Age as an Independent Risk Factor for Intensive Care Unit Admission or Death Due to 2009 Pandemic Influenza A (H1N1) Virus Infection

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ABSTRACT

Objective. This study evaluated risk factors for intensive care unit (ICU) admission or death among people hospitalized with 2009 pandemic influenza A (pH1N1) virus infection.

Methods. We based analyses on data collected in Washington State from April 27 to September 18, 2009, on deceased or hospitalized people with laboratory-confirmed pH1N1 infection reported by health-care providers and hospitals as part of enhanced public health surveillance. We used bivariate analyses and multivariable logistic regression to identify risk factors associated with ICU admission or death due to pH1N1.

Results. We identified 123 patients admitted to the hospital but not an ICU and 61 patients who were admitted to an ICU or died. Independent of high-risk medical conditions, both older age and delayed time to hospital admission were identified as risk factors for ICU admission or death due to pH1N1. Specifically, the odds of ICU admission or death were 4.44 times greater among adults aged 18–49 years (95% confidence interval [CI] 1.97, 10.02) and 5.93 times greater among adults aged 50–64 years (95% CI 2.24, 15.65) compared with pediatric patients <18 years of age. Likewise, hospitalized cases admitted more than two days after illness onset had 2.17 times higher odds of ICU admission or death than those admitted within two days of illness onset (95% CI 1.10, 4.25).

Conclusion. Although certain medical conditions clearly influence the need for hospitalization among people infected with pH1N1 virus, older age and delayed time to admission each played an independent role in the progression to ICU admission or death among hospitalized patients.

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On April 21, 2009, the Centers for Disease Control and Prevention reported that a novel influenza A virus had been detected in the United States.[1] Within a week of this report, cases of the new 2009 pandemic influenza A (pH1N1) were identified in Washington State. The pH1N1 outbreak spread in Washington State and throughout the country during the following months, and by the end of August 2009, more than 9,000 hospitalizations and nearly 600 deaths due to the pH1N1 virus were reported nationally.[2]

During annual seasonal influenza epidemics, risk factors for severe or complicated disease include age <5 years or ≥65 years and certain medical conditions (i.e., chronic pulmonary, hepatic, renal, or cardiovascular disease; cognitive, neurologic/neuromuscular, metabolic, and blood disorders; immunosuppression; and pregnancy).[3–7] Recent studies have shown that these medical conditions are also associated with hospitalization and death due to pH1N1.[8–11] In addition, delayed antiviral treatment and delayed hospital admission have been identified as risk factors for severe or complicated pH1N1 infection.[9–12] The objective of this study was to define risk factors for intensive care unit (ICU) admission or death among patients hospitalized for pH1N1 infections.

METHODS

From April 27 to September 18, 2009, the Washington State Department of Health (WA DOH) conducted statewide passive surveillance for laboratory-confirmed pH1N1 infections resulting in hospitalization or death. This surveillance system was aided by an emergency rule declaration that required all health-care providers and hospitals in Washington State to report all pH1N1 hospitalizations or deaths to public health. Initial diagnostic testing by rapid antigen, direct or indirect fluorescent antibody, or polymerase chain reaction (PCR) tests was based on clinical suspicion. Positive specimens were submitted to the Washington State Public Health Laboratories for confirmatory testing and subtyping using real-time reverse transcriptase PCR (rRT-PCR).

Local health department staff investigated all reports of hospitalized or deceased patients with laboratory-confirmed pH1N1 by reviewing medical records and/or interviewing patients or family members via telephone. Demographic and clinical information was collected using a standardized case report form and electronically submitted to WA DOH.

A case was defined as a Washington resident reported between April 27 and September 18, 2009, who was hospitalized or died due to rRT-PCR-confirmed pH1N1 infection. Cases were excluded if the case report was incomplete. Cases were divided into two outcome groups on the basis of disease severity: (*1*) patients who died or had a critical illness (defined as admission to an ICU) and (*2*) patients who were hospitalized but survived and did not become critically ill.

High-risk medical conditions were defined as those recognized by the Advisory Committee for Immunization Practices (ACIP) to increase the risk for severe or complicated influenza, as discribed previously.[3] Adults were defined as people ≥18 years of age and children as people <18 years of age. The time from illness onset to hospital admission was categorized into two groups based on whether the patient was hospitalized within two days, or more than two days, after illness onset.

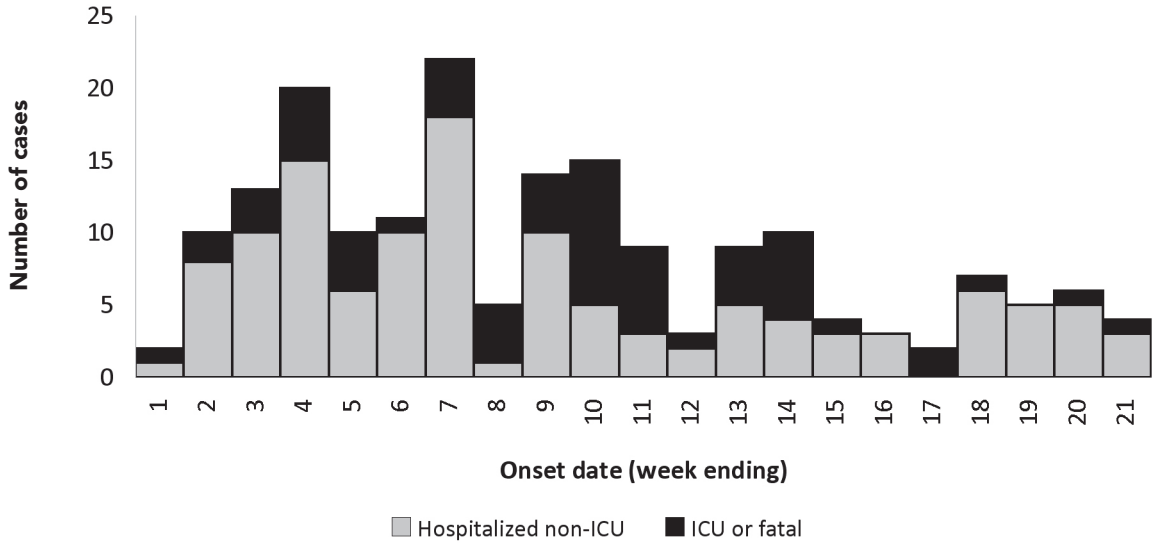
We assessed patient outcome in relation to age, gender, the presence of high-risk medical conditions, and time from illness onset to hospital admission. We used a Chi-square test for bivariate comparisons. We performed multivariable logistic regression analyses and calculated corresponding adjusted odds ratios and 95% confidence intervals (CIs) using SAS® version 9.1.[13]

RESULTS

A total of 189 hospitalized and fatal pH1N1 cases were reported between April 27 and September 18, 2009; 184 (97%) had completed case reports (Figure). Among the 184 cases, 123 (67%) were hospitalized but were not critically ill and 61 (33%) were critically ill or died (Table 1). Sixteen (9%) of the reported pH1N1 cases died. Adults represented 45% of the hospitalized patients who were not critically ill but 80% of the critically ill or deceased patients ($p<0.001$). Critically ill and fatal cases were more likely to be admitted to the hospital more than two days after illness onset than hospitalized patients who were not critically ill ($p=0.008$). Of the 184 cases, 104 (57%) were females and 116 (63%) had at least one high-risk medical condition. Neither gender nor the presence of a high-risk medical condition was associated with severe outcomes in bivariate analysis.

We examined age, gender, the time from illness onset to hospital admission, and the presence of at least one high-risk medical condition using a multivariable logistic regression model. The odds of critical illness or death were 4.44 times greater among adults aged 18–49 years (95% CI 1.97, 10.02) and 5.93 times greater among adults aged 50–64 years (95% CI 2.24, 15.65) compared with children aged <18 years (Table 2). We observed a non-significant increase among cases ≥65 years of age compared with cases <18 years of age.

Figure. Epidemic curve of pH1N1 cases in Washington State by disease severity: illness onset April 19–September 12, 2009



pH1N1 = 2009 pandemic influenza A

ICU = intensive care unit

Cases admitted more than two days after illness onset had 2.17 times higher odds of critical illness or death than those admitted within two days of illness onset (95% CI 1.10, 4.25). Neither gender nor the presence of a high-risk medical condition was a significant risk factor for critical illness or death.

Table 1. Characteristics of pH1N1 cases in Washington State by disease severity: reported April 27–September 18, 2009

Characteristic	*ICU or fatal* N *(percent)*	*Hospitalized (non-ICU)* N *(percent)*	P-*value*[a]
Total cases	61 (100)	123 (100)	
Age group (in years)			<0.001
0–17	12 (20)	68 (55)	
18–49	30 (49)	34 (28)	
50–64	16 (26)	14 (11)	
≥65	3 (5)	7 (6)	
Female	38 (62)	66 (54)	0.27
Hospitalization >2 days after illness onset	36 (59)	47 (38)	0.008
Any high-risk medical condition associated with severe influenza[b]	42 (69)	74 (60)	0.25
Any chronic lung condition	21 (34)	37 (30)	0.55
Immunocompromised	12 (20)	18 (15)	0.37
Diabetes	12 (20)	12 (10)	0.06
Chronic heart disease	5 (8)	14 (11)	0.50
Pregnant	4 (7)	6 (5)	0.60
Other high-risk medical condition	8 (13)	12 (10)	0.48

[a]Chi-square test

[b]As defined by the Advisory Committee for Immunization Practices in: Fiore AE, Shay DK, Broder K, Iskander JK, Uyeki TM, Mootrey G, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recomm Rep 2009;58(RR08):1-52.

pH1N1 = 2009 pandemic influenza A

ICU = intensive care unit

Table 2. Risk factors for ICU admission or death among people hospitalized in Washington State due to pH1N1: April 27–September 18, 2009

Variable	*AOR (95% CI)*[a]
Age (in years)	
0–17	Referent
18–49	4.44 (1.97, 10.02)
50–64	5.93 (2.24, 15.65)
≥65	2.53 (0.55, 11.57)
Hospitalization >2 days after illness onset	2.17 (1.10, 4.25)
Female	1.15 (0.57, 2.32)
Any high-risk medical condition associated with severe influenza[b]	1.22 (0.59, 2.52)

[a]AOR calculated using multivariable logistic regression

[b]As defined by the Advisory Committee for Immunization Practices in: Fiore AE, Shay DK, Broder K, Iskander JK, Uyeki TM, Mootrey G, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recomm Rep 2009;58(RR08):1-52.

ICU = intensive care unit

pH1N1 = 2009 pandemic influenza A

AOR = adjusted odds ratio

CI = confidence interval

DISCUSSION

In this study, adults aged 18–64 years were more likely to be critically ill or die than children, and people hospitalized more than two days after illness onset were also more likely to be critically ill or die. Previous studies have reported an increased risk of hospitalization due to pH1N1 infection among people with certain high-risk medical conditions.[8,10] We also observed this association (Unpublished data, WA DOH Communicable Disease Surveillance, 2009); however, in this study of hospitalized cases, the presence of any high-risk medical condition was not observed to be a risk factor for more severe outcomes.

To date, there have been mixed findings regarding the association between age and severe outcomes due to pH1N1 when controlling for other factors.[10–12] Studies examining hospitalized patients with pH1N1 infection in the United States and the Province of Manitoba, Canada, did not find age to be an independent risk factor for more severe outcomes.[10,11] Another study examined gender, age, and high-risk medical conditions among all pH1N1 hospitalizations in Canada.[12] Similar to our findings, they reported a significant association between adults and severe outcomes; however, in contrast to our findings, they identified a significant association between severe outcomes and high-risk medical conditions. More research is needed to evaluate the magnitude of age as a risk factor for severe outcomes, as well as potential biological and social explanations for this association.

Although children accounted for more than 50% of non-ICU hospitalizations due to pH1N1 virus, people aged 18–64 years comprised the majority of the severe illnesses. This finding is similar to what was seen during the 1918 influenza pandemic, when children aged 5–14 years were disproportionately ill with influenza, but adults in their 20s to 40s had higher mortality rates from influenza and pneumonia than typically seen with influenza in this age group. Several theories have been proposed as to why this distribution differs from traditional seasonal influenza mortality distribution. Possible explanations include antibody-dependent enhanced infection in adults in their 20s to 40s due to prior virus exposures, the presence of comorbidities or exposure to cofactors and medications in older age groups, and bacterial or viral coinfections that disproportionately affected this older age group.[14] Another possible explanation is that unlike young children, whose immune systems are developing, and elderly people, whose immune systems are aging, young adults may have a more profound inflammatory response in the lung resulting in acute lung injury and acute respiratory distress syndrome.

Unlike seasonal influenza, in the present study people ≥65 years of age accounted for a minority of hospitalizations and deaths due to pH1N1. Although we found that adults aged 18–64 years had higher odds of severe outcomes compared with children, we did not observe a significant association among people ≥65 years of age. This inability to detect an association may have been because hospitalizations were uncommon in this age group during the time frame of this study; only 10 cases (5%) were reported among people aged ≥65 years. This small number of cases in the oldest age group may be the result of lower transmission to seniors and fewer infections[15] or potential residual immunity to a virus similar to pH1N1 virus.[16,17] More hospitalized cases from the oldest age group should be examined to further explore age ≥65 years as a risk factor for severe outcomes.

In assessing ACIP-defined high-risk medical conditions as risk factors for critical illness or death due to pH1N1, we examined the presence of any high-risk medical condition as well as each condition separately. In multivariable analysis, none significantly contributed to the model as a predictor of critical illness or death among hospitalized pH1N1 cases. Likewise, other groupings of age, such as <25 and ≥25, <50 and ≥50, and 18–49 vs. others (<18 and ≥50), did not affect the finding that adults were more likely to have severe outcomes.

Limitations

These surveillance data had inherent limitations. Influenza surveillance in Washington State is a passive system, which is subject to underreporting. Also, this analysis was limited to cases with laboratory-confirmed pH1N1 infection and may not be representative of all people with pH1N1 infection due to potential biases in testing by age or other factors. Additionally, assessment and classification of medical conditions may have varied among local health departments. Lastly, we did not assess medical conditions that were not on the ACIP list; however, some conditions, such as obesity, may be important for pH1N1 disease progression.

CONCLUSION

This study demonstrated the importance of age as an independent risk factor for severe outcomes due to pH1N1. Specifically, hospitalized adults aged 18–64 years were more likely to be admitted to an ICU or die than hospitalized children. Most notably, this association between age and severe outcomes was independent of the presence of a high-risk medical condition, gender, and the time from illness onset to hospital admission. While certain medical conditions clearly influenced the need for hospitalization among people infected with pH1N1 virus, the presence of a high-risk medical condition was not associated with severe outcomes among hospitalized people.

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