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. 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. 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.

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. In addition, early 2008-2009 influenza season surveillance data suggest that oseltamivir resistance among influenza A(H1N1) viruses will most likely be higher during the upcoming season. 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 confer resistance, H274Y (N2 NA numbering) in the viral neuraminidase. Before the 2007-2008 influenza season,
detection of oseltamivir-resistant viruses in humans had typically been reported only among persons treated with oseltamivir and human-to-human transmission of an NAI-resistant virus had never been documented. In addition, clinical case reports and in vitro and animal studies suggested that the infectivity and replciative ability of NAI-resistant viruses were compromised. 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 inhibition assay with chemiluminescent substrate as previously described. 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. Testing for adamantane resistance was performed by a pyrosequencing assay for detection of markers of adamantane resistance in the M2 gene as previously described.

Clinical specimens from patients infected with oseltamivir-resistant influenza 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 χ² 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≤.05 was considered statistically significant. Statistical analysis was conducted by using SAS version 9.1 (SAS Institute Inc, Cary, North 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. 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. 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.
Infections with Oseltamivir-Resistant Influenza A(H1N1) Virus

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 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

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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 adaman- tane (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 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-
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. 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. The findings of this investigation informed interim guidelines released by the CDC on the use of antiviral agents for the 2008-2009 influenza season.

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. Before the 2007-2008 influenza season, resistance to oseltamivir had only been described in association with oseltamivir exposure. 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 study 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. 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%. Transmission of 1 virus with the H274Y mutation, originally recovered from a patient treated with oseltamivir, was demonstrated in a ferret model, but transmission of oseltamivir-resistant viruses among humans had never been documented previously.

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. 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 NAIs 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 NAIs-resistant viruses would be less viable than sensitive ones. 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 influenza 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.

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Author Affiliations: Epidemiologic Intelligence Service, Office of Workforce and Career Development Assigned to Influenza Division (Dr Dharan), and Influenza Division (Drs Gubareva, Okomo-Adhiambio, Klimov, Brosseau, 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-Adhiambio, McClintock, St. George, Epperson, Fry.

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

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

Critical revision of the manuscript for important intellectual content: Dharan, Gubareva, Meyer, Okomo-Adhiambio, McClintock, St. George, Epperson, Brammer, Klimov, Fry.

Statistical analysis: Dharan, Epperson, Fry.

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Osmeltamivir-Resistance Working Group Members: Farhad Ahmed, MBBS, MPH, Kumar Nalluswamy, MD, MPH, Pennsylvania Department of Health, Harrisburg; Susan D. Bascom, BSN, Communicable Disease Surveillance Section, New Hampshire Department of Health and Human Services, Concord; Vjalcja Berisha, MD, Office of Epidemiology, Maricopa County Department of Public Health, Phoenix, Arizona; Rachelle B. Boulton, MS, MPH, Utah Department of Health, Salt Lake City; Joyce Cohen, MPH, Edward Corkren, MPH, Molly Crockett, MPH, Massachusetts Department of Public Health, Boston; Christie Dao, Varoum M. Dedy, MSc, PhD, Henrietta Hall, Monica Patton, Tiffany G. Sheu, Teresa R. Wallace (Influenza Division), Craig 초 (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; Mike Harter, MD, DTM&H (Epidemic Intelligence Service Officer), Jenny Koepell, 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; Purisma Linnan, 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, Ranjanji Rajan, MPH, Hawaii State Department of Health, Honolulu; Cara J. Person, MPH, Kimberly Yousef-Hindes, MPH, CDC/CSTE Applied Epidemiology Fellow, New York 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, MLS (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; Alain 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 compensation for their contribution.

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INFECTIONS WITH OSELTAMIVIR-RESISTANT INFLUENZA A(H1N1) VIRUS


