

Epidemiology of 2009 Pandemic Influenza A (H1N1) Deaths in the United States, April–July 2009

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During the spring of 2009, pandemic influenza A (H1N1) virus (pH1N1) was recognized and rapidly spread worldwide. To describe the geographic distribution and patient characteristics of pH1N1-associated deaths in the United States, the Centers for Disease Control and Prevention requested information from health departments on all laboratory-confirmed pH1N1 deaths reported from 17 April through 23 July 2009. Data were collected using medical charts, medical examiner reports, and death certificates. A total of 377 pH1N1-associated deaths were identified, for a mortality rate of .12 deaths per 100 000 population. Activity was geographically localized, with the highest mortality rates in Hawaii, New York, and Utah. Seventy-six percent of deaths occurred in persons aged 18–65 years, and 9% occurred in persons aged ≥ 65 years. Underlying medical conditions were reported for 78% of deaths: chronic lung disease among adults (39%) and neurologic disease among children (54%). Overall mortality associated with pH1N1 was low; however, the majority of deaths occurred in persons aged < 65 years with underlying medical conditions.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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In April 2009, the 2009 pandemic influenza A (H1N1) virus (pH1N1), an influenza strain with a combination of gene segments not previously reported in swine or human influenza virus strains [1], was identified in the United States [2]. The majority of pH1N1 infections have resulted in a mild illness similar to that seen in seasonal influenza [3] in healthy persons, with a small proportion of more serious infections, resulting in

severe illness and death. Most severe illness has been reported in persons with underlying medical conditions, including chronic lung disease, diabetes, cardiovascular disease, neurologic disease, and pregnancy [4].

A major difference between the epidemiology of seasonal influenza and pH1N1 is the age distribution of influenza-related deaths. An estimated 90% of deaths due to seasonal influenza complications occur in persons aged ≥ 65 years, with only 6% occurring in persons aged 50–64 years, 3% in persons aged 5–49 years, and $< 1\%$ in children < 5 years of age [5]. In contrast, during the pH1N1 pandemic, only 14% of laboratory-confirmed influenza-related deaths occurred in persons ≥ 65 years of age, whereas 69% were reported in adults aged 25–64 years [6].

During the early weeks of the pH1N1 pandemic, deaths in the United States were uncommon [7]. However, after a substantial increase in the reported total number of pH1N1 cases and subsequent pH1N1-associated deaths in late May and early June, the Centers for Disease Control and Prevention (CDC) revised its data collection instrument to facilitate more rapid compilation of data for all pH1N1-associated deaths identified by state health departments in the United States. In this article, we describe the patient demographic characteristics, underlying medical conditions, causes of death, and geographic distribution of pH1N1-associated deaths from the beginning of the pandemic in April through 23 July 2009. The data collection end date coincided with a meeting on 26 July of the Advisory Committee on Immunization Practices (ACIP), for which data were provided to guide recommendations for influenza vaccination.

METHODS

For this report, a pH1N1-associated death was defined as a death occurring on or before 23 July 2009, with laboratory confirmation of pH1N1 virus infection. Laboratory confirmation was defined as a test positive for pH1N1 or influenza A but negative for human H1 and H3, as determined by real-time reverse-transcriptase polymerase chain reaction (RT-PCR). Laboratory testing was performed at either the CDC or the state health department with use of CDC-based primers.

State and local health departments were asked to complete a standard data collection form, using information from all available resources, including patient medical charts, medical examiner reports, and death certificates. Data elements included demographic information; occupation; date of illness onset; presence of underlying medical conditions, including pregnancy and obesity; documentation of diagnosis of pneumonia, if reported; results of microbiological cultures of specimens obtained from sterile sites; antiviral use; and date and location of death. Because influenza-associated deaths in children are nationally notifiable, case reports for children < 18 years of age

were verified by comparing them with reports from the CDC's influenza-associated pediatric mortality surveillance system. Occupation was categorized according to the occupational risk pyramid for pandemic influenza [8].

We classified pH1N1-associated deaths as having occurred in persons with high-risk medical conditions if the decedent had ≥ 1 underlying medical conditions recognized by the ACIP that place persons at increased risk for severe complications from influenza, including chronic pulmonary or cardiovascular disorders, immunosuppression, and neurologic conditions [9]. We classified persons who died and did not have at least 1 ACIP-recognized underlying medical condition as being previously healthy. Reported underlying medical conditions were systematically reviewed by clinicians (P.A. and S.B.) and were categorized for analysis. Additional factors, such as obesity, illicit drug use, and alcoholism were considered to be present if a report of such factors was included in the medical record. We compared the prevalence of underlying medical conditions among pH1N1-associated deaths with those in the US population with use of national estimates of prevalence from condition-specific data sources [10–13].

We calculated national and state-specific mortality rates with use of annual estimates of the resident population in the United States starting on 1 July 2008, excluding Puerto Rico [14]. Data were analyzed using SAS, version 9.2 (SAS Institute). Statistical differences in the frequency of underlying medical conditions, by age group, were evaluated using the Fisher's exact test.

RESULTS

pH1N1-Associated Deaths

The earliest reported pH1N1-associated death in the United States occurred on 27 April 2009 in Texas. From 17 April through 23 July 2009, 377 deaths due to pH1N1 infection occurred in 32 states, for an overall mortality rate of .12 deaths/100 000 US population (95% confidence interval [CI], .08–.16 deaths/100 000 population) during the 3-month surveillance period (Figure 1). Reports of fatal cases of pH1N1 virus infection were initially infrequent: only 45 were reported from 27 April through 12 June 2009. However, from 12–18 June 2009, the cumulative number of reported pH1N1-associated deaths nearly doubled to 87. Subsequently, a median of 42 additional deaths (range, 39–52 deaths) were reported to the CDC each week through 23 July 2009.

There was a wide geographic distribution of deaths but substantial rate variation by state (Figure 2). During May, deaths were reported from the western and midwestern United States and New York City; in June, deaths were reported in eastern states and Florida, Oklahoma, Nevada, and Oregon (Figure 3). The highest mortality rates were reported in Hawaii (.62

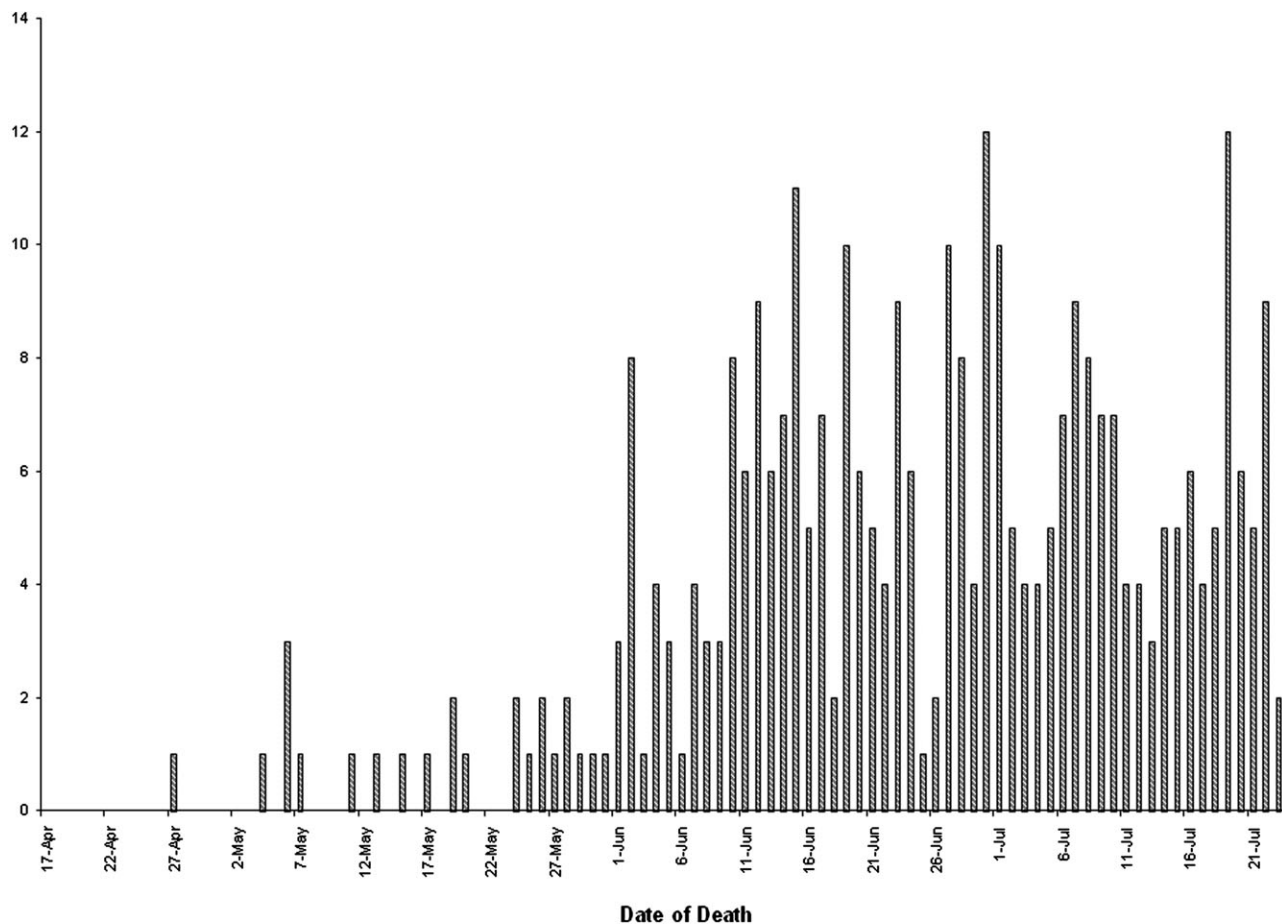


Figure 1. Epidemiologic curve of 2009 influenza A (H1N1)-associated deaths in the United States, 17 April–23 July 2009.

deaths/100 000 population; 95% CI, .19–1.05 deaths/100 000 population), New York City (.65 deaths/100 000 population; 95% CI, .47–.82 deaths/100 000 population) and Utah (.58 deaths/100 000 population; 95% CI, .29–.86 deaths/100 000 population).

Demographic Characteristics

Demographic data were available for 328 (87%) of 377 reported fatal pH1N1 cases, although data were not complete for all cases (Table 1). Among 327 pH1N1-associated deaths in persons with known age, the age ranged from 2 months to 85 years, with over three-quarters of deaths occurring in persons aged 18–64 years (Table 1). The mortality rate was .10 deaths/100 000 population (95% CI, .07–.13 deaths/100 000 population) among persons 18–29 years of age, 13 deaths/100 000 population (95% CI, 0.1–.15 deaths/100 000 population) among persons aged 30–49 years; .16 deaths/100 000 population (95% CI, .13–.2 deaths/100 000 population) among persons aged 50–64 years. In contrast, the mortality rate was lower (.07 deaths/100 000 population; 95% CI, .05–.1 deaths/100 000 population) among persons aged ≥ 65 years, and none of the deaths in this age group occurred before June. The mortality rate was lowest (.06 deaths/100 000

population; 95% CI, .05–.08 deaths/100 000 population) among persons aged < 18 years; only 7 reported pH1N1-associated deaths were reported in children < 2 years of age, including 2 infant deaths.

Race and ethnicity data were available for 266 fatal cases (71%). Overall, 75 (28%) of 266 pH1N1-associated deaths occurred in Hispanic persons; however, the proportional distribution of deaths shifted markedly during the study period. Before June, 61% of deaths occurred in Hispanic persons, but this percentage decreased to 25% during June and July, when the greatest proportion of deaths reported were in non-Hispanic white persons (44%) and non-Hispanic black persons (21%). The proportion of deaths among Asians or Pacific Islanders and American Indians or Alaska Natives did not differ during June and July (10%), compared with April and May (9%).

Underlying Medical Conditions

Information about the presence of underlying medical conditions was available for 324 (86%) of 377 fatal pH1N1 cases. Among persons who died, 253 (78%) had at least 1 reported underlying medical condition, and 182 (71%) had > 1 such condition (mean severe underlying medical conditions per fatal

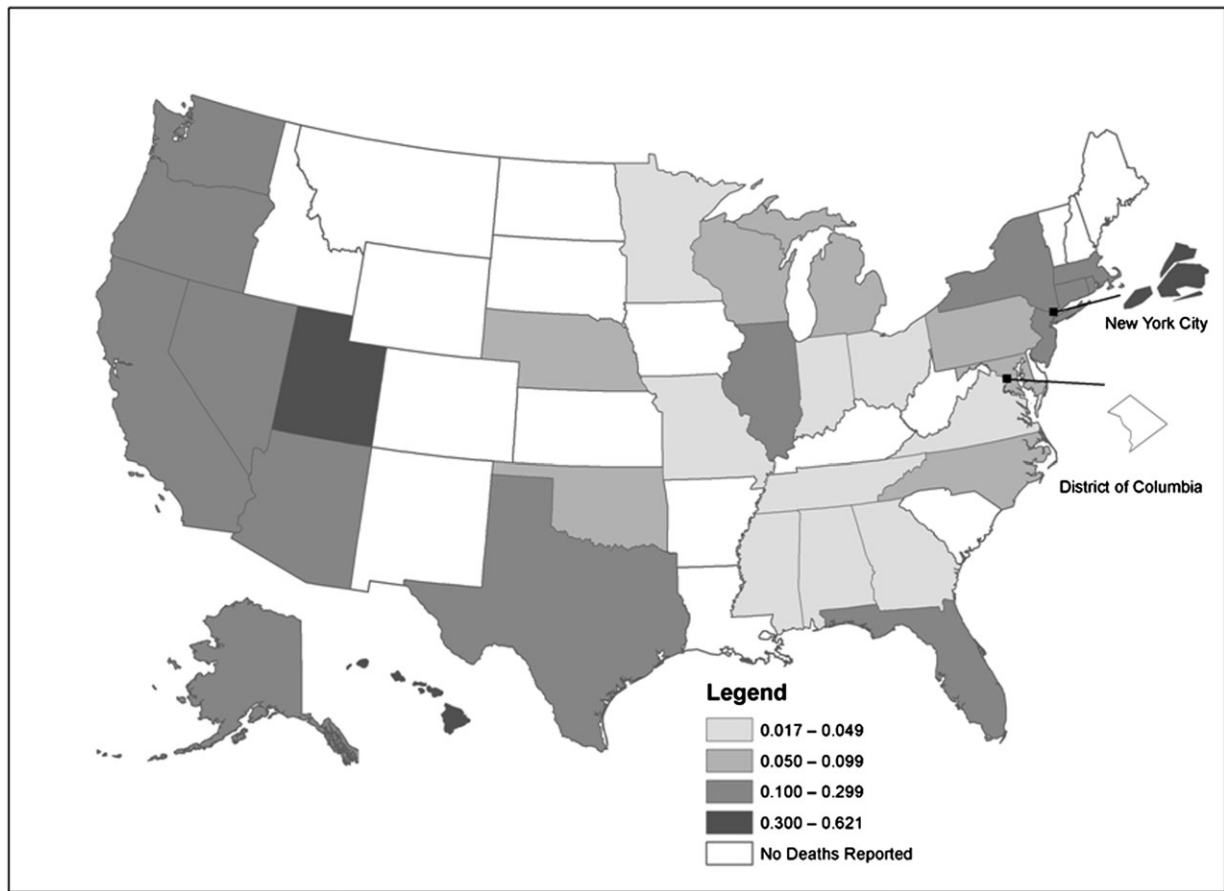


Figure 2. Density map of the United States, showing the rate per 100,000 population of pandemic influenza A (H1N1)-associated deaths occurring in each state, 17 April–23 July 2009.

case, 2.4; range 2–6) (Table 2). In a comparison of the frequency of underlying medical conditions considered by ACIP to confer an elevated risk for severe complications (including death) associated with influenza that were reported in persons who died of pH1N1 with that in the US population, all conditions were more frequently reported in persons who died. The prevalence of reported obesity (including morbid obesity), which is not currently an ACIP-defined high-risk underlying condition, was also elevated in pH1N1-associated deaths (Table 3).

Adult pH1N1-Associated Deaths

Chronic lung disease was the most frequently reported underlying medical condition, occurring in 106 (39%) of 276 pH1N1-associated adult deaths (Table 2), and among 103 persons who died for whom an underlying chronic lung condition was specified, 51 (50%) were reported to have asthma, 42 (41%) were reported to have chronic obstructive pulmonary disease (COPD), and 9 (12%) were reported to have both of these conditions. Other underlying chronic lung conditions, such as chronic thickening of respiratory secretions, chronic pleural effusion, pulmonary hypertension, or

lung impairment associated with cerebral palsy or scoliosis, were reported in 19 persons (18%) who died.

The prevalence of asthma and COPD among persons who died of pH1N1 infection varied by age. Forty-two (82%) of 51 pH1N1-associated deaths in persons with a reported medical history of asthma occurred in persons 30–64 years of age. Only 1 death occurred in an adult >65 years of age; however, 32 (76%) of 42 pH1N1-associated deaths in persons with underlying COPD were reported in adults aged ≥ 50 years.

Other ACIP high-risk underlying medical conditions were reported among pH1N1-associated deaths independently or in conjunction with pulmonary and/or other disease. Non-hypertensive cardiovascular disease was the second most frequently reported underlying medical condition after pulmonary disease. Among the 64 (23%) of 276 deaths in adults with underlying cardiovascular disease, 59 (92%) were reported in adults ≥ 30 years of age. Cardiovascular disease was also frequently reported in conjunction with other underlying medical conditions: 28 (44%) of 64 persons who died had chronic cardiovascular disease and chronic lung disease, and 23 (36%) of 64 had diabetes. Diabetes, reported among 65 (24%) of 276 persons

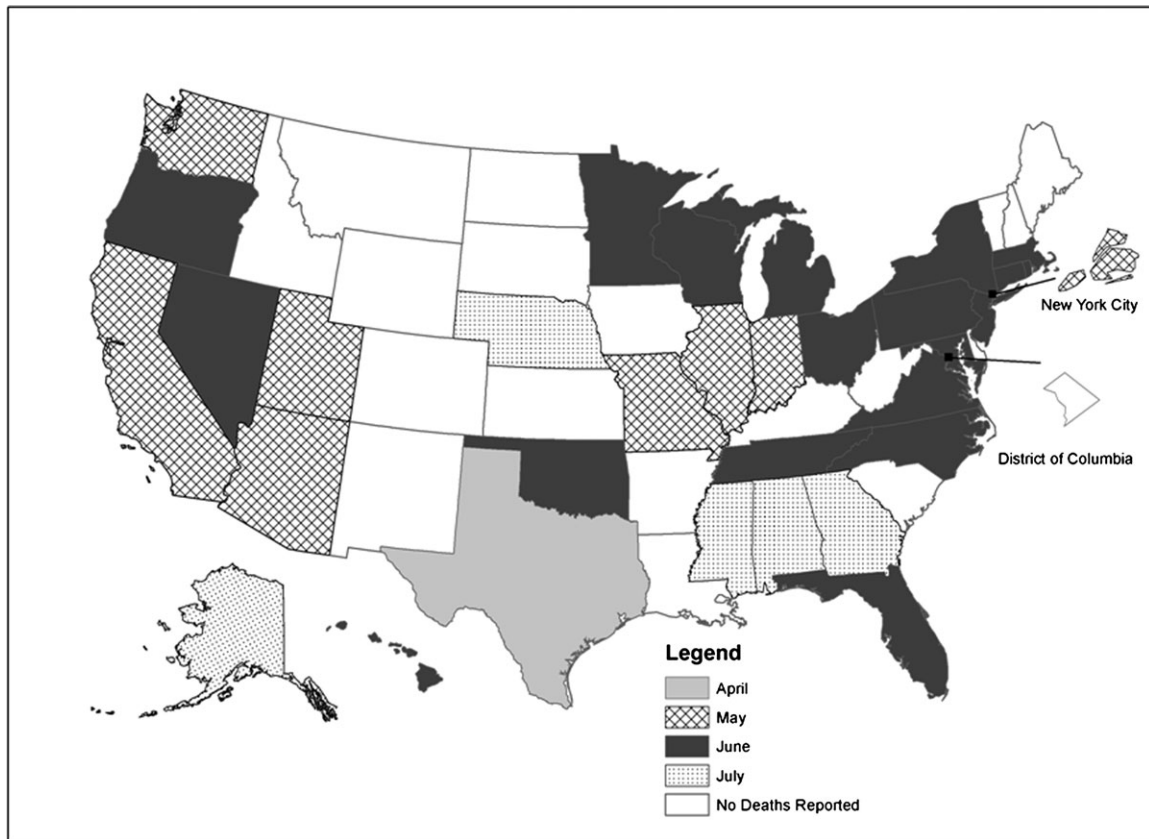


Figure 3. Month of first pandemic influenza A (H1N1)-associated death for all states, 17 April–23 July 2009.

with pH1N1-associated adult deaths, was also frequently associated with chronic lung disease (27 [42%] of 65). Forty-one (15%) of 276 pH1N1-associated deaths among adults were reported to have cancer; 27 (60%) were aged 50–64 years, and 12 (27%) were ≥ 65 years of age. Although immune suppression was frequently reported in conjunction with cancer because of chemotherapy (28 [49%] of 57), immune suppression in the absence of cancer chemotherapy was most frequently reported in persons aged 30–49 years (9 [31%] of 29) and 50–64 years (11 [38%] of 29). Specific diagnoses for immune suppression were rarely reported, but reports that were received included HIV infection, AIDS, and immunosuppressive drug therapy for organ transplantation.

Pediatric pH1N1-Associated Deaths

Among 48 pH1N1-associated deaths in children <18 years of age 33 (69%) had a reported underlying medical condition, among which neurologic disorders were reported most frequently, comprising 79% of deaths with a reported underlying medical condition. The majority of reported neurologic conditions included neurodevelopmental disorders, such as cerebral palsy, developmental delay, or Down syndrome (25 [96%] of 26). Three (12%) of 26 pediatric pH1N1-associated deaths

occurred in children with underlying neuromuscular disease, including 2 with muscular dystrophy and 1 with myasthenia gravis, and 12 (46%) occurred in children with underlying seizures. It was common for pH1N1-associated deaths among children with underlying neurologic disease to have multiple neurologic conditions: 22 (67%) of 33 children had 2–3 underlying neurologic conditions, and every child with a reported seizure also had at least 1 other neurologic disorder. In addition to multiple neurologic conditions, 78% of the deaths among children with neurologic disorders also had another underlying medical condition, such as chronic lung disease (60%).

Pregnancy-Associated Deaths

Seventeen deaths occurred in pregnant women, accounting for 5% of all pH1N1-associated deaths identified. The median age of pregnant women who died was 25 years (range, 18–38 years). Gestational age of the fetus at the time of illness onset was known for 14 (82%) of the pregnant women who died; 7 (50%) of these women were in the third trimester of pregnancy, 5 (36%) were in the second trimester, 1 (7%) was in the first trimester, and 1 (7%) was 1 week postpartum. Ten (59%) of the pregnant women who died were reported to have an additional underlying

Table 1. Demographic Characteristics of Persons Who Died of Pandemic Influenza A (H1N1) Virus Infection in the United States, 17 April–23 July 2009

Characteristic	Value	% or range
Male sex, proportion (%)	164/328	(50.0)
Age, median (range), years	43	(0.2–85)
Age, proportion (%)		
<18 years	48/327	(14.7)
18–29 years	51/327	(15.6)
30–49 years	107/327	(32.7)
50–64 years	91/327	(27.8)
>65 years	30/327	(9.2)
Race/ethnicity, proportion (%)		
White, non-Hispanic	110/266	(41.4)
Black, non-Hispanic	55/266	(20.7)
Hispanic	75/266	(28.2)
Asian/Pacific Islander	21/266	(7.9)
American Indian/Alaskan Native	5/266	(1.9)
Occupation, proportion (%)		
Employed	76/169	(45.0)
High risk ^a	3/76	(4.0)
Medium risk	31/76	(40.8)
Lower risk	42/76	(55.3)
Nonworking	51/169	(30.2)
Not applicable (student or child)	42/169	(24.9)
Time from onset of symptoms to death, median (range), days	8	(0–78)
Death location, proportion (%)		
Hospital	162/188	(86.2)
Emergency department	8/188	(4.3)
Home	15/188	(8.0)
Hospice	3/188	(1.6)

^a High-risk occupations were defined as having a high potential for exposure to known or suspected sources of pandemic H1N1, such as health care workers or emergency medical responders; medium risk for occupations that require contact within 1.8 meters 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 nonworker for retirees, disabled persons, students, and young children.

medical condition. Seven (70%) were reported to have asthma, and 4 of these women had as many as 3 additional underlying medical conditions, including a history of cancer, hematologic disorders, hepatic disorders, and immune suppression.

pH1N1-Associated Deaths in Previously Healthy Persons

More than one-fifth (21%) of persons who died of pH1N1 had no reported underlying ACIP high-risk medical condition. However, 46 (65%) had other potential health or behavioral risk factors reported. For example, 39 pH1N1-associated deaths (55%) were reported to have occurred in persons who were obese, including 11 (15%) who were reported to be morbidly obese, although body mass index was too rarely reported for verification. In addition, 7 persons (10%) who died were reported to have behavioral risk factors, including illicit drug use, alcohol abuse, and smoking; 10 (14%) had hypertension. As was observed among persons who died who had underlying medical conditions, many of these persons had >1 risk factor. For example, obesity was reported in 7 of 10 persons who died and

were reported to have hypertension and in 1 person with reported hypothyroidism.

Bacterial Coinfections

Among all 377 reported pH1N1-associate deaths, information regarding the presence of a bacterial coinfection was reported for 216 deaths (57%); among these 216, a coinfection was reported for 63 (29%). Among 40 adult pH1N1-associated deaths, 15 (38%) who had no other recognized underlying medical condition were reported to have a bacterial coinfection, compared with 32 (24%) of 135 adult pH1N1-associated deaths who had ≥1 underlying medical condition ($P < .01$). Among deaths in children <18 years of age, 9 (60%) of 14 in those with no underlying medical conditions and 7 (26%) of 27 in those with underlying medical conditions involved bacterial coinfection ($P < .05$). Although the specific pathogen was reported too infrequently for analysis, the majority of those reported were *Streptococcus* species.

Table 2. Comparison of Underlying Conditions Reported among Pandemic Influenza A (H1N1) Deaths in the United States, by Age Group, April–July 2009

Condition	All Ages (n = 324) ^a		<18 Years (n = 48)		18-64 Years (n = 246)		>65 Years (n = 30)		P for differences between age groups
	No.	% ^b	No.	%	No.	%	No.	%	
No preexisting medical condition	71	21.9	15	31.3	55	22.4	1	3.3	.007
Preexisting medical condition	253	78.1	33	68.8	191	77.6	29	96.7	
Chronic lung disease	125	39.0	19	39.6	93	37.8	13	43.3	NS
Asthma	60	18.6	9	18.8	50	20.4	1	3.3	.06
Chronic obstructive pulmonary disease	42	13.3	0.0	0.0	31	12.8	11	36.7	<.001
Cardiac/cardiovascular disease	74	23.0	10	20.8	50	20.5	14	46.7	.01
Neurologic disorder/developmental delay	58	18.1	26	54.2	28	11.5	4	13.8	<.001
Neurodevelopmental disorder	41	12.8	25	52.1	16	6.6	0	0.0	<.0001
Neuromuscular disorder	6	1.9	3	6.3	2	0.8	1	3.5	<.05
Seizure disorder	24	7.4	12	25.0	11	4.5	1	3.3	<.001
Pregnant	17	5.3	0	0.0	17	6.9	0	0.0	.06
Metabolic disorders	76	23.5	0	0.0	59	24.0	17	56.7	<.001
Diabetes	65	20.2	0	0.0	53	21.7	12	40.0	<.001
Cancer	45	13.9	4	8.3	29	11.8	12	40.0	<.001
Renal disease	41	12.7	1	2.1	28	11.4	12	40.0	<.001
Immunosuppressive condition ^c	61	23.5	4	9.8	44	22.7	13	52.0	<.001
Hematologic disease	30	9.4	1	2.1	25	10.3	4	13.8	NS
Hepatic disease	14	4.4	0	0.0	13	5.4	1	3.3	NS

^a Estimates vary on the basis of data availability for some conditions.

^b Many patients had multiple preexisting conditions.

^c Includes chemotherapy.

NS, not significant.

Cause of Death

Up to 3 causes of death was reported for 145 (45%) of 345 pH1N1-associated deaths, and among these, a single cause was listed for 38 (26%). Among the 107 deaths (74%) due to multiple causes, 42 (39%) involved 2 causes and 65 (61%) involved

3. The leading reported causes of death were pulmonary (62%), including pneumonia, acute respiratory distress syndrome, hypoxemic respiratory failure, and exacerbation of COPD or asthma. Other causes, such as sepsis syndromes, bacterial coinfection, and multi-organ failure, accounted for 15% of

Table 3. Prevalence of Reported Underlying Medical Conditions among Pandemic Influenza A (H1N1) (pH1N1)-Associated Deaths in Adults Compared with the Prevalence Reported in the General US Adult Population

Condition	Prevalence among pH1N1 adult deaths, %	Prevalence in general US adult population, %	References ^a
Asthma	18.8	7.3	10
Chronic obstructive pulmonary disorder	15.7	4.4	10
Diabetes	20.2	8.3	10
Cardiovascular disease ^b	23.7	11.8	10
Renal disease	12.7 ^c	1.7	10
Severe neurodevelopmental or neurocognitive disorders	10.0	1.2	11
Seizure disorder	4.0	<1	11
Pregnant	5.5	1	12
Hepatic disease	4.4	1.4	10
Cancer	13.9	7.9	10
Obesity	45.6	33.8	13
Morbid obesity	10.3	5.9	13

^a Compared with the prevalence an 30 years, compared with nt if a report of such factors was included in the medical record.

^b Excludes hypertension.

^c Nonspecific renal disease noted in the medical history.

the reported causes of death; cardiovascular causes, such as cardiac arrest and heart failure, accounted for 12% of the reports. Renal failure was listed among 5% of the reported causes of death, and a small proportion of causes were reported as hematologic (1.8%), gastrointestinal (1.8%), and neurologic (1.8%) origin.

DISCUSSION

This case series represents a comprehensive evaluation of early pH1N1-associated deaths in the United States. From April through late July 2009, the overall pH1N1-associated mortality rate was low (.12 deaths/100 000 population), compared with seasonal influenza epidemics [5] but was consistent with other reported pH1N1-associated mortality rates [15, 16] and varied widely by age. The most striking feature of pH1N1-associated deaths was the predominance among young and middle-aged adults. In sharp contrast to seasonal influenza, in which >90% of deaths [5, 16] typically occur in persons ≥ 65 years of age, >90% of pH1N1-associated deaths in this series occurred in persons <65 years of age, including 15% in children <18 years of age, who typically account for <1% of influenza-associated deaths [5]. More recent data from the CDC's pH1N1 national surveillance Aggregate Hospitalization and Death Reporting Activity indicate that $\sim 86\%$ of pH1N1-associated deaths during the pandemic occurred in persons <65 years of age [6]. pH1N1 influenza-associated deaths in the United States occurred in parallel with the geographic spread of the pandemic. The outbreak began in Mexico and was first detected in the United States in California and Texas, where the first fatal case was identified. Subsequently, the highest mortality rates occurred in states that experienced the largest outbreaks.

Differences in the age distribution of deaths during this pandemic, compared with seasonal influenza epidemics, may be explained, in part, by differences in cross-reactive immunity. Serologic studies have demonstrated a correlation between increasing age and prevalence of cross-reactive immunity to pH1N1 [17, 18]. Approximately one-third of persons >60 years of age have been found to have influenza antibody titers against pH1N1 that are likely to be explained by exposure to and infection with antigenically similar influenza A (H1N1) virus strains, including the 1918 pandemic influenza virus. Preexisting, cross-reactive antibody against pH1N1 is present in only 4% of persons aged <30 years, compared with 25%–35% of adults >60 years of age and nearly half of adults aged >80 years [17].

In all age groups, death was more prevalent among persons with underlying medical conditions. This is consistent with other reports of severe pH1N1 illness that reported that 67%–90% of hospitalized patients had a history of at least 1 identified underlying medical condition [4, 19, 20, 21]. Among all pH1N1-

associated deaths, chronic lung disease was the most frequently reported underlying medical condition, with asthma most frequently reported in children who died and COPD most frequently reported in adults. The association of other underlying conditions with pH1N1-associated mortality varied by age. For example, although underlying nonhypertensive cardiovascular disease was associated with almost one-quarter of all adult deaths, it was reported in nearly half of deaths in persons ≥ 65 years of age. Metabolic disorders, COPD, cancer, renal disease, and immunosuppressive conditions also occurred most frequently in older adults. Among childhood deaths, underlying neurologic disease emerged as a key underlying condition. Although only 12% of deaths in persons aged 18–64 years had an underlying neurologic condition, more than half of all pH1N1-associated deaths among children had an underlying neurologic condition. Only 23% of deaths occurred in children who did not have a known underlying medical condition; in comparison, earlier studies of seasonal influenza have shown that 45%–65% of deaths in children are among those considered to be previously healthy. [22, 23]. Sixty percent of the children who died and who did not have an underlying medical condition had a bacterial coinfection reported at the time of death.

The age-specific prevalence of certain underlying medical conditions likely affected the proportional distribution of deaths. We observed the highest mortality rate among persons aged 50–64 years, which could be related, in part, to a higher prevalence of underlying conditions, in addition to immunologic susceptibility because persons in this age group have been shown to have a lower prevalence of cross-reactive immunity, compared with older persons [17]. Therefore, the high prevalence of underlying conditions, combined with lower levels of cross-reactive immunity, appears to have led to a substantial increase in the risk for severe outcome.

This study has several limitations. Although laboratory testing during the pandemic was probably more complete than in typical influenza seasons, identification of pH1N1 infection may still have been incomplete; therefore, it is likely that the population mortality rate was underestimated [24]. In addition, although every effort was made to collect complete data on every reported death, it was not possible to standardize data collection among all reporting sites. Reports of bacterial coinfections were not verified, and autopsy reports were not obtained for every case. Health departments depended on multiple sources of information, some of which may have been incomplete or unavailable, and this may also have contributed to underascertainment of pH1N1-associated deaths. In addition, undiagnosed, unrecognized, or otherwise unreported underlying high-risk conditions may have resulted in misclassification. Finally, data on antiviral use and report of pneumonia were insufficiently reported for analysis.

This report underscores the importance of pH1N1 influenza vaccination for persons <65 years of age and children with underlying medical conditions. Although adults aged ≥65 years were less severely affected, they are still considered to be at high risk for severe influenza complications, including death, and should also be targeted for pH1N1 vaccination. The 2010–2011 trivalent seasonal influenza vaccine will contain the pH1N1 strain, which should reduce the prevalence of influenza-associated complications, particularly because universal vaccination of all persons >6 months of age is now recommended [9]. Health care providers should emphasize the importance of vaccination of patients with underlying medical conditions. Although our data did not permit the evaluation of treatment with antiviral medication, severely ill adults and children and adults with underlying medical conditions with suspected or confirmed influenza infection should be treated early and aggressively with appropriate antiviral medications [25]. This case series was conducted before disease was widespread, and these data contributed to pH1N1 vaccination policy and antiviral treatment recommendations for the fall and winter influenza season. Monitoring of pH1N1-associated deaths should continue, to enhance our understanding of the risks for severe complications, identify changes in the epidemiology of influenza illness, and contribute to new guidance for targeted intervention and risk communication in the future.

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References

- Garten RJ, Davis CT, Russell CA, et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. *Science* **2009**; 325:197–201.
- 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.
- Cauchemez S, Donnelly CA, Reed C, et al. Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States. *N Engl J Med* **2009**; 361:2619–2627.

- Jain S, Kamimoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April – June 2009. *N Engl J Med* **2009**; 361:1935–1944.
- 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.
- Centers for Disease Control and Prevention. 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 22 February 2010.
- CDC Influenza Emergency Response Team, CDC. Update: novel influenza A (H1N1) virus infections — worldwide, May 6, 2009. *MMWR Morb Mortal Wkly Rep* **2009**; 58(17):453–458.
- 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 27 May 2010.
- 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(RR-8):1–56.
- Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. *Vital Health Stat* **2009**; 10:242).
- Hirtz D, Thurman DJ, Gwinn-Hardy K, et al. How common are the “common” neurologic disorders? *Neurology* **2007**; 68:326–337.
- 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.
- Flegel KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999–2008. *JAMA* **2010**; 303:235–241.
- Annual estimates of the resident population for the United States, Regions, States, and Puerto Rico: April 1, 2000 to July 1, 2009 (NST-EST2008–01). Washington, D.C.: U.S. Census Bureau, Population Division, 2008. Available at: <http://www.census.gov/popest/states/NST-ann-est.html>. Accessed 20 January 2010.
- Donaldson LJ, Rutter PD, Ellis BM, et al. Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study. *BMJ* **2009**; 339:b5213.
- Presanis AM, Lipsitch M, De Angelis D, et al. The severity of pandemic H1N1 in the United States, April – July 2009. *Plos Curr* **2009**:RRN1042.
- 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.
- Miller E, Hoshler K, Hardelid P, et al. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. *Lancet* **2010**; 375:1100–1108.
- Epperson S, Blanton L, Dhara R, et al. Influenza activity — United States and worldwide, 2007–08 season. *MMWR Morb Mortal Wkly Rep* **2008**; 57:692–697.
- Jouvet P, Hutchison J, Pinto R, et al. Critical illness in children with influenza A/pH1N1 2009 infection in Canada. *Pediatr Crit Care Med* **2010**; 11:603–609.
- Vaillant L, LaRuche G, Tarantola A, et al. epidemic intelligence team at InVS. Epidemiology of fatal cases associated with pandemic H1N1 influenza 2009. *Euro Surveill* **2009**; 14:pii. 19309.
- Finelli L, Fiore A, Dhara R, et al. Influenza-associated pediatric mortality in the United States: increase of staphylococcus aureus co-infection. *Pediatrics* **2008**; 122:805–11.
- Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 2003–2004. *N Engl J Med* **2005**; 353:2559–67.
- Reed C, Angulo FJ, Swerdlow DL, et al. Estimates of the prevalence of pandemic (H1N1) 2009, United States, April–July 2009. *Emerg Infect Dis* **2009**; 15:2004–2007.
- Centers for Disease Control and Prevention. updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 season **2009**. Available at: <http://www.cdc.gov/h1n1flu/recommendations.htm> Accessed 25 February 2010.