Epidemiology of influenza A (H1N1)pdm09-associated deaths in the United States, September–October 2009

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Background From April to July 2009, the United States experienced a wave of influenza A (H1N1)pdm09 virus (H1N1pdm09) infection. The majority of the deaths during that period occurred in persons <65 years of age with underlying medical conditions.

Objective To describe the epidemiology of H1N1pdm09-associated deaths in the US during the fall of 2009.

Methods We collected demographic, medical history, and cause of death information on a nationally representative, stratified random sample of 323 H1N1pdm09-associated deaths that occurred during September 1–October 31, 2009.

Results Data were available for 302/323 (93%) deaths. Most cases (74%) were 18–64 years of age and had ≥1 underlying medical condition (72%). Among cases aged <18 years, 16/43 (37%) had a chronic lung disease, and 15/43 (35%) a

neurological disorder; among cases aged ≥18 years, 94/254 (37%) had a chronic lung disease and 84/254 (33%) had a metabolic disorder. The median number of days between symptom onset and death was six among children (range, 1–48) and 12 among adults (range, 0–109). Influenza antiviral agents were prescribed for 187/268 (70%) of cases, but only 48/153 (31%) received treatment within 2 days of illness onset.

Conclusions The characteristics of H1N1pdm09 deaths identified during the fall of 2009 were similar to those occurring April–July 2009. While most cases had conditions that were known to increase the risk for severe outcomes and were recommended to receive antiviral therapy, a minority of cases received antivirals early in the course of illness.

Keywords H1N1pdm09 subtype, influenza A virus, influenza antiviral agents, influenza fatal cases.

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Introduction

The influenza A (H1N1)pdm09 virus (H1N1pdm09) began to circulate in the United States in April 2009,¹ and in June 2009 the World Health Organization declared a global influenza pandemic. In the United States, a small focal pandemic wave in the spring was followed by a very large wave of widespread illness in all parts of the country in the fall.² Although for most persons infected, influenza is a mild, self-limited illness, influenza epidemics and pandemics are associated with substantial morbidity and mortality in a population. This is particularly true in vulnerable populations, such as pregnant women, young children, the elderly, and those with certain underlying medical condi-

tions.³ Identifying persons at greatest risk for severe outcomes from influenza helps to guide prevention and control efforts.⁴

The Centers for Disease Control and Prevention (CDC) monitored severe outcomes from H1N1pdm09 infection in the United States throughout the pandemic through individual reports and aggregate reporting by jurisdictions.^{5–7} A study of the characteristics of H1N1pdm09 influenza-associated deaths that occurred during April–July 2009 in the United States reported that 76% of deaths occurred in persons aged 18–64 years and 78% had underlying medical conditions.⁵ Chronic lung disease, including asthma, was the most common condition reported among cases aged ≥18 years (39%), while neurologic diseases were the most

common conditions reported among cases aged <18 years (54%). This and other reports suggested that the age groups most at risk of severe H1N1pdm09 disease differed from those for seasonal influenza where the highest number of deaths is seen in persons aged ≥ 65 years.^{3,6–8} Based on experience from past pandemics, there was concern that in subsequent waves the H1N1pdm09 virus would become more virulent and cause more severe disease.⁹ Thus, surveillance for severe and fatal H1N1pdm09 cases was necessary at the start of the fall wave to detect potential changes in the epidemiologic patterns observed during the early months of the pandemic and ensure that vaccination and treatment recommendations remained targeted to those at greatest risk.⁵ To monitor characteristics associated with death from H1N1pdm09, a nationally representative study of deaths that occurred during September–October 2009 was conducted.

Methods

A total of “4053 influenza-associated deaths” were reported to CDC from September 1 to October 31, 2009, from all 50 states, the District of Columbia, and several large municipal areas.⁶ Because individual reports could not be collected for such a large number of cases, we selected a sample of deaths to identify changes in demographic and clinical characteristics of cases from spring to fall.⁵ Initial data from the spring suggested that 76% of fatal H1N1pdm09 cases had at least one underlying medical condition (this proportion later increased to 78% once analysis of all spring data was completed). Basing calculations on a 10% decrease in the prevalence of this characteristic and employing $\alpha = 0.05$ and a desired power of 80%, we identified a sample size of 323 deaths. The probability of selection was proportional to the number of H1N1pdm09 laboratory-confirmed deaths either reported by or estimated to have occurred in each jurisdiction during this period. According to this sampling strategy, 40 states and New York City were asked to provide information for a specified number of H1N1pdm09-associated deaths; for the remaining jurisdictions, the number of laboratory-confirmed or estimated laboratory-confirmed deaths was <1 (i.e. zero or a fraction), and no case from that jurisdiction was included. Each jurisdiction was asked to randomly select the requested number from all laboratory-confirmed H1N1pdm09-associated deaths that occurred in the jurisdiction during the reporting period. The method of randomization was determined at the jurisdiction level.

We defined a case as death in a person of any age with laboratory confirmation of H1N1pdm09 virus infection occurring in the United States between September 1, 2009, and October 31, 2009. Laboratory confirmation included: a

positive reverse transcriptase–polymerase chain reaction (RT-PCR) test for the H1N1pdm09 virus, an influenza A-positive RT-PCR test that was negative for human H1 and H3, a positive rapid antigen test for influenza A, a positive direct immunofluorescence assay, or a positive viral culture. State and local public health officials used a standard data collection form to collect and report information about demographics, date of illness onset, underlying medical conditions, complications of influenza preceding death, and up to seven causes of death. Sources of information used to complete reports included state case report forms, laboratory reports, patient medical records, death certificates, and autopsy reports. The principal investigator reviewed all forms; when data were missing or incorrect, they were corrected via personal communication with the submitting jurisdiction.

High-risk medical conditions were defined as those recognized by the Advisory Committee on Immunization Practices (ACIP) as conferring an increased risk of severe complications from seasonal influenza. These conditions include chronic pulmonary (including asthma), cardiovascular (excluding hypertension), renal, hepatic, neurologic/neuromuscular, hematologic, and metabolic disorders (including diabetes mellitus); immune suppression, including immune suppression caused by medications or human immunodeficiency virus; and pregnancy, including 6 weeks post-partum.⁴ Information was also collected about smoking, history of alcohol or substance abuse, obesity, and morbid obesity. Morbid obesity was ultimately added to the list of high-risk medical conditions that should be targeted for influenza vaccine in the 2010 ACIP recommendations.¹⁰ In cases aged 18 years and older, obesity was defined as body mass index (BMI) of ≥ 30 kg/m² or use of the term “obesity” in the medical record; morbid obesity was defined as a BMI of ≥ 40 kg/m² or use of the term “morbid obesity” in the medical record. For cases aged 2–17 years, obesity was defined as a BMI above the 95th percentile or use of the term “obesity” in the medical record.¹¹ Obesity was not defined in cases aged <2 years, and morbid obesity was not defined in any patient <18 years old. Cases were defined as previously healthy if they did not have documentation of any ACIP high-risk condition, were not a current smoker, did not have a history of alcohol or substance abuse, and were not obese or morbidly obese. If information on any previous medical condition was available for a decedent, missing or unknown responses for other medical condition variables were considered to be negative responses; for all other variables, missing or unknown responses were excluded from the denominator. Medical conditions and causes of death were reviewed and categorized by physician-epidemiologists. Occupation was categorized according to the occupational risk pyramid for pandemic influenza, which classifies

occupations according to the likelihood of employees' exposure to pandemic influenza.¹²

Analysis was conducted using sas 9.2 statistical software (Research Triangle Institute, Cary, NC, USA). Statistical differences in categorical variables were evaluated using a chi-square test and in continuous variables a Wilcoxon rank-sum test; statistical significance was set at alpha (α) = 0.05. As part of the emergency public health response to the pandemic, this case series was deemed to be non-research in accordance with the federal human subjects protection regulations as defined in Title 45 Code of Federal Regulations parts 46.101c and 46.102d and CDC's Guidelines for Defining Public Health Research and Public Health Non-Research.

Results

Among the 323 requested H1N1pdm09 associated deaths from 41 jurisdictions, reports that met the inclusion criteria were submitted for 302 (93%) deaths from 36 states and New York City (for a jurisdictional response rate of 90%). Cases were not submitted from the following states: Idaho, Kentucky, Maine, Maryland, Massachusetts, Missouri, Nebraska, New Hampshire, New Jersey, North Dakota, Rhode Island, Vermont, Wisconsin, and Wyoming. The median number of deaths provided by jurisdictions was six (range, 1–42). Four reports were excluded because the date of death did not occur in September or October 2009, and for 17 cases from four states, the requested data collection was not completed. Complete information was not reported for each case; therefore, denominators vary according to the number of cases for which data were available.

Demographic characteristics

The median age was 45 years and ranged from 10 days to 86 years; 224 (74%) deaths occurred in persons aged 18–64 years (Figure 1). Among 294 (97%) cases with

Figure 1. Influenza A (H1N1)pdm09-associated deaths, by age group, United States, September 1–October 31, 2009.

available race and ethnicity data, 156 (53%) were white, non-Hispanic (NH), 62 (21%) were black, NH, and 48 (16%) were Hispanic (Table 1). Among 203 (67%) cases for whom occupation information was available, 90 (44%) were considered non-working, 52 (26%) were students or children, and 61 (30%) were employed. Of the 61 cases who were employed and who were classified using the occupational risk pyramid for pandemic influenza, 5 (8.2%) were working in a high-risk occupation, 15 (25%) in a medium-risk occupation, and 41 (67%) were in the lower-risk occupational group.

Underlying risk factors

Past medical history was reported for 297 (98%) cases, and 214 (72%) had an ACIP-defined high-risk underlying

Table 1. Demographic characteristics among influenza A (H1N1)pdm09-associated deaths, United States, September 1–October 31, 2009

Characteristic	Frequency (%)*
Male	148/302 (49)
Age group (in years)	
<18	45/302 (15)
18–29	41/302 (14)
30–49	96/302 (32)
50–64	87/302 (29)
≥65	33/302 (11)
Race/Ethnicity	
White	156/294 (53)
Black	62/294 (21)
Hispanic	48/294 (16)
Asian	8/294 (3)
American Indian/Alaska native	16/294 (5)
Other	4/294 (1)
Occupation	
Non-working**	90/203 (44)
Student or child	52/203 (26)
Employed	61/203 (30)
High risk***	5/61 (8)
Medium risk	15/61 (25)
Lower risk	41/61 (67)

*Denominators vary according to the number of deaths for which data were available.

**Classified as non-working: disabled ($n = 31$), unemployed ($n = 27$), retired ($n = 15$), homemaker ($n = 7$), unspecified non-working ($n = 10$).

***High-risk occupations were defined as having a high potential for exposure to known or suspected sources of H1N1pdm09, such as healthcare workers or emergency medical responders; medium risk for occupations that require contact within 6 feet of other persons, such as teachers and retail workers; lower risk for occupations without frequent close contact with the public, such as office workers or labor workers; and non-worker for retirees, disabled persons, students, and young children.

Table 2. Comparison of underlying conditions reported among influenza A (H1N1)pdm09-associated deaths by age group, United States, September–October, 2009, *n* = 302

Co-morbid conditions	All ages Frequency (%)	<18 years Frequency (%)	≥18 years Frequency (%)
Medical history reported	297/302 (98)	43/45 (96)	254/257 (99)
Chronic lung disease	110/297 (37)	16/43 (37)	94/254 (37)
Asthma	52/297 (18)	11/43 (26)	41/254 (16)
COPD	49/297 (17)	0/43 (0)	49/254 (19)
Other chronic lung	44/297 (15)	11/43 (26)	33/254 (13)
Cardiovascular disease	70/297 (24)	9/43 (21)	61/254 (24)
Neurologic disorder	62/297 (21)	15/43 (35)	47/254 (19)
Developmental delay	23/297 (7.7)	13/43 (30)	10/254 (3.9)
Neuromuscular disorder	29/297 (9.8)	8/43 (19)	21/254 (8.3)
Seizure disorder	27/297 (9.1)	11/43 (26)	16/254 (6.3)
Other neurologic	30/297 (10)	3/43 (7.0)	27/254 (11)
History of stroke	10/297 (3.4)	0/43 (0)	10/254 (3.9)
Pregnant	1/297 (0.34)	0/43 (0)	1/254 (0.39)
6 weeks post-partum	7/297 (2.4)	0/43 (0)	7/254 (2.8)
Metabolic disorders	87/297 (29)	3/43 (7)	84/254 (33)
Diabetes	75/297 (25)	0/43 (0)	75/254 (30)
Other metabolic	19/297 (6.4)	3/43 (7)	16/254 (6.3)
Immunosuppressive condition*	58/297 (20)	1/43 (2.3)	57/254 (22)
HIV/AIDS	6/297 (2.0)	0/43 (0)	6/254 (2.4)
Renal disease	41/297 (14)	2/43 (4.7)	39/254 (15)
Hematologic disorder	33/297 (11)	0/43 (0)	33/254 (13)
Hepatic disease	19/297 (6.4)	0/43 (0)	19/254 (7.5)
ACIP condition**	214/297 (72)	27/43 (63)	187/254 (74)
Obesity***	139/251 (55)	8/30 (27)	131/221 (59)
Morbid obesity†	56/221 (25)	–	56/221 (25)
ACIP condition or obesity	247/297 (83)	30/43 (70)	217/254 (85)
History of alcohol/substance abuse	33/184 (18)	0/37 (0)	33/147 (22)
Current smoker	38/213 (18)	0/38 (0)	38/175 (22)

ACIP, Advisory Committee on Immunization Practices.

*Includes chemotherapy and other medications, but does not include persons with HIV infection or AIDS.

**Conditions include chronic pulmonary (including asthma), cardiovascular (excluding hypertension), renal, hepatic, neurologic/neuromuscular, pregnancy or child delivery within 6 weeks, hematologic, and metabolic (including diabetes mellitus) disorders, immune suppression (including immune suppression caused by medications or human immunodeficiency virus).

***Not defined in patients aged <2 years; includes H1N1pdm09-associated deaths also defined as morbidly obese.

†Not defined in patients aged <18 years.

medical condition (Table 2). Of the 214 cases that had an ACIP underlying medical condition, 60 (28%) had one condition, 43 (20%) had two, and 111 (52%) had three or more. The median number of ACIP high-risk conditions reported among cases was 3 (range, 1–11). Among those 18 years of age and older (*n* = 254), the most common ACIP high-risk conditions were chronic lung disease (37%), metabolic disorders including diabetes (33%), and cardiovascular disease (24%). One adult woman who died was pregnant and seven women who died had delivered a baby during the preceding 6 weeks. Among those aged <18 years (*n* = 43), the most common medical conditions were chronic lung disease (37%) and neurological disorders (35%).

Among those aged ≥18 years, 131/221 (59%) were obese, 56/221 (25%) were morbidly obese, 33/147 (22%) had a history of alcohol or substance abuse, and 38/175 (22%) had been current smokers. There were 8/30 (27%) persons <18 years of age documented as obese. Among those without ACIP high-risk conditions for whom data were available, 28/53 (53%) were obese; among adults, 17/46 (37%) were morbidly obese, 6/28 (21%) had a history of alcohol or substance abuse, and 7/30 (23%) were current smokers. Among the 278 patients with information on both ACIP high-risk conditions and other factors, only 13 (4.7%) reported no conditions and were considered previously healthy; the majority 9/13 (69%) were <18 years of age, and none was 65 years of age or older.

With few exceptions, the prevalence of underlying medical conditions in adult cases from this series was not significantly different from adult cases from the spring (Table 3).

Medical care

The median interval between symptom onset and hospitalization varied significantly by age and was 3 days (range, 0–22 days) among adults aged ≥ 18 years old and 1 day (range, 0–7 days) among children < 18 years old ($P = 0.01$). Six cases had been hospitalized for three or more days before onset of their influenza symptoms and may have acquired influenza in the hospital. The median interval from symptom onset to death also varied significantly by age and was 12 days in adults (range, 0–109 days) and 6 days in children (range, 1–48 days) ($P < 0.01$). A total of 254/299 (85%) cases were hospitalized (Table 4). Of those hospitalized, 233/254 (91%) received intensive care unit (ICU) care and 224/254 (88%) required mechanical ventilation. Of those not hospitalized, 11/34 (32%) received outpatient medical care for their influenza-related illness. The most common location of death was the hospital (232/292; 80%), followed by hospice (26/292; 8.9%), the emergency department (20/292; 6.8%), and home (11/292; 3.8%).

Treatment and prevention

Influenza antiviral agents were prescribed for 187/268 (70%) cases (Table 4). Receipt of influenza antiviral agents did not vary significantly by age; they were received by

23/39 (59%) cases aged < 18 years, 140/198 (71%) cases aged 18–64, and 24/31 (77%) cases aged ≥ 65 years ($P = 0.21$). Receipt of antivirals did, however, vary significantly by race/ethnicity; they were received by 92/141 (65%) white, NHs, 42/59 (71%) black, NHs, and 35/41 (85%) Hispanics ($P = 0.046$). Among those who received influenza antiviral agents and for whom the interval from illness onset to start of antiviral treatment could be calculated, the median interval was 4 days, and 48/153 (31%) were treated within 2 days. The proportion of cases receiving antiviral agents within the recommended first 2 days after symptom onset was 11/20 (55%) for cases aged < 18 years, 24/115 (21%) for cases aged 18–64 years old, and 13/18 (72%) for cases aged ≥ 65 years old ($P < 0.01$). Oseltamivir was used either alone or in combination with other influenza antiviral agents for 185/187 (99%) cases who received influenza antiviral therapy; one case received only peramivir and one received only zanamivir. The H1N1pdm09 vaccine was not widely available before November 2009, and only 2/178 (1.1%) cases were reported to have received H1N1pdm09 vaccine.

Sequelae, complications, and co-infections

A clinical diagnosis of pneumonia was reported for 211/260 (81%) cases, and among these 142/163 (87%) had radiographic evidence of pneumonia (Table 4). Pneumonia etiology was reported as viral in 42/84 (50%) cases, bacterial in 22/84 (26%) cases, and both viral and bacterial in 20/84 (24%) cases. Acute Respiratory Distress Syndrome

Table 3. Comparison of underlying medical conditions among influenza A (H1N1)pdm09-associated deaths in adults with proportions reported in the United States

Condition	Prevalence, general US adult population (%)	Prevalence among 2009 H1N1 adult deaths, spring (%)	Prevalence among 2009 H1N1 adult deaths, fall (%)	P-value, Spring versus Fall	References
Current asthma	7.3	19	16	0.47	27
Chronic obstructive pulmonary disorder	4.4	15	19	0.24	27
Diabetes	8.3	24	30	0.13	27
Cardiovascular disease*	11.8	23	24	0.86	27
Chronic renal disease (stage III or IV)	1.7	14**	15**	0.79	27
Neurologic disorder	1.2	12	19	0.03	28
Seizure disorder	< 1	4	6	0.32	28
Pregnant	1	6	< 1	< 0.001	29
Hepatic disease	1.4	5	7	0.28	27
Cancer	7.9	15	4	< 0.001	27
Obesity	33.8	51	59	0.09	30
Morbid obesity	5.9	12	25	< 0.001	30

*Excludes hypertension.

**Non-specific renal disease noted in the medical record.

Table 4. Clinical characteristics reported among pandemic influenza A (H1N1)pdm09-associated, United States, September–October, 2009

Characteristic	Frequency (%)
Outpatient provider visit noted	99/176 (56)
Hospitalized	254/299 (85)
Admitted to ICU	233/254 (91)
Mechanical ventilation	224/254 (88)
Antiviral therapy	187/268 (70)
Within 2 days of onset of symptoms	48/153 (31)
H1N1pdm09 vaccination	2/178 (1)
Diagnosed with pneumonia	211/260 (81)
Radiographic evidence of pneumonia	142/163 (87)
Specified etiology	84/211 (39)
Viral pneumonia	42/84 (50)
Bacterial pneumonia	22/84 (26)
Both viral and bacterial pneumonia	20/84 (24)
Organism cultured from sterile site	39/263 (15)
Pulmonary hemorrhage or hemoptysis	26/217 (12)
Developed pulmonary embolism	13/213 (6.1)
New onset CHF	21/209 (10)
New onset MI	16/216 (7.4)
Diagnosis of ARDS	138/228 (61)
Location of death	
Hospital	232/292 (80)
ER	20/292 (6.8)
Home	11/292 (3.8)
Hospice	26/292 (8.9)
Other	3/292 (1.0)
Autopsy performed	70/217 (32)

ARDS, acute respiratory distress syndrome.

(ARDS) was reported for the majority (61%) of cases. Hemoptysis or signs of pulmonary hemorrhage were reported in 26/217 (12%) cases, and pulmonary embolism was reported in 13/213 (6.1%) cases. Acute myocardial infarction during the course of H1N1pdm09 infection was reported in 16/216 (7.4%) cases, and 21/209 (10%) cases developed a new diagnosis of congestive heart failure during the course of illness.

Organisms were cultured from samples taken from normally sterile sites in 39/263 (15%) cases (Table 3). The most common organisms identified were methicillin-resistant *Staphylococcus aureus* (cultured from 10 cases), followed by *Streptococcus* species (spp.) ($n = 7$), *Candida* spp. ($n = 5$), *Pseudomonas* spp. ($n = 4$), methicillin-sensitive *Staphylococcus aureus* (3), *Enterococcus* spp. (3), and *Klebsiella* spp. (2).

Autopsy was performed for 70/217 (32%) cases (Table 4). Among cases with any cause of death listed, 231/256 (90%) had at least one pulmonary cause of death listed, including influenza 175/231 (76%), pneumonia 125/231 (54%), ARDS 66/231 (29%), and viral pneumonitis 12/231 (5%).

Discussion

This H1N1pdm09 fatality case series is a nationally representative sample of deaths associated with H1N1pdm09 infection that occurred early in the fall pandemic wave during a period of widespread H1N1pdm09 activity in the United States. The majority of deaths occurred in the hospital among adults between the ages of 18–64 with underlying medical conditions; pneumonia and ARDS were common complications of infection. Most cases, and especially children, were admitted to the hospital within the first several days of symptom onset. Receipt of influenza antiviral therapy within 2 days of illness onset was more frequently reported in children and persons aged ≥ 65 years than in persons aged 18–64 years old.

The age distribution for H1N1pdm09-associated deaths was similar to the distribution observed during the spring 2009 pandemic wave.^{5,8} From April to July 2009, the median age of fatal cases was 43 years and 76% of all H1N1pdm09-associated deaths occurred in persons aged 18–64 years.⁵ In this case series, the median H1N1pdm09 decedent age was 45 years and 74% of all H1N1pdm09-associated deaths occurred in persons 18–64 years of age. Furthermore, studies from Germany,¹³ England,¹⁴ and Portugal,¹⁵ conducted at different times during the pandemic, demonstrated similar median ages among those who died from H1N1pdm09, ranging from 43 to 49 years. This age distribution differs markedly from that typically observed in outbreaks of seasonal influenza, where $>90\%$ of deaths occur in persons ≥ 65 years of age.³ This relative sparing of persons ≥ 65 years of age may be due to pre-existing immunity from previous exposure to H1N1 influenza strains closely related to the 1918 influenza virus.^{16,17} In addition, as has been reported,^{5,12,18} the majority of cases (72%) had one or more medical conditions that put them at risk of severe influenza; all persons over the age of 65 had at least one underlying medical condition.

Our study corroborates the findings of several other studies identifying obesity and morbid obesity as more common among persons with severe influenza than in the general US population.^{5,12,18,19} While 59% of adults in this sample were obese, the most recent National Health Interview Study demonstrated a prevalence of obesity of 28.3% in the US adult general population.²⁰ Before the 2009 pandemic, obesity and morbid obesity were not considered risk factors for severe influenza; however, following the pandemic morbid obesity was added by the ACIP to the list of underlying conditions that confer increased risk for severe outcome. Although it appears that morbid obesity was more common among fall 2009 cases than spring 2009 cases, caution should be used when interpreting this finding. Morbid obesity was identified as a potential risk factor for severe illness early in the pandemic;¹⁹ thus increased reporting of

this condition may have occurred in the fall study. Pregnancy and a history of cancer were less frequently reported in the fall when compared to the spring, and this may have been a result of prevention and treatment messages that were targeted to protect these populations when they were noted to be at risk in the spring.⁵

Information about smoking, alcohol, and substance abuse was collected in this study. Smoking was not more common among adults aged ≥ 18 years old in our case series than in the general US population (22% versus 19%).²⁰ However, 33/184 (18%) of our cases had a history of alcohol or substance abuse, while the 2009 National Survey on Drug Use and Health found that 8.9% of the general US population aged 12 or older had alcohol or substance dependence or abuse in the past year. Although not directly comparable, this evidence suggests that alcohol and substance abuse may have been more common in H1N1pdm09 deaths than in the general public.²¹ Further investigation of smoking, alcohol, and substance abuse as potential risk factors for severe outcomes from influenza is warranted. As noted by Epstein *et al.*,²² people with clearly defined risk factors could be specially targeted for influenza vaccination, even within current universal vaccine recommendations.

While a majority of cases in our study received influenza antiviral treatment, one-third of those treated received influenza antiviral agents within the recommended 2 days of symptom onset. Most of those who were not treated within the recommended time frame were in the 18- to 64-year-old age group who accounted for 75% of the deaths in this series. Prompt empiric treatment with influenza antiviral agents within 2 days of influenza illness onset can reduce the risk of severe illness or death.^{23–25} The benefits of antiviral treatment are likely to be greatest if treatment is started as soon as possible after illness onset, and evidence for benefit is strongest in studies in which treatment was started within 2 days of illness onset. However, antiviral treatment for any person with confirmed or suspected influenza who requires hospitalization is recommended, even if the patient presents >2 days after illness onset.^{23–25} This study is subject to several limitations. First, only cases from 36 states and NYC were included in this analysis. Thus, it is possible but unlikely that the results from this analysis may not be generalizable to the entire United States, given the wide geographical distribution of participating states and the $>90\%$ sample participation rate. Second, case ascertainment might have been biased toward hospitalized patients because people who die outside the hospital are less likely to be tested for influenza.²⁶ However, we encouraged participating states to use all sources of mortality data and to select randomly from all deaths that occurred during the study period; approximately 20% of deaths occurred in a location other than the hospital. Third, states had different methods for confirming and

identifying influenza deaths and used different data sources. Therefore, case ascertainment methods and data quality may vary by state. Finally, for a given decedent, if information was reported for one or more medical conditions, other medical conditions for which information was missing or unknown were assumed to be negative. This may have underestimated the prevalence of the underlying medical conditions included in this study.

Because of concerns about increased virulence in a subsequent pandemic wave, we conducted this study at the start of the fall wave to determine whether the epidemiologic patterns observed during the early months of the pandemic would persist and to ensure that vaccination and treatment recommendations remained targeted to those at greatest risk. We found that the characteristics of persons dying with H1N1pdm09 infection were similar to those who had died with H1N1pdm09 early in the pandemic. Close monitoring of H1N1pdm09-associated deaths was vital to the understanding of patient characteristics that occurred commonly in persons who died with H1N1pdm09 infection and helped to ensure that vaccine and antiviral treatment would be targeted to populations most likely to benefit from their use.

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Conflicts of interest

The authors have no conflicts of interest.

Appendix

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References

- 1 Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009; 360:2605–2615.
- 2 Jhung M, Swardlow D, Olsen S *et al.* Epidemiology of 2009 Pandemic Influenza A (H1N1) in the United States. *Clin Infect Dis* 2011; 52(Suppl 1):S13–S26.
- 3 Thompson WW, Shay DK, Weintraub E *et al.* Mortality associated with influenza viruses and respiratory syncytial virus in the United States. *JAMA* 2003; 289:170–186.
- 4 Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR Recomm Rep* 2009; 58:1–54.
- 5 Fowlkes A, Arguin P, Biggerstaff M *et al.* Epidemiology of 2009 Pandemic Influenza A (H1N1) deaths in the United States, April–July 2009. *Clin Infect Dis* 2011; 52(Suppl 1):860–868.
- 6 Centers for Disease Control. Flu-related hospitalizations and deaths in the United States from April 2009–January 30, 2010. Available at http://www.cdc.gov/H1N1flu/hosp_deaths_ahdra.htm (Accessed 28 February 2011).
- 7 Jhung MA, Davidson H, McIntyre A *et al.* Preliminary results of 2009 pandemic influenza surveillance in the United States using the aggregate hospitalization and death reporting activity. *Influenza Other Respir Viruses* 2011; 5:321–327.
- 8 Lee E, Wu C, Lee E *et al.* Fatalities associated with the 2009 H1N1 influenza A virus in New York city. *Clin Infect Dis* 2010; 50:1498–1504.
- 9 Taubenberger J, Morens D. 1918 Influenza: the mother of all pandemics. *Emerg Infect Dis* 2006; 12:15–22.
- 10 Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep* 2010; 59:1–62.
- 11 National Center for Health Statistics. 2000 CDC growth charts: clinical growth charts. Available at <http://www.cdc.gov/growthcharts> (Accessed 28 February 2011).
- 12 Occupational Safety and Health Administration. Guidance on preparing workplaces for an influenza pandemic. OSHA 3327-05R 2009. Available at http://www.osha.gov/Publications/influenza_pandemic.html (Accessed 28 February 2011).
- 13 Wilking H, Buda S, von der Lippe E *et al.* Mortality of 2009 pandemic influenza A(H1N1) in Germany. *Euro Surveill* 2010; 15:19741.
- 14 Pebody RG, McLean E, Zhao H *et al.* Pandemic Influenza A(H1N1) 2009 and mortality in the United Kingdom: risk factors for death, April 2009 to March 2010. *Euro Surveill* 2010; 15:19571.
- 15 Correia AM, Queiros L, Dias J. Pandemic influenza A(H1N1) in the North of Portugal: how did the Autumn–Winter wave behave? *Rev Port Pneumol* 2010; 16:880–886.
- 16 Hancock K, Veguilla V, Lu X *et al.* Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med* 2009; 361:1945–1952.
- 17 Skountzou J, Koutsouanos D, Kim J. Immunity to pre-1950 H1N1 influenza viruses confers cross-protection against the pandemic swine-origin 2009 A (H1N1) influenza virus. *J Immunol* 2010; 185:1642–1649.
- 18 Louie J, Acosta M, Winter K *et al.* Factors associated with death or hospitalization due to Pandemic 2009 Influenza A (H1N1) infection in California. *JAMA* 2009; 302:1896–1902.
- 19 Morgan O, Bramley A, Fowlkes A *et al.* Morbid obesity as a risk factor for hospitalization and death due to 2009 Pandemic influenza A(H1N1) disease. *PLoS ONE* 2010; 5:e9694.
- 20 Ward BW, Barnes PM, Freeman G, Schiller JS. Early release of selected estimates based on data from the 2010 National Health Interview Survey [online]. National Center for Health Statistics. 2011; Available at <http://www.cdc.gov/nchs/nhis.htm> (Accessed 16 July 2011).
- 21 Substance Abuse and Mental Health Services Administration. Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings. Rockville, MD: Office of Applied Studies (NSDUH Series H-38A, HHS Publication No. SMA 10-4586Findings), 2010.
- 22 Epstein M, Reynaldo S, El-Amin A. Is smoking a risk factor for influenza hospitalization and death? *J Infect Dis* 2010; 201:794–795.

- 23 Hanshaoworakul W, Simerman JM, Narueponjirukal U *et al.* Severe human influenza infections in Thailand: oseltamivir treatment and risk factors for fatal outcome. *PLoS ONE* 2009; 4:e6051.
- 24 McGeer A, Green KA, Plevneshi A *et al.* Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis* 2007; 45:1568–1575.
- 25 Centers for Disease Control and Prevention. Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2011; 60:1–25.
- 26 Centers for Disease Control and Prevention. Interim guidance for influenza surveillance: prioritizing RT-PCR testing in laboratories. Available at <http://www.cdc.gov/h1n1flu/screening.htm> (Accessed 7 April 2010).
- 27 Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. *Vital Health Stat* 2009; 10:242.
- 28 Hirtz D, Thurman DJ, Gwinn-Hardy K *et al.* How common are the “common” neurologic disorders? *Neurology* 2007; 68:326–337.
- 29 Ventura SJ, Abma JC, Mosher WD *et al.* Estimated pregnancy rates by outcome for the United States, 1990–2004. *Natl Vital Stat Rep* 2008; 56:1–26.
- 30 Flegel KM, Carroll MD, Ogden CL *et al.* Prevalence and trends in obesity among US adults, 1999–2008. *JAMA* 2010; 303:235–241.