JRHS
Journal of Research in Health Sciences
Original Article

Influenza A (H1N1) in Hamedan Province, Western Iran in 2009: A Case-Control Study

Zahra Cheraghi[a], Amin Doosti Irani[a], Shahab Rezaiean[a], Jamal Ahmadzadeh[a], Jalal Poorolajal[b]*, Hossein Erfani[c], Jalal Battaei[c], Ali Zahiri[c], Norooz Ali Noroozi[c], Ali Golshaeian[c], Mostafa Anvari[c], Ali Neshani[c], Hamid Padyar[c], Ali Mohammad Reza Alipoor[c], Mohsen Moradi[c], Mahdi Maleki[c], Samad Givi[c], Morad Esmaeili[c].

[a] *Department of Epidemiology & Biostatistics, School of Public Heath, Hamedan University of Medical Sciences, Hamedan, Iran*
[b] *Department of Epidemiology & Biostatistics, School of Public Heath and Research Center for Health Sciences, Hamedan University of Medical Sciences, Hamedan, Iran*
[c] *Deputy of Health, Hamedan University of Medical Sciences, Hamedan, Iran*

ARTICLE INFO

Article history:
Received: *11April 2010*
Revised: *26 April 2010*
Accepted: *15 May 2010*
Available online: *21 June 2010*

Keywords:

Influenza A (H1N1)
Case-Control Studies
Clinical manifestations
Iran

Corresponding author:

Poorolajal J. (MD, PhD)
Tel: +98 811 8260661
Fax: +98 811 8255301
E-mail addresses:
poorolajal@umsha.ac.ir
poorolajal@yahoo.com

ABSTRACT

Background: The novel influenza A (H1N1) virus was first detected in March 2009 in Mexico and then disseminated to many other countries worldwide. In this study, we assessed the potential risk factors of swine flu as well as the most important clinical manifestations of this infectious disease among confirmed cases during early phase of pandemic H1N1.

Methods: Subjects (cases and controls) were selected from those patients with signs and symptoms of respiratory tract infection who referred to health centers of eight cities throughout Hamedan Province, western Iran form July to December 2009. Characteristics of the participants were obtained by interviewers using pre-determined questionnaire. Cases were distinguished by pharyngeal soap specimens positive for influenza A virus using polymerase chain reaction (PCR). Logistic regression model was conducted at 0.05 significance level using Stata 9.1 statistical software to assess the effects of various risk factors on H1N1 influenza infection.

Results: Totally, 245 confirmed cases of H1N1 influenza were compared with 388 controls. Case fatality rate of influenza infection was about 2.86%. In comparison with age group of 1-19 yr old, adjusted odds ratio estimates was 1.91 [95% CI: 1.06, 3.46] for age group of 20-39 yr old, 0.94 [0.37, 2.38] for age group of 40-59 yr old, and 0.34 [0.09, 1.37] for age group of 60-79 yr old. Adjusted odds ratio estimates of influenza A infection was 8.12 [95% CI: 3.11, 21.6] for pregnant women compared to non-pregnant women; 1.84 [95% CI: 1.32, 2.86] for high educated individuals in comparison with low educated individuals; 2.11 [95% CI: 1.25, 3.57] for whose who had close contact with suspected influenza patients; and 2.15 [95% CI: 1.16, 3.98] for individuals with normal body mass index (BMI= 25-30) compared with underweight individuals (BMI< 20). There were no significant differences in clinical manifestations between cases and controls.

Conclusion: The risk of influenza A infection is highest among children and adolescents, pregnant women, high educated individuals, and those who had close contact with suspected influenza patients during pandemic phase. In addition, there is no pathognomonic sign or symptom to distinguish influenza infection clinically from other kinds of respiratory track infections.

Introduction

The swine influenza is an acute and highly contagious respiratory tract infection that is produced by influenza A (H1N1) virus [1]. The new influenza A (H1N1) virus spreads from person-to-person. It is transmitted like seasonal flu during close contact with infected individuals. The infected droplets expelled during coughing or sneezing [1]. The incubation as well as infectious periods are usually short from 1 to 3 days and from 3 to 5 days respectively, although infectious period in children may persist until 7 days [2].

Influenza A (H1N1) has multiple clinical signs and symptoms including fever, cough, myalgia, and sore throat [3, 4]. The children less than 5 or greater than 65 yr old, pregnant women, individuals who suffer from chronic disease, and the immune compromised people are at higher risk of infection in comparison with general population [5]. In addition, influenza A increases maternal and neonatal morbidity and mortality rate [6].

The novel H1N1 virus was first detected in March 2009 in Mexico and then disseminated to the US and many other countries worldwide. On 11 June 2009, the World Health Organization (WHO) declared pandemic influenza phase 6 [7]. Soon after that, in 10 July 2009, H1N1 influenza infection spread worldwide and at least 100,000 persons were infected by this novel H1N1 influenza virus [8]. Investigators predicted if this pandemic achieves virulence strong enough like 1981 pandemic flu, 62 million death would occurred [9].

The first case of H1N1 swine flu in Iran was detected in a student who lived in the US and came back to Iran for summer vacation and developed symptoms less than a week after his arrival [10]. From June to November 2009, 2662 confirmed influenza infected individuals were reported in Iran [11].

In his case-control study, we intended to assess the potential risk factors of H1N1 influenza A as well as the most important clinical signs and symptoms of this disease among confirmed cases detected in Hamedan province during early phase of pandemic H1N1.

Materials and Methods

This unmatched case control study was conducted in Hamedan Province, western Iran including 245 cases and 388 controls. Both cases and controls were selected from those patients with signs and symptoms of respiratory tract infection who referred to health centers of eight cities throughout Hamedan province during the early pandemic phase of swine flu form July to December 2009. Pharyngeal soap and gargle specimens were taken form all subjects under study for detection of influenza A (H1N1) virus. The specimens were sent to central laboratory of Ministry of Health in Tehran. All specimens were tested for H1N1 influenza A using polymerase chain reaction (PCR). Those individuals whose specimens were positive for H1N1 influenza were considered as cases otherwise as controls. Simultaneously, characteristics of the participants as well as data regarding to potential risk factors were collected by interviewers using a pre-determined questionnaire.

The potential risk factors of H1N1 influenza infection that were evaluated in this study included: age, body mass index (BMI), smoking, close contact with suspected influenza patients, chronic disease including coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), diabetes, dialysis, cancer, anemia, and transplantation, and history of influenza vaccination. Clinical signs and symptoms documented at the time of taking specimen and included fever, cough, sore throat, headache, rhinorrhea, fatigue, nausea, diarrhea, and abdominal pain. In addition, severity and suddenly onset of signs and symptoms were assessed.

Data were collected during five months follow-up. We conducted logistic regression model at 0.05 significance level using Stata 9.1 statistical software to assess the effects of various risk factors on H1N1 influenza infection. We considered adjusted odds ratios (OR) to assess covariates effects on influenza infection.

Results

In this study, 245 confirmed cases of H1N1 influenza patients were compared with 388 non-influenza patients with clinical signs and symptoms of respiratory tract infection (Table 1). Seven deaths occurred among 245 cases (Table 2). Accordingly, case fatality rate of influenza A infection was estimated to be 2.86%.

The effect of various potential risk factors on influenza infection was investigated using adjusted odds ratio (OR) (Table 3). Based on these findings, Compared to children and adolescents aged 1-19 yr, adjusted odds ratio estimate was 1.91 [95% CI: 1.06, 3.46] for adults aged 20-39 yr, 0.94 [95% CI: 0.37, 2.38] for adults aged 40-59 yr, and 0.34 [95% CI: 0.09, 1.37] for elders aged 60-79 yr. Although an apparent increased risk of influenza infection was seen among females [OR= 1.20; 95% CI: 0.70, 2.01], however, the association was not statistically significant (P= 0.514). On the other hand, the crude OR of influenza A infection for pregnant women compared with non-pregnant women was 2.91 [95% CI: 1.57, 5.42], the

adjusted OR estimate increased tremendously and reached 8.12 [95% CI: 3.11, 21.6]

We divided the participants into six groups according to their education level including illiterate, primary school, middle school, high school, and academic. There were no statistically significant differences between the chance of influenza infection either among the first three subgroups (illiterate, primary school, and middle school) or between the last two subgroups (high school and academic). Therefore, we combined the first and second homogenous subgroups and made two distinct subgroups including low educated individuals versus high-educated individuals respectively. Unexpectedly, adjusted OR estimate for high educated individuals was 1.84 [95% CI: 1.32, 2.86] compared to low educated individuals.

The adjusted OR estimate of influenza A infection was 2.11 [95% CI: 1.25, 3.57] for those individuals who mentioned a history of close contact with suspected influenza patients during the last week. In addition, unlike to our expectation, the risk of influenza infection was higher among non-smokers compared to smokers, although the association was not statistically significant (*P*= 0.095).

Based on these findings, the adjusted OR estimate was 1.22 [95% CI: 0.71, 2.10] for urban population compared to rural population (*P*= 0.461); 2.10 [95% CI: 0.95, 4.67] for people with positive history of chronic disease compared with general population (*P*= 0.068); and 1.01 [95% CI: 0.57, 1.79] for those who had a trip during the last week compared with those who did not have a trip (*P*= 0.972). In addition, there was not statistically difference between risk of influenza infection among recipients of seasonal influenza vaccine in comparison with those who had not received the vaccine (*P*= 0.739).

Compared with underweight individuals with body mass index (BMI) <20, adjusted OR estimate for individuals with normal body mass index (BMI= 20-25) was 2.15 [95% CI: 1.16, 3.98] and for overweight individuals (BMI> 25) was 1.40 [95% CI: 0.65, 3.05].

Clinical signs and symptoms, which were evaluated among cases and controls, included fever, sore throat, cough, headache, rhinorrhea, fatigue, nausea, diarrhea, and abdominal pain (Table 4 and Figure 1). There were no statistically significant differences in the proportion of clinical signs and symptoms between cases and controls. Although clinical signs and symptoms initiated more suddenly among cases (56%) than among controls (47%), but the difference was not statistically significant (*P*= 0.061).

About 30% of the cases and 25% of the controls were hospitalized. In addition, 9% of the cases and 4% of the controls were hospitalized in intensive care unit (ICU).

Table 1: Distribution of demographic characteristics and potential risk factors among cases and controls

Variable	Subgroup	Cases (%)	Controls (%)
Age (yr)	1-9	57 (23)	70 (18)
	10-19	59 (24)	123 (32)
	21-29	73 (30)	77 (20)
	31-39	24 (10)	40 (10)
	41-49	19 (8)	23 (6)
	51-59	5 (2)	16 (4)
	60-69	4 (2)	13 (3)
	70-79	3 (1)	17 (4)
	80-89	1 (0)	8 (2)
Sex	Male	107 (44)	184 (47)
	Female	138 (56)	204 (53)
Pregnancy	Yes	30 (22)	20 (10)
	No	108 (78)	184 (90)
Region	Rural	53(22)	120(31)
	Urban	186(76)	262(67)
	Unknown	6 (2)	6 (2)
Education	Illiterate	8 (3)	43 (11)
	Primary school	42 (17)	98 (25)
	Middle school	30 (12)	85 (22)
	High school	52 (21)	93 (24)
	Academic	31 (13)	33 (8)
	Child	41 (17)	33 (8)
	Unknown	41 (17)	3 (1)
Occupation	Child	26 (15)	28 (5)
	Student	51 (29)	136 (39)
	Collegian	10 (6)	9 (3)
	Soldier	1 (1)	2 (1)
	Housewife	49 (28)	94 (27)
	Teacher	3 (2)	4 (1)
	Employee	13 (7)	21 (6)
	Self-employment	20 (11)	55 (16)
	Retired	2 (1)	1 (1)
	Jobless	0 (0)	3 (1)
Chronic disease	Yes	20 (8)	45 (12)
	No	225 (92)	243 (88)
Smoking	Yes	6 (2)	32 (8)
	No	191 (78)	356 (92)
	Unknown	48 (20)	0 (0)
Severity	Outpatient	84 (34)	259 (67)
	Inpatient	41 (17)	92 (24)
	ICU	12 (5)	14 (3)
	Unknown	108 (44)	23 (6)
End outcome	Recovery	238 (97)	388 (100)
	Death	7 (3)	0 (0)

Table 2: Characteristics of the cases who died from influenza A (H1N1) infection

Variable	Subgroup	Number (%)
Age (yr)	0-9	1 (14)
	10-19	1 (14)
	20-29	1 (14)
	30-39	2 (28)
	≥60	2 (28)
Sex	Male	4 (57)
	Female	3 (43)
Pregnancy	Yes	0 (0)
	No	7 (100)
Region	Rural	2 (29)
	Urban	5 (71)
Smoking	Yes	1 (14)
	No	5 (71)
	Unknown	1 (14)
Vaccine	Yes	1 (14)
	No	6 (86)
Severity	Outpatient	2 (29)
	Inpatient	2 (29)
	ICU	3 (42)

Table 3: The effect of various potential risk factors on influenza A (H1N1) infection

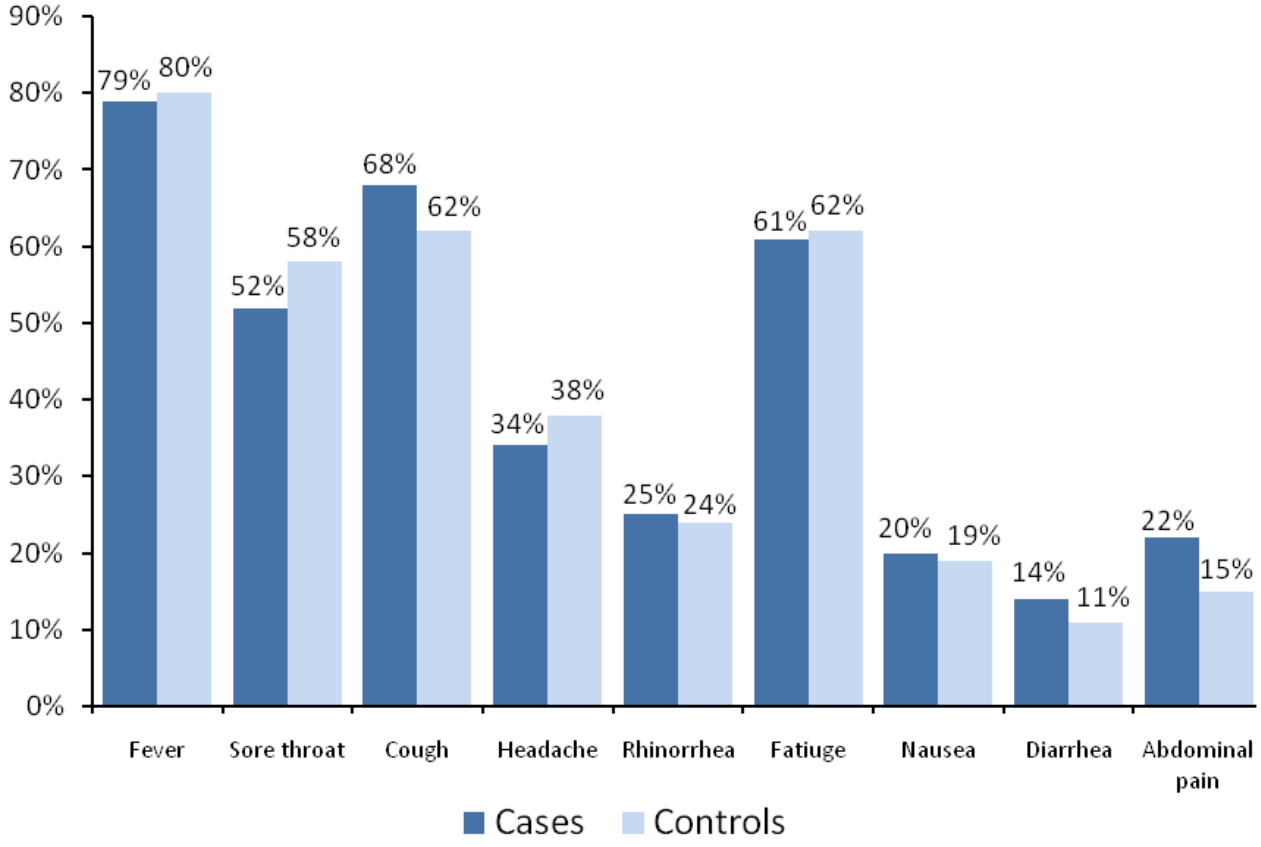
Variables	Adjusted OR [95% CI]	*P*
Age (20-39 years/1-19 years)	1.91 [1.06, 3.46]	**0.032**
Age (40-59 years/1-19 years)	0.94 [0.37, 2.38]	0.901
Age (60-79 years/1-19 years)	0.34 [0.09, 1.37]	0.130
Sex (female/male)	1.02 [0.61, 1.72]	0.938
Pregnancy	8.12 [3.11, 21.6]	**0.001**
Education[a] (high educated/low educated)	1.84 [1.32, 2.86]	**0.001**
Suspected contact (yes/no)	2.11 [1.25, 3.57]	**0.005**
Smoking (smokers/nonsmokers)	0.39 [0.13, 1.18]	0.095
Region (urban/rural)	1.22 [0.71, 2.10]	0.461
Chronic disease (yes/no)	2.10 [0.95, 4.67]	0.068
Trip (yes/no)	1.01 [0.57, 1.79]	0.972
Influenza vaccination (yes/no)	0.81 [0.23, 2.83]	0.739
BMI (normal weight/low weight)	2.15 [1.16, 3.98]	**0.015**
BMI (overweight/low weight)	1.40 [0.65, 3.05]	0.391

[a]: low education level included: illiterate, primary school, and middle school; high education level included high school and academic.

Table 4: Distribution of influenza A (H1N1) signs and symptoms among cases and controls

Clinical sign/Symptom	Proportion among		Difference
	Cases [95% CI]	Controls [95% CI]	*P*-value
Sudden onset	0.56 [0.47, 0.64]	0.47 [0.42, 0.52]	0.061
Fever	0.80 [0.73, 0.86]	0.81 [0.77, 0.85]	0.777
Sore throat	0.52 [0.44, 0.59]	0.59 [0.54, 0.64]	0.190
Cough	0.68 [0.61, 0.75]	0.63 [0.59, 0.68]	0.267
Headache	0.35 [0.28, 0.43]	0.41 [0.36, 0.45]	0.303
Rhinorrhea	0.24 [0.17, 0.31]	0.25 [0.21, 0.30]	0.833
Fatigue	0.62 [0.57, 0.68]	0.62 [0.57, 0.67]	0.870
Nausea	0.21 [0.15, 0.27]	0.20 [0.16, 0.24]	0.610
Diarrhea	0.15 [0.09, 0.20]	0.12 [0.09, 0.15]	0.253
Abdominal pain	0.22 [0.16, 0.29]	0.16 [0.12, 0.20]	0.078

Figure 1: Distribution of clinical signs and symptoms in among cases and controls



Discussion

According to the results of present study, pregnant women, urban population, high educated people, obese individuals, and those who mentioned close contact with suspected influenza patients were at higher risk of H1N1 influenza A infection.

Selection of controls from the patients with respiratory tract infection made them clinically similar to cases. However, because of logistic and financial limitation, it was not possible to select another control group from those non-patients clienteles who referred to health centers for other reasons.

In this study, pregnancy was detected as the strongest risk factor for influenza A infection. Accordingly, although pregnant women my be at higher risk if influenza infection [6], one reason that may explain such strong association is intensive health care that was conducted during early phase of pandemic H1N1 to detect pregnant women infected with influenza A. This practice introduced many pregnant women in the study participants so that pregnant women comprised 15.6% of the female participants. A relatively similar result was indicated in WHO report. This report stated that pregnant women had 13 times higher risk for hospitalizing due to influenza A in comparison with non-pregnant women [6].

Adults aged 40-59 yr and 60-79 yr had lower risk of influenza A infection in comparison with children and adolescents aged 1-19 yr. In other words, risk of influenza infection decreases with age. Nonetheless, adults aged 20-39 yr had higher risk of infection compared to children and adolescents. It may be attributed to greater proportion of high-risk pregnant women aged 20-39 yr among this age group.

We found an apparent inverse association between cigarette smoking and influenza infection so that the chance of influenza infection among non-smokers was nearly two times higher than among smokers. Although the association was not statistically significant, this may be the result of chance error due to sparse data in our study. As it was indicated in Table 1, only six out of 245 cases were

smokers. Such small number of data can lead to chance error.

As mentioned in the results section, adjusted OR estimates was statistically significant for high-educated individuals compared with low educated individuals. This increased risk of infection among high-educated individuals can be attributed to their occupation, which was not evaluated in this study. The occupation of the participants was not evaluated in this study because of sparse data due to diversity of the occupations among the participants.

We indicated that incidence of influenza infection was higher among individuals with positive history of chronic disease. However the association was not statistically significant (P= 0.127). This may also be due to sparse data, because only 20 out of 245 cases suffered from chronic diseases (Table 1).

A study conducted in California indicated that 35% of the cases had COPD, 17% were diabetic, and 17% had CHD [12]. Based on our findings, 11% of the cases suffered from at least one type of chronic diseases. Prevalence of chronic diseases among the cases reported by California study was much higher than our study. A reason that may explain this discrepancy is that the population of US is older than Iranian population. Thus, prevalence of chronic diseases is expected to be higher among US population.

A matched case-control study conducted in Mexico city revealed that none of the individuals in control group who had received seasonal influenza vaccine had not been infected with influenza A [13]. In our study, six individuals among cases group had already received seasonal influenza vaccine. This discrepancy may be due to sparse data in our study (only 6 out of 245 cases in our study received influenza vaccine).

Previous studies indicated that traveling had important role in increasing the incidence of influenza A infection [13]. In addition, the first report of confirmed cases of H1N1 2009 influenza in Iran confirmed this subject and revealed that 70% of the cases had either a history of traveling aboard during the last two weeks or having direct contact with someone who returned from abroad [11]. In this study, we indicated that there was not statistically significant positive relation between traveling abroad and influenza infection (P= 0.996). In addition, our findings revealed that the close contact to suspected influenza patients may increase nearly two times the chance of influenza infection.

One study that conducted in England estimated the overall case fatality rate of influenza infection to be 26 per 100,000. This estimate for children 5-14 yr old was reported to be the lowest (11 per 100000) and for elder over 65 yr old was estimated to be the highest (980 per 100000). The age mean of those who died due to influenza infection was 39 yr [14]. Another study that conducted in New York indicated that 62% of deaths were between 25-49 yr old with age mean 41.5 yr [15]. According to our findings, the age median of the cases was 35.57 yr which was rather younger than what reported in previous studies [14].

The similarity of clinical characteristics of cases and controls were because of selecting the control group from patients with respiratory tract infection who were clinically similar to cases at the enrolment in the study. We indicated that there is not a prominent clinical sign or symptom to distinct the cases from the controls. Two studies in Mexico and the US reported similar results and stated that there is no pathognomonic sign or symptom to distinguish influenza infection clinically from other respiratory tract infections [16].

Conclusion

According to the results of this study, we concluded that, children and adolescents, pregnant women, high-educated individuals, and those who had close contact with suspected influenza patients during the acute pandemic phase may be considered to be at higher risk of influenza A infection. In addition, there is no pathogonomonic sign or symptom to distinguish influenza infection clinically from other kinds of respiratory track infections. We also indicated that case fatality rate of influenza infection is estimated to be 2.86%. In addition, there is no pathogonomonic sign or symptom to distinguish influenza infection clinically from other kinds of respiratory track infections.

Acknowledgments

We would like to thank all health experts and health technicians of the Deputy of Health, Ha-

medan University of Medical Sciences who collaborated in data collection during the early phase of pandemic H1N1 influenza infection as well as Deputy of Research and Technology for financial support of this study. The authors declare that they have no conflicts of interest.

References

1. Word Health Organization. Swine influenza: frequentlyasked questions. *Weekly epidemiological record*. 2009;**84(18)**:149-60.
2. Hyemann DL. *Control of Communicable Disease*. Geneva: American Public Health Association; 2004.
3. Klontz KC, Hynes NA, Gunn RA, Welder HM, Harmon MW, Kendal AP. An outbreak of influenza A/TAIWAN/1/86 (H1N1) infections at a naval base and its association with airplane travel. *Am J Epidemiol*. 1989;**129(2)**:341-8.
4. Zambon M, Hays J, Webster A, Newman R, Keene O. Diagnosis of Influenza in the Community. *Arch Intern Med*. 2001;**161**:2116-22.
5. Dadras MN, Sorush M, Zahed-Anaraki S. *Guidelines for Surveillance & Control of Influenza*. Tehran: Ministry of Health and Medical Education 2009.
6. BMJ. Critical illness due to2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study. *BMJ*. 2010; 340: c1279.
7. Hatami H. *Emerging & Reemerging of Disease:Emerging & Pandemic Influenza A(H1N1) in 2009*. Comprihensive Textbook of Public Health. Tehran: Ministry of Health and Medical Education 2009.
8. Garske T, Legrand J, Donnelly CA, Ward H, Cauchemez S, Fraser C, et al. Assessing the severity of the novel influenza A/H1N1 pandemic. *BMJ*. 2009;**339**:b2840.
9. Chawla R, Sharma RK, Bhardwaj JR. influenza A (H1N1) outbreak and challenges for pharmacotherapy. *Indian J Physiol Pharmacol*. 2009;**53(2)**:113-26.
10. Cao B, Li XW, Mao Y, Wang J, Lu HZ, Chen YS, et al. Clinical Features of the Initial Cases of 2009 Pandemic Influenza A (H1N1) Virus Infection in China. *N Engl J Med*. 2009;**361**:1-10.
11. Gooya MM, Soroush M, Mokhtari-Azad T, Haghdoost AA, Hemati P, Moghadami M, et al. Influenza A (H1N1) Pandemic in Iran: Report of First Confirmed Cases from June to November 2009. *Arch Iran Med*. 2010;**13(2)**:91-8.
12. Cordova-Villalobos JA, Sarti E, Arzoz-Padres J, Manuell-Lee G, Mendez JR, Kuri-Morales P. The influenza A(H1N1) epidemic in Mexico. Lessons learned. *Health Res Policy Syst*. 2009;**7(21)**:1-7.
13. Garcia-Garcia L, Valdespino-Gómez JL, Lazcano-Ponce E, Jimenez-Corona A, Higuera-Iglesias A, Cruz-Hervert P, et al. Partial protection of seasonal trivalent inactivated vaccine against novel pandemic influenza A/H1N1 2009: case-control study in Mexico City. *BMJ*. 2009;**339**: b3928.
14. Donaldson LJ, Rutte P, Ellis BM, Greaves FEC, Mytton TO, Pebody RG, et al. Mortality frompandemic A/H1N1 2009 influenza in England: public health surveillance study. *BMJ*. 2009;**339**: b5213.
15. Gill JR, Sheng ZM, Ely SF, Guinee DG, Beasley MB, Suh J, et al. Pulmonary Pathologic Findings of Fatal 2009 Pandemic Influenza A/H1N1 Viral Infections. *Arch Pathol Lab Med*. 2010;**134**:235-43.
16. Chuang SK, Wong C, Li A, Li A, Li A, Ma E, et al. Update on Human Swine Influenza. *Communicable Diseases Watch*. 2009;**6(10)**:37-40.