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Pediatric hospitalizations for 2009 pandemic influenza A (H1N1) in Saurashtra region, India

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ABSTRACT

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

Methods: *From September, 2009 to February, 2010, we observed 62 children infected with 2009 influenza A (H1N1) virus who were 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 of the disease were closely monitored.*

Results: *Of 62 patients, median age was 2.5 years, and 56.5% were males. Median time of 5 days was observed from onset of illness to influenza A (H1N1) diagnosis, while median time of 7 days reported for hospital stay. All admitted patients received oseltamivir drug, but only 9.7% received it within 2 days of onset of illness. More than one fourth (29.0%) of admitted patients were expired. The most common symptoms were cough (69.4%), fever (61.3%), sore throat and shortness of breathing. Pneumonia was reported in 97.1% patients with chest radiography.*

Conclusion: *We have demonstrated that infection related illness affects children with survival of 71% patients after antiviral treatment. The median time for virus detection with use of real-time RT-PCR is 5 days. Mortality reported high among children with radiological evidence of pneumonia.*

Keywords: *Influenza A (H1N1), clinical features, epidemiology, RT-PCR, antiviral drug, intensive care*
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Introduction

Influenza causes significant morbidity and mortality in childhood [1]. Influenza A (H1N1) (earlier known as swine flu) is a new influenza virus causing illness in human beings. The scientists call this a 'quadruple reassortant' virus and hence this new (novel) virus is christened "Influenza A (H1N1) virus" [2, 3]. In early April, 2009, cases of human infection with 2009 pandemic influenza A (H1N1) virus were identified in the Mexico [4] and then in United States (US) [5, 6]. 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 [7, 8]. The first case of confirmed infection with the virus in India was documented in May, 2009 [9]. The positivity of patients remains low up to the August, 2009 but then large numbers of cases were reported throughout the India. Saurashtra region is a western most part of Gujarat state in India. From Gujarat state, first H1N1 positive confirmed case was found in June 2009 [10] while

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from Saurashtra region the first case was reported in August 2009 [11]. All positive patients were isolated and monitored carefully, which allowed us to keep track of various clinical features, results of laboratory and radiographic tests and outcome of admitted patients. This report summarizes the clinical and epidemiological characteristics of 62 confirmed pediatric cases of 2009 pandemic influenza A (H1N1) virus infection, hospitalized in various hospitals of Rajkot city of Saurashtra region from September, 2009 to February, 2010.

Methods
Data Sources & study period: From the first reported case of influenza A (H1N1) in May, 2009 in India, the Central Government started preparation regarding the management of infected patients. Gujarat state including Saurashtra region, has also started monitoring and surveillance activities as soon as the positive cases were reported from August, 2009 onwards. All those hospitals having intensive care units were involved in admitting and managing such positive patients in Rajkot. Total 62 pediatric patients found positive and admitted by Pediatric Department of Civil Hospital & two other pediatric hospitals of Rajkot city from 1st September, 2009 to 28th February, 2010 and were included for analysis.

Categorization of Influenza A (H1N1) cases [12]: Ministry of Health & Family Welfare, Government of India had issued guidelines for categorization of influenza A (H1N1).

Table 1 Categorization of influenza A (H1N1) patients as per clinical features		
Category & Clinical Features	**Antiviral treatment**	**RT-PCR* testing & Hospitalization**
Category A: **Mild fever, cough/sore throat, body ache, headache, diarrhea, vomiting. Patient should be monitored & reassessed after 24 to 48 hours**	Not needed	Not needed
Category B (1): **Signs of category A, and/or high grade fever, severe sore throat. Home isolation is advisable.**	May be given	Not needed
Category B (2): **Signs of category A, and/or any of the high risk conditions like, children with mild illness but with predisposing risk factors; pregnant women; persons aged 65 yrs or more; patients with lung, liver, hear, kidney diseases, blood disorders, diabetes, neurological disorders, cancer, HIV/AIDS; long term steroid therapy.**	Given	No testing required but hospitalization may be needed
Category C: **In addition to signs & symptoms of category A & B, any of the following: breathlessness, chest pain, drowsiness, fall in blood pressure, sputum mixed with blood, bluish discoloration of nails; children with red flag signs like somnolence, high & persistent fever, inability to feed well, convulsions, shortness of breath, difficulty in breathing; worsening of underlying chronic conditions;**	Start immediately	Immediate testing & hospitalization

*RT-PCR: Reverse transcriptase polymerase chain reaction.

cases during screening for home isolation, testing treatment, and hospitalization *Clinical case /suspected case definition*: A suspected case was defined as an influenza like illness (temperature $\geq$ 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) assay performed at a laboratory operated under the auspices of the state government [8]. A close contact was defined as a person who lived with or was exposed to the respiratory secretions or other bodily fluids of patients with suspected or confirmed influenza A (H1N1) infection.

Data variables, records & analysis: Children with lab confirmed influenza A (H1N1) admitted during study period were involved for the study. Several types of data collected from the pediatric patients and their records: date and time of admission to hospital/intensive care units (ICU); age; sex; religion; residential status; co-existing conditions; date and time of first symptoms. Also other variables were collected from medical record and statistics department of different hospitals including, duration of treatment in hospitals & ICU; duration between onset of illness and diagnosis; outcome of hospital/ICU admission; time from onset of illness to death; time from antivirus drug started to death.

Data collection and analysis was coordinated by the Community Medicine Department, P D U Medical College, Rajkot. All admitted pediatric patients' admission history and their medical records were assessed from swine flu ward for initial clinico-epidemiological details and from medical record and statistics department after patient discharge/death from Civil Hospital and private hospitals of Rajkot city. Line list number was given to every patient to avoid duplication at any time during study period. Approval by institutional review board was not required because of, this infectious disease was covered under epidemic act and state health department [13] has 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 viral 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 [14]. 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: For categorical variables, the percentages of patients in each category and median time of various variables were calculated and appropriate statistical test (chi square test) was applied. We calculated descriptive statistics for all study variables. All data was entered in MS Excel, and analyzed by using Epi Info software (version 3.5.1) from CDC [15].

Results

Demographic & clinical characteristics: from 1st September, 2009 to 28th February, 2010, total 62 pediatric cases infected with 2009 H1N1 influenza A (table 2) were diagnosed and hospitalized in the PDU Medical College & Civil Hospital and in two other super specialty hospitals in Rajkot. Lab confirmed pediatric cases were reported mainly from Rajkot city (40.3%), followed by Rajkot district (29.0%), while 30.6% cases were from other districts of Saurashtra region. Week wise distribution (figure 1) of influenza A (H1N1) infected patients in Saurashtra region shows that number of cases increases gradually from third week of December, 2009 onwards with sudden increase seen with highest positive cases (11) reported in 4th week of December, 2009 which then remains at high level during January, 2010 followed by gradual fall in number of positive cases in February, 2010. The median age of 2.5 years was reported in positive cases. The median duration of diagnosis of infection was 5 days after onset of illness (1-20 days range). Of the 62 children, majority patients reported with cough (69.4%) and fever (61.3%), vomiting (56.5%), followed by complain of shortness/difficulty in breathing (37.1%) and sore throat (32.3%) (table 3). Total 10 (16.1%) cases had an underlying medical condition. Seizure disorder (6.5%), followed by anemia and thalessemia (3.2%) were main reported co-existing conditions.

Laboratory & radiographic findings: Leukopenia was observed in 22.8% of 57 patients, and lymphopenia in 18.5% of 54 children (table 4). Two third children reported anemia, 21.1% had severe anemia. Thrombocytopenia was found in 22.4% of 49 tested children. Chest X-ray was done in 34 (54.8%) admitted children and among them pneumonia was found in 97.1%.

Treatment outcome: The median time for hospital stay found 7 days for influenza A (H1N1) infected children. Duration of hospital stay 6 days or more was observed in 53.2% patients. All the reported positive patients had received antiviral drug oseltamivir (table 1). Out of 62 positive patients, only 9.7% received antiviral drug within 2 days of onset of illness. After hospital admission, 71% cases survived and discharged, while 29% cases were expired even after receiving treatment including antiviral drugs and intensive care. Among 18 expired patients, two third children belong to < 5 age group. Even after receiving complete course (5 days) of antiviral

Table 2. Baseline characteristics, disease history, and outcomes of 62 hospitalized children infected with 2009 pandemic influenza A (H1N1) virus in Saurashtra region, India (September , 2009 to February, 2010)	
Characteristics	**Value**
Age in year	
Median - year	2.5
Range	4.5 mths – 15 yrs
Age group of positive patients – no. (%)	
<1 year	10 (16.1)
1-5 years	30 (48.4)
6-10 years	11 (17.7)
11-15 years	11 (17.7)
Sex – no. (%)	
Male	35 (56.5)
Female	27 (43.5)
Recent travel to infected region – no. (%)*	0
Referral from general practitioner/ pediatrician – no. (%)	26 (41.9)
Hospital stays in days – no. (%)	
Median (in days)	7
$\leq$2 days	9 (14.5)
3-5 days	11 (17.7)
6-10 days	33 (53.2)
$\geq$11 days	9 (14.5)
Time interval from onset of illness to hospital admission & diagnosis-no. (%)	
Median (in days)	5
<1 day	0
1-4 days	25 (40.3)
5-10 days	34 (54.8)
>10 days	3 (4.8)
Antiviral treatment – no. (%)	
Any antiviral drug received	62 (100)
$\leq$2 days after onset of symptoms	6 (9.7)
Outcome of patients – no. (%)	
Survived	44 (71.0)
Expired	18 (29.0)
Patients kept on ventilators – no. (%)	16 (25.8)
Duration on ventilators in days – median	2
Age group of expired H1N1 influenza A patients – no. (%)	
<1 year	4 (22.2)
1-5 years	8 (44.5)
6-10 years	2 (11.1)
11-15 years	4 (22.2)
Time interval from onset of illness to death – no. (%)	
<1 day	0
1-4 days	1 (5.6)
5-10 days	11 (61.1)
>10 days	6 (33.3)
Time interval from antivirus drug started to death – no. (%)	
<1 day	0
1-4 days	11 (61.1)
5-10 days	7 (38.9)
>10 days	0

* 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.
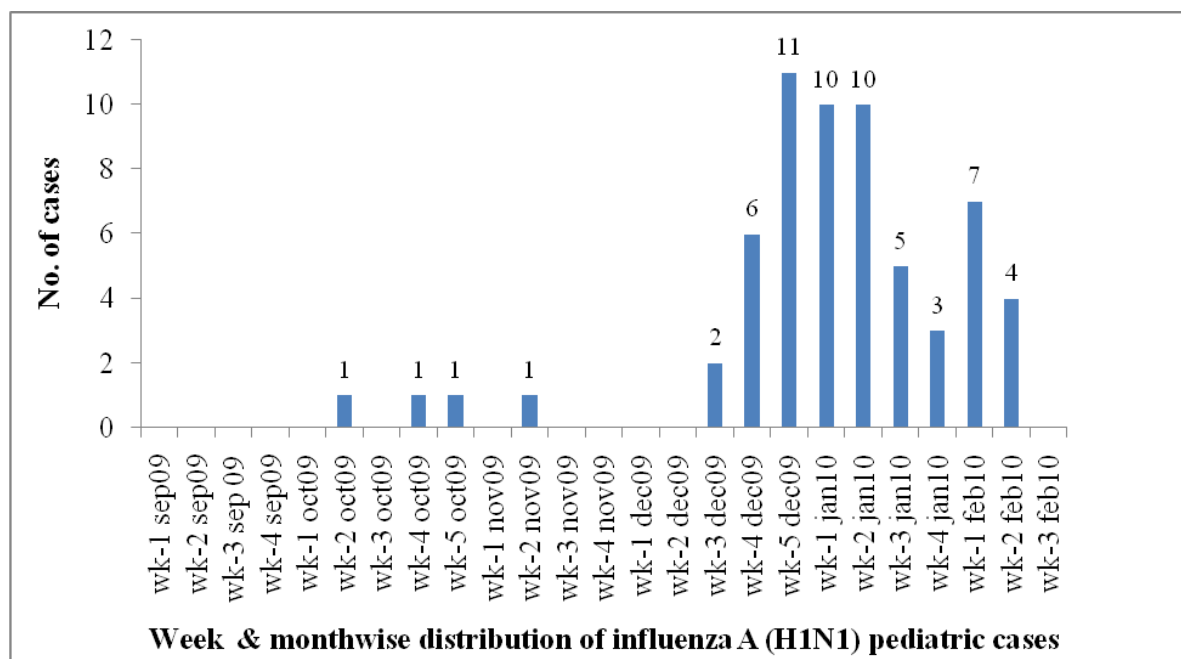
Figure 1. Week wise distribution of hospitalized children infected with influenza A (H1N1) from September 2009 to February 2010 in Saurashtra region, India.

drug oseltamivir 38.9% children were expired. Mortality was found more among children (p<0.05) with delayed referral from general practitioner/ pediatrician to tertiary care centre. Significant number (p<0.05) of critical children reported cough, fever, shortness of breath, presence of co-existing condition. Mortality was found more among children with radiological evidence of pneumonia (p<0.05).

Discussion
This study identified all pediatric patients with confirmed 2009 influenza A (H1N1) belonging to category C [12], who were hospitalized in P D U Medical College & Civil Hospital, and in two other super specialty hospitals in Rajkot from September, 2009 and February, 2010. As no confirmed 2009 influenza A (H1N1) case [11] was

Table 3. Clinical features and coexisting conditions of 62 influenza A (H1N1) infected hospitalized children in Saurashtra region, India	
Characteristics	**Value – no. (%)**
Clinical Features – no. (%)	
Cough	43 (69.4)
Fever ($\geq$37.5 ° Celsius)	38 (61.3)
Sore Throat	20 (32.3)
Shortness/difficulty in breathing	23 (37.1)
Nasal Catarrh	14 (22.6)
Headache	12 (19.4)
Vomiting	35 (56.5)
Coexisting conditions – no. (%)	
Any one condition	10 (16.1)
Seizure disorder	4 (6.5)
Congenital Heart Diseases	1 (1.6)
Thalessemia	2 (3.2)
Pleural Effusion	1 (1.6)

Table 4 Laboratory and radiographic findings on hospital admission in influenza A (H1N1) infected children in Saurashtra region, India*

Characteristic	No. /Total No. (%)
Leukocyte count	
Mean count	8104 ± 5138
Leukopenia (<4,000/ mm^3)	13/57 (22.8)
Leukocytosis (>10,000/ mm^3)	17/57 (29.8)
Hemoglobin gm/dl	9.49 ± 1.96
Anemia	38/57 (66.7)
Mild (10.0-11.0 gm/dl)	12/57 (21.1)
Moderate (8-10 gm/dl)	14/57 (24.6)
Severe (<8 gm/dl)	12/57 (21.1)
Lymphocyte count	
Lymphopenia (<3000/ mm^3)	10/54 (18.5)
Platelet count	
Mean count	$264,945 \pm 156,051$
Thrombocytopenia (<150,000/ mm^3)	11/49 (22.4)
Thrombocytosis (>350,000/ mm^3)	13/49 (26.5)
Elevated alanine aminotransferase (>40 U/liter)	
Any deviation	5/6 (83.3)
$\geq$ 2× the upper limit of normal range	5/6 (83.3)
Elevated aspartate aminotransferase (>40 U/liter)	
Any deviation	1/5 (20.0)
$\geq$ 2× the upper limit of normal range	1/5 (20.0)
Elevated total bilirubin (>1.2 mg/dl)	1/6 (16.7)
Erythrocyte sedimentation rate	
>15 mm/hr in male patients	3/5 (60.0)
>20 mm/hr in female patients	0
Chest X-ray findings	
Done	34/62 (54.8)
Pneumonia found	33/34 (97.1)
Antibiotic treatment received	62/62 (100)
Corticosteroid treatment received	22/62 (35.5)

* Plus-minus values are mean $\pm$ SD.

Table 5 Characteristics of hospitalized children who don't need intensive care and survived and children who need intensive care or died.

Characteristics	Children don't need intensive care & survived (N=43)	Children need intensive care or died (N=19)
Age		
Median – yr (range)	1 (6 mths – 15 yrs)	4 (4.5 mths– 15 yrs)
<5 years	27 (62.8)	12 (63.2)
Referral from general practitioner/ pediatrician* – no. (%)	12 (27.9)	14 (73.7)
Clinical features – no. (%)		
Cough*	25 (58.1)	18 (94.7)
Fever*	21 (48.8)	17 (89.5)
Shortness of breath*	11 (25.6)	12 (63.2)
Coexisting conditions – no. (%)		
Any one condition*	3 (7.0)	7 (36.8)
Seizure disorder	2 (4.7)	2 (10.5)
Congenital Heart Disease	0	1 (5.3)
Anemia	1 (2.3)	1 (5.3)
Thalessemia	0	2 (10.5)
Pleural effusion	0	1 (5.3)
Pneumonia on chest radiography on admission* – no. / total no. (%)	18 (41.9)	15 (78.9)
Antiviral treatment received ≤2 days after onset of symptoms – no. (%)	3 (7.0)	3 (15.8)
Corticosteroid treatment received– no. (%)*	11 (25.6)	11 (57.9)

p<0.05

reported upto 1st week of September, 2009, no data was available for analysis in Saurashtra region.Total 62 pediatric patients reported confirmed and hospitalized during study period and their different characteristics were analyzed. Since 5th October, 2009 guidelines were updated regarding high risk groups and it indicates hospitalization of only patients belonging to category C in separate isolation ward. The median age of pediatric patients found 2.5 years which is lower than in patients from Canada (4.8 yrs) [16] and Argentina (10 yrs) [17].

Present study reported 7 days median hospital stay (1-22 days range), compare to Canada (4 days) [18] and China (8 days) [19]. From onset of illness to hospital admission and diagnosis of infection 5 days median was reported, more than Argentina (4 days) [17]. Significant difference was observed between surviving patients and those who died regarding referral from general practitioner / pediatrician consultation, compare to US [20]. Delayed referral from general practitioner/ pediatrician was reported more among critical children (p<0.05).

The 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 [21]. 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 & 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 and was available in reported region also. Although the evidence of benefit from antiviral therapy is 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 [23]. In present study area, all the influenza A (H1N1) infected children received oseltamivir after hospital admission, but only 9.7% had received it within 2 days of onset of illness, like in Argentina (12%) [17]. Initial primary treatment at general practitioners or pediatrician level and delayed referral to higher center and investigation may be possible explanation for delayed start of oseltamivir in suspected or confirmed influenza A (H1N1) patients. Under an Emergency Use Authorization in US, oseltamivir therapy recommended for 2009 H1N1 infection even if it is initiated more than 48 hours after the onset of illness and also approved its use in children under the age of 1 year [24].

Week wise distribution (figure 1) of influenza A (H1N1) infected children in Saurashtra region shows that number of cases increases gradually from third week of December, 2009 onwards and sudden increase seen with highest positive cases (n=11) reported in 4th week of December, 2009 which then remains at high level during January, 2010 followed by gradual fall in number of positive cases in February, 2010. In India, monsoon season comes to an end in September and October months followed by start of winter from November upto February month end. The atmospheric temperature remains lowest in December, correlating increase in reported number of infected patients with influenza A (H1N1). It also continues in January and as the winter comes to an end by February, number of reported positive cases also shows fall in number. It signifies influenza virus relationship with cold season as maximum number of cases occurs during these months of winter season, also reported by other studies [25, 26].

Likewise in patients of Argentina [17], Canada [18], and France [27], we have reported majority patients having cough (69.4%) and fever (61.3). In a pattern that was similar to that in patients with seasonal influenza, the patients in our study had a low prevalence (16.1%) of underlying medical conditions than in United States (67%) [28]. Various studies reported that, 44 to 84% of adults who were hospitalized with seasonal influenza had an underlying condition [23, 29] and our reported prevalence is even less than the lower end of this range.

In present study, 22.8% of 57 patients had leukopenia; 66.7% of 57 patients had anemia including 21.1% patients having severe anemia [30]; 18.5% children had lymphopenia which is higher than patients in Argentina [17]. Chest radiography was done in 54.8% of 62 hospitalized children and 97.1% of hospitalized patients (p<0.05) had findings on it that were consistent with pneumonia. All hospitalized children with evidence of pneumonia received antiviral drugs and also antibiotics, similar to France (27) but Battinger JA et al [16] reported only 50% influenza A (H1N1) positive children received it in Canada. In the absence of accurate diagnostic methods, patients who are hospitalized with suspected influenza and lung infiltrates on chest radiography should be considered for treatment with both antibiotics and antiviral drugs [31].

Our study has a number of strengths. It represents one of largest series of pediatric patients with severe 2009 influenza A (H1N1) infection covering two seasons of monsoon and winter. It includes children from geographically similar areas, which improves the generalizability of our results to other regions. These observations of epidemiological 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 from only hospitalized children, so patients who become infected in the community and did not go to the hospital were not included in our study. Also, patients belonging to category B (i) or B (ii) who were treated on outpatient basis and not being tested were not included in present study. All diagnostic testing was clinically driven, and other investigations were not obtained in a standardized fashion. Despite the use of a standardized data collection form, not all information was collected for all patients. The findings may be different during future waves, owing to the timely deployment of an effective vaccine, to viral mutation, and to resistance to antiviral drugs.

Conclusion

We have demonstrated that infection related illness affects children with survival of 71% patients after antiviral treatment. The median time for virus detection with use of real-time RT-PCR is 5 days. Mortality reported high among children with radiological evidence of pneumonia.

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