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**Research Article**

# Clinical profile of the first 1000 fatalities for influenza A (H1N1) in Mexico

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## ABSTRACT

**Background:** Influenza is an acute respiratory disease responsible for several episodes of high mortality throughout human history. In 2009, Mexico experienced an atypical influenza outbreak caused by a mutant strain of the influenza A (H1N1) subtype, which generated significant mortality. The aim of this paper was to analyze the clinical and sociodemographic conditions of the first 1000 fatalities recorded during this outbreak.
**Methods:** We conducted a study based on an analysis of the clinical files of patients positive for influenza A (H1N1) using Real-Time-Polymerase Chain Reaction (RT-PCR) to conduct an analysis of deaths compared to deaths in the general population.
**Results:** The majority of deaths occurred in patients aged 35-84 years (65.8%). Average time between symptom onset and death was 13.8 days, with an average of 7.8 days from time of hospitalization until death. Ca. 25% of deaths occurred in residents from Mexico City and from the nearby State of Mexico. In the majority of cases, we found that patients who died had a low educational and socioeconomic status along with co-morbidities such as metabolic syndrome and its individual components, as well as respiratory illnesses. In 80% of cases, patients received mechanical ventilation, and a similar percentage received antiviral therapy (oseltamivir, zanamivir).
**Conclusions:** The primary-care level was not utilized by patients who died from influenza. The higher prevalence of chronic degenerative diseases among deaths compared with the general population indicates that these groups of patients should be considered and prioritized in the event of future outbreaks.

**Keywords:** Influenza A (H1N1), Clinical profile, Socioeconomic and educational status, Clinical features

## INTRODUCTION

Influenza is a disease that has accompanied humans throughout history, resulting in epidemics during various stages of human history and one that is often associated with a high mortality rate. Current advances in science and technology available to address the problem of epidemics are superior to those of the past century; however, influenza remains a challenge for health systems. In this era of globalization and due to the rapidity with which disease-causing virus mutations are disseminated and because of the high economic burden of medical care and resulting loss of life, health systems are

impelled to provide a quick and appropriate response to the new characteristics of the disease-causing virus.[1,2]

We reiterate lessons learned from previous epidemics. First, the emergence of epidemics has been estimated with a range of 10-50 years.[3] We have an ongoing ability to identify the involved agent more efficiently so that the association of symptoms with known types such as VIA, VIB, or VIC, which are pathogenic to humans, allows us to be better prepared. We also know that, even in the absence of cross-immunity among these agents, type A is particularly important due to its antigenicity, resulting in the Hemagglutinins (HA) and Neuraminidases (NA) that are triggered. There are 24 subtypes, of which only three HA (H1, H2, and H3) and three NA (N1, N2, and N8) have been associated with influenza infection. Clinical conditions range from mild to complicated but are usually self-limiting.[4] Despite our extensive knowledge, there is a latent danger that mutations or variations observed in viruses that cause influenza could give rise to a new virus for which there is no immunological memory and, therefore, one that would represent a greater risk to the public health.

In this context, the 2009 epidemic presented itself in Mexico. A mutant strain of the human influenza virus emerged globally, one now known as influenza A (H1N1). The virus was composed of four segments of different types of influenza (American swine, Eurasian swine, North American human, American bird), which began to cause deaths. The first cases were detected beginning in April 2009 in Mexico. During that month, the Ministry of Health of Mexico called for a rapid response team for this public health emergency. This team comprised Mexican physicians from several disciplines and included epidemiologists, pulmonologists, critical care physicians, and infectious disease and public health specialists, and a group of external experts from the World Health Organization (WHO) and the Pan American Health Organization (PAHO).[5,6]

Mexico experienced significant mortality from the beginning of the pandemic influenza A (H1N1) in 2009. In February 2010, the relevant experience was published with respect to the clinical characteristics of the first 100 deaths. The present article extends the analysis to the first 1000 deaths caused by human influenza virus A (H1N1)[7] and analyzes the national registry of the first 1000 confirmed deaths from the H1N1 virus in Mexico, a figure that on July 19, 2010 amounted to 1329/72548 confirmed cases.

## METHODS

An analysis of the clinical characteristics of the first 1000 patients who died as a result of influenza A (H1N1) in Mexico confirmed by Real-Time-Polymerase Chain Reaction (RT-PCR) was carried out by a review of medical records. All medical units of the National Health System sent medical records to the National Medical Arbitration Commission.

The information was organized in an encrypted database, determining clinical and sociodemographic variables, as well as the medical care that had been administered. There were 206 variables that were able to be identified from this information. In this manner, the information gathered would allow establishing a patient profile, identifying the disease evolution and related clinical characteristics with co-morbidities or prior risk factors.

The following are some variables of the patient profile: time of hospital admission (before or after the official warning of influenza in April 2009); pre-existing chronic degenerative conditions and the results of laboratory and imaging studies upon admission and during patient care, and the clinical symptoms at the time of admission and the patients' evolution during hospitalization were identified, as well as information on the treatment dose and duration with antiviral and antimicrobial agents. Additionally, information was obtained regarding the use of mechanical ventilator support, days of hospitalization until death, and the immediate cause of death as reported on the death certificate.

To confirm that patients were infected with human influenza A (H1N1), we included only cases that had the RT-PCR performed by the National Institute of Epidemiological Reference (INDRE). Samples collected prior to May 2009 were sent to the National Microbiology Laboratory in Winnipeg (Canada) and to the Influenza Division at the Centers for Disease Control in Atlanta, Georgia (U.S.).[6,7]

Similarly, co-morbidities or the incidence of other chronic conditions associated with increased severity, such as smoking, autoimmune diseases, diabetes, high blood pressure, cardiovascular disease, or respiratory conditions were reviewed. General descriptive comparisons were made among the database, the most recent information published, and mortality data, published in other countries such as the U.S., for this group of patients.

For sociodemographic comparisons, we used the 2005 population data of the national census from the National Institute of Statistics and Geography (INEGI 2005), the National Council of Population (CONAPO, 2008), and the National Survey of Health and Nutrition (ENSANUT 2006). For mortality statistics, the databases of the National Information Health System (SINAIS 1997-2007) were employed. All analyses were performed using SPSS for Windows (v.13) software.

## RESULTS

Results of the analysis of the patients' sociodemographic profile are shown in Table 1. The characteristics of patients who died are compared with deaths nationwide.

As is shown in Table 1, the age distribution among patients who died from influenza focuses on adults and older adults; 65.8% fall into the age group between 30 and 84 years, whereas 24% correspond to the age range of 10-29 years and ~10% are <10 years of age. When compared with national data, the distribution is different (19% for patients <10 years of age, 37.5% for patients 10-29 years of age, and 43.4% for patients aged 30-84 years). Gender analysis shows that there were more deaths in males (51.7%) than in females (48.3%), a slightly greater proportion for males than that observed according to the national data (49.2% for males).

**Table 1: Sociodemographic and clinical characteristics of the 1,000 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, years (n=1000)** | | | |
| 0-9 | 102 | 10.2 | 19.1 |
| 10-29 | 240 | 24.0 | 37.5 |
| 30-84 | 658 | 65.8 | 43.4 |
| **Gender (n=1000)** | | | |
| Masculine | 517 | 51.7 | 49.2 |
| **Area of residence (n=1000)** | | | |
| Mexico City | 131 | 13.1 | 8.2 |
| State of Mexico | 124 | 12.4 | 13.8 |
| Other states | 745 | 74.5 | 78 |
| **Clinical history (n=836)** | | | |
| Pre-existing chronic disease | | | |
| Metabolic syndrome | 365 | 43.7 (40.3-47.0) | 14.5 (13.9-15.1) |
| Cardiovascular disease | 197 | 23.6 (20.7-26.4) | 4.1 (3.8-4.4) |
| High blood pressure | 191 | 22.8 (20.0-25.7) | 15.4 (14.8-16.0) |
| Diabetes | 213 | 25.5 (22.5-28.4) | 7 (6.6-7.5) |
| Respiratory | 58 | 6.9 (5.2-8.7) | 0.4 (0.37-0.46) |
| Infectious | 19 | 2.3 (1.3-3.3) | 3.1 (2.9-3.4) |
| Autoimmune disease | 16 | 1.9 (1.0-2.8) | - |
| Cancer | 18 | 2.2 (1.2-3.1) | 0.8 (0.7-0.9) |
| **Tobacco use (n=836)** | | | |
| Nonsmoker | 669 | 80.0 | 70.3 |
| Current or former smoker | 167 | 20.0 | 29.7 |
| Not specified | - | - | 0 |
| **BMI, males (n=90)** | | | |
| Underweight | 3 | 3.3 (0.0-7.0) | 1.5 (1.2-1.9) |
| Normal weight | 29 | 32.2 (22.6-41.9) | 31.7 (30.2-33.2) |
| Overweight | 22 | 24.4 (15.6-33.3) | 42.5 (41.1-44.0) |
| Obesity | 36 | 40 (29.9-50.2) | 24.2 (23.0-25.6) |
| Missing values | 350 | | |
| **BMI, females (n=88)** | | | |
| Underweight | 2 | 2.3 (0.0-5.4) | 1.4 (1.1-1.8) |
| Normal weight | 25 | 28.4 (19.0-37.8) | 26.7 (25.6-27.8) |
| Overweight | 19 | 21.6 (13.0-30.2) | 37.4 (36.1-38.7) |
| Obesity | 42 | 47.7 (37.3-58.2) | 34.5 (33.4-35.7) |
| Missing values | 308 | | |

BMI: Body mass index

Regarding occupation, it was shown that the largest group of patients who died was made up of female homemakers (25%), 23.2% of patients were employees of private enterprises, and 18.3% of patients were self-employed. With regard to education, the majority of deaths occurred in subjects with low educational levels

(20.6% had completed basic schooling and 16.6% had incomplete basic education). According to place-of-residence, Mexico City occupies 13.1% of the total fatalities, followed by the State of Mexico (12.4%). The other Mexican states made up the remaining 74.5% of total fatalities. The percentage of deaths in Mexico City exceeded the habitual mortality of persons living in Mexico City residents by 5%. It is noteworthy that the deaths, despite being widespread throughout the country, were concentrated in the State of Mexico and in Mexico City (25% of all deaths due to influenza).

Analysis by level of HEALTH care shows that of the 1000 cases studied in this article, 82.5% were seen for the first time at the secondary healthcare level, and 17.2% of the cases were seen for the first time at the tertiary care level. Clinical files do not report any contact with physicians or healthcare providers at the primary healthcare level.

Table 1 also displays information on chronic diseases and pre-existing conditions. Thus, it was considered to include only deaths in subjects >20 years of age (n=836) to be comparable by age range with ENSANUT 2006 data. It is noteworthy that more than one half of the patients had at least one chronic disease. The most common diseases were, in order of frequency, metabolic syndrome (MetS) (diabetes, high blood pressure, and hyperlipidemia) 43.7%, diabetes alone 25.5%, cardiovascular disease 23.6%, high blood pressure alone 22.8%, and respiratory diseases, 6.9%. The Body Mass Index (BMI) calculation was able to be determined in only 17.8% of deaths (females in 88 cases and males in 90 cases, for which obesity was reported in 47.7 and in 40% of the cases, respectively.

**Table 2: Laboratory results.**

| Laboratory test | N | Mean ± SD | Number of cases outside normal parameters* (%) |
|---|---|---|---|
| **Blood gas analysis upon admission** | | | |
| pH | 668 | 7.3 ± 0.1 | 384 (57.5) |
| $HCO_3$ | 643 | 19.9 ± 6.8 | 635 (98.58) |
| BE | 528 | 0.5 ± 2.3 | 528 (100) |
| $SaO_2$ | 702 | 68.6 ± 25.8 | 573 (81.7) |
| **Blood gas analysis before intubation** | | | |
| pH | 275 | 7.6 ± 4.6 | 186 (67.6) |
| $HCO_3$ | 256 | 20.5 ± 7.9 | 255 (99.6) |
| BE | 217 | 0.4 ± 1.8 | 217 (100) |
| $SaO_2$ | 298 | 56.7 ± 26.3 | 287 (93.6) |
| **Blood gas analysis after intubation** | | | |
| pH | 506 | 7.5 ± 4.1 | 324 (64.0) |
| $HCO_3$ | 477 | 20.6 ± 6.3 | 471 (98.7) |
| BE | 404 | 0.8 ± 2.9 | 404 (100) |
| $SaO_2$ | 508 | 72.8 ± 32.4 | 278 (54.7) |

BE: Base excess; SD: Standard deviation

**Table 3: Patients' characteristics, symptoms, diagnosis, treatment, and type of medical facility.**

| Characteristic | N | % |
|---|---|---|
| **Type of medical facility (n=1000)** | | |
| None | 1 | 0.1 |
| Primary-level | 1 | 0.1 |
| Secondary-level | 825 | 82.5 |
| Tertiary-level | 172 | 17.2 |
| Missing values | 1 | 0.1 |
| **Primary symptoms (n=1000)** | | |
| Fever | 915 | 91.5 |
| Cough | 450 | 45.0 |
| Dyspnea | 619 | 61.9 |
| Myalgias | 349 | 34.9 |
| Headache | 407 | 40.7 |
| **Treatment schedule (n=1000)** | | |
| Steroids | 542 | 54.2 |
| Adrenalin | 202 | 20.2 |
| Norepinephrine | 196 | 19.6 |
| Dopamine | 263 | 26.3 |
| Antiviral therapy (oseltamivir or zanamivir) | 848 | 84.8 |
| Antimicrobial agents | 897 | 89.7 |
| Ceftriaxone | 574 | 57.4 |
| Clarithromycin | 283 | 28.3 |
| Cefotaxime | 247 | 24.7 |
| Amikacin | 229 | 22.9 |
| Vancomycin | 205 | 20.5 |
| Levofloxacin | 164 | 16.4 |
| Imipenem | 160 | 16.0 |
| Clindamycin | 156 | 15.6 |
| Moxifloxacin | 132 | 13.2 |
| Ciprofloxacin | 120 | 12.0 |
| Mechanical ventilation | 801 | 80.1 |
| **Radiological description (n=910)** | | |
| Multiple foci pneumonia | 831 | 83.1 |
| Pleural effusion | 79 | 7.9 |
| **Positive bacterial cultures (n=1000)** | | |
| *Staphylococcus epidermidis* | 7 | 0.7 |
| *Staphylococcus aureus* | 7 | 0.7 |
| *Pseudomona aeuruginosa* | 5 | 0.5 |
| *Candida albicans* | 5 | 0.5 |
| *Staphylococcus hominins* | 3 | 0.3 |
| *Staphylococcus haemolyticus* | 3 | 0.3 |
| Coagulase-negative *Staphylococcus* | 3 | 0.3 |
| Gram-positive moderate *Coccus* | 3 | 0.3 |
| *Acinetobacter baumannii, Staphylococcus aureus* | 3 | 0.3 |
| *Staphylococcus simulans* | 2 | 0.2 |
| **Cause of death (certificate) (n=1000)** | | |
| Pneumonia | 687 | 68.7 |
| Pneumonia associated with other diagnoses** | 247 | 24.7 |
| Other diagnosis | 43 | 4.3 |
| Missing values | 23 | 2.3 |
| Number of days from admission to death* | Range, 0-64 days; median, 5.0 days; mean, 7.8 days | |
| Number of days from initial symptoms to death* | Range, 1-65 days; median, 11.0 days; mean, 13.8 days | |

Regarding arterial blood gas tests, the results are summarized in Table 2, where it is noted that most of the patients had abnormal tests upon hospital admission in the three measured parameters and presented lower oxygen saturation. After intubation, only a slight improvement in the measured parameters was observed.

Table 3 shows clinical data and type of diagnosis, medical treatment, and level of care sought by patients. The main clinical symptoms in the data observed showed fever (91.5%), dyspnea (61.9%), cough (45.0%), headache (40.7%), and myalgia (34.9%). Average hospital stay from time of admission to time of death was 7.8 days, whereas the average time from symptom onset to death was 13.8 days.

A review of imaging studies, chest radiography, shows that 83.1% of the cases had multiple foci of pneumonia and pleural effusion in 7.9% of cases; 80.1% of cases required mechanical ventilation. In bacterial cultures, 4.1% tested positive for at least one antimicrobial agent. The two most frequently encountered microorganisms were *Staphylococcus epidermidis* and *Staphylococcus aureus*, both with a prevalence of 0.7%. Established medical management included the following drugs in order of frequency: antiviral (oseltamivir or zanamivir), 84.8%; steroids, 54.2%; dopamine, 26.3%; adrenalin 20.2%, and norepinephrine, 19.6%. With regard to antibacterial agents, these were used in 89.7% of cases, in order of frequency, and these were prescribed: ceftriaxone, 57.4%; clarithromycin, 28.3%; cefotaxime, 24.7%; amikacin, 22.9%, and vancomycin, 20.5%, among others.

Causes of death comprised pneumonia (68.7% of cases), pneumonia associated with other diagnoses (24.7%), and other diagnoses (4.3%). Of patients who were hospitalized, 16 patients died within the first 24 h and 230 patients died after 12 days. The remainder of the patients died after the first 24 h and before 12 days of hospitalization.

## DISCUSSION

The most common age range found in the registry of deaths was 30-80 years, and there were 22.4% more deaths than those observed nationally in the same age group. Regarding the population <10 years of age, the proportion of deaths was 10.2%, nine percentage points below that observed in the general population. This demonstrates that the pattern observed in the first 100 deaths was maintained, mainly affecting young adults. This profile is comparable to the Spanish experience, in which the majority of cases affected the younger population.[8]

The majority of cases had at least one pre-existing chronic disease at the time of admission. Among these was noted the high percentage of obesity found in males (40%) as well as in females (47.7%), which is above the prevalence in the national population (24 and 34%, respectively). Similarly, the prevalence of MetS was three-fold more common, cardiovascular disease was five times more common, and respiratory illnesses, even more so (17.25-fold among patients who died from influenza than in those recorded in the national statistics) (National Health Survey 2006). Type 2 diabetes mellitus (DM2) was also identified as a clinical entity whose prevalence is 7%, with a prevalence of 4% for cardiovascular diseases and 15.4% for high blood pressure.

This information allows us to state that these diseases are risk factors for death due to influenza. Special mention is made regarding DM2 because it is the leading cause of death reported in Mexico. This is consistent with CDC standards that recommend that patients with DM2 be vaccinated annually against influenza.

A similar situation was observed in Latino populations, such as those of Spain and Chile. In the first case, in patients who died (n=246) it was found that these were older patients (median age, 47 years) and that they had a greater number of co-morbidities than those who recovered [taking into account only patients who were hospitalized in an Intensive Care Unit (ICU)]. The main co-morbidities among the group of patients who died in Spain were any Chronic Obstructive Pulmonary Disease (COPD) or asthma, obesity, or immunodeficiencies.[9] In Chile, the affected age groups were similar to those in the Mexican population (15-49 years of age) and the principal co-morbidities reported were cardiovascular and respiratory diseases.[10]

This study also recommends important lessons from the experience in Mexico in the face of an outbreak of influenza. An important characteristic of the influenza outbreak was the time at which it presented, which was outside of the normal seasonal period. This may account for the earlier cases in which primary care was delayed, in which there was inadequate diagnosis, and in which there was a lack of specific antiviral treatment. From October 22 to December 2, 2009, the highest number of deaths from influenza was recorded, adding 416 cases.

These characteristics highlight the importance for all countries to implement a timely epidemiological alert that monitors epidemiological information systems, thus anticipating an abnormal resurgence of influenza.

Although these data are not analyzed in this article, the attack rate was actually similar to that of a flu season. In the case of Spain, this was also true, where the peak maximum incidence was reached during week 46 of the year 2009.

The overall responsiveness to performing an RT-PCR test became available in Mexico on May 1, 2009, which may have influenced the delay in identification and in performance of rapid intervention in these cases. This situation notwithstanding, these findings demonstrate the

importance of rapid implementation and active surveillance during the early stages of the epidemic. The Spanish experience for the most recent epidemic of Human influenza A (H1N1) virus shows that once phase 6 was established by the WHO, the planning of health services was established by searching for sentinel cases and by surveillance of severe cases.[8] A new monitoring strategy was established with several aspects that were required to meet the suspicious cases, including incubation period, clinical criteria, epidemiological criteria, laboratory criteria, and case classification.[11] Information and education of the population are key points for reducing the time between first symptoms and first medical care, in order to administer the antiviral treatment in timely fashion, in that this was one of the most important variables that affected the clinical outcome of these patients. In the case of Mexico, the same time period for reflection or availability of information during early stages of the epidemic was not available; therefore, greater uncertainty prevailed in the management of influenza, possibly explaining the increased number of deaths in the country.

## CONCLUSIONS

One limitation of this study is that the source of information was medical records. Not being able to control the accuracy of this information limits the ability to perform a more complete analysis, such as in the case of measuring BMI, which was referred in the methodology.

Comparisons with national data in our study are only descriptive and provide contextual information with which to interpret the study findings. The study examined only the deaths reported due to influenza A (H1N1) and confirmed by RT-PCR. Deaths that occurred at the homes of patients who did not receive medical care, thus undetected by the health system, were not taken into account. Similarly, cases with influenza A (H1N1) who survived were not able to be analyzed. This would have allowed us to analyze more clearly the weight of relevant risk factors such as co-morbidities, individual factors, and social factors, and in particular, the characteristics and responsiveness of government health systems. This is a limitation that must be resolved. In the UK, discussions on the need for a revolution in the area of health information are underway. Certainly, change at the global level is indispensable.

Recent studies suggest that mortality from influenza A (H1N1) is lower than previously thought and this underscores the need for more accurate warning systems that take into consideration the source, transmissibility, and pathogenicity of the new agent.[10,11] Absence of deaths among those in close contact with patients who died during the epidemic suggests a moderate degree of virulence. Although it was impossible to contain the first outbreak and transmission among countries, current evidence indicates a clear reduction in mortality with early detection and appropriate treatments and effective control of patients with influenza. In the case of Mexico, these attributes allowed the stabilization of new cases and reduced the number of deaths at the end of the epidemic to a certain degree.

Finally, this analysis suggests that it is important to strengthen the capacity of information systems and the epidemiological surveillance of countries. It is insufficient to possess only emergency plans. Information must be rapidly disseminated for effective epidemic control. In addition, a health system should strengthen primary healthcare and primary care in general. As noted, the majority of patients who died due to influenza generally had no contact at the primary healthcare level. This is the system of "first-point-of-contact" and it must be strengthened.

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