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Original Article:

Characteristics of Fatal Cases of Pandemic Influenza A (H1N1) from September 2009 to January 2010 in Saurashtra Region, India

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Abstract:
Background: India reported first case of 2009 pandemic influenza A (H1N1) virus infection in May, 2009 and Saurashtra region in August, 2009. We describe the characteristics of fatal cases of 2009 influenza A (H1N1) infection reported in Saurashtra region. **Methods:** From September, 2009 to January, 2010, we observed 71 fatal cases that were infected with 2009 influenza A (H1N1) virus and admitted in different hospitals in Rajkot city. Real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) testing was used to confirm infection; the clinico-epidemiological features were observed and documented. **Results:** Median age of the deceased (71) was 29 years, and 57.7% were females. Median time observed was 5 days from onset of illness to diagnosis of influenza A (H1N1), and 57.7% were referred from general practitioner (OR=0.42, CI=0.24-0.74). Median hospital stay reported was 3 days. All admitted patients received oseltamivir, but only 16.9% received it within 2 days of onset of illness. The most common symptoms were cough (97.2%), fever (93%), sore throat and shortness of breath. Co-morbid conditions were present in almost half of the patients who ultimately died, the most common of which was pregnancy (OR=0.15, CI=0.04-0.52). Radiological pneumonia was reported in 98% patients. **Conclusion:** Residing in urban area, delayed referral from general practitioner, presence of co-existing condition, especially pregnancy was responsible for mortality among influenza A (H1N1) infected positive.
Key Words: Influenza A (H1N1); Epidemiology; Fatal cases; RT-PCR; Pregnancy; Antiviral drug

Introduction:

The first human cases of infection with the 2009 pandemic influenza A (H1N1) virus were confirmed in the Southwest United States in April 2009, although an epidemic later confirmed to be caused by H1N1 (2009) had been occurring in Mexico in the weeks prior to detection.[1,2] The novel pandemic influenza A (H1N1) virus was later confirmed to be a triple re-assortant virus containing gene segments from swine, avian and human influenza A virus.[1,3,4] On June 11, 2009 the World Health Organization (WHO) raised the pandemic level from 5 to 6, highest level after the documentation of human to human transmission of the virus in at least three countries in two of the six world regions defined by the WHO.[5,6] Similarities with regards to the characteristics of the influenza A (H1N1) virus have been observed among populations of both the northern and southern hemispheres.[7-10] Further similarities have been observed globally in the risk factors contributing to severe disease and death, with underlying disease recorded in at least half of the fatal cases [11], mainly pregnancy and metabolic diseases.[11,12]

Although much has been published on the characteristics of pandemic influenza A (H1N1) infection globally[7-12], little published data are available from the Indian subcontinent. The characteristics of pandemic influenza may differ from other developed countries reporting the infection, considering the high prevalence of other infectious diseases and significant burden of non communicable conditions.

The first case of confirmed pandemic H1N1 infection in India was documented during May, 2009.[13] Incidence rate remained low until August, 2009 when large numbers of cases were reported throughout India. Saurashtra region which is the western-most part of Gujarat state in India, reported its first H1N1 positive case during August, 2009. The purpose of this manuscript is to describe the characteristics of reported pandemic H1N1-related deaths, from 1st September, 2009 to 31st January, 2010.

Methods:

The Ministry of Health and Family Welfare, Government of India, started preparations for the management of infected patients as soon as the first case was reported in May, 2009. Gujarat state (including Saurashtra Region) participated in active surveillance for pandemic H1N1 as of August 2009. Hospitals having an advanced life saving support were involved in admitting and managing influenza A (H1N1) positive patients in Rajkot.

***Clinical case /suspected case definition*[6]:** 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, rhinorrhea, 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. A confirmed case was defined by a positive result of a real-time reverse transcriptase polymerase chain reaction (RT-PCR).

***Variables*:** Several types of data collected from the patients include: demographic information, any coexisting conditions, regarding onset of illness and treatment taken. Data regarding hospitalization, whether intensive care was needed, duration of antiviral drug administration, and disease outcome were collected from medical record and statistics departments of various hospitals.

***Data Management*:** All expired patients' admission history and their medical records including certified cause of death were assessed for clinico-epidemiological details. Approval by institutional review board was not required because of this infectious disease was covered under epidemic act and the state health department[14] had implemented Epidemic Disease Control Act, 1897 from 18th August, 2009 and issued a notification that it was in the interest of the public health to collect data on an emerging pathogen.

***Laboratory confirmation of infection*:** The 2009 H1N1 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.[15] Two swabs from naso-pharynx and one from pharynx were collected from suspected patients and their contacts for detection of influenza A (H1N1) virus by real-time RT-PCR assay.

***Statistical analysis*:** All data was entered in MS Excel, and analyzed by using Epi Info software (version 3.5.1) from CDC.[16]

***Certification of cause of death*:** In India, all deaths are recorded on a standard death certificate, which distinguishes between direct causality (Part I) and contributory factors (Part II). Part I of the certificate records diseases or conditions directly leading to death and part II records conditions contributing to the death but not related to the disease or condition causing it. Death certificates were also analyzed according to the methods of ICD-10 (international classification of diseases, 10th revision) [17], used nationally and internationally to produce national mortality statistics.[18]

Results:

Total 274 patients were found positive (Figure 1) and admitted in different hospitals of Rajkot from 1st September, 2009 to 31st January, 2010. Out of them, 71 patients who expired were included for analysis.

Admission rate and mortality was highest among below five years (16.9%) children, and 25-45 years (40.8%) age group. Median age of 29 years (Table 1) was reported among expired patients (range 4 months to 68 years). Significant number of deaths were occurred in patients residing in urban areas then in rural areas (OR= 1.95, CI=1.15-3.41). But no such association was found for male / female. No fatal case reported to have recent travel history to infected region. Median time, from onset of illness to diagnosis of influenza A (H1N1), was 5 days. More than half (57.7%) of fatal cases were treated first at general practitioner and then referred to higher center for further investigation. Seventeen percent patients who expired had received antiviral treatment within 2 days of onset of illness. 87.1% deaths occurred 5 days after onset of illness.

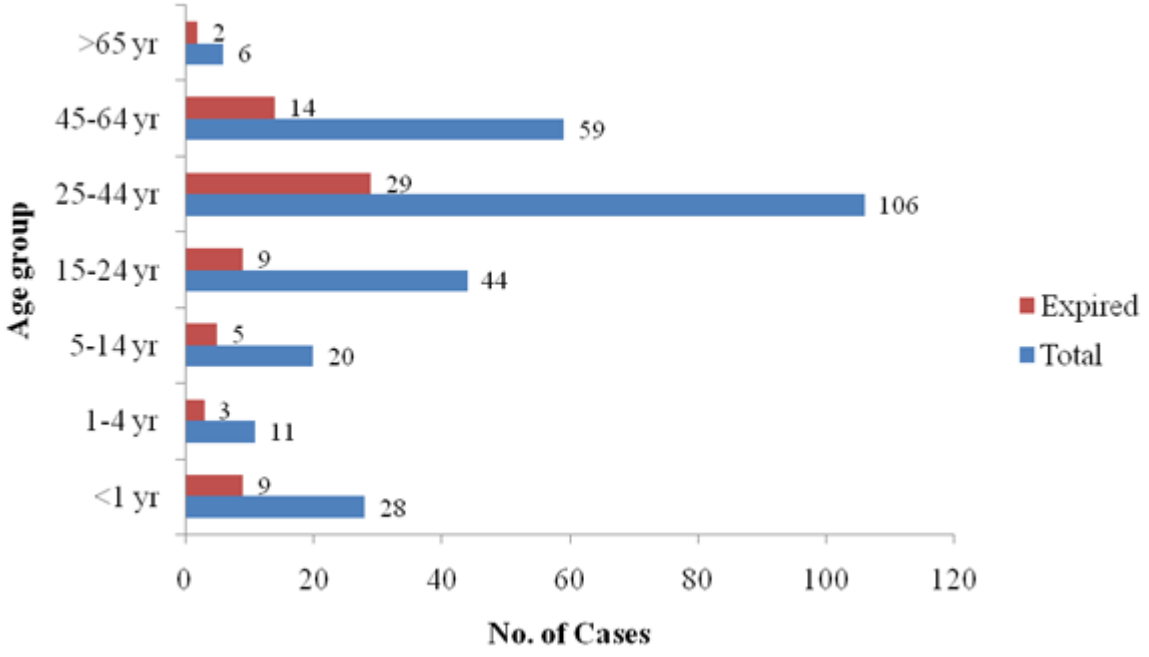

Figure 1: Age group wise distribution of influenza A (H1N1) positive total (n=274) and expired (n=71) patients in Saurashtra region from September, 2009 to February, 2010

Table 1: Baseline characteristics and disease history of 2009 pandemic influenza A (H1N1) virus infected patients in Saurashtra region (September, 2009 to January, 2010)

Characteristics	Non fatal cases (n=203) No. (%)	Fatal cases (n=71) No. (%)
Age in year		
Median – year	27	29
Range	4 mths-68 yrs	4 mths-68 yrs
Age group of positive expired patients – no. (%)		
< 5 yrs	27 (13.3)	12 (16.9)
5-24 yrs	50 (24.6)	14 (19.7)
25-44 yrs	77 (37.9)	29 (40.8)
45-64 yrs	45 (22.2)	14 (19.7)
≥ 65 yrs	4 (2.0)	2 (2.8)
Sex – no. (%)		
Male	111 (54.7)	30 (42.3)
Female	92 (45.3)	41 (57.7)
Residential status† – no. (%)		
Urban	143 (70.4)	39 (54.9)
Rural	60 (29.6)	32 (45.1)
Hospital stays in days – no. (%)		
Median (in days)	5	3
≤2 days	14 (6.9)	27 (38.0)
3-5 days	51 (25.1)	21 (29.6)
6-10 days	100 (49.3)	15 (21.1)
≥11 days	38 (18.7)	8 (11.3)
Time interval from onset of illness to hospital admission & diagnosis-no. (%)		
Median (in days)	5	5
<1 day	12 (5.9)	6 (8.5)
1-4 days	91 (44.8)	24 (33.8)
5-10 days	89 (43.8)	40 (56.3)
>10 days	11 (5.4)	1 (1.4)
Referral from general practitioner/physician‡ – no. (%)	75 (36.9)	41 (57.7)
Antiviral treatment – no. (%)		
Any antiviral drug received	203 (100)	71 (100)
≤2 days after onset of symptoms	32 (15.8)	12 (16.9)
Time interval from onset of illness to death – no. (%)		
<1 day	NA§	1 (1.4)
1-4 days		8 (11.3)
5-10 days		38 (53.5)
>10 days		24 (33.8)

*An infected region was defined as an area where one or more confirmed cases of 2009 pandemic influenza A (H1N1) virus infection had been found in the preceding 7 days.
† p<0.01, Odds Ratio (OR) = 1.95, Confidence Interval (CI) = 1.12-3.41
‡ p<0.01, OR = 0.42, CI = 0.24-0.74
§ NA- Not Applicable

Cough (97.2%), fever (93%), shortness of breathing (57.7%), and sore throat (52.1%) reported mainly among deaths due to influenza A (H1N1) (Table 2).

Little less than half (45.1%) deaths were reported having coexisting conditions, including 14.1% pregnant women. Significant association was found between pregnancy (p=0.01) and influenza A (H1N1) infection among fatal cases. Laboratory findings (Table 3) like, leukopenia (31%), anemia (44.8%), lymphopenia, thrombocytopenia (32.1%), elevated alanine aminotransferase (90.3%), aspartate aminotransferase (37.9%), pneumonia (98.3%) were reported among fatal cases.

Table 2: Clinical features and coexisting conditions of patients infected with influenza A (H1N1) at the time of hospital admission

Characteristics	Non fatal cases (n=203) No. (%)	Fatal cases (n=71) No. (%)
Clinical Features – no. (%)		
Cough	196 (96.6)	69 (97.2)
Fever (≥37.5˚ Celsius)	186 (91.6)	66 (93.0)
Shortness/difficulty in breathing	105 (51.7)	41 (57.7)
Sore Throat	112 (55.2)	37 (52.1)
Nasal Catarrh	40 (19.7)	16 (22.5)
Headache	52 (25.6)	19 (26.8)
Vomiting	13 (6.4)	14 (19.7)
Coexisting conditions – no. (%)		
Any one condition*	58 (28.6)	32 (45.1)
Pregnancy†	5 (2.5)	10 (14.1)
Diabetes Mellitus	22 (10.8)	5 (7.0)
Hypertension	19 (9.4)	5 (7.0)
Chronic Heart Diseases	9 (4.4)	4 (5.6)
Chronic Pulmonary Diseases	13 (6.4)	2 (2.8)
Seizure disorder	5 (2.5)	2 (2.8)

*P<0.01; † p<0.01, OR=0.15, CI=0.04-0.52

Table 3: Laboratory and radiographic findings on hospital admission in influenza A (H1N1) infected expired patients in Saurashtra region*

Characteristic	No. /Total No. (%)
Leukocyte count	
Mean count	7905 ± 7566
Leukopenia (<4,000/ mm^3)	18/58 (31.0)
Leukocytosis (>10,000/ mm^3)	14/58 (24.1)
Hemoglobin gm/dl	11.03 ± 2.65
Anemia	
Mild (10.0-11.0 gm/dl)	8/58 (13.8)
Moderate (8-10 gm/dl)	10/58 (17.2)
Severe (<8 gm/dl)	8/58 (13.8)
Lymphocyte count	
<1500/ mm^3 in adults	30/39 (76.9)
<3000/ mm^3 in children	2/10 (20.0)
Platelet count	
Mean count	212, 566 ± 151, 843
Thrombocytopenia (<150,000/ mm^3)	17/53 (32.1)
Thrombocytosis (>350,000/ mm^3)	6/53 (11.3)
Elevated alanine aminotransferase (>40 U/liter)	
Any deviation	28/31 (90.3)
≥2× the upper limit of normal range	27/31 (87.1)
Elevated aspartate aminotransferase (>40 U/liter)	
Any deviation	11/29 (37.9)
≥2× the upper limit of normal range	2/29 (6.9)
Elevated total bilirubin (>1.2 mg/dl)	9/35 (25.7)
Erythrocyte sedimentation rate	
>15 mm/hr in male patients	8/21 (38.1)
>20 mm/hr in female patients	6/21 (28.6)
Chest X-ray findings	
Done	59/71 (83.1)
Pneumonia found	58/59 (98.3)
Antibiotic treatment received	64/71 (90.1)
Corticosteroid treatment received	41/71 (57.7)

* ± values are mean ± SD.

Chest radiography was done in 59 (83.1%) of 71 fatal cases and among them 98.3% reported bilateral pneumonia. Among all reported deaths, the underlying cause of death was classified as influenza A (H1N1) in the causal chain directly leading to death (Table 4).

Table 4: Certification of direct causes of death in expired influenza A (H1N1) patients in Saurashtra region	
Certified causes of death	**Direct Cause (n=71) No. (%)**
Direct cause (Part I)	
Influenza A (H1N1)	71 (100)
Contributing cause (Part II)	
Pneumonia	3 (4.2)
Acute Respiratory Distress Syndrome (ARDS)	5 (7.0)
Pneumonia and ARDS	55 (77.5)
Other respiratory complications	3 (4.2)
Multi organ failure	6 (8.5)
Pre-existing disease (DM, Thalessemia, CHD, RHD)	5 (7.0)

Discussion:

During the previous pandemics of 20th century and during seasonal influenza, most cases involve transient illness, not requiring hospitalization. Deaths were described mainly in young adult population or those with underlying disease.[19] Seasonal influenza caused significant morbidity and mortality throughout the world.[20] Present study identified all patients with confirmed 2009 influenza A (H1N1) belonging to category C [21], who were hospitalized in various hospitals in Rajkot from September, 2009 to January, 2010. Category C includes patients having high grade fever, severe sore throat, any co-existing condition, breathlessness, chest pain, drowsiness, fall in blood pressure, sputum mixed with blood, and they were hospitalized immediately.

Total 274 patients were hospitalized during study period and among them 71 patients expired. The majority of expired patients (63%) belonged to age group 25-65 years, suggesting high fatality rate among adults. The median age of fatal cases was 29 years, which is lower than that reported in South Africa (33.5 years)[11] and in France (37 years).[22] Significant number of deaths were occurred in patients residing in urban areas then in rural areas (OR= 1.95, CI=1.15-3.41). But no such association was found for male / female sex among fatal and non fatal cases. Large number of people resides in congested areas with poor environmental and hygienic conditions may be the reason for spread of influenza A (H1N1) virus in urban area than rural area. Most ultimately fatal cases (57.7%) were first treated at a general practitioner and then referred to the higher center (OR=0.42, CI=0.24-0.74). The median time between onset of illness and hospital admission and diagnosis was more in this study than studies of other countries.[23,24] The possible justification is that patients seek treatment at local level from general practitioners and physicians, but with no or little improvement after initial treatment, they were referred to higher center for further investigation and management.

The vast majority of 2009 H1N1 viruses that have been tested at the CDC to date have been susceptible to two neuraminidase inhibitors, oseltamivir and zanamivir, and resistant to two adamantanes; amantadine and rimantadine.[4,25] 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 at high risk for complications.[26] Ministry of Health & Family Welfare, Government of India has recommended and supplied oseltamivir to the state governments for distribution in tertiary care centers and district hospitals in adequate quantity. Although the evidence of benefit from antiviral therapy was strongest when treatment is initiated within 48 hours after the onset of illness, a study with oseltamivir in hospitalized patients reported reduction in mortality even after 48 hours of onset of illness.[27] In present study, all the influenza A (H1N1) infected fatal cases received oseltamivir after hospitalization, but only 16.9% received it within 48 hours of onset of illness, compared to 45% in United States.[23] Initial treatment by general practitioners and delayed referral to higher center, may be possible explanations for late start of oseltamivir in suspected or confirmed influenza A (H1N1) patients.

Fatal cases, on hospitalization, mainly presented with cough (97.2%), fever (93%), shortness of breathing (57.7%), and sore throat (52.1%). These observations are similar to studies done by others in US [23], Australia and New Zealand.[24] In the present study, the proportion of fatal cases who had at least one coexisting condition was 45%, which was 36% in England[28], and 53% in France.[22] Pregnancy is a well documented risk factor for severe infection and death in seasonal influenza and in previous pandemics.[29-31] In this study, 14.1% of fatal cases were pregnant compared to 2.5% in non-fatal cases (OR=0.15, CI=0.04-0.52). Out of 10 fatal pregnant cases, 2 were in second trimester and 8 in third trimesters.

Our study has a number of strengths. It represents one of the largest series of fatal cases with severe 2009 influenza A (H1N1) infection covering two seasons of monsoon and winter. It includes both adults and children from geographically similar areas, which improves the generalizability of our results to other regions. These characteristics of risk factors, typical clinical features, response to therapy, and prognosis should aid in the recognition, diagnosis and clinical management of influenza A (H1N1).

Our study also has some limitations. The data was taken only from hospitalized fatal cases, so patients who became infected, remained undiagnosed, died in the community and did not go to the hospital were not included in our study. All diagnostic testing was clinically driven, and other investigations were not obtained in a standardized fashion. Though we used a standardized data collection form, we still could not collect all information for all the patients. The findings may be different during future waves, owing to timely deployment of an effective vaccine, viral mutation, and resistance to antiviral drugs.

Conclusion:

We have demonstrated the characteristics of fatal cases of 2009 influenza A (H1N1). Residing in urban area, delayed referral from general practitioner, presence of co-existing condition, especially pregnancy was responsible for mortality among influenza A (H1N1) infected positive.

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