

Quantifying the mortality caused by the H1N1 influenza virus during the 2009 pandemic in Mexico

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Abstract

Introduction: The frequency and mortality of the pandemic caused by influenza A(H1N1)pdm09 might have been underestimated, especially in developing countries. This study was designed to quantify the possible underestimation of pandemic influenza mortality and evaluate the concordance between the data reported for A(H1N1)pdm09 mortality and the causes of death reported during the pandemic period of April 2009 to February 2010.

Methodology: The death certificates of 754 confirmed cases of A(H1N1)pdm09 infection were included in the study. Data was analyzed using the United States Centers for Disease Control and Prevention's statistical model accounts for the variability in the proportion at each step using the Monte Carlo probabilistic model sampled from a uniform probability distribution.

Results: A total of 1,969 deaths were estimated, with an estimated lethality of 5.53 per 100,000 (range, 3.5-8.76 per 100,000) in contrast with the 754 deaths and a lethality of 1.98 per 100,000 infected patients officially reported. In 631 of 754 (83.7%) death certificates from A(H1N1)pdm09 influenza-positive patients, influenza was not mentioned as a cause of death.

Conclusions: It is possible that the mortality of the pandemic was three times higher than officially reported in Mexico. One source of error that could explain this underestimation is in the completion of death certificates, because in > 80% of confirmed cases of infection with influenza virus, it was not reported as the cause of death.

Key words: influenza A virus H1N1 subtype; pandemics; public health; disease outbreaks; statistics; population

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Introduction

Influenza infections cause substantial mortality and morbidity every year, and estimates of this burden have played a pivotal role in formulating influenza vaccination policies [1]. However, the number of deaths attributable to influenza is difficult to estimate directly because influenza infections are typically not confirmed by laboratory tests or are not specified on hospital discharge forms, including death certificates. In addition, many infected people who suffer moderate or mild symptoms do not seek medical care. Importantly, sometimes influenza-associated deaths occur from secondary complications, when influenza viruses are no longer detectable [2].

Confining the denominator to laboratory-confirmed cases may lead to gross underestimation of the incidence of true symptomatic cases and, therefore, will lead to a substantial overestimation of mortality for symptomatic cases. In Mexico, the lethality was calculated as 0.1%, but the denominator was restricted to patients presenting to primary care facilities [3,4].

Estimates based on death certificates may be subject to delays of weeks and depend on the accuracy and completeness of death certificates; they may, therefore, be unreliable. Mortality associated with the A(H1N1)pdm09 influenza strain has been reported with variable completeness worldwide and in particular subgroups, including inpatients, patients in critical care, pregnant women, and children [4].

The Instituto Mexicano del Seguro Social (IMSS) is the largest health institution in Mexico and provides health care services to around 43% of the total population of the country [3]. The IMSS is distributed across the entire Mexican territory, and has three levels of care. The first level includes family medicine, preventive medicine, and prenatal care; the second level includes general hospitalization; and the third level corresponds to specialized hospitalization.

To estimate the mortality during the 2009 influenza pandemic in the IMSS population, a simple model designed by the United States Centers for Disease Control (CDC) [5] was used; this model conforms to the leverage of multiple sources of uncertainty, taking into account the models mentioned above. In this model, the user can enter data from a population of interest, the number of reported cases in the population, and a range of possible values for each of the steps in the estimation of cases. The model accounts for the variability in proportion in each step using the Monte Carlo probabilistic model sampled from a uniform probability distribution.

This work had two main objectives: first, to quantify the possible underestimation of the pandemic influenza mortality between April 2009 and February 2010; and second, to evaluate the relationship between the data reported for A(H1N1)pdm09 mortality during the pandemic period of April 2009 to February 2010 and the causes of death reported on the death certificates of patients infected by the virus. These data should contribute further to the analysis of the response of the IMSS health care services during the pandemic emergency.

Methodology

Two databases were analyzed retrospectively. The first contained the death records of IMSS patients with A(H1N1)pdm09 diagnosis verified using the polymerase chain reaction (PCR) test at the laboratory of the IMSS Epidemiological Surveillance Coordination. The second database was an online epidemiological surveillance notification system called SINOLAVE. Both databases were created in response to the epidemic and recorded in the Epidemiological Surveillance and Contingency Support attached to the Public Health Unit of the Directorate of Medical Benefits of the IMSS. The information analyzed was for the period between February 2009 and April 2010. The two databases comprise electronic records from 1,099 family medicine units and 259 hospitals (general zone, regional general, and high-specialty medical units).

The information on mortality from the A(H1N1)pdm09 influenza virus was recorded in a Microsoft Excel file. Each record in the mortality database was assigned a unique identifier, and the information was homogenized to give it a statistical structure. Subsequently, the categories of variables such as age, date of death, medical units of origin, and occurrence of death were established.

Seven hundred fifty-four death certificates were validated by completing and rectifying those that exhibited any inaccuracy, inadequacy, or duplicity. Patients' dates of death were grouped according to epidemiological week. The results are expressed as frequencies, percentages, and rates. Mortality was calculated using the number of recorded deaths from A(H1N1)pdm09 influenza as the numerator, according to age and sex, and the rights-holder population of the IMSS as the denominator, according to age and sex, for June 2009 [5].

A simple model designed by the US CDC was used. The main feature of the estimation method is that it is a simple multiplier model that adjusts for multiple sources of uncertainty. In this model, the user can enter data from a population of interest, the number of reported cases in the population, and a range of possible values for each of the steps in the estimation of cases. The model accounts for the variability in the proportion at each step using a probabilistic Monte Carlo model sampled from a uniform probability distribution. It calculates a total multiplier that is used to estimate the probability of the occurrence of cases and deaths from A(H1N1)pdm09 influenza. This model provides a simple approach to estimate the burden imposed by the A(H1N1)pdm09 influenza virus on human health.

The death certificates of 754 confirmed cases were analyzed to assess whether the physicians had recorded infection with A(H1N1)pdm09 as the immediate basic cause of death or as the background cause of death.

This study was approved by the Ethics Board of the National Commission of Scientific Investigation (Registry No. 2010-785-019).

Results

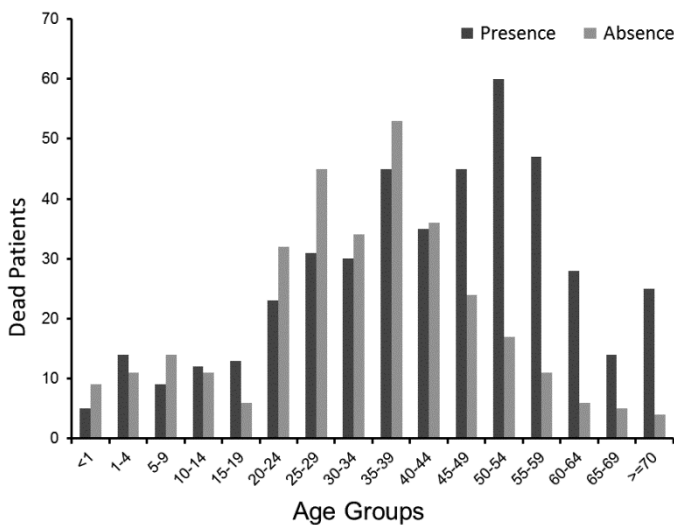
Mortality by A(H1N1)pdm09 influenza in Mexico during the pandemic

By April 30, 2010, the IMSS had recorded 173,392 cases of suspected influenza-like illness (ILI), 20,000 confirmed cases, 15,606 hospitalized cases, and 754 deaths.

Table 1. Number and percentage of patients who died of A H1N1 influenza according to co-morbidity

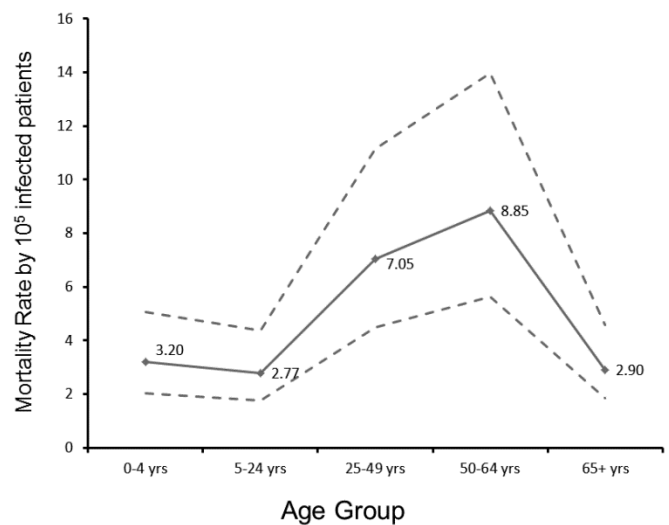
Co-morbidity	Frequency (n = 754)	%
None	318	42.2
Hypertension	174	23.1
Diabetes	43	5.7
Neurological diseases	32	4.0
Obesity	32	4.2
Renal diseases	29	3.8
Pneumopathy	28	3.7
Cancer	16	2.1
Arthritis-Lupus	11	1.5
Cardiopathies	8	1.1
AIDS	3	0.4
Other	60	8.0
Total	754	100.0

Figure 1. Comorbidity by age group in patients who died from pandemic 2009 H1N1 influenza



Comorbidities present in 754 dead patients were analyzed by quinquennial age groups. Dark bars indicate the number of patients that presented comorbidities; gray bars indicate the number of patients who did not present comorbidities.

Figure 2. Estimate of the mortality of influenza A (H1N1)pdm09 per 100,000 infected patients by age group



Estimated mortality value is represented by the gray line and the confidence intervals are represented by dotted lines. The estimated mortality in each age group is indicated by the numbers on the gray line.

Table 2. Mortality by influenza A H1N1 by age and sex groups

Age group (years)	Rights-holder population in 2009			Cases numbers during between April 2009 and February 2010			Lethality		
	Sex		Total	Sex		Total	Sex		Total
	Female	Male		Female	Male		Female	Male	
< 1	242,177	254,636	496,813	3	11	14	1.24	4.32	2.82
1 to 4	1,315,304	1,383,362	2,698,666	11	14	25	0.84	1.01	0.93
5 to 9	1,762,922	1,832,314	3,595,236	14	9	23	0.79	0.49	0.64
10 to 14	1,620,745	1,685,798	3,306,543	14	9	23	0.86	0.53	0.70
15 to 19	1,037,381	899,765	1,937,146	9	10	19	0.87	1.11	0.98
20 to 24	1,404,523	1,119,209	2,523,732	38	17	55	2.71	1.52	2.18
25 to 29	1,674,739	1,401,106	3,075,845	42	34	76	2.51	2.43	2.47
30 to 34	1,731,907	1,462,321	3,194,228	26	38	64	1.50	2.60	2.00
35 to 39	1,654,876	1,424,038	3,078,914	34	64	98	2.05	4.49	3.18
40 to 44	1,371,812	1,158,646	2,530,458	28	43	71	2.04	3.71	2.81
45 to 49	1,202,906	980,821	2,183,727	31	38	69	2.58	3.87	3.16
50 to 54	1,069,754	826,013	1,895,767	40	37	77	3.74	4.48	4.06
55 to 59	923,915	702,012	1,625,927	29	29	58	3.14	4.13	3.57
60 to 64	822,937	669,501	1,492,438	13	21	34	1.58	3.14	2.28
65+	2,264,125	2,105,912	4,370,037	15	33	48	0.66	1.57	1.10
Total	20,100,023	17,905,454	38,005,477	347	407	754	1.73	2.27	1.98

Using the CDC method, the number of infected patients in the IMSS population was estimated to be ~1.11 million, with a minimum of 234,700 and a maximum of 2.09 million. Estimates developed using this method yielded the following results: a median of 65,700 inpatients (range: 41,500-104,000) and a median number of deaths of 1,969 (range: 1,246-3,118).

During the study period, 754 deaths were recorded, 54% of which were men. There was no comorbidity in 42.2% of the deaths (Table 1), and only 8% had a combination of comorbidities. In the 44 years and younger age group, about half of all deaths occurred in individuals without comorbidities, whereas in the patients 45 years of age and older, most deaths occurred in patients with comorbidities (Figure 1). Lethality was high for the less-than-one-year age group and increased again from ages 35 to 60 years (Table 2).

Grouping the patients into five age groups showed that the highest mortality was in the 25-49 and 50-64-year age groups (Figure 2). The initial reported lethality of 1.98 per 100,000 appeared to have been underestimated. This rate could have been as high as 5.2 per 100,000 infected; also, 1,980 deaths (95% confidence interval: 1,263-3,129) may have occurred during the epidemic period (Table 3). The estimated lethality for these age groups was 2.5-3 times higher than what was recorded officially.

Death certificates

The underestimation was assessed by reviewing the death certificate of each patient positive for

A(H1N1)pdm09 influenza. This revealed that the presence of influenza infection was not recorded in 83.7% of cases (Table 4).

The diagnoses of influenza or A(H1N1)pdm09 influenza, together or separately, recorded in death certificates during the study period were as follows: the underlying cause of death in 58 cases (7.7%), the direct cause of death in 23 cases (3.0%), and as an antecedent in 42 cases (5.6%), for a total of 123 cases (16.3%). There was no recorded diagnosis of A(H1N1)pdm09 influenza in 631 (83.7%) of the total number of cases. The most frequent diagnosis recorded on death certificates was viral atypical pneumonia or severe respiratory failure.

Discussion

An accurate assessment of the exact number of people infected is one of the main difficulties during an influenza epidemic. This number cannot be established directly; it can only be determined through representative serum samples and antibody titers or through estimates using mathematical models [6].

The first influenza pandemic of the twenty-first century was considerably less lethal than expected [4]. This assertion was possible by estimating the total number of people infected with the A(H1N1)pdm09 influenza virus, which was achieved using the results of laboratory tests and/or estimates based on mathematical models. The evaluation of the number of fatal cases was one of the main challenges faced by health care systems, because some patients were asymptomatic and others did not seek medical care despite the presence of symptoms. Given the

Table 3. Estimation of the number of deaths from influenza between April 2009 and February 2010

<i>Number of deaths by A(H1N1) influenza</i>	<i>Count</i>			<i>Rate per 10⁵ IMSS rights-holders</i>		
	90% limits			90% limits		
	Median	Min	Max	Median	Min	Max
0-4 yrs	102	65	162	3.20	2.04	5.06
5-24 yrs	315	201	498	2.77	1.77	4.38
25-49 yrs	992	633	1,567	7.05	4.50	11.15
50-64 yrs	444	283	701	8.85	5.64	13.98
65+ yrs	127	81	200	2.90	1.85	4.58
Total	1,980	1,263	3,129	5.21	3.32	8.23

Table 4. Number and percentage of records of A (H1N1) influenza diagnosis in death certificates

<i>Total death certificates without record of influenza and/or A (H1N1) diagnosis</i>	<i>Record as direct cause of death</i>	<i>Record as underlying cause of death</i>	<i>Record as an antecedent or morbid condition that led to death</i>	<i>Total death certificates with record of A (H1N1) influenza diagnosis</i>
631/754 (83.7%)	23/754 (3.0%)	58/754 (7.7%)	42/754 (5.6%)	123 (16.3%)

conditions described above, few cases that required hospitalization or admission to an intensive care unit and involved patient death were recorded accurately; this resulted in underreporting or underestimation of the number of victims. Despite these difficulties, with the help of laboratory test data, the World Health Organization determined the official death toll of A(H1N1)pdm09 influenza worldwide to be 17,483 deaths up to March 28, 2010. This figure is lower than the estimated annual global mortality for seasonal influenza [7].

Thus, the final figure reflects what happens with other pandemics – surveillance systems significantly underestimated the burden of the A(H1N1)pdm09 influenza virus because only confirmed A(H1N1)pdm09 hospitalizations and deaths were reported. For example, an epidemiological study performed in the United States found that the mortality associated with A(H1N1)pdm09 influenza was lower than for other pandemics, with only 12 deaths per 100,000 inhabitants from April to July 2009 [8]. Similarly, a study conducted in the United Kingdom reported a lethality of 0.026%, which was very low compared with other worldwide reports. In other reports, the mortality rates were 0.1% to 0.9%; however, these studies used cases confirmed by laboratory testing as the denominator [4]. Lethality as low as 0.005% was reported in New Zealand [8]. Our first study, published in November 2009, also reported a mortality < 1%, although we were able to adjust the first estimate using the Emerging Infections Program of the CDC and the death certificates obtained from the IMSS.

The influenza surveillance system of the CDC comprises a series of sentinel systems that continuously monitors patients with ILI and associated morbidity throughout the territory using reports of hospitalizations and deaths. These systems can help monitor the trend of a disease and the speed at which it spreads over time by comparing it according to geographic regions. However, one disadvantage of these systems compared with other models is that they fail to consider the full burden of influenza on a population, because identifying and including all individuals in epidemiological studies requires that each patient visits a clinic. Although the model has some shortcomings, these were adjusted for, thus overcoming the limitations. In our case, five age groups were considered: 0-4 years, 5-24 years, 25-49 years, 50-64 years, and 65 years and older, which is in keeping with the CDC model [5]. Additionally, the cause of death was adjusted using death certificates;

thus, only cases in which the main cause of death was A(H1N1)pdm09 influenza were considered. Finally, comorbidity was considered, leading to the exclusion of cases for which A(H1N1)pdm09 influenza was not the leading cause of death.

Using the method described above, we recorded the following: 58 cases (7.7%) had A(H1N1)pdm09 influenza as the underlying cause of death, 23 cases (3.0%) had A(H1N1)pdm09 influenza as the direct cause of death, and 42 cases (5.6%) had A(H1N1)pdm09 influenza as an antecedent, for a total of 123 cases (16.3%). The underestimation of the mortality rate is noteworthy because, although the initial mortality rate reported was 1.98 per 100,000 rights-holders, it was estimated that this rate could be as high as 5.2 per 100,000 rights-holders, surpassing the United States' mortality estimation of 4 per 100,000 rights-holders [9]. This was, however, still lower than the rate noted by another Mexican group that estimated it could have been as high as 11.1 per 100,000 rights-holders [10]. These differences might reflect the different time periods studied, because the range was only from April 2009 to December 2009, in which both the mortality and morbidity were higher than at the beginning of 2010 [3,8].

One advantage of the CDC model is that the user can enter data from a population of interest, the number of reported cases in the population, and a range of possible values for each of the steps in the estimation of cases. The model also accounts for the variability in the proportion at each step using a Monte Carlo probabilistic model sampled from a uniform probability distribution. This model provided a simple approach to estimating the burden of the A(H1N1)pdm09 influenza virus on human health. Our results were consistent with those reported recently by other groups from the IMSS on the possible underestimation of the recorded mortality of A(H1N1)pdm09 influenza [10]. However, our work is the first to evaluate whether death certificates in Mexico reported A(H1N1)pdm09 influenza infection as the cause of death. In the United States, only 60% of the deaths associated with A(H1N1)pdm09 influenza reported influenza as the cause of death [11]. In contrast, in the United Kingdom, the cause of death of 80% of the people infected with A(H1N1)pdm09 influenza was reported as influenza [12].

Continuous monitoring of the severity of A(H1N1)pdm09 influenza will allow the identification of needs within our health system regarding hospitalization, access to intensive care units, and special needs for each age group. The estimated

mortality rate will allow health authorities to develop long-term strategies to ensure the quality of medical care provided by all health care systems. It will also allow the evaluation of responses to the epidemic and determination of the efficiency of use of available resources and proper administration of specific treatments, and will enable us to advise the administration on the appropriate antiviral drugs to be used in future epidemics.

Inadequate recording of the basic and direct causes of death on death certificates is a widespread problem that was identified in our study and requires attention. It must be addressed as a matter of urgency during the training of hospital medical staff to ensure that death certificates are completed accurately and fully.

Conclusion

Based on the number of sick people and deaths registered in the IMSS, the 2009 influenza pandemic was considered to be less lethal and less severe than expected. However, it is possible that the mortality and lethality of the 2009 influenza pandemic were three times higher than officially reported. One source of error in this underestimation is the completion of death certificates, because in > 80% of confirmed cases of infection, influenza was not reported as a cause of death.

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Conflict of interests: No conflict of interests is declared.