An Analysis of 332 Fatalities Infected with Pandemic 2009 Influenza A (H1N1) in Argentina

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Abstract

Background: The apparent high number of deaths in Argentina during the 2009 pandemic led to concern that the influenza A H1N1pdm disease was different there. We report the characteristics and risk factors for influenza A H1N1pdm fatalities.

Methods: We identified laboratory-confirmed influenza A H1N1pdm fatalities occurring during June-July 2009. Physicians abstracted data on age, sex, time of onset of illness, medical history, clinical presentation at admission, laboratory, treatment, and outcomes using standardize questionnaires. We explored the characteristics of fatalities according to their age and risk group.

Results: Of 332 influenza A H1N1pdm fatalities, 226 (68%) were among persons aged <50 years. Acute respiratory failure was the leading cause of death. Of all cases, 249 (75%) had at least one comorbidity as defined by Advisory Committee on Immunization Practices. Obesity was reported in 32% with data and chronic pulmonary disease in 28%. Among the 40 deaths in children aged <5 years, chronic pulmonary disease (42%) and neonatal pathologies (35%) were the most common co-morbidities. Twenty (6%) fatalities were among pregnant or postpartum women of which only 47% had diagnosed co-morbidities. Only 13% of patients received antiviral treatment within 48 hours of symptom onset. None of children aged <5 years or the pregnant women received antivirals within 48 h of symptom onset. As the pandemic progressed, the time from symptom-onset to medical care and to antiviral treatment decreased significantly among case-patients who subsequently died (p<0.001).

Conclusion: Persons with co-morbidities, pregnant and who received antivirals late were over-represented among influenza A H1N1pdm deaths in Argentina, though timeliness of antiviral treatment improved during the pandemic.

Introduction

In April 2009, pandemic influenza H1N1 2009 (influenza A H1N1pdm virus emerged in Mexico and the United States [1]. Argentina was one of the first countries to experience pandemic H1N1 virus transmission during the usual influenza season [2], [3]. The first influenza A H1N1pdm-confirmed case was identified on April 29th, 2009. This and subsequent cases were among travelers arriving from North America. The virus did not spread in the community until mid-May. The first group affected was school-aged children in Buenos Aires.

On June 15th, 2009, the first fatal influenza A H1N1pdm case in Argentina was confirmed [4]. Ten days later, 22 additional influenza A H1N1pdm fatalities were confirmed in the province of Buenos Aires. During July (epidemiological weeks 26–30), the number of laboratory-confirmed influenza A H1N1pdm cases rose from 2,409 to 5,712 and the number of confirmed deaths from 55 to 337 which represented an increase in case-fatality proportion among reported cases from 2.2% to 5.9%. This was the largest number of influenza A H1N1pdm deaths reported from any country at that time. Although the initial elevated mortality was considered a surveillance artifact, concerns remained that influenza A H1N1pdm disease evolution was somehow different in Argentina. Public health officials were also concerned that prevention and treatment measures might not have been sufficiently targeted, given the limited size of local oseltamivir stockpiles for presumptive treatment of case-patients.

On June 26th, 2009, the National Ministry of Health of Argentina (NMHA) created the National Commission for the Assessment of Influenza A (H1N1) to assess clinical aspects of
influenza A H1N1pdm illness among fatalities, adequacy and
timeliness of treatment, and possible risk factors for severe illness
[5]. In this report, we describe the features of 332 laboratory-
confirmed influenza A H1N1pdm fatalities with available clinical
data that occurred during June 15–July 31 2009, at the peak of
influenza A H1N1pdm transmission in Argentina.

Methods
In April 2009, the Government of Argentina activated the
national Emergency Situation Room (ESR). Each province
reported laboratory and epidemiological data on confirmed
influenza A H1N1pdm fatalities and hospitalizations through the
National Health Surveillance System and from laboratories
performing real-time reverse-transcription polymerase-chain-reac-
tion (rRT-PCR) for influenza A H1N1pdm through the
Laboratory Surveillance System [6], [7]. Public and private health
institutions were mandated to notify the ESR of hospitalized
influenza A H1N1pdm case-patients who subsequently died.

For this study, a confirmed fatal case was defined as a patient
who tested positive for influenza A H1N1pdm and who died in the
period June 15–July 31 2009 (i.e. the peak of the pandemic). To
identify cases, we searched a list of influenza A H1N1pdm
laboratory-confirmed fatalities reported to the ESR by private and
public institutions from the city of Buenos Aires and the seven
provinces with the highest number of reported confirmed cases
(i.e. Buenos Aires, Santa Fe, Córdoba, Neuquén, Río Negro,
Tucumán, and Entre Ríos).

Physicians abstracted data on age, sex, medical history,
comorbidities (i.e. chronic pulmonary, cardiovascular, renal,
hepatic, hematological, metabolic, neurologic, immunologic and
neonatal disorders), selected risk factors (e.g. obesity, defined as
BMI>30 or subjectively assessed; pregnancy, alcoholism, and
smoking), previous hospitalizations, signs and symptoms, clinical

Table 1. Age and sex distribution of fatalities reported from June 15th to July 31st 2009, Argentina.

| Age       | Fatalities reported | Fatalities reported (%) | Population* (N) | Population (%) | No. fatalities reported per 100,000 pop |
|-----------|---------------------|-------------------------|-----------------|---------------|-------------------------------------|
| 0 to 4    | 48                  | 14                      | 3,349,278       | 9             | 1.4                                 |
| 5 to 18   | 45                  | 14                      | 9,442,608       | 26            | 0.5                                 |
| 19 to 49  | 134                 | 40                      | 15,241,760      | 42            | 0.9                                 |
| 50 to 64  | 75                  | 23                      | 4,638,864       | 13            | 1.6                                 |
| 65+       | 30                  | 9                       | 3,587,620       | 10            | 0.8                                 |
| Sex       |                      |                         |                 |               |                                     |
| Male      | 177                 | 53                      | 17,659,072      | 49            | 1.0                                 |
| Female    | 155                 | 47                      | 18,601,058      | 51            | 0.8                                 |

*Argentina census data (INDEC. Censo Nacional de Población, Hogares y Viviendas 2001).
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presentation, diagnosis at admission, duration of hospitalization and intensive care, radiographic findings, use of oseltamivir, and laboratory results using a standardized form. Nosocomial influenza A H1N1pdm virus infection was defined as a patient who developed respiratory symptoms >48 hours after admission for a non-respiratory cause and who later tested positive for influenza A H1N1pdm. Organ failures were defined according to international definitions [8,9]. If a patient was mechanically ventilated, but not admitted to intensive care unit (ICU) because of space limitations, the case was still classified as an ICU patient.

Respiratory specimens were collected from suspected cases and were tested for influenza A H1N1pdm by rRT-PCR assay initially in Argentina’s National Reference Laboratory. As the pandemic progressed, an additional 18 laboratories were trained to use this technique and provided data for the study.

Differences in categorical variables among the three age groups (i.e. <5, 5–49, and >50 years) were analyzed by χ² tests and Fisher’s exact test. Student t-tests and one-way analysis of variance (ANOVA) were used to compare means and Wilcoxon Rank sum test to compare medians.

**Results**

During 2009, 626 patients died with laboratory-confirmed influenza A H1N1pdm infection in Argentina [10]. The proportion of confirmed hospitalized case-patients who died peaked during June (i.e. 48 [18%] of 272) (Figure 1). Of the 626 fatalities, 377 were reported during June 15-July 31 (the study period). Forty-five were excluded because 37 were not confirmed by RT-PCR and eight had incomplete medical charts.

The remaining 332 fatalities had a median age of 36 years (IQR = 13–53 years) and 177 (53%) were male. Children aged <18 years accounted for 93 (26%) of fatalities, those aged <5 years comprised 48 (52%), and infants aged less <6 months comprised 16 (33%). Although more fatalities were reported among patients aged 19–49 years, laboratory-confirmed influenza A H1N1pdm fatalities per 100,000 population were more common among children aged <5 years and persons aged 50–64 years (Table 1).

**Table 2.** Selected symptoms and physical signs at time of admission by age group in influenza A H1N1pdm confirmed fatalities (excluding patients with influenza A H1N1pdm nosocomial infections unless otherwise reported), Argentina, June 15th–July 31st, 2009.

| Age groups (years) | <5 N = 48 | 5–49 N = 179 | 50+ N = 105 | All ages N = 332 |
|--------------------|-----------|--------------|-------------|-----------------|
| Symptoms reported at presentation | | | | |
| Fever | 25/30 (83) | 118/132 (89) | 59/76 (78) | 202/238 (85) |
| Dyspnea | 34/38 (89) | 133/141 (94) | 87/91 (96) | 254/270 (94) |
| Cough | 14/19 (75) | 124/133 (93) | 84/88 (96) | 222/240 (93) |
| Gastrointestinal | 4/21 (19) | 34/96 (35) | 13/66 (20) | 51/183 (28) |
| Headache | 1/4 (25) | 28/48 (58) | 15/39 (38) | 44/91 (48) |
| Sore throat | 1/6 (17) | 18/55 (33) | 10/37 (27) | 29/96 (30) |
| Physical signs at admission | | | | |
| Temperature | 36.5 (36, 37.4) | 38 (36.9, 38.4) | 37.2 (36.5, 38.3) | 37.5 (36.5, 38.2) |
| Temperature >38 °C | 5/32 (16) | 68/135 (50) | 36/86 (42) | 109/253 (43) |
| Respiration rate | 51 (40, 64) | 30 (25, 40) | 28 (24, 36) | 32 (25, 40) |
| Elevated respiration rate | 24/30 (80) | 90/120 (75) | 50/75 (67) | 164/225 (73) |
| Heart Rate | 150 (130, 180) | 112 (100, 120) | 100 (82, 120) | 110 (90, 128) |
| Elevated heart rate | 31/37 (84) | 113/148 (76) | 47/92 (51) | 191/277 (69) |
| Systolic Blood Pressure | 89 (79, 97) | 110 (100, 130) | 120 (100, 139.5) | 110 (97, 130) |
| Low Systolic Blood Pressure | 6/13 (46) | 16/138 (12) | 11/92 (12) | 33/243 (14) |
| Crackles | 19/30 (63) | 121/132 (92) | 70/80 (88) | 210/242 (87) |
| Wheezing | 17/27 (63) | 39/88 (44) | 40/64 (63) | 96/179 (54) |

*Unless otherwise stated.

**Ethics statement**

To maintain data confidentiality, unique identifiers on medical records were coded. Institutional review board approval was not required as the NMHA empowered the commission to confidentially review medical records of influenza A H1N1pdm fatalities through a ministerial resolution [5] during this public health emergency.
Thirty fatalities were not hospitalized for influenza symptoms but rather acquired nosocomial influenza A H1N1pdm infections. Excluding these cases, the most common symptoms at admission were dyspnea (94%), cough (93%), and history of fever (85%). During admission, most patients had elevated respiration rates (73%) and heart rates (69%). On auscultation, crackles were more common among fatalities aged ≥5 years compared to fatalities <5 years (89% vs. 63%, \(p<0.01\)). Anemia was present in 54% of patients, and more common among those aged <5 years old, less than 11.5 g/dl Hb for patients 5–12 years old, less than 12 g/dl Hb for patients 12–15 years old and non-pregnant women (>15 years old), and less than 13 g/dl Hb for men 15 years and older.

Anemia was defined as less than 11 g/dl of hemoglobin (Hb) for patients less than 5 years old and for pregnant women (≥15 years old), less than 11.5 g/dl Hb for patients 5–12 years old, less than 12 g/dl Hb for patients 12–15 years old and for non-pregnant women (>15 years old), and less than 13 g/dl Hb for men 15 years and older.

**Acidosis or hypoxemia** is defined as pH under 7.36 or oxygen saturation less than 96%.

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Table 3. Selected hematology at time of admission by age group in influenza A H1N1pdm confirmed fatalities (excluding patients with influenza A H1N1pdm nosocomial infections unless otherwise reported), Argentina, June 15–July 31, 2009.

| Hematology                  | <4,500 cells/ml | >11,000 cells/ml | >150,000 cells/ml |
|-----------------------------|-----------------|------------------|-------------------|
| Leukopenia                  | 8/31 (26)       | 38/124 (31)      | 20/85 (24)        |
| Leukocytosis                | 13/31 (42)      | 25/124 (20)      | 30/85 (35)        |
| Lymphopenia**               | 15/21 (71)      | 56/71 (79)       | 38/41 (93)        |
| Anemia†                     | 28/41 (68)      | 66/162 (41)      | 44/99 (44)        |
| Thrombocytopenia (<150,000 cells/ml) | 6/25 (24) | 40/81 (49) | 19/53 (36) |

Table 4. Selected X-ray patterns at time of admission by age group in influenza A H1N1pdm confirmed fatalities (excluding patients with influenza A H1N1pdm nosocomial infections unless otherwise reported), Argentina, June 15th–July 31st, 2009.

| X-Ray patterns at admission |
|-----------------------------|-----------------|------------------|
| Consolidation only          | 14/26 (54)      | 37/93 (40)       |
| Bilateral                   | 12/14 (86)      | 26/36 (72)       |
|Interstitial only            | 8/26 (31)       | 29/93 (31)       |
| Bilateral                   | 8/8 (100)       | 28/29 (97)       |
|Consolidation + Interstitial | 3/26 (12)       | 23/93 (25)       |
| Bilateral                   | 3/3 (100)       | 21/23 (91)       |

Primary Diagnosis at admission (includes patients that developed influenza A H1N1pdm nosocomial infections)

| Pneumonia                    | 26/48 (54)      | 133/179 (74)     | 78/105 (74)      | 237/332 (71) |
| Other respiratory diagnosis* | 16/48 (33)      | 28/179 (16)      | 21/105 (20)      | 65/332 (20)  |
| No record of any respiratory diagnosis *** | 6/48 (10) | 18/179 (13) | 6/105 (6) | 30/332 (9) |

* COPD, Asthma, atelectasis, tuberculosis, respiratory failure.
** Fever syndrome, septic shock, leukemia, gastrointestinal problems, pregnancy, HIV/AIDS.
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**Lymphopenia was defined as <3000 cells/ml for patients under 5 years old, <2000 cells/ml for patients 5-12 years old and <1500 cells/ml for patients over 12 years old.

**Anemia was defined as less than 11 g/dl of hemoglobin (Hb) for patients less than 5 years old and for pregnant women (≥15 years old), less than 11.5 g/dl Hb for patients 5–12 years old, less than 12 g/dl Hb for patients 12–15 years old and non-pregnant women (≥15 years old), and less than 13 g/dl Hb for men 15 years and older.

**Acidosis or hypoxemia” is defined as pH under 7.36 or oxygen saturation less than 96%.

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common among patients aged ≥50 compared to the other age groups (p<0.001). Eighty-two percent of patients had oxygen saturation <96%, which was more common among patients ≥5 years (p<0.01); while acidosis (pH<7.36) and elevated pCO2 (>44 mmHg) were more common among patients <5 years (p<0.01) (Table 3).

Among 176 patients with admission radiographs, (79%) had bilateral chest infiltrates, 71 (40%) had consolidation, 61 (35%) had interstitial pattern, 37 (21%) had both, and six (3%) had other findings (Table 4). For 236 (71%) of the 332 patients (including those with nosocomial infections), the primary hospital admission diagnosis was pneumonia. Pneumonia, however, only accounted for 54% of the primary diagnoses among children aged <5 years, with other respiratory illnesses accounting for over one third of the admission diagnosis among this age group.

Of 304 patients admitted for influenza A H1N1pdm-associated illness (excluding nosocomial infections), the median time from symptom onset to admission was five days (IQR, 3–7 days). Most patients (299 [95%] of 315) needed ICU admission and, 292 were mechanically ventilated for a median of six days (IQR, 2–12 days).

Among the 252 patients with available information on the start date of their mechanical ventilation, 207 (82%) were mechanically ventilated outside of the ICU because of space-limitations. Hematologic failure was diagnosed in 44%, hepatic failure in 5% and multiorgan failure in 71% of influenza A H1N1pdm fatalities.

Of all 332 patients, 290 (87%) received antiviral treatment; 103 (76%) ≤2 days of admission but only 33 (13%) of 253 with information on timing of administration received antivirals ≤48 hours of symptom onset. None of the 40 fatalities aged <5 years received antivirals ≤48 hours of symptom onset; 20% of these children received antivirals ≤48 hours of a doctor’s visit, and only 55% received antivirals ≤48 hours of hospitalization compared to at least 78% in older age groups (Table 5).

As the pandemic progressed, the mean time from symptom onset to first doctor visit and symptom onset to hospitalization among fatalities decreased (p<0.001). Similarly, the mean time from symptom onset to antiviral treatment decreased from 19 days during epidemiologic week 22 to four days during week 28 (p<0.001). The time from the first doctor visit to antiviral treatment also decreased as the pandemic progressed (p<0.001) while the time from hospitalization to antiviral treatment remained brief (Figure 2A–E).

At least one comorbidity [1] was reported in 75% of cases with such information in their charts. The most common comorbidities were chronic pulmonary disease (including asthma) in 28%, metabolic disorder (including diabetes) in 25%, and immunosup-

| Table 5. Treatment and Clinical course of 332 influenza A H1N1pdm-confirmed fatalities, June 15th–July 31st, 2009. |
|---------------------------------------------------------------|
| N (%) total | N (%) total | N (%) total | N (%) total |
| Antiviral use (ATV) | 40/48 (83) | 156/179 (87) | 94/105 (90) | 290/332 (87) |
| Received ATV treatment | 0/36 (0) | 23/139 (17) | 12/79 (15) | 33/253 (13) |
| <48 hr after onset (early treatment) | 6/30 (20) | 56/112 (50) | 43/68 (63) | 105/210 (50) |
| <48 hr after first doctor visit | 18/33 (55) | 103/129 (80) | 62/79 (78) | 183/241 (76) |
| <48 hr after admission | 46/47 (98) | 162/170 (95) | 91/98 (93) | 299/315 (95) |
| Intensive care | 47/47 (100) | 160/174 (92) | 85/99 (86) | 292/320 (91)** |
| Mechanical ventilation (MV) | 0 (0–0)/140 | 0 (0–0)/73 | 0 (0–0)/233 |
| Median No. Days: ICU to MV (IQR) | 7 (4–13)/41 | 6 (2–12)/152 | 5 (2–11)/81 | 6 (2–12)/252 |
| Timelines Median Days (IQR)/N*** |
| Onset—First doctor visit | 1 (0–3)/31 | 2 (0–4)/116 | 3 (1–5)/75 | 2 (0–4)/222 |
| First doctor visit—ATV treatment | 6 (3–10)/29 | 2 (0–5)/103 | 1 (0–5)/64 | 2 (0–5)/196 |
| Onset—Hospitalization | 6 (2–9)/27 | 4 (3–6)/125 | 5 (3–7)/79 | 5 (3–7)/231 |
| Hospitalization—ATV treatment | 1 (0–4)/27 | 0 (0–2)/118 | 0 (0–1)/73 | 0 (0–2)/218 |
| Hospitalization—ICU | 0 (0–2)/32 | 1 (0–2)/127 | 0 (0–1)/75 | 0 (0–1)/234 |
| Onset—Death | 15 (8.5–22)/32 | 12 (7–20.5)/140 | 13 (7–20)/87 | 13 (7–20)/259 |

*eleven case-patients were ventilated outside of the ICU because of space-limitations.
**excluding influenza A H1N1pdm nosocomial infections.
***excluding influenza A H1N1pdm-associated illness.
expression in 24% of fatalities. Among children aged <5 years, chronic pulmonary disease (42%) was also the most common comorbidity followed by neonatal pathologies (i.e. genetic disorders, congenital malformations, and preterm births) (35%) and neurologic disease (19%) (Table 6). The prevalence of asthma was low among fatalities (6%). In contrast, 4% of patients were HIV positive, a proportion higher than the 0.4% country prevalence [12]. Similarly, 32% of fatalities were obese, a proportion higher than the 15% country prevalence [13].

We identified 16 pregnant women and four postpartum women among fatalities. Four of the pregnant women were in their second trimester while 11 were in their third trimester. Eight delivered by caesarean section after being admitted to the ICU, two whom had stillbirths. Pregnant women had significantly longer ICU stays than non-pregnant women aged 15–44 years (11 vs. 4 days, p = 0.01). One pregnant and two postpartum women did not receive any antiviral treatment during the course of their illness. Among the 17 pregnant or postpartum women that received

Figure 2. Mean number of days from date of onset to date of first doctor visit (A), hospitalization (B), and antiviral treatment (C); Mean number of days from first doctor visit (D) and hospitalization (E) to antiviral treatment among influenza A H1N1pdm fatalities by epidemiological week of onset.
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antivirals, none received them within the recommended 48 hours after illness onset but a median of seven days (IQR: 5–9 days) later. Fifty percent received antivirals 1 day after hospitalization (Table 7).

Discussion

Most fatal cases presented to the hospital with acute severe respiratory compromise or ARDS and required immediate mechanical ventilation with respiratory failure as their main cause of death. The median age of fatalities was consistent with those found in other influenza A H1N1pdm studies [14], [15], [16], [17], [18], [19]. Three-quarters of confirmed influenza A H1N1pdm fatalities occurred among persons aged <50 years, however, the highest incidence of H1N1pdm fatalities occurred among persons aged 50–65 years and children <5 years (half of them <1 year).

Two-thirds of all cases had at least one comorbidity as defined by ACIP [11]. In addition, healthy pregnant women were disproportionately affected as has been found in other studies [2], [20], [21], [22]. The unusually high proportion of decedents who were obese in our case-series (i.e. 33%) is consistent with studies [2] [23], [24] that suggest that obesity may be a risk factor for severe influenza disease. Although our study did not determine which fatalities had acquired immunodeficiency syndrome or were on antiretroviral therapy, we found a higher prevalence of influenza A H1N1pdm co-infection among HIV positive fatalities when compared to the general population. Such data are important because early reports suggested that HIV-infected individuals might experience more severe complications from influenza A H1N1pdm infection [20], [24], [25], [26], a finding not confirmed in later studies [27], [28], [29].

Even though the government of Argentina recommended oseltamivir treatment to high-risk persons [30], fewer than 15% of fatalities received antiviral treatment during the recommended 48 hours after symptom onset and only half within 48 hours of a physician visit. No children aged <5 years received early treatment.

Table 6. Comorbidities* and underlying conditions among influenza A H1N1pdm confirmed fatalities by age groups, Argentina, June 15th–July 31st, 2009.

| Age groups | <5 | 5–49 | 50+ | Total |
|------------|----|------|-----|-------|
| N = 48 | N = 179 | N = 105 | N = 332 |
| **Comorbidities*** | N (%) total |
| Chronic pulmonary disease† | 20/48 (42) | 29/152 (19) | 33/94 (35) | 82/294 (28) |
| Asthma | 0/41 (0) | 11/142 (8) | 5/89 (6) | 16/272 (6) |
| Cardiovascular disease§ | 5/41 (12) | 16/154 (10) | 35/94 (37) | 56/289 (19) |
| Renal disease | 2/41 (5) | 11/151 (7) | 18/88 (21) | 31/280 (11) |
| Hepatic disease | 1/39 (3) | 6/151 (5) | 4/85 (5) | 13/275 (5) |
| Hematological disease | 3/38 (8) | 22/148 (15) | 8/88 (9) | 33/274 (12) |
| Metabolic disorder¶ | 3/42 (7) | 34/156 (22) | 35/91 (39) | 72/289 (25) |
| Diabetes | 0/40 (0) | 22/150 (15) | 22/87 (26) | 44/277 (16) |
| Immunosuppression# | 4/42 (10) | 43/163 (26) | 24/92 (26) | 71/297 (24) |
| HIV/AIDS | 0/38 (0) | 10/155 (7) | 1/85 (1) | 11/278 (4) |
| Other comorbidities** | 29/48 (60) | 34/160 (21) | 12/93 (13) | 75/301 (25) |
| Neurologic disease†† | 9/48 (19) | 33/160 (21) | 12/93 (13) | 54/301 (18) |
| Neonatal pathologies | 17/48 (35) | n/a | n/a | n/a |
| At least 1 comorbidity* | 39/48 (81) | 115/170 (68) | 85/101 (84) | 239/319 (75) |

**Underlying conditions**

| | <5 | 5–49 | 50+ | Total |
|----------------|----|------|-----|-------|
| Obesity | 0/40 (0) | 54/154 (35) | 34/82 (42) | 88/276 (32) |
| Hypertension | 1/40 (3) | 28/153 (18) | 58/94 (62) | 87/287 (30) |
| Smoking§§ | n/a | 35/171 (20) | 29/103 (28) | 64/321 (20) |
| Alcohol dependence | n/a | 9/145 (6) | 15/86 (17) | 24/269 (9) |
| Substance abuse | n/a | 6/142 (4) | 2/81 (3) | 8/261 (3) |
| Pregnancy/postpartum¶¶ | n/a | 20/91 (22) | 0/44 (0) | 20/155 (13) |

* Comorbidities as defined by the Advisory Committee on Immunization Practices 10.
† Including asthma.
§ Excluding hypertension.
¶ Persons who have diabetes (including diabetes caused by medications or by type 2 diabetes).
# Persons who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration.
†† Including cerebrovascular disease, cerebral palsy, epilepsy, down syndrome, neurochronic disease.
‡‡ Does not include former and passive smokers.
* Women only.
n/a not applicable.

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women were identified as high-risk and the government of 
[N = 44]. During the pandemic, pregnant pregnancy as a risk factor for severe influenza illness and death 
case-series of decedents is concordant with reports that identify 
supervision to children aged 
clinicians were required to provide antiviral treatment to children 
among very young children. Indeed, at the onset of the pandemic, 
may have been caused by the clinician’s lack of familiarity with the 
use of oseltamivir and their concerns over potential adverse 
events among pregnant women and their unborn children. 

Although other studies have shown a high frequency of dyspnea 
in critically ill patients, our analyses demonstrates our case-patients 
also frequently had tachypnea (73%), tachycardia (69%) and 
acidosis and/or hypoxemia (88%) on admission. Gastrointestinal 
symptoms were more frequently reported than in adults infected 
with seasonal influenza but not as frequently as in other influenza 
A H1N1pdm studies [14], [20], [21], [36]. Thrombocytopenia 
on admission was frequently observed among decedents, and 
was more prevalent than previously reported among patients with 
influenza A H1N1pdm infection [37], [38], [39]. 

During the pandemic, an insufficient number of ICU beds were 
available for all patients. Critically ill patients occasionally 
mechanical ventilation outside the ICU, at the emergency 
department or special facilities [40], [41]. In most patients, ARDS 
with respiratory failure was the leading cause of death. This is in 
contrast to ARDS caused by other etiologies where respiratory 
failure accounts for <20% of deaths [42], [43], [44]. This finding 
has also been observed in other influenza A H1N1pdm studies [2], 
[45], [46]. Acute renal failure requiring dialysis was observed 
frequently among patients aged ≥5.

Our analysis indicates that time from symptom onset to clinic 
visit and to hospitalization decreased as the pandemic progressed. 
Time to antiviral treatment also decreased during the first two 
weeks of the study. These data suggest that affected persons sought 
care earlier and physicians used antivirals more rapidly as the 
pandemic progressed and may explain why the case fatality 
proportion of hospitalized patients decreased from a peak at the 
beginning of the pandemic. The initial delay in health seeking may 
have been caused by high risk persons that did not suspect that 
they had influenza illness or that were not aware of the need to 
seek care within 48 hours of symptom onset when antivirals are 
most effective. The initial delay in treatment could have been 
caused by unavailability of antivirals or by primary care physicians 
unfamiliar with their use. In Argentina, only a small stockpile of 

treatment was available at the beginning of the pandemic which 
was insufficient to treat all patients once influenza A H1N1pdm 
spread throughout the country.

Our study has several limitations. Our case-series design did not 
allow us to collect information from controls to further substantiate 
whether potential risk factors were indeed associated with death 
from H1N1pdm. The data obtained was limited to non-
standardized medical records and there was no opportunity to 
confirm details with family members. Due to the limited 
availability of laboratory testing during the study period, the 
number of confirmed fatalities represented only about half of the 
currently confirmed fatalities and may not be representative of other 
fatalities during this period or of those who occurred at home. Moreover, we only assessed hospitalized laboratory-
confirmed influenza A H1N1pdm fatalities for which we had 
medical records, and these cases might have manifested differently

| Table 7. Description of pregnant, postpartum and fertile age 
women among influenza A H1N1pdm confirmed deceased 
patients, Argentina, June 15th–July 31st, 2009. |
|-----------------|-----------------|
| Pregnant and | Non-pregnant |
| Postpartum (N = 20) | (N = 44) |
| Median age (range) | 26.5 (19–41) | 32.5 (16–44) |
| Postpartum at symptom onset | 4 | n/a |
| Pregnant at symptom onset | 16 | n/a |
| Second trimester | 4/15 | n/a |
| Third trimester | 11/15 | n/a |
| Stillbirths | 2/16 | n/a |
| Delivered after ICU admittance | 8/16 | n/a |
| C-sections | 13/14 | n/a |
| Comorbidities | | |
| Chronic pulmonary disease | 1/15 | 9/40 (23%) |
| Cardiovascular disease | 1/17 | 3/39 (8%) |
| Renal disease | 0/16 | 2/40 (5%) |
| Hepatic disease | 0/16 | 4/39 (10%) |
| Hematological disease | 3/18 | 3/37 (8%) |
| Metabolic disorder (diabetes) | 3/18 | 16/39 (41%) |
| Immunosuppression | 1/18 | 12/41 (29%) |
| Other condition | 2/18 | 4/39 (10%) |
| At least 1 condition | 9/19 | 29/42 (70%) |
| Obesity | 2/16 | 16/38 (42%) |
| Hypertension | 2/16 | 7/40 (18%) |
| Antiviral (ATV) treatment | 17/20 | 39/44 (89%) |
| <48hrs from symptom onset | 0/17 | 4/29 (14%) |
| Timelines: Median Days (IQR) | | |
| Onset—ATV treatment | 7 (5–9) | 5 (3–7) |
| First doctor visit—ATV treatment | 4 (2.5–6) | 1 (0–5) |
| Hospitalization—ATV treatment | 1 (1–3) | 0 (0–2) |
| Onset—Hospitalization | 4 (2–6) | 4 (2–5) |
| ICU— Death | 11 (6–16) | 4 (2–12) |
| Onset— Death | 14 (13–17) | 9 (5–18) |

n/a not applicable.
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Argentina approved social distancing measures to protect them 
such as strongly urging them to stay home from work with paid 
leave. We observed that <50% of pregnant women had 
comorbidities, compared to 70% of influenza A H1N1pdm 
infected non-pregnant women and 80% of pregnant women in 
the U.S. [34]. In our study, these predominantly healthy pregnant 
and postpartum women received antivirals a median of seven days 
after symptom onset compared to five days among non-pregnant 
women. Such finding that suggests that although antiviral 
treatment ≤4 days after symptom onset was associated with 
milder influenza A H1N1pdm disease [34], clinicians may have 
been hesitant to use them possibly due to lack of familiarity with the 
use of oseltamivir and their concerns over potential adverse 


events among pregnant women and their unborn children.

The high proportion of pregnant or postpartum women in our 
case-series of decedents is concordant with reports that identify 
pregnancy as a risk factor for severe influenza illness and death 
[21], [32], [32], [34], [35]. During the pandemic, pregnant 
women were identified as high-risk and the government of

![Table 7. Description of pregnant, postpartum and fertile age women among influenza A H1N1pdm confirmed deceased patients, Argentina, June 15th–July 31st, 2009.](https://www.plosone.org/article/file/10.1371/journal.pone.0033670.t007)
to those occurring at home or those not tested for influenza. Laboratory samples and tests did not follow a study protocol but represented the choices made by clinicians during the management of patients. Our study did not include autopsy data. Several parameters that define risk factors and underlying conditions, such as height and weight data, smoking history and alcohol consumption, were not available for all case-patients. We were unable to compare risk factors for death compared to severe disease and the effect of antiviral treatment as we did not review charts from surviving hospitalized patients.

After the study was conducted, Argentina has emphasized protecting young children and pregnant women. The 2010 monovalent influenza A H1N1pdm influenza vaccination campaign in Argentina aimed at a 95% coverage among pregnant women and 85% coverage among children aged <4 years [47]. Continued efforts should be made to promote influenza vaccination among groups at high risk of complications from influenza infection, ensure national surge capacity for intensive care and mechanical ventilation, secure antiviral stocks, guarantee their availability and accessibility, and to provide guidelines to health care providers on appropriate and timely use especially in vulnerable populations.

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Author Contributions

Data analyzed: the EC FEB PRC MAW. Wrote the paper: AMB CH CA PB AG OR MGC. Interpreted findings in the context of the international literature and assisted in manuscript development: FC EAB PRC MAW.

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