DOI:10.1111/j.1750-2659.2012.00405.x
www.influenzajournal.com

Original Article

Clinical features of the hospitalized patients with 2009 pandemic influenza A (H1N1) in Santa Fe, Argentina

Gabriela Kusznierz,[a] Andrea Uboldi,[b] Gabriela Sosa,[b] Santiago Torales,[c] Javier Colombo,[d] Cecilia Moyano,[e] Hernan Escobar[f], Sergio Lejona,[g] Eduardo Anchart,[h] Alejandra Gómez,[a] Susana Imaz[a]

[a]Instituto Nacional de Respiratorias 'Dr. Emilio Coni', Santa Fe, Argentina. [b]Dirección Provincial de Promoción y Protección de la Salud, Ministerio de Salud, Santa Fe, Argentina. [c]Instituto Autárquico Provincial de Obra Social, Santa Fe, Argentina. [d]Programa de Zoonosis, Ministerio de Salud, Santa Fe, Argentina. [e]Secretaría de Salud, Ministerio de Salud, Santa Fe, Argentina. [f]Dirección Provincial de Planificación, control de gestión y estadísticas, Rosario, Argentina. [g]Centro de Especialidades Médicas de Rosario, Rosario, Argentina. [h]Red Provincial de Laboratorios, Rosario, Argentina.

Correspondence: Kusznierz Gabriela Fabiana, Instituto Nacional Enfermedades Respiratorias 'Dr. Emilio Coni', Blas Parera 8260, 3000 Santa Fe, Argentina.
E-mail: labconi@yahoo.com.ar

Accepted 6 June 2012. Published online 23 July 2012.

Background During 2009 occurred the emergence and global spread of a novel influenza A (H1N1) virus. We describe the clinical and epidemiologic features of hospitalized patients who survived and patients who died because of pandemic 2009 influenza A (H1N1) infection reported in Santa Fe, Argentina, from May to July 2009.

Methods Using medical charts, we collected data on 242 patients who were hospitalized with confirmed laboratory results (defined as positive by specific PCR for pandemic 2009 influenza A H1N1).

Results During the study period, there were 242 cases of hospitalization or death. Of the 242, 46% were admitted to an intensive care unit (ICU) and 33·5% died. The mean age was 27·8 years for surviving and 39·6 for those who died. Twenty-eight percent of hospitalizations involved persons under the age of 15 years; 33% of the patients were between the age of 15 and 44 years; and only 3·3% were 65 years of age or older. Sixty-seven percent had an underlying medical conditions, including diabetes, obesity, heart and lung diseases, and pregnancy. Of the 242 patients, 68% had findings consistent with pneumonia. Treatment with oseltamivir was administered to 227 (93·8%) patients from which 38 received oseltamivir within 48 hours after the onset of symptoms.

Conclusions The pandemic strain caused severe illness, including pneumonia and acute respiratory distress syndrome, and resulted in ICU admissions in 46% of patients and death in 33·5%. The mean age of hospitalized infected cases was lower than is common with seasonal influenza. Underlying medical conditions were common in the 67% the evaluated patients. Patients who died had a higher prevalence of comorbidities (86·4%) than those who survived (57%), suggesting that the presence of chronic illness may increase the likelihood of death. However, the severe illness was also identified among young, healthy persons.

Keywords Clinical features, fatal cases, hospitalized, influenza A (H1N1)pdm2009, treatment.

Please cite this paper as: Kusznierz *et al.* (2013) Clinical features of the hospitalized patients with 2009 pandemic influenza A (H1N1) in Santa Fe, Argentina. Influenza and Other Respiratory Viruses 7(3), 410–417.

Introduction

On 11 June 2009, the World Health Organization[1] raised the pandemic alert level to phase 6, the pandemic phase, in response to the emergence and global spread of a novel influenza A (H1N1) virus. The 2009 H1N1 virus contained a unique combination of gene segments that had not previously been identified in humans or animals.[2,3]

As of March 2010, almost all countries had reported cases, and more than 17 700 deaths among laboratory-confirmed cases had been reported to the World Health Organization (WHO).[4] In the Argentina, 626 laboratory-confirmed deaths had been caused by the 2009 H1N1 virus.

Although 2009 influenza A (H1N1) has generally been characterized as a uncomplicated infection, severe illnesses and deaths have been reported among some patients.[4–8] Recent studies have shown that health conditions typically associated with risk for seasonal influenza complications were also found among individuals with 2009 influenza A (H1N1) admitted to an intensive care unit (ICU).[4–7] Information on the clinical features and populations at risk of

complications from infection is still emerging in Argentina. In this report, we describe the clinical and epidemiologic features of hospitalized patients who survived or died because of pandemic 2009 influenza A (H1N1) infection reported in the Province of Santa Fe, Argentina, from May to July 2009.

Methods

Design, setting, and participants

Argentina is divided into 23 provinces and the autonomous city of Buenos Aires. The Province of Santa Fe is located in the central region of Argentina. The province of Santa Fe has 19 departments and a population of 3 285 170 of inhabitants.[9] Rosario and La Capital are the most populated departments.

We conducted a retrospective study involving patients who were hospitalized in Santa Fe from 1 May to 31 July 2009. We included patients with confirmed laboratory results (defined as positive by specific real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay for pandemic 2009 influenza A(H1N1) according to the protocol recommended by the U.S. Centers for Disease Control and Prevention (CDC).[10] Disease outcome included two possible options: patients who survived or died.

We included all patients who died from the whole province, whereas a sample of patients who survived was incorporated in the study, all of them from the department La Capital, Santa Fe.

To determine the sample size of patients with confirmed influenza who survived, 50% was used as an estimated frequency for the clinical features, which would be explored in the whole cases included in the study; this percentage allows the largest possible sample size to be calculated for a determined level of confidence. The least reliable sample size was 155, considering that the number of patients with confirmed influenza survived accounted during the study period in Santa Fe province was 731 and using 95% confidence level and an error of 7%. As we mentioned above, we used the convenience sampling method, randomly selecting the survival cases from those hospitalized at La Capital Department. As the study was coordinated in this department, this method allowed an easy access to the medical records. The surviving patients were hospitalized at three public hospitals and six private facilities. They account for 90% of the facilities of the department La Capital.

In the case of the deceased, all cases of the Province were studied because the small number of cases allowed us to study them all.

Data collection

Data regarding the hospitalized patients were extracted from medical records, using a standardized report form that included demographic data, clinical presentation and course, comorbid conditions, and laboratory and radiographic findings, and treatment course.

Statistical analysis

Continuous variables were summarized as means (with interquartile ranges). For categorical variables, the percentages of patients in each category were calculated. For pregnancy, proportions were calculated as a percentage of pregnant patients among female patients of reproductive age (15–44 years).

We performed a bivariate analysis to compare the outcomes for patients who survived and who died. The Mantel–Haenszel chi-square test was used to compare discrete variables and the Mann–Whitney test to compare continuous variables. A P-value of $<0{\cdot}05$ was considered to indicate statistical significance.

Results

Study population and demographic data

The first case of confirmed infection was identified on May 2009. From May to December 2009, a total of 7689 hospitalizations by acute lower respiratory infection (ALRI) were reported and 1536 (of which 731 were hospitalized) were confirmed cases of infection with H1N1 influenza in Santa Fe. We analyzed 242 clinical records of patients with confirmed Influenza A (H1N1). This patients represented 15·7% (242/1536) of all confirmed cases and 3·1% (242/7689) of ALRI.

Of the 242 patients, 161 survived and 81 were fatal cases. Of the 242 patients, 121 (50%) were females and 14 were pregnant (17·7% of female patients of childbearing age).

The mean age of surviving patients was 27·8 (range, 2 months to 86 years); 84 patients (52·2%) were male (Table 1). Eighty-one patients died, 34·5% from Rosario, and 18·5% from The Capital. The mean age of fatal patients was 39·6 (range, 4 months–88 years); 37 patients (45·7%) were male (Table 1).

Underlying medical conditions

Of the 242 patients, 162 (67%) had an underlying medical condition (Table 2). Of the 161 surviving patients, 57·1% had one or more underlying medical condition, and of the 81 patients who died, 86·4% had comorbidities. Chronic lung disease was the most common condition seen, plus metabolic disease and heart disease in both surviving patients and patients who died (Table 2). Fifty-seven cases with hypertension had comorbidities that are established risk factors[11] for severe influenza including 19 with heart disease, chronic lung disease ($n = 12$), or metabolic disease ($n = 37$). Thirty-eight adults patients with obesity had underlying conditions associated with influenza complications, including 12

Table 1. Distribution by age group and sex in patients who survived and who died, 2009, Santa Fe, Argentina

Age group (years)	Patients Who survived (*n* = 161)			Patients Who died (*n* = 81)		
	Female	Male	Total *n* (%)	Female	Male	Total *n* (%)
<1	10	23	33 (20·4)	2	3	5 (6·2)
2–4	5	4	9 (5·6)	1	2	3 (3·7)
5–9	6	6	12 (7·4)		2	2 (2·5)
10–14	2		2 (1·2)	2		2 (2·5)
15–24	11	7	18 (11·2)	7	1	8 (9·8)
25–34	7	8	15 (9·3)	4	4	8 (9·9)
35–44	10	8	18 (11·1)	7	5	12 (14·8)
45–54	16	12	28 (17·4)	11	10	21 (25·9)
55–65	6	11	17 (10·5)	8	10	18 (22·2)
>65	3	3	6 (3·7)	2		2 (2·5)
Non-specified		3	3 (1·9)			
Total	77	84	161 (100)	44	37	81 (100)

Table 2. Pre-existing conditions of hospitalized patients who survived and patients who died according to age group (years), 2009, Santa Fe, Argentina

Pre-existing condition	Hospitalized patients Who survived (*n* = 158)				Hospitalized patients Patients who died (*n* = 81)				*P*-value
	<15 *n* = 56	15–44 *n* = 51	>45 *n* = 51	Total no. (%)	<15 *n* = 12	15–44 *n* = 28	>45 *n* = 41	Total no. (%)	
Obesity		1	5	6 (4)		11	21	32 (40)	<0·001
Diabetes		4	6	10 (6)		3	12	15 (19)	0·002
Heart disease			10	10 (6)	2	1	9	12 (15)	0·02
Hypertension		5	21	26 (16)	1	4	26	31 (38)	0·03
Renal disease		3	4	7 (4)	3		6	9 (11)	0·04
Preterm	8			8 (5)	1			1 (1)	0·14
Chronic lung disease	18*	3**	10**	31 (20)	4	6	11	21 (26)	0·23
Cancer and/or immunosuppression		6***	2	8 (5)	1	2	4	7 (7)	0·26
Other metabolic disorder†			5	5 (3)		2	3	5 (6)	0·27
Pregnancy		11		11 (7)		3		3 (4)	0·32
Asthma	1	3	6	10 (6)	1	1	1	3 (4)	0·41
Neurologic disease	5	1	2	8 (5)	4	1	1	6 (7)	0·44
Total (any pre-existing condition)	16 (28·6)	30 (58·6)	43 (84·3)	89 (56)	9 (75)	22 (78·6)	39 (95)	70 (86)	<0·001

*Respiratory obstructive bronchitis and bronchopulmonary dysplasia.
**Chronic obstructive pulmonary disease.
***HIV, transplant.
†Hypothyroidism, Cushi's disease.

with diabetes mellitus and cardiac disease ($n = 19$). All 5 adult patients with obesity without risk factors associated with influenza complications had hypertension.

A total of 11 (6·8%) surviving patients were pregnant, 1 of whom had another underlying medical condition (hypertension and obesity). Of the 11 pregnant patients, one was in the first trimester, three were in the second trimester, and seven were in the third trimester (Table 3). Among the three pregnant patient deaths, one had asthma (Table 3). Maternal mean age was 20 years (range, 23–29). Of the three women, one was in their first, one was in their second, and one was in third trimester.

Table 3. Characteristics of pregnant women with 2009 influenza A (H1N1) illness, 2009, Santa Fe, Argentina

Characteristics	No. of pregnant women (n = 14)
Maternal age (year)	
<18	6
18–29	5
30–39	3
Trimester of pregnancy (week)	
First trimester (0–13)	2
Second trimester (14–28)	4
Third trimester (>29)	8
Pre-existing condition	
Hypertension/obesity	1
Asthma	1
Oseltamivir treatment	
Received <48 hour after symptom onset	4
Admitted to intensive care unit	7
Assisted ventilation	4
Oxygen supplementation	9
Maternal deaths	3
Delivery type	
Cesarean delivery	5
Vaginal delivery	1

Clinical manifestations and treatments

The most common symptoms included cough, crackles, dyspnea, and fever. Wheezing was noted in 43% of the patients. Gastrointestinal symptoms were reported in (66) 27·6% of patients, including (17) 32% of children (i.e., patients under the age of 5 years) and (49) 26% in patients >6 years (Table 4). Progressive dyspnea and cyanosis were more frequent in fatal cases ($P < 0{\cdot}01$).

The diagnoses were pneumonia 68%, ALRI 5·8%, influenza 3·7%, bronchiolitis 2·8%, bronchitis 2·5%, chronic obstructive pulmonary disease (COPD) 2·5% (Table 5).

Treatment with oseltamivir was administered in a total of 227 (93·8%) patients; 16·7% of patients received therapy within 48 hours after the onset of symptoms (Table 5). Among the patients who survived, 33% received oseltamivir 3–5 days after the onset of symptoms, 28% 6–10 days, and 12% after than 10 days. The mean time from the first consultation to the initiation of treatment was 2·1 days (range, 0–16) in surviving patients and 5·4 days (range, 0–30) in patients who died ($P < 0{\cdot}001$). Fifty-eight percent of patients who survived and 30% the patients who died were treated the day of the consultation or the day before. All pregnant women received oseltamivir, in this analysis (Table 3). The time from onset symptoms to initiation of therapy was 6–10 days in the three pregnant patients who died. From five live-birth deliveries for which gestational age was known, two were preterm.

Fifty-nine percent of surviving hospitalized patients received oxygen supplementation for a mean duration of 6·8 days (range, 1–80). Of the non-surviving patients, 71·6% received oxygen supplementation for a mean duration of 8·7 days (range, 1–32).

Two hundred and seventeen patients (89%) received antibiotic therapy during hospitalization. Of patients for whom the date of initiation of antibiotics was available, such therapy was started before admission in 79 (32·6%) patients. Of these, 20% survived and 56% died. In the case of patient receiving several types of antibiotics, patients received a mean of 2·3 (survived) and 2·8 (fatal) antibiotics (range, 1–7); 40% of patients received more than one antibiotic. Commonly used antibiotics included ceftriaxone, clarithromycin, amoxiclavulanic, and ampi sulbactam. Vancomycin, piperacilin/tazobactam, and imipenem were more frequent in patients who died.

The mean length of hospitalization was 5 days, (range, 1–88) for survivors and 6·5 days (range, 0–32) for non-survivors ($P = 0{\cdot}10$).

Of the 242 patients evaluated, (112) 46% were admitted to an ICU, 81 of whom died. Of the 31 patients who survived, 30% was <5 years old and 60% >15 years. Of the patients who survived, 74% had an underlying medical condition, including metabolic disease (in seven cases), asthma (in one case), COPD (in one case), and neurologic diseases (in three cases); seven patients were pregnant. The mean length of ICU stay was 9·75 days (range, 1–80) for survivors and 13·3 (range, 1–32) days for non-survivors ($P = 0{\cdot}28$). Eighty-one (79·4%) required assisted ventilation (Table 5). The mean duration of ventilation was 9·3 days (range, 1–27) for survivors and 6·5 (range, 1–32) days for non-survivors ($P = 0{\cdot}12$).

Among fatal cases, the mean time from the onset of symptoms to death was 14·2 days (range, 1–47), 22·9% cases died within 7 days after the onset of symptoms, 45·7% between 7–15 days and 31·4% more the 15 days.

In the three pregnant, the time from the onset of illness to death ranged from 11 to 26 days. The mean time from the onset of symptoms to admission into an ICU was 7 days (range, 1–29). All three pregnant required mechanical ventilation on the day of admission (5–9 days from the onset of symptoms).

Laboratory testing

Leukocytosis (absolute leukocyte count, >1000 per cubic millimeter) was present in the 44·8% among those who survived and 34% among those who died. Among those who survived (109), 68% had neutrophilia and (22) 14% had thrombocytopenia (platelet count, <150 000 per cubic millimeter) and who died had (55) 68·6% and (28) 35%, respectively (Table 4).

Table 4. Characteristics of hospitalized patients who survived and patients who died in Santa Fe, 2009 on admission, Santa Fe, Argentina

Signs and symptoms no. (%)	All cases *n* = 239	Cases aged 0–5 years		Cases aged > 6 years	
		Fatal *n* = 9	Non-fatal *n* = 44	Fatal *n* = 72	Non-fatal *n* = 114
Cough	212 (89)	9 (100)	37 (84)	62 (86)	104 (91)
Fever	172 (72)	9 (100)	30 (68)	57 (79)	76 (66)
Crackles	155 (65)	3 (33)	12 (27)	49 (68)	91 (79)
Dyspnea	169 (71)	7 (77)	30 (68)	64 (88)	68 (59)
Wheezing	102 (43)	4 (44)	18 (41)	24 (33)	56 (49)
Tachypnea	137 (57)	9 (100)	30 (68)	57 (79)	41 (36)
Asthenia	93 (39)	3 (33)	6 (14)	29 (40)	55 (48)
Myalgia	72 (30)			23 (32)	49 (43)
Progressive dyspnea	74 (31)	6 (66)		47 (65)	21 (18)
Rhinorrhea	47 (20)	2 (22)	20 (45)	5 (7)	20 (17)
Headache	49 (21)			16 (22)	33 (29)
Vomiting	42 (17)		10 (23)	10 (14)	22 (19)
Chills	32 (14)	1 (11)		10 (14)	21 (18)
Conjunctivitis	4 (2)			2 (3)	2 (2)
Nauseas	15 (6)			8 (11)	7 (6)
Cyanosis	25 (11)	3 (33)	5 (11)	17 (24)	
Diarrhea	24 (10)	1 (11)	6 (14)	4 (6)	13 (11)
Laboratory findings					
Leukocyte count, $\times 10^9$/l mean (range)		17 292 (4900–45 700)	12 483 (2500–59 000)	8688 (1000–27 900)	9828 (400–30 060)
Lymphocytes %, mean range		28·5 (20–60)	28 (7–62)	13·9 (0–45)	15 (2–59)
Neutrophils %, mean (range)		65·8 (40–84)	62 (27–88)	80 (51–96)	78·9 (15–93)
Platelet count, mean		237 928	307 487	223 500	230 010

From the patients for whom data were available, 7 (2·9%) had microbiologic evidence of a secondary bacterial infection. The pathogens identified were *Streptococcus pneumoniae*, *Pseudomona aeruginosa*, *Staphylococcus viridians*, and *Staphylococcus hominis*.

Radiographic findings

Of the 175 patients (72%) who underwent chest radiography obtained on admission, the most frequent diagnosis was pneumonia (68%). The most frequent radiographic findings included consolidation (60%) and interstitial pattern (36%), was observed bilateral infiltrates in 72% of those who died and 59% of those who survived, (Table 5).

Discussion

We describe a case series of 242 patients in Santa Fe who were hospitalized for 2009 H1N1 virus infection between May and July 2009.

When influenza hospitalizations are more common among people >65 years of age and those under the age of 5 years, in our dataset, 50 (20%) of the hospitalizations involved persons under the age of 5 years; 163 (67%) of the patients were between the age of 15 and 65 years; and only 8 (3·3%) were 65 years of age or older, as previously described for this pandemic.[8,12–24] The mean age (39·6 days) was higher among patients who died. Our data suggest that severe disease and mortality are concentrated in adolescents and adults between the ages of 15 and 65 years (76%). A potential biological basis for this observation is that patients >65 years of age have a cross-reactive antibody to 2009 influenza A (H1N1) at much higher rates than younger patients.

The signs and symptoms of patients who were hospitalized were generally similar to those reported during seasonal influenza, and other reports related to the pandemic.[13,25,26] Whereas diarrhea or vomiting has occasionally been reported in children and in <5% of adults during peak periods of seasonal influenza, these symptoms were reported in 28% of patients in our study, much higher than previously reported.[12] Other studies of patients with influenza A (H1N1) pdm2009 have reported an incidence much lower (2% and 10%).[8,13,22,26,27]

The patients in our study had a high prevalence of underlying medical conditions 159 (67%), as found by other studies, 25 (36%) of patients under 15 years old and 134 (78%) of adults.[12,13,15,17–19,21,27] Patients who died had

Table 5. Clinical course and outcomes of hospitalized patients who survived and patients who died, 2009, Santa Fe, Argentina

	Fatal *n* = 81	Non-fatal *n* = 161	*P*-value
Age, mean	39·6	27·8	<0·001
Male sex, no. (%)	37 (45·7)	84 (52·2)	0·34
Comorbidities, no. (%)	70 (86·4)	92 (57·1)	<0·001
Radiographic findings on admission – no./total no. (%)			
Consolidation	26/69 (37·7)	80/106 (75·5)	<0·001
Interstitial pattern	24/69 (34·8)	39/106 (36·7)	0·78
Air bronchogram	4/69 (5·8)	22/106 (20·8)	0·006
Atelectasis	1/69 (1·4)	39/106 (7·5)	<0·001
Complete opacification	8/69 (11·6)	1/106 (0·9)	0·001
Pleural effusion	1/69 (1·4)	6/106 (5·6)	0·16
Days from onset symptoms to first consultation, means	2·6 (1–22)	4·26 (1–21)	<0·001
Days from first consultation to hospital admission, means	3·4 (0–29)	5·1 (1–21)	<0·001
Days from hospitalization to ICU admission, means	1·8 (0–31)	1·41 (0–10)	0·99
Admitted to intensive care unit – no./total no. (%)	81/81 (100)	31/161 (19·2)	<0·001
Assisted ventilation no./total no. (%)	68/81 (83·9)	13/161 (8)	<0·001
Diagnosis- no./total no. (%)			
Pneumonia	58/81 (72)	108/161(67)	0·47
Influenza		9/161(5·6)	
ALRI	7/81 (8·6)	7/161(4·3)	0·17
Bronchiolitis	1/81 (1·2)	6/161(3·7)	0·27
Bronchitis		6/161(3·7)	
DPOC	2/81 (2·5)	4/161 (2·5)	0·98
Febril syndrome	1/81 (1·2)		
Secondary bacterial infections	6/81 (7)	1/161 (0·6)	0·002
Complications- no./total no. (%)			
Acute respiratory distress syndrome (ARDS)	58/81 (72)	6/31 (19)	<0·001
Sepsis and shock	44/81 (54)	2/31 (6)	<0·001
Renal insufficiency with dialysis	10/81 (12)	1/31 (3)	0·10
Neurologic complications	7/81 (8)		
Respiratory arrest	3/81 (4)		
Liver failure		1/31 (3)	
Acute lung injury	38/81 (47)		
Pneumothorax	7/81 (9)		
CIS	3/81 (4)		
Heart failure	18/81 (22)		
Antibiotic treatment no./total no. (%)	80/81 (98·7)	137/161 (85)	<0·001
Antiviral treatment (oseltamivir)	*n* = 70	*n* = 157	
Received <48 hours after symptom onset – no./total no. (%)	6/46 (13)	32/119 (27)	0·05
Days from onset symptoms to initiation of antiviral therapy, mean, (range)	7·4 (1–30)	5·4 (0–24)	0·012

ALRI, acute lower respiratory infection; ICU, intensive care unit.

a higher prevalence of comorbidities 70 (86·4%) than those who survived 89 (56%), suggesting that the presence of chronic illness may increase the likelihood of death. However, 11 (13·6%) of those who died were previously healthy people, similar other studies.[15,21,23] Chronic lung disease, diabetes, obesity, and heart disease were the most frequently identified underlying conditions. These findings are in line with published reports from other countries.[12,13,15,21,23,28] Among critically ill patients, obesity and diabetes have been shown to be a risk factor for increased mortality. A majority of these patients had an underlying condition associated with an increased risk of influenza-related complications. Although the prevalence of obesity among adults in our study (22%) was much lower than previously reported, in this report we found a significant difference between survivors and non-survivors.[13,15,28] The association of obesity with severe 2009 influenza A (H1N1) infection has been reported by others[12,13,15,23,28] and may be a novel finding of this pandemic. As observed in our cases, obesity is associated with many comorbidities that are severe influenza risk factors, such as diabetes, cardiovascular disease, and pulmonary disease.[15,28] The role of

obesity remains to be further analyzed to ascertain whether the risk is linked with complications of obesity during intensive care or with a severe course of disease because of diabetes frequently associated with obesity. A large proportion of our adult cases had other comorbidities that are not established risk factors for severe influenza, including hypertension.[11] Nevertheless, as observed in our cases, hypertension (57/59) is associated with many comorbidities that are severe influenza risk factors. Hypertension has not previously been identified as an independent risk factor for seasonal influenza complications, a fact that we also observed in our study. A high proportion of young children who survived 40 (71% of the 0–15 year olds) and young adults who survived 21 (41% of the 15–44 year olds) had no documented underlying disease.

The prevalence among pregnant women in our study – 14 (17·7%) – was similar to other studies.[21] Among them, pregnant women accounted for up to 5·7% of hospitalized patients and 3·7% of patients who died. The data reported herein were lower than previous studies.[12,29] Eighty-six percent of the pregnant patients were infected in the second or third trimester and 50% required intensive care. This is being consistent with previous studies.[29,30] Only 14% of cases had medical conditions besides pregnancy that are recognized risk factors for complications from influenza. These findings were different from other studies.[29,30] None of the pregnant patients who died were treated within 48 hours of illness onset. Although pregnant women frequently presented with mild or moderate symptoms, many had a rapid clinical progression and deterioration, different from the course of seasonal influenza observed previously.[29,31,32] In line with other studies, the three women who died required mechanical ventilation and were severely ill at the time of presentation requiring intubation on the day of admission.[29]

Disease progression was rapid in patients who died, with a mean time from the onset of symptom to ICU admission 7 days and to death of 14 days, which is similar to what others have reported.[13] Critically ill patients experienced a rapid worsening that required intensive care within 24–48 hours of hospital admission, as described in other studies.[23] acute respiratory distress syndrome (ARDS), sepsis, and shock were the most frequent complications, each occurring in 45–60% of critically ill patients, a finding which is consistent with reports from other countries.[12,13,21,23]

Few bacterial coinfections were detected, but bacterial diagnostic test is not known if it was performed in all patients.

Additionally, a significant proportion of patients had findings on chest radiography that were consistent with pneumonia.

In our study, a high proportion (93·8%) of patients received antiviral treatment. However, only around 23% received it within 48 hours from the onset of symptoms. The mean time of initiation of treatment was later (7·4 days among those who died and 5·4 days among those who survived). This may be due to the fact that generally patients do not seek medical care immediately (mean of 2·6–4·6 days from symptom onset to consultation). Only 30% of the patients who died received treatment the day of the consultation or the following day and 58% of the patients who survived. Our data suggest that the use of antiviral drugs can reduce disease severity and mortality, especially when such therapy is started early.[8,12,15,21,29,30]

Our study had several limitations. Despite being a retrospective study, not all information was collected for all patients. Surviving cases belonged to one department from the province, but the sampling method may not allow to draw conclusions applicable to the whole province. Nevertheless, the sampling size is appropriate; furthermore, the mean ages and the percentage of males were not significantly different between all surviving cases accounted in the province and those included in this study (Mann–Whitney test and chi-square test for the comparison of mean ages and percentages of males, respectively, $P < 0{\cdot}05$; data not shown in Results section). The two populations studied were not from the same geographic area and this could introduce a bias in the analysis. However, factors that could influence results in our analyses in studying different populations, such as hospital care access and antiviral treatment access and availability, were similar in all departments.

The patients evaluated represented 3·1% of total hospitalizations that were reported.

The data of the initiation of treatment were available in 66% in deceased and in 78% in survivors. Only patients with confirmed infection we evaluated, so the group may not be the representative of hospitalized patients who were not tested. Moreover, the difficulty in determining whether the cause of death is attributable to influenza A (H1N1) infection or to associated factors remains a major limitation.

In conclusion, the pandemic strain caused severe illness, including pneumonia and ARDS, and resulted in ICU admissions in 46% of patients and death in 33·5%. Underlying medical conditions were common in the 67% the evaluated patients. Patients who died had a higher prevalence of comorbidities (86·4%) than those who survived (57·1%), suggesting that the presence of chronic illness may increase the likelihood of death. However, the severe illness was also identified among young, healthy persons. Delayed initiation of antiviral therapy, comorbidities, and age may have contributed to an increased severity of illness.

References

1 World Health Organization. Global alert and response, pandemic (H1N1) 2009, frequently asked questions: what is phase 6? Available at http://www.who.int/csr/disease/swineflu/frequently_asked_questions/level_pandemic_alert/en/index.html (Accessed 8 October 2009).

2 Novel Swine-origin Influenza A (H1N1) Virus Investigation Team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009; 360:2605–2615.

3 Garten RJ, Davis CT, Russell CA *et al.* Antigenic and genetic characteristics of swine-origin 2009 A (H1N1) influenza viruses circulating in humans. Science 2009; 325:197–201.

4 World Health organization. Pandemic (H1N1) 2009- UPDATE 94. Geneva: World Health organization, 2010. Available at http://www.who.int/csr/don/2010_04_01/en/index.html (Accessed 9 April 2010).

5 Center for Disease Control and Prevention. Prevention and control of influenza: recommendations of the advisory Committee on Immunization Practices (ACIP), 2008. MMWR Recomm Rep 2008; 57:1–60.

6 Thompson WW, Shay DK, Weintraub E *et al.* Influenza-associated hospitalizations in the United States. JAMA 2004; 292:1333–1340.

7 Committee of the WHO Consultation on Clinical Aspects. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. N Engl J Med 2010; 362:1708–1719.

8 Baehr F, Morín G, Del Solar J, Olive H, Torres J. Clinical features of adults younger and older and than 50 years hospitalized with influenza A H1N1 2009 in a private hospital in Santiago, Chile. Rev Chilena Infectol 2010; 27:139–143.

9 National Institute of Statistics and Censuses. 2010. Available at: http:/http://www.indec.gov.ar/ (Accessed 3 April 2011).

10 Centers for Disease Control and Prevention (CDC). CDC realtime RTPCR (rRTPCR) protocol for detection and characterization of influenza A (H1N1). Available at http://www.who.int/csr/resources/publications/swineflu/CDCrealtimeRTPCRprotocol_20090428.pdf (Accessed 3 November 2009).

11 Fiore AE, Shay DK, Broder K *et al.* Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on immunization Practices (ACIP), 2009. MMWR Recomm Rep 2009; 58:1–52.

12 Jain S, Kaminoto L, Bramley AM *et al.* Hospitalized Patients with 2009 H1H1 Influenza in the United States, April–June 2009. N Engl J Med 2009; 361:1935–1944.

13 Cui W, Zhao H, Lu X *et al.* Factors associated with death in hospitalized pneumonia patients with 2009 H1N1 influenza in Shenyang, China. BMC Infect Dis 2010; 10:145.

14 Chowell G, Bertozzi S, Colchero MA *et al.* Severe respiratory disease concurrent with the circulation of H1N1 influenza. N Engl J Med 2009; 361:674–679.

15 Louie JK, Acosta M, Winter K *et al.* Factors associated with death or hospitalization due to pandemic 2009 Influenza A (H1N1) infection in California. JAMA 2009; 302:1896–1902.

16 Vaillant L, La Ruche G, Tarantola A, Barboza P. Epidemiology of fatal cases associated with pandemic H1N1 Influenza 2009. Euro Surveill 2009; 14:pii: 19309.

17 Center for Disease Control and Prevention. Hospitalized Patients with Novel Influenza A (H1N1) Virus Infection –California, April–May, 2009. MMWR Morb Mortal Wkly Rep 2009; 58:536–541.

18 Center for Disease Control and Prevention. Deaths and hospitalizations related to 2009 pandemic influenza A (H1N1)- Greece, May 2009–February 2010. MMWR Morb Mortal Wkly Rep 2010; 59:682–686.

19 Center for Disease Control and Prevention. Intensive- care patients with severe novel influenza A (H1N1) virus infection- Michigan, June 2009. MMWR Morb Mortal Wkly Rep 2009; 58:749–752.

20 Karadeli E, Koç Z, Ulusan S, Erbay G, Demiroglu Y, Sen N. Chest radiography and CT finding in patients with the 2009 pandemic (H1N1) influenza. Diagn Interv Radiol 2010; DOI 10.4261/1305-3825 DIR.3337-10.1.

21 Peralta Olalla P, Garcia M, Herrero MV *et al.* Risk factor for disease severity among hospitalised patients with 2009 pandemic influenza A (H1N1) in Spain, April–December 2009. Euro Surveill 2010; 15:1–9.

22 Cao B, Li XW, Mao Y *et al.* Clinical features of the initial cases of 2009 pandemic influenza A(H1N1) virus infection in China. N Engl J Med 2009; 361:2507–2517.

23 Kumar A, Zarychanski R, Pinto R *et al.* Critically ill patients with 2009 influenza A (H1N1) infection in Canada. JAMA 2009; 302:1872–1879.

24 Kamigaki T, Oshitani H. Epidemiological characteristics and low case fatality rate of pandemic (H1N1) 2009 in Japan. PLoS Curr 2009; 1:RRN1139.

25 Tamma P, Turnbull A, Rove S *et al.* Clinical outcomes of seasonal influenza and pandemic influenza A (H1N1) in pediatric in patients. BMC Pediatr 2010; 10:72.

26 Winzer R, Kanig N, Schneitler S *et al.* Early clinical experiences with the new influenza A (H1N1/09). Dtsch Arztebl Int 2009; 106:770–776.

27 Libster R, Bugna J, Coviello S *et al.* Pediatric hospitalization associated with 2009 pandemic influenza A (H1N1) in Argentina. N Engl J Med 2010; 362:45–55.

28 Morgan O, Bramley A, Fowlkes A *et al.* Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A (H1N1) disease. PLoS ONE 2010; 5:e9694 Doi 10.1371/journal.pone.0009694.

29 Siston A, Rasmussen S, Honei M *et al.* Pandemic 2009 influenza A (H1N1) virus illness among pregnant women in the United States. JAMA 2010; 303:1517–1525.

30 Louie J, Acosta M, Jamieson D, Honein M. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. N Engl J Med 2010; 362:27–35.

31 Dodds L, McNeil SA, Fell DB *et al.* Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. CMAJ 2007; 176:463–468.

32 Jamieson D, Honein M, Rasmussen S *et al.* H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 2009; 374:451–458.