A Two Wave Analysis of Hospitalizations and Mortality from Seasonal and Pandemic 2009 A (H1N1) Influenza in Saurashtra, India: 2009-2011

Chudasama RK, Patel UV1, Verma PB1, Banerjee A1, Buch P2, Patel P3

Department of Community Medicine, Meghji Pethraj Shali Medical College, Jamnagar, 1Departments of Community Medicine, 2Pediatric, 3Microbiology, Pandit Deendayal Upadhyay Medical College, Rajkot, Gujarat, India

Abstract

Background: During May 2009, India reported the confirmed case of 2009 A (H1N1) influenza reported and in August 2009, Saurashtra region made the first report. Aim: We describe the clinico-epidemiological characteristics of patients who were hospitalized with 2009 A (H1N1) influenza infection and seasonal influenza in Saurashtra region. Subjects and Methods: A total of 1726 patients suffering from A (H1N1) influenza and seasonal influenza were admitted in the different hospitals of Rajkot city of Saurashtra region during September 2009-February 2011. Real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) testing was used to confirm the infection. The clinico-epidemiological features of the patients were closely monitored. Data were analyzed by Chi square or Fisher's exact test, using Epi Info software (version 3.5.1) of the Center for Disease Control (CDC). Results: Among the patients hospitalized due to influenza, 29.6% (511/1726) were laboratory confirmed cases of A (H1N1) influenza while the rest 70.4% (1215/1726) were cases of seasonal influenza. A median time of 3 days was observed from the onset of illness to laboratory confirmed diagnosis of A (H1N1) influenza. The median duration of hospital stay of such patients was 2-32 days. All admitted A (H1N1) influenza patients received Oseltamivir drug, but only 14.9% (76/511) received it within 2 days of onset of illness. 24.9% (127/511) of those admitted for A (H1N1) influenza died as compared to 5.3% (65/1215) of those suffering from seasonal influenza. The most common symptoms were cough, fever, sore throat and shortness of breath in both the groups of patients. The prevalence of any coexisting morbidity in those with A (H1N1) influenza was 31.3% (160/511) while in those with seasonal influenza it was 19.4% (236/1215). The common coexisting morbidities were hypertension, diabetes mellitus, chronic pulmonary diseases and pregnancy. Pneumonia was reported in 91% positive patients with chest radiography. Conclusion: Though the clinico-epidemiological pattern of the A (H1N1) influenza patients were comparable to that of those suffering from seasonal influenza, a fivefold higher mortality was noted in A (H1N1) influenza patients. Hypertension, pregnancy, pneumonia on chest X-ray, and receiving antiviral treatment within 2 days of illness onset were mainly reported among A (H1N1) influenza patients.

Keywords: Africa, Epidemiology, Influenza A (H1N1), Seasonal influenza

Introduction

The novel A (H1N1) influenza virus was first identified in Mexico in April, 2009,[1] and then in United States (US).[2,3] This was originally referred to as “swine flu” because many of the genes in this new virus were found in pigs of North America. On further analysis, it was found that this new virus had gene segments from the swine, avian and human flu virus genes. This led to the scientists rechristening this ‘quadraple reassortant’, novel (new) virus as “A (H1N1) influenza virus”.[4,5] This virus spread rapidly worldwide, and hence the World Health Organization (WHO) declared the pandemic to the maximum alert level of ‘6’, after the documentation of human to human transmission of the virus in at least three countries in two of the six WHO regions.[7]
Ministry of Health and Family Welfare, Government of India, started preparation regarding the management of infected patients as soon as the first laboratory confirmed case of A(H1N1) influenza was detected in India in May 2009.[9] The number of such confirmed cases saw a step rise from August 2009 onwards. The state of Gujarat of Western India reported the first laboratory confirmed A(H1N1) influenza positive case in June 2009.[9] Saurashtra region (located in the westernmost part of the Gujarat state of India) reported its first laboratory confirmed A(H1N1) influenza positive case in August 2009.[10]

Present study was conducted with objective to study the clinico-epidemiological characteristics of the patients who were hospitalized with either the A (H1N1) influenza infection or seasonal influenza infection. The study helps in understanding the different clinical and epidemiological characteristics in a developing country to help further for future management of the infection in a country like India with scarcity of data on influenza.

Subjects and Methods

Demographic characteristics, data collection and management

Gujarat state started monitoring and surveillance activities as soon as the first confirmed case was reported in August 2009. All patients with positive test for A (H1N1) influenza were hospitalized, treated and carefully monitored for their changing clinical, laboratory and radiological profile. From September 2009-February 2011, a total of 1726 patients were admitted in different hospitals including Civil Hospital and nine other private hospitals of Rajkot city with influenza like illness. These included 511 (29.6%) patients with A (H1N1) influenza and 1215 with seasonal influenza A(H1N1) influenza negative. Though cases were not reported from November 2010 onwards, nonetheless, surveillance activities were continued till February 2011. The study covers two waves of the pandemic A (H1N1) influenza: The first wave from September 2009 to March 2010, and the second wave from June 2010 to November 2010. Approval by institutional review board was not required because this infectious disease was covered under epidemic act and state health department, [11] who has implemented Epidemic Disease Control Act, 1897 from 18th August 2009 and issued a notification that it was of public health interest to collect data on an emerging pathogen.

Categorization of A (H1N1) influenza case

The Ministry of Health and Family Welfare, Government of India had issued guidelines regarding the segregation of A (H1N1) influenza cases to facilitate laboratory testing, isolation, hospitalization, treatment with specific antiviral medicine. The guideline described three categories namely: (1) Category-A, (2) Category-B 1 and 2, (3) Category-C [12]

Patients of category A and B were treated on outpatient basis and of category C were hospitalized. This study describes a total 511 patients belonging to category ‘C’ who were found positive for A (H1N1) influenza over a period of eighteen months.

Clinical case/suspected case definition

A suspected case was defined as an influenza like illness (temperature > 37.5°C and at least one of the following symptoms; sore throat, cough, rhinorhea, or nasal congestion, and either a history of travel to a country where infection had been reported in the previous 7 days or an epidemiologic link to a person with confirmed or suspected infection in the previous 7 days).[13] A confirmed case was defined by a positive result of a real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay performed at a laboratory operated under the auspices of the state government.

Data variables

In this study data collected from the patients included their basic epidemiological details like age, sex, religion, residential status, date and time of admission to the hospital, clinical details like coexisting morbid and physiological conditions (like pregnancy), date and time of first symptoms etc., Details pertaining to their changing clinical profile and outcome (e.g., presence and type of influenza syndrome, duration between onset of illness and diagnosis, duration of treatment in the hospitals and intensive care units, outcome of hospital admission, time from onset of illness to death, time between starting of antiviral drug and death, etc.) was obtained from the medical record and statistics department of hospitals.

The admitted A (H1N1) influenza patients were grouped again for further analysis, into two more categories: ‘Severe A(H1N1) influenza cases – those who needed intensive care or died during the course of treatment and ‘non severe A (H1N1) influenza cases - those who did not require intensive care and survived.’

Data management

Data collection and analysis were coordinated by the Community Medicine Department, PDU Medical College, Rajkot. Clinical and epidemiological details of the patients admitted in the Civil Hospital (attached to the Medical College, Rajkot) and nine other private hospitals having the required facilities for isolation and treatment of the A (H1N1) influenza cases were looked into detail for the pertinent data. Unique ‘line list number’ was given to every patient to avoid duplication (due to inter-hospital transfer during any time of the study period). No assumptions regarding missing data were made; all proportions were calculated as percentages of the patients with available data.

Laboratory confirmation of infection

The 2009 A (H1N1) influenza virus was detected with the use of a real time RT-PCR assay in accordance with the protocol from the US centers for Disease Control and Prevention, as recommended by the WHO.[14] Those persons who were
suspected of being infected and those who were identified as their close contacts were investigated by taking two swabs: One from the naso-pharynx and the other from the pharynx for detection of virus by real time RT-PCR assay. Because of limited resources, only 2009 A (H1N1) influenza virus was tested, and no other subtypes were tested. At state level, initially laboratory was started in BJ Medical College, Ahmedabad for the investigation and samples were sent there from Rajkot, but results were available after 24 hours. So, from 26th January 2010, another laboratory was started in Microbiology Department, PDU Medical College and Civil Hospital, Rajkot for testing samples by real time RT-PCR and results were available within 24 hours.

Statistical analysis
All the data were entered into MS Excel and analyzed by Chi square or Fisher's exact test, proportions and percentages, using Epi Info software (version 3.5.1) of the Center for Disease Control (CDC). The cut off used for significant value was 95% confidence interval, and \( P<0.05 \).

Results

Demographic and clinical characteristics of patients
Month wise distribution [Figure 1] of hospitalized patients with influenza A (H1N1) and seasonal influenza in Saurashtra region shows that during first wave, highest number of cases reported during December 2009 and January 2010. During second wave maximum numbers of cases were reported during months of August and September 2010.

The median age for those having A (H1N1) influenza was 27 years (range 4 months-68 years) while for those having seasonal influenza, it was 25 years (range 1 month-85 years). The median duration between onset of infection and its diagnosis was 5 days (range: 1-20) [Table 1]. Only 0.01% (03/511) of the A (H1N1) influenza positive patients had a recent history of travel to another country. During admission, those positive for A (H1N1) influenza reported with cough (93.9%), fever (90.8%), shortness/difficulty in breathing (66.5%) and sore throat (59.9%) [Table 2]. Coexisting morbid conditions (like diabetes, hypertension, etc.) were reported in 31.3% of A (H1N1) influenza positive cases and 19.4% of seasonal influenza cases. 8.7% (22/253) females having A (H1N1) influenza and 1.3% (07/521) females having seasonal influenza were found to be pregnant. During study period, twenty two pregnant women reported positive for A (H1N1) influenza. Among them, fourteen women were died and 8 were cured and discharged from the hospital [Table 3].

Laboratory and radiographic findings
Leukopenia was observed in 20.8% (94/453) A (H1N1) influenza positive patients. Lymphopenia was found in 50.3% of adult patients (172/342) and 17.0% (18/106) of children having A (H1N1) influenza infection [Table 4]. Among those having A (H1N1) influenza infection, 32.1% (164/456) had anemia. Thrombocytopenia was found in 22.3% (93/417) A (H1N1) influenza patients who were tested. Chest X-ray was done in 97.7% (499/511) of the A (H1N1) influenza patients: And among them pneumonia was found in 91% (454/499) patients.

Treatment outcome
All those detected with A (H1N1) influenza were given the recommended antiviral drug ‘Oseltamivir’. However, out of the 511 positive patients, 76 (14.9%) received Oseltamivir...
Within 2 days of onset of illness, 75.1% (384/511) of A (H1N1) influenza cases survived and were discharged, while 94.7% (1150/1215) of seasonal influenza cases survived the morbid episode. The median duration of hospital stay for A (H1N1) influenza cases was 6 days, while it was 4 days for seasonal influenza cases. Among those who expired, 48% (61/127) of A (H1N1) influenza cases and 32.3% (21/65) of seasonal influenza cases belonged to the productive age group of 15-44 years [Table 1].

**Discussion**

The current study found 29.6% of cases having influenza...
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like symptoms as positive for A (H1N1) influenza. Studies in Panama[16] and Chile,[17] reported figures of 40.9% and 45.9% as positive. In China, the majority (76.5%) of the infected patients had a history of travel to countries infected with A (H1N1) influenza,[18] while only 0.01% infected patients of this study had a similar history of travel. A median time interval (from onset of illness to hospital admission and diagnosis of infection) of 5 days is found in this study as compared to 3 days in studies done in the United States,[19] 4 days in Australia and New Zealand,[20] and similar to Mexico.[21] The period between onset of illness and hospital admission and diagnosis of this study is more than that of other countries.[19,26] These patients of this study, were initially treated at a local level by the general practitioners; when no improvement was reported (after few days of treatment), they were then referred to the higher centers for further investigation and treatment. This could be the reason for longer time duration between onset of illness to diagnosis.

Current interim CDC guidelines for pandemic and seasonal influenza recommend the use of either oseltamivir or zanamivir for hospitalized patients with suspected or confirmed influenza and for outpatients who are at high risk for complications.[22]

Ministry of Health and Family Welfare, Government of India had recommended and supplied oseltamivir to the state governments for distribution. In the present study, though all the A (H1N1) influenza infected patients received oseltamivir after hospitalization, only 14.9% (76/511) had received it within 2 days of the onset of illness, in contrast to 45% in the United States.[19] Initial primary treatment at the level of the general practitioners or local physician led to a delay in the referral: This could be the most plausible explanation for the delayed start of oseltamivir in suspected or confirmed A (H1N1) influenza patients.

The prevalence of cough and fever of those positive for A (H1N1) influenza was similar to studies reported from...
other countries.\textsuperscript{[23,24] In the present study, A (H1N1) influenza patients reported a low prevalence (31.3\%) of underlying medical conditions as compared to studies from the United States (73\%).\textsuperscript{[19] The presence of underlying morbidities in A (H1N1) influenza patients ranges from 52-74\% in other studies.\textsuperscript{[23,25,26] Hypertension and diabetes mellitus were the most common underlying conditions in both the hospitalized groups of our study in contrast to studies done elsewhere, where in patients with seasonal influenza,\textsuperscript{[27] and A (H1N1) influenza,\textsuperscript{[19] asthma and Chronic Obstructive Pulmonary Disease (COPD) were the most common underlying conditions. The 4.3\% (22/511) patients reported pregnancy [Table 4] in this study among A (H1N1) influenza patients was higher than the expected prevalence in the general population (1\%),\textsuperscript{[28]} in contrast, 7\% was reported in US,\textsuperscript{[19]} 11\% in New Zealand,\textsuperscript{[21]} and 16.7\% in Australia.\textsuperscript{[29] During periods of seasonal influenza and past pandemics, pregnant women have been at higher risk for influenza associated morbidity and mortality.\textsuperscript{[28-31]} Chest radiography was done in 97.7\% (499/511) of the A (H1N1) influenza patients: 91\% (454/499) of these patients had findings that were consistent with pneumonia. Significant number of patients with severe A (H1N1) influenza 96\% (311/324) reported pneumonia ($P = 0.001$) on chest radiography compared to 82.4\% (103/125) patients with non severe influenza. Similar findings were also reported by other studies.\textsuperscript{[10,32,33] In the absence of accurate diagnostic methods, patients who were hospitalized with suspected influenza and lung infiltrates on chest radiography should be considered for treatment with both antibiotics and antiviral drugs.\textsuperscript{[34]}

Limitations

The data was taken from only hospitalized patients; ence persons who became ill (with symptoms pertaining to influenza like illness) but who did not go to any hospital, could not be included in the study. As per the guidelines of the Ministry of Health, Government of India, patients belonging to category B (1) or (2) were treated on an outpatient basis: They were not being tested for A (H1N1) influenza. Such patients could thus not be included for this study. All diagnostic testing were clinically driven and other investigations were not obtained in a standardized fashion. Despite the use of a standardized data collection form, not all information could be collected from all the patients as the diagnostic testing, clinical management and their documentation on the medical records did not always follow a standard operating protocol. Besides, the findings from this study may be different during future waves of the pandemic (owing to the timely deployment of an effective vaccine, viral mutation, resistance to antiviral drugs etc.)

Conclusion

Though the clinico-epidemiological pattern of the A (H1N1) influenza patients were comparable to that of those suffering from seasonal influenza, a fivefold higher mortality was noted in A (H1N1) influenza patients. Hypertension, pregnancy, pneumonia on chest X-ray and receiving antiviral treatment within 2 days of illness onset were mainly reported among A (H1N1) influenza patients. These observations of the epidemiological risk factors, typical clinical features, response to their therapy and prognosis should aid in the recognition, diagnosis and clinical management of A (H1N1) influenza.

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References


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