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Research Article

Epidemiological and clinical profile of Influenza A(H1N1) pdm09 in Odisha, eastern India

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ABSTRACT

Epidemic of flu is highly contagious and it spreads through air. In 2009 H1N1 influenza virus emerged after reassortment of North American TRIG and Eurasia Avian like virus of swine and started epidemic in Mexico. The first cases were reported from Hyderabad city on 16th May 2009 in India that spread rapidly within a short span of time. During this period large population of Odisha situated at the eastern side of India was also affected and incidences of H1N1 cases were recorded through state Government surveillance system. In this study real time RT-PCR based diagnosis was conducted for the throat swabs collected from suspected H1N1 cases in Odisha during 2009–2017. A total of 2872 throat swabs were received from 23 different Government and private hospitals and 21.1% positivity was confirmed. The disease affected mostly 46–60 years age group, males (50.6%) being more affected. The clinical features had shown that fever with cough (89.6%) was the most common symptom followed by shortness of breath (72.7%). Post monsoon was the peak season in which most of the cases were reported. Neurological signs, pregnancy, diabetes and hypertension were found to be risk factors for H1N1. The case fatality rate (CFR) was 15%.

1. Introduction

Flu epidemics occur every 6–10 years due to antigenic shift and that exposes human population with a new strain of influenza leading to higher or lower morbidity or mortality. The first human influenza epidemic of 21st century was an Influenza A(H1N1)pdm09 subtype virus that emerged through reassortment of North American Triple reassortment (TRIG) and Eurasian Avian (EA) like viruses of swine [1]. In 2009 world encountered a pandemic due to a novel Influenza A(H1N1)pdm09. First case was reported from Mexico in 2009 which was characterized by rapid spread and caused high morbidity [2] that subsequently spread to more than 214 countries with more than 18,366 deaths [3]. The first case of pandemic Influenza A(H1N1)pdm09 in India was reported from Hyderabad city on 16th May 2009 [2]. After that the virus soon spread to almost all major cities in India.

The pandemic A(H1N1)pdm09 started in the eastern part of Odisha in September, 2009 and spread rapidly to all parts of the state and lasted until the end of year 2010. A large number of Influenza A(H1N1)pdm09 cases (n = 118) and deaths (n = 32) were reported during this pandemic. In next two-three years only sporadic influenza activity was reported i.e. 2 confirmed cases of Influenza A(H1N1)pdm09 were reported in 2012, while only one case confirmed in 2013. Virulence of Influenza A(H1N1) pdm09 virus became once again active and caused another epidemic in 2015. The number of new cases, including fatal cases continued to increase since September, 2015. In this period, we reported 60 new Influenza A(H1N1)pdm09 cases and 5 deaths. We carried out a retrospective analysis of the available information, in order to study the clinico-epidemiological features and establish the magnitude and severity of recent Influenza A(H1N1)pdm09 epidemics in hospitalized patients from the state of Odisha.

2. Materials and methods

This retrospective record based study was conducted among patients

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of all age groups who were hospitalized and suspected of Influenza A(H1N1)pdm09 virus infection. The study was carried out at Virology Laboratory specially designated for influenza testing at Regional Medical Research Centre (ICMR), Bhubaneswar, Odisha, India from 2009 to2017.

A suspected case of Influenza A(H1N1)pdm09 virus infection was defined as per WHO classification of category A and B patients or a patient with influenza-like illness (ILI) with a history of international travel from the country of confirmed Influenza A(H1N1)pdm09, or a close contact with a confirmed H1N1 infected person. ILI was defined as a case presenting with fever $\geq$38 °C with at least one respiratory symptom such as cough, rhinorrhea, or sore throat. Confirmed case defined as a probable case that was tested positive for pandemic Influenza A(H1N1) pdm09 by real-time reverse transcription polymerase chain reaction (rRT-PCR) [4].

All patients with ILI belonging to Category B and C were screened at different Government and private hospitals and medical colleges as per the state health programme and samples referred to viral laboratory of RMRC, Bhubaneswar for laboratory confirmation. The clinico-epidemiological information about all referred cases from these hospitals of the state was collected along with the respiratory sample using proforma prepared by the Ministry of Health and Family Welfare, Government of India. An additional proforma designed by the lab was also used to gather relevant information from all suspects and deaths from Influenza A(H1N1)pdm09. The four medical colleges namely SCB Medical College and Hospital at Cuttack, VIMSAR Medical College at Sambalpur, MKCG Medical College, Berhampur, AIIMS, Bhubaneswar and state capital hospital at Bhubaneswar acted as five nodal centres for screening of Swine flu cases in the state. Besides private or public sector hospitals and medical colleges providing critical care to patients were also part of the Pandemic Flu management chain. After screening samples were referred to virology laboratory, Regional Medical Research Centre, ICMR, Bhubaneswar maintaining cold chain. Laboratory investigations were done with adequate quality control (QC) measures monitored by the National Institute of Virology (NIV), Pune. The QC measures included periodic training of the laboratory staff, standardizing reagents for RealTime PCR and EQAS proficiency testing.

Upper respiratory tract specimens including nasal and throat swabs were collected using plastic shafted dacron swabs placed into viral transport medium (VTM). RNA was extracted using the QIAamp viral RNA mini kit (QIAGEN, Germany) according to the manufacturer instruction. Amplification and detection for each RNA isolate was performed on Applied Biosystem's RealTime PCR 7500 instrument by using primers and probe sets for Influenza A, Universal Swine (swA), Swine H1 (swH1) and RNaseP (Applied Biosystems, USA) as per the CDC real-time RT-PCR protocol (RealTime PCR, Applied Biosystems, USA) [5].

The epidemiological parameters were analysed which included demography, clinical profile and disease outcome. Case Fatality Rate (CFR) was calculated by calculating numbers of deaths out of positive cases. All the relevant data collected and analyzed using Microsoft Excel.

3. Result

Odisha experienced the first pandemic during last quarter of 2009 when 16 districts (58 suspected cases) reported the outbreak. The outbreak was more widespread during 2017 in terms of more number of affected districts (n = 30) and suspected cases (n = 1703). A total of 2872 acute phase nasal/throat/nasopharyngeal swabs, tracheal aspirates from patients hospitalised in 23 different Government and private hospitals in the state of Odisha were referred to the virology laboratory during 2009–2017. Year wise distribution of cases is detailed in Table 1. Of these, 955 (33.2%) samples were positive for Influenza A and out of these cases, 606 (21.1%) samples were positive for Influenza A(H1N1)pdm09 through Real Time PCR. Remaining 349 cases were only Flu A positive. No sample was found positive for Influenza B. During this period 91 deaths occurred with CFR of 15% among the Influenza A(H1N1)pdm09 positive cases. The year wise distribution of Influenza A(H1N1)pdm09 cases (Table 1) reveals highest numbers of cases (n = 1703) received during 2017 with 67.33% H1N1 positivity followed by16.34% during 2010. It was observed that CFR was high with 30.3% in 2010 followed by 15.79% in 2009. During 2015 though the number of confirmed Influenza A(H1N1)pdm09 cases was 12.54% but the CFR was low (6.58).

Table 1
Year wise distribution of suspected/confirmed Influenza A(H1N1)pdm09 cases.

Year	No. of districts	No. of cases	Flu A Positive	No. of confirmed Influenza A(H1N1) pdm09 Cases (%)	No. of deaths (%)	Case fatality (%) of Influenza A(H1N1) pdm09
2009	16	58	28	19(3.14)	3(3.2)	15.79
2010	27	430	167	99(16.34)	30(32.9)	30.30
2011	12	31	3	0(0.00)	0	0
2012	16	52	3	2(0.33)	0	0
2013	13	33	1	1(0.17)	0	0
2014	8	19	0	0(0.00)	0	0
2015	25	444	97	76(12.54)	5(5.4)	6.58
2016	20	102	4	1(0.17)	0	0
2017	30	1703	652	408(67.33)	53(58.2)	12.99
Total	30	2872	955	606 (21.1)	91	15.02

Analysis of age and sex distribution of pandemic Influenza A(H1N1) pdm09 virus suspected and positive cases shown in Table 2. Out of the 606 positive cases; 307 (50.6%) were males representing 10.6% of suspected cases enrolled for laboratory testing. It was observed that the number of positive cases increased with age up to 60 years. Pandemic Influenza A(H1N1)pdm09 positivity rate was higher (29.70%) in the age group of 46–60 years followed by 31–45 years age group i.e. 22.77%.

The clinical features of the confirmed Influenza A(H1N1)pdm09 infected cases had shown that fever and cough were the most common (89.6%) symptom followed by shortness of breath (72.7%) where as sore throat and nasal catarrh were less common symptoms. As per chest radiograph, 47.5% positive cases had signs of pneumonia. It was observed that 18.15% of patients among positives were staying in the community where one or more infected people were Influenza A(H1N1) pdm09 positive (Table 3).

Similarly, among the cases of pandemic Influenza A(H1N1)pdm09 negative but influenza A positives; fever (91.4%) and cough (87.67%) were most common symptoms followed by shortness of breath (77.6%). No follow up data was available for deaths among pandemic Influenza A(H1N1)pdm09 negative cases. It was also noted that there was no difference among pandemic Influenza A(H1N1)pdm09 and Influenza A positives as far as affection of age group is concerned.

During this period 91 deaths were reported among hospitalized Influenza A(H1N1)pdm09 lab confirmed patients (n = 606) (Table 4) belonged to the age group of 46–60 years (Fig. 1). Number of deaths was more among male patients (n = 50, 54.9 %)) than females (n = 41, 45.1%). Out of 91, 52.74% (48) had other underlying conditions like CNS involvement (15.4%) and ARDS (13.2%) etc. Other co-morbid conditions like hypertension, diabetes, coronary artery disease and pregnancy were also noted in low frequency (Table 4).

It was observed that among the deaths there was a mean gap of 5.7 days when the patients were admitted to the hospital after onset of the symptoms. Also a mean gap of 6.4 days between onset of symptom and intake of Tamiflu was noted among the hospitalized patients. Tamiflu was given on same day of admission as per requirement of C-category in 7 cases and 2nd day in 3 cases and beyond 2nd day in 3 cases when respiratory signs progressed. Only 4 cases reported to local doctor's consultation before attending referral hospitals.

Year wise analysis of influenza activity revealed no case of Influenza A(H1N1)pdm09 in 2011 and 2014, whereas only one case was found positive during the years 2013 and 2016. Month wise break up showed highest number of positive cases admitted in the months of August during the respective years with larger case load i.e. in 2010, 2015 and 2017

Table 2
Proportion of suspected and confirmed cases of influenza by age group and gender.

Age group (yrs)	Male			Female			Total		
	Suspected cases	Positive	% Positive*	Suspected cases	Positive	% Positive*	Suspected cases	Positive	%Positive*
<5	88	20	6.51	58	11	3.67	146	31	5.11
5 to 15	70	21	6.84	77	22	7.35	147	43	7.09
16 to 30	304	49	15.96	277	62	20.73	581	111	18.31
31 to 45	323	64	20.84	269	74	24.74	592	138	22.77
46 to 60	426	89	28.9	334	91	30.43	760	180	29.70
>60	437	64	20.84	209	39	13.04	646	103	16.99
Total	1648	307		1224	299		2872	606	

* % positive was calculated for each age group among total positive cases for all age groups.

Table 3
Comparison of clinical features and travel history of suspected and confirmed cases of H1N1.

Clinical condition	Suspected ILI cases (n = 2872)		Positive for H1N1 (n = 606)		Negative for H1N1 (n = 2266)	
	No. of cases	%	No. of cases	%	No. of cases	%
Fever	2481	86.39	543	89.60	1938	85.53
Cough	2417	84.16	543	89.60	1874	82.70
Sore throat	1512	52.65	343	56.60	1169	51.59
Nasal catarrh	895	31.16	197	32.51	698	30.80
Shortness of breath	2284	79.53	441	72.77	1843	81.33
Pneumonia signs	1555	54.14	288	47.52	1267	55.91
Travel details						
Visit to other locality/ state/country	114	3.97	27	4.46	87	3.84
History of close contact with confirmed case of H1N1 positive (within 7 day)	172	5.99	37	6.11	135	5.96
Travel to a community reported of H1N1 cases	237	8.25	53	8.75	184	8.12
Resides in the community where there are one or more confirmed influenza cases	444	15.4	110	18.15	334	14.74

Table 4
Conditions associated with Influenza A(H1N1)pdm09 confirmed deaths(n = 91).

Parameters	Number (%)
Age group(Years)	
<15	8 (8.8)
16–30	15 (16.5)
31–45	19 (20.9)
46–60	35 (38.6)
>60	14 (15.4)
Hypertension	4 (4.4%)
Diabetes	6 (6.6%)
Coronary artery disease	4 (4.4%)
Chronic renal failure	4 (4.4%)
Pregnancy	4 (4.4%)
Neurological complication	14 (15.4)
Acute Respiratory Distress Syndrome	12 (13.2)
Mean gap between onset of illness & hospitalization	5.7 days (Median 5.5)
Mean gap between onset of illness & Tamiflu intake	6.4 days (Median 6)
Mean gap between hospital admission & Tamiflu intake	1.2 days
Survival after hospitalization (Mean period)	3.4 days (Median 2.5)

(Fig. 2). Apart from this a shorter peak was observed during the month of March in 2015.

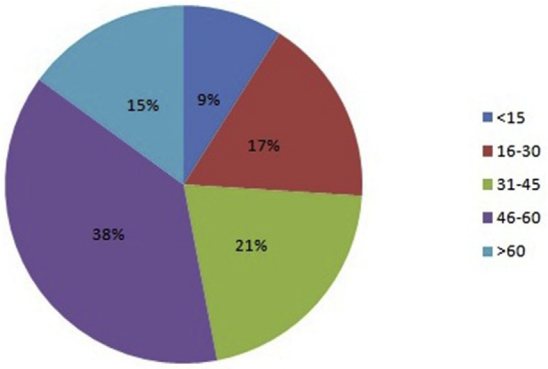

Fig. 1. Numbers of Influenza A 2009 associated deaths by year and age distribution.

4. Discussion

India reported its first case of pandemic Influenza A(H1N1)pdm09 in May 2009 from Hyderabad city, Telangana [2] and Odisha reported first confirmed case of Influenza A(H1N1)pdm09 in October 2009. Through 2009 to 2017, a total of 2872 suspected patients with flu like symptoms were hospitalized and tested for pandemic influenza Influenza A(H1N1) pdm09 infection, of which 606 (21.1%) were found to be positive.

The characteristic feature of this pandemic influenza infection was that, case distribution was disproportionate among all age groups but the patients belonging to 46–60 years followed by 30–45 years of age group found to be more affected than the other age groups, which was also reflected in other studies [6]. This finding also corroborates with the study of Jin Lv et. al, 2017 [7] reporting higher prevalence in elder age group which was not exposed previously. In our study it was observed that infection rate was higher among male individuals (50.6%) than females (49.3%) though the difference is not significant. Similar observation was reported in some studies indicating different behaviour, hormone response and susceptibility to infectious diseases may be the reason for this difference among males and females [8].

Among the confirmed positive cases for Influenza A(H1N1)pdm09 common symptoms observed were fever with cough (89.6%) followed by shortness of breath (72.7%). Similar symptoms of positive cases were also observed in various other studies [9, 10, 11]. This can be used for preliminary diagnosis of Influenza A infection during the influenza season prior to lab diagnosis report.

Month-wise analysis of influenza activity in the present study showed that in our region two peaks of epidemic of Influenza A(H1N1)pdm09 were observed. First peak started in winter season during February–March and second peak was observed in post monsoon season i.e. August–September where second was dominant. Increased influenza activity in monsoon and post monsoon seasons also observed in other studies [12, 13, 14]. First peak started in February–March i.e, in cold &

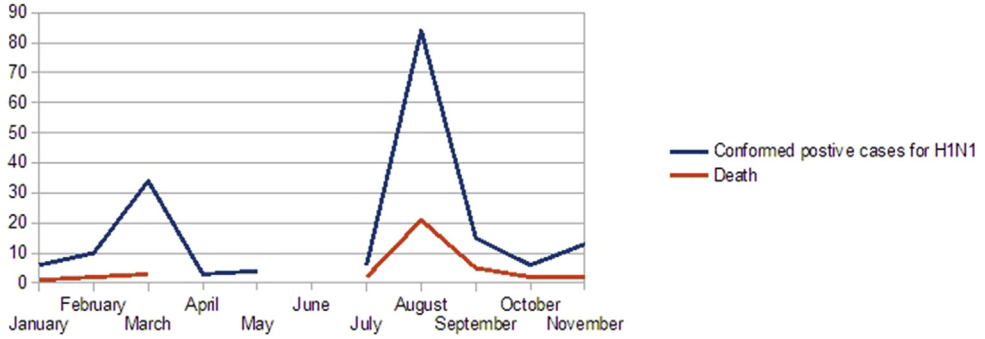

Fig. 2. Month-wise analysis of influenza H1N1 positive cases.

low solar radiation season with a decreasing trend in number of cases during April–June; dry and sunny season which indicated increased influenza activity in cold temperature and in low solar radiation [15, 16, 17]. Exact reason for increased influenza activity in winter is not known but when temperature drops people spend more time indoors, making it easier for the virus to spread in-house (8). No/low number of cases were reported in 2011, 2013–14 and 2016 which may indicate that most of the people were vaccinated during 2009–10 out of Influenza A(H1N1)pdm09 positives for which decline in transmission occurred over 2013–14. On lowering of the host immunity over few years, the population was again susceptible to acquire infection and thus, epidemic resurgence again in 2015. Presumably the situation was repeated in 2016 and again due to lack of immunity majority of the population affected in 2017. This could be due to absence of a programme for flu vaccination in the country, where pandemic panic was the driving force for the community to take a preventive vaccine. This force became weak over time possibly because of the increase in the health system preparedness in handling emergencies and early diagnosis cum treatment measures that reduced the population fear to face the situation.

Studies showed that various risk factors like age, co-existence of chronic diseases, pregnancy and the time from symptom onset to hospital admission, with particularly elevated risk among elders, infants, pregnant women, hypertension, immune-suppression, or delayed hospital admission [18, 19, 20, 21, 22, 23, 24, 25] were associated with severity of morbidity and mortality of Influenza A(H1N1)pdm09. There was underlying disease in at least 49% of documented fatal cases worldwide which is comparable to our study, where 52.74% of the deaths among patients with Influenza A(H1N1)pdm09 infection had reported co-existing chronic illness. In contrast few studies that had shown up to 90% patients having any one underlying conditions like pregnancy, obesity etc. [26]. Neurological complication has been reported in 15.4% among H1N1 2009 associated deaths in our study. A study from California reported neurological complication among 20% of H1N1 infected patients [27]. Although it is not possible to exclude a coincidental association between Influenza A(H1N1)pdm09 infection and neurological illness. Similarly, the infection in some cases might have accentuated an underlying chronic neurological disorder [28]. Pregnancy is a well documented risk factor for severe infection and death in previous pandemics [13, 25] which was also noted in our investigation. It was noted that hypertension and diabetes were other co-morbid conditions, those were associated with 4 (4.4%) and 6 (6.6%) death cases among Influenza A(H1N1)pdm09 infected patients during 2009 which was also reported by previous studies identifying diabetes to be significantly associated with death and severity of disease [14, 15, 16, 17, 18, 19]. We also found presence of other syndromes like Down syndrome with immune compromised state, cerebral malaria and hypothyroidism.

There is considerable variation depending on country and continent as far as age is considered as risk factor for mortality. In some studies it was suggested that Influenza A(H1N1)pdm09 occurred mostly in children [29, 30] where as in other studies age group of 20–49 years was suggested to be more affected [30]. In our investigation age group 20–50 year was also found to have significantly high CFR.

Among the Influenza A(H1N1)pdm09 deaths, average time lag between onset of illness and hospital admission was 5.7 days (Range 0–15 days) and the mean duration of hospital stay of cases leading to death was 3.4 days (Range 0–13 days). There was an average delay of 6.4 days for Tamiflu use. Hence it can be presumed that delay in antiviral therapy can be a main determinant for mortality.

Though our study gives an impression on associated risk factors for mortality, it is limited by certain amount of missing clinical data like pre-existing respiratory disease, small numbers, incomplete records on epidemic dynamics within the population and health structure/referral chain.

According to the data from WHO till March 2010, this new Influenza A(H1N1)pdm09 was estimated to have a case-fatality rate (CFR) of 1.28%. The CFR in our study was much higher (15%) in comparison to other studies [30] which may be due to under reporting of cases of H1N1 especially those of mild illness. The CFR during the wave was high in the fall season.

5. Conclusion

The study results are worth noting on its strengths and limitations. We used detailed hospitalization data from an enhanced surveillance system that covered all hospitals in the state, and individual-level clinical data also allowed us to assess the effect of age, gender and underlying co-morbidities on the risk of death among Influenza A(H1N1)pdm09 patients. It reflects that adults as well as young aged were mostly affected by the wave of this pandemic Influenza A(H1N1)pdm09 suggesting risk of acquisition of infection by most active and productive age group which should be considered in any future preventive plan. Although children are the principal targets in any immunization programme, the adults also need emphasis in such a situation where they are equally susceptible and risk is high due to movement and exposure. The co-morbid conditions associated with mortality should be taken into account and health providers can recommend influenza vaccination on priority to patients with discussed medical conditions. These high-risk patients also need careful attention when become hospitalized with flu like illness. Besides, early antiviral therapy can be targeted during such pandemics in countries like India, where laboratory investigation for all suspected patients may not be feasible.

The ethical clearance for the study was not required since samples were referred to us for diagnosis as a public health concern to mitigate the pandemic. However the investigations were performed following GCP guideline of ICMR as well as Institutional Ethics Committee recommendations for the ICMR Virology grade-1 laboratory project.

Declarations

Author contribution statement

B.Dwibedi: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

J.Sabat: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

S.Dixit; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper. S.Rathore, S.Panda, S.S.Pati, M.Mandal: Performed the experiments; Contributed reagents, materials, analysis tools or data.

S.Subhadra: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

L.M.Ho, B.Thakur: Contributed reagents, materials, analysis tools or data.

S.K.Kar: Conceived and designed the experiments; Analyzed and interpreted the data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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