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RESEARCH ARTICLE

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS OF PANDEMIC A(H1N1)pdm09 IN CASABLANCA-MOROCCO : MAY 2009– MAY 2010

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ABSTRACT

Influenza A(H1N1)pdm09 emerged in Mexico and United States and spread throughout the world over a short period of time. The aim of this study was to investigate the demographic, clinical manifestations and epidemiologic characteristics of influenza H1N1pdm09 associated to confirmed influenza A(H1N1)pdm09 in Casablanca. From 07 May, 2009 to 17 May 2010, 1347 nasopharyngeal swab from patients with clinical evidence of influenza-like illness (ILI) were tested for pandemic A(H1N1)pdm09 virus, using One-Step Real-Time RT-PCR. Demographic data, symptoms, exposure and co-morbidity conditions were documented. Of 1347 nasopharyngeal swab 489 (36.3%) were positive and 858 (63.7%) were negative. The Maximum positive cases were found in the age group of 15-44 yr, (46.4%) followed by 5-14 yr (32.3%) and the low positive cases was found in the age group > 65 yr(1.7%). Fever (82.4%), Cough (80.2%), Sore throat (47%), Headache (44.6%), Rhinitis (46.4%) and Myalgia (28.6%), were the most commonly reported symptoms in the A(H1N1)pdm09 positive group, but gastrointestinal symptoms, including vomiting and diarrhea, were not commonly reported (9.2%), (4.7%) respectively. The prevalence of Influenza A(H1N1 is high in the younger population. Continuous monitoring is essential for evaluation and surveillance to be prepared for and able to control future influenza activities.

INTRODUCTION

Influenza pandemics are the most important infectious diseases unpredictable requiring monitoring and surveillance around the world (Suzue *et al*., 2012). In April 2009, influenza A(H1N1)pdm09 emerged in Mexico and United States (Perez-Padilla *et al*., 2009; Jain et Goldman 2009) and spread rapidly worldwide causing the first pandemics of the 21st century that affected 214 countries and resulted in 18449 virologically confirmed deaths (« WHO | Pandemic (H1N1) 2009 - update 112 » 2013) (WHO update on Pandemic H1N1 2009, 6th August 2010). The expeditious global spread of this virus led the World Health Organization to raise the pandemic alert level to phase-6 on 11 June 2009 (« PMNCH | WHO: Influenza pandemic alert raised to level 6 » 2013) (« Epidemiological Summary of Pandemic Influenza A(H1N1)PDM09Virus - Ontario, Canada, June 2009 » 2009). Infection with pandemic A(H1N1)pdm09, causes a broad spectrum of clinical expressions ranging from a febrile upper respiratory illness to pulmonary complications that required hospitalization, neurological complications, myocarditis or pericarditis, invasive bacterial infection, or other severe conditions (Centers for Disease Control and Prevention (CDC) 2009). In context, and given that pandemic influenza may represent global health risks, we analyzed the demographic, clinical manifestations and epidemiologic characteristics associated to confirmed influenza A(H1N1)pdm09 in Casablanca. It represents the first medical report about H1N1 pandemic in this city and this experience will draw conclusions and lessons for a better preparation for future pandemics.

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MATERIALS AND METHODS

Cases definitions and sample

The case definitions recommended by WHO guidelines were used for probable and confirmed cases with an acute febrile respiratory illness and disease spectrum from influenza-like illness to pneumonia (« WHO | Influenza » 2013). During the early months of the pandemic A(H1N1)pdm09, Nasal/ Nasopharyngeal swab/Broncho Alveolar Lavage (BAL) samples were collected in viral transport medium under triple packaging cold chain conditions from suspected cases to the Institute Pasteur of Morocco Casablanca. The samples were accompanied with completed questionnaire will indicating demographic characteristics, date of onset of symptoms, co-

morbidities, travel history to areas of high prevalence and/or close contact with a confirmed.

Laboratory Diagnosis (Real-time RT-PCR)

All samples were processed in Bio Safety level 3 (BSL 3) laboratory after reception. The Viral nucleic acid was extracted from 200 µl of nasal/nasopharyngeal swabs using the High Pure Viral Nucleic Acid Kit (Roche Diagnostics). The respiratory samples were tested using Real-time RT-PCR protocol Centers for Disease Control and Prevention (CDC). For each sample, four target genes were amplified; Influenza A, Swine Influenza A, Swine H1 and RNaseP by Real Time CDC RT PCR protocol previously described by WOH(« WHO | CDC protocol of realtime RTPCR for influenza A (H1N1) » 2013)) and performed on the Light Cycler 2.0 or Fast 7500 Instrument. A sample was declared positive when it showed amplification in all 4 target genes.

Statistical analysis

The Analyses were performed using the SPSS software package (version 21.0) for Windows® in the statistical analysis. We applied descriptive methods for frequencies and percentages of the different variables. The positivity rate was defined as the number of individuals testing positive for A(H1N1)pdm09, out of all the tested individuals. We used the $\chi 2$, test or Fischer Exact Test for bivariate analysis. A p-value < 0.05 was considered statistically significant. The associations between H1N1 and the various predictive demographic and clinical symptoms were assessed using multi- variable logistic regression. The dependent outcome variable was A(H1N1)pdm09, while the predictor variables were age, gender, fever, cough, headache, vomiting, diarrhea, exposure to a confirmed case and travel.

RESULTS

From 07 May, 2009 to 17 May 2010, 1347 specimens from patients were tested for pandemic A(H1N1) pdm09 virus, of them 657 (48.8%) males and 676 (50.2%) females. The mean age was 24 years, with a range of 5 month to 80 years of which 489 (36.3%) were positive and 858 (63.7%) were negative. The transmission was began in June, reached its peak in November and declined dramatically subsequently. The demographic information, Clinical characteristics, co-morbidity, exposure history, and travel history of the study are presented in Table 1.

The Maximum positive cases were found in the age group of 15-44 yr, (46.4%) followed by 5-14 yr (32.3%) and the low positive cases was found in the age group > 65 yr (1.7%) . The distribution by age categories and pandemic (H1N1) 2009 virus infection showed a significant association and none were previously vaccinated against influenza (Fig.1).

At the start of the pandemic period from 12 June 2009 to 21 October 2009, 48 (9.8%) cases were imported in travelers, ten from Canada, four from London, nineteen from Spain, eight from U.S.A, four from France and one respective case from Italy, Germany and Saudi Arabia. The proportion of cases with no travel history increased in the end of October. Initially, after laboratory confirmation of the infection, the patients were quarantined in the Influenza A (H1N1) 2009isolation ward to contain spread of pandemic. They received antiviral treatment with neuraminidase inhibitors (Oseltamivir) immediately. During the later period of the pandemic, only sick patients with identifiable underlying conditions as pregnancy, asthma and respiratory distress required a few days of hospitalization. Confirmed infection were identified early in the investigation

Table 1. Demographic and clinical characteristics of the study by H1N1 status (N = 1347)

	ALL (n=1347)	Negative (n = 858; 63.7%)	Positive (n = 489; 36.3%)	p- Value
Demographic characteristics				<0.001
Age group (years)	1238(91.9%)	777(62.8%)	461(37.2%)	
0-4	198(16%)	(n = 152; 19.6%)	(n =46; 10%)	
5-14	281(22.7%)	(n = 132; 17%)	(n =149; 32.3%)	
15-44	556(44.9%)	(n =342; 44%)	(n = 214;46.4%)	
45-65	160(12.9%)	(n =116; 14.9%)	(n = 44; 9.5%)	
>65	43(3.5%)	(n = 35; 4.5%)	(n = 8;1.7%)	
MALE	657(48.8%)	427(49.8%)	230(47.0%)	0.231
FEMALE	676(50.2%)	418(48.7%)	258(52.8%)	
Travel	175(13%)	127(8.14%)	48(9.8%)	0.009
MEDICAL	31(2.3%)	24(2.8%)	7(1.4%)	0.108
School	168(12.5%)	71(8.3%)	97(19.8%)	<0.001
Prison	14(1%)	3(0.4%)	11(2.2%)	0.001
Exposure	69(5.1%)	50(5.8%)	19(3.9%)	0.119
Clinical characteristics				
FEVER	933(69.3%)	530(61.8%)	403(82.4%)	<0.001
Cough	935(69.4%)	543(63.3%)	392(80.2%)	<0.001
Sore throat	516(38.3%)	284(33.1%)	232(47.%)	<0.001
Headache	489(36.3%)	271(31.6%)	218(44.6%)	<0.001
Myalgia	373(27.7%)	233(27.2%)	140(28.6%)	0.79
Vomiting	79(5.9%)	34(4.0%)	45(9.2%)	<0.001
Diarrhoea	73(5.4%)	50(5.8%)	23(4.7%)	0.381
Rhinitis	581(43.1%)	354(41.3%)	227(46.4%)	0.224
Co-morbidity				
Asthma	158(11.7%)	61(7.1%)	97(19.8%)	<0.001
HTA	16(1.2%)	9(1%)	7(1.4%)	0.533
Diabetes	40(3%)	23(2.7%)	17(3.5%)	0.408
Pregnancy	81(6.1%)	41(4.8%)	40(8.2%)	0.040
HEART	26(1.9%)	13(1.5%)	13(2.7%)	0.143

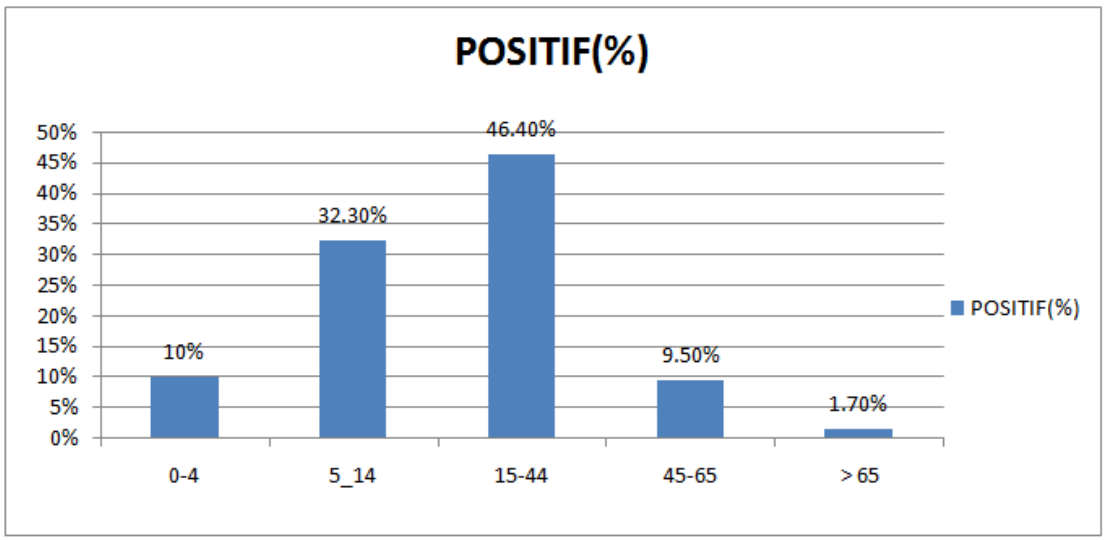

Figure 1. The age distribution of patients infected with pandemic influenza A (H1N1) 2009

in schools and universities in Casablanca from 23 October 2009, to 10 December 2009. Out off 168 (12.5%) Schoolchildren and student, 97(19.8%) were positive so, school closure were effective at reducing the final attack rate. Fever (82.4%), cough (80.2%), sore throat (47%), headache (44.6%), Rhinitis (46.4%) and myalgia (28.6%), were the most commonly reported symptoms in the H1N1-positive group as compared to the swab-negative group, but gastrointestinal symptoms, including vomiting (9.2%) and diarrhea(4.7%), were not commonly reported. Information on obesity was not systematically collected. Out of the 489 (36.3%) laboratory-confirmed cases, five cases had confirmed pneumonia, six respiratory distress admitted to an intensive care unit. Among 81 pregnant women, 40 were infected with A(H1N1)pdm09. Utilizing the stepwise-backward elimination method, the multivariable logistic model (Table 2) demonstrated that significant variables included younger age, school, fever, headache constitute a risk factor to develop this infection.

Table 2. Predictive symptoms of H1N1 in the study cohort using multivariable logistic regression

	OR	95.0% CI	P-value
AGE	0.982	0.97-0.994	0.004
TRAVEL	0.932	0.524-1.658	0.81
MEDICAL	0.43	0.11-1.676	0.224
SCHOOL	3.005	1.433-6.302	0.004
EXPOSURE	0.848	0.351-2.046	0.713
FEVER	3.823	2.162-6.761	<0.001
COUGH	1.672	0.979-2.856	0.06
SORETHROST	1.072	0.73-1.574	0.723
HEADACHE	1.923	1.282-2.886	0.002
MYALGIES	1.094	0.722-1.658	0.672
VOMITING	2.48	1.129-5.445	0.024
LDIARRHEA	1.391	0.606-3.192	0.436
RHINITE	0.995	0.672-1.472	0.979
ASTHMA	3.296	1.862-5.834	<0.001
HTA	3.903	0.9-16.917	0.069
DIABETES	1.314	0.447-3.858	0.619
PREGNANCY	2.273	1.274-4.056	0.004
HEAT	1.934	0.537-6.965	0.313

AOR, adjusted odds ratio; CI, confidence interval

DISCUSSION

During summer 2009, international travel have facilitated the geographical spread from the initial foci of A(H1N1) pdm09 infection in Mexico and the United States to many countries throughout the world (team 2009). Casablanca the high population density, was the first city in Morocco to reported the firsts confirmed cases of A(H1N1)pdm09 infection on jun12, 2009. They concern two travelers : a young girl and a young man who were pursuing their studies in Montreal, Canada. A national active surveillance system was established with thermal scanners installed in airports to detect fevers in recent travelers to areas affected by pandemic A(H1N1)pdm09. The surveillance systems was used to monitor track and characterize the influenza A(H1N1)pdm09, occurring primarily outside the period when influenza virus typically circulates generally, and predominantly affecting younger age groups. The positivity rate for pandemic A(H1N1)pdm09 virus infection represented 36.3% of the group of patients presenting with influenza-like illnesses in the ambulatory setting but this infection rate was higher than in other regions of the European Community (Potdar *et al*., 2010). The incidence of influenza-like illness with a negative result for pandemic rates A(H1N1) pdm09 was very high (63.7%). This event could be tied to the circulation of other respiratory viruses. Vaccines against pandemic influenza were not widely available during its first wave and Antiviral (oseltamivir) therapy and prophylaxis were used extensively as a strategy against pandemic influenza. It has been shown that they may aid in the prevention of infection, reduce the level of its transmission and the severity of the associated disease (Ward *et al*., 2005). The distribution of influenza A (H1N1)pdm09 cases by age was high attack rates among group of 15-44 yr, (46.4%) followed by school-age 5-14 yr (32.3%) but relatively low infection in the elderly population. The mean age was 24 years old as reported in several studies of confirmed pandemic cases in Canada and the U.S. (23-27) years old (Campbell *et al*., 2010) (Louie *et al*., 2009). The age distribution of patients in this study was similar to what has been described elsewhere in several European

countries which may have a climate almost similar to that of Casablanca like Spain (Scalera et Mossad 2009).The WHO reported that most patients worldwide were reported in adolescent and young adults contrary to seasonal flu which the elderly are most affected(Harcourt *et al*., 2012; Yang *et al*., 2012).

The predominance of infection in young people and children play an important role in the spread of influenza A(H1N1)pdm09 virus than has been reported by other authors (Scalera et Mossad 2009; Peiris, Poon, et Guan 2009) and because of their high contact rates, are thought to amplify and accelerate spread in the general population (Mikolajczyk *et al*., 2008). Similarities in epidemiological behavior of this new influenza strain were observed among populations of both the northern and southern hemispheres (Scalera et Mossad 2009). School were found to be a risk of infection and play an important role in transmission. Among 168 (12.5%), 97 (19.8%) were positive and were closed worldwide during the first wave of 2009 influenza pandemic to prevent the viral spread. The $H1N1_{2009}$ infection can easily spread in enclosed units as prison (Finnie, Hall, et Leach 2012). Of the 14 respiratory tract specimens prison in Casablanca, 11 Influenza A virus was detected. The impact of influenza tends to increase transmission and the risk of secondary infection. Therefore vaccination, administration of antiviral drugs and implementation of control measures can result in the majority of the enclosed population to moderating outbreaks of influenza pandemic and epidemic. Fever and cough were more commonly seen in patients with H1N1 virus infection in this study similar to other studies amongst H1N1-infected patients (Scalera et Mossad 2009; Cao *et al*., 2009; Crum-Cianflone *et al*., 2009). Patients with H1N1 virus infection were also more likely to report sore throat, headache and rhinitis but they were less likely to have diarrhea and vomiting. According to our results, 9.2% of H1N1 patients complained of diarrhea and 4,7% reported vomiting such as (Lahlou Amine *e et al*., 2011). The frequencies of both these symptoms were lower than those reported by (Al-Tawfiq *et al*., 2011) but higher than those reported in other studies. Differences in these findings may be related to diverse geographical, cultural, and health care environments.

We found that pregnancy was associated with H1N1 virus infection. Previous reports from pregnant women have demonstrated an increased risk of infection during previous pandemics and influenza epidemics(Louie, Acosta, Jamieson, Honein, *et al*., 2010). During pregnancy, physiologic adaptations in the respiratory, cardiovascular, and immune systems place women at increased risk for certain infections and complications that are associated with influenza viruses(Creanga *et al*., 2010; Louie, Acosta, Jamieson, et Honein 2010) particularly those with a coexisting medical condition, such as asthma. These data highlight the importance of vaccines against H1N1 influenza in pregnant women (Conlin *et al*.,. 2013). These data insist the importance of assessing the safety of H1N1 vaccines among pregnant women. These data document the importance of vaccinating pregnant women against influenza, and demonstrate the value of administration of antiviral with suspected or confirmed influenza. Asthma was also found to be associated to severity of pandemic influenza infection in the global pooled analysis (McKenna *et al*., 2013). In this study among patients with an history of asthma 158 (11.7%), 97 (19.8%) were found to be associated to pandemic influenza infection and hospitalization. Data from international studies reported similar proportions of asthma among hospitalized patients with pH1N1 infection than that reported from Syria (20%) (Alsadat *et al*., 2012), Australia (31%) (Hewagama *et al*., 2010), Ireland (18%), Singapore (19%), Spain (23%), and the United Kingdom (25%) (Nguyen-Van-Tam *et al*., 2010). Medical conditions, such as arterial hypertension or diabetes, were not associated with infection by the H1N1 virus. This can be attributed to the small number of H1N1 infections in older groups. Clinical disease commonly appears benign, but complications leading to hospitalization may occur, especially in persons with underlying lung or heart disease, diabetes or those on immunosuppressive therapies or pregnant women (González-Candelas *et al*., 2012). Six death with influenza A (H1N1)pdm09 virus infection have been attributed to respiratory failure in Casablanca among sixty four in Morocco. This study contributed to the epidemiological surveillance of A(H1N1)2009 virus infections during the pandemic allowed to enrich national and international databases. The transmissibility of this virus in Casablanca was comparable to that observed in more developed countries and greater efforts are needed to mitigate future, and possibly more severe, pandemics.

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