

# H1N1 influenza A

## *Preliminary evaluation in hospitalized patients in a secondary care facility in Saudi Arabia*

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### ABSTRACT

**الأهداف:** معرفة الخصائص السريرية والوبائية للموجة الأولى لإنفلونزا الخنازير H1N1.

**الطريقة:** أجريت دراسة استيعادية على جميع المرضى الذين تم إدخالهم لمجمع الملك سعود الطبي و تشخيص إصابتهم بإنفلونزا الخنازير H1N1 خلال الفترة ما بين 22 مايو 2009 حتى 31 أغسطس 2009. و كان ضابط دخول الدراسة وجود مسحة البلعوم الموجبة. و تم فحص القوائم للعلامات السريرية والوبائية

**النتائج:** تم إدخال العدد الإجمالي للمرضى 153 مريض مصاب بإنفلونزا الخنازير H1N1 الأكثرية ذكور (108 (71%). كانت أغلبية المرضى من الجنسية السعودية 111 (73%) مع وجود 83 ذكور (75%) و 28 إناث (25%). كان العمر المتوسط 25 عام. و من أكثر الأعراض حسب الأغلبية كانت السخونة 143 مريض، سعال 126 مريض، التهاب البلعوم 70 مريض، صداع 18 مريض، ضيق التنفس 17 مريض، آلام العضلات 11 مريض، إسهال 9 مريض، قيء 7 مريض. كان معدل وجود الأعراض قبل التنويم 3.55 يوم، معدل أيام التنويم 4.8 يوم. وقد حصل تحسن تام لـ 150 مريض. بينما حدثت الوفاة عند 3 مريض.

**خاتمة:** تعتبر جائحة إنفلونزا الخنازير H1N1 كوباء عالمي صحيحة وقد وصلت إلى المملكة العربية السعودية و يعتبر خطر لمواطنيها الصغار في السن و الذين بدون مناعة و المصابين بأمراض أخرى خاصة في الرئة مثل المصابين بالربو الشعبي و أيضا الحوامل. و بغرم شراستها في العدوى، كانت الوفاة أقل من المتوقع لمثل هذا الفيروس الحديث. الابتعاد عن التجمعات الاجتماعية قد وجد مفيداً، و لكن لا بد من المراقبة فيما بعد لتأكد من النتائج المبدئية.

**Objectives:** To assess the epidemiologic and clinical manifestations of the first wave of H1N1 influenza A patients.

**Methods:** This study is a retrospective chart review of all patients admitted in King Saud Medical Complex, Riyadh, Kingdom of Saudi Arabia, from 22nd May to 31st August 2009, with a proven diagnosis of H1N1 influenza A. Only patients with a positive

nasopharyngeal swab were included, and excluded when the swab was negative. Charts were then analyzed for epidemiological and clinical data.

**Results:** A total of 153 patients with proven H1N1 infection were admitted, with a predominance of male patients (108 [71%]). Most patients were Saudis (111 [73%]), with 83 males (75%), and 28 females (25%). The mean age was 25 years (standard deviation; 9.45 years), and median age was 24 years. The most common symptoms in order of frequency were; fever (143 patients), cough (126 patients), sore throat (70 patients), headache (18 patients), shortness of breath (17 patients), myalgia (11 patients), diarrhea (9 patients), and vomiting (7 patients). Average duration of symptoms before admission was 3.55 days, and the average time of hospitalization was 4.8 days. Full recovery was obtained in 150 patients. Death occurred in 3 patients.

**Conclusion:** True to its designation as a pandemic, H1N1 influenza A, has reached Saudi Arabia and poses a risk to the young population without immunity, and those with co-morbid disease, particularly of the lungs (bronchial asthma), and the pregnant. Despite its virulence in infecting people, deaths are far less than anticipated for such a novel virus. Social distancing can be recommended. However, further observation has to continue to substantiate these tentative preliminary findings.

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Orthomyxoviridae, the family of influenza viruses, is known for its potential to cause worldwide pandemics, with the one that swept the world in 1918 killing more people than the preceding Great war itself.<sup>1</sup> An outbreak in late March 2009 in Mexico of a novel influenza virus infection, which spread rapidly to neighboring countries caused the World Health Organization (WHO) to announce a pandemic alert phase 6 implying that a pandemic is under way.<sup>2,3</sup> The triple re-assortment virus was designated "swine-origin influenza A H1N1 virus (S-OIV)," and is an enveloped single stranded ribonucleic acid virus that contains 8 genes from 3 different species of North American and Eurasian swine, avian, and human influenza viruses.<sup>2,4</sup> Saudi Arabia being a Muslim country has been spared in the past, due to the non-existence of swine domestication, vast distances between its major cities (protecting it from avian influenza), however, remains vulnerable due to international travel, the yearly pilgrimage (Hajj), and a young population. In this study, we present the epidemiology, demographics, and clinical features of patients admitted with H1N1 over the first 3 months of this pandemic.

**Methods.** We performed a retrospective chart review of all patients admitted with a diagnosis of H1N1 influenza A at King Saud Medical Complex, a secondary care hospital of the Ministry of Health, Riyadh, Kingdom of Saudi Arabia, and subsequently found to be positive upon real time reverse transcriptase-polymerase chain reaction testing between 22nd May (admission date of the first confirmed patient), and 31st August 2009. No ethical consent was needed according to our review board, as no personal information was to be published. All patients were admitted after a nasopharyngeal swab was obtained, through a specially created clinic, according to the WHO guidelines for suspected, probable, and confirmed cases, the presence of fever more than 38°C with influenza-like symptoms, including presence of chills, headache, upper respiratory tract symptoms (cough, sore throat, rhinorrhea, shortness of breath), myalgia, arthralgias, fatigue, vomiting, or diarrhea, the finding of an infiltrate on chest radiograph, or belonging to a high risk group with chronic medical conditions, especially pulmonary, immunocompromised, pregnant, and nursing home resident. The charts were analyzed for gender, nationality, age distribution, school attendance, history of recent travel within 7 days of symptom onset, irrespective of the point of origin of the journey, source of contact, occupational risk such as, hospital staff, airline staff, history of vaccination for seasonal flu, symptoms of influenza, fever, cough, sore throat, diarrhea, vomiting, myalgia, shortness of breath, headache, duration of symptoms prior to presentation,

presence of an infiltrate on chest radiograph, need for intensive care admission, and ventilation treatment with oseltamivir, and duration of hospitalization, co-morbid conditions, including major organ disease, especially pulmonary, pregnancy, immunocompromised state, and finally, outcome defined by recovery, or death.

For descriptive and inferential statistical analyses, the Statistical Package for Social Sciences for Windows version 16 (SPSS Inc., Chicago, IL., USA) was used. Means and standard deviations were generated.

**Results.** Our review included 153 charts of patients admitted with confirmed H1N1 infection. Most patients are Saudis with 111 cases (73%), with 83 (75%) male, and 28 (25%) female cases, foreigners comprised 42 cases (27%), with only 18 (43%) male cases. The median age of all patients was 24 years with a range of 3-51 years. Overall, 39 students were infected, and 17 students were from the same school. A total of 29 patients developed influenza H1N1 after returning from travel abroad. The countries involved include 4 continents. The most common international destination was Great Britain with 6 patients, followed by the Philippines (4 patients), United States (East and West Coast) and Syria (both 3 patients), and Indonesia (2 patients). The United Arab Emirates, Egypt, Kuwait, Morocco, Australia each had one patient. Local travel involved 2 patients coming from Mecca, one from Jeddah, and 2 from unknown destinations. Destinations indicate routes of spread. Contacts were traced in 12 (8%) patients to household contacts with H1N1 patients. Three patients were stewardesses, 15 (10%) patients were hospital employees, 9 nurses, one medical secretary, 3 laboratory technicians, one porter, one security guard, and 14 of them are from King Saud Medical Complex. Co-morbid conditions included in order of frequency were; bronchial asthma (15 [10%] patients), smoking (5 [3%] patients), community acquired pneumonia (5 [3%] patients), diabetes mellitus (4 [3%] patients), hypertension (3 [2%] patients), pregnancy (2 [1%] patients), alcohol abuse (2 [1%] patients), obesity, rheumatoid arthritis, sickle cell disease, hepatitis B virus infection, gastroenteritis, diabetes insipidus, hypothyroidism, iron deficiency anemia, one patient each. The most common symptoms in order of frequency were fever as most common, and vomiting as the least common (Table 1). The chest radiographs of 9 patients showed infiltrates, 10 were admitted to the intensive care unit (ICU), and 6 needed ventilatory support. All patients received oseltamivir. No patient had been previously vaccinated for seasonal influenza. The average duration of symptoms before admission was 3.55 days, and the average time of hospitalization was 4.8 days. Full recovery was obtained in 150 patients.

Death occurred in 3 patients, one was a female prisoner with an acute physiology and chronic health evaluation score (APACHE) score of 117, one was a one week post-partum with an APACHE score of 132, and one morbidly obese male with an APACHE score of 76, and those who died had an average age of 28 years, and an average duration of 9 days stay in the ICU.

**Discussion.** This present study examined the epidemiological characteristics and clinical features of the first wave of H1N1 influenza A to hit Saudi Arabia in cases admitted to a secondary care facility. The government of Saudi Arabia through the Ministry of Health recommended the establishment of special screening clinics for suspected cases, isolation wards, strict hand hygiene, the use of disposable N95 respirators, and provided anti-viral agents in the form of neuraminidase inhibitors oral oseltamivir, and inhalable zanamivir. The so called top-down approach

was adopted by developed countries.<sup>5</sup> Screening, case definition, admission, and treatment criteria were according to the WHO guidelines.<sup>6</sup>

Our results were found to be similar to the findings of the Novel S-OIV Investigation Team (NIT), which studied 642 confirmed cases in the United States.<sup>7</sup> Conforming to their study, we identified a notable predominance of male patients (71%), though our median age was higher (24 years instead of 20 years), our age range (3-51 years) was similar to their team's finding (19 months - 51 years for hospitalized patients).<sup>7</sup> In a Mexican study of patients with H1N1 infection and respiratory failure for comparison, the age range was 13-47 years old,<sup>8</sup> while the Mexican National Epidemiologic Surveillance System noted a particular increase of cases in adults between the ages of 20-40 years.<sup>8</sup> Hence, it has been established that the illness targets the young, and people in the reproductive age group. The preponderance of males raises the question of whether males are more susceptible. The apparent population effect of S-OIV infection has several signature features of previous pandemics including atypical timing, and ages shifts in the disease' activity.<sup>8</sup> Persons under the age of 30 years have been found to have little evidence of cross-reactive antibodies to the pandemic virus, however, a proportion of older adults had pre-existing cross-reactive antibodies.<sup>9</sup> This was also suggested from virologic studies of the 1976 swine influenza vaccine.<sup>10,11</sup>

Students comprised 25% of the patients in our study, with a small cohort of students identified in the same school (44% of the total students affected), emphasizing the importance of crowding and closed settings, as a risk factor for transmission. Therefore, the activation of social distancing is an important strategy to prevent future spread.<sup>12</sup> However, investigators of a simulation of the spread of pandemic influenza in Australia commented that the intervention of social distancing such as school closure, increased isolation of symptomatic individuals in their households, workplace non-attendance (now recommended in Saudi Arabia to last 7 days by a Ministerial directive, namely, expected period of infectivity from one day before the onset of symptoms through 5-7 days following infection),<sup>13</sup> and reduction of contact in the wider community are capable of arresting influenza epidemic development if used in combination, activated without delay, and maintained for a relatively long period.<sup>12</sup> The question remains for how long? Workplace related infection was 10% in hospital employees, and more in those health care providers (HCP) with direct patient contact (9 out of 15 were nurses from our institution). The point of whether HCP can avoid influenza was raised in an article on "ethical concern in an influenza pandemic," and the consensus was that caring for patients with a potential

**Table 1** - Demographics and symptoms in 153 hospitalized patients with confirmed H1N1 influenza A receiving oseltamivir.

Characteristic	n	(%)
Male	108	(71)
Median age	24	
Age range, years	3-51	
<i>Age group, years</i>		
3-12	7	(5)
13-19	32	(21)
20-29	78	(51)
30-39	20	(14)
40-49	12	(8)
50-51	2	(1)
Students attending school	39	(25)
Students in school outbreak, n=39	17	(44)
Travel history	29	(19)
Most common destination-UK, n=29	6	(14)
History of vaccination with seasonal flu vaccine	none	
<i>Clinical symptoms</i>		
Fever	143	(93)
Cough	126	(82)
Sore throat	70	(46)
Headache	18	(12)
Shortness of breath	17	(11)
Myalgia	11	(7)
Diarrhea	9	(6)
Vomiting	7	(5)
Average length of hospitalization in days	4.8	
Infiltrate on chest radiograph	9	(6)
Admission to intensive care	10	(7)
Ventilation required	6	(60)
Full recovery	150	(98)
Died	3	(2)

lethal illness for the HCP is not a moral obligation, but remains a moral option.<sup>14</sup>

Patients with a history of national, as well as international travel (29 [19%] in this study) became probably infected at the point of origin, or during flight in the crowded airplane cabin. The National Institute of Occupational Health and Safety in the US is modeling airflow, and migration of airborne biological agents throughout typical aircraft cabins. With this model, exposure for crew members and passengers could be estimated and measured, to minimize such exposure, could be evaluated.<sup>15</sup> Most travelers came from the United Kingdom. Symptoms and signs were similar in frequency as in the study by the NIT group (Table 1). In decreasing order they were fever, cough, sore throat, shortness of breath, myalgia, diarrhea, and vomiting. Shortness of breath may point to the involvement of the lower respiratory tract, while diarrhea stands out as an unusual sign of this influenza.<sup>16</sup> The clinical spectrum of the disease has become more defined with suspected subclinical cases, self-limited outcomes, and death from severe respiratory failure, either by primary viral pneumonia, or secondary bacterial infection, or viral pneumonia super added on community acquired pneumonia.<sup>2,6</sup>

Bronchial asthma has been mentioned as a condition at high risk for complications.<sup>17</sup> In our study, bronchial asthmatics compromised 15 patients (10%), but no one had complications. The greater susceptibility of asthmatics can be explained by the cellular pathogenesis of the influenza virus, which once attached to the respiratory tract epithelium, can attach to, and penetrate columnar epithelial cells if not prevented from doing so by specific secretory antibody immunoglobulin A (IgA).<sup>18</sup> Subtle immunodeficiency of IgA in severe asthma has recently been recognized.<sup>19</sup>

From the 9 patients admitted to the ICU, 6 needed ventilatory support, and 6 patients had no identifiable underlying health condition. Three patients died with an average age of 28 years. As predicted, the high APACHE scores were associated with a worse outcome. One was obese with a body mass index above 35. Obese persons are more vulnerable to influenza, maybe because it is now well-established that obesity, in particular abdominal obesity, interferes with lung function, although the underlying mechanism is yet to be clarified.<sup>20</sup> The other patient was a week post-partum, but came from another hospital already on a ventilator, apparently having contracted her illness just before, or shortly after delivery. Pregnancy as such, poses a state of immunodeficiency with decreased levels of T helper cells as a possible cause.<sup>21</sup> That T cells are important in the immunity against the influenza virus is emphasized in the centers of disease control statement that human immunodeficiency virus-infected adults

and adolescents, and especially persons with low CD4 cell count, or acquired immune deficiency syndrome can experience more severe complications of seasonal influenza.<sup>22</sup>

All patients received oseltamivir on admission, without delay. Most patients improved fast on this medication, so that they could be discharged within 3 hospital days, with an average stay of 4.8 days. Whether they continued shedding the virus should have been confirmed after 7 days of infection, with a repeat nasopharyngeal swab, which however, was not carried out due to financial considerations. Not all countries can afford medication like oseltamivir, and some developing countries have turned to medications, which either decrease the impact of the complications of H1N1, like statins for pneumonia, which in studies have shown to decrease the 30-day mortality rates by 50%, or medications which boost host defenses against the virus like chloroquine, that acts as an antiviral agent by impairing virus release into the cytosol.<sup>5</sup> This is the so called "bottom-up" approach as opposed to the "top-down approach" mentioned earlier.<sup>5</sup>

The low rate of mortality in our study (2%), despite a higher rate of infections in a naïve populace however, is intriguing, even more so after Webster and Campbell<sup>23</sup> showed in an experiment *in vivo* in turkeys, that genetic reassortment gave rise to a new influenza virus that leads to a total population collapse. Even though we do not have all the answers, as Baden et al<sup>24</sup> in an editorial pointed out: "We now have important tools to fight this outbreak: a clear case definition, an aware health care system, and an informed public. We await the availability of a vaccine."

It is noteworthy that our study was preliminary and observed only a small segment of patients in a single institution, therefore, results are to be interpreted in this context.

In conclusion, we have examined the first wave of patients admitted with a novel influenza virus designated H1N1, which appears to be more virulent than its seasonal counterpart by virtue of the number of infected patients, but so far is less lethal as anticipated theoretically. Bronchial asthmatics are particularly vulnerable, and treatment for this group should be initiated swiftly. Social distancing, especially school closure for at least a fortnight after the return from holidays can be recommended. More patients will have to be studied in detail as the pandemic unfolds to arrive at further recommendations.

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