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# Differences in the Epidemiological Characteristics and Clinical Outcomes of Pandemic (H1N1) 2009 Influenza, Compared with Seasonal Influenza

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## Abstract

**BACKGROUND—**There are limited data comparing the clinical presentations, comorbidities, and outcomes of patients with infections due to seasonal influenza with patients with infections due to pandemic (H1N1) 2009 influenza.

**OBJECTIVE—**To compare the epidemiological characteristics and outcomes of pandemic (H1N1) 2009 influenza with those of seasonal influenza.

**METHODS—**A cross-sectional study was conducted among patients who received diagnoses during emergency department and inpatient encounters at 2 affiliated academic medical centers in Philadelphia, Pennsylvania. Cases of seasonal influenza during the period November 1, 2005, through June 1, 2008, and cases of pandemic influenza during the period from May 1, 2009, through August 7, 2009, were identified retrospectively.

**RESULTS—**Forty-nine cases of pandemic influenza and 503 cases of seasonal influenza were identified. Patients with pandemic H1N1 were younger (median age, 29 years) than patients with seasonal influenza (median age, 59 years) ($P < .001$). More patients with pandemic H1N1 (35 [71%] of 49) were African American, compared with patients with seasonal influenza (267 [53%] of 503; $P = .02$). Several symptoms were more common among patients with pandemic influenza infections than among patients with seasonal influenza infections: cough (98% vs 83%; $P = .007$), myalgias (71% vs 46%; $P = .001$), and pleuritic chest pain (45% vs 15%; $P < .001$). Pregnancy was the only comorbidity that occurred significantly more often in the pandemic influenza group than in the seasonal influenza group (16% vs 1%; $P < .001$). There were no significant differences in frequencies of deaths of hospitalized patients, intensive care unit admission, or length of hospitalization between groups.

**CONCLUSION—**Other than pregnancy, there were few clinically important differences between infections due to seasonal influenza and those due to pandemic influenza. The greater rate of lower respiratory tract symptoms in pandemic cases might serve to differentiate pandemic influenza from seasonal influenza.



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On June 11, 2009, the World Health Organization declared an influenza pandemic on the basis of the widespread incidence of H1N1 2009 influenza cases observed globally.[1] Early reports from Mexico, where the virus was first identified, revealed a disproportionate incidence of severe pneumonia and related deaths among previously healthy people aged 5–59 years.[2] Indeed, the highest rate of mortality seen in the initial Mexican epidemic (15%) was noted in patients aged 35–39 years.[2] Subsequent reports of pandemic (H1N1) 2009 influenza (hereafter "pandemic H1N1 influenza") infections in other regions have revealed variable disease severity but an overall lower mortality rate than that of the initial epidemic observed in Mexico.[3–6] During the 2009–2010 influenza season, pandemic H1N1 influenza was a substantial contributor to the incidence of influenza infections, as evidenced by reported epidemiologic trends in the United States and elsewhere.[7,8]

There are few published systematic comparisons of presentation or outcomes of pandemic H1N1 influenza and seasonal influenza.[9–11] Case series describing pandemic H1N1 influenza have suggested that pandemic H1N1 influenza predominantly affects younger age groups.[2,5,6,12] Likewise, reports of series of severe and fatal cases of pandemic H1N1 influenza have revealed that pregnancy, obesity, diabetes, and other underlying comorbid conditions commonly occur with severe disease.[13,14] Despite these preliminary data, it remains unknown whether pandemic H1N1 influenza differs substantially from seasonal influenza in its presentation and clinical course.

Comparing the epidemiological characteristics of pandemic H1N1 influenza and seasonal influenza is of utmost importance. If pandemic H1N1 influenza is a substantial contributor to the 2010–2011 influenza season, then it becomes crucial to design and implement appropriate triage systems for healthcare providers. Before doing so, a basic understanding of how pandemic H1N1 influenza differs from seasonal influenza is necessary. We retrospectively analyzed the presentations and outcomes of patients with influenza infections treated in the emergency departments and inpatient units of a large, urban, university-based health system and compared these cases with cases of pandemic H1N1 influenza encountered during the early pandemic H1N1 influenza epidemic at the same institution.

## METHODS

This study was approved by the institutional review board of the University of Pennsylvania and was compliant with the Health Insurance Portability and Accountability Act. We conducted a cross-sectional study of cases of seasonal influenza and pandemic H1N1 influenza diagnosed during emergency department and inpatient encounters at the Hospital of the University of Pennsylvania, Philadelphia, and its affiliate, Penn Presbyterian Medical Center, Philadelphia. The Hospital of the University of Pennsylvania is a 725-bed academic medical center that serves as the tertiary care center for the University of Pennsylvania health system. It has approximately 32,000 patient admissions, 633,000 outpatient visits, and 40,000 emergency department visits annually. Penn Presbyterian Medical Center is a 324-bed urban community hospital located in West Philadelphia with approximately 12,000 patient admissions, 130,000 outpatient visits, and 26,000 emergency department visits annually.

Cases of seasonal influenza A or B infection diagnosed during the period from November 1, 2005, through June 1, 2008, among emergency department and hospital inpatient visits were identified by searching the health system's comprehensive infection control database and molecular diagnostics laboratory records. The databases were queried by searching for all polymerase chain reaction (PCR) assay results positive for influenza among patients aged 18 years and older who were treated in either the emergency department or the hospital inpatient units during the above-specified time periods. Only positive assay results were

considered diagnostic; indeterminate assay results were not included in the analysis. Cases of pandemic H1N1 influenza were identified by searching the same database for PCR assay results positive for influenza A during the period May 1, 2009, through August 7, 2009, using the same search criteria as for seasonal influenza. All cases of influenza A identified in May of 2009 were sent to the state health department laboratory for typing. If these were found to be due to nontypeable virus, the sample was then forwarded to the Centers for Disease Control and Prevention (CDC) for confirmatory testing for pandemic H1N1 influenza virus. On June 12, 2009, the Pennsylvania State Department of Health announced that it would no longer accept specimens for analysis, because more than 90% of influenza A specimens were found to be pandemic H1N1 influenza virus.[15] Subsequent specimens positive for influenza A were considered probable pandemic H1N1 influenza, and no further identification was sought except in cases of severe illness, for which all cases were confirmed to be due to pandemic H1N1 influenza virus by staff of the state laboratory.

Initial diagnoses of influenza A and influenza B infections were based on nucleic acid testing of nasopharyngeal swab samples obtained during an emergency department or in-patient encounter. Nucleic acid amplification was performed as a partially multiplexed real-time reverse transcription polymerase chain reaction. All assays were performed on an ABI 7900 with TaqMan probes (Applied Biosystems). We used $\beta_2$-microglobulin as a control gene to control for the presence of inhibitors or poor sample quality.

Hospital and emergency department medical records of patients with influenza were reviewed to determine demographic characteristics (ie, age, sex, and race), vital signs (ie, maximum temperature, minimum systolic blood pressure, maximum pulse rate, and maximum respiratory rate during the first 24 hours of hospitalization), symptoms (ie, cough, dyspnea, sputum production, myalgias, pleuritic chest pain, or headache), and examination findings (ie, wheezing, confusion, or acute need for supplemental oxygen). Comorbid conditions were also ascertained and included diagnoses of asthma, chronic obstructive pulmonary disease, congestive heart failure, diabetes mellitus, active malignancy, transplant recipient status, pregnancy, human immunodeficiency virus–positive status, chronic corticosteroid use (equivalent to at least 20 mg/day prednisone), nursing home residency, and recent hospitalization (30 or fewer days prior). In addition, presenting total white blood cell count, serum creatinine level, and chest radiography findings (from the first radiograph obtained at admission) were collected. Outcome measures of death during hospitalization, need for intensive care unit (ICU) admission, need for mechanical ventilation, length of hospital stay (calculated for admitted patients only), and readmission within 30 days or less were also determined from the health system's electronic medical record.

Bivariable analyses were conducted to compare pandemic H1N1 influenza and seasonal influenza cases with regard to demographic characteristics, comorbidities, presenting vital signs and symptoms, laboratory and radiographic findings, and clinical outcomes. The Fisher exact test was used to compare categorical data, and the Wilcoxon rank sum test was used for continuous variables. All *P* values reported are 2 sided, and a *P* value of less than . 05 was considered to reveal a significant difference. Statistical analysis was performed with Stata, version 10 (Stata Corp).

## RESULTS

A total of 526 cases of seasonal influenza were identified from November 1, 2005, through June 1, 2008. Five hundred three cases had complete records available for review. Of these, 381 cases (76%) were diagnosed in hospitalized patients and 122 (24%) during emergency department visits that did not lead to hospital admission. Within the seasonal influenza group, 364 (72%) of 503 cases were influenza A and 139 cases (28%) were influenza B.

Forty-nine novel pandemic H1N1 influenza cases were diagnosed during the period from May 1, 2009, through August 7, 2009, and all had adequate records available for review. Twenty-five cases (51%) of pandemic H1N1 influenza occurred in hospitalized patients, and 24 cases (49%) of pandemic H1N1 influenza were diagnosed during emergency department visits that did not lead to hospitalization. Patients diagnosed with seasonal influenza were significantly more likely to be hospitalized, compared with those with pandemic H1N1 influenza (76% vs 51%; OR, 2.99 [95% CI, 1.57–5.68]; $P = .005$). Baseline demographic data are summarized in Table 1. Patients with pandemic H1N1 influenza typically presented at a younger age (median, 29 years) than patients with seasonal influenza (median, 59 years; $P < .001$). More patients with pandemic H1N1 influenza (35 [71%] of 49) were African American, compared with patients with seasonal influenza (267 [53%] of 503; $P = .02$). The median time from presentation to diagnostic testing was not significantly different across groups ($P = .71$).

The frequencies of most comorbid conditions were similar for patients with seasonal influenza and patients with pandemic H1N1 influenza (Table 1). However, pregnancy was significantly more common in the pandemic H1N1 influenza group (8 [16%] of 49 vs 7 [1%] of 503; OR, 13.83 [95% CI, 4.11–46.75]; $P < .001$). Presenting signs and symptoms are summarized in Table 2. Among patients with pandemic H1N1 influenza, significantly higher rates of self-reported cough (48 [98%] vs 419 [83%]; OR, 9.62 [95% CI, 1.59–392.38]; $P = .01$), pharyngitis (12 [24%] vs 61 [12%]; OR, 2.35 [95% CI, 1.05–4.91]; $P = .02$), myalgia (35 [71%] vs 233 [46%]; OR, 2.90 [95% CI, 1.47–5.97]; $P < .001$), and pleuritic pain (22 [45%] vs 75 [15%]; OR, 2.67 [95% CI, 1.44–4.82]; $P < .001$) were observed, compared with the seasonal influenza group. Admission chest radiographic findings were similar between groups: radiographic shadowing indicative of an infiltrate was noted in 8 (16%) of patients with pandemic H1N1 influenza and 87 (17%) of those with seasonal influenza.

Rates of ICU admission, requirement for invasive mechanical ventilation, and death were similar between groups (Table 3). The median age of patients who were admitted to the ICU was 59 years (range, 29–71) for the pandemic H1N1 influenza group and 55 years (range, 22–98) for the seasonal influenza group ($P = .99$). Among patients admitted to the ICU, radiographic shadowing suggestive of pulmonary infiltrates was found in 4 (67%) of 6 patients with pandemic H1N1 influenza and 28 (42%) of 66 patients with seasonal influenza ($P = .54$). One previously healthy pregnant woman with pandemic H1N1 influenza was admitted to the ICU with respiratory failure and ultimately required cardiopulmonary bypass for several days because of severe acute respiratory distress syndrome. No pregnant women with seasonal influenza died or required ICU admission. The mortality rate among patients with pandemic H1N1 influenza was 3 (6%) of 49, compared with 12 (2%) of 503 for patients with seasonal influenza; however, this difference was not statistically significant ($P = .13$). The median length of hospital stay was greater in the seasonal influenza group (4 days [range, 1–56]) than in the pandemic H1N1 influenza group (2 days [range, 1–48]); however, this difference was not statistically significant ($P = .20$). Likewise, rehospitalization rates did not differ between groups.

## DISCUSSION

A common question posed to public health officials and clinicians is how pandemic H1N1 influenza differs from typical seasonal influenza. These results suggest some notable differences, as well as many similarities, between seasonal influenza and pandemic H1N1 influenza. Patients with seasonal influenza were significantly more likely to be hospitalized after visiting the emergency department. Symptomatically, patients with pandemic H1N1 influenza were more apt to complain of cough, myalgia, and pleuritic chest pain than

patients with seasonal influenza. Among the most notable epidemiologic differences was the disproportionate rate of cases involving pregnant women and the significantly lower median age of patients with pandemic H1N1 influenza, compared with patients with seasonal influenza. Important similarities were also observed between groups, particularly with respect to complications of influenza, as measured with use of ICU admission rates, mortality rates, length of stay, rates of rehospitalization, and the low incidence of pulmonary infiltrates on initial chest radiograph.

Cough and pleuritic pain, which were both more common in patients with pandemic H1N1 influenza, are suggestive of lower respiratory tract infection. The implications of increased complaints suggesting lower respiratory tract disease in the pandemic H1N1 influenza group are not trivial.[16] Historically, secondary bacterial pneumonia has been among the more common causes of severe disease and death during prior pandemics.[14,17–24] It is not unreasonable to hypothesize, therefore, that providers would be more likely to triage patients with these complaints to a higher level of care (eg, emergency department vs outpatient clinic). Likewise, antibiotic prescriptions might increase with concern for lower respiratory tract disease.[25–27] Frequent reports of pleuritic pain also raise other diagnostic considerations for clinicians. These include pulmonary embolism and acute coronary syndrome, both of which necessitate additional testing and interventions that could further tax an already stressed medical infrastructure.[28,29]

Despite the increased rate of lower respiratory tract symptoms in the pandemic H1N1 influenza group, other markers associated with severe pulmonary compromise occurred with similar infrequency between groups. Indeed, the need for supplemental oxygen and mechanical ventilation was uncommon in both groups. These observations suggest that severe pulmonary compromise does not occur with greater frequency in pandemic H1N1 influenza, which echoes earlier assertions that pandemic H1N1 influenza is typically a mild illness.[6] Likewise, pulmonary infiltrates at initial chest radiography were uncommon with both groups, which argues against frank pneumonia in the majority of cases at presentation. This observation should be interpreted with some caution, however, because there are few data on how chest imaging findings correlate with the severity of influenza disease.[19,30–32] In fact, a large portion of patients in both groups who required ICU admission had initial chest radiographs *without* evidence of radiographic shadowing, which suggests that chest radiography is not a reliable predictor of severe influenza infection. Further research on the subject of chest imaging and influenza may be useful to determine whether such observations hold true.

The similarity in outcomes observed between pandemic H1N1 influenza and seasonal influenza infections is worth noting. Indeed, the frequency of hospitalization was significantly higher for patients with seasonal influenza than for patients with pandemic H1N1 influenza, whereas hospitalization durations and rates of rehospitalization and death were similar between the groups. Although these results should offer some reassurance to those affected by pandemic H1N1 influenza, they should also highlight the fact that influenza, in any form, can be a serious and sometimes fatal illness.

Perhaps the greatest contrast between pandemic H1N1 influenza and seasonal influenza was the significantly higher rate of pregnant women seeking care in the pandemic H1N1 influenza group. It is evident here, and in prior reports,[5,14,33] that pandemic H1N1 influenza affects pregnant women at disproportionately higher rates than the rest of the population. Of the 503 patients with seasonal influenza examined (spanning 2 seasons), no pregnant women required ICU admission. In contrast, 1 of 6 patients requiring ICU admission with pandemic H1N1 influenza was pregnant. Several reports have highlighted the association of pandemic H1N1 influenza with pregnancy.[5,13,14,33] Indeed, pregnancy has been considered a risk

factor for severe disease with both seasonal influenza infection and in prior influenza pandemics.[34–37] Similarly, our results reveal that pandemic H1N1 influenza also poses a particularly high risk to pregnant women when compared with seasonal influenza. The reason for this incongruity is unclear. One possibility is that pregnant women were vaccinated against seasonal influenza and therefore less likely to present with seasonal influenza. Indeed, for several years, the CDC's Advisory Committee on Immunization Practices has recommended annual vaccination against seasonal influenza for pregnant women.[38] This probably does not account for the entire difference, however, because the rate of influenza vaccination reported among pregnant women was consistently less than 20% in several prior studies.[35,39–41] Alternatively, the higher incidence of pandemic H1N1 influenza among pregnant women could simply result from the lower age range of patients affected by the pandemic virus, compared with patients affected by seasonal influenza. In either case, an effort toward vaccination of pregnant women against pandemic H1N1 influenza becomes even more important as a result of these data.

Potential limitations of this study include the retrospective collection of data from preexisting medical records. As such, some variables, such as presenting symptoms, may be subject to bias in terms of healthcare practitioners' lines of questioning, particularly during the initial pandemic H1N1 influenza epidemic when media coverage on the subject was prominent. These data are also limited by a small number of pandemic H1N1 influenza cases, which potentially hampers the ability to reveal smaller significant differences between groups. Furthermore, the data presented are limited to cases observed in academic centers in Philadelphia, and the epidemiologic characteristics of pandemic H1N1 influenza may differ in other settings. Because these data were collected on only patients seeking emergency medical care and hospital care, the results may not reflect episodes of milder disease occurring simultaneously in the community.

In summary, these results suggest that pandemic H1N1 influenza and seasonal influenza were similar with regard to overall disease severity and rates of complications. Most patients had favorable outcomes, even among traditionally high-risk groups. Notable differences in presentation between groups included higher rates of lower respiratory tract symptoms, such as cough and pleuritic chest pain, among patients with pandemic H1N1 influenza, although these findings did not translate into increased rates of respiratory failure. These data support the hypothesis that pandemic H1N1 influenza poses risks to the population that are similar to those of seasonal influenza. The increased incidence of pandemic H1N1 influenza among pregnant women should be emphasized, however, and vaccination should be encouraged for these women.

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## TABLE 1

Baseline Demographic Characteristics and Comorbid Conditions of Patients with Pandemic (H1N1) 2009 Influenza or Seasonal Influenza

| Variable | No. (%) of patients | | OR (95% CI) | *P* |
|---|---|---|---|---|
| | Pandemic (H1N1) 2009 influenza (*n* = 49) | Seasonal influenza (*n* = 503) | | |
| Demographic characteristics | | | | |
| Age, median (range) | 29 (18–71) | 59 (18–99) | | <.001 |
| African American race | 35 (71) | 267 (53) | 2.21 (1.12–4.55) | .02 |
| Male sex | 21 (43) | 211 (42) | 1.04 (0.54–1.95) | >.99 |
| Comorbidities | | | | |
| Pregnancy | 8 (16) | 7 (1) | 13.83 (4.11–46.75) | <.001 |
| COPD | 2 (4) | 57 (11) | 0.33 (0.04–1.33) | .12 |
| Asthma | 11 (22) | 87 (17) | 1.38 (0.61–2.90) | .37 |
| Diabetes mellitus | 11 (22) | 135 (27) | 0.79 (0.35–1.63) | .51 |
| Malignancy | 2 (4) | 50 (10) | 0.39 (0.04–1.55) | .18 |
| Past receipt of transplant | 5 (10) | 30 (6) | 1.79 (0.52–4.99) | .25 |
| CHF | 4 (8) | 83 (17) | 0.45 (0.11–1.29) | .13 |
| HIV positive | 3 (6) | 31 (6) | 0.99 (0.19–3.38) | .99 |
| Chronic corticosteroid treatment[a] | 4 (8) | 48 (10) | 0.84 (0.21–2.46) | .75 |
| Recent hospitalization[b] | 3 (6) | 54 (11) | 0.54 (0.10–1.78) | .31 |
| Residence in nursing home | 0 (0) | 21 (4) | 0 (0–1.82) | .15 |

NOTE. CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; OR, odds ratio.

[a] Defined as 30 days or more of 20 mg prednisone (or equivalent) daily.

[b] Within the past 30 days.

## TABLE 2

Presenting Symptoms, Vital Signs, and Evaluation of Patients with Pandemic (H1N1) 2009 Influenza or Seasonal Influenza

| Variable | No. (%) of patients | | OR (95% CI) | *P* |
|---|---|---|---|---|
| | Pandemic (H1N1) 2009 influenza (*n* = 49) | Seasonal influenza (*n* = 503) | | |
| Sign or symptom | | | | |
| Cough | 48 (98) | 419 (83) | 9.62 (1.59–392.38) | .01 |
| Dyspnea | 21 (43) | 268 (53) | 0.66 (0.35–1.24) | .18 |
| Sputum production | 24 (49) | 200 (40) | 1.45 (0.77–2.73) | .21 |
| Myalgia | 35 (71) | 233 (46) | 2.90 (1.47–5.97) | .001 |
| Pleuritic pain | 22 (45) | 75 (15) | 2.67 (1.44–4.82) | <.001 |
| Nasal congestion or coryza | 18 (37) | 150 (30) | 1.37 (0.70–2.61) | .32 |
| Pharyngitis | 12 (24) | 61 (12) | 2.35 (1.05–4.91) | .02 |
| Headache | 13 (27) | 109 (22) | 1.31 (0.61–2.63) | .43 |
| Delirium | 4 (8) | 73 (15) | 0.52 (0.13–1.50) | .22 |
| Wheezing | 8 (16) | 96 (19) | 0.83 (0.32–1.86) | .64 |
| Sick contacts | 14 (29) | 63 (13) | 2.79 (1.31–5.67) | .002 |
| Vital signs | | | | |
| Maximum temperature, °C, median (95% CI) | 38.6 (38.2–38.8) | 38.3 (38.2–38.6) | … | .40 |
| Tachycardia[a] | 7 (14) | 63 (13) | 1.16 (0.42–2.77) | .72 |
| Hypotension[b] | 1 (2) | 26 (5) | 0.38 (0.01–2.44) | .33 |
| Tachypnea[c] | 3 (6) | 36 (7) | 0.85 (0.16–2.85) | .79 |
| Requirement of oxygen treatment | 7 (14) | 82 (16) | 0.86 (0.37–1.97) | .71 |
| Evaluation | | | | |
| Serum creatinine level, mg/dL, median (95% CI) | 0.9 (0.78–1.29) | 1.1 (1.0–1.2) | … | .12 |
| White blood cell count, thousands/$\mu$L, median (95% CI) | 6.7 (6.1–8.2) | 7.1 (6.6–7.7) | … | .80 |
| Infiltrate on chest radiograph | 8 (16) | 87 (17) | 0.93 (0.36–2.11) | .86 |

NOTE. CI, confidence interval; OR, odds ratio.

[a] Defined as a pulse rate of more than 125 beats per minute.

[b] Defined as systolic blood pressure of less than 90 mm Hg.

[c] Defined as a respiration rate of more than 30 breaths per minute.

## TABLE 3

Outcomes and Severe Disease among Patients with Pandemic (H1N1) 2009 Influenza or Seasonal Influenza

| | No. (%) of patients | | | |
|---|---|---|---|---|
| **Variable** | **Pandemic (H1N1) 2009 influenza (*n* = 49)** | **Seasonal influenza (*n* = 503)** | **OR (95% CI)** | ***P*** |
| Death | 3 (6) | 12 (2) | 2.67 (0.47–10.36) | .13 |
| ICU admission | 6 (12) | 66 (13) | 0.92 (0.31–2.30) | .86 |
| Use of mechanical ventilation | 4 (8) | 35 (7) | 1.19 (0.29–3.55) | .75 |
| Rehospitalization within 30 days | 7 (14) | 56 (11) | 1.33 (0.48–3.18) | .51 |
| Length of stay,[a] median (range) | 2 (1–48) | 4 (1–56) | … | .20 |

NOTE. CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

[a] Length of stay calculation based on hospitalized patients only.