Clinical characteristics of fatalities due to influenza A (H1N1) virus in Mexico

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ABSTRACT

Background Mexico has experienced a disproportionate mortality burden due to the influenza A(HIN1) pandemic. A study was undertaken to investigate the sociodemographic and clinical characteristics of the first 100 patients who died from confirmed influenza A(H1N1).

Methods A clinical evaluation was made of the first 100 consecutive deaths of confirmed cases between 10 April and 28 May 2009 reported by the Federal Ministry of Health. Statistical analysis included disease frequencies and descriptive comparisons with national health data.

Results Most patients (60%) were aged 30—79 years, 53% were female and 40% were residents of Mexico City. On admission, 50% had one or more chronic medical conditions including metabolic syndrome (40%), cardiovascular disease (21%), diabetes (20%), hypertension (20%) and respiratory disease (8%). 38% of women and 26% of men were obese based on body mass index). The main clinical symptoms were fever (84%), cough (85%), dyspnoea (75%) and myalgia (30%). The frequency of all chronic diseases was higher in this sample than in the national statistics. Most (82%) developed symptoms before the Mexican government issued the influenza alert (24 April). Median hospital stay prior to death was 4 days (range 0—58).

Conclusions Patients, mostly young adults, who died from A(HIN1) influenza had a high frequency of one or more chronic diseases upon admission. Most died shortly after the health authorities initiated national influenza control measures.

INTRODUCTION

A new swine origin influenza virus A(H1N1) in humans which emerged in Mexico has captured the worldwide attention of health organisations, the press and the public.[1–3] Swine influenza is common in industrial pig farms. Over the past 40 years it has caused small self-limited outbreaks in humans, mostly among people with occupational exposure to pigs.[4 5] The new A(H1N1) strain is the first known to have sustained human-to-human transmission.[6–9] However, it appears to share some characteristics with past epidemics of 1918, 1957 and 1970, including its occurrence outside the normal influenza season, greater transmissibility than seasonal influenza and severe disease in younger age groups.[6 10–12] La Gloria, a town in the state of Veracruz, was the apparent site of the first outbreak in Mexico, although it is now thought that the new A(H1N1) virus had been circulating in humans in previous months. The characteristics of the new infection fed suspicions about the possible emergence of a new and highly virulent reassortant influenza in humans.[7 13 14] The World Health Organization (WHO) declared A(H1N1) to be a phase 6 pandemic on 11 June after reports of sustained transmission in at least two continents.[15] As of January 2010, the pandemic had spread to over 220 countries with over 15 147 confirmed deaths worldwide.[16] Mexico reported the vast majority of officially confirmed deaths in the first 6 months of the outbreak, and the region as a whole continues to report the majority of deaths (7261 at 5 February 2010).[17]

Within a week of Mexico confirming the first case of A(H1N1) influenza on 12 April 2009, the Mexican government launched a national influenza response in coordination with global health organisations. This included prevention and control measures in hospitals (masks, disinfectants and antiviral agents), enhanced case detection, quarantine and social distancing measures (a nationwide 10-day closure of schools, large public events and movie theatres, and suspension of non-essential work and travel within the metropolitan area of Mexico City). The aim of this paper is to describe the sociodemographic and clinical characteristics of the first 100 consecutive deaths caused by the A(H1N1) virus in Mexico in order to identify possible risk factors for disease and to improve the medical care of susceptible individuals.

METHODS

The patients described here represent the first 100 consecutive confirmed deaths due to influenza A(H1N1) in Mexico who were admitted to secondary and tertiary hospitals throughout the country between 14 March and 16 May 2009. The quality and type of data obtained from medical records vary since they were gathered from different medical institutions and overseeing physicians were under significant pressure to attend to the new surge of patients needing medical care for influenza-like conditions. All medical records of patients who died with a laboratory-confirmed diagnosis of H1N1 were sent to the Federal Ministry of Health (MOH) in Mexico City. In mid-April a rapid response team convened at the MOH headquarters, which included infectious diseases researchers, epidemiologists and a small group of external experts (WHO Epidemiology Division, Geneva). The team gathered to extract the most relevant information from the charts and compiled a database of all confirmed deaths. The updated

case definition of confirmed cases of influenza A(H1N1) included a positive real-time PCR (RT-PCR) plus fever and respiratory disturbances. A general influenza A marker and H1 swine marker were used. Confirmatory tests were carried out by the National Reference Laboratory (Instituto Nacional de Referencia Epidemiologica, INDRE) in Mexico on the samples sent by the medical facilities where the patients were treated. All samples collected after early May were sent to INDRE once local RT-PCR testing capacity was available, while those collected before that time were sent either to the National Microbiology Laboratory in Winnipeg, the Influenza Division at the Centers for Disease Control in Atlanta or the Naval Health Research Laboratory in San Diego.

The information available in the patient database included time of hospital admission before or after the official influenza alert on 24 April 2009, sociodemographic data, self-reported pre-existing chronic diseases and laboratory studies performed upon admission. We were particularly interested in analysing weight, height and body mass index (BMI) as these factors might increase the risk of diabetes and hypertension which have been shown to be associated with increased severity of influenza-related disease.[17–19] We calculated BMI for all cases who had height and weight data (97%). Chronic conditions that are suspected risk factors for more severe disease due to influenza were recorded including smoking, autoimmune diseases, diabetes, hypertension, cardiovascular disease and respiratory disorders. All patients admitted to hospital had thorax imaging studies. Clinical symptoms at admission and during the course of the illness were recorded. Clinical and laboratory tests included blood gases (oxygen and carbon dioxide) at admission and before and after intubation. Dosage and duration of antiviral and antimicrobial treatments were collected. We also recorded use of mechanical ventilation and radiology studies. In addition, we recorded the number of days from initial symptoms until death, days hospitalised until death and immediate cause of deaths reported in the medical charts. This national dataset consists only of H1N1-related deaths that had been reported to the Federal Ministry of Health and did not contain cases who were admitted to hospital and survived.

General descriptive comparisons were made between this dataset and the most recently published national health and mortality data, as has been done in H1N1 case reports in the USA.[20] We used national census data from the National Institute of Statistics and Geography (INEGI, 2005) and the National Population Council (CONAPO, 2008) for the sociodemographic comparison and the 2006 National Survey on Health and Nutrition (ENSANUT, in Spanish).[21–24] For mortality statistics we used mortality databases from the National Health Information System (SINAIS, 1979–2007).[25] All analyses were performed using SPSS Version 13.0.

RESULTS

Sociodemographic profile of patients

Between 10 April and 28 May 2009, 100 people died in Mexico as a result of the influenza A(H1N1) virus. Table 1 presents the sociodemographic characteristics of the sample compared with national data. There was a wide age distribution among the cases who died; 30% were aged 10–29 years, 60% were aged 30–79 years and only 10% were aged <10 years. In contrast, the national age distribution is somewhat younger, with 19% aged <10 years, 38% aged 10–29 years and 43% aged 30–79 years. There were slightly more women than men (53% vs 47%), similar to the national data. Most of the cases were employed (48%) or homemakers (29%). The majority had either primary (43%) or secondary (22%) education.

Over half of the patients were residents of Mexico City and the neighbouring state of Mexico (61%), while others were residents of central states including San Luis Potosi (6%,) Hidalgo (5%) and Zacatecas (4%). The greater proportion of residents from the capital and neighbouring states in this sample compared with national data can be partly explained by the greater concentration of health services in Mexico City, and those patients from outlying areas who sought medical care for H1N1 were probably referred to central hospitals. In this sample there was an even distribution of admission to secondary (53%) and tertiary (47%) care facilities.

Clinical characteristics of patients on admission

Data on chronic diseases/pre-existing conditions in the sample compared with national prevalence data are shown in table 1. Only cases aged >20 years (n=86) were included in order to correspond with the age range used in the 2006 National Survey on Health and Nutrition. Approximately half of the patients had at least one chronic disease on admission. The most common were metabolic syndrome (40%), hypertension (20%), cardiovascular disease (21%), diabetes (20%) and respiratory disease (8%). These percentages are much higher than the 2006 national data, which reported a prevalence of 15% for metabolic syndrome, 15% for hypertension, 7% for diabetes and <1% for respiratory disease.[22] BMI was calculated on admission for the 97 cases for whom height and weight data were available. There was a greater proportion of obese women (38%) and men (26%) in this sample than in the national survey data (35% and 24%, respectively), but these differences were not statistically significant.

The results of blood gas studies conducted on admission and before and after intubation are summarised in table 2. The majority had abnormal values for three of the four determinations and all patients had low measures of arterial oxygen saturation (Sao_2). In general, blood gases improved only slightly after intubation, which suggests a significant decline in respiratory function probably due to severe lung tissue damage. The fraction of inspired oxygen (Fio_2) varied from 80% to 100% cm H_2O, according to how each patient progressed.

The main clinical symptoms were fever (84%), cough (85%), dyspnoea (75%), myalgia (30%) and headache (22%).The majority of patients (82%) reported having experienced influenza symptoms before the national influenza alert issued on 24 April, and the average stay in hospital before death was 7 days. Over half of the cases (55%) were admitted to the hospital before the influenza alert and the remainder (45%) afterwards. All 100 cases had received positive confirmatory RT-PCR tests for influenza A(H1N1) virus prior to or upon admission.

Based on imaging studies, 94% of the patients had multiple foci pneumonia and 84% required mechanical ventilation. However, only two cases had positive bacterial cultures. Treatment for infection included antibiotics (94%), steroids (59%) and antiviral therapy (oseltamivir and zanamivir) (56%).

All patients died in the hospital to which they were originally admitted. The median number of days between hospital admission and death was 4 (range 0–58). However, 16% were hospitalised for >12 days before death while 11% died within the first 24 h of admission. The median number of days between initial onset of symptoms and death was 10.5. The immediate causes of death were pneumonia due to H1N1 (68%) and pneumonia due to H1N1 plus other diagnoses such as septic shock, viral encephalitis and chronic pulmonary disease (26%). These findings are summarised in table 3.

Table 1 Sociodemographic and clinical characteristics of the first 100 confirmed deaths due to influenza A(H1N1) compared with sociodemographic and clinical characteristics of the total population, Mexico 2009

	Cases of influenza A(H1N1)		National*
	N	% (95% CI)	% (95% CI)
Age range†			
0–9	10	10.0	19.2
10–29	30	30.0	37.8
30–79	60	60.0	43.1
Gender†			
Male‡	47	47	49.2
Area of residence†			
Mexico City	40	40	8.2
State of Mexico	21	21	13.8
Other states	39	39	78
Clinical background§			
Pre-existing chronic disease			
Metabolic syndrome¶	34	39.5 (29.0 to 50.1)	14.5 (13.9 to 15.1)
Cardiovascular diseases**	18	20.9 (12.2 to 29.7)	4.1 (3.8 to 4.4)
Hypertension††	17	19.8 (11.2 to 28.4)	15.4 (14.8 to 16.0)
Diabetes††	17	19.8 (11.2 to 28.4)	7 (6.6 to 7.5)
Respiratory‡‡	7	8.1 (2.2 to 14.0)	0.4 (0.37 to 0.46)
Infectious§§	3	3.5 (0.4 to 7.4)	3.1 (2.9 to 3.4)
Autoimmune diseases¶¶	2	2.3 (0 to 5.6)	–
Cancer	1	1.2 (1.1 to 3.5)	0.8 (0.7 to 0.9)
Tobacco use			
Non-smoker	35	40.7	70.3
Current or former smoker	29	33.7	29.7
Not specified	22	25.6	0
*BMI men****			
Underweight	2	5.1 (0.0 to 12.4)	1.5 (1.2 to 1.9)
Normal	19	48.7 (22.3 to 65.1)	31.7 (30.2 to 33.2)
Overweight	8	20.5 (7.3 to 33.8)	42.5 (41.1 to 44.0)
Obesity	10	25.7 (11.3 to 40.0)	24.2 (23.0 to 25.6)
*BMI women****			
Underweight	1	2.1 (0.0 to 6.4)	1.4 (1.1 to 1.8)
Normal	19	40.4 (25.9 to 55.0)	26.7 (25.6 to 27.8)
Overweight	9	19.1 (7.5 to 30.8)	37.4 (36.1 to 38.7)
Obesity	18	38.3 (23.9 to 52.7)	34.5 (33.4 to 35.7)

*Only the population at the beginning of the year 2009 aged <80 years was considered (N=105 878 876).
†Estimates from Consejo Nacional de Población (National Population Council).[21]
‡Three women were pregnant with 24, 34 and 38 weeks gestation.
§Cases under 20 years were excluded because National Health Survey 2006 only calculates chronic disease in persons aged ≥20 years.
¶For H1N1 deaths that had a prior diagnosis of metabolic syndrome, we included obesity, diabetes mellitus or hypothyroidism. For ENSANUT, metabolic syndrome also includes prior diagnosis of obesity and diabetes using data from ENSANUT adult questionnaire.
**Using ENSANUT adult questionnaire data, we calculated prior diagnosis of cardiovascular disease (infarct, cardiac insufficiency and other heart conditions).
††Using ENSANUT adult questionnaire data, we calculated prior diagnosis of diabetes.
‡‡Asthma and tuberculosis were calculated from ENSANUT list of chronic diseases.
§§Using ENSANUT, we calculated the occurrence of respiratory, urinary and sexually transmitted infections 2 weeks prior to the 2006 national survey.
¶¶The ENSANUT sample size was insufficient to carry out an estimate.
***Underweight (BMI <18.5 kg/m^2), normal (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), obese (BMI ≥30.0 kg/m^2).

Using the mortality data and published epidemiological data, we calculated the attack rate and the disease-specific death rate due to H1N1. The attack rate due to H1N1 (total deaths due to H1N1 divided by all confirmed cases during the study period between April and May 2009) was 100/4974 or 2%.[26] This rate is similar to that reported by Fajardo-Dolci *et al*.[27] The total number of reported confirmed deaths due to H1N1 in Mexico from 28 March to 30 November 2009 was 656 cases.[28] Divided by the mid-year population in 2009 (107 550 697), this yields a rate of 0.61 H1N1-related deaths per 100 000 persons.[21] This rate is lower than the latest reported death rates due to non-H1N1 influenza in Mexico between 2005 and 2007. In 2007, the most recent data available,[25] the death rate was 13.6 per 100 000 persons, a slight decline from 14.4 in 2006 and 14.5 in 2005, and most deaths occurred in those aged <10 years and >60 years.

DISCUSSION

Mexico has experienced a disproportionate burden of mortality since the beginning of the influenza A(HIN1) pandemic. This is the first study to analyse a national sample of the first 100 consecutive deaths due to H1N1 in Mexico. The most common age range in the sample was 30–79 years, which is higher than the national age distribution and higher than the typical age distribution for seasonal influenza. The majority of cases had at least one pre-existing chronic disease upon admission. Notably,

Table 2 Laboratory results

Laboratory tests	N	Mean	SD	Number of cases outside normal parameters*(%)
Blood gas analysis upon admission				
pH	53	7.3	0.4	22 (41.5)
Pco_2	53	32.4	8.8	40 (75.5)
Po_2	53	49.9	24.2	53 (100)
Sao_2	50	71.7	21.3	39 (78)
Blood gas analysis before intubation				
pH	41	7.3	0.1	22 (53.7)
Pco_2	40	34.2	8.9	22 (57.9)
Po_2	42	41.3	14.4	41 (97.6)
Sao_2	41	63.15	21.26	37 (90.2)
Blood gas analysis after intubation				
pH	63	8.1	6.1	42 (67.7)
Pco_2	63	42.3	21.8	32 (59.3)
Po_2	63	69.0	79.6	56 (88.9)
Sao_2	62	78.35	19.04	39 (62.9)

Pco_2, partial pressure of blood carbon dioxide; Po_2, partial pressure of blood oxygen; Sao_2, blood saturation of oxygen.
*Normal parameters: pH 7.35–7.45; Po_2 80–100 mm Hg; Pco_2 35–45 mm Hg; Sao_2 90–100%.

Table 3 Patient characteristics, symptoms, diagnosis, treatment and type of medical facility

Characteristics	N	%
Type of medical facility†		
Secondary level	52	53
Tertiary level	47	47
Main symptoms		
Fever	84	84
Cough	85	85
Dyspnoea	75	75
Myalgias	30	30
Headache	22	22
Treatment schedules		
Steroids	59	59
Adrenaline	13	13
Norepinephrine	25	25
Dopamine	22	22
Antiviral therapy (oseltamivir or zanamivir)	56	56
Antimicrobial agents‡	94	94
Mechanical ventilation	84	84
Radiological description (n=82)		
Multiple foci pneumonia§	77	93.9
Pleural effusion	5	6.1
Positive bacterial cultures (n=2)		
Staphylococcus epidermidis	1	1
Staphylococcus ominis	1	1
Cause of death certificate		
Pneumonia¶	68	68
Pneumonia associated with other diagnoses**	26	26
Other diagnoses††	6	6
Number of days from admission to death*	Range 0–58, median 4.0, mean 6.9	
Number of days from initial symptoms to death	Range 2–71, median 10.5, mean 13.1	

*One case was excluded because that individual was never hospitalised.
†The medical facility where patients were admitted for treatment for H1N1 and where they died was the same in all cases.
‡Antimicrobial agents included cephalosporins (cefuroxime, cefotaxime, ceftriaxone, ceftazidime and cefepime), quinolones (ciprofloxacin, ofloxacin, norfloxacin, levofloxacin and gatifloxacin) and macrolides (erythromycin and clarithromycin).
§Multiple foci pneumonia: diagnosis was made when we noted two or more consolidation zones in the lungs, outside the base of the lung.
¶Death due to H1N1 was defined as having more than three of the following clinical symptoms: cough, fever, coughing, malaise, myalgia, homeostasis, runny nose, cyanosis, headache, chest pain, sore throat and conjunctival hyperemia. All deaths had confirmed A (H1N1) influenza by PCR studies.
**A patient was defined as being infected with H1N1 when he or she had more than three clinical symptoms. Other conditions included refractory metabolic acidosis, hydroelectric imbalance, viral encephalitis, septic shock, bilateral bacterial pneumonia, type 2 diabetes mellitus, epilepsy, acute respiratory failure, hypertension, chronic obstructive pulmonary disease and lupus erythematosus.
††Uraemic syndrome, acute lung oedema, acute respiratory failure, lower respiratory tract infection, sudden death, ventricular fibrillation, massive pleural effusion, probable influenza, probable whooping cough syndrome. They also had confirmed A(H1N1) influenza by PCR studies.

all diseases were more common in this sample than in the general population, based on the most recent national health statistics.[23 24] Comparing reported percentages between this study sample and the national dataset, we found that cardiovascular disease was five times more common in our sample, metabolic disorders and diabetes were nearly three times more common, respiratory diseases were 20 times more common and hypertension was 30% more common. In addition, in this sample we observed higher proportions of obesity among women (38%) and men (26%) compared with the national data for women (35%) and men (24%), although these differences were not significant. Cardiovascular disease, diabetes and pulmonary disease—all common in our study sample—have been shown to be risk factors for complications due to influenza.[10 19 25 29] Type 2 diabetes is the leading cause of death in Mexico and has been shown to be a risk factor for hospitalisation and complications from influenza. The CDC now recommends that patients with diabetes should have annual influenza vaccinations.[30] There is also an increasing prevalence of obesity and hypertension in Mexico.[18]

It is intriguing that the majority of the sample was middle-aged while only 15% were <10 years and >60 years. This age distribution of deaths from influenza has been reported in previous pandemics and confirmed in a recent study of H1N1 cases in Mexico.[6 25–27 29]

An unsurprising finding to emerge from the study was that most of the deaths in this sample occurred at or before early May, only 2 weeks after the Mexican government initiated its national influenza response measures. This factor may explain why other countries reported lower mortality, as they were not affected until after the WHO issued the pandemic alert and could respond more effectively as the first cases were being identified.

This study also suggests important lessons for Mexico's influenza response. One hallmark of the outbreak was its emergence outside the normal influenza season which, in the initial cases, led to delays, inadequate diagnosis and lack of specific antiviral treatment. This highlights the importance for all countries to implement epidemiological alert monitoring systems all year round and anticipate the resurgence of unusual influenza strains. In addition, most of the A(HIN1)-related hospitalisations and deaths in Mexico occurred around the time when the federal health authorities issued an alert and while they were organising a national response plan in the context of significant global uncertainty about the scope and severity of the disease. Widespread RT-PCR testing capacity was not available in Mexico until 1 May, which may have delayed confirmed case identification and early intervention. Regardless, these findings draw attention to the importance of implementing rapid and active surveillance at early stages of an epidemic.

This study has limitations. To date there has been one published case-control study on H1N1 in Mexico from a single tertiary care hospital.[31] The comparisons with national datasets in our study are only descriptive and serve to provide contextual information with which to interpret study findings. At the time of analysis we did not have data on non-reported H1N1 deaths—that is, those

who died of H1N1 at home without being admitted to a health facility. However, this is the first national-level study to document the sociodemographic and clinical characteristics of the first H1N1 deaths in Mexico. In addition, the dates of symptom onset were based on self-reports so we do not have an exact clinical picture of the early stages of the infection in order to understand reasons for delays in admission. Our findings suggest the need for follow-up case-control studies to assess risk factors for H1N1-related hospitalisation and death in Mexico.

The influenza A(HIN1) pandemic has tested the global influenza response systems put in place in 2005 following SARS.[32 33] Recent studies show that the influenza A(HIN1) pandemic has a lower case fatality than was previously thought, and points to the need for a more precise alert system which considers the origin, transmissibility and pathogenicity of the new agent. Also, the lack of mortality among close contacts of the deceased cases in this study suggests only moderate virulence. At the same time, the WHO's latest declaration of the influenza A(HIN1) pandemic as level 6 sent a clear message to prevent the false sense of security that the worst may be over.[15] Mexico experienced the highest number of influenza A(HIN1)-related fatalities in the first 6 months of the pandemic and most occurred in the initial weeks of the outbreak, primarily affecting individuals with pre-existing conditions. However, the implementation of a costly but effective response early in the outbreak, using lessons learnt from SARS and avian (H5N1) influenza,[34] has made a significant contribution to the global response. Although it was impossible to contain the initial outbreak and transmission to other countries, current evidence indicates a clear decline in mortality due to early detection of cases and proper treatment schedules and stabilisation of new cases.[35] These lessons also reaffirm the importance of global collaboration to respond rapidly and effectively. Now that a human influenza strain of swine origin is a reality, global collaboration is vital to prevent the resurgence of new and potentially more infectious strains.

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All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. Data sharing: no additional data available.

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