Journal of Tropical Pediatrics, 2021, 67(4), 1–14
doi: 10.1093/tropej/fmab084
Original Paper

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An Eight-Year Profile of Children with Influenza A(H1N1) in a Large Hospital in India

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ABSTRACT

As influenza virus A(H1N1) continues to circulate, reports from India have documented mainly respiratory involvement in children. This retrospective chart review of children at a medical college found that from August 2009 to July 2017, 855 children aged 3 months to 15 years had H1N1 influenza of whom 310 (36.3%) were admitted and 29 (9.4% admissions) died. In 2009–12, 76.5% patients presented in August–October but from 2015 to 2017, 89.3% came in January–March. The proportion of under-fives increased from 54.0% in 2009–10 to 77.7% in 2015–17. Among admitted children, 82.6% were under 5 years, 96.1% had respiratory symptoms and 11% had seizures. Six children had encephalopathy of whom four died; two survivors had severe neurological sequelae. Other features included gastroenteritis, otitis media, myositis and hepatitis. Complications included shock (10.7%) and acute respiratory distress syndrome (6.1%). Evidence of bacterial/fungal infection was present in 71 (22.9%). Oxygen was required by 123 children (39.7%), high-dependency/intensive care by 47 (15.2%), 17 (5.5%) received high-flow oxygen and 29 (9.4%) required mechanical ventilation. There were no significantly increased odds of needing intensive care or of dying in children with underlying diseases or among different age groups but those with underlying central nervous system (CNS) diseases had higher odds of needing high-dependency/intensive care [odds ratio (OR) 2.35, $p = 0.046$]. Significantly, children with CNS symptoms had nearly seven times higher odds of needing mechanical ventilation (OR 6.85, $p < 0.001$) and over three times higher odds of dying (OR 3.31, $p = 0.009$).

LAY SUMMARY

H1N1 Influenza ("swine flu") emerged as a global pandemic in 2009 and continues to affect children all over the world. This review of records from a medical college hospital in southern India found that 855 children aged 3 months to 15 years came with H1N1 influenza over 8 years from

August 2009 to July 2017. In 2009-12, over three-quarters of them presented in the rainy season but from 2015-17, almost 90% came in the winter and spring, suggesting a change in the seasonality of the outbreaks, which could impact the choice of dates for annual influenza vaccination. The proportion under 5 years of age increased from 54% in 2009-10 to 78% in 2015-17, suggesting possible immunity in children exposed to earlier outbreaks. Over a third of the children needed admission of whom almost 40% needed oxygen, one-sixth needed high-dependency/intensive care and 1 in 11 admitted children died, emphasizing the severity of this disease. While most children had respiratory symptoms, all organs of the body were affected; 11% of those admitted had seizures and 6 had encephalitis. Children admitted with central nervous system symptoms had an almost 7-fold higher risk of needing high-dependency/intensive care and an over 3-fold higher risk of dying.

KEYWORDS: clinical features, paediatric, swine flu, pandemic influenza

INTRODUCTION

Influenza viruses have caused four of the five global pandemics of the 20th and 21st centuries [1, 2]. In March 2009, swine-origin influenza virus A(H1N1)pdm2009 emerged from Mexico [3], spread to USA and reached India by May [4]. In June, a pandemic was declared by the World Health Organization (WHO) [5], which ended in August 2010 [6], but outbreaks continued in India [7–9], and almost 40% cases were children [10]. Most Indian reports of paediatric H1N1 influenza are from 2009 to 2010 and describe predominantly respiratory symptoms with mortality rates varying from 0% to 29% [10–22]. Though encephalopathy in children had been documented internationally [23–27], only a few cases have been reported from India [15, 21, 28, 29]. We reviewed the clinical features of children treated in our hospital from 2009 to 2017 to provide a comprehensive picture of H1N1 infection among paediatric admissions.

METHODOLOGY

This retrospective study was conducted in a medical college in a semi-rural town in southern India, after obtaining institutional research board clearance. From 1 August 2009 to 31 July 2017, children aged 3 days to 15 years with 'influenza-like illness'(ILI) [30] with fever and respiratory symptoms had had nasal, nasopharyngeal or throat swabs tested for H1N1, using real-time reverse transcriptase–polymerase chain reaction assay (PCR) by an in-house standardized PCR, based on Centers for Disease Control (CDC) protocol [31], using an ABI 7500 machine. In 2009–10, all children with influenza-like illnesses were screened after which only those with underlying diseases, tachypnoea or chest in-drawing were tested. As reports of non-respiratory symptoms emerged, some whose symptoms could be explained by H1N1 infection were also tested. The medical records of all patients aged 3 days to 15 years who were positive for H1N1 influenza in this 8-year period were included in the study and those admitted were further analysed for clinical features, associated diseases, treatment given and mortality.

Descriptive statistics were used for qualitative variables; number and percentage were used for categorical variables. Chi-square test was done to test the association between categorical variables. Association between continuous variables and mortality was assessed using independent Student's *t*-test for normally distributed risk variables. A *p*-value at 5% level significance was considered statistical significant. Analysis was carried out using SPSS software 21.0 version.

RESULTS

A total of 855 of the 6752 (12.7%) children tested were positive for H1N1 influenza in the 8 years of the study (Table 1). Of these, 310 (36.3%) were admitted and 29 died (3.4%, 9.4% of admissions). In 2009, 38.1% children were admitted after which the percentage gradually decreased. As cases again increased after 2015, the admission rate increased to over 50% every year.

Annual and seasonal variation

In the first 6 months from August 2009 to February 2010, 221 children tested positive. The next wave occurred 1 year later, from July to October 2010 when 194 children were positive. In 2011, a smaller

Table 1. Year-wise testing, admissions and deaths of H1N1 positive children from August 2009 to July 2017

Year	2009 (5 months)	2010	2011	2012	2013	2014	2015	2016	2017 (7 months)	Total
H1N1 samples	1046	1366	560	1116	665	241	792	237	699	6752
H1N1 positive	215	200	40	95	1	4	93	8	199	855
(%)	(20.6)	(14.6)	(7.1)	(8.5)	(0.2)	(1.5)	(11.7)	(3.4)	(23.5)	(12.7)
Admitted	82	34	5	17	0	0	51	7	114	310
(%)	(38.1)	(17)	(12.5)	(17.9)	(0.0)	(0.0)	(54.8)	(87.5)	(57.3)	(36.3)
Died	5	4	0	1	0	0	7	1	11	29
(%)	(2.3)	(2.0)	(0.0)	(1.1)	(0.0)	(0.0)	(7.5)	(12.5)	(5.5)	(3.4)
Percentage of deaths among admissions	6.1	11.8	0.0	5.9	0.0	0.0	13.7	14.3	9.6	9.4

peak of 41 children occurred from July to January 2012, followed by 12 cases from March to June 2012 in the fourth year. For the next 2 years, only five cases were detected. Then from November 2014 to May 2015, 89 new cases were diagnosed. There were only nine cases from August 2015 to February 2016. Another large wave of 206 patients started from December 2016 to June 2017, 7 years after the initial pandemic started (Fig. 1).

From 2009 to 2012, the peak number of patients came in the rainy seasons with two-thirds (364 of 550 patients, 66.2%) coming in August and September and three-quarters (421 of 550 patients, 76.5%) from August to October. In 2012, cases appeared even in summer when it was dry with temperatures above 40°C. The last two waves were in winter and spring; from 2015 to 2017, almost 90% patients came from January to March (268 of 300 patients, 89.3%).

Age of patients

The youngest patient was 2 months old and the oldest was 15 years old. Infants and 1-year olds (129 cases, 68 admissions and 7 deaths) had similar rates of admission and death and together contributed to 28.8% of cases, 43.8% of admissions and 44.8% of deaths. The statistics for 2-year olds (102 cases, 41 admissions and 3 deaths), 3-year olds (105 cases, 45 admissions and 4 deaths) and 4-year olds (101 cases, 34 admissions and 3 deaths) were similar to each other. After that, there was a decrease in the percentage contribution to cases, admissions and deaths with increasing age. Adolescents (10–15 years) contributed to only 5.5% of admissions but had the highest death rate among those admitted (23.5%) (Table 2).

Overall, 64.8% cases, 82.5% admissions and 79.3% deaths were under 5 years of age. In 2009–10, 191 of the 415 H1N1 positive children (46.0%) were 5 years of age or above and 71 (17.1%) were 10 years and above. From 2015 to 2017, of the 300 H1N1 positive children, only 67 (22.3%) were 5 years of age or above and 12 (4.0%) were 10 years and above, showing a downward trend in the ages of children presenting to the hospital with H1N1 influenza (Fig. 2).

Presenting symptoms

Of the 310 children who were admitted, all had fever (100%) and 298 (96.1%) had respiratory symptoms at presentation. The next most common was seizures in 34 children (11.0%); 28 (9.0%) came with a history of seizures and 6 developed seizures after admission. This was followed by vomiting and/or diarrhoea as the predominant symptoms in 24 (7.7%). Five children presented with myositis (all of whom were aged 4 years or more), five had otitis media (all of whom were aged 2 years or less), three had hepatitis (elevated alanine transaminase), two had drowsiness without seizures, two had fever alone and one each had stridor, epistaxis, haematemesis (with gastric erosions), headache with neck stiffness and congestive cardiac failure (with underlying mitral regurgitation).

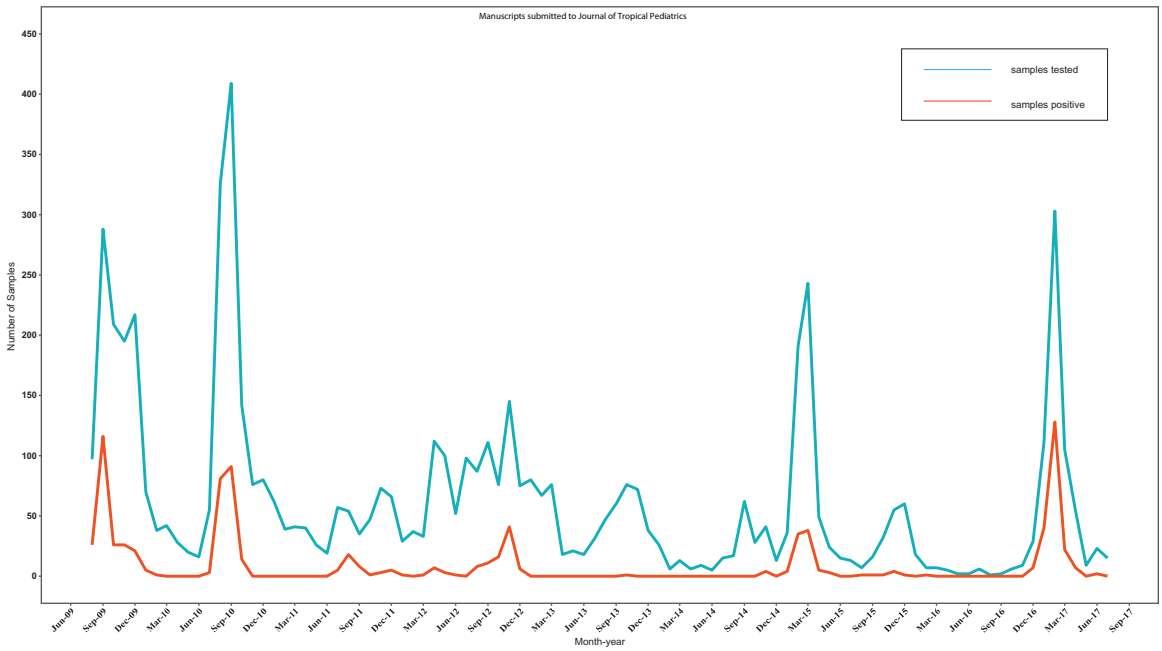

Fig. 1. Seasonal incidence of H1N1 positive children from August 2009 to July 2017.

TABLE 2. Age distribution of cases, admissions and deaths of children with H1N1 influenza

Age (years)	<1	1–4	5–9	10–15	Total
H1N1 positive (% of all cases)	117 (13.7)	437 (51.1)	206 (24.1)	95 (11.1)	855 (100)
Admitted (%)	68 (58.1)	188 (43.0)	37 (18.0)	17 (17.9)	310 (36.3)
Age-wise percentage of all admissions	21.9	60.6	11.9	5.5	100
Death (%)	6 (5.1)	17 (3.9)	2 (1.0)	4 (4.2)	29 (3.4)
Percentage of deaths among admissions	8.8	9.0	5.4	23.5	9.4
Age-wise percentage of deaths	20.7	58.6	6.9	13.8	100

Of the 12 children who did not have respiratory symptoms, 7 had seizures of whom 4 had H1N1 encephalopathy (3 of them also had vomiting and 1 had diarrhoea), 1 (with Dravet syndrome) had status epilepticus and diarrhoea and 2 had febrile seizures with no other symptoms. Of the other five children without respiratory symptoms, two had vomiting alone, one had myositis and two had no other symptom besides fever.

Central nervous system involvement

All 37 children with central nervous system (CNS) symptoms during the H1N1 illness were admitted (11.9% of all admissions); 34 had seizures, 3 of whom had status epilepticus. Two had depressed sensorium without seizures. One child with headache and neck stiffness had been treated for meningitis for 5 days elsewhere; his cerebrospinal fluid (CSF) examination was suggestive of partially treated pyogenic meningitis. Of the children with CNS symptoms, 21 (56.8%) had no underlying CNS disease, including one of those who developed status epilepticus. A past history of seizures was present in 56 of the admitted children but only 13 (23.2%) of them had seizures during the H1N1 influenza illness. Eight of the 37 children died (21.6%).

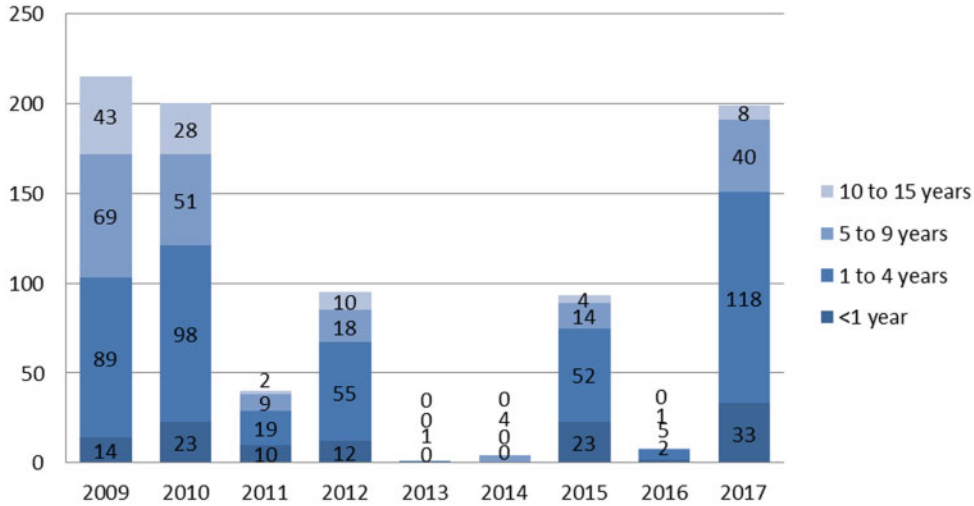

Fig. 2. Year-wise age distribution of children with H1N1 influenza infection from 2009 to 2017.

H1N1 encephalopathy was present in six children (Table 3). The first was diagnosed in 2010. Four years later five more children were diagnosed. All had fever, seizures and depressed sensorium; only one had respiratory symptoms. None had a past history of seizures or neurological problems. One was on treatment for acute lymphoblastic leukaemia with no previous CNS disease and one with congenital adrenal hyperplasia (21-hydroxylase deficiency) was neuro-developmentally normal. The other three were pre-morbidly normal. Two of the three CSF examinations performed had elevated protein levels. There was no pleocytosis but polymorphs were present. The magnetic resonance imaging brain scans showed acute haemorrhagic leukoencephalopathy in one child, features of haemorrhagic viral encephalitis in another and the last had features of viral encephalitis (Fig. 3). Four of the six children with H1N1 encephalopathy died within 14 days of admission. Both the survivors had spastic quadriplegia and severe cognitive impairment at 1 year and 4 months of follow-up, respectively.

Associated disorders

Of the 855 H1N1 patients, 334 (39.1%) had another associated illness; 65 (19.5%) of them had more than one associated disorder. Of the 310 admissions, 166 (53.5%) had an associated disorder. Significantly more of those with associated disorders (166 of 334; 49.7%) were admitted compared to 144 of 521 (27.6%) who had no other disorder ($p \leq 0.001$).

Complications

Like the presenting symptoms, the complications affected almost all organs and systems of the body. The commonest was shock which affected 33 (10.7%) admitted children followed by acute respiratory distress syndrome (ARDS) in 19 (6.1%). Six each (1.9% each) had acute kidney injury, depressed sensorium due to encephalopathy and bleeding diathesis [pulmonary haemorrhage, upper gastrointestinal haemorrhage, disseminated intravascular coagulation (DIC), isolated thrombocytopenia]. Five (1.6%) had pneumothorax, four each (1.3% each) had ventilator-associated pneumonia or liver cell failure, three (1.0%) had status epilepticus and one each had myocardial dysfunction, abdominal compartment syndrome, severe dehydration, neutropenia, hyponatremia, hypoglycaemia and rhabdomyolysis (with diabetic ketoacidosis). Chest X-rays were taken for 294 (94.8%), bacterial/fungal cultures for 267 (86.1%), total and differential leukocyte counts for 295 (95.2%) and C-reactive protein for 60 (19.4%) of the admitted children. Secondary bacterial/fungal infection based on positive cultures and/or radiological evidence of bacterial pneumonia, supported by neutrophilic leukocytosis and elevated CRP, was present in 71 admitted children (22.9%).

Table 3. Case series of children with H1N1 encephalitis

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)	14	4	6	1	10	4
Sex	Male	Female	Female	Female	Female	Male
Date of diagnosis	18 August 2010	20 February 2015	28 March 2015	27 January 2017	30 January 2017	21 February 2017
Underlying Illness	Acute lymphoblastic leukaemia; CSF normal at admission before chemotherapy	Nil	Congenital adrenal hyperplasia (21 hydroxylase deficiency)	Nil	Nil	Nil
Symptoms	Fever and respiratory distress for 4 days, focal seizures, hemiparesis, agitation followed by depressed sensorium for 1 day	Cough for 4 days, fever for 2 days, single seizure followed by depressed sensorium for 1 day	Fever, vomiting, recurrent seizures, depressed sensorium for 1 day	Fever, recurrent seizures, depressed sensorium for 1 day	Fever, vomiting, recurrent seizures, depressed sensorium for 1 day	Fever, vomiting, loose stools for 2 days, recurrent seizures, depressed sensorium for 1 day
CSF	Not done as child was too sick	5 WBC, 4 RBC P60%L40%, protein 153 mg/dl Glucose 58 mg/dl Culture: No growth	Not done as child was too sick	Not done as child was too sick	2 WBC, 40 RBC P20%L80% protein 450 mg/dl glucose 115 mg/dl Culture: No growth Pneumococcal antigen latex negative Viral PCR negative Tuberculosis MGIT culture negative	2 WBC 3 RBC P20%, L 80%. protein 31 mg/dl glucose 64 mg/dl Culture: No growth Viral PCR negative
MRI brain with contrast	Acute haemorrhagic leukoencephalopathy	Haemorrhagic viral encephalitis (possible acute necrotizing	Not done as child was too sick	Not done as child was too sick	Not done as child was too sick	Features of viral encephalitis

(continued)

Table 3. (continued)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
		encephalopathy although characteristic enhancement is not seen)				
Duration of illness (days)	8	19	6	14	3	47
Outcome	Death	Spastic quadriplegia, blind, deaf, severe cognitive impairment (at 1 year follow-up)	Death	Death	Death	Spastic quadriplegia, severe cognitive impairment (at 4 month follow-up)

Note: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

Treatment given

The mean duration of admission was 6.7 days (SD ±6.2 days) and the median was 5 days (IQR 3–7 days). Intensive (ICU) or high-dependency (HDU) care unit was needed by 47 (15.2%) admitted children (36 needed ICU and 11 needed HDU care). Oxygen was given to 123 children (39.7% admissions); 17 of them received high-flow oxygen and 29 required mechanical ventilation, i.e. 37.4% of those needing oxygen received either high-flow oxygen or mechanical ventilation. Of those given oxygen, 109 (88.6%) were under 5 years of age, as were 16 of those needing high-flow oxygen (94.1%) and 21 (72.4%) mechanically ventilated children. Of the 68 admitted infants, 35 (51.5%) needed oxygen. Four of the 17 adolescents aged 10 years and older needed oxygen (23.5%); all (100%) of them required mechanical ventilation. However, there was no statistically significant difference in the need for ICU/HDU care or the need for ventilation among the different age groups ($p = 0.956$). Forty admitted children required inotrope infusions (12.9%), 4 required dialysis (1.3%) and 1 needed a tracheostomy (0.3%). Oseltamivir was given to 277 of the 310 admitted children (89.4%). Those who did not receive oseltamivir were recovering and past the fifth day of illness, except two who died within 48 h of admission, before their test results came. There was no significant difference in the incidence of bacteria/fungal infection or pneumonia, nor was there a significant difference in the need for ICU/HDU care or death, between children who received oseltamivir and those who did not and between children who received oseltamivir within 48 h of the onset of symptoms compared to those who received it later (Table 4). Antibiotics were given to 304 (98.1%) admitted children. The six children who did not receive antibiotics recovered fully without requiring ICU/HDU care.

Mortality

Twenty-nine children died among 855 (3.4%) totally and 310 (9.4%) admissions. Of them, 24 (82.8%) had shock, 18 (62.1%) had ARDS, 13 (44.8%) had hospital-acquired sepsis or ventilator-associated pneumonia, 11 (37.9%) had seizures, 11 (37.9%) had thrombocytopenia or DIC, 7 (24.1%) had acute

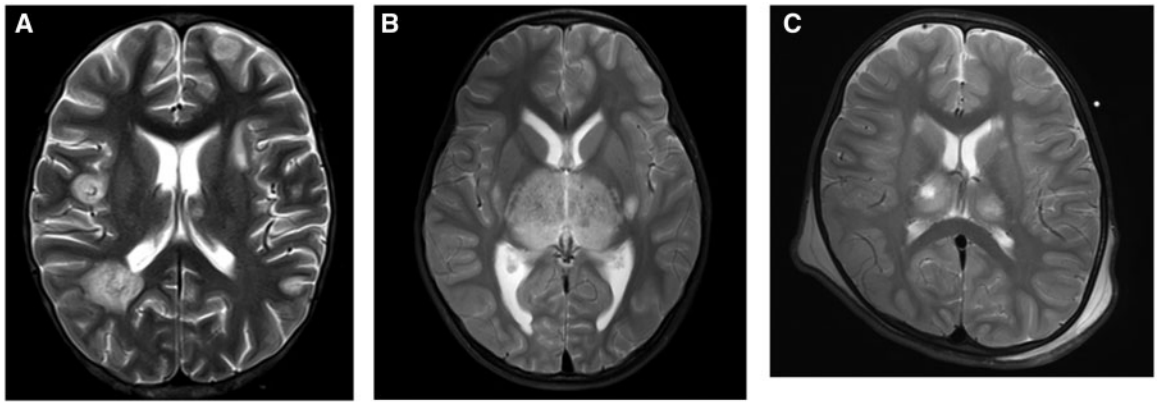

Fig. 3. Magnetic resonance imaging images of the brain of three children with H1N1 encephalopathy. (**A**) An 11-year-old boy (case 1) with acute lymphoblastic leukaemia with no evidence of central nervous system disease; T2W axial image of the brain shows multiple rounded hyper-intense lesions in both grey and white matter of bilateral cerebral hemispheres with hypo-intense foci within (bleeds) suggestive of acute haemorrhagic leukoencephalopathy. (**B**) A previously well 4-year-old girl (case 2) whose T2W axial image of the brain shows bilateral symmetrically swollen thalami and posterior putamen with long TR hyper-intensities and multiple hypo-intense foci within (bleeds) suggestive of haemorrhagic viral encephalitis. (**C**) A previously well 4-year-old boy (case 6) whose T2W axial image of brain shows multiple rounded hyper-intense lesions in bilateral internal capsules, basal ganglia and thalami with cystic areas within suggesting viral encephalitis.

kidney injury, 5 (17.2%) had pneumothorax, 2 (6.9%) had myocardial dysfunction, 1 (3.4%) had hepatitis and 1 (3.4%) had abdominal compartment syndrome. In 2009–10, the mortality rate among admitted children was 7.8% compared to 11.0% in 2015–17 (Table 1), but this difference was not statistically significant ($p = 0.356$).

Risk factors

When comparing the duration of admission, children with underlying diseases, those needing ICU/HDU care, those needing mechanical ventilation and those who died had significantly longer durations of admission ($p < 0.001$). There was no significant difference in the duration of admission required for children of different age groups ($p = 0.956$) (Supplementary Table S1).

When comparing the need for ICU/HDU admission (Table 5), those with CNS symptoms had a nearly seven times higher chance of ICU/HDU admission compared to those who did not [odds ratio (OR) 6.89, $p < 0.001$]. In the multivariate logistic regression, after adjusting with the presence of CNS underlying disease, the odds [OR 6.83, 95% confidence interval (CI) 2.96–15.47] were still statistically significant ($p < 0.001$). There was no significant difference between the different age groups or between those with or without other associated disorders. The OR of those with no underlying disease was similar to those with a non-CNS underlying disease. However, if there was an underlying CNS disease then the OR was more than twice that of children who had no underlying disease (OR 2.35, $p = 0.046$) or those who had non-CNS underlying diseases (OR 2.29, $p = 0.036$), which were statistically significant.

When comparing the need for mechanical ventilation, those with CNS symptoms had a nearly seven times higher odds of needing mechanical ventilation compared to those who did not (OR 6.85, $p < 0.001$) which was statistically significant. Compared to children with no other associated disease, the OR of requiring mechanical ventilation was 1.62 in those with an associated disease, 1.42 in those with non-CNS underlying diseases and more than double (OR 2.22) in those with CNS underlying diseases. However, none of these was statistically significant. There was no statistically significant difference in need for ventilation between children of different age groups.

When comparing mortality, those with CNS symptoms had over three times higher chance of dying

Table 4. Oseltamivir use and bacterial/fungal infections and serious disease (intensive/high-dependency care or death)

(*n*)	Bacterial/fungal infection	*p*	Intensive/high-dependency care or death	*p*
Oseltamivir (277)	65 (23.5%)	0.495	46 (16.6%)	0.263
No oseltamivir (33)	6 (18.2%)		3 (9.1%)	
Oseltamivir within 48 h of onset of symptoms (27)	7 (25.9%)	0.751	6 (22.2%)	0.416
Oseltamivir after 48 h of onset of symptoms (250)	58 (23.2%)		40 (16.0%)	

compared to those who did not (OR 3.31, $p = 0.009$) which was statistically significant. The risk of dying was double if the child had an underlying disease compared to those who did not have an underlying disease (OR 2.08), whether it was a CNS underlying disease or not (OR 2.04 and OR 2.10, respectively) though these differences were not statistically significant. There was no statistically significant difference in deaths between children of different age groups though the OR of death was over three times more among admitted adolescents compared to other age groups.

There were 138 children with asthma/recurrent wheeze as their only associated disorder of whom 38 needed admission, 1 of whom required HDU care and died. The admission rate (27.5%), ICU/HDU admission (OR 0.13, 95% CI 0.02–0.99), mechanical ventilation (OR 0.20, 95% CI 0.03–1.53) and mortality rate (OR 0.24, 95% CI 0.03–1.78) were not more than those of children who had no underlying disease.

DISCUSSION

The WHO declared H1N1 influenza pandemic over in August 2016. In India, 2009 and 2010 had over 20 000 reported cases each year while 2015, 2017 and 2019 had over 42 000, 38 000 and 28 000 cases, respectively [7–9], i.e. the outbreaks occurring 5, 7 and 9 years later had more cases/year than the initial pandemic. Similarly, our study showed large peaks of cases in 2015 and 2017, after the initial peaks in 2009 and 2010. Cases were also reported every year, justifying the label, 'a smouldering pandemic' [32]. H1N1 influenza is considered a 'seasonal' influenza and though this is more pronounced in temperate climates, there is a known predilection for the rainy season in the tropics [33, 34]. This was apparent in the first 4 years of our study. Subsequent waves of patients came more in late winter and spring and cases were also diagnosed throughout the year including summer with temperatures over 40°C. Therefore, the prediction of outbreaks (and advising the timing of vaccination) becomes more difficult and possibly less relevant compared to countries with temperate climates.

When viewed over time, a downward trend in the age of the maximum number of cases was seen. In 2009, 60% of the H1N1 children in our study were under 5 years of age; this gradually increased to 83% in 2017. In USA, in the initial outbreak [35], 60% of cases were under 19 years of age but only 12.9% of them were under five and two-thirds were adolescents aged 10 years and above. In Mexico in 2009, under-fives made up 58% admitted children [3], similar to our study. In Indian studies from 2009 to 2010, 25–40% children presenting to hospitals were under 6 years of age [10, 12, 15]. By 2015, over two-thirds of the children in this study were under 6 years of age [21]. This could suggest that the immunity acquired by children in 2009–10 protected them in subsequent years, so that by 2017, most of the infected children were those who were born after

Table 5. Risk factors for intensive and high-density care, mechanical ventilation and death in children admitted with H1N1 influenza

Variables	Total, *n* (%)	ICU/HDU admission			Mechanical ventilation			Death		
		n (%)	OR (95% CI)	*p*	*n* (%)	OR (95% CI)	*p*	*n* (%)	OR (95% CI)	*p*
Age group (years)										
<1	69 (22.3)	10 (14.5)	1.00		5 (7.2)	1.00		6 (8.7)	1.00	
1–4	187 (60.3)	28 (15.0)	1.04 (0.48–2.27)	0.924	19 (10.2)	1.45 (0.52–4.04)	0.480	17 (9.1)	1.05 (0.40–2.78)	0.922
5–9	37 (11.9)	5 (13.5)	0.92 (0.29–2.93)	0.890	5 (13.5)	2.00 (0.54–7.41)	0.300	2 (5.4)	0.60 (0.12–3.13)	0.545
10–15	17 (5.5)	4 (23.5)	1.82 (0.49–6.70)	0.371	4 (23.5)	3.94 (0.93–16.68)	0.063	4 (23.5)	3.23 (0.80–13.09)	0.100
Underlying disease										
No underlying disease	144 (46.5)	19 (13.2)	1.00		12 (8.3)	1.00		9 (6.3)	1.00	
Any underlying disease	166 (53.5)	28 (16.9)	1.34 (0.71–2.51)	0.370	21 (12.7)	1.62 (0.77–3.41)	0.208	20 (12.0)	2.08 (0.92–4.74)	0.079
Underlying disease—CNS underlying disease										
No underlying disease	144 (46.5)	19 (13.2)	1.00		12 (8.3)	1.00		9 (6.3)	1.00	
CNS underlying disease	42 (13.5)	11 (26.2)	2.35 (1.02–5.45)	0.046	7 (16.7)	2.22 (0.81–6.05)	0.120	5 (11.9)	2.04 (0.65–6.46)	0.225
Non-CNS underlying disease	123 (39.7)	17 (13.8)	1.06 (0.53–2.15)	0.864	14 (11.4)	1.42 (0.63–3.21)	0.394	15 (12.2)	2.10 (0.88–4.98)	0.093
Non-CNS underlying disease vs. CNS underlying disease										
Non-CNS underlying disease	42 (13.5)	11 (26.2)	1.00		7 (16.7)	1.00		5 (11.9)	1.00	
CNS underlying disease	268 (86.5)	36 (13.4)	2.29 (1.06–4.95)	0.036	26 (9.7)	1.86 (0.75–4.61)	0.179	24 (9.0)	1.37 (0.49–3.82)	0.543
Presence of CNS symptoms during this illness										
No CNS symptoms	37 (11.9)	17 (45.9)	1.00		13 (35.1)	1.00		8 (21.6)	1.00	
CNS symptoms	273 (88.1)	30 (11.0)	6.89 (3.25–14.57)	<0.001	20 (7.3)	6.85 (3.04–15.47)	<0.001	21 (7.7)	3.31 (1.35–8.15)	0.009

Note: CNS, central nervous system.

2009–10 and had not been previously exposed to the virus.

Definitions of 'influenza-like illness' as an acute respiratory illness with fever and cough [30, 36, 37] are used as criteria for testing algorithms, though recently body-ache, headache, gastroenteritis, coryza and atypical presentations in infants have been added [30, 36–38]. Most studies of Indian children noted only respiratory symptoms [10–22]. In our study, children presented with symptoms from almost all body systems and one in nine admitted children had CNS symptoms that led to a 7-fold risk of ICU/HDU care and mechanical ventilation requirement and a 3-fold risk of death compared to other children. Though CNS involvement has been reported [15, 21, 23–29], it does not feature in algorithms for H1N1 influenza testing despite this increased risk, as well as the fact that it contributes to the acute encephalitis syndrome cases among children in India [39].

Among children with underlying diseases, the odds for needing ICU/HDU care or mechanical ventilation were significantly higher only in those with underlying CNS diseases. Though the odds of dying were double in children with underlying disease, this was not statistically significant. If the underlying disease was only asthma then there was no increased risk of severe disease or death. The Indian Academy of Pediatrics (IAP) guidelines give those with underlying chronic underlying diseases (except asthma) the second highest priority (after the elderly) and those with asthma the third highest priority for influenza vaccination [40]. The CDC guidelines for vaccination also state that those with asthma as well as children with neurologic conditions as having a higher risk of severe disease [41]. Our study suggests that those with underlying CNS diseases could be placed in a higher priority group and those with asthma alone do not need to be prioritized above others.

There was no significant difference in the risks for intensive care, mechanical ventilation or death in any age group in our study. Both IAP and CDC guidelines [40, 41] state that children under 2 years old should be prioritized for vaccination as they were at risk for more severe disease. This was not evident in this study but it did find that over 44% admitted children were under 2 years of age and 80% admissions were under-fives; thus prioritizing the under-5 population for influenza vaccination could greatly decrease admissions.

A third of the admitted children (and all the adolescents) who needed oxygen needed high-flow oxygen or mechanical ventilation and one in six admissions needed ICU/HDU care. The need for intensive care ranged from 5% to 13% in some developed countries [24, 39, 40] and 28% to 56% in other Indian studies [14, 16, 18]. Thus there is a need for adequate secondary and tertiary care facilities around the country to care for the children with H1N1 influenza.

In this study, the case fatality rate of children admitted with H1N1 influenza was 9.6%, most commonly associated with shock or ARDS, compared to 0–2.3% in developed countries [42–45] and 0–29% [10–22] in other Indian studies. The overall case fatality rate of H1N1 influenza from 2009 to 2019 in India was 6.4%, increasing from 3.6% in 2009 to 8.6% in 2010, with rates of 7.0%, 5.8% and 4.3% in the waves of 2015, 2017 and 2019, respectively [7–9]. This is much higher than global estimates of 0.1–5% with rates as low as 0.01% among children [46]. The higher admission rates and mortality rates from 2015 onwards in this study could have been because in 2009–10, almost all children with ILI were tested, whereas subsequently, mainly those with tachypnoea or risk factors were tested, leading to a higher proportion being admitted, so an inference regarding an increased virulence of the virus could not be inferred.

CONCLUSION

This hospital-based retrospective study showed that H1N1 influenza continues to affect children in India with varying seasonality. There was a downward shift in the age of children over the 8 years of the study. Over 80% of children admitted were under 5 years of age. The children presented with diverse symptoms other than respiratory, including encephalitis; these should be recognized as part of 'influenza-like illnesses' in children. The mortality rate among admitted children was 9.4%. Children admitted with CNS symptoms had a significantly higher risk of needing ICU/HDU care (OR 6.89) or mechanical ventilation (OR 6.85) and of dying (OR 3.31) compared to other children. Among admitted children with

underlying diseases only those with underlying CNS diseases had a significantly higher risk of needing ICU/HDU care (OR 2.35). Recognizing that children presenting with CNS symptoms are at the highest risk of severe disease and mortality and prioritizing the vaccination of under-5 children and those with underlying CNS diseases could decrease the burden of hospitalization and mortality of children with H1N1 infection.

This study was limited by being a retrospective review of hospital records. It was not representative of the disease in the community. Almost 90% of the children had cultures done to look for bacterial infections, but they were not screened for any other respiratory viruses besides influenza viruses, which could possibly have been co-infecting them. Three of the six children with encephalopathy were clinically stable enough to have their CSF tested and of these, only two children had their CSF tested for multiple viruses by PCR. However, as viral co-infections have been documented in only 20–30% children with influenza, we feel this omission may not have had a significant impact [47, 48].

SUPPLEMENTARY DATA

Supplementary data are available at *Journal of Tropical Pediatrics* online.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the contribution of Dr Thenmozhi Mani, PhD, Senior Demonstrator, Department of Biostatistics, Christian Medical College, Vellore for her statistical analysis of the data in this study.

FUNDING

No funding was used for this study.

ETHICS APPROVAL

Institutional Review board clearance obtained.

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