

Clinical Outcome of Patients Hospitalized in a Tertiary Care Hospital of Nepal with Confirmed Influenza A/pdm 09(H1N1) in 2018/2019

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ABSTRACT

Background: It is important to monitor the cases affected by Influenza A/pdm09 as it is difficult to predict the behavior of Influenza A/pdm09 virus as a seasonal influenza. This study aimed to measure the clinical outcomes of patients with Influenza A/pdm 09 in a tertiary care hospital of Nepal in post pandemic period.

Methods: A retrospective study was conducted in a tertiary care hospital of central Nepal to record the confirmed cases of Influenza A/pdm 09 from April 2018 to March 2019. The medical records of those patients whose throat sample had been sent to laboratory for testing Influenza A/pdm 09 were referred. The outcomes were then abstracted from the hospital system/medical record department.

Results: Among 141 influenza suspected cases, 35.5%(N=50) were Influenza A/Pdm 09 positive. Both male and female were equal in distribution (N=25). Most positive cases were from the age group of 15-64 yrs. Out of total, 72% (N=36) with Influenza A/pdm 09 were discharged after treatment whereas case fatality rate was 22% (N=11). Twenty-one positive cases were admitted in intensive care unit in which 52.4% expired. The average length of stay in I.C.U and mechanical ventilation were 6.4 days and 5.8 days respectively.

Conclusions: This study in post pandemic period in Nepal shows the outcomes of patients with confirmed influenza A/pdm 09 in a year time period with comparably high case fatality rate.

Keywords: Influenza A/pdm 09; Nepal; post pandemic, retrospective

INTRODUCTION

Influenza caused by virus (A and B) can cause varying severity from asymptomatic to complicated illness or death.^{1,2} After WHO declared that Influenza A/pdm 09 (H1N1) is post pandemics(2010), the level of concern has decreased but it is not clear if post pandemic influenza differ substantially with pandemic influenza in terms of clinical manifestation and outcomes.^{3,4} There have been several studies which explain that the morbidity and mortality caused after influenza pandemics on later years are high every year in other parts of world but not a single study has been carried out in our country Nepal.⁵⁻⁸ This retrospective study tries to narrow this knowledge gap by providing the initial information on behavior of Influenza A/pdm 09 (H1N1) in post pandemic era in Nepalese society. The objective of this study was to demographic profile, seasonal variation and case fatality rate of Influenza a/pdm in tertiary care hospital of Nepal.

METHODS

A retrospective study was done in a tertiary care hospital of Nepal. Grande International hospital is a 200 bed (ICU 17 beds) referral hospital located in Central Nepal. All the admitted cases from March 2018 to February 2019 whose throat sample had been sent to test influenza panel to laboratory with the suspicion from Clinicians were included in the study. Firstly, the cases were identified from the pharmacy record by selecting the patients to whom oseltamivir medicine was dispensed with suspicion of H1N1 in that specific time period. Once the cases were identified, the individual medical file was accessed from medical record department to note the details. The occupancy of the hospital in the year 2018 was 0.6. The reason for selecting specified time period was due to availability of good number of confirmed cases and to include the waves during a year period based on the literature reviews. The throat samples were sent mainly to National Influenza Center

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under National Public Health Laboratory (NPHL) as epidemiology department and control division (EDCD) of Nepal provides free antiviral medicine (oseltamivir) to the positive cases but the test report of influenza should be of NPHL. The samples were only sent to test for influenza based on IDSA guidelines on seasonal influenza.⁹ The sample (throat swab) was collected into viral transport medium (VTM) provided by NPHL itself which should be transported on ice box within 48 hours after collection. In few cases, when the patient was critical requiring Intensive care, the sample was sent simultaneously to NPHL and private laboratories named DECODE genomics and research center. The reason for choosing private laboratory was solely for speed test report. Both laboratories employ real time polymerase chain reaction (RT PCR) method to determine the strain of Influenza.

All confirmed cases were classified into three age groups i.e 0-14yr (children), 15-64yr (adult) and 65+ yr (elderly).¹⁰ Further, gender classifications was also made as male and female. The clinical outcomes of positive cases influenza A/pdm 09(H1N1) were classified into four classes: 1) Discharged after treatment 2) Expired 3) Leave against medical advice(LAMA) and 4) Discharge on patient's request(DOPR). The length of stay in ICU and mechanical ventilator were also calculated. All the information was entered and calculated using Microsoft Excel 2007.

Mean, standard deviation was calculated for age variables.

RESULTS

A total of 141 admitted cases were suspected of influenza A (H1N1) in a period between April 2018 to March 2019. Among these 50 cases were positive for Influenza A/pdm 09 (H1N1) and four were positive for Influenza B. The age and gender distribution of patients with positive Influenza A/pdm 09 are as below:

Table 1. Age distribution of H1N1 confirmed cases.

Age Group	Total	Male	Female	SD
0-14 yr	1	1	0	1
15-64	44	22	22	13.3
65+yr	5	2	3	7.2
Overall	50	25	25	

As per province, majority of positive cases are from province 3.

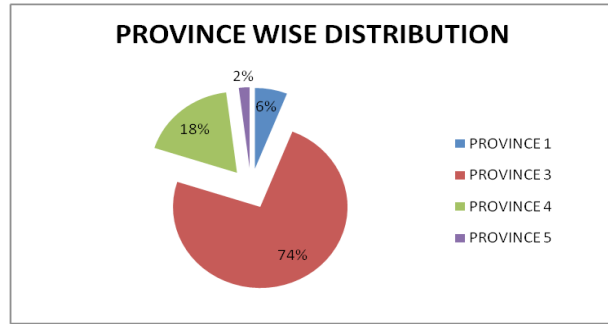


Figure 1. Distribution of positive cases (H1N1) as per province of Nepal.

The clinical outcomes of influenza A/pdm 09(H1N1) positive cases were as follows:

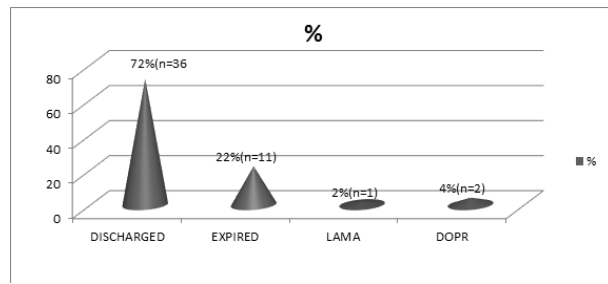


Figure 2. Clinical outcomes of patients with confirmed H1N1/pdm 09.

The cases of influenza A/pdm 09 were observed maximum during January and February.

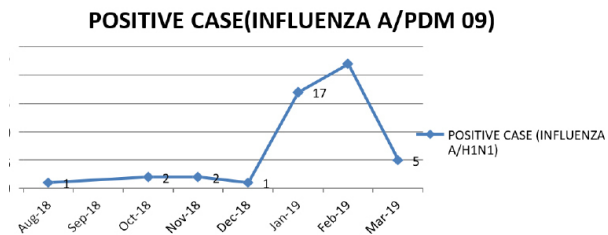


Figure 3- Epidemic curve of confirmed cases of H1N1/pdm 09 in 2018/2019.

Table 2. Parameters for H1N1 confirmed cases admitted in ICU

Variables	Number(N)
ICU Admission	21 (42%)
LOS(I.C.U)	6.1d
LOS(Total)	9.8d
LOS(Ventilator)	5.8d

Out of 87 negative cases (with suspicion of H1N1), 9 were expired whereas others 78 got discharged after receiving appropriate treatment. On average negative cases received antiviral (oseltamivir) for at least 3 days.

DISCUSSION

In order to understand the behavior of influenza A/pdm 09 on post pandemic period, this was a small-scale study conducted in a tertiary level health care of Nepal. Since this study includes the data from one organization, it is difficult to predict the overall picture of a country; however, this hospital serves as a referral center for entire Nepalese population, and so rough estimation on the overall status of influenza A might be possible.

In context of Nepal, there is only one study done by Adhikari et al in 2009 to address epidemiology of outbreak of pandemic influenza A/pdm 09 in Nepal but not a single study done on post pandemic period. In our study, the mean age of patients with influenza A(H1N1) is 44 years whereas it was only 21 years in a national level study done in Nepal in pandemic period.¹¹ Whereas, a study done in one of the hospital in Spain in post pandemic period showed 64 years as mean age of cases with influenza A/H1N1 positive.¹² The demographics and age/gender distribution is quite similar to the cohort study done in United states (mean age-48 yrs and male-51%).¹³ Other studies done during pandemic era too showed that younger age group were mainly affected by H1N1 which contradicts our finding.^{13,14}

Since the hospital is province 3, majority of cases are from the districts in province 3 itself and some from nearby province 4 which is similar to the finding during pandemic period.¹¹

With respect to waves of seasonal influenza in a year period, the positive cases (H1N1/Pdm 09) were identified to be in increasing trend from the first week of January which continued to rise to maximum 22 cases till end of February, after that there was a sharp decline in positive cases. The study done by Adhikari et al. showed the peak on November month. On contrary, a large study done in seven states' hospitals in eastern India showed the peak on August and July.¹⁵ A recent large scale United States study published in February 2018 too showed maximum cases during January and February but in this study case of H3N2 were reported maximum.¹⁶

The admitted patients were followed only up to the time of discharge from the hospital by the concerned consultants.

The outcome of patients with confirmed laboratory report (H1N1/pdm 09) was basically classified into four groups:

1) Discharged 2) Expired 3) Leave against medical advice. 4) Discharge on patient request.

Out of 50 positive patients, 36(72%) were discharged after the resolution of symptoms and associated complications. Eleven(22%) patients got expired from ICU among which 10 patients (91%) were transferred to Grande hospital only after getting some days of treatment on other centers and on most cases the samples to confirm influenza was not made. The samples were sent from this center to confirm the strain of influenza. Even though the antiviral medicine (oseltamivir) was started immediately on this center after the suspicion of influenza A(H1N1) was made, the delay in sending samples from previous center might have deteriorated the condition of patients.¹⁷ It had been observed in this study that patients were continued the antiviral treatment for at least 3 days after starting even for negative cases. There are basically two reasons for it. Firstly, delay in getting the report from the test center and secondly the critically ill patients were continued the antiviral despite negative test report if the clinicians strongly suspected on clinical judgement. Since the national influenza center is the only test center all over Nepal for authorized influenza testing, the reporting usually takes 3-4 days and even longer in some cases and till then Physicians had to continue the antiviral on clinical ground. Since the patient received antiviral till the test report, it is quite difficult to establish the role of antiviral (oseltamivir) in positive and negative cases. The co-relation between mortality and use of antiviral (oseltamivir) in test negative patients have not been studied.

The case fatality rate(CFR) in this study was 22% which is about three times greater than the International cohort studies carried out over three years' time period.¹² A similar study done in tertiary care hospital in south India over seven year period reports the death rate to be 9.4 which is nearly the half of our finding.¹⁸ Our death rate is significantly higher compared to data from states 'hospital in eastern india(1.4%) in pandemic period.¹⁵ Furthermore, a study from the global influenza hospital surveillance network too showed only 2% mortality in post pandemic period (2013-2014).¹⁹ Another study done in Michigan Hospital in 2015/2016 showed only 1% mortality among 90 cases with influenza A (H1N1) positive.²⁰ As per Nepali study done by Adhikari et al, there were only three deaths (all females) reported during pandemic influenza A/pdm 09 period (case fatality ratio(CFR) =1.74) and mean age for mortality cases were below 35 yrs.¹¹ Our finding significantly differs from this finding as mean age for deaths cases is 44 yrs and about equal mortality was observed in both gender(Female 5, Male 6) and CFR has increased drastically to 22% which

needs to be addressed as it may be the unpredictable behavior of post pandemic influenza A/pdm 09. The another possibility for high mortality in this study could be due to study site as this is a tertiary care hospital and more complicated and severe cases got admitted here. Retrospective identification of cases might also include some bias and increase mortality. Inclusion of risk factors (co-morbidity/age/severity) for confirmed cases would make this study more authentic. Limited studies done in similar setting and design could also have made comparison quite unrealistic. Whereas, increased mortality rate in post pandemic period is similar to some studies done in Europe. A study done in a university hospital of Germany showed about three fold increase(12% versus 5%) in mortality rate in first post pandemic period and another post pandemic study done in Oulu university showed 16.7% mortality(0% in pandemic period).^{21,22} The percentage of patients with influenza A/pdm 09/ H1N1 that were admitted to I.C.U is 42% which is comparable to the study done in Germany(46%) in post pandemic period but nearly three times higher than the study done in U.S in more recent year 2016.²³ The length of stay in I.C.U has increased from 1.9 to 4.3 days in later four years study but it is less than our finding (4.3d vs 6.1d) whereas this study has shorter length of stay(total) when compared to the study done in 900 bed tertiary care hospital(9.8d vs 13d).²²

In our case, 36% of H1N1 positive cases were ventilated which is about three fold high as compared to the study, which was carried over longer period from 2004/05 to 2012 to compare clinical variation between seasonal influenza and pandemic H1N1.²³

CONCLUSIONS

Influenza A/pdm 09 is associated with high incidence in March to December, associated with high fatality rate and more stay in in the intensive care unit. It seems that contributing factors (such as comorbidity) need to be studied and more data from other sites of same nation are required to sensitize the regulatory bodies to interpret if the behavior of post pandemic influenza A is responsible for increased fatality so that general public can be made aware.

REFERENCES

1. Bunthi C, Thamthitawat S, Baggett HC, Akarasewi P, Ruangchira-urai R, Maloney SA, et al. Influenza A(H1N1) pdm09-associated pneumonia deaths in Thailand. *PLoS One*. 2013;8(2):e54946. [PubMed]
2. Oshansky CM, Thomas PG. The human side of influenza. *J Leukoc Biol*. 2012;92(1):83-96. [PubMed]
3. WHO. WHO recommendations for the post-pandemic period. Pandemic H1N1 (2009) briefing note 2009 [inter-

net]. Available from: <https://www.who.int/csr/disease/swineflu/notes/briefing-20100810/en/>

4. 4. Ambrozaitis A RD, Žagminas K, Kuprevičienė N, Gravenstein S, Janorienė L. Influenza A(H1N1) pdm09 and postpandemic influenza in Lithuania. *Open Med (Wars)*. 2016;11(october):341-53. [PubMed]
5. 5. Mishra B. 2015 Resurgence of influenza A (H1N1) 09: Smoldering pandemic in India? *J Glob Infect Dis*. 2015;7(2):56-9. [PubMed]
6. 6. Minchole E, Figueredo AL, Omenaca M, Panadero C, Royo L, et al. Seasonal influenza A H1N1pdm09 virus and severe outcomes: A reason for broader vaccination in non-elderly, at-risk people. *PLoS One*. 2016;11(11):e0165711. [PubMed]
7. 7. Myttoon OT RP, Donaldson LJ. Influenza A(H1N1) pdm 09 in England, 2009 to 2011: a greater burden of severe illness in the year after the pandemic than in the pandemic year. *Euro Surveill*. 2012;17. [PubMed]
8. 8. Sherbany H, McCauley J, Meningher T, Hindiyeh M, Dichtiar R. Return of pandemic H1N1 influenza virus. *BMC Infect Dis*. 2014;14:710. [Link]
9. 9. Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File Jr TM, Fry AM, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;68(6):e1-47. [PubMed]
10. 10. Nepal UNFA. Population situation Analysis of Nepal 2017. [FullText]
11. 11. Adhikari BR, Shakya G, Upadhyay BP, Prakash Kc K, Shrestha SD, Dhungana GR. Outbreak of pandemic influenza A/H1N1 2009 in Nepal. *Virol J*. 2011;8:133. [PubMed]
12. 12. Lynfield R, Davey R, Dwyer DE, Losso MH, Wentworth D, Cozzi-Lepri A, et al. Outcomes of influenza A(H1N1)pdm09 virus infection: results from two international cohort studies. *PLoS One*. 2014;9(7):e101785. [PubMed]
13. 13. Almozroc MA MZ, Alwadey AM. Pandemic influenza A/H1N1 in Saudi Arabia: description of first one hundred cases. *Ann Saudi Med*. 2010;30:11-4. [PubMed]
14. 14. Swine N. Virus Investigation Team, Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med*. 2009;360(25):2605-15. [PubMed]
15. 15. Mukherjee A, Roy T, Agrawal AS, Sarkar M, Lal R, Chakrabarti S, et al. Prevalence and epidemiology of pandemic H1N1 strains in hospitals of Eastern India. *J Public*

- Health Epidemiol. 2010;2(7):171-4. [\[FullText\]](#)
16. Budd AP, Wentworth DE, Blanton L, Elal AI, Alabi N, Barnes J, et al. Update: influenza activity—United States, October 1, 2017–February 3, 2018. *MMWR Morb Mortal Wkly Rep.* 2018;67(6):169-79. [\[PubMed\]](#)
 17. Álvarez-Lerma F, Marín-Corral J, Vila C, Masclans JR, de Molina FJ, Loeches IM, et al. Delay in diagnosis of influenza A (H1N1) pdm09 virus infection in critically ill patients and impact on clinical outcome. *Crit Care.* 2016;20(1):337. [\[Link\]](#)
 18. Jacob K, Jacob SKJ, Suma Samuel, P G Renjith, Abin Mathew. Incidence and Outcome of H1N1 Cases in a Tertiary Care Hospital in South India: A Retrospective Observational Study. *International Journal of Scientific Study.* 2016;4(7):39-43.
 19. Puig-Barberà J, Natividad-Sancho A, Trushakova S, Somina A, Pisareva M, Ciblak MA, et al. Epidemiology of hospital admissions with influenza during the 2013/2014 northern hemisphere influenza season: results from the global influenza hospital surveillance network. *PLoS One.* 2016;11(5):e0154970. [\[PubMed\]](#)
 20. Segaloff HE, Petrie JG, Malosh RE, Cheng CK, McSpadden EJ, Ferdinands JM, et al. Severe morbidity among hospitalised adults with acute influenza and other respiratory infections: 2014–2015 and 2015–2016. *Epidemiol Infect.* 2018;146(11):1350-8. [\[PubMed\]](#)
 21. Lehnert N, Geis S, Eisenbach C, Neben K, Schnitzler P. Changes in severity of influenza A (H1N1) pdm09 infection from pandemic to first postpandemic season, Germany. *Emerg Infect Dis.* 2013;19(5):748-55. [\[PubMed\]](#)
 22. Ylipalosaari P, Ala-Kokko TI, Laurila J, Ahvenjarvi L, Syrjala H. ICU-treated influenza A(H1N1) pdm09 infections more severe post pandemic than during 2009 pandemic: a retrospective analysis. *BMC Infect Dis.* 2017;17(1):728. [\[PubMed\]](#)
 23. Von der Beck D, Seeger W, Herold S, Gunther A, Loh B. Characteristics and outcomes of a cohort hospitalized for pandemic and seasonal influenza in Germany based on nationwide inpatient data. *PLoS One.* 2017;12(7):e0180920. [\[PubMed\]](#)