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Clinical Characteristics and Mortality of Influenza A H1N1 and Influenza-Like Illness in Mexico City in the 2013-2014 Winter Season

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ABSTRACT

Background: The 2013-2014 influenza season in Mexico City was severe and mainly due to influenza A H1N1, as was the 2009 pandemic. **Objective:** To describe features of the outbreak and to compare the characteristics of patients with and without viral identification. **Methods:** We reviewed the medical charts of all individuals with influenza or influenza-like illness admitted to a referral hospital for respiratory diseases in Mexico City from January 2013 to March 2014, whether influenza virus was identified or not. **Results**: We included 233 patients with influenza-like illness, 99 of whom had laboratory confirmed influenza; one-half of all patients required mechanical ventilation and 25% were admitted to the intensive care unit. Patients with confirmed influenza had a more severe disease than those without confirmation. A total of 52 (22.3%) patients died in hospital; survival was greater among patients hospitalized in the intensive care unit compared with those who remained in regular wards. **Conclusions:** Influenza A H1N1 continues to cause significant outbreaks in Mexico City. Patients with influenza-like illness had a similar clinical course regardless of laboratory confirmation of influenza, suggesting that their illness likely belonged to the same outbreak. Mechanical ventilation in regular hospital wards may be lifesaving, although the outcome is worse than at an intensive care unit. (REV INVES CLIN. 2016;68:147-53)

Key words: Influenza. Mechanical ventilation. Intensive care unit. Mortality.

INTRODUCTION

In March 2009, the novel influenza A (H1N1) was first reported in the southwestern USA and in Mexico, becoming the first pandemic of the 21st century. The population and healthcare system in Mexico City experienced the first and greatest early burden of the critical illness[1]. The 2009 influenza A H1N1 pandemic caused the deaths of 18,449 individuals with laboratory confirmed infection worldwide[2]. However, recent data increase the estimates to 200,000, including persons who died from influenza-like illness (ILI) or

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from diverse complications and who had no viral testing in countries or regions without access to the standard influenza virus real-time polymerase chain reaction (RT-PCR)[3]. In December 2013 we identified a rapidly growing number of persons with ILI, including severe cases, many of whom had laboratory confirmed influenza A H1N1. In 2011 Mexico experienced another winter outbreak of influenza A H1N1[4]. This report describes the clinical characteristics of patients hospitalized in our center from December 1, 2013 to February 28, 2014 with ILI as well as confirmed cases of influenza A H1N1 virus infection. In addition, we explored potential cofactors involved with mortality.

MATERIAL AND METHODS

Design and population study

We carried out a cross-sectional study collecting, in a standardized questionnaire, information from the clinical records of patients who were admitted from January 1, 2013 to March 3, 2014 to the National Institute of Respiratory Diseases of Mexico (INER). We included patients 18 years of age or older with confirmed influenza A H1N1 or ILI. Influenza-like illness was defined according to the World Health Organization (WHO) as sudden-onset fever (> 38°C) with cough or sore throat, in the absence of other diagnoses. A case of confirmed influenza A H1N1 is usually defined as the presence of ILI plus a positive RT-PCR or viral culture[5], but for the present work, influenza confirmation was obtained by RT-PCR. Sociodemographic variables comprised age, gender, and place of residence. We measured weight and height and estimated the body mass index (BMI) of patients. As clinical variables, we included respiratory signs and symptoms as well as smoking status, days of hospitalization, the presence and duration of mechanical ventilation, admission to the intensive care unit (ICU), vaccine against influenza, and in-hospital death. Laboratory measurements included hemoglobin (g/dl), platelet count ($\times 10^3$/µl), leukocytes ($\times 10^3$/µl), lymphocytes ($\times 10^3$/µl), creatinine (mg/dl), blood urea nitrogen (BUN, mg/dl), albumin (g/dl), bilirubin (mg/dl), creatine phosphokinase (CPK, U/ml), and lactate dehydrogenase (LDH, U/l).

We recorded the presence of comorbidities for each patient as the following dichotomous variables (yes/no): overweight/obesity; systemic arterial hypertension; asthma; type 2 diabetes mellitus (DM2); heart disease (most common was chronic heart failure [CHF]); chronic obstructive pulmonary disease (COPD); interstitial lung disease (ILD); human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS), and pulmonary tuberculosis (TB). Data on the number of medical emergency consultations, hospital admissions, and patients on mechanical ventilation due to ILI were obtained from the Department of Epidemiological Surveillance of the INER.

Statistical analysis

We compared all the variables, stratifying by condition of influenza (ILI vs. laboratory confirmed influenza A H1N1) and death to identify risk factors. Continuous variables were compared using Student's *t* test and categorical variables, with Pearson's chi-square test. Risk of in-hospital death was estimated by fitting logistic regression models and survival function, employing Kaplan-Meier models and Cox proportional hazard models as function of influenza confirmation, mechanical ventilation, place of care, presence of exposure, and comorbidities. A p value of < 0.05 was considered as statistically significant for all tests. Analysis was conducted using STATA v.12 statistical software (Stata Corp., College Station, TX, USA).

RESULTS

A total of 233 patients were included; mean age was 46.9 years (standard deviation [SD]: 13.8 years), and 137 (58.8%) were male. Patients were hospitalized for 19 days on average (SD: 18 days). Influenza was confirmed in 99 patients (42.5%), whereas 134 (57.5%) had ILI with negative RT-PCR tests, missing tests, or insufficient samples. Most of the patients (68.2%) resided in Mexico City, while the rest came from another state. Less than 5% of the included patients were vaccinated for the season when the illness occurred. A comorbid condition was identified in 92.3% of all patients. One-half of the patients (50.6%) received mechanical ventilation and 25.3% were admitted to the ICU. Sixty-one patients had worsening respiratory failure and required mechanical ventilation while in a general hospital ward since there were no beds available in the ICU. Fifty-two patients (22.3%) died in hospital (Table 1).

Table 1. Sociodemographic and clinical characteristics of the entire group (n = 233)

Variable	Value*
Age, years	46.9 (13.8)
Male, n (%)	137.0 (58.8)
Residence in Mexico City, n (%)	159.0 (68.2)
Influenza A H1N1, n (%)	99.0 (42.5)
BMI, kg/m^2	30.9 (6.9)
Influenza vaccine, n (%)	10.0 (4.3)
Hospitalization, days	18.8 (17.9)
Active smoker, n (%)	69.0 (29.6)
Mechanical ventilation, n (%)	118.0 (50.6)
Admitted to ICU, n (%)	59.0 (25.3)
Platelet count, × 10^3/µl	223.9 (107.3)
Creatinine, mg/dl	1.2 (0.91)
BUN, mg/dl	19.1 (16.1)
Albumin, g/dl	3.0 (0.7)
Bilirubin, mg/dl	0.8 (0.5)
CPK, U/ml†	157.0 (67.0, 411.0)
LDH, U/l	482.7 (419.5)
Hemoptysis, n (%)	39.0 (16.7)
Diabetes mellitus, n (%)	20.0 (8.6)
COPD, n (%)	12.0 (5.2)
Any comorbidity‡, n (%)	215.0 (92.3)
Death, n (%)	52.0 (22.3)

*Mean and standard deviation (SD) or number and percentage when indicated; †Represent median, 25th and 75th percentile. ‡Obesity, hypertension, asthma, heart disease (most common, chronic heart failure), interstitial lung disease, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), tuberculosis. BMI: body mass index; ICU: intensive care unit; BUN: blood urea nitrogen; CPK: creatinine phosphokinase; LDH: lactic dehydrogenase; COPD: chronic obstructive pulmonary disease.

The clinical characteristics and laboratory results of the patients on hospital admission stratified by the condition of influenza are presented in table 2. No difference was found between the two groups in the proportion of patients who lived in Mexico City. Individuals with confirmed influenza had more severe disease compared with those with ILI. Patients with confirmed influenza required more mechanical ventilation and ICU admission and had higher levels of LDH and CPK, but the difference in mortality, although higher in confirmed cases, was not statistically significant. Confirmed cases also had a higher BMI than those with ILI.

Patients who died were often older ($p < 0.01$), male ($p < 0.05$), on mechanical ventilation ($p < 0.01$), and had hemoptysis ($p < 0.01$) or diabetes mellitus ($p < 0.05$). In addition, deceased patients had more abnormalities in several laboratory tests: higher than normal BUN, bilirubin, CPK and LDH, or lower albumin. The BMI was not different between groups (Table 3).

Of 118 patients who received mechanical ventilation, 61 (51.7%) were cared for outside the ICU (regular hospital wards, emergency room), and 57 (48.3%) at the ICU. Of the 61 patients treated outside the ICU, 35 (57.4%) died, compared with 14 of 57 (24.6%) admitted to the ICU ($p < 0.01$) (Table 4).

Results of logistic regression suggest no differences between patients with confirmed influenza or ILI in most measurements, except for a lower platelet count in individuals with confirmed influenza (odds ratio [OR]: 0.99; $p < 0.01$) (Table 5).

A Cox proportional hazard model confirmed that ICU admission reduced the risk for death (hazard ratio [HR]: 0.27; $p < 0.01$), while hemoptysis (HR: 2.24; $p < 0.01$), mechanical ventilation (HR: 6.23; $p < 0.05$), age (HR: 1.04; $p < 0.05$), and being male (HR: 4.72; $p < 0.01$) were associated with death. No statistical difference in mortality was found between patients with confirmed influenza and those with ILI (HR: 0.99; $p = 0.99$) (Table 6).

Figure 1 depicts Kaplan-Meier survival curves for patients who were ventilated, stratifying by place of care (ICU vs. ward). Survival was higher among patients admitted to the ICU than among those treated in wards ($p < 0.01$). Mean 95% confidence interval [95% CI] of survivor days were 89.8 days (range, 75.0-104.5 days) for patients in the ICU and 33.4 days (range, 25.0-41.8 days) for those cared for in wards. Data were confirmed in multivariate Cox proportional hazard models (HR: 0.27; $p < 0.01$) (Table 6), also demonstrating an increased risk of death in patients receiving mechanical ventilation (HR: 6.23; $p < 0.05$). Figure 2 illustrates the survival functions obtained from the model in table 6 for patient care at ICU and in wards. The functions were evaluated using the average values reported in table 1 for continuous variables and considering a male patient with hemoptysis, diabetes mellitus, and mechanical ventilation. The figure presents higher survival for patients admitted to the ICU compared with those cared for in regular wards under similar conditions. Figure 3 describes the number of medical consultations, hospital admissions, and patients on mechanical ventilation in the 2013-2014 winter season compared to previous outbreaks since the 2009 H1N1 pandemic.

Table 2. Sociodemographic and clinical characteristics by influenza condition

Variable*	ILI n = 134	Influenza A H1N1 n = 99	P value
Age, years	46.9 (14.5)	46.9 (12.8)	0.994
Male, n (%)	74.0 (55.2)	63.0 (63.6)	0.197
Residence in Mexico City, n (%)	98.0 (73.1)	61.0 (61.6)	0.062
BMI, kg/m^2	29.6 (6.6)	32.5 (6.9)	**< 0.01**
Hospitalization, days	16.8 (15.4)	21.4 (20.7)	0.062
Active smoker, n (%)	40.0 (29.9)	29.0 (29.3)	0.475
Mechanical ventilation, n (%)	60.0 (44.8)	58.0 (58.7)	**< 0.05**
Admitted to ICU, n (%)	27.0 (20.2)	32.0 (32.3)	**< 0.05**
Platelet count, × 10^3/µl	241.4 (115.6)	200.1 (89.9)	**< 0.01**
Creatinine, mg/dl	1.1 (1.0)	1.2 (0.8)	0.177
BUN, mg/dl	17.7 (16.6)	21.1 (15.1)	0.114
Albumin, g/dl	3.9 (0.7)	2.9 (0.6)	0.076
Bilirubin, mg/dl	0.7 (0.5)	0.8 (0.6)	0.827
CPK, U/ml†	122.0 (58, 361)	195.0 (99, 575)	**< 0.01**
LDH, U/l	396.3 (312.5)	599.6 (510.1)	**< 0.01**
Hemoptysis, n (%)	22.0 (16.4)	17.0 (17.2)	0.879
Diabetes mellitus, n (%)	12.0 (8.9)	8.0 (8.1)	0.814
COPD, n (%)	6.0 (4.5)	6.0 (6.1)	0.589
Any comorbidity, n (%)	123.0 (91.8)	92.0 (92.9)	0.748
Death, n (%)	27.0 (20.2)	25.0 (25.3)	0.355

*Data are mean and standard deviation (SD) or number and percentage when indicated; †Represent median, 25th and 75th percentile; medians compared by Wilcoxon rank-sum test.
ILI: influenza-like illness; BMI: body mass index; ICU: intensive care unit; BUN: blood urea nitrogen; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; COPD: chronic obstructive pulmonary disease.

Table 3. Sociodemographic and clinical characteristics by mortality

Variable*	Surviving patients n = 181	Deceased patients n = 52	P value
Age, years	44.9 (13.6)	53.7(12.4)	**< 0.01**
Male, n (%)	99.0 (54.7)	38.0 (73.1)	**0.018**
Residence in Mexico City, n (%)	128.0 (70.7)	31.0 (59.6)	0.130
BMI, kg/m^2	30.7 (7.2)	31.3 (5.5)	0.570
Hospitalization, days	18.5 (16.8)	19.6 (21.7)	0.756
Active smoker, n (%)	58.0 (32.0)	11.0 (21.2)	0.450
Influenza A H1N1, n (%)	74.0 (40.9)	25.0 (48.1)	0.355
Mechanical ventilation, n (%)	69.0 (38.1)	9.0 (94.2)	**< 0.01**
Admitted to ICU, n (%)	45.0 (24.9)	14.0 (26.9)	0.763
Platelet count, × 10^3/µl	235.1 (109.1)	184.4 (91.1)	0.136
Creatinine, mg/dl	1.1 (0.9)	1.5 (1.0)	0.140
BUN, mg/dl	15.9 (12.2)	30.6 (22.1)	**< 0.01**
Albumin, g/dl	3.1 (0.7)	2.6 (0.5)	**< 0.01**
Bilirubin, mg/dl	0.7 (0.4)	0.9 (0.7)	**< 0.01**
CPK, U/ml †	130.0 (63, 341)	251.0 (102, 662)	**0.011**
LDH, U/l	386.5 (281.1)	821.1 (613.0)	**< 0.01**
Hemoptysis, n (%)	21.0 (11.6)	18.0 (34.6)	**< 0.01**
Diabetes mellitus, n (%)	11.0 (6.1)	9.0 (17.3)	**0.011**
COPD, n (%)	10.0 (5.5)	2.0 (3.9)	0.629
Any comorbidity, n (%)	165.0 (91.2)	50.0 (96.2)	0.235

*Data are mean and standard deviation (SD) or number and percentage when indicated; †Represent median, 25th and 75th percentile; medians compared by Wilcoxon rank-sum test.
BMI: body mass index; ICU: intensive care unit; BUN: blood urea nitrogen; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; COPD: chronic obstructive pulmonary disease.

Table 4. Sociodemographic and clinical characteristics by place of care

Variable*	Hospital ward n = 174	ICU n = 59	P value
Age, years	47.54 (14.1)	44.9 (12.7)	0.204
Male, n (%)	99.0 (56.9)	38.0 (64.4)	0.311
Residence in Mexico City, n (%)	115.0 (66.1)	44.0 (74.5)	0.226
BMI, kg/m^2	30.7 (6.9)	31.3 (6.8)	0.599
Inpatient days	13.2 (12.7)	34.9 (21.2)	< **0.01**
Active smoker, n (%)	45.0 (25.9)	24.0 (40.7)	< **0.01**
Influenza A H1N1, n (%)	67.0 (38.5)	32.0 (54.2)	< **0.05**
Mechanical ventilation, n (%)	61.0 (35.1)	57.0 (96.6)	< **0.01**
Platelet count, × 10^3/µl	223.80 (104.9)	224.4 (114.9)	0.970
Creatinine, mg/dl	1.1 (0.8)	1.3 (1.1)	0.212
BUN, mg/dl	17.8 (15.1)	23.1 (18.3)	< **0.05**
Albumin, g/dl	3.2 (0.7)	2.6 (0.5)	< **0.01**
Bilirubin, mg/dl	0.8 (0.6)	0.7 (0.3)	0.051
CPK, U/ml†	122.0 (64, 305)	328.0 (130, 753)	< **0.01**
LDH, U/l	425.2 (420.0)	649.1 (374.2)	< **0.01**
Hemoptysis, n (%)	28.0 (16.1)	11.0 (18.6)	0.650
Diabetes mellitus, n (%)	15.0 (8.6)	5.0 (8.5)	0.972
COPD, n (%)	12.0 (6.9)	0 (0)	< **0.05**
Any comorbidity, n (%)	164.0 (94.3)	51.0 (86.4)	0.052
Death, n (%)	38.0 (21.8)	14.0 (23.7)	0.763

*Data are mean and standard deviation (SD) or number and percentage when indicated. †Represent median and percentile 25th and 75th; medians compared with the Wilcoxon rank-sum test.
BMI: body mass index; BUN: blood urea nitrogen; CPK: creatinine phosphokinase; LDH: lactic dehydrogenase; COPD: chronic obstructive pulmonary disease.

Table 5. Logistic models for influenza A H1N1 (vs. influenza-like illness without viral confirmation)*

Variables	OR (95% CI)	P value
Death	0.84 (0.34-2.03)	0.69
Age, years	0.99 (0.97-1.01)	0.28
Masculine gender	1.42 (0.80-2.54)	0.23
BMI, kg/m^2	1.01 (0.98-1.04)	0.46
Inpatient days	1.01 (0.99-0.03)	0.51
Platelet count, × 10^3/µl	0.99 (0.994-0.999)	< **0.01**
CPK, U/ml	1 (1.00-1.001)	0.58
LDH, U/l	1 (1.00-1.00)	0.10
Mechanical ventilation	0.76 (0.32-1.79)	0.53
Cared for at ICU	1.36 (0.57-3.25)	0.48
Observations	217*	

*Models use patients with complete information in all variables. In this case, 93% (217/233) of patients had complete information in all the variables included in model.
OR: odds ratio; 95% CI: 95% confidence interval; BMI: body mass index; CPK: creatinine phosphokinase; LDH: lactic dehydrogenase; ICU: intensive care unit.

Table 6. Cox proportional hazard models of factors associated with death for all patients*

Variables	HR (95% CI)	P value
Cared for at ICU	0.27 (0.21-0.59)	< **0.01**
Hemoptysis	2.24 (1.08-4.64)	< **0.05**
Mechanical ventilation	6.23 (1.39-27.87)	< **0.05**
Influenza A H1N1	0.99 (0.50-1.08)	0.99
Age, years	1.04 (1.00-1.08)	< **0.05**
Masculine gender	4.72 (1.73-12.87)	< **0.01**
BMI, kg/m^2	1.04 (0.97-1.11)	0.231
Observations	210†	

*Model included lactic dehydrogenase, bilirubin levels, albumin, blood urea nitrogen, creatinine phosphokinase, platelet count, and diabetes mellitus, but no significant association was observed.
†Models (n = 210/233 or 90%) include patients with complete information in all variables.
HR: hazard ratio; 95% CI: 95% confidence interval; ICU: intensive care unit; BMI: body mass index.

Figure 1. Crude survival function for ventilated patients stratifying by place of care.

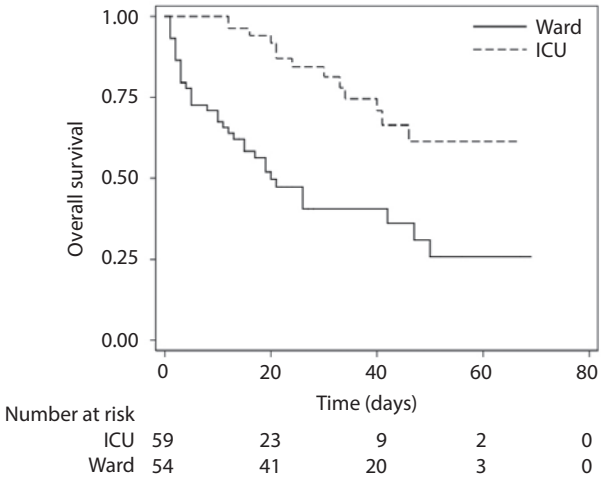


Figure 2. Adjusted survival function for all patients stratifying by place of care.
*Survival curves were estimated using coefficients from table 5, and mean values are reported in table 1 for continuous variables and considering a male patient with hemoptysis, diabetes mellitus, and mechanical ventilation

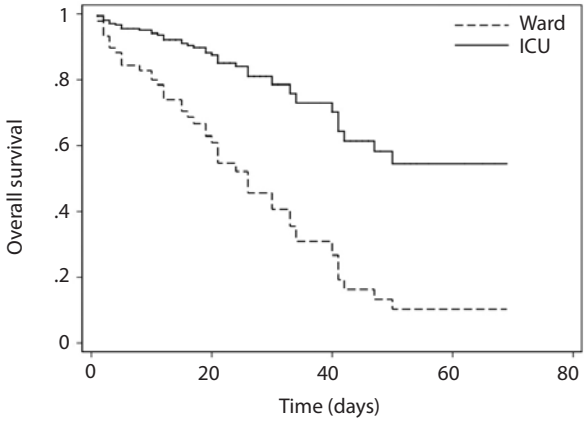
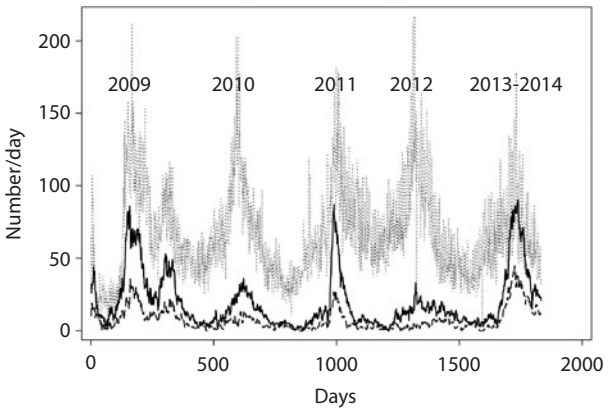


Figure 3. Historical number of emergency room consultations (upper graph), hospital admissions (middle continuous line), and patients on mechanical ventilation (lower line) with influenza-like illness from INER as a function of time from April 23, 2009, during the influenza pandemic when surveillance started.
We observed an annual outbreak of influenza-like illness, although years with severe cases alternated with milder years. The incidence in the 2013-2014 season was as high as that in the second pandemic peak.



DISCUSSION

The influenza outbreak in Mexico City in the winter of 2013-2014 was predominantly due to influenza A H1N1, as it was in 2009 and 2011, and tended to be more severe than the outbreaks of 2012 and 2010, when influenza virus subtype H3N2 variants predominated. During 2013 we observed a severe outbreak with a significant number of individuals requiring hospitalization (with a maximum of 90 out of 180 hospital beds available) and mechanical ventilation (maximum of 45 patients simultaneously), and with a number of hospital deaths similar to what we had seen during the 2009 pandemic (Fig. 3). Nearly all hospitalized individuals (96%) lacked the seasonal influenza vaccine; unfortunately, vaccination rates in Mexico are low, even in individuals with special risk factors for influenza complications. Again, individuals with ILI, similar to patients with confirmed influenza in most of the features studied although with a slightly milder disease, comprised about 50% of patients cared for[6]. A negative RT-PCR may have been due to several factors, such as delay in sampling (although with lung damage already in course), an inadequate sample, or upper airway sampling instead of samples obtained from lung secretions. In general, during an influenza outbreak, individuals with ILI should be considered as having influenza and be treated without delay with oseltamivir (Tamiflu®) or equivalent drugs accordingly, as we did in our hospital. This is important since estimates of influenza severity are often lower because counts are based mostly on confirmed cases. Recently, however, official reports from the Ministry of Health in Mexico included several indicators based on the clinical definition of cases without requiring viral confirmation.

Hemoptysis has only been described as a predictor of hospitalization or care at the ICU[7,8]; however, in our patients its presence increased the risk of death, even though we had a lower prevalence (16%) than in other studies (30%)[7].

Nearly all patients were obese and had a high number of comorbidities, both risk factors for hospitalization and death from influenza[7-9]. The latter suggest that patients with chronic diseases were particularly vulnerable in this outbreak. Patients with the described characteristics should be immunized. By focusing on populations with chronic diseases, we may be able to prevent cases, hospitalization, and mortality from influenza.

Patients admitted to the ICU had a better outcome compared with those cared for in regular hospital wards, even after adjusting for mechanical ventilation and disease severity. In our hospital, during severe outbreaks, mechanical ventilation in patients with respiratory failure is initiated in regular wards when the ICU is saturated, which is life-saving in the short term but, as seen in this outbreak, prognosis may be worse for those not admitted to the ICU. This was likely due to a shortage of trained personnel for the surveillance of critical patients 24 hours a day and during weekends, as important as the lack of sufficient mechanical ventilators outside the ICU. In reference hospitals for respiratory diseases, an increase in requirements for ICU beds is observed during the influenza season, and having additional personnel trained in ICU is very important for improving care in the regular wards or for increasing the permanent ICU facilities.

Influenza remains a significant health risk and is preventable; however, immunization must cover a higher proportion of the population and the vaccine should be administered prior to the winter season. Influenza H1N1 has become a seasonal strain and continues to cause severe outbreaks, possibly because small variants of the virus may still be present in several outbreaks, such as those reported[10], alternating in Mexico in winter with a predominance of H3N2, the variant causing more severe outbreaks in the USA.

Our study has limitations derived from the information available in clinical charts obtained during an important influenza outbreak in a referral hospital for respiratory diseases. Outcomes were worse than in population or regional hospitals outbreaks, representing the most severe portion of cases. However, this does not imply that case mortality was similar to that in general hospitals or even less in outpatients.

In conclusion, Mexico continues to experience winter outbreaks with influenza A H1N1, likely due to incomplete vaccine coverage and small viral variants. During these outbreaks, the requirement for ICU beds and appropriate personnel increases. An alternative would be to open, for influenza, fully equipped and staffed ICU beds in other hospitals.

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