Pandemic influenza A (2009 H1N1) in hospitalized patients in a Saudi Arabian hospital: Epidemiology and clinical comparison with H1N1-negative patients

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KEYWORDS
Influenza; Vaccination; H1N1; Pandemic

Summary
Background and objectives: The World Health Organization (WHO) declared that pandemic influenza A (H1N1) was a public health emergency of international concern in April 2009. Herein, we describe the characteristics of patients in a Saudi Arabian hospital with and without H1N1 infection.

Methods: We reviewed the records of patients admitted with influenza-like illness and compared confirmed pandemic H1N1 cases to the H1N1-negative patients admitted to the hospital. Infections due to the novel H1N1 virus were confirmed using real-time reverse transcriptase polymerase chain reaction (rRT-PCR).

Results: During the study period, a total of 165 patients were admitted with influenza-like illness and underwent rRT-PCR testing. Of these patients, 47 (28.4%) had confirmed novel H1N1 virus infection. Thus, the hospitalization incidence rate was 13.4 cases per 100,000 persons. The remaining patients had negative H1N1 rRT-PCR test results. The mean age ± SD of the H1N1-positive patients was 30.3 ± 28.5 years compared with 25.3 ± 23 years for the H1N1-negative group (P = 0.28). Severe obesity was observed in 6.7% and 8.5% of H1N1-positive and H1N1-negative patients, respectively (P = 0.74). The clinical picture was similar between the two groups, except for the higher prevalence of nausea (25.5% vs. 11%) and diarrhea (21.3% vs. 7.6%) in the H1N1-positive group than in the H1N1-negative group (P = 0.03). The mortality rate was low in both groups.

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Introduction

A novel influenza virus (H1N1) was initially recognized to cause influenza-like illness in March 2009 in Mexico; subsequently, the H1N1 virus spread worldwide. On June 11, 2009, the World Health Organization (WHO) declared a phase 6 pandemic of moderate severity [1]. The first case of pandemic H1N1 infection in Saudi Arabia was reported on June 3, 2009 [2]; subsequently, the infection became widespread within the country. Three studies of the outbreak were conducted in different regions of Saudi Arabia. One study reported the clinical features of the first 100 cases [3], and the other two studies addressed the clinical features of hospitalized H1N1 patients [4,5]. This paper reports the clinical characteristics of hospitalized H1N1-positive patients and compares these characteristics with those of H1N1-negative patients. In addition, we aimed to determine if any specific disease characteristics could help distinguish between pandemic H1N1 and other causes of influenza-like illness (ILI).

Methods

This was a prospective, observational study of all hospitalized patients admitted with ILI from July 18 to December 22, 2009. The Saudi Aramco Medical Services Organization (SAMSO) provides medical care for Saudi Aramco employees and their dependents. Approximately 370,000 individuals are eligible for medical care at SAMSO. The main hospital is a 380-bed referral institution, and the hospital has five intensive care units (cardiac, medical, surgical, pediatric, and neonatal). Admissions to the hospital cover a whole range of patients and include general admissions, intensive care, and patients receiving chemotherapy for hematological and solid organ malignancies. However, SAMSO does not provide solid organ or bone marrow transplant services. On average, there are 36,426 admissions annually, with an average length of stay of 5.3 days.

During the initial phase of the H1N1 pandemic, patients were screened for the presence of ILI. Patients requiring hospitalization with ILI were tested for the H1N1 virus based on recommendations from the Centers for Disease Control and Prevention (CDC) [6]. Patients were tested if they reported fever (>38°C) and at least two of the following symptoms: cough, sore throat, headache, myalgia, and rhinorrhea [3]. A nasopharyngeal (NP) swab sample was obtained for real-time reverse transcriptase polymerase chain reaction (rRT-PCR) testing.

All admitted patients with ILI during the study period were reported to the epidemiology and infection control committee using a standardized form. The following data were collected from the medical records: age, sex, pre-existing chronic conditions, body mass index (BMI), previous vaccination for 2009–2010 seasonal influenza, and presenting clinical symptoms and signs. Severe obesity was defined as a BMI of ≥35 and morbid obesity as a BMI of ≥40. We also collected the following laboratory data: WBC, neutrophil and lymphocyte percentages. Admission to the intensive care unit, mechanical ventilation and mortality were also recorded.

Statistical analyses were performed using SPSS, and descriptive statistics were used. Fisher’s exact test was used to compare the two groups. A two-sided P value of <0.05 was considered significant.

Results

During the study period from July 18 to December 22, 2009, a total of 165 patients were admitted with ILI and underwent rRT-PCR testing for the H1N1 influenza A virus. Of all the included patients, 118 (71.6%) were negative for H1N1, and the remaining 47 (28.4%) were confirmed to have a novel H1N1 virus infection. Thus, the hospitalization incidence rate for H1N1-positive cases was 13.4 cases per 100,000 persons. Based on the small sample size of 118 controls and 47 H1N1-positive patients, the study had a power of 41% to detect a significant difference. The weekly number of cases exhibited two waves: weeks 3–6, from August 1 to August 28, and weeks 13–20, from October 10 to December 4, 2009 (Fig. 1). There was a significant difference among
seasons in the percentage of patients with H1N1 infection (Fig. 2). There were more H1N1-positive patients in the fall than in the summer \( (P = 0.034) \) and the winter \( (P = 0.024) \).

The mean age ± SD of the H1N1-positive patients was 30.3 ± 28.5 years compared to 25.3 ± 23 years for the negative group \( (P = 0.28) \). The highest percentage of cases was in the age group of 1–29 years (Table 1). This age group constituted 41.3% of the H1N1-positive patients and 49.8% of the H1N1-negative patients \( (P = 0.56) \). Bronchial asthma was present in 23.4% of hospitalized patients with H1N1 infection compared with 19.5% among H1N1-negative patients \( (P = 0.67) \). There was no difference between the groups in terms of underlying medical conditions or previous vaccination with the seasonal influenza vaccine \( (25.4\% \text{ vs. } 30.9\%; P = 0.39) \) (Table 2).

Severe obesity \( (\text{BMI of } \geq 35) \) was observed in 8 patients \( (6.7\%) \) and in 4 patients \( (8.5\%) \) of the H1N1-positive and H1N1-negative groups, respectively \( (P = 0.74) \). According to the hospital protocol, all the patients admitted with ILI during the study period, which coincided with the H1N1 pandemic, received oseltamivir.

Of the 165 admitted patients, 41 \( (14.4\%) \) were admitted to the intensive care unit, with equal proportions of H1N1-positive and H1N1-negative patients. One pregnant woman in each group was admitted to the hospital during the study period. The average lengths of hospital stay (ALOS) were 8.5 and 7.5 days for the H1N1-positive and H1N1-negative groups, respectively \( (P = 0.78) \).

<p>| Table 2 | Underlying conditions of hospitalized patients with and without 2009 H1N1 influenza virus infection. |
|-------------------------|------------------------------------------|------------------------------------------|-------------|</p>
<table>
<thead>
<tr>
<th>H1N1-negative; n (%)</th>
<th>H1N1-positive; n (%)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>23 (19.5)</td>
<td>11 (23.4)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td>8 (6.8)</td>
<td>3 (6.4)</td>
</tr>
<tr>
<td>Coronary artery disease (CAD)</td>
<td>21 (17.8)</td>
<td>7 (14.9)</td>
</tr>
<tr>
<td>Diabetes mellitus (DM)</td>
<td>24 (20.3)</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Sickle-cell disease (SCD)</td>
<td>10 (8.5)</td>
<td>6 (12.8)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1 (0.8)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Severe obesity (BMI of ( \geq 35 ))</td>
<td>8 (6.7%)</td>
<td>4 (8.5%)</td>
</tr>
<tr>
<td>Previous seasonal influenza vaccine</td>
<td>30 (25.4%)</td>
<td>15 (30.9%)</td>
</tr>
</tbody>
</table>
Table 3  Clinical features and laboratory data of hospitalized patients with and without 2009 H1N1 influenza virus infection.

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>H1N1-negative (N=118); n (%)</th>
<th>H1N1-positive (N=47); n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (≥38)</td>
<td>98 (83.1)</td>
<td>41 (87.2)</td>
<td>0.69</td>
</tr>
<tr>
<td>Sore throat</td>
<td>28 (23.7)</td>
<td>17 (36.2)</td>
<td>0.18</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (11)</td>
<td>12 (25.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22 (18)</td>
<td>15 (31.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (7.6)</td>
<td>10 (21.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (7.6)</td>
<td>7 (14.9)</td>
<td>0.34</td>
</tr>
<tr>
<td>Cough</td>
<td>85 (72)</td>
<td>40 (85.1)</td>
<td>0.18</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>34 (28.8)</td>
<td>16 (34)</td>
<td>0.76</td>
</tr>
<tr>
<td>Myalgia</td>
<td>25 (21.2)</td>
<td>10 (21.3)</td>
<td>0.72</td>
</tr>
<tr>
<td>WBC, mean ± SD</td>
<td>10.8 ± 7.3</td>
<td>6.9 ± 4.5</td>
<td>0.008</td>
</tr>
<tr>
<td>Neutrophil %, mean ± SD</td>
<td>58 ± 21</td>
<td>54 ± 19.3</td>
<td>0.26</td>
</tr>
<tr>
<td>Lymphocyte %, mean ± SD</td>
<td>25 ± 17.5</td>
<td>29.5 ± 17</td>
<td>0.20</td>
</tr>
<tr>
<td>CXR done</td>
<td>113 (95.8)</td>
<td>45 (95.7)</td>
<td>0.79</td>
</tr>
<tr>
<td>Pneumonia on CXR</td>
<td>74 (62.7)</td>
<td>30 (63.8)</td>
<td>0.81</td>
</tr>
<tr>
<td>ICU admission</td>
<td>17 (14.4)</td>
<td>7 (14.5)</td>
<td>0.8</td>
</tr>
<tr>
<td>Intubation</td>
<td>8 (6.8)</td>
<td>4 (8.5)</td>
<td>0.74</td>
</tr>
<tr>
<td>Average length of stay (ALOS)</td>
<td>7.5 ± 14</td>
<td>8.2 ± 12.1</td>
<td>0.78</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.8)</td>
<td>1 (2.1)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

This difference is related to occurrence of the first wave of the disease in the summer followed by the second wave in the fall. Although it was expected that a third wave might occur in the winter, such an event did not occur; the percentage of patients in the winter was only 11%, compared with 27% in the summer and 48% in the fall.

The mean age of the hospitalized patients was 30.3 years. In previous studies, the mean age of the hospitalized patients positive for H1N1 infection was 25 years [5,8]. The hospitalized patients in this study had a lower mean age than those reported recently by the Mayo Clinic [9]. In the current study, the highest percentages of cases were in the age group of 1—29 years (41.3%). The finding is similar to other published results showing that the highest proportion of cases, both overall and among hospitalized patients, was among individuals aged 5—29 (>60%) [4]. The differential age group involvement may be related to the fact that older persons have pre-existing immunity to the 2009 H1N1 virus. Alternatively, children and adolescents may have greater contact rates [10—12].

Most patients with pandemic H1N1 influenza experience mild disease; however, approximately 12% of those admitted to the hospital require high-dependency or intensive care [8]. The hospitalization rate was reported to be 26% in an earlier study from Saudi Arabia [4]. The hospitalization rate was 32—45% in those under the age of 18 years in the United States [13,14]. The ICU admission in this cohort of patients was 14.4%, which is in accordance with the previously reported ICU admissions.
in the USA. In those studies, 9–31% of hospitalized patients were admitted to ICUs [13−17]. In general, the hospitalization rates may differ from country to country due to differences in utilization of the health care system and the timing of the study. Earlier studies may have higher admission rates due to the uncertainty of the disease at the start of the pandemic [18]. Similar to a previous study performed in Chile, a high proportion of patients were admitted with pneumonia. In the current study, the rate of pneumonia was 63.8%, compared with 75% in that study [19].

Pregnant women accounted for 0.8% of the admitted patients. Similarly, among 117 cases of laboratory-confirmed cases from Riyadh, one patient (0.85%) was pregnant [4]. In contrast, in published studies from other parts of the world, pregnant women represented 7−10% of hospitalized patients and 6−9% of ICU patients [13,14]. Since the early phase of the 2009 H1N1 pandemic, pregnancy was thought to be a risk factor for infection and poor outcome. However, the findings of this study do not support this risk. A possible explanation for the discrepancy between these studies could be differences in the countries reporting the data and in the patients included. In the current study, we only included hospitalized patients, which would be expected to result in a greater number of complications in pregnant women. Among patients with severe or fatal cases of 2009 H1N1 virus infection, severe obesity (BMI ≥ 35) or morbid obesity (BMI ≥ 40) has been reported at rates that are higher—by a factor of 5 to 15—than the rate in the general population [16,17,20]. However, in the current study, the mortality rate was low among both H1N1-positive and -negative patients. The ALOS in our study was 7.5 days compared to 4.8 days in a previous study from Saudi Arabia [5] and from the United Kingdom [8]. The difference in the ALOS is probably related to the differences in clinical protocol among the institutions. The ALOS did not differ between H1N1-positive and H1N1-negative patients in our study. The mortality rate of less than 1% in our study was similar to that observed in previous studies from Saudi Arabia. In a study from Saudi Arabia, 3 of 150 hospitalized patients (2%) died [5]. However, the overall case fatality rate was less than 0.5%, with a wide range of estimates (0.0004−1.47%) [21]. The fatality rate for symptomatic illness was estimated to be 0.026−0.048% in the United States and the United Kingdom [22−25]. This difference may reflect uncertainty regarding case ascertainment [24−26].

The clinical presentation of H1N1-positive patients was similar to that of H1N1-negative patients apart from significantly greater prevalences of nausea and diarrhea in the former group. Because the CDC ILI criteria were used to identify patients for inclusion in the study, it was expected that there would be no differences between the groups with respect to fever, sore throat, headache, cough, rhinorrhea or myalgia. Thus, the fact that there was no difference in cough between the groups is expected. Our finding of more frequent gastrointestinal illness among patients with H1N1 echoes findings from the United Kingdom, where diarrhea was reported in 27% of H1N1-positive patients [18]. It was also reported in the USA that gastrointestinal symptoms were more common with H1N1 than with seasonal influenza [10]. However, this finding has been inconsistent, with no clear explanation proposed.

Anti-viral therapy was not used prior to presentation of the included patients. Because the clinical presentation of H1N1-positive and H1N1-negative patients with ILI is similar, it is difficult to diagnose H1N1 infection on clinical grounds. One method for differentiation among the different viral causes of ILI is the Winthrop-University Hospital Infectious Disease Division’s diagnostic weighted point-score system [27]. In that system, point scores were used to make a probable diagnosis of H1N1 influenza pneumonia in admitted adults with ILI [27].

The limitations of this study are the inclusion of only admitted patients and the failure to include all patients with ILI. National policy restricts testing to those with severe disease manifestations and to admitted patients. Thus, the true number H1N1 cases and the incidence of H1N1 within the community were underestimated. Second, there was no testing for seasonal influenza viruses; thus, no firm conclusion can be made about the comparison between H1N1 and seasonal influenza patients. Third, this study included the experience from a single center with a relatively small number of patients. Thus, the findings might not be generalizable to all patients with H1N1 infection in Saudi Arabia. A fourth limitation of the study is that it included a small cohort; thus the study was unlikely to detect small but potentially important differences between the groups. To have a power of 80%, the study should have included a total of 510 cases (170 H1N1-positive cases and 340 H1N1-negative cases).

In conclusion, we described the clinical presentation and the outcomes of laboratory-confirmed hospitalized pandemic H1N1 cases from Saudi Arabia. The comparison of admitted H1N1-positive and H1N1-negative patients with ILI showed that the two groups were similar except with respect to the prevalences of nausea and diarrhea and that the
mean WBC count was slightly higher in the H1N1-positive group. The strength of these findings may be tempered by the failure to identify seasonal and other human influenza viruses.

Conflict of interest statement

None to disclose.

Funding source

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Approval

Public department according to our institute’s requirements (Number 10-3136).

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