# A Concurrent Comparison of the Epidemiology and Clinical Presentation of Patients Hospitalized with Pandemic 2009 (H1N1) Influenza and Seasonal Influenza-A in Sub-himalayan Region of Himachal Pradesh

**Thakur C[1*], Singh DV[2], Sharma A, Kumar V[1], Kanga A[2]**


## Abstract

**Background:** Pandemic influenza (H1N1) 2009 emerged in April 2009 and spread widely in India. Although an unprecedented number of cases required intensive care, comparative community-based studies with seasonal influenza strains have not shown any significant differences in clinical symptoms or severity.

**Methods:** The authors performed active surveillance on confirmed influenza-related admissions and compared the clinical profile of patients with pandemic (H1N1) 2009 influenza and patients with seasonal influenza at a tertiary care hospital in Shimla, Himachal Pradesh.

**Results:** A total of 309 patients with flu like illness (category-C) admitted at IGMC were tested for influenza A infection and 58 (18.77%) patients had laboratory confirmed influenza A infection. Out of 58 patients, 22 with pandemic A (H1N1) and 36 with seasonal influenza A infection were analyzed. Compared with seasonal influenza, pandemic A (H1N1) patients were more likely to have sore throat (68.2% vs 16.7%, p=0.001),g.i.t symptoms (63.6% vs 16.7%, p=0.001),myalgia (36.4% vs 13.9%, p=0.047), radiologically confirmed pneumonia(81.8% vs 55.6%, p=0.042), multifocal changes on CXRs (72.7% vs 36.1%, p=0.012) and hypothyroidism as a risk factor(22.7% v 0%, p= 0.002) Patients with pandemic A (H1N1) were more likely to receive oseltamivir (91.3% vs 40.2%, p=0.002). ARDS was the major reason for intensive care unit admission in both the groups. There were no statistical significant differences in the other clinical features, comorbidities, rate of intensive care unit admission and mortality.

**Conclusions:** The clinical features and outcomes of pandemic (H1N1) 2009 influenza and current circulating seasonal influenza A strains were comparable in hospitalised patients. However, since both seasonal and pandemic influenza can lead to significant morbidity and mortality, the impact of pre-existing seasonal influenza should not be underestimated during the pandemic period.


## Introduction

In late March and early April 2009, an outbreak of H1N1 influenza A virus infection was detected in Mexico with subsequent cases observed in many other countries including India and the USA.[1] WHO declared H1N1 as a pandemic on 11th June, 2009. In India first case was seen in Gujarat on July 6th, 2009.

The pandemic 2009 (H1N1) influenza A virus is a novel reassortant virus comprising two swine strains (North American and Eurasian swine viruses lineages), one human strain and one avian strain of influenza A. On the basis of early estimates from Mexico, pandemic 2009 (H1N1) appeared to have higher transmissibility than seasonal influenza but lower clinical severity than the 1918 influenza pandemic. Transmission is mainly person-to-person by droplet infection or droplet nuclei created by sneezing, coughing or talking.

According to other studies, there are some points that differentiate H1N1 2009 from seasonal influenza A like more virulence younger age distribution,[2,3] young age as principal mortality risk factor, novel risk factors such as obesity,[1,4] new symptoms previously not frequently associated with influenza infection, such as diarrhea and vomiting[3,5] and more hospitalization without coexisting medical conditions.[6] Other reports found similarities between 2009 H1N1 and seasonal influenza with regard to rates of viral shedding and transmissibility[7], basic reproduction number, range of severity, clinical symptoms of hospitalized patients, and risk factors for severe disease. The most common risk factors associated with complications in both 2009 H1N1 and seasonal influenza patients were chronic pulmonary, cardiovascular, hepatic, renal, metabolic disorders, neurological diseases, chronic smoking, pregnancy and underlying immune compromise. Confirmation of pandemic 2009 (H1N1) virus infection can be made with rRT–PCR, viral culture or four-fold rise in virus specific neutralizing antibodies.[1]

There are little data directly comparing confirmed pandemic (H1N1) 2009 with contemporaneous seasonal influenza over the same influenza season. The purpose of the study was to compare the epidemiology, clinical features, and outcome of hospitalized patients with pandemic and seasonal influenza A over the same influenza season.

## Methods

This prospective study was conducted in a tertiary care Indira Gandhi Medical College and Hospital (IGMC), Shimla, HP in Category-C patients with flu-like symptoms hospitalized in IGMC, Shimla.

[1]Department of Microbiology, Dr. YSP Government Medical College, Nahan, Himachal Pradesh; [2]IGMC Medical College, Shimla, Himachal Pradesh; *Corresponding Author
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**Table 1: Demographic characteristics**

| Characteristics | | 2009 H1N1 n=22 (%) | Seasonal influenza n=36 (%) |
|---|---|---|---|
| Age (yrs.) | <18 | 2 (9.1%) | 5 (13.9%) |
| | 18-40 | 8 (36.4%) | 19 (52.8%) |
| | 41-60 | 8 (36.4%) | 7 (19.4%) |
| | >60 | 4 (18.2%) | 5 (13.9%) |
| | Mean (Range in years) | 41.88 (0.5-74) | 35.29 (0.5-73) |
| Sex | Female | 11 (50%) | 15 (41.7%) |
| | Male | 11 (50%) | 21 (58.3%) |
| Nosocomial | | 00 | 5 (13.9%) |

All the enrolled patients for this study were categorized as per the recommendations of Ministry of Health and Family Welfare, Government of India[8]. Appropriate clinical specimens (nasopharyngeal or throat swabs, broncho-alveolar lavage, tracheal aspirates and nasopharyngeal or oropharyngeal aspirates as washes) were collected in a viral transport medium,[8] as per the guidelines of the Centers for Disease Control and Prevention (CDC), Atlanta. All the collected clinical specimens were subjected to real-time polymerase chain reaction (rRT-PCR) analysis as per CDC protocol for the detection of the pandemic H1N1-2009 virus.[9]

Pandemic influenza case was defined as PCR-confirmed pandemic (H1N1) 2009 influenza infection and seasonal influenza case was defined as any PCR-confirmed influenza A infection for which infection with pandemic (H1N1) 2009 virus had been excluded. All the positive cases were followed up in their respective wards and their demographic characteristics, clinical profile and outcome was noted.

Statistical analysis were performed using Epi Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA, USA) and SPSS student version 16.0(SPSS Inc, Chicago,USA). Univariate analyses were performed to compare patients with pandemic influenza with those with seasonal influenza with respect to reported symptoms, underlying medical conditions, and treatment. A p value < 0.05 was considered significant.

## Results

During the study period, a total of 309 patients with flu like illness (category-C) admitted at IGMC were tested for influenza A infection. A total of 58 (18.77%) patients had laboratory confirmed influenza A infection and 251 (81.23%) patients did not have influenza A infection. Out of these 58 patients, a total of 22 (37.93%) patients had 2009 H1N1 infection and 36 (62.07%) patients had seasonal influenza A infection.

**Table 2: Interval between onset of symptoms and admission**

| Interval (Days) | 2009 H1N1 n=22 (%) | Seasonal influenza n=36 (%) |
|---|---|---|
| 0-4 | 7 (31.8%) | 17 (47.2%) |
| 5-9 | 15 (68.2%) | 18 (50%) |
| >10 | 00 | 1 (2.8%) |

The number of males (32) were more than the females (26) with the male to female ratio of 1.23:1 in the influenza A positive cases (Table 1). For 2009 H1N1 positive cases (n=22) the number of males were equal to the number of females (11 each) and in seasonal influenza A positive cases (n=36), the number of males (n= 21) were more than the number of females (n=15). Most of the pandemic and seasonal influenza patients in the study were male but the proportion of male patients among the seasonal influenza patients was greater than that among patients with pandemic influenza, 58.3% and 50%, respectively (p=0.139).

In this study the minimum age group for seasonal influenza A was 5 months while the maximum was 73 years. Majority of the patients were in the age group 18-40 years (52.8%). Mean and median age was 35.29 years and 33 years, respectively. The minimum age for 2009 H1N1 was 5 months while the maximum was 74 years. Majority of the patients were in the age group 18-40 years and 41-60 years (both 36.4%). Mean and median age was 41.88 years and 41.50 years, respectively. The pandemic and seasonal influenza affected all the age groups but only 18% (n=4) of the cases with pandemic influenza were > 55 years of age compared with 25 % (n=9) of those with seasonal influenza.

Nosocomial infection was detected in 5 (13.9%) cases in the seasonal influenza group and no case was detected in 2009 H1N1 influenza group.

The percentage of the patients with pandemic influenza who got admitted within 5 to 9 days of onset of symptoms was 68.2% as compared with 50% of patients with seasonal influenza (Table 2).

### Clinical and Diagnostic Features

The most common symptoms in pandemic influenza cases were fever (100%), cough (95.5%) and dyspnoea (90.9%) followed by sore throat (68.2%), g.i.t symptoms (63.6%), cyanosis (50%), rhinorrhea (36.4%), myalgia (36.4%) and conjunctivitis (22.7%)and in seasonal influenza the most common symptoms were cough (94.4%), fever (91.7%), and dyspnoea (77.8%) followed by rhinorrhea (38.9%), cyanosis (25%), chest pain (16.7%), g.i.t symptoms (16.7%) and sore throat (16.7%) (Table 3). Sore throat, myalgia and g.i.t symptoms (diarrhoea and vomiting) were significantly more common in patients with pandemic influenza than seasonal influenza (p=.0001, p=.047 and p=.0001, respectively).

Overall 31.8% of patients with pandemic influenza and 38.9% of patients with seasonal influenza had leucocytosis and none of the patient in both groups had leucopenia. Only 9.1% of patients with pandemic influenza and 11.1% of patients with seasonal influenza had lymphopenia and none of the patient in both groups had lymphocytosis. Pneumonia was reported in significantly higher proportion of patients with pandemic influenza as compared with seasonal influenza (81.8% v 55.6%, respectively; p=.042).

Chest X-rays (CXR) were taken of all the patients in the study and normal CXR was significantly more common in patients with seasonal influenza as compared with pandemic influenza (41.7% v 18.2%, respectively; p=.012). In CXRs with abnormal findings, multifocal changes were significantly more common in patients with pandemic influenza as compared with seasonal influenza (72.7% v 36.1%, respectively; p=.012), whereas the unifocal changes and pleural effusion were more common in patients with seasonal influenza. Blood and sputum culture were taken in all the patients with pneumonia. Blood cultures were taken in 18 patients with pandemic influenza and only in one patient, S aureus was isolated and out of 20 seasonal influenza patients only in four patients significant pathogen was isolated (S. aureus 2, K pneumoniae 1, CoNS 1). Sputum cultures were positive in two patients with pandemic influenza (S pneumoniae 2) and in three patients with seasonal influenza pneumonia (S

**Table 3: Clinical and diagnostic features**

| Feature | 2009 H1N1 n=22 (%) | Seasonal influenza (n=36) n=36 (%) | p value |
|---|---|---|---|
| Fever | 22 (100%) | 33 (91.7%) | 0.170 |
| Rhinorrhoea | 8 (36.4%) | 14 (38.9%) | 0.851 |
| Sore throat | 15 (68.2%) | 6 (16.7%) | 0.0001 |
| Cough | 21 (95.5%) | 34 (94.4%) | 0.869 |
| Chest pain | 4 (18.2%) | 6 (16.7%) | 0.885 |
| Dysnoea | 20 (90.9%) | 28 (77.8%) | 0.206 |
| GIT symptoms | 14 (63.6%) | 6 (16.7%) | 0.0001 |
| Myalgia | 8 (36.4%) | 5 (13.9%) | 0.047 |
| Hemoptysis | 3 (13.6%) | 2 (5.6%) | 0.296 |
| Cyanosis | 11 (50%) | 9 (25%) | 0.053 |
| Hypotension | 00 | 3 (8.3%) | 0.170 |
| Altered sensorium | 1 (4.5%) | 2 (5.6%) | 0.869 |
| Conjuctivitis | 5 (22.7%) | 1 (2.7%) | |
| TLC | | | 0.594 |
| Normal | 15 (68.2%) | 22 (61.1%) | |
| Leucocytosis | 7 (31.8%) | 14 (38.9%) | |
| Leucopenia | 00 | 00 | |
| Lymphocyte count | | | 0.810 |
| Normal | 20 (90.9%) | 32 (88.9%) | |
| Lymphocytosis | 00 | 00 | |
| Lymphopenia | 2 (9.1%) | 4 (11.1%) | |
| Positive blood culture | 1/18 (5.5%) (*S. aureus*) | 4/20 (20%) (*S. aureus* 2, *K. pneumoniae* 1, *CoNS* 1) | |
| Positive sputum culture | 2/18 (11.1%) (*S. pneumoniae* 2) | 3/20 (15%) (*S. pneumoniae* 2, *K pneumoniae* 1) | |
| Pneumonia (radiologically confirmed) | 18 (81.8%) | 20 (55.6%) | 0.042 |
| CXR findings | | | |
| Normal | 4 (18.2%) | 15 (41.7%) | |
| Unifocal changes | 2 (9.1%) | 8 (22.2%) | |
| Mutifocal changes | 16 (72.7%) | 13 (36.1%) | 0.012 |
| PLEF | 1 (4.5%) | 5 (13.9%) | |

**Table 4: Risk factors**

| Risk Factor | 2009 H1N1 n=22 (%) | Seasonal influenza n=36 (%) | p value |
|---|---|---|---|
| Smoking | 9 (40.9%) | 15 (41.7%) | 0.956 |
| Asthma | 2 (9.1%) | 4 (11.1%) | 0.810 |
| COPD | 6 (27.3%) | 10 (27.8%) | 0.967 |
| Diabetes | 4 (18.2%) | 3 (8.3%) | 0.272 |
| Obesity | 4 (18.2%) | 2 (5.6%) | 0.130 |
| Immunocompromised | 1 (4.5%) | 3 (8.3%) | 0.588 |
| Cardiac disorders | 6 (27.3%) | 5 (13.9%) | 0.214 |
| Chronic Liver Ds. | 1 (4.5%) | 0 | 0.204 |
| Chronic Kidney Ds. | 2 (9.1%) | 2 (5.6%) | 0.614 |
| Thyroid Dysfunction | 5 (22.7%) | 0 | 0.002 |
| Other concurrent infections | 3 (13.6%) | 10 (27.8%) | |

**Table 5: Management and outcome**

| Treatment and outcome | 2009 H1N1 n=22 (%) | Seasonal influenza n=36 (%) | p value |
|---|---|---|---|
| Oseltamavir | 22 (100%) | 24 (66.7%) | 0.002 |
| Antibiotics given | 22 (100%) | 35 (97.2%) | 0.439 |
| Oral steroids | 5 (22.7%) | 9 (25%) | 0.889 |
| ARDS | 3 (13.6%) | 4 (11.1%) | 0.779 |
| ICU admission | 4( 18.2%) | 5 (13.9%) | 0.668 |
| Hospital stay (median; range in days) | 7 (1-14) | 5 (2-26) | 0.606 |
| Mortality | 4 (18.2%) | 4 (11.1%) | 0.779 |
| Interval b/w symptom onset and start of oseltamavir (mean) | 5.3 days | 5.9 days | 0.139 |

pneumoniae 2, K pneumoniae 1).

## Risk Factors

The most common risk factors/ underlying medical disorders (Table 4) in pandemic influenza cases were smoking (40.9%), COPD (27.3%), cardiac disorders (27.3%), and thyroid dysfunction (22.7%). The most common risk factors/underlying medical disorders in seasonal influenza cases were smoking (41.7%), COPD (27.8%), other concurrent infections (27.8%) and cardiac disorders (13.9%). Univariate analysis showed that thyroid dysfunction as a risk factor was significantly more common for pandemic influenza patients (**p=0.002**). Other concurrent infections were reported in three pandemic influenza patients (HIV 1, pulmonary tuberculosis 2) and in ten seasonal influenza patients (tuberculosis-4, Scrub typhus-2, purpeural sepsis-2, *K pneumoniae* septicemia-1, SABE with CoNS-1). Obesity was reported more commonly in patients with pandemic influenza as compared with seasonal influenza (18.2% vs 5.6%), though not statistically significant (p=0.13).

## Management and Outcome

The proportion of patients treated with oseltamivir (Table 5) was significantly higher in pandemic influenza as compared with seasonal influenza (100% v 66.7%, respectively; **p=.002**). The mean lag time between illness onset and starting antiviral treatment was 5.3 days for patients with pandemic influenza and 5.9 days for patients with seasonal influenza (p = 0.39).Similar proportion of patients in both groups were treated with antibiotics and oral steroids. The median duration of hospitalization was 7 days for patients with pandemic influenza and 5 days for those with seasonal influenza (p = 0.13). Although the findings were not significant, a trend toward longer hospital stays did appear for those with pandemic (H1N1) 2009 versus seasonal illness, based on the proportion of patients hospitalized an additional ≥7 days (54.5%% vs. 44.4%, respectively). Similar proportion of patients in both groups had ARDS and required ICU admission. Patients with radiologically confirmed pneumonia commonly required admission to ICU; 23.6% of patients with pneumonia (9/38) were admitted to ICU- four with pandemic and five with seasonal influenza. The mortality was higher in pandemic influenza patients than in seasonal influenza patients (18.2% vs. 11.1%, respectively), though statistically not significant (p=.779). Out of eight patients in both the groups(four each) who expired, five (62.5%) had ≥1 underlying risk factor/comorbidities. One pandemic influenza patient and two seasonal influenza patients expired without any underlying risk factor/ comorbidities.

## Discussion

This study compares the demographic characteristics, clinical profile and outcome of hospitalised patients with pandemic H1N12009 influenza with the other seasonal influenza A strains infection. A major strength of our study was that the cases of seasonal and pandemic H1N12009 influenza occurred concurrently, which allowed us to make a direct comparison.

Our study shows that there was significant co-circulation of other seasonal A viruses in India during the current pandemic also shown in a study by Chudasama et al[10] done in Gujarat.

This study showed that pandemic and seasonal influenza affected all age groups and the mean age of pandemic influenza cases was higher than the seasonal influenza cases (41.8 years vs. 35.3 years). However, less number of cases with pandemic influenza was observed in > 55 years of age. Similar findings were reported by 6% (49/871) of the study participants with pandemic influenza were >55 years Carcione et al[3] only 3.15% were older than 60 years Chang et al[11] 9.2% positive cases were reported in 2015 in a age group of >65 years in a recent study from Rajasthan by Sharma et al.[12] The relative sparing of adults in this age group is presumably due to the exposure of persons in this age group to antigenically related influenza viruses earlier in life resulting in the development of cross-protective antibodies.[13]

We observed that there was no difference in terms of sex distribution of the cases similar to other studies.[14,15] Maximum number of patients in both the groups in our study got admitted within mean time of 5 days which is similar to that reported by Chudasama et al[10] and comparable to mean of 4 days reported by Chang et al.[11]

In our study, the most common symptoms in both the groups (pandemic influenza and seasonal influenza) were fever, cough and dyspnoea similar to[11,15,16] common clinical features, fever (100%), cough (90·7%), sore throat (85·7%) as reported in a recent study done by Gurav et al[17] but sore throat, myalgia and g.i.t symptoms (diarrhoea and vomiting) were significantly more common in patients with pandemic influenza than seasonal influenza, p=.0001, p=.047 and p=.0001, respectively.

There was no difference between the two groups in the mean total white blood cell count and lymphocyte count. Positive blood cultures were observed more commonly in seasonal than in pandemic influenza cases (20% vs. 5.5%). This is consistent with other studies suggesting that bacterial pneumonia following H1N1/09 influenza is less common than viral pneumonitis. Pneumonia (radiologically confirmed) was reported in significantly higher proportion of patients with pandemic influenza as compared with seasonal influenza (81.8% v 55.6%, respectively; p=.042). Abnormal chest radiographs and multifocal changes were also significantly more common in pandemic influenza group (p=0.012).

We observed that smoking and COPD were the most common risk factors/underlying medical disorders in both the groups also reported by Carcione et al,[3] Cheng et al[16] and Murata et al.[18]

In our study thyroid dysfunction (hypothyroidism) as a risk factor was found to be significantly more common for pandemic influenza patients (p=0.002). Obesity was reported more commonly in patients with pandemic influenza in this study, though not statistically significant (p=0.13) and also by Bautista et al,[13] To et al,[19] Cui et al[20] and Cheng et al.[16] This is similar to the previous study of Morgan et al.[14] The complication-rate in patients with respiratory co-morbid conditions was significantly higher as compared to those without.

In our study the proportion of patients treated with oseltamivir was significantly higher in pandemic influenza as compared with seasonal influenza (p=.002) probably due to the perceived higher risk of complications in this group of patients. All other similar studies done by Carcione et al,[3] Chang et al,[11] Cheng et al[16] and To et al[19] have reported the same. Most studies of oseltamivir were performed in patients with seasonal influenza, and it was shown that treatment with an antiviral reduced the mortality rate in hospitalised patients with seasonal influenza.

The median duration of hospitalization in both the groups was not statistically significant in this study and also in studies by Chang et al,[11] Cheng et al[16] and Carcione et al.[3]

Similar proportion of patients in both groups had ARDS and required ICU admission in our study, in contrast to higher proportion of pandemic influenza cases reported by Chang et al[11] and Cheng et al[16]. All the patients in both the groups admitted to ICU had multifocal changes in their chest X-rays and our finding highlights the importance of lower respiratory tract involvement, regardless of strain, as a marker of severity of disease and admission to intensive care. The mortality was higher in pandemic influenza patients in our study, though it was not found to be statistically significant. Six out of the eight deaths in the study were due to ARDS.

### Conclusion

During the study period it was found that patients hospitalized with symptoms of flu like illness were predominantly suffering from seasonal influenza A infection as compared to pandemic 2009 (H1N1) infection. Our findings show that the clinical profile and outcome of the patients with pandemic 2009 (H1N1) influenza infection is comparable to those with seasonal influenza A infection in terms of sex distribution, symptomatology, total white blood cell count and lymphocyte count, blood and sputum culture positivity for bacterial infections, common risk factors, treatment with antibiotics and oral steroids, duration of hospitalization, ARDS and ICU admission, mortality and mode of death. However, pandemic influenza patients reported sore throat, myalgia, g.i.t symptoms, hypothyroidism, multifocal changes on chest radiographs, pneumonia and treatment with oseltamivir significantly more commonly than seasonal influenza patients. We must not lose sight of the fact that influenza remains an important cause of illness and death. Therefore, influenza vaccination should be advised to all the high risk groups, which currently is not being done in our setting.

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