JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Different features of influenza A H1N1pdm09 virus infection among adults in 2009/10 and 2010/11

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Abstract

Introduction: Influenza A H1N1pdm09 virus infection causes an epidemiologically and clinically severe disease mostly characterized by pneumonia, resulting in a high mortality rate. The purpose of this study was to investigate and compare epidemiological and clinical characteristics of influenza A H1N1pdm09 virus infection in patients hospitalized during the pandemic (2009/10) and post-pandemic seasons (2010/11).

Methodology: The data of patients with laboratory-confirmed influenza A H1N1pdm09 virus infection hospitalized and treated at the University Hospital for Infectious Diseases Dr. Fran Mihaljevic in Zagreb, Croatia in the first two seasons of appearance were analyzed.

Results: Compared to the pandemic season, in the post-pandemic season, patients were hospitalized longer, had higher values of inflammatory parameters, and were more often treated with antibiotics. The total number of risk factors in patients did not vary significantly between the two seasons. In the pandemic season, a significantly higher number of obese patients and patients with chronic lung disease was observed, whereas in the post-pandemic season, a statistically significant number of patients presented with symptoms of chronic cardiac and neuromuscular diseases. Primary viral pneumonia was frequently registered in younger adults during the pandemic season, whereas in the post-pandemic season, there were more cases of bacterial pneumonia.

Conclusions: During the pandemic season, the influenza A H1N1pdm09 virus infection caused a severe disease with rare bacterial complications, especially in adult patients. The common characteristics of the influenza A H1N1pdm09 virus were lost in the post-pandemic season, assuming the shape and characteristics of the seasonal influenza A virus.

Key words: influenza A virus; H1N1 subtype; risk factors; complications; mortality.

J Infect Dev Ctries 2016; 10(2):155-162. doi:10.3855/jidc.6040

(Received 08 October 2014 – Accepted 22 June 2015)

Introduction

In March 2009, a new type of influenza virus was diagnosed in infected persons in Mexico and California, causing a new pandemic in the 21st century. Forty years after the last recorded influenza pandemic, a completely new influenza A virus, so-called swine flu, was recombined among as many as four types of influenza A viruses (two swine flu, one bird flu, and one human flu strain) in an organism of a swine, representing a novel influenza A virus [1-3].

The pandemic season is characterized by an atypical off-seasonal occurrence and rapid spread, lasting several months and taking place in several waves. The size of the affected population and the clinical presentation are significantly different compared to seasonal influenza [3,4]. The most important difference with respect to the seasonal flu is the higher morbidity and the greater number of complications, including fatal outcomes, in younger patients infected with influenza A H1N1pdm09 virus [4,5]. In 2009, persons over the age of 60 had a lower morbidity rate due to a degree of pre-existing immunity, *i.e.,* the presence of antibodies highly compatible with the pandemic virus antigens, since the majority of the elderly population had already come into contact with the original form of the seasonal influenza A H1N1pdm09 virus circulating until 1957. The protective antibodies in the 18–60 age group of subjects were found in lower percentages [6-8].

Most patients infected by the pandemic virus develop a mild form of the disease, but occasionally the virus can cause severe and fatal forms of the disease, affecting and eventually leading to the collapse of function of various organ systems. In addition to respiratory system complications, a pandemic virus

causes complications in other organ systems as well, such as a range of neurological syndromes, damage to the myocardium, kidneys, liver, joints, *etc*. Very rarely, it also induces the development of secondary bacterial infections [6,9,10].

Two separate viruses, which cause the pandemic and seasonal influenza, respectively, have a similar clinical presentation, and only by laboratory testing we can determine the exact causal virus [3,11]. In September 2009, the World Health Organization (WHO) approved the only valid test for diagnosing influenza, known as real-time reverse-transcriptase polymerase chain reaction (RT-PCR), which has superior sensitivity and allows the differentiation of sub-types and phylogenetic analyses [12].

The influenza A H1N1pdm09 virus is especially associated with a higher number of primary viral pneumonias in younger patients, with an early onset and a very rapid progression, occasionally accompanied by the development of acute respiratory distress syndrome (ARDS) and secondary pneumonias as result of bacterial super-infections [13,4]. Also, during an influenza pandemic, it has been known that patients (especially children) can suffer a higher number of neurological complications [14,15]. In this study, we attempted to differentiate either characteristics of clinical symptoms and epidemiological features or their consequences in patients who presented with influenza A H1N1pdm09 virus infection during the pandemic season (2009/10) or post-pandemic season (2010/11).

Methodology

Patients

Based on the prospective monitoring of numerous parameters at the University Hospital for Infectious Diseases Dr. Fran Mihaljevic (UHID) in Zagreb, Croatia, demographic, epidemiological, clinical, and basic laboratory indicators of 105 adult patients hospitalized with the confirmed influenza A H1N1pdm09 virus infection diagnosis in the period between 1 July 2009 and 31 March 2010 (pandemic season) were retrospectively analyzed. The same set of data was collected and analyzed for 123 adult patients hospitalized due to influenza A H1N1pdm09 virus infection in the subsequent season, from 15 November 2010 to 31 March 2011 (post-pandemic season). The patients' data were gathered from medical records. The patients were stratified according to their age, sex, date of admission to the hospital, duration of the disease preceding hospitalization (in days), and the duration of hospitalization (in days). Symptoms of the disease, including their severity, complications and the final outcome, risk factors, basic laboratory results (together with the chest radiographs), and applied treatment were analyzed. Ethical approval was obtained from the ethical committee at the University Hospital for Infectious Diseases Dr. Fran Mihaljevic in Zagreb.

Classification of the severity of the disease

The severity of the disease was divided into four categories (internal coding) according to the clinical presentation, accompanying chronic diseases, complications, and final outcome: (1) mild (as a rule, without complications and chronic diseases); (2) moderate (complications and/or aggravation of the chronic diseases); (3) severe (treated in the intensive care unit [ICU]); and (4) very severe (fatal outcome). Risk factors and complications due to influenza A H1N1pdm09 were defined according to the International Classification of Diseases (ICD)-10 disease classification and the internal coding of UHID. Due to its importance, diabetes was classified as an exceptional risk factor. The term encephalopathy was used generally for all disorders of consciousness, including primary and secondary affection of the central nervous system.

Laboratory testing

The clinical criteria for diagnosing of influenza were presenting symptoms (high fever, headache, fatigue, muscle and joint aches, cough), together with the indicative (highest recorded values) laboratory tests (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], leukocyte count [L]), and epidemiological data. The laboratory testing with basic biochemical analysis (blood glucose level, urea, creatinine, liver enzymes – AST, ALT, GGT, LDH) was performed for all patients, and creatine kinase (CK) was analyzed for half of the patients, using automated biochemistry analyzers Olympus AU640 and/or Olympus AU400 (Hamburg, Germany). All patients had chest radiographs taken, and 85% of them had electrocardiography (ECG) done. Any deviation from the normal electrocardiogram, with or without pharmacological treatment, was considered as a sign of pathological ECG.

Respiratory samples (pharyngeal swab and/or bronchoalveolar aspirate) were analyzed and tested using RT-PCR in the Croatian National Influenza Centre, which exchanges information with the Influenza Centre in London [12].

Statistical analysis

Statistical analysis included the Kolmogorov-Smirnov test for testing the equality of the distribution of continuous variables. To describe their grouping and dispersion, a median and interquartile range was used for the distribution of data that deviated significantly from the normal. The two asymmetrically distributed independent variables were compared using the Mann-Whitney U test. To analyze the difference in proportions of the nominal and ordinal variables, the Chi-squared test (χ^2) was used, and in the lack of expected frequency, the Fisher's exact test was additionally applied. The probability of error was set at $\alpha < 0.05$, and the differences between groups were accepted as statistically relevant for $p < 0.05$. The statistical analysis was performed using SPSS software version 17.0 and Microsoft Excel version 11.

Results

In the pandemic season, the influenza A H1N1pdm09 virus infection was confirmed by RT-PCR in 105 adult patients, whereas in the post-pandemic season, it was confirmed in 123 adult patients. In the pandemic season, 56 males (53.3%), and 49 females (46.7%) were studied, whereas in post-pandemic season, 75 (61.0%) males and 48 (39.0%) females suffering from influenza A H1N1pdm09 virus infection were studied. Other epidemiological characteristics of pandemic influenza A H1N1pdm09 virus infection between two observed groups of patients are presented in Table 1. In the pandemic season, 62.1% of the total number of hospitalized and etiologically confirmed subjects were adults, and in the post-pandemic season, adults accounted for 73.6% of all hospitalized and etiologically confirmed patients. Although a slightly lower number of elderly patients (> 65 years old) was studied in the pandemic season (14 patients or 13.3%) as compared to the post-pandemic season (26 patients or 21.1%), those differences were not statistically significant (χ^2 test = 0.659; df = 1; p = 0.416. Distribution of age groups is presented in Table 2.

The average duration of illness prior to hospitalization was 4.0 ± 4.0 days (range 1–12 days) in the pandemic, compared to 3.0 ± 3.0 days (range 1–21 days) in the post-pandemic season (Mann-Whitney U = 5,743.00; p = 0.145). The average of hospitalization lasted 8.0 ± 7.0 days (range 2–119 days) in the pandemic season, while in the post-pandemic season, it was 9.0 ± 6.0 days (range 1–98 days) (Mann-Whitney U = 5,778.00; p = 0.203). The average highest body temperature in patients with pandemic influenza at admission was 39.0°C ± 1.2°C (range 37.0°C –41.2°C),

Table 1. Epidemiological features of influenza A H1N1pdm09 virus infection during pandemic and post-pandemic seasons.

Feature	Pandemic season	Post-pandemic season
Outbreak	July 2009	December 2010
Duration of the epidemic	9 months	4 months
Peak of the epidemic	November 2009	January 2011
Number of examined/hospitalized	3,856/562	2,883/458
Hospitalized with confirmed infection	169	167
Adults: n (%)	105 (62.1)	123 (73.6)
Male: n (%)	56 (53.3)	75 (61.0)
Female: n (%)	49 (46.7)	48 (39.0)
Average age (years)	42.0 ± 27.0	49.0 ± 30.0
Most common complication	Primary viral pneumonia	Bacterial pneumonia
Died with confirmed infection: n (%)	4 (3.8)	8 (6.5)
Average age of deceased (years)	35.3 ± 7.8	44.7 ± 16.3

Table 2. Age distribution of patients infected with influenza A H1N1pdm09 virus infection during pandemic and post-pandemic seasons.

Age group	Pandemic season n (%)	Post-pandemic season n (%)
18–29	21 (20.0)	23 (18.7)
30–39	19 (18.1)	20 (16.3)
40–49	25 (23.8)	19 (15.4)
50–59	16 (15.2)	27 (22.0)
60–64	10 (9.5)	8 (6.5)
> 65	14 (13.3)	26 (21.1)
Total	**105 (100)**	**123 (100)**

whereas in those with post-pandemic influenza, it was 39.0°C ± 0.9°C (range 37.5°C –40.5°C) (Mann-Whitney U = 5,990.50, p = 0.553). No statistically significant differences in ESR, L, CRP, and CK were found between the pandemic and post-pandemic groups of patients (Table 3). Furthermore, liver damage was also not observed as a statistically significant difference among these groups, but statistically significant differences in ECG changes were found. ECG changes were observed in 59/105 (56.2%) patients hospitalized in the pandemic season as compared to 49/123 (39.8%) patients in the post-pandemic season (χ^2 test = 5.018; df = 1; $p < 0.025$). In the pandemic season, 94/105 (89.5%) patients were treated with oseltamivir, while in the post-pandemic season, 107/123 (86.9%) patients were treated with this antiviral drug (χ^2 test = 1.622; df = 1; p = 0.203). In the pandemic season, 79/105 (75.2%) patients were treated with antibiotics, as compared to 97/123 (78.9%) patients in the post-pandemic season (χ^2 test = 0.422; df = 1; p = 0.516). In the pandemic season, 18/105 patients (17.1%) were admitted to the ICU, whereas in the post-pandemic season, a statistically significant number of patients was admitted to the ICU – 36/123 patients (29.3%) (χ^2 test = 4.608; df = 1; $p < 0.031$). The average age of patients admitted to the ICU in the pandemic season was 29.7 ± 17.0, while in the post-pandemic season, it was 48.8 ± 20.0, and although a trend of differences was present, this difference was not statistically significant (χ^2 test = 1.570; df = 1; p = 0.209). Four patients (3.8%) (three males and one female) died in the pandemic season, whereas in the post-pandemic season, eight patients (6.5%) (six males and two females) died (χ^2 test = 2.068; df = 1; p = 0.153) (Table 3). Among all groups of patients, the moderate form of the disease dominated, and no statistically significant difference regarding the severity of illness between patients in both seasons was found (Table 4).

In the pandemic season, 68/105 (64.8%) patients had 188 risk factors (2.7 risk factors per each patient), whereas 76/123 (61.8%) patients in the post-pandemic season had 205 risk factors (2.7 risk factors per patient). Statistically significant differences among risk factors, when comparing patients in the pandemic to those in the

Table 3. Clinical and laboratory features of patients with influenza A H1N1pdm09 virus infection during pandemic and post-pandemic seasons.

Clinical features	**Pandemic season**	**Post-pandemic season**	**P (Mann-Whitney U)**
	Median [interquartile range]	**Median [interquartile range]**	
Average age (years)	42 [27]	49 [30]	0.170
Duration of illness prior hospitalization (days)	4 [4]	3 [3]	0.145
Duration of hospitalization (days)	8 [7]	9 [6]	0.203
Average max temperature (ºC)	39 [1.2]	39 [0.9]	0.553
ESR (mm/h)	40 [42]	32 [46]	0.403
L ($x10^9$/L)	7.2 [4.5]	8.7 [5.3]	0.087
CRP (mg/L)	63.7 [79]	79.1 [120.7]	0.200
CK (U/L)	191 [492]	161 [256]	0.508
Laboratory features	**Pandemic season**	**Post-pandemic season**	**P (χ^2)**
	n (%)	**n (%)**	
Liver damage	38 (36.2)	40 (32.5)	0.560
Abnormal ECG	59 (56.2)	49 (39.8)	0.025
Patients treated with antivirals	94 (89.5)	107 (86.9)	0.203
Patients treated with antibiotics	79 (75.2)	97 (78.9)	0.516
Patients treated in ICU	18 (17.1)	36 (29.3)	0.031
Died	4 (3.8)	8 (6.5)	0.153

ESR: erythrocyte sedimentation rate; L: leukocyte count; CRP: C-reactive protein; CK: creatine kinase; ECG: electrocardiography; ICU: intensive care unit

Table 4. Illness severity of patients with influenza A H1N1pdm09 virus infection during pandemic and post-pandemic seasons.

Clinical form of disease	**Pandemic season**	**Post-pandemic season**	**P (χ^2)**
	n (%)	**n (%)**	
Mild	6 (5.7)	13 (10.6)	0.186
Moderate	73 (69.5)	88 (71.5)	0.797
Severe	22 (21.0)	6 (13.0)	0.075
Very severe	4 (3.8)	6 (4.9)	0.695
Total	**105 (100)**	**123 (100)**	

post-pandemic season, were chronic lung disease such as asthma (23/105; 21.9%), chronic obstructive pulmonary disease (COPD) (23/105; 21.9%), and obesity (10/105; 9.5%) patients. Contrary to the post-pandemic season, chronic cardiac disease was a significant risk factor in 52/123 (42.3%) patients, and neuromuscular diseases were present in 17 (13.8%) patients. The third-most common risk factor, although it bore no statistical significance, was immunodeficiency, observed in 24 patients (19.5%), and diabetes mellitus, observed in 10 (8.1%) patients (Table 5).

The most common and statistically significant risk factors in adult patients < 65 years of age during the pandemic and post-pandemic seasons were asthma and COPD (Suppl. Table 1), whereas in the post-pandemic season, chronic cardiac disease was observed as a significant risk factor in elderly patients (> 65 years of age) (Suppl. Table 2.)

In both seasons, approximately the same number of complications of influenza A H1N1pdm09 virus infection was observed. Accordingly, 82/105 (78.1%) patients in the pandemic season had 179 complications, whereas 93/123 (75.6%) patients in the post-pandemic season presented with 188 complications; these differences were not statistically significant (χ^2 test = 0.196; df = 1; p < 0.657). In the pandemic season, viral pneumonia was observed in 45/105 (42.8%) patients, as

Table 5. Risk factors in patients with influenza A H1N1pdm09 virus infection during pandemic and post-pandemic seasons.

Risk factors	Pandemic season	Post-pandemic season	P (χ^2)
	n (%)	n (%)	
Chronic cardiac disease	31 (29.5)	52 (42.3)	0.046
Asthma	23 (21.9)	5 (4.1)	0.001
COPD	23 (21.9)	13 (10.6)	0.019
Hypertension	21 (20.0)	32 (26.0)	0.283
Immunological disease	11 (10.4)	24 (19.5)	0.059
Chronic kidney disease	13 (12.4)	10 (8.1)	0.287
Malignant disease	14 (13.3)	11 (8.9)	0.290
Neuromuscular disease	5 (4.7)	17 (13.8)	0.020
Diabetes mellitus	11 (10.4)	10 (8.1)	0.540
Obesity	10 (9.5)	4 (3.3)	0.049
Chronic liver disease	11 (10.4)	8 (6.5)	0.279
Congenital deformities	2 (1.9)	0	0.123
Chronic alcoholism	6 (5.7)	12 (9.7)	0.259
Pregnancy	4 (3.8)	1 (0.8)	0.123
Residents of institutions	3 (2.8)	6 (4.8)	0.434
Total	**188**	**205**	

COPD: chronic obstructive pulmonary disease.

Table 6. Distribution of complications due to influenza A H1N1pdm09 virus infection during pandemic and post-pandemic seasons.

Complications	Pandemic season	Post-pandemic season	P (χ^2)
	n (%)	n (%)	
Primary viral pneumonia	45 (42.8)	25 (20.3)	0.001
Bacterial pneumonia	21 (20.0)	34 (27.6)	0.178
Liver damage	38 (36.2)	41 (33.3)	0.651
Myositis	11 (10.5)	23 (18.7)	0.082
Encephalopathy	11 (10.5)	3 (2.4)	0.011
Acute bronchitis	7 (6.7)	3 (2.4)	0.120
Kidney damage	11 (10.5)	12 (9.8)	0.858
ARDS	10 (9.5)	8 (6.5)	0.399
Sinusitis	4 (3.8)	2 (1.6)	0.304
Multi-organ failure	4 (3.8)	7 (5.7)	0.508
Otitis media	2 (1.9)	0	0.124
Myocarditis	2 (1.9)	2 (1.6)	0.871
Other complications	13 (12.4)	28 (22.8)	0.041
Total	**179**	**188**	

ARDS: acute respiratory distress syndrome

compared to 25/123 (20.3%) patients in the post-pandemic season, and this difference was statistically significant (χ^2 test = 8.342; df = 1; $p < 0.001$). Of note is that encephalopathy was observed in 11 (10.5%) patients in the pandemic season, which was significantly higher compared to 3 (2.4%) patients in the post-pandemic season ($p = 0.011$). In the pandemic season, 13 (12.4%) patients had other complications, whereas 28 (22.8%) patients in the post-pandemic season had other complications; this difference was statistically significant ($\chi 2$ test = 28.342, df = 12, $p < 0.005$) (Table 6.).

Discussion

During the pandemic season, patients were, in most cases, admitted to a hospital on the fourth day of illness following the onset of the disease, and the average length of stay in the hospital was eight days, whereas in the post-pandemic season, hospitalization commenced on the third day of illness and lasted for nine days on average. The longer length of stay in the hospital could be explained by the greater number of older hospitalized patients, resulting in more bacterial complications.

The post-pandemic season was characterized by higher recorded values of the inflammation parameters (L and CRP) due to a greater number of bacterial complications, resulting in a more frequent use of antibiotics, more frequent ICU admissions, and a higher mortality rate. Higher values of CK, liver damage, as well as short-term ECG changes were more often registered in the pandemic season due to a stronger immune response of the body to the influenza A H1N1pdm09 virus. According to the results of the study conducted by Viasus *et al*., H1N1pmd09-positive patients hospitalized during the post-pandemic season were considerably older than those hospitalized during the pandemic season [16]. In our study, patients were more often treated with antiviral therapy in the pandemic season, and with antibiotics and antivirals in the post-pandemic season, which corresponds to the data reported previously [16,17]. Risk factors were more often registered in the pandemic season. However, both seasons had a greater number of patients with two or more risk factors as opposed to those with only one. Compared to the pandemic season, during the post-pandemic season, patients were older by an average of seven years, indicating that the patient's age is an important risk factor for the severity of the disease, *i.e.,* grounds for hospitalization during the post-pandemic season. According to some European reports and our own study, patients with chronic pulmonary and cardiac diseases, obese people, and pregnant women form the highest-risk group for contracting the pandemic virus [4,17].

The most important risk factors in the pandemic season were chronic pulmonary diseases asthma and COPD, followed by the chronic cardiac diseases that were also reported in other similar studies, where the frequencies varied from 5% to more than 80% [18-20,11]. According to reports from the United States and United Kingdom, nearly half of the hospitalized adult patients with COPD acquired the severe form of the disease [19-21]. In the post-pandemic season, the most frequent risk factors in our patients were chronic cardiac diseases and hypertension. Obesity, chronic liver and kidney diseases, and pregnancy were occurred more frequently in the pandemic season. According to North American and some European reports, pathological obesity and pregnancy are also important risk factors; however, in our patients, these factors did not rank particularly high [6,17,19,20,22].

In the first two influenza seasons, we recorded similar distribution of complications in our patients. In our study, various complications were observed, which were altogether more frequent in the post-pandemic season. Due to a greater number of hospitalized elderly patients, complications were more frequent and more severe in the post-pandemic season, which leads us to conclude that the virus had higher potential to cause complications in persons with risk factors. A special characteristic of the influenza A H1N1pdm09 virus was its correlation with the great number of primary viral pneumonias in younger adult patients, occurring at the very onset of the disease [4,11,17]. Similarly, in our study, during the pandemic season, primary viral pneumonia was recorded twice as often as secondary bacterial pneumonia, whereas during the post-pandemic season, secondary bacterial pneumonia became a more frequent complication as the age of the affected patients increased.

ARDS was a complication often accompanying viral pneumonia and was the key cause of respiratory insufficiency requiring the use of mechanical ventilation [4,17,22,23]. In addition to primary viral pneumonia, our study showed a higher prevalence of encephalopathy cases in the pandemic season and other bacterial complications in the post-pandemic season.

However, our study showed a relatively low mortality rate compared to previous studies (3.8% versus 6.5%) among patients in these two seasons [23-25]. Moreover, noteworthy is the occurrence of relatively frequent severe forms of the disease,

including those with fatal outcomes in previously healthy young individuals.

Some reports suggest that 20%–45% of the deceased patients were younger than 50 years of age and had no previously recorded risk factors [4,19-21,24,26]. In our study, the average age of deceased patients during the pandemic season was 35.3, and most of these patients had some risk factors. Conversely, the average age of the deceased in the post-pandemic season was 44.7 (9.4 years older, on average), and these patients had more risk factors (data not shown). The majority of the deceased in both seasons suffered from viral pneumonia and, consequently, ARDS. Although the post-pandemic season was characterized by a greater number of secondary bacterial pneumonias, in our study, they were not a common cause of death as previously described [4,7,17]. The relatively low mortality presented in our study, despite the high number of patients with severe forms of the disease accompanied by pneumonia, could be connected to the antiviral drug treatment of patients, as confirmed by other authors, which stresses the importance of early dispensing of antiviral drugs [26]. Furthermore, in our study, the decreased number of viral pneumonia cases in the second season could not be explained by vaccination against influenza A (data not shown) or treatment by oseltamivir because we did not find any difference regarding vaccination rate or oseltamivir treatment in both seasons.

Conclusions

Altogether, our study showed that influenza A H1N1pdm09 virus infection in the post-pandemic season had similar clinical manifestations and risk factors as seasonal flu.

Authors' contributions

SG, SS, ECT, JN, JA, and IK analyzed results. SG, SS, and JA wrote the manuscript. IK and JA supervised the writing of the manuscript.

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Conflict of interests: No conflict of interests is declared.

Annex 1: Supplementary Items

Supplementary Table 1. Distribution of risk factors in patients (< 65 years) with influenza A H1N1pdm09 virus infection during pandemic and post-pandemic seasons.

Risk factors	Pandemic season	Post-pandemic season	P (χ^2)
	n (%)	n (%)	
Chronic cardiac disease	25 (23.8)	28 (22.8)	0.531
Asthma	18 (17.1)	4 (3.3)	0.001
COPD	17 (16.2)	5 (4.6)	0.005
Hypertension	20 (19.0)	30 (24.4)	0.782
Chronic kidney disease	11 (10.4)	24 (19.5)	0.243
Malignant disease	9 (8.6)	7 (5.7)	0.300
Neuromuscular disease	9 (8.6)	8 (6.5)	0.410
Diabetes mellitus	4 (3.8)	15 (12.2)	0.079
Obesity	8 (7.6)	7 (5.7)	0.430
Chronic alcoholism	5 (4.7)	0	
Residents of institutions	11 (10.4)	8 (6.5)	0.218
Total	**150**	**151**	

COPD: chronic obstructive pulmonary disease.

Supplementary Table 2. Distribution of risk factors in patients (> 65 years) with influenza A H1N1pdm09 virus infection during pandemic and post-pandemic seasons.

Risk factors	Pandemic season	Post-pandemic season	P (χ^2)
	n (%)	n (%)	
Chronic cardiac disease	6 (5.7)	24 (19.5)	0.021
Asthma	5 (4.7)	1 (0.8)	0.067
COPD	6 (5.7)	8 (6.5)	0.964
Hypertension	1 (0.8)	2 (1.6)	0.693
Chronic kidney disease	4 (3.8)	3 (2.4)	0.453
Malignant disease	5 (4.7)	3 (2.4)	0.289
Neuromuscular disease	1 (0.8)	2 (1.6)	0.693
Diabetes mellitus	3 (2.9)	3 (2.4)	0.692
Obesity	5 (4.7)	4 (3.3)	0.479
Chronic alcoholism	2 (1.6)	2 (1.6)	0.887
Residents of institutions	2 (1.6)	2 (1.6)	0.887
Total	**38 (36.2)**	**54 (43.9)**	

COPD: chronic obstructive pulmonary disease.