Clinical and epidemiological characteristics of 2009 pandemic influenza A in hospitalized pediatric patients of the Saurashtra region, India

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Background: **The first case of 2009 pandemic influenza A or H1N1 virus infection in India was reported in May 2009 and in the Saurashtra region in August 2009. We describe the two waves clinico-epidemiological characteristics of children who were hospitalized with 2009 influenza A infection in the Saurashtra region.**

Methods: **From September 2009 to February 2011, we treated 117 children infected with 2009 influenza A virus who were admitted in different hospitals in Rajkot city. Real-time reverse transcriptase polymerase chain reaction (RT-PCR) test was used to confirm infection, and the clinico-epidemiological features of the disease were closely monitored.**

Results: **In the 117 patients, with a median age of 2 years, 59.8% were male. The median time from onset of the disease to influenza A diagnosis was 5 days, and that from onset of the disease to hospitalization was 7 days. The admitted patients took oseltamivir, but only 11.1% of them took it within 2 days after onset of the disease. More than one fourth (29.1%) of the admitted patients died. The most common symptoms of the patients were cough (98.3%), fever (94.0%), sore throat and shortness of breathing. Pneumonia was detected by chest radiography in 80.2% of the patients.**

Conclusions: **In children with infection-related illness, the survival rate was about 71% after oseltamivir treatment. The median time for virus detection with real-time RT-PCR is 5 days. Early diagnosis and treatment may reduce the severity of the disease.**

World J Pediatr 2012;8(4):321-327

Key words: **antiviral drug;**
clinical features;
epidemiology;
influenza A;
intensive care

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doi: 10.1007/s12519-012-0376-y

Introduction

Novel swine origin influenza A or H1N1 virus has become 21st century's first pandemic.[1] The new influenza virus of H1N1 strain undergoing triple reassortants contains genes from avian, swine and human viruses.[2,3] In early April 2009, cases of human infection with 2009 pandemic influenza A virus were identified in Mexico[4] and then in the United States.[5] The World Health Organization (WHO) raised the pandemic level from 5 to 6, the highest level after 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.[6,7] The first case of confirmed infection with the virus in India was documented in May 2009.[8] The Saurashtra region is a western part of Gujarat state in India. In Gujarat state, the first H1N1 positive case was reported in June 2009[9] and in the Saurashtra region in August 2009.[10] The symptoms of 2009 influenza A were expected to be similar to the symptoms of regular human seasonal influenza, including fever, cough, sore throat, and myalgia.[11] This report summarizes the clinical and epidemiological characteristics of the 117 children with 2009 influenza A virus infection, hospitalized in various hospitals of Rajkot city in the Saurashtra region. The study included the two waves of influenza A: the first wave from September 2009 to February 2010 and the second wave from August 2010 to October 2010.

Methods

Data sources and study period

The central government made preparation, from the first reported case of influenza A in May 2009 in India, for the management of infected patients. Gujarat state including the Saurashtra region had started monitoring and surveillance activities as soon as the positive cases were reported since August 2009. The Saurashtra region includes following districts, namely Rajkot, Junagadh, Jamnagar, Porbandar, Surendranagar, Kutch, Bhavnagar and Amreli. Rajkot city is in the center of the above mentioned districts. Due to availability of all treating facilities including intensive and ventilatory support, state government established 80-bed swine flu isolation wards in PDU Medical College and Civil Hospital in Rajkot city. All the private hospitals having an advanced life-saving support were also involved in admitting and managing such positive patients. Special isolation ward was started in Civil Hospital for admission of suspected/confirmed patients for diagnosis, treatment, and monitoring. A control room was started for regular monitoring, reporting and surveillance activities in PDU Medical College, Rajkot and managed by the Community Medicine Department with support from District Health Authorities since September 2009. During the period, a total of 775 children had undergone laboratory investigation, including 117 (15.1%) positive for influenza A and 658 (84.9%) negative for influenza A. The 117 children who had been admitted to the Pediatric Department of Civil Hospital and other two pediatric hospitals of Rajkot from September 2009 to February 2011 were included in the study. They were 64 patients found in the first wave of influenza A from September 2009 to February 2010 and 53 patients in the second wave from August 2010 to October 2010. Although no case was reported from November 2010, surveillance was done continuously up to February 2011.

Classification of influenza A cases[12]

The Ministry of Health and Family Welfare of India issued guidelines for classification of influenza A cases during screening for home isolation, testing, treatment, and hospitalization: (1) Type A: patients have mild fever plus cough/sore throat with or without body ache, headache, diarrhea and vomiting; they require no oseltamivir treatment but treatment of symptoms only; no test required for influenza A; they should be monitored for the progress of disease and reassessed at 24 to 48 hours. (2) Type B: (i) In addition to the signs and symptoms mentioned in type A, if the patient has high grade fever and severe sore throat, he or she may require home isolation and oseltamivir treatment, but no testing is required for influenza A; (ii) In addition to type A signs and symptoms, one who has one or more of the following high-risk conditions shall be treated with oseltamivir: children with mild illness but predisposing risk factors; pregnant women; persons aged 65 years or more; patients with lung diseases, heart disease, liver disease, kidney disease, blood disorders, diabetes, neurological disorders, cancer and HIV/AIDS; patients on long-term steroid therapy; no testing required for influenza A. (3) Type C: in addition to the above signs and symptoms in types A and B, if the child has one or more of the following symptoms and signs: breathlessness, chest pain, drowsiness, fall in blood pressure, sputum mixed with blood, and bluish discoloration of nails; children with influenza like illness who have a severe disease as manifested by red flag signs (somnolence, high and persistent fever, inability to feed well, convulsions, shortness of breath, difficulty in breathing, etc); worsening of underlying chronic conditions; all children in this type require testing, immediate hospitalization and treatment. In the present study, a total of 117 children of type C were confirmed, hospitalized, and monitored.

Definition of clinical case/suspected case[7]

A suspected patient was defined as a person with an influenza like illness (temperature ≥37.5˚C and at least one of the following symptoms: sore throat, cough, rhinorrhea, or nasal congestion) and with either a history of travel to a country where infection had been reported in the previous 7 days or an epidemiologic link to another person with confirmed or suspected infection in the previous 7 days. A confirmed patient was defined by a positive result of a real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay performed at a laboratory under the auspices of the state government. A close contact was defined as a person who lived with or was exposed to the respiratory secretions or other body fluids of patients with suspected or confirmed influenza A infection.

Variables, records and analysis

The data collected from children and their records included date and time of admission to hospital/intensive care unit (ICU), age, sex, religion, residential status, co-existing conditions, and date and time of first symptoms. Other variables collected from departments of medical records and statistics at different hospitals included duration of treatment in hospitals and ICU, duration between onset of illness and diagnosis, outcome of hospital/ICU admission, time from onset of illness to death, and time from antivirus treatment

to death. The children were classified into two groups: severe influenza A and non severe influenza A. In the severe influenza A group, children needed intensive care or died, and in the non severe influenza A group, children were not given intensive care and survived. For intensive care, the following signs were used by pediatricians: PAO_2<60 mmHg, hypercapnoea (PCO_2 >55 mmHg), severe metabolic acidosis (pH<7.2), severe respiratory distress (respiratory rate, >70/min), severe lower chest wall indrawing, altered sensorium, grasping or apnea, and shock.

Data collection and analysis were coordinated by the Community Medicine Department, PDU Medical College, Rajkot. Admission history and medical records of children were assessed for clinico-epidemiological changes or after their discharge/death from Civil Hospital and private hospitals of Rajkot. Line list number was given to every patient to avoid duplication at any time during the study period. No assumptions on missing data were made, and proportions were calculated as percentages of the children with available data. No approval of the institutional review board was required because this infectious disease was covered by the epidemic act[13] and the Epidemic Disease Control Act.

Laboratory confirmation of viral infection

The 2009 influenza A virus was detected by a real-time RT-PCR assay in accordance with the protocol from the USA Center for Disease Control (CDC) as recommended by the WHO.[14] Persons suspected of being infected and persons identified with close contacts were investigated by taking two swabs from the naso-pharynx and one from the pharynx for detection of virus by a real-time RT-PCR assay. At state level, initially laboratory study was started in BJ Medical College, Ahmedabad and samples were collected from Rajkot, but results were available after 24 hours. Thus, from January 26, 2010 another laboratory study was started in the Microbiology Department, PDU Medical College and Civil Hospital, Rajkot for testing samples by a real-time RT-PCR. Laboratory testing was made free of cost for all patients even they were admitted into private hospitals.

Statistical analysis

The percentages of children in each class and the median time of various variables were calculated, and chi-square test was used. We calculated descriptive statistics for all variables. All data were entered in MS Excel, and analyzed by using Epi Info software (version 3.5.1) from CDC.[15]

Results

Demographic and clinical characteristics

Totally 117 children from September 2009 to February 2011, who had been infected with 2009 influenza A (Table 1) were diagnosed and hospitalized in the PDU Medical College and Civil Hospital and in another two super specialty hospitals in Rajkot. Positive pediatric cases were reported from Rajkot city (35.0%), Rajkot district (31.6%), and other districts of the Saurashtra region (33.3%).

Monthly distribution (Fig.) of influenza A infected patients in the Saurashtra region shows that during the first wave, the number of cases increased from 16 in November 2009 to 31 in December 2009, and then decreased to 11 in January 2010. In the second wave, abrupt cases of the disease were reported from August 2010 up to October 2010.

The median age of children with positive findings was 2 years (IQR: 1-4 years). The median time of diagnosis of infection was 5 days after onset of illness (IQR: 4-7 days). Most of the 117 children had cough (98.3%), fever (94.0%), shortness/difficulty in breathing (70.9%), and sore throat (53.8%). Altogether 25 (21.4%) children reported underlying medical conditions, including seizures in 11 (9.4%), asthma in 4 (3.4%), and thalassemia in 4 (3.4%) (Table 2).

Laboratory and radiographic findings

Leukopenia was observed in 16 (15.1%) of 106 children and lymphopenia in 18 (17.6%) of 102 children (Table 3). Anemia was found in more than three fourth children (79/106), including 21 (19.8%) with severe anemia. Anemia was defined by a hemoglobin level <11 g/dL in children by the WHO criteria. It was further classified into mild anemia (10-10.9 g/dL), moderate anemia (8-9.9 g/dL) and severe anemia (<8 g/dL). All children with anemia survived except one child who died of severe anemia. Thrombocytopenia was found in 25.0% of 92 children. Chest X-ray was done in 86 (73.5%) children, and among them pneumonia was found in 69 (80.2%) children. Among children with pneumonia (n=69), 23 (33.3%) had severe influenza A; 21 (91.3%) of the 23 children were kept on ventilation therapy.

Treatment outcome

The median time for hospital stay was 7 days for influenza A infected children (IQR: 4-11 days). The duration of hospital stay was 6 days or more in 81 (69.2%) children. All children with positive findings received antiviral treatment with oseltamivir (Table 1). Of the 117 children with positive results, only 13 (11.1%) received antiviral treatment within 2 days after

Table 1. Baseline characteristics, disease history, and outcomes of the 117 hospitalized children with 2009 pandemic influenza A virus in the Saurashtra region during the two waves (Sept. 2009 to Feb. 2011)

Characteristics	Values
Age	
Median	2 y
Range	1 mon – 15 y
Age group of positive patients, *n* (%)	
<1 y	26 (22.2)
1-5 y	65 (55.6)
6-10 y	14 (12.0)
11-15 y	12 (10.3)
Sex, *n* (%)	
Male	70 (59.8)
Female	47 (40.2)
Religion, *n* (%)	
Hindu	109 (93.2)
Muslim	8 (6.8)
Residential status, *n* (%)	
Rajkot city	41 (35.0)
Rajkot district	37 (31.6)
Other districts	39 (33.3)
Recent travel to infected region, *n* (%)*	0 (0.0)
Referral from general practitioner/pediatrician, *n* (%)	66 (56.4)
Hospital stay, *n* (%)	
Median (in days)	7
<2 d	14 (12.0)
3-5 d	22 (18.8)
6-10 d	58 (49.6)
>11 d	23 (19.7)
Time interval from onset of the disease to hospital admission and diagnosis, *n* (%)	
Median (in days)	5
<1 d	0 (0.0)
1-4 d	45 (38.5)
5-10 d	59 (50.4)
>10 d	13 (11.1)
Antiviral treatment, *n* (%)	
Any antiviral drug received	117 (100.0)
<2 days after onset of symptoms	13 (11.1)
Outcome of patients, *n* (%)	
Survived	83 (70.9)
Expired	34 (29.1)
Patients kept on ventilators, *n* (%)	26 (22.2)
Duration on ventilators in days, median	2
Age group of expired H1N1 patients, *n* (%)	
<1 y	8 (23.5)
1-5 y	18 (52.9)
6-10 y	4 (11.8)
11-15 y	4 (11.8)
Time interval from onset of illness to death, *n* (%)	
<1 d	0 (0.0)
1-4 d	1 (2.9)
5-10 d	8 (23.5)
>10 d	25 (73.5)
Time interval from antivirus drug started to death, *n* (%)	
<1 d	0 (0.0)
1-4 d	13 (38.2)
5-10 d	5 (14.7)
>10 d	16 (47.1)

*: An infected region was defined as an area where one or more confirmed cases of 2009 pandemic influenza A virus infection had been found in the preceding 7 days.

onset of the disease (age range: 7 months to 9 years). After admission, 83 (70.9%) children survived and were discharged from hospitals, while 34 (29.1%) children died after treatment with antiviral agents and life-saving support. Among 34 deaths, more than three fourths (76.4%) were at age of ≤5 years. Even after a complete course of 5-day treatment with oseltamivir, 21 (61.8%) children died.

Table 2. Clinical features and coexisting conditions in the 117 influenza A infected children at the time of hospitalization in the Saurashtra region

Characteristics	*n* (%)
Clinical features, *n* (%)	
Cough	115 (98.3)
Fever (>37.5ºC)	110 (94.0)
Sore throat	63 (53.8)
Shortness/difficulty in breathing	83 (70.9)
Nasal catarrh	54 (46.2)
Headache	43 (36.8)
Vomiting	39 (33.3)
Coexisting conditions, *n* (%)	
Any one condition	25 (21.4)
Seizure disorder	11 (9.4)
Thalassemia	4 (3.4)
Asthma	4 (3.4)
Anemia	2 (1.7)
Congenital heart diseases	1 (0.9)

Table 3. Laboratory and radiographic findings at hospital admission in influenza A infected children in the Saurashtra region*

Characteristics	*n*/total *n* (%)
Leukocyte count	
Mean count	10 245±8657
Leukopenia (<4000/mm^3)	16/106 (15.1)
Leukocytosis (>10 000/mm^3)	37/106 (34.9)
Hemoglobin (g/dL)	9.60±1.98
Anemia	
Mild (10.0-11.0 g/dL)	25/106 (23.6)
Moderate (8-10 g/dL)	33/106 (31.1)
Severe (<8 g/dL)	21/106 (19.8)
Lymphocyte count	
Lymphopenia (<3000/mm^3)	18/102 (17.6)
Platelet count	
Mean count	276 760±169 988
Thrombocytopenia (<150 000/mm^3)	23/92 (25.0)
Thrombocytosis (>350 000/mm^3)	28/92 (30.4)
Elevated alanine aminotransferase (>40 U/L)	
Any deviation	7/8 (87.5)
≥2 × the upper limit of normal range	7/8 (87.5)
Elevated aspartate aminotransferase (>40 U/L)	
Any deviation	4/9 (44.4)
≥2 × the upper limit of normal range	3/8 (37.5)
Elevated total bilirubin (>1.2 mg/dL)	1/9 (11.1)
Erythrocyte sedimentation rate	
>15 mm/h in male patients	6/12 (50.0)
>20 mm/h in female patients	0 (0.0)
Chest X-ray findings	
Done	86/117 (73.5)
Pneumonia found	69/86 (80.2)
Antibiotic treatment received	105/117 (89.7)
Corticosteroid treatment received	39/117 (33.3)

*: Plus-minus values are mean ± SD.

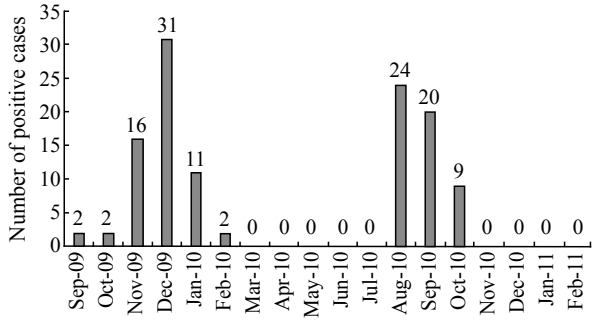

Fig. Month wise distribution of the 117 hospitalized children infected with influenza A (H1N1) from September 2009 to February 2011 in the Saurashtra region.

Table 4. Characteristics of hospitalized children with severe and non severe influenza A (H1N1)

Characteristics	Severe influenza A* (*n*=35)	Non-severe influenza A† (*n*=82)
Age		
Median (range), y	4 (4.5 mon - 15 y)	2 (1 mon - 15 y)
<5 y, *n* (%)	26 (74.3)	64 (78.0)
Referral from general practitioner/ pediatrician, *n* (%)	24 (68.6)	42 (51.2)
Clinical features, *n* (%)		
Cough‡	34 (97.1)	60 (73.2)
Fever‡	33 (94.3)	56 (68.3)
Shortness of breath‡	28 (80.0)	33 (40.2)
Coexisting conditions, *n* (%)		
Any one condition	9 (25.7)	16 (19.5)
Seizure disorder	3 (8.6)	8 (9.8)
Thalassemia	3 (8.6)	1 (1.2)
Asthma	0 (0.0)	4 (4.9)
Congenital heart disease	1 (2.9)	0 (0.0)
Pneumonia on chest radiography on admission, *n*/total *n* (%)	23 (65.7)	46 (56.1)
Antiviral treatment received ≤2 days after onset of symptoms,‡ *n* (%)	8 (22.9)	5 (6.1)
Corticosteroid treatment received, *n* (%)	14 (40.0)	25 (30.5)

*: Severe influenza A (H1N1): patients need intensive care or died; †: Non-severe influenza A (H1N1): patients do not need intensive care and survived; ‡: $P<0.05$ on bivariate analysis (χ^2 or Fisher's exact test).

Table 5. Certified causes of death in expired pediatric influenza A (H1N1) patients in the Saurashtra region

Certified causes of death	Direct cause (*n*=34), *n* (%)
Direct cause (Part I)	
Influenza A	34 (100.0)
Contributing cause (Part II)	
Pneumonia	4 (11.8)
Acute respiratory distress syndrome (ARDS)	6 (17.6)
Pneumonia and ARDS	24 (70.6)
Other respiratory complications	2 (5.9)
Multi-organ failure	5 (14.7)
Pre-existing disease (thalassemia, seizure disorder)	7 (20.6)

Children with severe influenza A were more likely to have cough, fever, shortness of breath; initiation of antiviral treatment within 2 days after onset of the disease was more common in severe cases than in non severe cases (Table 4).

All the 34 deaths were due to influenza A-realated causes: pneumonia with acute respiratory distress syndrome (ARDS) (70.6%), pre-existing conditions (thalassemia, seizure), ARDS (17.6%) or pneumonia alone (11.8%), and multi-organ failure (14.7%) (Table 5).

Discussion

In the present study, the 117 children with influenza A were confirmed and their clinical and laboratory findings were analyzed. We found that the median age of children was 2 years which was lower than that in patients with similar findings reported in Canada (4.8 years),[16] the USA (6 years)[17] and Argentina (10 years).[18] In our study, the median time for hospital stay was 7 days, with a range from less than 1 day to 30 days. It was 4 days (range: 2-7 days) in Canada[19] and 8.1 days (range: 6-16 days) in China.[20] The median time was 5 days from onset of illness to hospital admission or diagnosis of infection in contrast to 4 days in Argentina.[18] In the present study, 97% of the children died 5 days after onset of illness compared with 3 days for influenza related deaths in the USA.[21]

Most of 2009 influenza A viruses that have been tested by the CDC of the USA are susceptible to oseltamivir and zanamivir and also resistant to amantadine and rimantadine.[22] 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 of complications.[23] The Ministry of Health and Family Welfare of India has recommended the use of oseltamivir in tertiary care centers and district hospitals. In the present study, the influenza A infected children received treatment with oseltamivir after hospitalization, but only 11.1% of them were treated within 2 days after onset of the disease, while it was 12% in Argentina[18] and 48.1% in the USA.[17] Initial treatment by general practitioners or pediatricians and delayed referral to central hospitals may explain delayed treatment with oseltamivir for suspected or confirmed influenza A patients. In the USA, treatment with oseltamivir has been recommended for patients with 2009 influenza A infection even more than 48 hours after onset of the disease. The treatment was also recommended for children under 1 year old.[24]

The monthly distribution of influenza A infected

patients in the Saurashtra region showed that during the first wave the number of cases increased from 16 in November 2009 to 31 in December 2009 and then decreased to 11 in January 2010. In the second wave, abrupt cases were seen during the period of August 2010 to October 2010. Low atmospheric temperature in December leads to an increased number of patients infected with influenza A. The infection may last to January and February. By the end of February, no positive cases were reported from the study area, indicating that influenza virus is related to cold season as a large number of cases occur in winter during the first wave.[25,26] The second wave took place from August to October, suggesting that high humidity may promote the spread of infection.

Most patients had cough (98.3%) and fever (94.0%) as reported elsewhere.[18,19,27-30] The prevalence (21.4%) of underlying conditions was lower in our study than in the United States (67%)[31] and Argentina (35%).[18] Studies[24,32] revealed that 44%-84% of adults hospitalized with seasonal influenza had an underlying condition and that the prevalence of the disease was lower than that reported by others.

Obviously, the present study has some limitations. The data were collected from hospitalized children, those who were infected in the community or not hospitalized were not included. Also, children of type B who were treated in outpatient clinics but not tested were excluded in the study. Few investigations like creatinine phosphokinase, C reactive protein, and respiratory syncytial virus were not conducted as the kits were not available. Despite the use of a standardized form for data collection, some information was missed. The findings may be different in different waves because of the timely deployment of an effective vaccine, viral mutation, and resistance to antiviral agents.

In conclusion, influenza A infection-related disease affects children with a survival rate of 71% after treatment with oseltamivir. The period during which the virus can be detected with a real-time RT-PCR is 5 days. Early diagnosis and treatment may reduce the severity of the disease.

Acknowledgements

We are grateful to chief medical officer, Civil Hospital, Rajkot and other private hospitals for providing the necessary data. We are also grateful to the nursing staff of swine flu ward and medical record department of Civil Hospital, Rajkot for their assistance in providing necessary records and information.

Funding: None.
Ethical approval: Not needed.
Competing interest: None stated.
Contributors: Chudasama RK involved in designing the study, preparation, data collection and analysis, acts as a guarantor of study. Patel UV and Verma PB assisted in analysis and in manuscript writing. Agarwal P, Bhalodiya S and Dholakiya D helped in data collection, analysis and manuscript writing.

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Received July 6, 2011
Accepted after revision September 28, 2011