Occurrence of AH1N1 viral infection and clinical features in symptomatic patients who received medical care during the 2009 influenza pandemic in Central Mexico

Juan Pablo Castillo-Palencia1,2, Lucie Laflamme3 and Joel Monárrez-Espino1,3*

Abstract

Background: In 2009 a new influenza serotype (AH1N1) was identified in Mexico that spread rapidly generating worldwide alarm. San Luis Potosi (SLP) was the third state with more cases reported in that year. The clinical identification of this flu posed a challenge to medical staff. This study aimed at estimating the AH1N1 infection, hospitalization and mortality rates, and at identifying related clinical features in persons who received medical care during the influenza pandemic.

Methods: Retrospective study with persons with flu-like illness who received public or private medical care in SLP from 15.03.09 to 30.10.09. Physicians purposely recorded many clinical variables. Samples from pharyngeal exudate or bronchoalveolar lavage were taken to diagnose AH1N1 using real-time PCR. Clinical predictors were identified using multivariate logistic regression with infection as a dependent variable. Odds ratios (OR) with 95% confidence intervals (CI) were computed. Analyses were stratified by age group based on the distribution of positive cases.

Results: From the 6922 persons with flu symptoms 6158 had available laboratory results from which 44.9% turned out to be positive for AH1N1. From those, 5.8% were hospitalized and 0.7% died. Most positive cases were aged 5–14 years and, in this subgroup, older age was positively associated with AH1N1 infection (95% CI 1.05-1.1); conversely, in patients aged 15 years or more, older age was negatively associated with the infection (95% CI 0.97-0.98). Fever was related in those aged 15 years or more (95% CI 1.4-3.5), and headache (95% CI 1.2-2.2) only in the 0–14 years group. Clear rhinorrhea and cough were positively related in both groups (p < 0.05). Arthralgia, dyspnea and vaccination history were related to lesser risk in persons aged 15 years or more, just as dyspnea, purulent rhinorrhea and leukocytosis were in the 0–14 years group.

Conclusion: This study identified various signs and symptoms for the clinical diagnosis of AH1N1 influenza and revealed that some of them can be age-specific.

Background

Influenza A virus is a main cause of winter epidemics that results in increments in respiratory morbidity. It constitutes a public health concern due to the burden that it represents for the health system and labor market, and for its potential to evolve into a pandemic [1-3]. The virus is sub-classified based on its surface glycoproteins, hemaglutinin and neuroaminidase, which confer the pathogenicity [1,3-6]. Its high antigenic mutation capability is responsible for the cyclic outbreaks observed annually [1,5].

Transmission is mainly person to person through aerosol particles expelled by ill individuals when coughing or sneezing, but also through contact with hands or contaminated fomites [5]. The incubation period ranges from hours to days [5], with an average of two days [6]. Although some patients might be asymptomatic, most present signs and symptoms of varying severity after a few
days of contracting the disease [6,7], but the majority usually recover within one or two weeks [1].

The first flu pandemic was recorded in 1538 [5]. In the last century three pandemics reached the equivalent of Category 2 on the CDC pandemic severity index (case-fatality ratio >0.1%), and all were attributed to the subtype A [1]: The Spanish flu (AH1N1) from 1918–1920 disseminated in Europe and the US causing about 50 million deaths [3,5,6,8]; the Asian flu (AH2N2) from 1957–1958, responsible for 1–4 million deaths, was caused by a viral mutation that resulted in a combination of avian and human strains; and the Hong Kong flu (AH3N2) from 1968–1969 that resulted from an antigenic shift caused nearly 1 million deaths [5,8].

The last pandemic started in Mexico in March 2009, when the Ministry of Health recognized an unexpected outbreak of respiratory disease [9] that would later be identified as AH1N1, a new viral strain resulting from a genetic combination of bird, pig and human influenza viruses [10]. The mutation detected in the nuclear M protein, responsible for the resistance to amantadine compounds, similar to that found in the AH5N1 Hong Kong virus from 1997, caused concern due to the high lethality seen with this kind of strain, and because of the high infectivity of this new virus [8].

By May, many countries started reporting cases, and as a result WHO defined the event of international importance [9], and governments implemented an emergency response plan to limit the viral spread and consequences [11]. In Mexico, educational and other non-essential activities were suspended for weeks to prevent people from getting infected [12]. By June 11, the WHO officially declared a pandemic [13].

Fortunately, this pandemic was less lethal than expected, resulting in about 18 500 deaths worldwide in 2009 [13]. In Mexico around 73 000 cases with nearly 1 350 deaths were confirmed, resulting in a lethality rate of ~1.8% [14,15]. San Luis Potosi (SLP) state, where this study was conducted, accounted for 6.1% of the cases registered in the country, in spite of having only 2% of the Mexican population (2.5 million) [14]. It was in fact the state with the third most cases reported [15].

The limited knowledge about the symptomatology associated with the presence of AH1N1 made it very difficult for physicians to clinically distinguish this flu virus from other respiratory infections. A better understanding of the association between symptomatology and the presence of the virus could assist in future diagnostic efforts.

This study estimated the AH1N1 infection, hospitalization and mortality rates in SLP during the 2009 pandemic, and aimed at identifying clinical features associated with AH1N1 infection in individuals with flu-like illness who sought medical care.

### Methods

#### Study design

This study retrospectively investigated data gathered on patients suspected to be infected by AH1N1 virus during the 2009 outbreak and for which a set of clinical data was systematically collected.

Individuals of all ages with flu symptomatology who sought medical attention from 15.03.09 to 30.10.09 at any of the nearly 500 public or private health care facilities that integrated the Epidemiological Surveillance System for Influenza (ESSI) in the central Mexican state of SLP [16,17] were eligible for these analyses.

A working clinical definition was set during the pandemic to screen for all persons presenting fever, cough and headache [18,19], who were considered potentially infected, and respiratory tract samples were obtained to confirm the diagnosis; for infants irritability was used instead of headache, and in the elderly population fever could be missing [13,19]. In addition to these symptoms, many other clinical variables were systematically measured and recorded. In some cases, physicians decided to include patients for laboratory screening in spite of not having the pre-required three clinical manifestations.

#### Data source

Data was extracted from the ESSI, administered by SLP State Health Services [16]. When a patient fulfilled the criteria for a probable case, physicians had to complete a specific questionnaire that included information about the patient’s basic socio-demographic characteristics, the unit where the health care was provided, the complete clinical symptomatology, the use of previous treatment, and data on specific epidemiological risk factors. These formats were then sent to one of the six health jurisdictions of SLP where data were coded and manually entered into the ESSI.

Samples from pharyngeal or nasopharyngeal exudate, or bronchoalveolar lavage were taken from all patients who fulfilled the operational definition to confirm the diagnosis of AH1N1 using real-time polymerase chain reaction (RT-PCR), which has been reported to have a very high sensitivity and specificity [20]. Specimens were placed in normal saline solution or viral transport media, and were kept cooled at 2-4°C [21] before analyses were carried out at the Public Health Laboratory of SLP and confirmed by the National Institute for Diagnostic and Epidemiological Reference in Mexico City, based on the primers designed by the CDC to detect the AH1N1 virus [22].

This study was carried out in compliance with the Helsinki Declaration. Potential ethical concerns derived from the use of human data were carefully considered; informed consent was not obtained as data was collected routinely for epidemiologic surveillance purposes. The
proposal was reviewed and approved by the Ethics and Research Committee of SLP State Health Services (registration number SLP/070-2012) and authorization to use the data was provided by SLP State Health Services (approval reference number 19089).

Data selection
For the purpose of this study, the clinical data extracted from the ESSI registry were recorded when necessary (e.g., tachypnea from respiratory rate) and classified into signs (i.e., objective medical characteristic that can be detected), symptoms (i.e., subjective feature noticed by the patient that cannot be directly observed), and epidemiological risk factors related to flu infection. Except for few continuous variables (e.g., age, fever or respiratory rate), most of these variables were coded dichotomously in the original questionnaire.

Variables were selected for the analyses if they were related to respiratory tract infections. However, some had to be excluded as they contained similar information (e.g., pharyngitis and sore throat) or because they were considered irrelevant for this study (e.g., contact with animals and recent travel). Complete data was available for all the clinical variables included.

The signs included were fever (arm temperature ≥38°C), cough, clear or purulent rhinorrhea, nasal congestion, sore throat, conjunctivitis, dysphonia, tachypnea (≥20 breaths/min; ≥40 for infants aged ≤5 years), cyanosis and leukocytosis (≥12000/μL); the symptoms included headache, malaise, chills, myalgia, irritability, arthralgia, thoracic pain and dyspnea; and the epidemiological risk factors included recent contact with persons with flu and history of antiviral treatment within two weeks prior to the interview, immunization against seasonal influenza, current smoking, and history of diagnosed asthma and chronic obstructive pulmonary disease.

Statistical analyses
Infection, hospitalization and mortality rates were estimated per 100 individuals and defined as: Infection rate = Infected cases confirmed by laboratory / Total number of persons tested with available laboratory result; Hospitalization rate = Hospitalized with confirmed laboratory result / Total number of infected persons; and Mortality rate = Deaths with confirmed laboratory result / Total number of infected persons.

The proportion of persons with positive and negative AH1N1 infection was plotted by five-year age groups and compared with the distribution of the state population to identify the age categories with the highest incidence. Individuals with positive and negative infection confirmed by laboratory were compared using crude odds ratios (OR) with 95% confidence intervals (CI) for every clinical feature under study.

Clinical predictors were identified using backward stepwise logistic regression with infection confirmed by laboratory as a dependent variable, and all clinical data as independent variables. Adjusted regression models were produced for the two age group categories defined: 0–14 years (children), and ≥15 years. All signs, symptoms, and epidemiological risk factors that showed significant crude ORs in the bivariate analyses were entered into the initial models. Cases with missing laboratory data were excluded from the multivariate analyses (n = 794). Only variables with significant adjusted ORs, as judged by the 95% CI, remained in the final models.

The accuracy of the model was evaluated by subtracting the proportional by chance accuracy rate (PCHAR) to the overall percentage of accurate predictions seen in the classification matrix of the final model. The accuracy was considered acceptable if a ≥25% increase was observed over the PCHAR. The model fit was assessed using the Hosmer-Lemeshow goodness-of-fit statistic. A good model fit was indicated by a non-significant Chi-square value (p > 0.05). All data was analyzed with IBM® SPSS® version 18 (IBM, New York, USA).

Results
Table 1 presents the infection, hospitalization and mortality rates for AH1N1 in SLP compared with geographic regions of North America with documented statistics of the like [23-25]. Laboratory results were available for 89.9% of the 6922 persons screened who fulfilled the definition for probable case. Positive results lead to an infection rate of 44.9%. The hospitalization rate was markedly higher than the national rate (5.8 vs. 1.5%), but considerably lower than the American and Canadian figures (~14-15%). The mortality rate (0.7%) was very similar to the national and Canadian estimates (0.6 and 0.8, respectively), but notably lower than that reported in other geographic regions. Except for the mortality rates between Canada, Mexico and SLP, all other rates presented were statistically different (p < 0.01).

Figure 1 plots the percent distribution of confirmed cases by age group. From the 2767 patients with AH1N1 infection, 1409 (50.9%) were aged 0–14 years (731 males, 51.9%; 678 females, 48.1%), and 1358 (49.1%) were ≥15 years old (598 males, 44%; 760 females, 56%). There was a clear overrepresentation of positive cases (dark line) among children compared with the state population distribution (grey line). Consequently, the proportion of cases was lower in the adult groups compared with the population distribution, including the elderly.

Table 2 presents bivariate analyses for clinical manifestations associated with AH1N1 infection. Based on the crude associations (crude OR, 95% CI), most clinical signs and
symptoms studied were significantly associated: The strongest positive associations with the infection were observed for fever (4.1, 3.3-5.1), cough (3.3, 2.7-4.0), headache (3.2, 2.6-3.8), and clear rhinorrhea (1.8, 1.6-2.1); and the strongest negative ones, with leukocytosis (0.13, 0.04-0.42), purulent rhinorrhea (0.56, 0.41-0.77) and dyspnea (0.57, 0.48-0.68). Sex was not related to infection (1.0, 0.9-1.1).

Except for contact with other persons with flu (1.4, 1.2-1.7), all other epidemiological risk factors considered were not statistically associated.

Table 3 presents the final logistic regression models by age group. For children, the model included six variables with statistically significant positive adjusted ORs (age in years 1.07, cough 1.5, headache 1.6, clear rhinorrhea 1.3, contact with flu person 1.6, and conjunctivitis 1.2), and three with negative adjusted ORs (dyspnea 0.51, purulent

![Figure 1](image.png)

**Figure 1** Distribution of individuals by age group with confirmed AH1N1 diagnosis who received medical care for flu symptoms from March to October 2009 compared with the population distribution of San Luis Potosi State, Mexico.
rhinorrhea 0.47, and leukocytosis 0.07). The model fitted well (p 0.11), and the accuracy was 25% more than the PCHAR (0.62 vs. 0.50). For those aged 15 years or more, three variables showed statistically significant positive adjusted ORs (fever 2.2, cough 1.7, and clear rhinorrhea 1.5), and four had negative adjusted ORs (age in years 0.98, arthralgia 0.81, dyspnea 0.73, and seasonal flu vaccine 0.73). The accuracy of the model was 24% more than the PCHAR (0.63 vs. 0.52), and the model also fitted well (p 0.72).

**Discussion**

An objective of this study was to estimate the AH1N1 infection, hospitalization and mortality rates in this representative population sample. We observed that 62.7% of the AH1N1 positive cases occurred in persons aged 0–18 years, which was very similar to the 60% reported from April 15 to May 5, 2009 in the US [10], and to the 61.8% national Mexican figure registered from March 11 to May 27, 2009 in those aged 0–19 years [2] (64.2% in this study). Based on a longer observation period, our study reinforces the observation that the AH1H1 virus affected mostly infant and adolescent populations.

The high infection rate seen indicated a rapid transmission of this virus, since nearly one out of two persons presenting respiratory symptoms such as fever, headache and cough had a confirmed laboratory diagnosis, and this supports the value of the operational definition used to screen individuals.

The hospitalization rate is more problematic to interpret and compare, as no data regarding the criteria used for hospitalization was available. While different viral pathogenicity and/or clinical severity cannot be completely ruled out, it seems that hospitalization criteria varied considerably across geographic areas, as indicated by the relatively large variation observed (5.8% in SLP , 1.5% in Mexico, and 14-15% in the US and Canada) [23].

The infection, hospitalization, and mortality rates can be compared with those of seasonal influenza in SLP during the same period, which were 5.3% (0-14y 3.7%, ≥15y 4.8%), 9.6% (0-14y 4.9%, ≥15y 12.5%), and 1.8% (0-14y 0.8%, ≥15y 2.4%).

| Clinical characteristics | Confirmed AH1N1 infection, n (%) | Crude OR [95% CI] |
|--------------------------|----------------------------------|-------------------|
| Signs                    |                                  |                   |
| Fever                    | 2665 (96.3)                      | 2927 (86.3)       | 4.14 [3.32–5.16] |
| Cough                    | 2610 (94.3)                      | 2825 (83.3)       | 3.33 [2.76–4.00] |
| Clear rhinorrhea          | 2071 (74.8)                      | 2077 (61.3)       | 1.88 [1.68–2.10] |
| Nasal congestion          | 1376 (49.7)                      | 1361 (40.1)       | 1.47 [1.33–1.63] |
| Sore throat               | 1498 (54.1)                      | 1547 (45.6)       | 1.40 [1.27–1.55] |
| Conjunctivitis            | 728 (26.3)                       | 702 (20.7)        | 1.36 [1.21–1.54] |
| Dysphonia                 | 476 (17.2)                       | 505 (14.9)        | 1.18 [1.03–1.36] |
| Tachypnea                 | 107 (3.9)                        | 209 (6.2)         | 0.61 [0.48–0.77] |
| Cyanosis                  | 28 (1.0)                         | 57 (1.7)          | 0.59 [0.37–0.94] |
| Purulent rhinorrhea       | 57 (2.1)                         | 122 (3.6)         | 0.56 [0.41–0.77] |
| Leukocytosis              | 3 (0.1)                          | 28 (0.8)          | 0.13 [0.04–0.42] |
| Symptoms                  |                                  |                   |
| Headache                  | 2591 (93.6)                      | 2785 (82.1)       | 3.20 [2.68–3.82] |
| Malaise                   | 2087 (75.4)                      | 2252 (66.4)       | 1.55 [1.38–1.76] |
| Chills                    | 1356 (49.0)                      | 1423 (42.0)       | 1.32 [1.20–1.47] |
| Myalgia                   | 1775 (64.1)                      | 1977 (58.3)       | 1.28 [1.15–1.41] |
| Irritability              | 262 (9.5)                        | 267 (7.9)         | 1.22 [1.02–1.46] |
| Arthralgia                | 1570 (56.7)                      | 1785 (52.6)       | 1.18 [1.06–1.30] |
| Thoracic pain             | 449 (16.2)                       | 548 (16.2)        | 1.00 [0.87–1.15] |
| Dyspnea                   | 218 (7.9)                        | 439 (12.9)        | 0.57 [0.48–0.68] |
| Risk factors              |                                  |                   |
| Contact with infected (flu)| 433 (15.6)                      | 374 (11.0)        | 1.49 [1.29–1.73] |
| Antiviral treatment 1     | 47 (1.7)                         | 48 (1.4)          | 1.20 [0.80–1.80] |
| Seasonal flu vaccine      | 258 (9.3)                        | 343 (10.1)        | 0.91 [0.77–1.08] |
| Asthma/COPD               | 36 (1.3)                         | 45 (1.3)          | 0.98 [0.63–1.52] |
| Smoking                   | 44 (1.6)                         | 62 (1.8)          | 0.86 [0.58–1.28] |

1 Includes mainly acyclovir, amantadine, ribavirin and rimantadine given within 2 weeks prior to the interview.
Table 3 Adjusted logistic regression models with clinical features associated with AH1N1 infection in persons with flu symptoms who received medical care in San Luis Potosi from March 15 to October 30, 2009, stratified by age group

| Variables included in the final model | Coefficient | Adjusted OR [95% CI] | P-value | Coefficient | Adjusted OR [95% CI] | P-value |
|--------------------------------------|-------------|----------------------|---------|-------------|----------------------|---------|
| **0-14 years (n = 2698)**             |             |                      |         |             |                      |         |
| Age in years                         | 0.07        | 1.07 [1.05-1.10]     | 0.000   | -0.02       | 0.98 [0.97-0.98]     | 0.000   |
| Fever                                |             |                      |         |             |                      |         |
| Cough                                | 0.46        | 1.59 [1.12-2.24]     | 0.009   | 0.57        | 1.78 [1.19-2.67]     | 0.005   |
| Headache                             | 0.50        | 1.65 [1.21-2.25]     | 0.001   |             |                      |         |
| Clear rhinorrhea                     | 0.26        | 1.30 [1.08-1.57]     | 0.005   | 0.41        | 1.50 [1.28-1.77]     | 0.000   |
| Arthralgia                           |             |                      |         | -0.20       | 0.81 [0.69-0.96]     | 0.014   |
| Seasonal flu vaccine                 |             |                      |         | -0.31       | 0.73 [0.57-0.93]     | 0.011   |
| Contact with infected                | 0.52        | 1.68 [1.33-2.13]     | 0.000   |             |                      |         |
| Conjunctivitis                       | 0.25        | 1.29 [1.07-1.56]     | 0.007   |             |                      |         |
| Dyspnea                              | -0.65       | 0.51 [0.35-0.75]     | 0.001   | -0.31       | 0.73 [0.59-0.90]     | 0.003   |
| Purulent rhinorrhea                  | -0.75       | 0.47 [0.28-0.78]     | 0.004   |             |                      |         |
| Leukocytosis                         | -2.56       | 0.07 [0.00-0.62]     | 0.017   |             |                      |         |
| Intercept                            | -1.61       |                      |         |             |                      | -1.11   |

| **≥15 years (n = 3430)**             |             |                      |         |             |                      |         |
| Age in years                         |             |                      |         |             |                      |         |
| Fever                                |             |                      |         |             |                      |         |
| Cough                                |             |                      |         |             |                      |         |
| Headache                             |             |                      |         |             |                      |         |
| Clear rhinorrhea                     |             |                      |         |             |                      |         |
| Arthralgia                           |             |                      |         |             |                      |         |
| Seasonal flu vaccine                 |             |                      |         |             |                      |         |
| Contact with infected                |             |                      |         |             |                      |         |
| Conjunctivitis                       |             |                      |         |             |                      |         |
| Dyspnea                              |             |                      |         |             |                      |         |
| Purulent rhinorrhea                  |             |                      |         |             |                      |         |
| Leukocytosis                         |             |                      |         |             |                      |         |
| Intercept                            |             |                      |         |             |                      |         |

0.9%, ≥15y 2.4%), respectively [26]. While the seasonal infection rate contrasts with the much higher rate seen for AH1N1 (44.9%), the mortality rate is nearly 2.5 times higher (1.7 vs. 0.7%), pointing to the high infectivity, but low lethality of this virus, as previously observed [2,6]. The mortality rate was also similar to that of the Mexican (0.6%) and Canadian (0.8%) national estimates [23,24] though clearly lower than the US figure (1.9%). This difference is also difficult to explain, but it is unlikely to be due to underreporting in SLP, as health authorities mobilized most resources to track down any potential case of infection during the pandemic.

This study also looked at the association between clinical features and the presence of AH1N1 infection in persons who received medical care during the influenza pandemic in central Mexico, and the role played by age for the magnitude and direction of the association.

The main findings were that fever was associated, but only in those aged ≥15 years, while headache only in the 0–14 year group. Clear rhinorrhea and cough were positively related in both groups. Arthralgia, dyspnea and vaccination history were related to lesser risk in those aged ≥15 years, as dyspnea, purulent rhinorrhea and leukocytosis were in children.

The frequency of signs and symptoms found among infected individuals can be compared with that from other published studies. Fever, cough and sore throat were present in 96, 94, and 54%, respectively, compared to 94, 92 and 66% in the American Investigation Team [10]. According to the CDC morbidity and mortality weekly report (May 6, 2009) the most frequent clinical features reported in Mexico were fever (98%), cough (94%), rhinorrhea (83%), and headache (80%) [27]; these proportions were relatively similar to those found in SLP (96, 94, 75, 93%, respectively). However, comparisons must be treated with caution, especially with clinical signs, as diagnostic criteria used by physicians could have varied across studies. The results of this study are also in line with previous ones showing that AH1N1 infection was not sex specific [28-30].

Although several attempts have been made to relate clinical characteristics with the presence of the AH1N1 influenza virus, this study has three major strengths. A first merit lies in the size of the study population, which comprises the largest population-based sample (more than 6000 individuals) reported thus far. A second strength relates to the inclusion of both hospitalized subjects and outpatients of all ages. The third strength is related to the data treatment itself where multivariate regression analyses were used stratified by age group (0–14 and ≥15 years) defined based on the cut-off seen for the observed distribution of individuals with confirmed AH1N1 PCR-diagnosis.

The protective odds for infection found with seasonal vaccination against influenza in the adult population add to the controversy on this topic, as previous studies have reported protection [31-35], no effect [36-40], and even increased risk of infection [41]. While the potential cross-reactive protection of seasonal influenza vaccines through humoral and cell-mediated immune responses [42,43] needs further investigation, an upcoming review to assess the protection offered by influenza vaccines against circulating influenza A or B viruses that are not antigenically well-matched to vaccine strains will help elucidating this issue [44].

An additional finding is that clinical manifestations commonly related to bacterial respiratory infections, such as purulent rhinorrhea or leukocytosis, were negatively
associated with the likelihood of positivity. This finding is similar to that reported by other authors. In a sample of 362 patients presenting with flu syndrome to an emergency unit in Spain, nasopharyngeal swabs were taken for AH1N1 detection with PCR; results showed that positive cases had significantly lower mean leucocyte counts, and the association remained in the multivariate logistic regression analysis when the lymphocyte count was used [45]. However, it is worth noting that purulent rhinorrhea could also result from a superimposed bacterial respiratory infection [6].

Similarly, the symptomatology associated with lower respiratory tract infections and its severity (e.g. cyanosis, dyspnea and tachypnea) was also related to protective odds. This finding might have to do with the time period between the onset of the symptoms and the visit to the health unit, as an indicator of the progression of the infection. However, no differences were seen in the mean number of days elapsed from the reported start of the symptoms to the health visit (~3 days) between those who had and did not have these symptoms (p > 0.05).

Very few clinical features might be relatively specific to flu viral infections [27,46,47], such as the presence of clear rhinorrhea that relates to the hemagglutinin inhibiting effect on the surface glycoproteins that protect the respiratory tract cilia [4]. Respiratory diseases caused by influenza and parainfluenza viruses, adenoviruses or syncytial respiratory virus usually produce similar unspecific clinical symptomatology, characterized by fever, chills, malaise, headache, myalgia or cough [48]. In fact, a recent review of multivariate models devised to clinically diagnose influenza reported that only the combination of fever, cough and acute onset has a modest accuracy [49].

Compared with confirmed cases of seasonal influenza in SLP during the same period, those with AH1N1 infection aged ≥15 years showed significantly (p < 0.05) higher proportions of cough, clear rhinorrhea, nasal congestion, sore throat, malaise, chills, and myalgia (ranging from 8.3 to 16.4% higher), but had lower proportion of dyspnea (5.3% less); however, among those aged 0–14 years, the proportions were significantly higher only for cough (8.3%) and clear rhinorrhea (8.7%) [26].

For the AH1N1 influenza virus infection, various studies have not been able to identify symptoms that could predict the presence of AH1N1 infection using various designs and analytical procedures [50–52]. However, others have identified signs and symptoms associated to positive status. A retrospective study with 117 adult cases and 236 matched controls presenting with respiratory symptoms to hospital emergency departments in Toronto, Canada, showed higher associations for AH1N1 when various combinations of signs, symptoms and laboratory indicators were used, though only age, cough and fever remained associated in the multivariate analyses [53]. Another study with military personnel who visited primary health care clinics for febrile respiratory illness (i.e. fever, cough and sore throat) compared the signs and symptoms between those with positive and negative AH1N1 influenza virus using real-time PCR. Of the 2858 subjects recruited 821 were influenza cases, of which 434 were 2009 pandemic influenza AH1N1. The comparison of clinical features using multivariate logistic regression showed that sore throat, photophobia, injected pharynx and nausea/vomiting were negatively associated, while running nose, chills, fever and eye symptoms were positively related [54].

Conclusion
This study estimated the frequency and progression on the AH1N1 influenza infection in symptomatic individuals, and was able to identify various associated clinical features that revealed the age specificity of several of them, indicating the importance of this factor when establishing the presumptive clinical diagnosis.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
JPCP, LL and JME participated in designing the study. JPCP and JME performed the data analysis and drafted the manuscript. All authors participated in the interpretation of the results, and critically reviewed and approved the final manuscript.

Acknowledgements
The authors would like to express their thanks for the facilities provided by the San Luis Potosi State Health Services and for the use of the influenza database.

Author details
1Master in Public Health Program, San Luis Potosí Autonomous University, San Luis Potosí, Mexico. 2Department of Epidemiological Surveillance, San Luis Potosi Health Services, San Luis Potosí, Mexico. 3Division of Global Health (IHCAR), Department of Public Health Sciences, Karolinska Institutet, Nobelst väg 8, 17177, Stockholm, Sweden.

Received: 15 June 2012 Accepted: 18 December 2012 Published: 20 December 2012

References
1. Kuri-Morales P, Galván E, Cravioto P, Zárraga Rosas LA, Tapia-Coney R. Mortality due to influenza and pneumonia in Mexico between 1990 and 2005. Salud Publica Mex 2006, 48:379–384.
2. Fajardo-Dolci GE, Hernández-Torres F, Santacruz-Varela J, Rodríguez-Suárez J, Lamy P, Arboleya-Casanova H, Gutiérrez-Vega R, Manusell-Lee G, Córdova-Villalobos JA. Epidemiological profile of mortality due to human influenza A (H1N1) in Mexico. Salud Publica Mex 2006, 51:361–371.
3. Kuri-Morales P. The influenza pandemic: possible scenarios in Mexico. Gac Med Mex 2008, 144:285–290.
4. Arias CF, Escalera-Zamudio M, Soto-Del Río MD, Cobón-Gámez AG, Isa P, López S. Molecular Anatomy of 2009 Influenza Virus A (H1N1). Arch Med Res 2009, 40:643–654.
5. García-Garcia J, Ramos C. Influenza, an existing public health problem. Salud Publica Mex 2006, 48:244–267.
6. Cunha BA: Swine Influenza (H1N1) pneumonia: clinical considerations. Infect Dis Clin North Am 2010, 24:203–228.
7. World Health Organization: WHO guidelines for pharmacological management of pandemic influenza A (H1N1) 2009 and other influenza viruses. Part 1. Recommendations. 2010:3–32. http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf.
11. Tang JW, Shetty N, Tsan-Yuk T: Influenza pandemic: Mexico's response. Salud Publica Mex 2006, 48:72–79.

12. Cameron MJ, Rowe T, Kelvin DJ: Possible link between the severe respiratory illness outbreak in Mexico and swine influenza in southwestern United States? J Infect Dis 2009, 20:157–158.

13. World Health Organization: Pandemic (H1N1) 2009. Update 109. 2010 (July).

14. Consejo Nacional de Población: Situación actual de la epidemia, 17 Julio 2010 [Current situation of the pandemic, 17 July 2010]. Available at: http://www.conapo.gob.mx/index.php?option=com_content&view=article&id=36&Itemid=234.

15. Cameron MJ, Shetty N, Tsan-Yuk T: Features of the new pandemic influenza A/H1N1/2009 virus: virology, epidemiology, clinical and public health aspects. Curr Opin Pulm Med 2010, 16:235–241.

16. de Salud S: Manual para la vigilancia epidemiológica de influenza [Manual for the epidemiological surveillance of influenza]. México: Primera edición; 2006.

17. Secretaría de Salud: Sistema Nacional de Vigilancia Epidemiológica (SINAVE) [National System of Epidemiological Surveillance]. México: Available at: www.sineg.gob.mx.

18. Chowell G, Bertozzi SM, Arantxa-Colchero M, López-Gatell H, Secretaría de Salud: Situación de influenza A/H1N1/2009 en el Estado de San Luis Potosí [Situación de la influenza A/H1N1/2009 in the state of San Luis Potosí]. Available at: http://portal.salud.gob.mx/contenidos/noticias/influenza/estadisticasmx/2010/52/689.

19. Alpuche-Aranda C, Hernández M, Miller MA: Severe pneumonia associated with concurrent with the circulation of H1N1 influenza. N Engl J Med 2009, 361:674–679.

20. World Health Organization: Pandemic (H1N1) 2009. Guideline for the detection, treatment of cases and prophylaxis of the AH1N1 influenza pandemic in the state of San Luis Potosí. Available at: www.salsalud.gob.mx/lineamientos-para-la-deteccion-tratamiento-y-profilaxis-ante-la-pandemia-de-influenza-AH1N1-en-el estado-de-San-Luis-Potosi.html.

21. Di Giambenedetto S, Zileri Dal Verme L, Sali M, Farina S, Di Cristo V, Manzano S, De Luca A, Pignotato G, Prosperi M, Di Franco A, Gentiloni Silveri N, Delogu G, Cauda R, Fabbiani M, Fadda G: Clinical presentation, microbiological features and correlates of disease severity of 2009 pandemic influenza A (H1N1) infection. Eur J Clin Microbiol Infect Dis 2011, 30:541–549.

22. Carcione D, Giele C, Goggin LS, Kwan KS, Smith DW, Dowse GK, Mak DB, Lessler J, Reich NG, Cummings DA, New York City Department of Health and Mental Hygiene Swine Influenza Investigation Team, Nair HP, JT, Frédaire RF, Sanchez JL: Seasonal influenza vaccine and protection against pandemic (H1N1) 2009-associated illness among US military personnel. PLoS One 2010, 1:e10722.

23. Orellano PW, Reynoso JL, Carillo O, Uez O: Protection of trivalent inactivated influenza vaccine against hospitalizations among pandemic influenza A (H1N1) cases in Argentina. Vaccine 2010, 28:5298–5311.

24. Selvage D, Baumbach J, Sewell M: Influenza A (H1N1)-related hospitalization and death among racial/ethnic groups in New Mexico. Am J Public Health 2011, 101:1776–1784.

25. Yu H, Feng Z, Ueyki TM, Liao Q, Zhou L, Feng Y, Li M, Xiang N, Huiy Y, Yuan J, Jiang H, Zheng Y, Gargulillo P, Feng Z, Feng Y, Zheng J, Xu C, Zeng Y, Shu Y, Geo Z, Yang W, Wang Y: Risk factors for severe illness with 2009 pandemic influenza A (H1N1) virus infection in China. Clin Infect Dis 2011, 52:457–465.

26. Lessler J, Reich NG, Cummings DA, New York City Department of Health and Mental Hygiene Swine Influenza Investigation Team, Nair HP, JT, Frédaire RF, Sanchez JL: Seasonal influenza vaccine and protection against pandemic (H1N1) 2009-associated illness among US military personnel. PLoS One 2010, 1:e10722.

27. Cecilliano M, Del Rio C, Arce-Aguilera J, Acosta-Acosta H, Núñez-Aguilera J, Cruz-Castillo J, Cano-Arellano B, Garcia-Anaya A, Ferre-Guerrero E, Baez-Saltafia R, Ferreyra-Reyes L, Ponce-de-León-Rosas S, Alpuche-Aranda C, Rodriguez-López MH, Perez-Padilla R, Hernandez-Avila M: Partial protection of seasonal trivalent inactivated vaccine against novel pandemic influenza A/H1N1 2009: case–control study in Mexico City. BMJ 2009, 339:b3928.

28. Johns MC, Eck AA, Blaese DL, Lee SE, Perdue CL, Lipnick R, Vest KG, Russell DL: Prevention of seasonal influenza. BMJ 2009, 339:b3928.

29. Kelley H, Grant K: Interim analysis of pandemic influenza (H1N1) 2009 in Australia: surveillance trends, age of infection and effectiveness of seasonal vaccination. Euro Surveill 2009, 14(31):pii: 19208.

30. Carcione D, Giele C, Goggin LS, Smith DW, Dowse GK, Mak DB, Effler P: Association between 2009 seasonal influenza vaccine and influenza-like illness during the 2009 pandemic: preliminary results of a large household transmission study in Western Australia. Euro Surveill 2010, 15(28):pii: 19616.

31. Lallauri A, Savulescu C, Jiménez-Jorge S, Pérez-Brefa R, Pozo F, Casas I, Ledesma J, de Mateo S, Spanish Influenza Surveillance System (SIS): Influenza pandemic (H1N1) 2009 activity during summer 2009. Euro Surveill 2010, 15(28):pii: 19616.

32. Castillo-Palencia et al. BMC Infectious Diseases 2012, 12:363

http://www.biomedcentral.com/1471-2334/12/363
influenza vaccine and pandemic H1N1 illness during Spring-Summer 2009: four observational studies from Canada. PLoS Med 2010, 7:e1000258.

42. Xing Z, Cardona CJ. Preexisting immunity to pandemic (H1N1) 2009. Emerg Infect Dis 2009, 15:1847–9.

43. Greenbaum JA, Kotturi MF, Kim Y, Osteroff C, Vaughn K, Salimi N, Vira R, Ponomarenko J, Scheuermann RH, Sette A, Peters B. Pre-existing immunity against swine-origin H1N1 influenza viruses in the general human population. Proc Natl Acad Sci USA 2009, 106:20365–70.

44. Tricco AC, Hallett D, Soobiah C, Meier G, Chen M, Taishkandi M, Bauch C, Loeb M. Effect of influenza vaccines against mismatched strains: a systematic review protocol. Syst Rev 2012, 1:35.

45. Supervia A, Del Baño F, Maldonado G, Paillas O, Aguirre A, Vilaplana C, Horcajada JP, Martínez-Izquierdo MT. Predictive factors of 2009 H1N1 virus infection in patients with influenza syndrome. Rev Esp Quimioter 2011, 24:25–31.

46. Schout D, Hajjar LA, Galas FR, Uip DE, Levin AS, Caiaffa Filho HH, Sakane PT, Suslik CA, Teixeira JM, Bonfa E, Barone AA, Martins Mde A, Boulos M, Auler JO Jr. Epidemiology of human infection with the novel virus influenza A (H1N1) in the Hospital das Clínicas, São Paulo, Brazil-June-September 200. Clinics (Sao Paulo) 2009, 64:1025–1030.

47. Ornek T, Yağcı FD, Ekin S, Yalçın S, Yemişen M. Pneumonia in patients with novel influenza A (H1N1) virus in Southeastern Turkey. Wien Klin Wochenschr 2011, 123:106–111.

48. Díaz A, Zaraogoza R, Coronado R, Salavert M. Acute viral infections in immunocompetent patients. Med Intensiva 2011, 35:179–185.

49. Ebell MH, Afonso A. A systematic review of clinical decision rules for the diagnosis of influenza. Ann Fam Med 2011, 9:69–77.

50. Martín-Ruíz N, Sánchez-Ventura JG, García-Sánchez N, Ruiz-Andrés MA. Estudio de la epidemia de gripe A h1N1 de 2009–2010. Síntomas guía en atención primaria. comparación clínica con los casos hospitalizados [Study of the flu epidemic A h1N1 of 2009–2010. Leading symptoms in primary care. Clinical comparison with hospitalized cases]. Rev Pediatr Aten Primaria 2011, 13:519–530.

51. Elizondo-Montemayor L, Hernández-Torre M, Ugalde-Casas PA, Santos-Guzmán M, Serrano-Gonzalez M, Gutierrez NG, Lam-Franco L, Tamargo-Barrera D, Martinez U, Bustamante-Carreaga H, Alvarez MM, Schultz-Cherry S. Clinical and epidemiological features of 2009 pandemic H1N1 influenza differ slightly according to seroprevalence status during the second wave in the general population in Mexico. Respir Care 2012, 57:1586–93.

52. Bryant PA, Tebruegge M, Papadakis G, Clarke C, Barnett P, Daley AJ, South M, Curtis N. Clinical and microbiologic features associated with novel swine-origin influenza A pandemic 2009 (H1N1) virus in children: a prospective cohort study. Pediatr Infect Dis J 2010, 29:694–698.

53. Lee TC, Taggart LR, Mater B, Katz K, McGeer A. Predictors of pandemic influenza infection in adults presenting to two urban emergency departments, Toronto, 2009. CJEM 2011, 13:7–12.

54. Lee VJ, Yap J, Cook AR, Tan CH, Loh JP, Koh WH, Lim EA, Liaw JC, Chew JS, Hossain I, Chan KW, Ting PJ, Ng SH, Gao Q, Kelly PM, Chen MI, Tambayah PA, Tan BH. A clinical diagnostic model for predicting influenza among young adult military personnel with febrile respiratory illness in Singapore. PLoS One 2011, 6:e17468.

doi:10.1186/1471-2334-12-363

Cite this article as: Castillo-Palencia et al: Occurrence of AH1N1 viral infection and clinical features in symptomatic patients who received medical care during the 2009 influenza pandemic in Central Mexico. BMC Infectious Diseases 2012 12:363.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at www.biomedcentral.com/submit