentation: Presented in part at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy/Infectious Diseases Society of America (ICAAC/IDSA) 46th Annual Meeting; October 24, 2008; Washington, DC.

Additional Information: Online eFigure is available at <http://www.jama.com>.

REFERENCES

- Centers for Disease Control and Prevention (CDC). High levels of adamantane resistance among influenza A (H3N2) viruses and interim guidelines for use of antiviral agents—United States, 2005-06 influenza season. *MMWR Morb Mortal Wkly Rep*. 2006; 55(2):44-46.
- Bright RA, Shay DK, Shu B, Cox NJ, Klimov AI. Adamantane resistance among influenza A viruses isolated early during the 2005-2006 influenza season

- in the United States. *JAMA*. 2006;295(8):891-894.
3. Monto AS, McKimm-Breschkin JL, Macken C, et al. Detection of influenza viruses resistant to neuraminidase inhibitors in global surveillance during the first 3 years of their use. *Antimicrob Agents Chemother*. 2006;50(7):2395-2402.
 4. Sheu TG, Deyde VM, Okomo-Adhiambo M, et al. Surveillance for neuraminidase inhibitor resistance among human influenza A and B viruses circulating worldwide from 2004 to 2008. *Antimicrob Agents Chemother*. 2008;52(9):3284-3292.
 5. Mungall BA, Xu X, Klimov A. Surveillance of influenza isolates for susceptibility to neuraminidase inhibitors during the 2000-2002 influenza seasons. *Virus Res*. 2004;103(1-2):195-197.
 6. World Health Organization. Influenza A(H1N1) virus resistance to oseltamivir; last quarter 2007 to first quarter 2008. http://www.who.int/csr/disease/influenza/oseltamivir_summary/en/index.html. Accessed January 2, 2009.
 7. Centers for Disease Control and Prevention (CDC). Influenza activity—United States and worldwide, 2007-08 season. *MMWR Morb Mortal Wkly Rep*. 2008;57(25):692-697.
 8. Centers for Disease Control and Prevention (CDC). Update: influenza activity—United States, September 28-November 29, 2008. *MMWR Morb Mortal Wkly Rep*. 2008;57(49):1329-1332.
 9. Ward P, Small I, Smith J, Suter P, Dutkowski R. Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. *J Antimicrob Chemother*. 2005;55(suppl 1):i5-i21.
 10. Weinstock DM, Gubareva LV, Zuccotti G. Prolonged shedding of multidrug-resistant influenza A virus in an immunocompromised patient. *N Engl J Med*. 2003;348(9):867-868.
 11. Gubareva LV, Kaiser L, Matrosovich MN, Soo-Hoo Y, Hayden FG. Selection of influenza virus mutants in experimentally infected volunteers treated with oseltamivir. *J Infect Dis*. 2001;183(4):523-531.
 12. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J*. 2001;20(2):127-133.
 13. Kiso M, Mitamura K, Sakai-Tagawa Y, et al. Resistant influenza A viruses in children treated with oseltamivir: descriptive study. *Lancet*. 2004;364(9436):759-765.
 14. Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med*. 2005;353(13):1363-1373.
 15. Aoki FY, Boivin G, Roberts N. Influenza virus susceptibility and resistance to oseltamivir. *Antivir Ther*. 2007;12(4 pt B)(4 pt B):603-616.
 16. Ives JA, Carr JA, Mendel DB, et al. The H274Y mutation in the influenza A/H1N1 neuraminidase active site following oseltamivir phosphate treatment leave virus severely compromised both in vitro and in vivo. *Antiviral Res*. 2002;55(2):307-317.
 17. Roberts NA. Treatment of influenza with neuraminidase inhibitors: virological implications. *Philos Trans R Soc Lond B Biol Sci*. 2001;356(1416):1895-1897.
 18. Herlocher ML, Truscon R, Elias S, et al. Influenza viruses resistant to the antiviral drug oseltamivir: transmission studies in ferrets. *J Infect Dis*. 2004;190(9):1627-1630.
 19. Deyde VM, Okomo-Adhiambo M, Sheu TG, et al. Pyrosequencing as a tool to detect molecular markers of resistance to neuraminidase inhibitors in seasonal influenza A viruses. *Antiviral Res*. 2009;81(1):16-24.
 20. Bright RA, Medina MJ, Xu X, et al. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. *Lancet*. 2005;366(9492):1175-1181.
 21. Laplante J, Marshall SA, Van T, et al. Surveillance of antiviral resistant influenza from 2006-2008 by a network of U.S. state public health laboratories. Presented at: 24th Annual Clinical Virology Symposium; April 27-30, 2008; Daytona Beach, FL.
 22. Loonsk JW. BioSense: a national initiative for early detection and quantification of public health emergencies. *MMWR Morb Mortal Wkly Rep*. 2004;53(suppl):53-55.
 23. RelayHealth. <http://www.relayhealth.com/>. Accessed January 2, 2009.
 24. Centers for Disease Control and Prevention (CDC). Update: influenza activity—United States, September 30-December 1, 2007. *MMWR Morb Mortal Wkly Rep*. 2007;56(49):1287-1291.
 25. Centers for Disease Control and Prevention (CDC). Update: influenza activity—United States, September 30, 2007-February 9, 2008. *MMWR Morb Mortal Wkly Rep*. 2008;57(7):179-183.
 26. Fluview. A weekly influenza surveillance report prepared by the Influenza Division. <http://www.cdc.gov/flu/weekly>. Accessed February 3, 2009.
 27. Centers for Disease Control and Prevention. Issues Interim Recommendations for the Use of Influenza Antiviral Medications in the Setting of Oseltamivir Resistance among Circulating Influenza A (H1N1) Viruses, 2008-09 Influenza Season. <http://www2a.cdc.gov/HAN/ArchiveSys/ViewMsgV.asp?AlertNum=00279>. Accessed January 2, 2009.
 28. Hauge SH, Dudman S, Borgen K, Lackenby A, Hungnes O. Oseltamivir-resistant influenza viruses A (H1N1), Norway, 2007-08. *Emerg Infect Dis*. 2009;15(2):155-162.
 29. World Health Organization. Influenza A (H1N1) virus resistance to oseltamivir; 14 October 2008. <http://www.who.int/csr/disease/influenza/H1N1200801013.pdf>. Accessed January 2, 2009.
 30. World Health Organization. Influenza A (H1N1) virus resistance to oseltamivir; 20 August, 2008. http://www.who.int/csr/disease/influenza/H1N1webupdate20082008_kf.pdf. Accessed January 2, 2009.
 31. Lackenby A, Thompson CI, Democratis J. The potential impact of neuraminidase inhibitor resistant influenza. *Curr Opin Infect Dis*. 2008;21(6):626-638.
 32. van der Vries E, van den Berg B, Schutten M. Fatal oseltamivir-resistant influenza virus infection. *N Engl J Med*. 2008;359(10):1074-1076.