Infection and death from influenza A H1N1 virus in Mexico: a retrospective analysis

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Lancet 2009; 374: 2072–79

Published Online November 12, 2009 DOI:10.1016/S0140-6736(09)61638-X

See Online/Comment DOI:10.1016/S0140-6736(09)61916-4

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Summary

Background **In April, 2009, the first cases of influenza A H1N1 were registered in Mexico and associated with an unexpected number of deaths. We report the timing and spread of H1N1 in cases, and explore protective and risk factors for infection, severe disease, and death.**

Methods **We analysed information gathered by the influenza surveillance system from April 28 to July 31, 2009, for patients with influenza-like illness who attended clinics that were part of the Mexican Institute for Social Security network. We calculated odds ratios (ORs) to compare risks of testing positive for H1N1 in those with influenza-like illness at clinic visits, the risk of admission for laboratory-confirmed cases of H1N1, and of death for inpatients according to demographic characteristics, clinical symptoms, seasonal influenza vaccine status, and elapsed time from symptom onset to admission.**

Findings **By July 31, 63 479 cases of influenza-like illness were reported; 6945 (11%) cases of H1N1 were confirmed, 6407 (92%) were outpatients, 475 (7%) were admitted and survived, and 63 (<1%) died. Those aged 10–39 years were most affected (3922 [56%]). Mortality rates showed a J-shaped curve, with greatest risk in those aged 70 years and older (10·3%). Risk of infection was lowered in those who had been vaccinated for seasonal influenza (OR 0·65 [95% CI 0·55–0·77]). Delayed admission (1·19 [1·11–1·28] per day) and presence of chronic diseases (6·1 [2·37–15·99]) were associated with increased risk of dying.**

Interpretation **Risk communication and hospital preparedness are key factors to reduce mortality from H1N1 infection. Protective effects of seasonal influenza vaccination for the virus need to be investigated.**

Funding **None.**

Introduction

At the beginning of April, 2009, the medical care units of the Mexican Institute for Social Security (Instituto Mexicano del Seguro Social, IMSS) were alerted because the number of seasonal influenza cases did not decrease as expected from March to May. Additionally, three outbreaks of influenza-like illness were reported in the Mexican States of Veracruz, Tlaxcala, and San Luis Potosí from March to April.[1] These events, in conjunction with a report[2] of a suspected case of non-typical pneumonia in the State of Oaxaca on April 15, triggered both an epidemiological alert on April 17, and intensified surveillance of severe acute respiratory infections in inpatients. On April 23, Mexican officials announced that a novel influenza A H1N1 virus (pandemic H1N1) had been identified in two samples—one from the outbreak in Veracruz[3] and another from Oaxaca. By then, 18 confirmed H1N1 cases had been reported.[4]

By Sept 27, more than 4100 deaths were associated with the pandemic worldwide,[5] with 3020 deaths in the Americas mainly occurring in the USA, Argentina, Mexico, Brazil, and Canada. Mexico has one of the highest numbers of registered deaths at that date for this pandemic, with 146 cases[6]—63 of which have been reported by IMSS. IMSS is a Mexican public institution that provides health-care services to a population of nearly 40 million people, manages 1099 primary health-care units and 259 hospitals across the country, and has reported the largest number of cases and deaths of H1N1 within the country. In a pandemic, infection and death rates are expected to affect countries in different ways.[7] Individual host factors (eg, immune function, nutritional status, acquired immunity through previous influenza infection, and comorbidity) and community factors (population density and mixing rates, quality and access to health care, and the physical environment) can explain variations in mortality between communities.[7]

The epidemic in Mexico had a transmissibility rate of 1·2% and an estimated disease-specific mortality rate of 0·4%;[8] however, in view of new data, ranges for mortality have been set between 0·20% and 1·23%, with the lowest rates reported in the European Union (EU) and the highest in Mexico. At present, the pandemic has spread to more than 168 countries.[5] We therefore need to stay alert—especially in countries with similar socio-demographic characteristics to Mexico, which might share conditions that could potentially contribute to H1N1 mortality. An important step is to assess international strategies and programmes to control domestic epidemics, such as the controversial school-closure policy to prevent transmission.[9,10] Mexico has been the only country to shut down the school system

nationwide—from nurseries to universities—at the beginning of the pandemic.

We report the IMSS experience of the timing and spread of H1N1, and investigate some protective and risk factors for infection, severe disease, and death.

Methods

Data collection and surveillance

Before the H1N1 epidemic, Mexico had an active but incomplete influenza surveillance system. This surveillance allowed detection of the first cases of the new influenza but was not effective in assessment of the extent of the epidemic. After the first alert on April 17, active surveillance for severe pneumonia was started in all IMSS hospitals. Therefore, surveillance was only of patients in hospital, although almost all reported cases up to April 28, were the most severe.

On April 28, IMSS began active surveillance for influenza-like illness in outpatients within all primary health-care units and in inpatients, and began mortality surveillance in hospitals. Patients attending any primary-care clinic or hospital who met the case definition of influenza-like illness and those who were admitted with such an illness were entered into the surveillance system online by hospital or clinic epidemiologists, and the database was updated every day. Influenza-like illness was defined as fever, cough, and headache, with one or more of the following symptoms: sore throat, rhinorrhoea, arthralgias, myalgia, prostration, thoracic pain, abdominal pain, nasal congestion or diarrhoea, and irritability in infants (fever was not needed as a symptom for people older than 65 years). Requested information for case notification consisted of name, address, age, sex, occupation, symptoms, presence of a chronic disease, treatment, and whether influenza vaccination had been given during 2008 or 2009.

At the start of the epidemic, when influenza was suspected, clinicians obtained respiratory swabs for the rapid QuickVue Influenza A+B test (Quidel, San Diego, CA, USA) and for H1N1 virus testing with real-time PCR (rtPCR) on the same day. Additionally, an average of four household or co-worker contacts of confirmed patients were tested with rapid and confirmatory tests. Some inpatients did not have a rapid test—ie, cases confirmed before April 28, or when rapid tests were unavailable at clinics. By July 31, 49 196 QuickVue tests had been done, 9475 (19%) of which were positive. By July 31, confirmatory tests were ordered for 7130 patients with negative QuickVue results (figure 1). The decision to treat with antiviral drugs was based on clinical and epidemiological information and not solely on rapid test results.

With this surveillance system, the start of the epidemic was documented mainly for the most severe cases and for some mild cases, because active surveillance began at different times. Additionally, IMSS headquarters gathered medical records of all deaths to extract further detailed information to describe severe cases. From April 17 to May 25, all specimens were submitted to state laboratories and results were confirmed by the Instituto de Diagnóstico y Referencia Epidemiológica (InDRE) with direct antigen detection of influenza-specific RNA by real-time reverse-transcriptase (rtRT)-PCR, according to US Centers for Disease Control and Prevention (CDC) and WHO recommendations for collection and testing.[11] Since May 25, most specimens have been confirmed at La Raza, which is the IMSS laboratory authorised by InDRE.

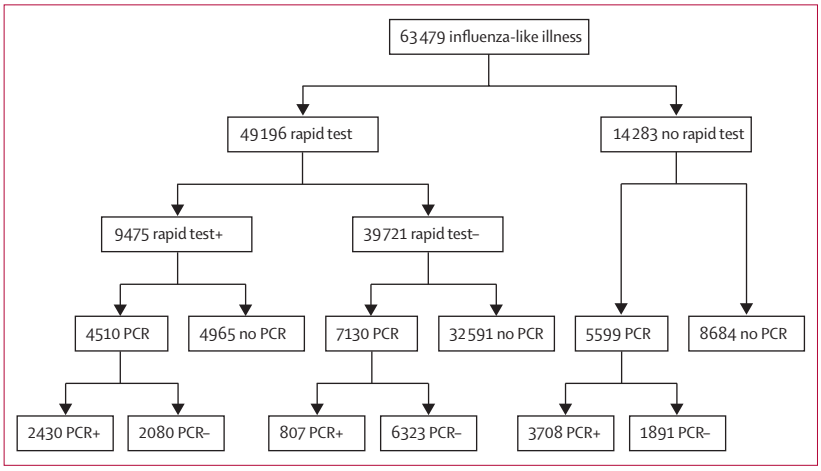

Figure 1: **Flow of patients with influenza-like illness and rapid and RT-PCR tests at IMSS, April–July, 2009**
RT=reverse transcriptase. IMSS=Mexican Institute for Social Security.

Statistical analysis

We used graphical analysis to describe the epidemic and show the time of alert and interventions used to prevent propagation of the virus. We estimated rates of clinical infection, admission, and deaths, with the population with a family doctor as the denominator.[12] Since H1N1 mortality rates could be misleading, we calculated different measures to estimate numbers of deaths, with influenza-like illness, laboratory-confirmed infection, and inpatients as denominators, as recommended by Fraser and co-workers.[3,8]

To identify symptoms with an increased association with testing positive for H1N1 infection and demographic characteristics, we used odds ratios (ORs) and 95% CIs to compare outpatients who were laboratory-confirmed positive cases with those confirmed negative, with unconditional logistical regression, adjusted by age and sex. With ORs, we compared laboratory-confirmed cases and grouped cases by severity as outpatients, inpatients, and deaths. We calculated field assessment of sensitivity and specificity of QuickVue tests in patients who were tested with both the rapid and rRT-PCR tests. This study did not need approval from a scientific committee; all individual data were kept confidential and patients could not be identified.

	Population	ILI (incidence ILI*)	Confirmed H1N1 (incidence confirmed H1N1*)	ILI cases admitted to hospital with severe acute respiratory infection (%)	Admitted with confirmed H1N1 (H1N1 admission rate*)	H1N1 deaths confirmed (population H1N1 mortality rate*)	Proportion H1N1 admissions†	ILI mortality rate‡	Confirmed H1N1 mortality rate§	Confirmed H1N1 admission mortality rate‖
Age (years)										
<1	503 236	1636 (325·10)	248 (49·28)	184 (11%)	33 (6·56)	4 (0·79)	0·10	0·24%	1·6%	12·1%
1–9	5 968 658	11 452 (191·87)	1584 (26·54)	495 (4%)	112 (1·88)	4 (0·07)	0·07	0·03%	0·3%	3·6%
10–19	4 961 194	10 071 (203·00)	1880 (37·89)	306 (3%)	90 (1·81)	3 (0·06)	0·05	0·03%	0·2%	3·3%
20–29	5 261 106	11 502 (218·62)	1381 (26·25)	483 (4%)	105 (2·00)	12 (0·23)	0·08	0·10%	0·9%	11·4%
30–39	5 889 209	8204 (139·31)	661 (11·22)	373 (5%)	76 (1·29)	13 (0·22)	0·11	0·16%	2·0%	17·1%
40–49	4 373 824	5550 (126·89)	410 (9·37)	326 (6%)	47 (1·07)	11 (0·25)	0·11	0·20%	2·7%	23·4%
50–59	3 254 339	3129 (96·15)	200 (6·15)	254 (8%)	37 (1·14)	9 (0·28)	0·19	0·29%	4·5%	24·3%
60–69	2 547 855	1319 (51·77)	70 (2·75)	182 (14%)	19 (0·75)	4 (0·16)	0·27	0·30%	5·7%	21·1%
≥70	2 852 758	1173 (41·12)	29 (1·02)	322 (27%)	7 (0·25)	3 (0·11)	0·24	0·26%	10·3%	42·9%
Missing data	NA	9443	482	64	12	NA	NA	NA	NA	NA
Total	35 612 179	63 479 (178·25)	6945 (19·50)	2989 (5%)	538 (1·51)	63 (0·18)	0·08	0·10%	0·9%	11·7%
Region										
Central Mexico outbreak	9 754 553	12 632 (129·50)	486 (4·98)	924 (7%)	130 (1·33)	45 (0·46)	0·27	0·36%	9·3%	34·6%
Southeast Mexico outbreak	4 022 996	14 196 (352·87)	3511 (87·27)	489 (3%)	160 (3·98)	5 (0·12)	0·05	0·04%	0·1%	3·1%

Data from Mexican Institute for Social Security, July 31, 2009. ILI=influenza-like illness. H1N1= influenza A H1N1. NA=not applicable. *Per 100 000 people affiliated with the Mexican Institute for Social Security. †Admitted to hospital with confirmed H1N1÷total confirmed H1N1. ‡(Deaths÷ILI)×100. §(Deaths÷confirmed H1N1)×100. ‖(Deaths÷H1N1 admissions)×100.

Table 1: **Effects of influenza A H1N1 by age-group and region, April–July 2009**

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

The first large outbreak of H1N1 in Mexico affected the Mexico City metropolitan area, San Luis Potosí, and Zacatecas in April, 2009, and lasted until June 6, 2009. Figure 2 shows results of intensive surveillance for influenza-like illness after April 28, in which up to 2800 cases were reported on May 2, during the peak of the epidemic. Since laboratory capabilities were initially overwhelmed, the number of confirmed cases as a proportion of suspected cases was very low. During this first outbreak, the mortality rate was high (table 1). Almost all deaths occurred in the Mexico City area, where most teaching hospitals are located. However, the population was not yet informed about cardinal symptoms, and health services were not prepared for this new disease (figure 2).

During June and July, a second large outbreak occurred in southeast Mexico, affecting Yucatán first, then Tabasco, Chiapas, and Veracruz, separated by intervals of about 1 week. Laboratory capabilities had improved, and more cases were confirmed with rRT-PCR than was previously possible. Most cases in this area were mild and only a few deaths occurred (figure 3). Most cases were from urban areas; however, a few outbreaks were reported in small towns in rural areas. Infection was transmitted mostly between young people but affected the old age-groups more severely than it did any other group (table 1). Time from symptom onset to admission diminished (figure 4) after a wide-reaching and intensive publicity campaign that started April 24, 2009, and remained in the media during the next few months, with decreasing intensity, which had a beneficial effect on mortality rates.

Fever, cough, headache, muscular pain, and rhinorrhoea were the main symptoms (table 2). People who had had seasonal influenza vaccination in the previous year had a reduced risk of H1N1 infection. Table 3 shows symptoms and other risk factors that were reported when patients were first diagnosed or admitted. Sex was not associated with severity of disease. Dyspnoea, tachypnoea, cyanosis, and being confined to bed were prognostic factors for admission and death. Patients with a chronic disease had an increased risk of death from H1N1. Reported chronic diseases of those who died were hypertension, diabetes mellitus, and obesity.

Four pregnant patients aged between 20 and 31 years died; two had only 6 years of education, one was a smoker, one had hypothyroidism, and another was obese, three were confined to bed, all had dyspnoea, and all received oseltamivir within 5–9 days of onset of symptoms. Time from onset of symptoms to admission was longer for people who died than for those who survived in hospital (7 *vs* 3 days). The OR (1·19, table 3) increased with every day of delay. Sensitivity of the QuickVue influenza A+B test was 75·1% (95% CI 73·56–76·58) and specificity 75·2% (74·32–76·18).

Discussion

Our surveillance analysis showed a large outbreak in April, 2009, that mainly affected the population in Mexico city. A second large outbreak took place in the southeast of Mexico during June and July. Mortality rates from pandemic H1N1 differed from those reported in other countries, probably because Mexico was the first country to have intensive virus circulation. The disease-specific mortality rate was high during the first outbreak but was similar to that recorded in other countries in the second outbreak in the southeast region. This finding could be attributable to delayed health care for the first cases.[12] Infants and people aged 10–19 years were at increased risk of infection, but disease was more severe in infants and those older than 60 years than in other age-groups. Patients with chronic diseases and delayed hospital admission were at heightened risk of severe H1N1 influenza, as were pregnant women. Our data suggest that seasonal influenza vaccination could reduce risk of H1N1 infection.

We had difficulty assessing the effectiveness of single control measures that were taken during the first outbreak, such as school suspension and restriction of mass gatherings, to mitigate the effect of the epidemic. Closing of schools might have reduced within-school transmission, and potentially reduced overall transmission within the community because transmission was more frequent between school-aged children, although evidence for this effect is inconclusive.[10] During the days after closure of schools nationwide, numbers of cases of influenza-like illness and confirmed H1N1 were clearly reduced. However, such a reduction is expected in an influenza outbreak that has just peaked—even if no intervention has been implemented.[10] Other measures taken at the same time to reduce transmissibility could have had an effect, such as frequent handwashing, barrier measures (ie, wearing of masks), and isolation of people with suspected respiratory-tract infections.[13] Additionally, numbers did not increase after classes restarted. Jefferson and colleagues[10] reported that closure of schools would

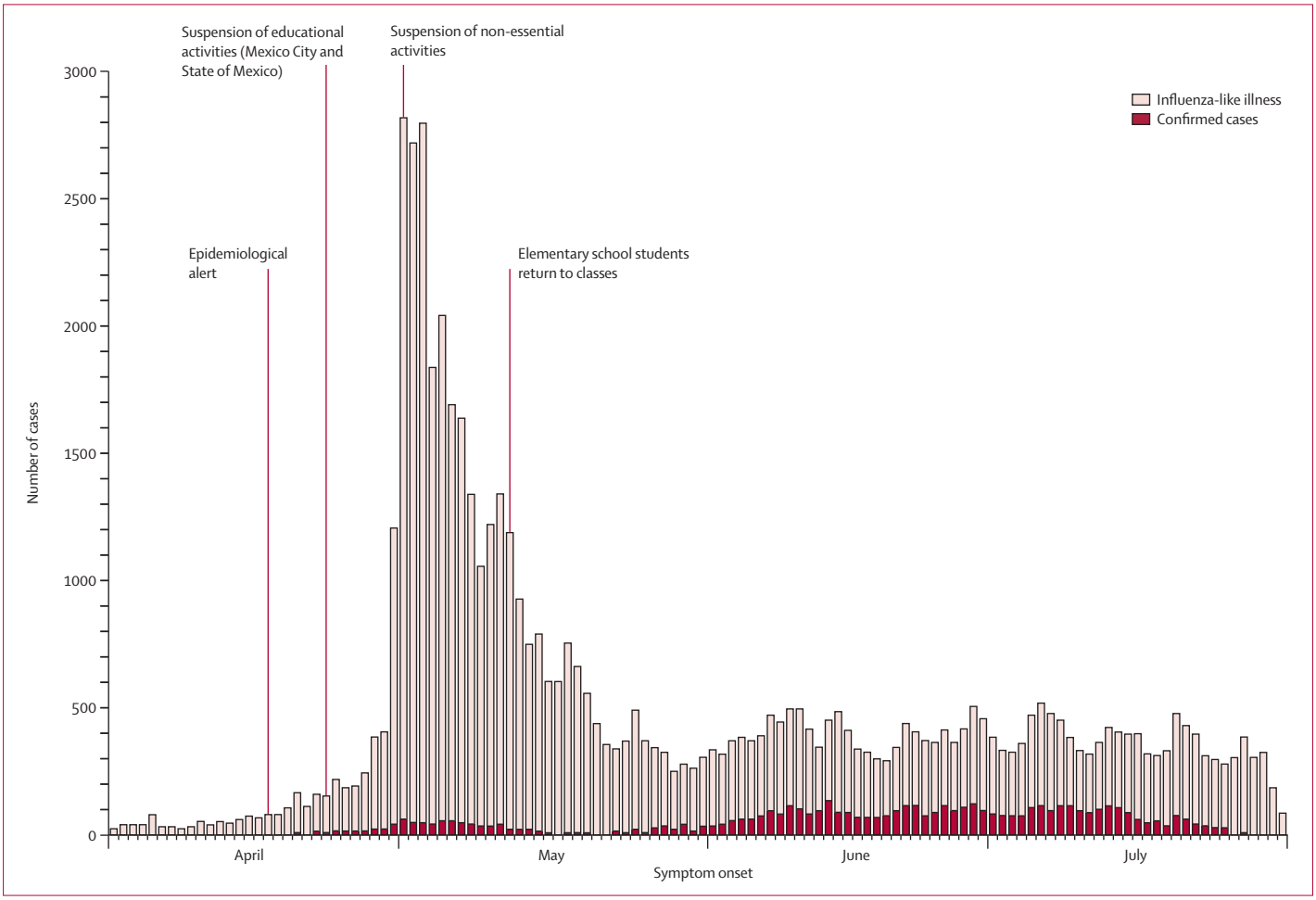

Figure 2: **Numbers of cases with influenza-like illness and laboratory-confirmed H1N1 and time of symptoms onset between April 1, and July 30, 2009**
Data are from the Mexican Institute for Social Security, July 31, 2009.

Figure 3: **Distribution of H1N1 laboratory-confirmed cases (and deaths) recorded by the Mexican Institute for Social Security, April 28, to July 31, 2009**
Data in parentheses indicate number of deaths.

decrease numbers of cases by 15%, but cause reductions of about 40% in peak attack rates. However, this reduction would be substantially undermined if children were not sufficiently isolated; hence, children's activities after school hours are crucial to the health effects of school closure. If schools are closed for a long time, apart from during holidays, contact between children might increase in other settings.[10]

We confirmed that fever, cough, headache, muscle aches, and rhinorrhoea are the main symptoms of H1N1.[2,12,14] Additionally, prostration, dyspnoea, cyanosis, and tachypnoea reported at the first visit were most strongly related to risk of admission and death. In the USA,[15] more than 70% of H1N1 admissions were for individuals with underlying medical problems, such as asthma and other lung diseases, diabetes, morbid obesity, autoimmune disorders, and neurological or cardiovascular disorders, and for those on immunosuppressive therapies.[16]

In previous H1N1 epidemics, Cutler[14] and co-workers reported a predominance of infection in young people. The first report[3] of the present epidemic showed that attack rates were increased in those younger than 15 years. Investigators in the USA reported[17] 60% of their first cases were in those younger than 18 years. Another report from Mexico[12] noted that most cases occurred in people younger than 50 years, and concluded that the highest mortality was in a young population group.[2,12] However, age-specific mortality rates are a combination of incidence and deaths and do not assess severity of disease. Proportions of admissions and disease-specific mortality rates are more indicative of disease severity than are overall mortality rates.[8]

During the 1918 influenza pandemic, the overall disease-specific mortality rate in pregnant women was 27%, establishing that pregnancy is a condition of risk during an influenza pandemic.[18] At IMSS, pregnant women accounted for four of 63 deaths (6·3%), whereas the USA reported seven of 87 deaths (8%). In Mexico, all pregnant workers were sent home during the peak of the pandemic, which probably accounts for this difference. Information about pregnancy in ambulatory confirmed cases was not available in the surveillance system, and we were unable to estimate the case fatality rate for pregnant women. None of the pregnant patients who died received antiviral drugs during the first 48 h and none had received influenza vaccine. Treatment should begin immediately after onset of symptoms in

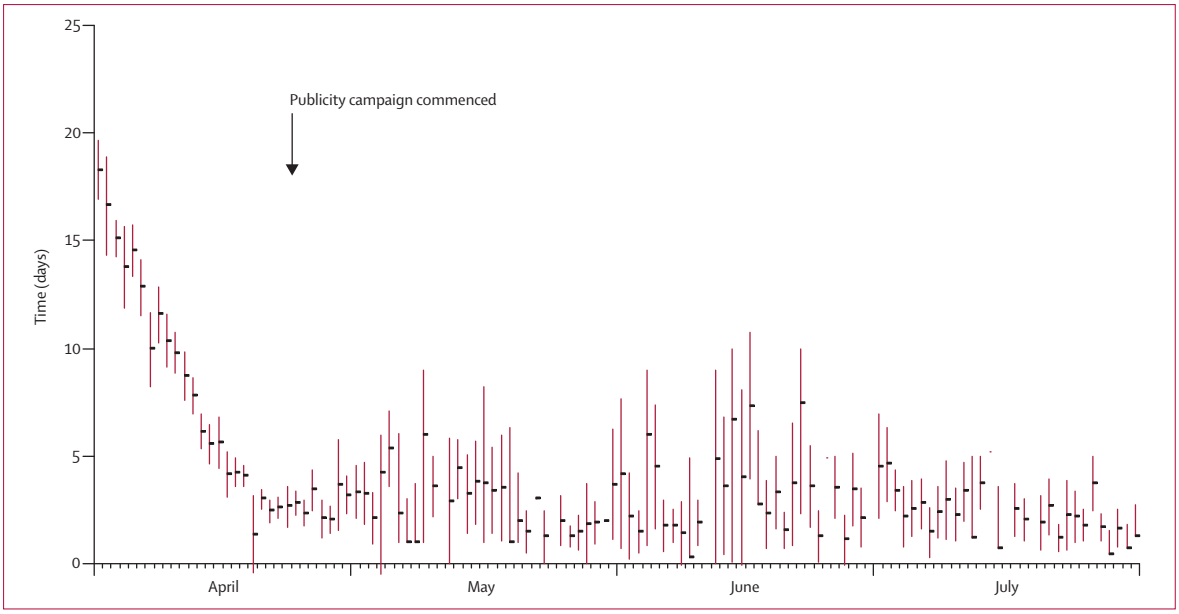

Figure 4: **Delay between symptoms onset to admission, April 28–July 31, 2009**
Mean and 95% CI are shown.

	Influenza-like illness (n=46240, %)	Laboratory-confirmed H1N1 negative (n=10 294, %)	Laboratory-confirmed H1N1 positive (n=6945, %)	H1N1-negative *vs* H1N1-positive odds ratio (95% CI)
Characteristics				
Male sex*	21 887 (47%)	4915 (48%)	3460 (50%)	1·00 (0·94–1·07)
Median age (years)	24 (<1–104)	25 (<1–109)	16 (0–91)	NA
Contact with with possible H1N1	4964/25 547 (19%)	1660/7307 (23%)	138/525 (26%)	0·98 (0·75–1·28)
Chronic diseases	16/46240 (<1%)	38/10 294 (<1%)	..	..
Clinical symptoms				
Fever	26 478/39 413 (67%)	7070/10 027 (71%)	4967/5416 (92%)	4·35 (3·89–4·87)
Cough	11 965/13 864 (86%)	2316/2721 (85%)	4455/4891 (91%)	1·78 (1·54–2·08)
Headache	29 079/39 371 (74%)	7634/10 011 (76%)	4741/5416 (88%)	2·14 (1·93–2·37)
Sore throat	7704/13 792 (56%)	1523/2670 (57%)	2441/4891 (50%)	0·76 (0·68–0·83)
Muscle aches	9327/13 796 (68%)	1833/2670 (69%)	3535/4891 (72%)	1·26 (1·13–1·40)
Rhinorrhoea	10 694/14 303 (75%)	2013/2809 (72%)	3879/5033 (77%)	1·30 (1·17–1·45)
Nasal congestion	7400/13 791 (54%)	1542/2670 (58%)	2948/4891 (60%)	1·08 (0·98–1·20)
Vaccinated 2008–09 or 2008†	3643/25 595 (14%)	1433/8096 (18%)	190/1766 (11%)	0·65 (0·55–0·77)

Data are n (%), median (range), or n/N (%). NA=not applicable. ..=data not available *Adjusted by age. Others variables are adjusted by age and sex. †With influenza vaccine.

Table 2: **Characteristics and clinical symptoms of suspected and confirmed outpatients with influenza-like illness**

this group, and vaccination during pregnancy is not contraindicated and therefore can be considered.[16,18]

Possible protection of seasonal influenza vaccine against H1N1 is controversial. In a Canadian report,[14] investigators did not identify this protective effect for H1N1. However, the Mexican population who has received seasonal influenza vaccination since 1977, including H1N1 components, could have benefited from cross immunity.[19] The high incidence of infection in young people could show not only their different exposure related to their daily activities but also that people older than 60 years might have some immunity against the H1N1 virus.[2] Cytotoxic T lymphocytes that are generated by seasonal influenza viruses against conserved epitopes might provide heterotypical immune responses that could reduce transmission—even without measurable antibody protection.[19] Garten and co-workers[20] reported that ferret postinfection antisera raised against the circulating seasonal human H1N1 viruses did not react with the 2009 H1N1 strains. However, results of age-stratified human seroprevalence studies[16] show that although children and young adults have little or no crossreacting antibodies by H1N1 virus, those older than 60 years have such antibodies against haemaglutinin

	Outpatients	Inpatients		Deaths	
	n=6407	n=475	Odds ratio (95% CI)	n=63	Odds ratio (95% CI)
Characteristics					
Male sex*	3196 (50%)	208 (44%)	0·84 (0·70–1·02)	34 (54%)	1·62 (0·93–2·82)
Age (years)	16 (0–91)	21 (<1–85)	NA	34 (0–79)	NA
Chronic diseases	..	11/475 (2%)	..	27/63 (43%)	6·1 (2·37–15·99)
Clinical symptoms					
Confined to bed	1503/4891 (31%)	206/410 (50%)	2·25 (1·83–2·77)	40/51 (78%)	2·76 (1·34–5·65)
Tachypnoea	187/4890 (4%)	49/408 (12%)	3·03 (2·15–4·27)	20/50 (40%)	4·26 (2·14–8·47)
Dyspnoea	604/4890 (12%)	184/408 (45%)	5·38 (4·32–6·71)	57/58 (98%)	2·33 (1·16–4·68)
Cyanosis	187/4890 (4%)	44/383 (11%)	2·87 (2·00–4·09)	16/45 (36%)	3·46 (1·63–7·31)
ICU	..	..	..	27/63 (43%)	..
Infiltrate on chest radiography	..	..	..	49/63 (78%)	..
Respiratory failure†	..	..	..	57/63 (90%)	..
Antivirals‡	466/623 (75%)	22/27 (81%)	1·21 (0·39–3·74)	40/61 (66%)	0·43 (0·14–1·31)
Time from onset to admission (days)	..	2·94 (3·43)		6·58 (5·09)	1·19 (1·11–1·28)

Data are n (%), median (range), n/N (%), or mean (SD). *Adjusted by age. †Needing mechanical ventilation. ‡Not adjusted. Others variables are adjusted by age and sex. NA=not applicable. ..=data not available.

Table 3: **Characteristics of H1N1 laboratory-confirmed cases that were not admitted to hospital, were admitted and fatal**

glycoprotein H1. Unfortunately, seroprevalence studies to identify antibodies against influenza in Mexico have not been done.

Validity of the rapid test remains questionable. In our study, sensitivity and specificity were about 75%. Although we cannot exclude potential selection bias, the decision to do both tests was guided more by availability of resources to transport samples than by characteristics of patients. Additionally, laboratory staff were unaware of the rapid-test result. Our results for this test are higher than those reported for Quidel.[21,22] In a report from Canada,[14] investigators do not recommend use of rapid tests, because confirmatory tests are needed irrespective of rapid-test results. Even guidance from CDC[23] as to whether rapid tests are useful is unclear. IMSS has recommended use of these tests as an aid for clinicians specifically during the epidemic. A positive rapid test during the pandemic in a symptomatic patient is highly suggestive of influenza; however, a negative test does not exclude infection and an rtRT-PCR confirmation test is needed.[21]

Our study has several limitations. The information sources are provided by staff who have different training for handling this type of illness. Some data are incomplete, but this drawback is inherent in epidemic outbreaks. To have complete information is difficult, and in the most advanced epidemiological surveillance systems information losses higher than 37% can arise.[17] A major difficulty is that this pandemic is still active and surveillance systems are still evolving.

All nations worldwide are closely monitoring whether the disease will continue to be less severe than it has been so far. However, the world has the biotechnological and communication methods to deal with this pandemic. Although H1N1 has spread to 168 countries and territories worldwide,[5] it has not reached the dimensions of its great predecessor in 1918, and some researchers believe, with the information available up to now, that the present H1N1 influenza virus will not cause a pandemic on the scale of those during the 20th century.[24,25] This pandemic might not be the one we expected; however, the virus is evolving and the threat continues.

Contributors

SEZ, JMMA, AJMO, and VBA participated in the study design, analysis, report development, and interpretation of study findings. VBA, JMMA, and CRGB participated in writing the report. CRGB, CGM, and MGL participated in data collection, data analysis, and assessment of data quality. ERP, MCOA, and ARP participated in data collection, assessment of data quality, and interpretation of study findings. SEZ and JMMA contributed equally to development of this report. All authors participated in revision of the report and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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