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JAMA. published online Oct 12, 2009; (doi:10.1001/jama.2009.1536)

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Critically Ill Patients With 2009 Influenza A(H1N1) in Mexico

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Context In March 2009, novel 2009 influenza A(H1N1) was first reported in the southwestern United States and Mexico. The population and health care system in Mexico City experienced the first and greatest early burden of critical illness.

Objective To describe baseline characteristics, treatment, and outcomes of consecutive critically ill patients in Mexico hospitals that treated the majority of such patients with confirmed, probable, or suspected 2009 influenza A(H1N1).

Design, Setting, and Patients Observational study of 58 critically ill patients with 2009 influenza A(H1N1) at 6 hospitals between March 24 and June 1, 2009. Demographic data, symptoms, comorbid conditions, illness progression, treatments, and clinical outcomes were collected using a piloted case report form.

Main Outcome Measures The primary outcome measure was mortality. Secondary outcomes included rate of 2009 influenza (A)H1N1–related critical illness and mechanical ventilation as well as intensive care unit (ICU) and hospital length of stay.

Results Critical illness occurred in 58 of 899 patients (6.5%) admitted to the hospital with confirmed, probable, or suspected 2009 influenza (A)H1N1. Patients were young (median, 44.0 [range, 10-83] years); all presented with fever and all but 1 with respiratory symptoms. Few patients had comorbid respiratory disorders, but 21 (36%) were obese. Time from hospital to ICU admission was short (median, 1 day [interquartile range {IQR}, 0-3 days]), and all patients but 2 received mechanical ventilation for severe acute respiratory distress syndrome and refractory hypoxemia (median day 1 ratio of PaO_2 to fraction of inspired oxygen, 83 [IQR, 59-145] mm Hg). By 60 days, 24 patients had died (41.4%; 95% confidence interval, 28.9%-55.0%). Patients who died had greater initial severity of illness, worse hypoxemia, higher creatine kinase levels, higher creatinine levels, and ongoing organ dysfunction. After adjusting for a reduced opportunity of patients dying early to receive neuraminidase inhibitors, neuraminidase inhibitor treatment (vs no treatment) was associated with improved survival (odds ratio, 7.4; 95% confidence interval, 1.8-31.0).

Conclusion Critical illness from 2009 influenza A(H1N1) in Mexico occurred in young individuals, was associated with severe acute respiratory distress syndrome and shock, and had a high case-fatality rate.

JAMA. 2009;302(17):(doi:10.1001/jama.2009.1536) www.jama.com

On April 21, 2009, the Centers for Disease Control and Prevention reported the detection of 2 cases of human infection with 2009 influenza A(H1N1) in California.[1] The greatest initial burden of critical illness and death occurred in Mexico[2] between March 18, 2009, and June 1, 2009, with 5029 cases and 97 documented deaths.[2-6] By August 30, 2009, there were more than 116 046 cases with 2234 deaths in the Americas and 277 607 documented cases and at least 3205 deaths worldwide.[2,7]

We report on 58 patients in Mexico who developed critical illness from confirmed, probable, or suspected 2009 influenza A(H1N1). This early information may be of considerable value for (1) the early identification of individuals at risk of becoming critically ill and who may benefit from targeted interventions including vaccination and antiviral therapy; (2) pandemic health care resource planning; and (3) providing baseline 2009 influenza A(H1N1)–associated morbidity and mortality data, comparing experiences in different jurisdictions, and identifying changes in disease virulence over time.

See related articles.

METHODS

Study Design

We retrospectively studied all critically ill patients with confirmed, prob-

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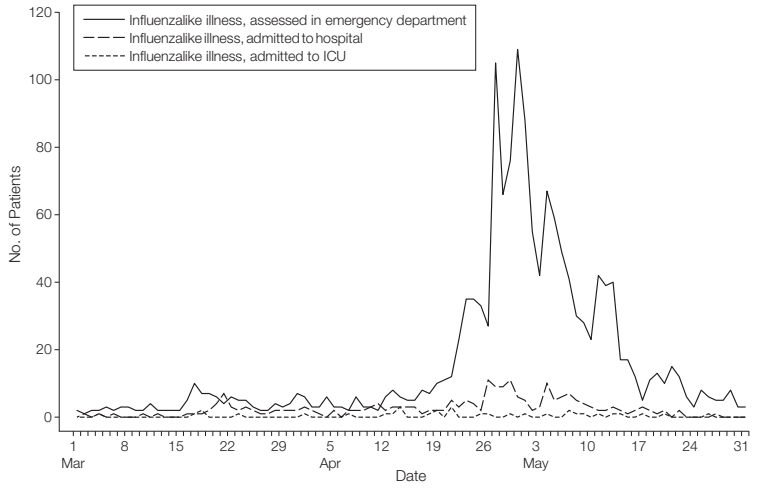
Figure 1. Admissions to Emergency Department, Hospital, and Intensive Care Unit (ICU) in a Single Study Hospital During the 2009 Influenza A(H1N1) Outbreak Period, Mexico, 2009



Hospitalized patients represent a subset of those assessed in the emergency department; patients admitted to ICU represent a subset of those hospitalized.

able, or suspected 2009 influenza A(H1N1) in Mexico admitted between March 24, 2009, and June 1, 2009, to 6 hospitals that were reference centers for the care of patients with influenza (FIGURE 1). Identification of all such patients was achieved by examining admission logs for all patient care areas, in collaboration with critical care and infectious diseases physicians in each participating hospital and with regional health authorities in Mexico.

We classified patients according to case definitions (confirmed, probable, or suspected) developed by the World Health Organization, Centers for Disease Control and Prevention, and the National Microbiology Laboratory (see eAppendix at http://www.jama.com).[8-10] We defined critically ill patients as those admitted to an adult or pediatric intensive care unit (ICU); requiring mechanical ventilation; having a fraction of inspired oxygen (FIO_2) greater than or equal to 60%; or receiving intravenous infusion of inotropic or vasopressor medication during the hospitalization.

To evaluate the proportion of patients who became critically ill, we compared our study population with the total number of inpatients diagnosed with confirmed, probable, or suspected 2009 influenza A(H1N1) and treated at any of the participating hospitals by June 1, 2009. All patients admitted to these 6 hospitals with respiratory symptoms or fever were routinely screened for 2009 influenza A(H1N1) during the outbreak period.

Case Report Generation, Dissemination, and Ethics Approval

Investigators in Canada collaborated with colleagues in Mexico and developed a data collection form with input from critical care personnel, infectious diseases clinicians, and clinical researchers, including the Canadian Critical Care Trials Group.[11] Research ethics board review and approval was granted by Sunnybrook Health Sciences Centre on April 30, 2009, and subsequently by the ethics boards of participating jurisdictions in Mexico. The data collection form was posted on academic institutional and critical care society Web sites on or after May 3, 2009.[12-14] Data collection in Mexico commenced on May 1, 2009, was entered by study site personnel, transmitted to the coordinating center in Toronto, then checked for errors through manual and electronic inspection using prespecified range limits.

Data Collection

Data collection included 2009 influenza A(H1N1) and critical illness eligibility criteria, demographic data, and details of influenza contact, symptoms, comorbid conditions, clinical characteristics, time course of the acute illness, microbiology samples, and treatments (eAppendix). Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score for adults or Pediatric Risk of Mortality III score for children.[15,16] Reporting of ventilatory parameters, arterial blood gas values, and chest radiograph findings, as well as Sequential Organ Failure Assessment (SOFA) scores, was performed on days 1, 3, 7, 14, and 28, using the values closest to 8:00 AM where appropriate.[17] Outcome variables included duration of mechanical ventilation, ICU and hospital length of stay, and ICU and hospital mortality at 14, 28, and 60 days from onset of critical illness.

From the largest referral centers, we were able to collect more detailed information on the total number of patients presenting to the emergency department with influenzalike illness as well as those admitted to the hospital and to the ICU, and to calculate the proportion of patients critically ill with influenza-related pneumonia as a function of total number of ICU beds. In the largest centers, we also collected detailed information on health care worker exposure and illness to assess risk posed to health care professionals through care of patients with 2009 influenza A(H1N1).

Analysis

Descriptive data are presented as frequencies (percentages) for discrete variables and as means (SDs) or medi-

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ans (interquartile ranges [IQRs]) for continuous variables. Because few patients remained alive and in the ICU at 28 days, nonoutcome variables are presented on days 1, 3, 7, and 14 but not day 28. To determine if there were differences in baseline characteristics between patients who survived vs those who died, we used a 2-sample *t* test or the Wilcoxon rank sum test for continuous variables and a χ^2 test or Fisher exact test for the discrete variables. Analyses to detect differences in treatment variables between survivors and nonsurvivors are at risk of confounding due to immortal time bias—ie, patients who die quickly have less "opportunity" to be exposed to certain therapies. Therefore, we restricted comparisons of neuraminidase use to patients who did not die within the first 3 days after admission to the hospital and adjusted for differences in severity of illness using the APACHE II score in a multiple logistic regression model.

The Kaplan-Meier method was used to determine the probability of survival over the duration of follow-up and to generate survival curves, censoring at 60 days all individuals discharged from the hospital alive. We compared the discriminative ability of the day-1 SOFA and APACHE II scores on mortality by testing the difference in C statistics (area under the receiver operating characteristic curve).

All statistical tests were 2-tailed, and factors were considered statistically significant at $\alpha < .05$. SAS version 9.2 (SAS Institute Inc, Cary, North Carolina) was used for all analyses.

RESULTS

Characteristics of Study Patients and Hospitals

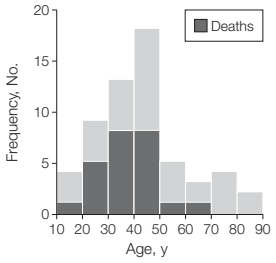
During the study period 899 patients with confirmed, probable, or suspected 2009 influenza A(H1N1) were assessed and admitted to study hospitals having a mean of 289 (SD, 167) beds and 16 (SD, 8) critical care beds. Critical illness occurred in 58 patients (6.5%) admitted to the hospital (29 confirmed, 14 probable, 15 suspected). There were no significant differences in demographics, severity of illness, comorbid conditions, or mortality among those with confirmed, probable, or suspected 2009 influenza A(H1N1), and they are described as a single group.

As a result of increased patient volumes, many experienced delay in admission to the ICU, and 4 remained in the emergency department until death. During the period of data collection, there were 5029 cases of 2009 influenza A(H1N1) and 97 deaths in all of Mexico.[18] This cohort from 6 hospitals represents approximately one-quarter of all deaths in Mexico during the study period. We have described the temporal burden of influenza and H1N1 on the largest study center, outlining the number of cases of influenzalike illness presenting to the emergency department and admitted to the hospital and cases of influenza-related illness admitted to the ICU (Figure 1). The usual capacity to care for critically ill patients was exceeded, necessitating care in other patient care areas and the addition of ICU beds and ventilators on 2 occasions.

Study patients were a median age of 44 (range, 10-83) years (FIGURE 2), 53% were female, and 2 were health care workers (TABLE 1). Only 2 children (10 and 14 years) were admitted to study centers with critical illness and had mean admission Pediatric Risk of Mortality III scores of 6.5 (SD, 2.1). Among all patients, symptoms included fever in 58 (100%); respiratory complaints (cough, dyspnea, or wheeze) in 57 (98%); generalized weakness in 41 (71%); myalgias in 35 (60%); headache in 33 (57%); and gastrointestinal symptoms of nausea, vomiting, or diarrhea in 18 (30%).

The median number of comorbid conditions was 2 (IQR, 1-4) (Table 1). Only 2 patients had a history of chronic obstructive pulmonary disease. Obesity was the most common comorbid condition (mean body mass index [BMI], 32 [SD, 12], calculated as weight in kilograms divided by height in me-

Figure 2. Age Distribution of 58 Critically Ill Patients With Confirmed, Probable, or Suspected 2009 Influenza A(H1N1) Infection



Intervals on the x-axis are equal to the lower limit and less than the upper limit.

Table 1. Characteristics of Critically Ill Patients With Confirmed, Probable, or Suspected 2009 Influenza A(H1N1) Infection, March 24, 2009, to June 1, 2009

Characteristic	No. (%) (N = 58)
Age, median (range), y	44.0 (10-83)
Female sex	31 (53.4)
Health care workers	2 (3.5)
Influenza vaccination in 2008 or 2009	2 (3.5)
APACHE II score, mean (SD)[a]	20.1 (11.9)
No. of comorbidities, median (IQR)	2 (1-4)
Any comorbidity	49 (84.5)
Obesity[b]	21 (36.2)
Ever smoker	20 (34.5)
Hypertension	15 (25.9)
Diabetes (type 1 or 2)	10 (17.2)
Gastrointestinal disease	6 (10.3)
Hyperlipidemia	5 (8.6)
Chronic renal insufficiency	4 (6.9)
Peripheral vascular disease	3 (5.2)
Arrhythmia	3 (5.2)
Valvular heart disease	3 (5.2)
Hypothyroidism	3 (5.2)
COPD	2 (3.4)
Asthma	2 (3.4)
Immune suppression	2 (3.4)
Ischemic heart disease, congestive heart failure, cirrhosis, cerebrovascular disease, pregnancy (each)	1 (1.7)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.
[a] Score range, 0-71; higher values indicate more severe disease.
[b] Defined as body mass index greater than 30. Calculated as weight in kilograms divided by height in meters squared.

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Table 2. Organ Dysfunction Over Time Among 58 Critically Ill Patients With Confirmed, Probable, or Suspected 2009 Influenza A(H1N1) Infection[a]

Organ Dysfunction	Day 1 (n = 58)	Day 3 (n = 52)	Day 7 (n = 44)	Day 14 (n = 28)
SOFA score, mean (SD)[b]	9.0 (4.3)	8.3 (4.1)	7.4 (4.1)	7.3 (4.1)
Ratio of PaO_2 to FIO_2, median (IQR), mm Hg	83 (59-145)	122 (67-169)	121 (70-167)	138 (89-190)
Lowest SBP, mean (SD), mm Hg	98 (22)	109 (24)	103 (24)	101 (20)
Vasopressors (ICU patients), No. (%)[c]	34 (58.6)	32 (61.5)	23 (52.3)	14 (50.0)
Heart rate, mean (SD), beats/min	103 (27)	92 (20)	96 (32)	101 (27)
Creatinine level, median (IQR), mg/dL	1.0 (0.8-1.8)	1.0 (0.77-1.5)	0.87 (0.59-1.46)	0.75 (0.52-1.1)
Platelet count, mean (SD), $\times 10^3/\mu L$	222 (112)	241 (145)	293 (139)	337 (171)
Bilirubin, median (IQR), mg/dL	0.77 (0.45-1.48)	0.72 (0.41-1.28)	0.83 (0.60-1.18)	0.69 (0.50-1.34)
White blood cell count, mean (SD), $\times 1000$ cells/mm^3	9.9 (5.9)	9.9 (5.8)	11.2 (5.5)	13.1 (7.1)
AST, median (IQR), U/L	63 (45-135)	66 (39-108)	33 (28-56)	30.5 (22.5-54)
INR, median (IQR)	1.1 (0.94-1.34)	1.12 (1.07-1.30)	1.13 (1.01-1.20)	1.19 (1.06-1.27)
Glasgow coma scale, median (IQR)	12 (5-15)	13 (5-15)	13 (9-15)	13 (13-15)

Abbreviations: AST, aspartate aminotransferase; FIO_2, fraction of inspired oxygen; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; SBP, systolic blood pressure; SOFA, Sequential Organ Failure Assessment.
SI conversion factors: To convert AST to μkat/L, multiply by 0.0167; bilirubin to μmol/L, multiply by 17.104; creatinine to μmol/L, multiply by 88.4.
[a] Denominators vary over time.
[b] Score range, 0-24; higher values indicate more severe disease.
[c] See eAppendix at http://www.jama.com for description of vasopressors used.

Table 3. Clinical Course and Outcomes of Patients With Confirmed, Probable, or Suspected 2009 Influenza A(H1N1) Infection

Mortality	No. (%) of Patients [95% CI] (N = 58)
From ICU admission	
Day 14	19 (33) [21.4-46.5]
Day 28	23 (40) [27.3-53.4]
Day 60	24 (41) [28.9-55.0]
Time course of illness, d	**Median (IQR)**
Symptoms to hospital admission	6 (4-8)
Hospitalization to ICU admission	1 (0-3)
Hospitalization to death	10 (4-14)
ICU length of stay, d	**Median (IQR) [95% CI]**
Survivors	13.5 (6-24) [8-22]
Nonsurvivors	7.0 (2-13) [4-13]
Duration of ventilation, d	**Median (IQR) [95% CI]**
Survivors	15.0 (8-26) [9-24]
Nonsurvivors	7.5 (3-13.5) [5-13]
Location of death (n = 24)	**No. (%)**
ICU	20 (83)
Emergency department[a]	4 (17)

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; IQR, interquartile range.
[a] Three patients died within 8 hours and 1 within 24 hours of presentation to the hospital.

ters squared). Twenty-one patients (36%) had a BMI greater than 30; 8 (14%) were morbidly obese (BMI >40).

Course of Illness and Treatments Received

Medical Therapies. Patients developed first symptoms a median of 6 (IQR, 4-8) days prior to hospitalization. Time from hospitalization to ICU admission was 1 (IQR, 0-3) day. Among 55 patients confirmed to have received medical therapies (unknown for 3), 52 (95%) were treated with antibiotics, while 45 (78%) received neuraminidase inhibitors (oseltamivir [44], zanamivir [6]), 8 received amantidine (14%), 1 rimantidine (2%), and 40 (69%) corticosteroids. Two patients received recombinant activated protein C. Two had received an influenza vaccination in 2008 or 2009.

Ventilation Support. Fifty-four patients, including 1 of 2 children, required mechanical ventilation (48 invasive, 22 noninvasive, 16 both) during the course of hospitalization (**TABLE 2** and eTable).[19] On the first day of critical illness, the mean FIO_2 was 72% (SD, 26%), set positive end-expiratory pressure (PEEP) was 13 (SD, 5) cm H_2O, and plateau pressure was 27 (SD, 7) cm H_2O. Median ratio of PaO_2 to FIO_2 was 83 (IQR, 59-145) mm Hg, with oxygen saturation of 88% (SD, 13%). Four patients received prone ventilation on their first day in the ICU, owing to severe hypoxia. Tidal volume per ideal body weight was 8.3 (SD, 3) mL/kg. Day 1 chest radiographs demonstrated bilateral disease in 95.6% of patients. Barotrauma occurred in 6 patients (10.3%) over the study. Patients received high FIO_2, high PEEP, and were commonly ventilated in the prone position. Only 1 patient received high-frequency oscillatory ventilation, and none was known to receive nitric oxide or extracorporeal membrane oxygenation.

Nonrespiratory Organ Dysfunction. A large number of patients (34 [58.6%]) initially required inotropic or vasoactive medications at day 1 (Table 2). Creatine kinase level was elevated (285 [IQR, 136-1159] IU/L). Initial other organ dysfunction was mild. Over the course of follow-up, hypotension requiring vasoactive medication support remained common at days 3, 7, and 14. *Staphylococcus aureus* was the most commonly identified cause of secondary bacterial pneumonia (4 patients).

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Outcomes. After 60 days from the onset of critical illness, 24 of 58 patients (41.4%; 95% confidence interval [CI], 28.9%-55.0%) had died (TABLE 3, FIGURE 3). In Mexico, most (19) patients died within the first 2 weeks after becoming critically ill. An additional 4 patients died by day 28, with only 1 additional death occurring within 60 days.

Four patients died in the emergency department, 3 within 8 hours and 1 within 24 hours of arrival. All deaths within 28 days were primarily related to respiratory failure, with only 1 late death primarily related to multisystem organ dysfunction. The 2 included children both survived and were discharged from the hospital. Intensive care unit length of stay among survivors was 13.5 (IQR, 6-24) days, while nonsurvivors died 7.0 (IQR, 2-13) days after ICU admission (Table 3). Duration of mechanical ventilation among survivors was 15 (IQR, 8-26) days and among nonsurvivors was 7.5 (IQR, 3-13.5) days. Many patients received ventilation outside of the ICU.

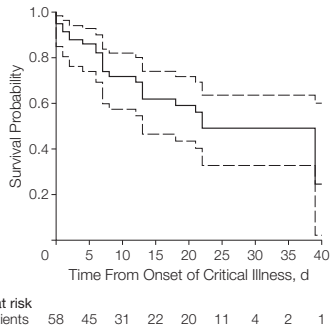
Comparison of Survivors and Nonsurvivors. Patients who died were more likely to have a higher APACHE II and SOFA score, lower mean arterial pressure at admission, evidence of renal and hepatic organ injury, lower ratio of PaO_2 to FIO_2, and higher set PEEP at admission to the ICU (TABLE 4). There were no significant differences in tidal volume or ventilation strategies between survivors and nonsurvivors. Patients with higher creatine kinase levels had a greater likelihood of dying at 28 days. Both APACHE II and day-1 SOFA score were significantly associated with 28-day mortality ($P<.001$ for both), and there was no difference in predictive value (C=0.83 and C=0.87, respectively; $P=.52$). After excluding patients dying early (within 72 hours of illness onset), who may have had less opportunity to be exposed to neuraminidase inhibitors, survivors were more likely to have received treatment with neuraminidase inhibitors (odds ratio, 7.4; 95% CI, 1.8-31.0; $P=.006$).

Risk to Health Care Workers. Among the 3 largest centers caring for 65.6% of the patients in this series, 40 of 6755 health care workers (0.6%) developed 2009 influenza A(H1N1), including 10 of 2421 workers (0.5%) from clinical areas. Only 1 health care worker became critically ill, and this patient was believed to have acquired H1N1 outside of the workplace.

COMMENT

Our analysis of critically ill patients with 2009 influenza A(H1N1) reveals that this disease affected a young patient group. Fever and respiratory symptoms were harbingers of disease in almost all cases. There was a relatively long period of illness prior to presentation to the hospital, followed by a short period of acute and severe respiratory deterioration. These patients had severe hypoxia and acute respiratory distress syndrome and required high FIO_2, PEEP, and ventilatory pressures. Within 60 days, 41% of critically ill patients had died.

Figure 3. Survival of Patients Critically Ill With Confirmed, Probable, or Suspected 2009 Influenza A(H1N1) Infection



Dashed lines indicate 95% confidence intervals.

Table 4. Comparison of Survivors and Nonsurvivors

Patient Characteristic	Survivors (n = 33)	Nonsurvivors[a] (n = 23)	*P* Value
Age, median (IQR), y	45 (33-60)	39 (30.5-45.5)	.09
Female sex, No. (%)	19 (56)	12 (50)	.66
Comorbidities, No. (%)	30 (88)	22 (92)	.67
Ever smoker, No. (%)	12 (35)	8 (33)	.72
BMI, median (IQR)[b]	28 (25-32)	32 (25-42)	.11
Time course of illness, median (IQR), d			
Symptoms to hospital admission	7 (4-8)	6 (3-8)	.47
Hospitalization to ICU admission	1 (0-2)	1 (0-3)	.81
Characteristics at ICU admission			
APACHE II score, mean (SD)	14 (7)	28 (13)	<.001
Ratio of PaO_2 to FIO_2, median (IQR), mm Hg	120 (62-161)	70 (51-105)	.03
Initial MAP, mean (SD), mm Hg	76 (15)	63 (14)	<.001
Ventilation at ICU admission, mean (SD)			
Tidal volume per ideal body weight, mL/kg	8.97 (3.2)	7.8 (1.8)	.19
Plateau pressure, cm H_2O	25 (9)	28 (5)	.34
Set PEEP, cm H_2O	10 (4)	15 (5)	.006
Organ dysfunction			
SOFA score on day 1, mean (SD)	6.7 (3.4)	12.3 (3.2)	<.001
Creatinine, median (IQR), mg/dL	0.90 (0.67-1.10)	1.4 (1.1-3.1)	<.001
AST, median (IQR), U/L	56 (38-81)	97 (48-163)	.07
White blood cell count, mean (SD), $\times 1000$ cells/mm^3	9.5 (5.5)	10.6 (6.6)	.46
Platelet count, mean (SD), $\times 10^3/\mu L$	242 (120)	195 (95)	.12
Bilirubin, median (IQR), mg/dL	0.74 (0.45-1.06)	1.24 (0.50-1.78)	.26
Creatine kinase, median (IQR), U/L	121 (51-231)	1059 (652-2449)	.003

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; AST, aspartate aminotransferase; BMI, body mass index; FIO_2, fraction of inspired oxygen; IQR, interquartile range; MAP, mean arterial pressure; PEEP, positive end-expiratory pressure; SOFA, Sequential Organ Failure Assessment.
SI conversion factors: To convert AST to μkat/L, multiply by 0.0167; bilirubin to μmol/L, multiply by 17.104; creatinine to μmol/L, multiply by 88.4; creatine kinase to μkat/L, multiply by 0.0167.
[a] All in-hospital deaths to September 11, 2009.
[b] Calculated as weight in kilograms divided by height in meters squared.

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The mortality rate of 41% for 2009 influenza A(H1N1)–associated critical illness is not dissimilar to that for acute respiratory distress syndrome resulting from other influenza but is higher than that for severe acute respiratory syndrome (SARS), and deaths in Mexico appear to have been more directly related to respiratory rather than multiorgan failure.[20-22] The low median age and relatively good prior health of this critically ill group are different from those for seasonal influenza and SARS,[22] in which older patients appear more susceptible to severe disease.

Although serologic studies suggest that 2009 influenza A(H1N1) is a novel influenza strain with little protection afforded by seasonal influenza vaccination, adults older than 60 years appear to have some preexisting immunity to this novel virus.[23] While a degree of cross-immunity might be afforded through a long history of annual vaccination, the specific effect of uncommon prior seasonal influenza vaccination, if any, is unclear. The age distribution of the general population in Mexico differs from that in many developed nations, with a much larger proportion of the population in lower age categories, and therefore it may not be surprising that young individuals comprise a greater proportion of those infected.[24]

Approximately 18% of critically ill patients with SARS were health care workers.[22] With SARS, viral shedding appeared to peak at about 7 days, coinciding with the time of ICU admission for many patients. Viral shedding in seasonal influenza is maximal near onset of the disease, then decreases rapidly.[25] These patients presented to the hospital and were admitted to the ICU a median of 6 days after disease onset, which may in part explain the apparent lack of nosocomial transmission among critically ill patients. Avian influenza A(H5N1) outbreaks would appear to have a significantly higher mortality than 2009 influenza A(H1N1) in patients requiring advanced organ support (approximately 90%, with median time from hospital admission to death of 6 days).[26-28] These baseline data will allow evaluation of whether the morbidity and mortality of this infection are worsening over time, which has been the case in many other pandemics.[29]

We found that certain baseline characteristics of critically ill patients with 2009 influenza A(H1N1) may be associated with increased mortality, including cardiovascular, respiratory, and renal organ dysfunction. Novel findings include possible worse outcomes among patients presenting with an elevated creatine kinase level. Elevated creatine kinase levels and rhabdomyolysis have been previously reported to complicate seasonal influenza, although more commonly in children.[30,31] Obesity was the most common comorbid condition in these patients and was more prevalent (36%) in this series than the general population prevalence (30%) in Mexico.[32] However, mortality was not significantly higher among obese patients compared with nonobese patients. Among other patient cohorts with undifferentiated acute respiratory distress syndrome, increased BMI has not emerged as a predictor of mortality.[33]

A better understanding of these factors, which were common, or those that suggest a higher mortality may provide health care professionals an earlier opportunity to identify and treat high-risk groups. Importantly, we found in this cohort that either SOFA or APACHE II scores may help to identify patients at high risk of death. Some authors have previously suggested the use of SOFA scores for triage during pandemic periods, owing to their relative ease of calculation.[34]

The strengths of this study include a large and detailed description of patients critically ill as a result of 2009 influenza A(H1N1). We have highlighted what appear to be differences in severity of illness, associations, and outcomes from other recent infectious respiratory outbreaks. The methods of rapid case report modification, research ethics approval, international dissemination, and analysis provide a potential example for future outbreak characterization[11] and potential for international comparisons among countries with different health care systems and capacity for care.

This study has several potential limitations. First, it represents a relatively early examination of the epidemiology of a severe infectious disease. Early reports risk overestimating the case-fatality rate through selective recognition and screening of the most severely ill patients. This may partially explain a high mortality in Mexico early in the outbreak; however, our cohort included all patients hospitalized with critical illness, not only those selected for admission to an ICU, thus minimizing the effect of selective triaging of critically ill patients (by age, comorbidity, etc) and minimizing the potential for overrepresentation of patients with certain characteristics or severity of illness. Also, the 6 hospitals participating in this cohort study had specific criteria for 2009 influenza A(H1N1) screening among all hospitalized patients, minimizing the risk of exposure ascertainment bias through overestimation of disease among only the sickest patients. For this early report, we deliberately included suspected, in addition to confirmed and probable, cases of 2009 influenza A(H1N1) because in the earliest stages of the outbreak, confirmatory testing was sometimes unavailable for patients who died rapidly and in settings with resources that did not initially permit testing. We performed all analyses in duplicate and found no significant differences in outcomes when including only confirmed and probable cases.

It is possible that the 2009 influenza A(H1N1) experience described here is somewhat unique to Mexico and may be related to a variety of factors, including climate, air quality, and altitude (2240 m above sea level) in Mexico City; or, noting the long duration between illness onset and presentation to the hospital with severe dis-

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ease, potential differences in the timing of access or presentation of the population to acute care compared with other settings. These critically ill patients presented to the hospital already very ill. Four patients died before admission to the ICU, 3 of these within 8 hours of presentation to the hospital. Despite these potential differences with other recently characterized outbreaks, the experience in Mexico may well represent a global "median" of illness presentation and outcome for 2009 influenza A(H1N1) more appropriate than reports only from the most well-resourced health care settings.[22]

As of August 30, 2009, the World Health Organization reported 254 206 cases of 2009 influenza A(H1N1) and 2837 deaths, for a case-fatality rate of approximately 1%—yet this may well be an overestimate, because testing is no longer being reported in many jurisdictions.[2] The case-fatality rate in previous influenza pandemics has varied widely, and all such reports may be inaccurate owing to difficulty in assessing the denominator (ie, the total number of cases).[35] The Spanish flu of 1918 is reported as causing 50 million deaths in 500 million individuals infected (10% case-fatality rate), while the Hong Kong flu of 1968-1969 caused 33 000 deaths among 50 million infected (<0.1% case-fatality rate).[36] The case-fatality rate of avian influenza A(H5N1) was initially reported to be as high as 60% but is more likely in the range of 14% to 33%.[28]

From the Mexico experience, it is clear that in certain environments, critical illness from 2009 influenza A(H1N1) may be associated with severe acute lung injury, refractory hypoxia, and a high mortality rate in young individuals. Influenza pandemics of the past century have been associated with a remarkably consistent epidemiologic curve, with peaks in the spring, fall, and later winter.[7] Early recognition of disease by the consistent symptoms of fever and a respiratory illness during times of outbreak, with prompt medical attention including neuraminidase inhibitors and aggressive support of oxygenation failure and subsequent organ dysfunction, may provide opportunities to mitigate the progression of illness and mortality observed in Mexico.

Published Online: October 12, 2009 (doi:10.1001/jama.2009.1536).
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Financial Disclosures: None reported.
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Previous Presentations: Presented in part at the International Conference of the American Thoracic Society; May 20, 2009; San Diego, California.
Additional Information: An eAppendix and eTable are available at http://www.jama.com.
Additional Contributions: We thank the following persons for providing input on the study design and conduct: **Mexico:** *Instituto Nacional de Ciencias Medicas y Nutrición "Salvador Zubiran":* Delia Borunda-Nava, MD, Carlos Rodriguez-Osorio, MD, Silvio Antonio Ñamendys, MD, MSc, Antonio Fonseca, MD, Guadalupe Morales, RN, Martha Huertas, RN; Patricia Leal, MD, Arturo Galindo Fraga, MD, Rafael Franco, MD, Sarbelio Moreno-Espinosa, MD, MSc; *Hospital General "Dr Manuel Gea Gonzalez" Influenza Committee:* Simon Kawa Karasik, MD, Araceli Contreras Molina, RN, Rafael Figueroa Moreno, MD, Jose Jesús Acevedo Mariles, MD, Carlos Alberto San Juan Martínez, MD, Guillermo Bierzwinsky Sneider, MD, Laura Ramírez Preciado, MD, Alejandro Avalos Bracho, MD, Lucina Gutierrez Sánchez, RN, Antonio Martínez Conde, MD, Antonio Lavalle Villalobos, MD, Lorena Hernández Delgado, MD, Gerardo Lara Figueroa, MD, Hector Prado Calleros, MD, Jeremy Farrar, MD, Alejandro Flores (emergency room technician); *Hospital de Especialidades CMN la Raza IMSS:* Alejandro Sanchez Hurtado, MD, Claudia Lopez Nava, MD; *Hospital Juarez de México:* Jose M. Conde-Mercado, MD, Monica Cureño-Diaz, MD, Ariel Estrada-Aguilera, MD, Claudia Vazquez-Zamora, MD, Mayte Martinez-Velazquez, MD, David Hernandez-Lopez, MD; *Hospital San Jose Tec de Monterrey:* Javier Valero Gomez, MD, Carlos Diaz Olachea, MD, Estrella Gonzalez, MD; *School of Medicine Tecnologico de Monterrey:* Rocio Cabrera (bioengineer); and all the Intensive Care Unit and Medical Intensive Care Unit nurse staff for all the effort and devotion of their work at the Inistituto Nacional de Enferemedades Respiratorias. **Canada and United States:** John Marshall, MD, Arthur Slutsky, MD, Phil Hebert, MD, PhD, Blair Henry, MSc, Francois Lamontagne, MD, Gordon Rubenfeld, MD, MSc, Andy Simor, MD, Muhammad Mamdani, PharmD, MA, MPH, Judith Hall, MSc, Bryan Boodhoo, and the Li Ka Shing Knowledge Institute of St. Michael's Hospital; Neill Adhikari, MDCM, MSc, Damon Scales, MD, PhD, Richard Mraz, PEng, Barry McLellan, MD, Karen Choong, MD, Kusem Menon, MD, MSc, Dominique Piquette, MD, MSc, Michael Christian, MD, Jeff Singh, MD, MSc, Orla Smith, MSc, Ellen McDonald, RN, Claudio Martin, MD, MSc, Francois Lellouche, MD, Nicole Zytaruk, RN, Lauralyn McIntyre, MD, MSc, Tom Stelfox, MD, PHD, John Granton, MD, Anand Kumar, MD, Ryan Zarychanski, MD, MSc, David Wensley, MD, Dermot Doherty, MD, Sandra Dial, MD, Sean Keenan, MD, MSc, Sheldon Magder, MD, David Hornstein, MD, David Leasa, MD, Rick Hall, MD, Mark Crowther, MD, MSc, Donald Griesdale, MD, Jamie Hutchison, MD, Jan Friedrich, MD, DPhil, Nial Ferguson, MD, MSc, Jacques Lacroix, MD, Peter Dodek, MD, MHSc, Philippe Jouvet, MD, PhD, Steve Webb, MD, Simon Finfer, MD, Jamie Cooper, MD, Allison McGeer, MD, Tex Kissoon, MD, Brian Cuthbertson, MB, ChB, Cathy Tansey, PhD, Ari Joffe, MD, Craig Coopersmith, MD, the American Thoracic Society, the Society of Critical Care Medicine, the University of Toronto Interdepartmental Division of Critical Care Medicine, and the Canadian Critical Care Trials Group.

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