



# A Five Year Profile of Clinical, Epidemiological and Radiological Characteristics of H1N1 Influenza in Children Admitted to Tertiary Care Center in South India

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## Abstract

**Introduction:** Influenza viruses are common etiological agents of acute respiratory illness in children. Clinical presentation varies from flu like illness to severe respiratory and multi organ involvement. This study is done to describe the clinical profile and outcome of hospitalized children diagnosed with H1N1 influenza.

**Methods:** A retrospective descriptive study was done at a tertiary care hospital in South India. It included children with swine flu diagnosed by RT-PCR assay of nasopharyngeal swab during the study period of five years. Data included clinical features, radiological findings, laboratory parameters, clinical course, complications and outcome.

**Results:** There were 118 children with H1N1 Influenza. Median age was 4.35 years (IQR 0.8 - 10.7) with male:female ratio of 0.8:1. Fever was the commonest symptom present in 113 children (95.7%) followed by cough in 103 (87.2%) and nasal discharge (39.8%). Lower respiratory tract signs were present in 38 (27.9%) of the children. Co-morbid illness included malnutrition (33%), pre-existing wheeze (9.3%) and anaemia (6.8%). Anaemia was the common laboratory (36%) followed by thrombocytopenia (21.2%) and leucopenia (18.6%). Interstitial pattern was the commonest radiological finding (27.9%). Complications included secondary bacterial infection (27.1%), severe respiratory distress (16.2%), septic shock and MODS (5.9%), pleural effusion (3.4%), ARDS (2.5%), pneumothorax (1.7%) and PAH (1.7%). Mortality was observed in 5 (4.2%) children.

**Conclusion:** The presence of co-morbid illness is a risk factor for severity of illness. Malnutrition and anaemia were risk factors for hospitalization and mortality.

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## Introduction

Influenza is an acute infectious disease caused by member of ortho-myxo virus family. The clinical presentation of H1N1 infection varies from a usually mild influenza like illness to rapidly worsening pneumonia with ARDS.<sup>1</sup> The seasonal epidemics cause mortality mostly in extremes of age i.e. elderly (> 65 years) and in children. Very few studies are available in India relevant to the clinical profile and outcome of seasonal H1N1 Influenza in children. This study was done to study the clinical and laboratory characteristics of hospitalized children with seasonal H1N1 influenza. Risk factors for hospitalization, severity of illness and mortality were also studied.



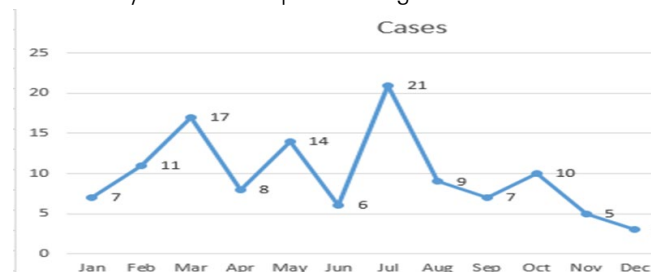
## Methods

This was a retrospective descriptive study conducted in a tertiary care hospital in South India. The study population included children one month to 18 years of age diagnosed with H1N1 Influenza admitted to the Department of Paediatrics during the study period of five years (September 2014 to August 2019). The diagnosis of H1N1 influenza was confirmed by RT-PCR (reverse transcription polymerase chain reaction) assay of the nasopharyngeal / throat swab. Ethical approval for study was obtained from the Institutional Ethics Committee (IEC number 955/2019). Baseline demographic, clinical and laboratory data were collected in the designated pro-forma. Clinical data included signs and symptoms, severity of respiratory distress and concomitant comorbid illness. Subjective symptoms such as headache, sore throat and myalgia were assessed in older children. According to clinical presentation subjects were divided into Category A, Category B, and Category C as per MOHFW (Ministry Of Health and Family Welfare) guidelines.<sup>2</sup> Case definitions included: 1. Suspected case: A person with acute febrile respiratory illness (reported or documented fever, and one of the following: cough, sore throat, shortness of breath, difficulty in breathing or chest pains) with onset: - within seven days of close contact with a person who is a probable or confirmed case of the new influenza (H1N1) virus infection, or - resides in a community where there are one or more confirmed new influenza cases 2. Confirmed case: A confirmed case of Pandemic Influenza (H1N1) virus infection is defined as an individual with laboratory confirmed new influenza (H1N1) virus infection by positive real time reverse transcriptase polymerase chain reaction (RT-PCR).<sup>2</sup> As per orders of central government, MOHFW (Ministry Of Health and Family Welfare) has categorized patients into three (A, B and C) categories: Category A: Those with mild fever, cough and sore throat, body ache, headache, nausea and diarrhoea are included in Category A. Category B: In addition to symptoms mentioned in Category A, they have high-grade fever and are in the high-risk category; they need treatment with oseltamivir. High-risk category includes children with mild illness, pregnant women, and persons over 65, those with lung, liver, heart, kidney, blood or neurological diseases or have been on long-term steroid therapy. Category C: They have breathlessness, chest pain, drowsiness, hypotension, hemoptysis, cyanosis requiring immediate hospitalization. This category also includes children with high and persistent fever, inability to feed, convulsions and difficulty in breathing. Laboratory data including complete blood count, renal function tests and liver function tests. A total leucocyte count of  $< 4000 / \text{mm}^3$  was considered as leukocytopenia and  $> 11000 / \text{mm}^3$  was considered as leukocytosis. Haemoglobin concentrations were assessed according the age specific guidelines of WHO. Thrombocytopenia was categorized into mild, moderate and severe when platelet count was between one to 1.5 lakh /  $\text{mm}^3$ , 50,000 - 1 lakh /  $\text{mm}^3$  and less than 50,000 /  $\text{mm}^3$  respectively. Hepatic transaminase level of

more than two times of the normal level was considered as elevated. CRP (C reactive protein) level of  $> 30 \text{ mg / L}$  was considered as elevated. The PRESS (Paediatric Respiratory Severity Score) score was calculated retrospectively from the clinical documents and respiratory distress was classified into mild, moderate and severe respiratory distress.<sup>3</sup> It includes objective assessment by the clinician in contrast to WHO staging of severe pneumonia and very severe pneumonia. Chest X-ray findings were documented and confirmed by a radiologist. X ray finding was considered to be "diffuse" if there was extensive area involved bilaterally. The pattern of abnormal findings was further classified into four categories namely interstitial pattern (Reticular or peribronchial interstitial shadowing), patchy areas of consolidation, lobar consolidation or diffuse air space consolidation. Treatment details including oseltamivir, supportive therapy and mechanical ventilation were collected. The length of hospital stay was recorded. Outcome was defined in terms of mortality and survival. Descriptive data was expressed as frequencies and percentages. Mean and standard deviation were computed for the variables following normal distribution curve, while median and inter-quartile range were computed for non-parametric data.

## Results

During the study period 118 children with H1N1 Influenza were admitted. The median age of study population was 4.35 years (IQR 0.8 - 10.7) with range of two months to 15.4 years. There was slight female preponderance with male to female ratio of 0.8:1 (44.6% vs.55.4%). According to the clinical category, majority children belonged to category B (69; 58.5%), followed by Category A (27; 22.9%) and Category C (22; 18.6%). 30 (25.4%) children had a family history of contact with swine flu. Prior vaccination history was present in five children. The mean duration of symptoms prior to admission was  $3.5 \pm 1.78$  days with a range of 1 one to five days. The peak incidence was observed in monsoon season followed by winter as depicted in figure 1.



**Fig 1:** Line diagram showing month wise distribution of H1N1 Influenza

Symptoms and signs at presentation are summarized in table 1. Fever was the commonest symptom in 113 children (95.7%), cough in 103 (87.2%), nasal discharge (39.8%), vomiting in 30 (25.4%) children and diarrhoea in 12 (10.2%) children. Five (4.2%) children presented with seizures and altered sensorium. The prevalence of URTI was 68 (57.6%).

LRTI as evidenced by crepitations and rhonchi was noticed in 38 (27.9%) children.

**Table 1:** Signs and symptoms of H1N1 Influenza

Symptom	N (%)	Sign	N (%)
Fever	113 (95.7)	Pharyngitis	69 (58.4)
Cough	103 (87.2)	Tachypnoea	42 (35.6)
Nasal discharge	47 (39.8)	Rhonchi	38 (32.2)
Hurried breathing	36 (30.5)	Crepitations	38 (32.2)
Sore throat	21 (17.7)	Chest retractions	32 (27.1)
Chest indrawing	21 (21.1)	Pallor	30 (25.4)
Myalgia	20 (16.9)	Rhinitis	28 (23.7)
Abdominal pain	12 (5.9)	Spo2 <90%	20 (16.9)
Vomiting	30 (25.4)	Tachycardia	20 (16.9)
Diarrhoea	12 (8.5)	Hepatomegaly	20 (16.9)
Headache	10 (8.5)	Hypotension	8 (6.7)
Seizures	5 (4.2)	Splenomegaly	7 (5.9)
Altered Sensorium	5 (4.2)	Delayed CFT (> 3 sec)	7 (5.9)

**Table 2:** Co-morbidities, laboratory characteristics and complications H1N1 Influenza

Parameter (N = 118)	N (%)
Comorbidities	78 (66.1)
-Malnutrition	39 (33)
-Reactive airway disease	11 (9.3)
-Iron deficiency Anemia	8 (6.8)
-Neurological illness	6 (5)
-Congenital heart disease	5 (4.2)
-Malignancy	3 (2.5)
-Chronic liver disease	2 (1.7)
-Chronic kidney disease	2 (1.7)
-Steroid use	2 (1.7)
Laboratory Parameters	
-Anaemia	43 (36.4)
-Leucopenia	22 (18.6)
-Leukocytosis	15 (12.7)
-Thrombocytopenia	25 (21.2)
-Elevated CRP	26 (22)
-Raised AST	62 (62.5)
-Raised ALT	24 (20.3)
-Hypoalbuminemia	13 (11%)

Complications	
-Secondary bacterial infection	32 (27.1)
-PICU admission	28 (23.7)
-Spo2 <90%	20 (16.9)
-Severe respiratory distress	19 (16.2)
-Inotropic requirement	9 (7.6)
-Mechanical Ventilation	8 (6.7)
-Septic shock/MODS	7 (5.9)
-Pleural effusion	4 (3.4)
-ARDS	3 (2.5)
-PAH	3 (2.5)
-Pneumothorax	2 (1.7)
-AKI	2 (1.7)
Mortality	5 (4.2)

The presence of pre-existing co-morbid illness was present in 44 (37.3%) of children (Table 2). Malnutrition was the most common risk factor present in 39 (33%) children. Baseline laboratory characteristics are depicted in table 2. Anaemia was present in 43 (36.4%) children with a mean haemoglobin of  $10.2 \pm 1.54$  g/dL. Leukopenia was present in 22 (18.6%) children while leukocytosis was present in 15 (12.7%) children. The median total leucocyte count was  $11.2 \times 10^9$  cells/L (6.7, 18.2). Thrombocytopenia was present in 25 (21.2%) children of which 17 (14.4%) had mild, seven (5.9%) had moderate

and one (0.8%) child had severe thrombocytopenia. Serum CRP was elevated in 26 (22%) children.

Chest x-ray was obtained in 86 children where it was normal in 12 (13.9%), interstitial pattern in 24 (27.9%) children, patchy consolidation in 12 (13.9%), diffuse air space consolidation in eight (9.3%) children and lobar consolidation in two (2.3%) children, hyperinflation in eight (9.3%) children. Lesions were bilateral in 38 (82.6%) children and unilateral in remaining eight (17.4%) children. Radiological findings are described in table 3.

**Table 3:** Radiological findings in children with H1N1 Influenza

Radiological Finding	N (%)
1. Interstitial pattern	24 (27.9)
2. Patchy consolidation	12 (13.9)
3. Diffuse air space consolidation	8 (9.3)
4. Hyperinflation	8 (9.3)
5. Pleural effusion	4 (4.6)
6. Lobar consolidation	2 (2.3)
7. Pneumothorax	2 (2.3)

All hospitalized children were treated with oral oseltamivir as per the recommendation.<sup>4</sup> Thirty two (27.1%) children were treated with broad spectrum intravenous antibiotics for secondary bacterial infection. Mean length of hospitalization was  $7.8 \pm 3.12$  (Range: 3 – 20 days). Among complications 28 (23.7%) children required admission to Paediatric Intensive Care Unit (PICU). Mean duration of PICU stay was  $8.2 \pm 4.02$  days (range 3-19 days).

system, 10 (8.5%) children had mild respiratory distress, 13 (11%) had moderate respiratory distress and 19 (16.2%) children had severe respiratory distress. Oxygen saturation of < 90% was found in 20 (16.9%) children. Among 42 (35.5%) children having respiratory distress, 32 (27.1%) children required supplemental oxygen. Twelve (10.2%) children required low flow oxygen via nasal prongs and 13 (11%) children required HFNC (High flow nasal cannula) support. Seven (5.9%) required invasive mechanical ventilation and five (4.2%) children developed ARDS. Three children had severe pulmonary artery hypertension (PAH) in echocardiography. Two children had acute kidney injury (AKI) of which one was diagnosed with acute glomerulonephritis. Considering the outcome, two children left against medical advice. Mortality was observed in five (4.2%) children. Significant clinical characteristics and complications of non-survivors are described in table 4.

## Discussion

Influenza viruses are classified into three types, namely Types A, B, C. The Pandemic Influenza A (H1N1) 2009 virus that caused Pandemic [2009 - 2010] still continues to cause outbreaks of Seasonal Influenza in India, accounting for the disease burden in elderly and children.<sup>5</sup> Studies have shown a preponderance in the incidence of H1N1 influenza during winter season and post-monsoon season.<sup>5-7</sup> We observed peak incidence in monsoon and winter season. This may be attributed to lower ambient temperature during the season.

In this study, positive family history of contact with H1N1 illness was obtained in 30%.

**Table 4:** Clinical, laboratory and radiological characteristics of non-survivors

	Parameter	Case 1	Case 2	Case 3	Case 4	Case 5
1	Age (years)	7	0.9	2	1	3
2	Gender	Female	Male	Female	Male	Male
3	Duration of illness (days)	6	7	5	6	10
4	Underlying comorbid illness/ risk factor	Underweight, Anaemia	None	Malnutrition	Malnutrition, Anaemia	B cell ALL
5	Chest x ray finding	B/L Patchy consolidation	B/L diffuse consolidation	B/L diffuse opacities	B/L diffuse air space opacities	Left Lobar consolidation
6	Laboratory findings	Anaemia, leucocytosis, hypoalbuminemia High CRP	Leukocytosis, High CRP	Anaemia, leukocytosis, elevated AST/ALT, low albumin	Anaemia, leukocytosis, low albumin High CRP	Anaemia, neutropenia, mbocytopenia, AKI
7	Complications	Secondary bacterial sepsis, Septic Shock, MODS	PAH, ARDS, Septic shock, Pneumo-thorax	ARDS, MODS, Refractory shock	ARDS, Pneumothorax	Pseudomonas sepsis, VAP, MODS

Two children required prolonged ICU stay (> 10 days). Nine (7.6%) children required inotropic or fluid support. According to the assessment of respiratory distress by PRESS scoring

In a study done by RR Das et al, 26% children had positive history of contact.<sup>5</sup> Majority of children diagnosed with H1N1 Influenza were in < 5 years age group (72.2 %). This is similar

to most of the studies where under five children were more affected. In our study, majority of the children were in category B (58.5%) followed by category A (22.9%) and C (18.6%). In the studies done by Ramya H S et al, category A comprised 81.4 %, category B 8.6% and category C 10 % respectively.<sup>6</sup>

The commonest symptom among children diagnosed with H1N1 was fever (95.7%) followed by cough (87.2%) and nasal discharge (39.8%). In the current study only hospitalized children were included. However a large proportion of mild H1N1 will never reach the hospital or treated on outpatient basis as illness being self-limited. Gastrointestinal symptoms were seen in about 1/3<sup>rd</sup> of the study population. This finding was also observed by a study done at Pune India by Chaitanya K et al.<sup>7</sup> A high incidence of gastrointestinal symptoms (42%) was found in a study done by Jain S et al.<sup>8</sup> CNS involvement in other studies ranged from 8 - 11% while five children in current study presented with seizures and altered sensorium. In the study done by Chaitanya K et al, pharyngitis (38.88%) was the most common finding followed by crepitations (27.77%) and bronchial breathing (22.22%).

Previous studies have described various risk factors for hospitalization including chronic wheeze, malnutrition, anaemia, immunodeficiency, prematurity, congenital heart disease, developmental delay, chronic kidney / liver disease etc.<sup>6-9</sup> In our study, malnutrition was found in 39 (33%) children followed by wheeze in 11 (9.3%) children. Six children were on immunosuppressive therapy (Three leukaemia on chemotherapy; two steroid therapy, one Nephrotic Syndrome)

We found anaemia in majority of children (36%). This can be explained by high prevalence malnutrition in the study population. High incidence of anaemia was reported from a study done by Chudasama RK et al.<sup>9</sup> Leucopenia was common (18.6%) while leukocytosis was observed in 12.7%. However, in a study done by Virkki R et al, it was found that the finding of leucocytosis and increased CRP was similar in both bacterial and viral pneumonia (48% v 47% and 66% v 60%, respectively), while CRP > 40 mg / L predicted bacterial pneumonia.<sup>10</sup> In the present study, CRP (> 30 mg / L) was elevated in 26 (22%) children. We found elevated hepatic transaminases in majority of children (AST in 62.5%; ALT in 20.3%). Papic et al have also observed frequent elevation of transaminases in influenza infections.<sup>11</sup>

Lobar pneumonia is classically described in bacterial pneumonia while interstitial opacities occur in viral pneumonia.<sup>12</sup> However in a retrospective study done by Guo W et al, it was found that most common radiological finding was bilateral patchy areas of consolidation (63.4%) followed by interstitial opacities (15.7%), diffuse air space consolidation (13.8%) and lobar consolidation (7.1%).<sup>13</sup> However in the current study, we observed interstitial pattern in majority (27.9%) followed by patchy areas of consolidation

(13.9%), diffuse air space consolidation (9.3%) and lobar consolidation (2.3%) in others. Management includes oral oseltamivir, oxygen supplementation, non-invasive / invasive respiratory support and prevention of secondary bacterial infection. In the study done by RR Das it was found that delay in the initiation of oseltamivir was a risk factor for hospitalization and severe illness. However in another study by Ghosh U et al there was no association between early initiation of oseltamivir and severity of illness.<sup>14</sup> Common complications associated with swine flu include acute respiratory failure requiring mechanical ventilation, secondary bacterial infection, sepsis, MODS, ARDS, pneumothorax, pleural effusion. Other rare complications reported include myocarditis, rhabdomyolysis and bleeding diathesis.<sup>15</sup> In the present study, eight (6.7%) required mechanical ventilation. Septic shock and MODS were observed in seven (5.9%) children. Other complications included pleural effusion (N = 4), PAH (N = 3) and pneumothorax (N = 2). Mortality was observed in five (4.2%) children. Mortality reported in various studies ranges from 3-5%.<sup>14,15</sup> Gosh U et al observed a case fatality rate 9.6%, most commonly associated with shock or ARDS. Presence of malnutrition, anaemia and leukocytosis, hypoalbuminemia was common among non-survivors. A three year old male child with B cell ALL who acquired H1N1 pneumonia during consolidation phase of chemotherapy developed pseudomonas sepsis and succumbed. Increased severity and poor outcome of H1N1 in children is known in children with ALL.<sup>16</sup>

## Conclusion

H1N1 influenza usually follows benign course in majority of children. The presence of co-morbid illness is a risk factor for severity of illness. We also found malnutrition and anaemia as risk factors for hospitalization and mortality. Hence improvement of nutritional status and correction of anaemia play a vital role in preventing of pneumonia and its complications. The descriptive nature of the study and data collection performed retrospectively account for its limitations.

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**Conflict of Interest** None

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