Original Article

A new wave of influenza A: Description of a cohort of patients in 2013 from a general hospital in Buenos Aires, Argentina

Adrian Ceccato, Alejandra Gonzalez, Elsa Oshiro, Liliana Aguilar[1], Luciana Ferrando, Maria Sol Sigismondo, Silvina Delarrosa, Jorge Andrada, Graciela Cabral[2], Marcelo Villaverde

Department of Medicine, Hospital Nacional Prof. Alejandro Posadas, [1]Depatment of Intensive Care, Intensive Care Unit, Hospital Nacional Prof. Alejandro Posadas, [2]Department of Diagnosis, Virology Laboratory, Hospital Nacional Prof. Alejandro Posadas, El Palomar, Buenos Aires, Argentina

ABSTRACT

Background and Objectives: The first pandemic of the 21st century was caused in 2009 by influenza A(H1N1). An increase in the number of cases caused by influenza A(H1N1) pdm09 was observed in 2013. The aim was to describe the number of influenza cases observed during 2013 in a general hospital of Argentina. **Materials and Methods:** A prospective, observational cohort of adult patients with influenza was confirmed by reverse transcription-polymerase chain reaction. **Results:** We analyzed 428 patients between epidemiological weeks 21 and 31, resulting in 134 (31%) patients who were positive for influenza A. Of these patients, 78% were infected with H1N1 (2009), 17% with H3, and 5% with a subtype that could not be determined. The mean patients' age was 53 ± 18 years. Eighty-three percent of patients had not been vaccinated, and no differences between vaccinated and nonvaccinated patients were observed. Seventy-five percent of patients had underlying conditions. Twenty-eight patients were treated as outpatients, and 86 required admission to the general ward, and 20 to the Intensive Care Unit. A significant difference in patient's age was observed between individuals infected with influenza H1N1 and those infected with other non-H1N1 subtypes. The mortality rate was 11%. In the multivariable analysis, mechanical ventilation (odds ratio: 27.66; 95% confidence interval [CI]: 6.43–119; $P < 0.001$) and cancer (odds ratio: 6.81; 95% CI: 1.25–37.13; $P = 0.02$) were predictors of mortality. **Conclusions:** We report a new wave of influenza A(H1N1). Most patients had underlying conditions, and a significant number of patients had not been vaccinated. Mortality was high; the only predictors of mortality were cancer and the need for mechanical ventilation.

Key words: Influenza, pneumonia, vaccine, viral infection

Address for correspondence:
Dr. Adrian Ceccato, Avenue Marconi and Illia Street. s/n, El Palomar 1684, Buenos Aires, Argentina.
E-mail: adrianceccato@gmail.com

Access this article online	
Quick Response Code:	Website: www.caijournal.com
	DOI: 10.4103/2225-6482.198497

How to cite this article: Ceccato A, Gonzalez A, Oshiro E, Aguilar L, Ferrando L, Sigismondo MS, *et al*. A new wave of influenza A: Description of a cohort of patients in 2013 from a general hospital in Buenos Aires, Argentina. Community Acquir Infect 2016;3:123-8.

INTRODUCTION

In April 2009, a novel swine-derived influenza virus was reported.[1] This virus was responsible for the first pandemic of the 21st century and caused influenza-like illness, pneumonia, acute respiratory distress syndrome, and death predominantly in young people.[2] Some conditions, such as pregnancy[3] or obesity, were associated with poor prognoses including increased medical complications and mortality.

The emergence of a virulent strain of influenza through antigenic shift and drift remains a significant threat to public health. In 2009, there were 1,390,566 cases of influenza-like illness in Argentina; of these cases, 14,034 were admitted to the hospital and 617 patients died.[4]

The effectiveness of nonadjuvant influenza A(H1N1) pdm09 vaccines in preventing disease is controversial, and these vaccines may prevent 50–63% of hospitalizations.[5,6] Vaccines can provide moderate protection against virologically confirmed influenza, but such protection is greatly reduced or absent in some seasons. Evidence for vaccine-mediated protection in adults aged 65 years or older is lacking.[7]

After the 2009 pandemic, additional cases of influenza A(H1N1) pdm09 infection were observed, but this virus was not the predominant agent of influenza infection. Some studies described the events that transpired during the first postpandemic season (2010–2011).[8,9] In addition, increased mortality and rates of infection among elderly patients with comorbidities have been observed during the post-2009 influenza infection seasons.

In the late fall of 2013, the appearance of influenza cases similar to those observed during the 2009 pandemic alerted the public health community.

According to data reported by the Ministry of Health in our country, a sustained increase in reported cases of influenza was observed beginning at epidemiological week (EW) 19 and peaking at EW 27. Between EWs 22 and 32, 5180 cases of influenza were reported for a total of 5600 cases in that year. From those cases, 5052 corresponded to Type A influenza, of which 2675 were identified as H1N1pdm and 596 as seasonal H3.[10]

The aim of this study was to describe the cases of influenza that occurred during 2013 in Prof. Alejandro Posadas Hospital.

MATERIALS AND METHODS

We conducted a prospective, observational study of a cohort of adult patients who tested positive for influenza infection by real-time reverse transcription-polymerase chain reaction (RT-PCR) analysis of nasopharyngeal swabs. Our institution is a referral center for acute respiratory diseases with 500 beds and a patient territory including 4 million people.

We performed nasopharyngeal swabs for influenza for all patients with influenza-like illness or pneumonia who may have also had associated conditions such as obesity (body mass index >30), pregnancy, cardiovascular disease, chronic obstructive pulmonary disease (COPD), asthma, immune compromise, or age >65 years. We described cases that occurred between EWs 21 and 31.

Age, sex, underlying conditions, previous vaccination, clinical conditions, and outcomes (length of stay, Intensive Care unit (ICU) requirements, and mortality) were recorded.

Informed consent was obtained from patients or their family members.

The initial management was decided according to the algorithm developed in 2009 by Sala *et al*.[11] based on oxygen saturation (SO_2) and the presence of crackles. Hospital department admission and antibiotic treatment were determined according to the recommendations of the Argentine pneumonia guidelines.[12] All patients received oseltamivir (150 mg/day) until they tested negative for influenza infection by nasopharyngeal swab. Patients admitted to the Intensive Care Unit (ICU) received a double dose of oseltamivir (300 mg/day). Pneumonia was defined according to the criteria described by Fang *et al*.,[13] and each patient's pneumonia severity index (PSI)[14] and confusion, urea, rate respiratory, blood pressure and age >65-years-old (CURB-65) score[15] were used to determine disease severity.

Flexible swabs and transport medium (COPAN) were used to obtain nasopharyngeal swabs from adults patients with influenza-like illness and pneumonia; tracheal aspirates were obtained from intubated patients. All samples were sent to the virology laboratory.

All samples were tested by real-time RT-PCR to detect influenza A (FLU-A) and influenza B (FLU-B) genomes. Samples that tested positive for FLU-A were subtyped using real-time RT-PCR to differentiate the H1N1 (2009) from H3 subtypes. Nucleic acid extraction was performed using QIAamp Viral RNA Mini Kit, QIAgen columns in an automated extractor (QIAcube). The Centers for Disease Control and Prevention (CDC)-designed protocol was used for amplification (CDC human influenza virus real-time RT-PCR detection and characterization panel September 2010 and CDC real-time RT-PCR detection and characterization of swine influenza 2009). All assays were performed using CFX96 Touch real-time equipment.

Routine cultures were performed; blood cultures were performed in all patients while sputum, tracheal aspirates,

or bronchoalveolar lavages were performed according availability.

The descriptive statistics used were the means ± standard deviation [SD] for quantitative data and frequency analysis (as percentages) for categorical data. Most data comparisons were performed by unpaired *t*-test or Chi-square test for categorical data. A $P < 0.05$ was considered statistically significant.

A multivariable logistic regression model was constructed to determine predictors of mortality.

RESULTS

We analyzed 428 patients between EWs 21 and 31, resulting in 134 patients (31%) positive for influenza A. Of these cases, 104 (78%) were H1N1 (2009), 23 (17%) were H3, and 7 (5%) were a subtype that could not be determined. The clinical, radiological, and laboratory tests are listed in Table 1.

The mean age was 53 ± 18 (SD) years, 49% were female, and 75% had associated conditions. The most frequently associated condition was elderly age, followed by obesity and heart failure.

The patients with influenza H1N1 presented with tachycardia more frequently exhibited lower urea values and were significantly younger than those patients infected by other strains [Table 1].

Eighty-six patients (64%) were admitted to the general ward, 20 (15%) were admitted to the ICU, and 28 (21%) were treated as outpatients.

The majority of patients had pneumonia [Figure 1] and 50% had bilateral infiltrates.

Eighty-three percent of patients did not receive the trivalent influenza vaccine despite the fact that 72% of them met the indications for vaccination according to the Ministry of

Table 1: Age, sex, comorbidities, clinical conditions, and coinfections; comparisons between patients with H1N1 influenza and non-H1N1 influenza

	All (*n*=134)	Influenza H1N1 (*n*=104)	Influenza non-H1N1 (*n*=30)	*P*
Age (mean±SD)	53±18.6	50±17	63±17	0.01
Female (%)	66 (49)	51 (49)	17 (56)	NS
Elderly (>65 years old, %)	36 (27)	22 (21)	14 (46)	NS
Obesity (BMI >30), (%)	31 (23)	24 (23)	7 (23)	NS
Heart failure (%)	24 (18)	18 (17)	6 (20)	NS
COPD (%)	19 (14)	15 (14)	4 (13)	NS
Diabetes (%)	15 (11)	9 (9)	6 (20)	NS
Cancer (%)	11 (8)	9 (9)	2 (6.7)	NS
Asthma (%)	11 (8)	7 (7)	4 (13)	NS
Chronic renal failure (%)	7 (5)	3 (10)	4 (4)	NS
HIV infection (%)	6 (4)	5 (5)	1 (3)	NS
Mean onset of symptoms, days (mean±SD)	4±3	4±2	4±4	NS
Length hospital stay, days (mean±SD)	7±6	8±6	7±5	NS
Pulse rates (mean±SD)	103±19	112±17	101±19	0.03
Respiratory rates (mean±SD)	25±5	25±5	25±5	NS
BMI (mean±SD)	28±8	29±9	28±5	NS
Hematocrit (%, mean±SD)	39±7	39±6	37±8	NS
Leukocytes/mm^3 (mean±SD)	9862±5578	9541±5192	10812±6616	NS
Urea (g/L), mean±SD	0.41±0.32	0.35±0.22	0.52±0.44	0.01
$PaFiO_2$ (mean±SD)	306±92	305±95	310±85	NS
pH (mean±SD)	7.42±0.07	7.41±0.07	7.42±0.04	NS
Glucose (mg/dL), mean±SD	146±82	139±62	168±122	NS
Pneumonia (%)	122 (91)	94 (90)	28 (93)	NS
Bilateral infiltrates (%)	61 (50)	49 (52)	13 (46)	NS
Coinfection (%)	12 (9)	9 (9)	3 (10)	NS
Streptococcus pneumoniae (%)	6 (4.5)	4 (4)	2 (6)	NS
Mycobacterium tuberculosis (%)	2 (1.5)	1 (1)	1 (3)	NS
Escherichia coli (%)	1 (0.7)	1 (1)	0	
Moraxella catarrhalis (%)	1 (0.7)	1 (1)	0	
Haemophilus influenzae (%)	1 (0.7)	1 (1)	0	
Citrobacter freundii (%)	1 (0.7)	1 (1)	0	
Vaccine (%)	22 (17)	14 (13)	8 (26)	NS
Mechanical ventilation (%)	17 (12)	15 (14)	2 (7)	NS
Mortality (%)	15 (11)	13 (12)	2 (7)	NS

COPD: Chronic obstructive pulmonary disease, HIV: Human immunodeficiency virus, BMI: Body mass index, $PaFiO_2$: Relationship between alveolar oxygen pressure and the inspired oxygen fraction, NS: Not statistically significant, SD: Standard deviation.

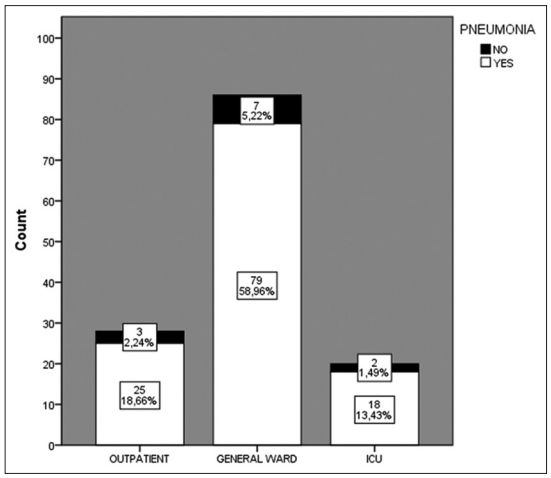

Figure 1: Location of hospital admission and proportions of patients with pneumonia

Health recommendations. These criteria included elderly age, obesity, diabetes, pregnancy, cancer, and cardiac or pulmonary disease. No significant difference was observed between the vaccinated and nonvaccinated patients with regard to the presence of pneumonia (84% *vs.* 91%, respectively, $P = 0.4$), admissions (72% *vs.* 80%, $P = 0.09$), or coinfections (13% *vs.* 8%, $P = 0.4$). No vaccinated patient died.

Patients admitted to the general ward had a mean SO_2 of 91.45%±5.75% and average ratio of arterial oxygen partial pressure to fractional inspired oxygen (Pa/Fi O_2) of 313 ± 94 at the time of admission. For patients admitted to the ICU, the mean SO_2 was 87.7 ± 10.4 and $PaFiO_2$ 246.5 ± 72. Patients' severity scores were not good predictors of disease intensity because 80% of patients admitted to the general ward presented with CURB-65 scores ≤2 and 64% had a PSI ≤ Group 3. For patients in the ICU, 60% had a CURB-65 score ≤2 and 70% had a PSI in Group 4 or 5 [Table 2]. Thus, PSI scores were the most reliable for predicting disease severity.

Twenty patients were admitted to the ICU, of which 17 required invasive mechanical ventilation, and 7 were initially hospitalized in the general ward and were then moved to the ICU. Only one patient admitted to the ICU was vaccinated.

Twelve patients presented with coinfections, of which *Streptococcus pneumoniae* was the most frequent and affected six patients. One of these patients presented with pleural empyema. Two of the coinfected cases had associated *Mycobacterium tuberculosis* infections, and one of these patients also had AIDS. In the ICU, three patients developed ventilator-associated pneumonia.

A total of 15 patients with an average age of 64 years died (11%). In univariate analysis for mortality, the statistically significant variables were age >65 years ($P = 0.01$), malignancy ($P < 0.03$), diabetes ($P < 0.02$), and the requirement for mechanical ventilation ($P < 0.001$).

Table 2: Comparative table of patients admitted to the intensive care unit and general ward

	General ward (*n*=86)	ICU (*n*=20)	*P*
Edad (mean±SD)	56.69±17	55.35±14	NS
Pneumonia (%)	79 (92)	18 (90)	NS
$PaFiO_2$ (mean±SD)	316.49±87	244.19±87	0.004
SO_2	91.45±5.75	87.72±10.40	0.04
Mortality (%)	6 (7)	9 (45)	0.0001
CURB-65 (%)			
0	20 (25)	2 (11)	NS
1	34 (44)	5 (28)	NS
2	10 (12)	3 (17)	NS
3	10 (12)	1 (5)	NS
4	4 (6)	7 (39)	0.001
5	1 (1)	0	NS
PSI (%)			
I	11 (14)	1 (5)	NS
II	22 (28)	3 (17)	NS
III	18 (23)	2 (11)	NS
IV	20 (25)	9 (50)	0.02
V	8 (10)	3 (17)	NS

$PaFiO_2$: Relationship between alveolar oxygen pressure and the inspired oxygen fraction, SO_2: Oxygen saturation, CURB-65: Confusion, urea, rate respiratory; blood pressure and age >65 years old, PSI: Pneumonia severity index, NS: Not statistically significant, SD: Standard deviation, ICU: Intensive Care Unit.

However, in the multivariate analysis, the variables that maintained significance differences were mechanical ventilation (odds ratio: 27.66; 95% confidence interval [CI]: 6.43–119; $P < 0.001$) and cancer (odds ratio: 6.81; 95% CI: 1.25–37.13; $P = 0.02$).

DISCUSSION

We report an important number of influenza cases, predominantly of the H1N1pdm09 subtype, that occurred in Argentina during 2013.

In our cohort, the analyzed patients had comorbidities or were elderly. An increase in the number of cases in the elderly population was observed during this influenza season although the patients who were infected with H1N1 were significantly younger than those infected with non-H1N1 subtypes. This result is in marked contrast to what occurred in 2009 when young patients predominated the infected population. Around 200,000 deaths are the estimated globally mortality in 2009, 80% of them were people younger than 65 years old.[16] It was suggested that elderly patients had some level of relative protection if they had been exposed to a pandemic influenza during childhood before 1957.[17] This hypothesis was also proposed to explain the infection trends of the Spanish flu pandemic that occurred in 1918. In one meta-analysis of seroprevalence for influenza H1N1, it was observed that 5% of the population had cross-reactive antibody before 2009, with the highest rates (14–34%) among people aged 65 years old and older.[18,19] In the postpandemic years, an increase in the seroprevalence was observed in all age groups, except in the elderly.

Some investigators propose that developing immunological memory to an antigenically dissimilar influenza subtype early in life may actually subvert the immune system, thereby increasing the risk of death when the individual is infected by a novel strain in later life.[20] These theories do not explain why the second pandemic influenza wave affected mostly older patients.

Numerous studies have demonstrated the role of host genetic susceptibility to severe disease and mortality for influenza; however, very large studies will be required to identify genetic effects on susceptibility to severe influenza.[21]

Obesity was the most frequently observed comorbidity, followed by cardiac and respiratory diseases. Although obesity was proposed as an independent risk factor for influenza with poor prognosis and mortality,[22,23] in our country, there was no difference in the prevalence of this condition between infected individuals and the general population.[4] Only one pregnant woman was treated without complications.

Although many patients fit the indications for influenza vaccination according to the National Health Ministry Guidelines, they did not receive the immunization. Seventeen percent of patients had been vaccinated, and no differences were observed with regard to pneumonia, hospitalization rates, or coinfections between the vaccinated and unvaccinated populations. The effectiveness of the vaccine is controversial, and many studies evaluating effectiveness used a serology-based end-point, which resulted in overestimation of efficacy. In a meta-analysis that used only specific end-points, such as virologically confirmed cases, the effectiveness of the monovalent vaccine for influenza H1N1pdm09 was 69%.[7] Other studies revealed that the monovalent vaccine administered during 2009–2010 was ineffective the following season. The trivalent inactive vaccine was effective in 77% of cases during the same period. This result supports the need for annual vaccination.[6]

Major efforts should be undertaken to annually vaccinate patients with risk factors.

The severity scores were not good predictors of disease course in these patients. The CURB-65 and PSI scores were validated in cases of nonviral pneumonia.

We found a significant difference in the urea value, pulse rates, and age between patients with influenza A H1N1 and patients with influenza non-H1N1; these factors were included in the CURB-65 and PSI scores;[14,15] however, no difference in outcomes such as mortality or mechanical ventilation was observed. We thought that the differences in urea value and pulse rates would be associated with the differences in the age.

Seven of the patients hospitalized in the ICU were previously admitted to the general ward and their conditions worsened during the first days. A few patients did not have pneumonia, but they were admitted predominantly with acute exacerbations of COPD or asthma. In addition, there were three cases of febrile neutropenic patients, of which two exhibited worsening disease status.

Elevated mortality was observed predominantly in the ICU patients. This result was similar to what was described in 2009.[4] In contrast, during the pandemic of 1918, the highest mortality was observed during the second wave of infection.[24] All patients were treated with oseltamivir from the beginning, including the initial patients due to the similarity between these cases and those observed in 2009. The mean number of days from the onset of symptoms to consultation with a physician was 4, which could have resulted in reduced treatment efficacy.[25] Patients had serious underlying conditions, such as cancer. In the multivariate analysis, only the requirement for invasive mechanical ventilation and the presence of cancer were predictors of mortality.

Two patients were coinfected with tuberculosis. This associated condition was not described in the patients documented in 2009 but was a serious problem in the 1918 pandemic and increased mortality predominantly in male patients.[26]

CONCLUSIONS

A new wave of cases produced by influenza H1N1 was observed during the late fall and winter of 2013. Most patients affected had associated risk factors, including elderly age and other comorbidities. A significant number of patients had not been vaccinated, and greater effort should be devoted to achieve annual vaccination. The severity scores were not useful for predicting disease course. Patient mortality was high, and the only independent predictors of mortality were the need for mechanical ventilation and the presence of cancer.

Acknowledgments

We thank Dr. Alfredo Monteverde for his help and advice during this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Novel Swine-Origin Influenza A (HN) Virus Investigation Team, Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, *et al.*

Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009;360:2605-15.
2. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, *et al.* Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. N Engl J Med 2009;361:1935-44.
3. Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, *et al.* H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 2009;374:451-8.
4. Estenssoro E, Ríos FG, Apezteguía C, Reina R, Neira J, Ceraso DH, *et al.* Pandemic 2009 influenza A in Argentina: A study of 337 patients on mechanical ventilation. Am J Respir Crit Care Med 2010;182:41-8.
5. Kwong JC, Campitelli MA, Gubbay JB, Peci A, Winter AL, Olsha R, *et al.* Vaccine effectiveness against laboratory-confirmed influenza hospitalizations among elderly adults during the 2010-2011 season. Clin Infect Dis 2013;57:820-7.
6. Bateman AC, Kieke BA, Irving SA, Meece JK, Shay DK, Belongia EA. Effectiveness of monovalent 2009 pandemic influenza A virus subtype H1N1 and 2010-2011 trivalent inactivated influenza vaccines in Wisconsin during the 2010-2011 influenza season. J Infect Dis 2013;207:1262-9.
7. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: A systematic review and meta-analysis. Lancet Infect Dis 2012;12:36-44.
8. Rodríguez A, Martin-Loeches I, Bonastre J, Olaechea P, Alvarez-Lerma F, Zaragoza R, *et al.* First influenza season after the 2009 pandemic influenza: Report of the first 300 ICU admissions in Spain. Med Intensiva 2011;35:208-16.
9. Viasus D, Cordero E, Rodríguez-Baño J, Oteo JA, Fernández-Navarro A, Ortega L, *et al.* Changes in epidemiology, clinical features and severity of influenza A (H1N1) 2009 pneumonia in the first post-pandemic influenza season. Clin Microbiol Infect 2012;18:E55-62.
10. Integrated Surveillance Bulletin. Presidency of the Nation Argentina. Secretary of Promotion and Health Programs. Available from: http://www.msal.gob.ar/index.php/home/boletin-integrado-de-vigilancia.
11. Sala H, Roca JS, Zerbo C, Garcia R, Cabral G, Fernandez A, *et al.* Initial clinical management of symptomatic adult patients during influenza A (H1N1) epidemics. J Emerg Med 2011;41:435-40.
12. Luna CM, Calmaggi A, Caberloto O, Gentile J, Valentini R, Ciruzzi J, *et al.* Neumonía acquired in the community. Practical guide elaborated by a committee intersocieties. Medicina (B Aires) 2003;63:319-43.
13. Fang GD, Fine M, Orloff J, Arisumi D, Yu VL, Kapoor W, *et al.* New and emerging etiologies for community-acquired pneumonia with implications for therapy. A prospective multicenter study of 359 cases. Medicine (Baltimore) 1990;69:307-16.
14. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;336:243-50.
15. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, *et al.* Defining community acquired pneumonia severity on presentation to hospital: An international derivation and validation study. Thorax 2003;58:377-82.
16. Dawood FS, Iuliano AD, Reed C, Meltzer MI, Shay DK, Cheng PY, *et al.* Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: A modelling study. Lancet Infect Dis 2012;12:687-95.
17. Chowell G, Bertozzi SM, Colchero MA, Lopez-Gatell H, Alpuche-Aranda C, Hernandez M, *et al.* Severe respiratory disease concurrent with the circulation of H1N1 influenza. N Engl J Med 2009;361:674-9.
18. Van Kerkhove MD, Hirve S, Koukounari A, Mounts AW; HNpdm Serology Working Group. Estimating age-specific cumulative incidence for the 2009 influenza pandemic: A meta-analysis of A(H1N1) pdm09 serological studies from 19 countries. Influenza Other Respir Viruses 2013;7:872-86.
19. Broberg E, Nicoll A, Amato-Gauci A. Seroprevalence to influenza A(H1N1) 2009 virus-where are we? Clin Vaccine Immunol 2011;18:1205-12.
20. Gagnon A, Miller MS, Hallman SA, Bourbeau R, Herring DA, Earn DJ, *et al.* Age-specific mortality during the 1918 influenza pandemic: Unravelling the mystery of high young adult mortality. PLoS One 2013;8:e69586.
21. Horby P, Nguyen NY, Dunstan SJ, Baillie JK. An updated systematic review of the role of host genetics in susceptibility to influenza. Influenza Other Respir Viruses 2013;7 Suppl 2:37-41.
22. Louie JK, Acosta M, Samuel MC, Schechter R, Vugia DJ, Harriman K, *et al.* A novel risk factor for a novel virus: Obesity and 2009 pandemic influenza A (H1N1). Clin Infect Dis 2011;52:301-12.
23. Díaz E, Rodríguez A, Martin-Loeches I, Lorente L, del Mar Martín M, Pozo JC, *et al.* Impact of obesity in patients infected with 2009 influenza A(H1N1). Chest 2011;139:382-6.
24. Taubenberger JK, Morens DM. 1918 influenza: The mother of all pandemics. Emerg Infect Dis 2006;12:15-22.
25. Hiba V, Chowers M, Levi-Vinograd I, Rubinovitch B, Leibovici L, Paul M. Benefit of early treatment with oseltamivir in hospitalized patients with documented 2009 influenza A (H1N1): Retrospective cohort study. J Antimicrob Chemother 2011;66:1150-5.
26. Noymer A, Garenne M. The 1918 influenza epidemic's effects on sex differentials in mortality in the United States. Popul Dev Rev 2000;26:565-81.