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Review Article

Epidemiological Review of Pandemic Influenza A (H1N1) Virus

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ABSTRACT

Influenza virus has been known to be a major pathogen affecting the respiratory health of human beings worldwide. Since the emergence of pandemic (H1N1) 2009, several epidemics with mild or moderate severity have been reported. We studied the resurgence of this virus in Indian context and analysed the epidemic situation of 2018. The data obtained by government agencies from various parts of country revealed that there has been an approximate 3 fold decrease in the number of cases and an approximate 2.3 fold decrease in the number of deaths in 2018 compared to the year 2017 but the case fatality rate was increased by 1.4 fold. The increased severity of the viral infection may be attributed to mutation in the haemagglutinin gene of the circulating strains of the virus. We concluded that an active surveillance to monitor the drift or shift in viral genome and dynamic role of health care agencies to create awareness among the people is mandatory to limit the rate of morbidity and mortality due to pandemic (H1N1) 2009.

INTRODUCTION

The H1N1 strain of influenza A virus has been creating havoc amongst the human population since 1918 when it caused the first major pandemic affecting 500 million people globally and leading to the death of almost 50 million people across the world [1]. Following the first pandemic, the 20th century witnessed two more pandemics in the year 1957 (the Asian flu) that led to ~115,700 excess deaths and in the year 1968 (the Hong Kong flu) with an estimated 98,100 excess deaths over the 4-year period 1968–1971 [2,3]. In 2009, the H1N1 strain re-emerged as a "quadruple reassortant" virus for which the human population had no immunity [4,5]. This novel strain, later termed as the pandemic influenza A (H1N1) 2009 virus or pandemic (H1N1) 2009, was a fourth generation descendent of the 1918 H1N1 virus that spread worldwide with unprecedented speed having the ability of sustained human-to-human transmission and killing more than 18,449 people across the globe including 981 deaths reported in India [6-8]. The WHO declared a post-pandemic period in August 2010, soon after a year of its emergence [9]. In India, the pandemic (H1N1) 2009 virus spread in three waves during the period of pandemic. The first wave came in September 2009 followed by the second and third waves in December 2009 and August 2010 respectively. The novel pandemic (H1N1) 2009 subtype is now considered a seasonal strain and has been in circulation since its emergence, like any other pandemic strain. Several waves of influenza epidemic were reported from

different parts of India during the post pandemic period. In this short communication, we discuss the resurgence of the pandemic (H1N1) 2009 virus infections reported in the year 2018 in India.

Seasonal Circulation of Pandemic (H1N1) 2009 Virus and Post Pandemic Resurgence in India

In India and many other countries, the seasonal H1N1 and H3N2 strains were completely replaced by the novel pandemic (H1N1) 2009 strain soon after its emergence. After the post-pandemic stage in 2010, the H1N1 still remained in co-circulation with influenza A (H3N2), influenza B and completely replaced seasonal influenza A (H1N1) virus. The trio remained in circulation as seasonal strains till the winter of 2012 when India witnessed a sudden resurgence of the pandemic (H1N1) 2009strains [10]. Several parts of India have been seeing the resurgence of pandemic (H1N1) 2009 strain in almost every winter. An epidemiological study conducted on 1726 influenza infected patients in Saurashtra region during 2009-2011 revealed that almost 30% of the patients suffered from confirmed infection with pandemic (H1N1) 2009 strain and almost 25% of patients with pandemic (H1N1) 2009 influenza died as compared to 5.3% of those suffering from seasonal influenza [11].

Similarly in the year 2015, the pandemic (H1N1) 2009 outbreak was again observed across the different states of India. The number of infected patients and death toll surpassed the previous years with 39,000 confirmed cases and 2,500 associated deaths [12]. This was unusual as the resurgence occurred in the first quarter of the year as compared to the usual that takes place during the monsoon season (June-September). A recent study, conducted in West Bengal from January to December 2015, identified several mutations in the Haemagglutinin (HA) gene of influenza A (H1N1) 2009 strain compared to the viral gene isolated in 2009. The authors concluded that this could be a possible reason of increased virulence and disease severity during recent resurgence [13]. Another study conducted during the first quarter of 2015 also revealed the emergence of pandemic (H1N1) 2009 geno-group 6B and drug resistant strains from Madhya Pradesh, India [14].

Current Resurgence of Pandemic Influenza A (H1N1) 2009 Virus in India

In the post-pandemic period, India experienced several waves of epidemics caused by the pandemic (H1N1) 2009. The viral genome sequences submitted by Indian researchers, to the global database in 2015, indicated that the mutated virus with an increased virulence could be circulating in the Indian sub-continent. In 2018, the disease caused by pandemic (H1N1) 2009, commonly referred to as "Swine Flu" in India showed a major resurgence in the post pandemic era, though less severe than that in 2017.

CASE REPORTING

In a developing country like India, significant number of people having cough, cold and fever do not report to the clinicians and get recovered within few days by taking home remedies and precautions. An almost 13,447 positive cases were reported in 2018 from different parts of the country against 38,811 cases which were reported in 2017 with the death toll reaching up to 969 in 2018 against 2,266 death cases reported in 2017 [15]. The reports show that there was almost a 22 fold increase in the number of flu cases and about 8.5 fold increase in the death toll in 2017 as compared to the year 2016, which again decreased in 2018 by 3 and a 2.3 fold respectively (Figure 1a and 1b). Many states in India were affected by this resurgence. Maharashtra was the most affected state with almost 19% of the H1N1 casualties followed by Tamil Nadu [15]. Integrated Disease Surveillance Program (IDSP) of Government of India gathered the morbidity and mortality reports from different states which showed that the situation, though better than 2017, had been worrisome and needed to be brought under control as soon as possible.

It is also important to note that though the number of cases and deaths has been much higher in 2015 and 2017, the case fatality ratio was up to three times higher in other years viz. 2011, 2013, 2014, 2016 and 2018 (Figure 1c). This may be accounted to the infection in high risk group individuals which might have resulted in high mortality rate. The overall reduction in the number of reported cases in these years may be attributed to the overlapping immunity development in larger proportion of population as a result of widespread viral infection in 2010 and 2015.

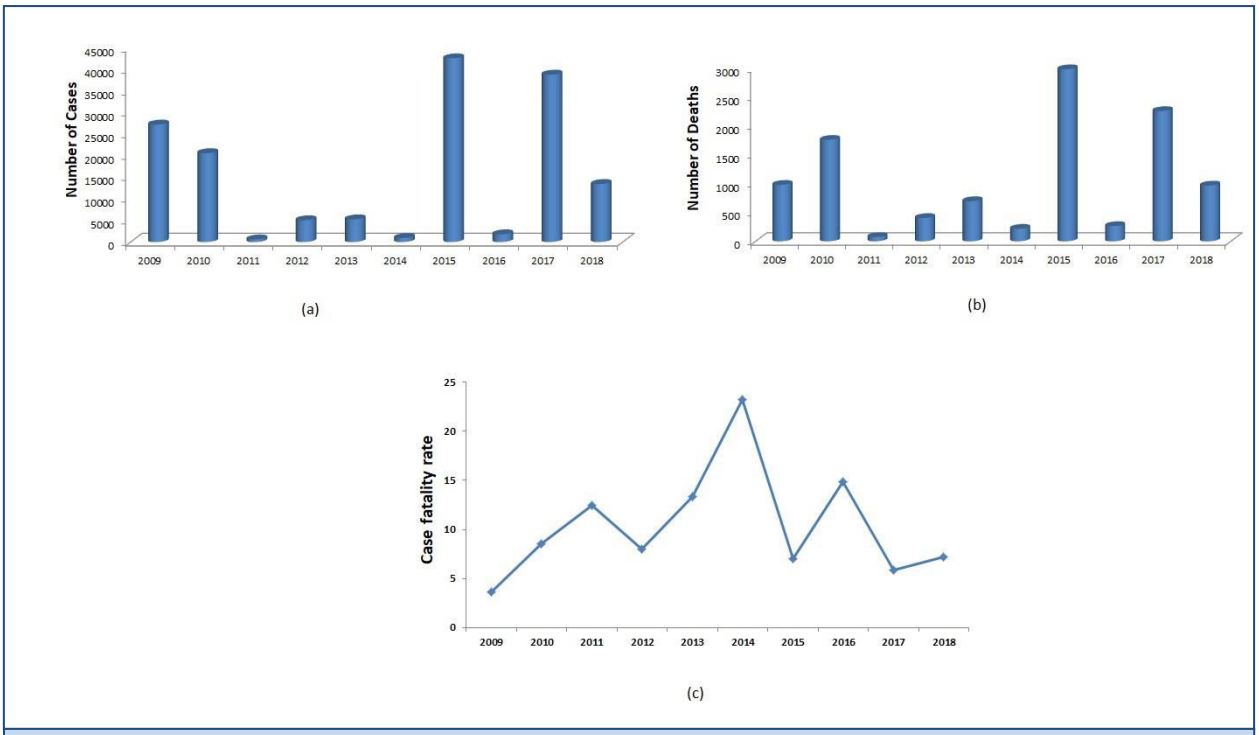

Figure 1: Year-wise morbidity and mortality due to swine flu. a) Number of cases reported to be affected by swine flu since 2009. b) Number of deaths due to swine flu since 2009 up to 9th December 2018. c) Case fatality ratio due to swine flu till 9th December 2018.

ENVIRONMENT AND VIRAL INFECTION

The attack rate of influenza virus has always been discussed to be dependent on the environmental conditions [16,17]. As per the general observation, in sub-tropical countries where the climatic conditions ranges from cold and humid to hot and dry, influenza cases rise with the arrival of monsoon when the humidity as well as temperature is conducive for the activity of the virus while a minor peak of the disease is also observed in winter season when the temperature favours the prolonged survival of the virus [18]. The recent trend in the outbreak of disease, however, does not seem to correlate with any specific climatic conditions. Although the number of cases of pandemic (H1N1) 2009 increases abruptly in mid monsoon season, the cases of such infections have been reported almost throughout the year. In 2017, the first case of pandemic (H1N1) 2009 was reported on 6th January when the climate was cold and humid and the number of cases kept increasing thereafter. There was an abrupt increase in the number of cases from July 2017 when the monsoon arrived and the climate was warm and humid. In 2018, 13447 cases and 969 deaths have been reported in India up to 9th December 2018, with Maharashtra being the most affected state where the average climatic condition has been warm and humid [15].

Virus Evolution and Host Immunity Behind Pandemic (H1N1) 2009 resurgence

Type A influenza viruses, based upon the presence of two glycoproteins HA (Haemagglutinin) and NA (Neuraminidase) on the surface of the virus are divided into subtypes. There are 18 different known H antigens (H1 to H18) and numerous types of known N antigens (N1 to N11), but only H1, H2, H3 and N1, N2 have been positively linked to influenza epidemics in humans. Each virus subtype has undergone mutation to form a variety of strains with different pathogenic profiles resulting in some strains being pathogenic to one species while other affecting multiple species.

The influenza A virus subtypes (confirmed in humans) are:

- H1N1 - "Spanish flu" (1918) and swine flu outbreak (2009)
- H2N2 - "Asian flu" (late 1950s)
- H3N2 - "Hong Kong flu" (1960s)
- H5N1 - global influenza pandemic threat through its spread (mid-2000s)

- H7N9 - on-going epidemic in China and considered to have the greatest pandemic threat of the Influenza A viruses
- H7N7 - unusual zoonotic potential
- H1N2 -endemic in humansand pigs
- H9N2, H7N2, H7N3, H5N2, and H10N7.

Influenza virus, like any other RNA virus, mutates rapidly due to lack of proofreading ability in its polymerase, resulting in an event called the "genetic drift" generating approximately one error per replicated genome [19]. Such an event can lead to a production of almost 10,000 new mutant viruses ready to infect neighbouring cells. The increasing rate of antigenic drift helps the virus in evading the host immune response. The scientists across the world, involved in the influenza surveillance program, submit viral genome sequences from their respective countries to Centre for Disease Control (CDC) and based on these sequences, CDC/WHO determines the composition of trivalent/tetravalent annual influenza vaccines. Until 2016, A/California/7/2009(H1N1) was included in the annual vaccine composition but in 2014-2015, it was observed that immunization with such vaccines could not completely protect the susceptible individuals. Again, the year 2017 marked a major resurgence of the virus which has been attributed tospecific mutations in the HA gene of virus. Indian strains exhibited two mutations in the HA gene viz. T200A and D225N. T200A mutation improved human glycan receptor binding of the virus and D225N mutation was linked to increased virulence and disease severity in concerned patients [20,21]. Specimens collected from different regions of India have also shown the presence of virus harbouring K166Q mutations. It has been suggested that the strains having this specific mutation spreads faster and is more virulent than the pandemic (H1N1) 2009 strain [22-24]. On the basis of these findings, CDC/ WHO has recommended there placement of A/California/7/2009(H1N1) with A/Michigan/45/2015 (H1N1) in the trivalent vaccine composition and it is expected that the newly formulated vaccine will protect the individuals against the mutated virus. Annual updating of the vaccine composition is must to counter the viral infection and therefore, as per the need of time, several strategies are being explored to develop a universal vaccine which may provide cross-protection against the newly emerging strains of the virus [25].

Table 1: Categorization of patients suffering from flu like symptoms.

	Category A	Category B	Category C
Signs & Symptoms	Mild fever; Cough/ Sore throat; Bodyache; Headache; Diarrhoea; Vomiting	High grade fever; Sever sore throat; Risk groups having signs of category A	Signs and symptoms of category A &B; Breathlessness; Chest pain; Drowsiness; Convulsions; Fall in BP; Blood in sputum; Blue nails or worsening of underlying chronic conditions
Need for diagnosis	No testing required for H1N1	No testing required for H1N1	Test for H1N1 infection required
Management of symptoms	1. Stay at home 2. Oseltamivir treatment not required 3. Only symptomatic treatment 4. Should not mix with public & high risk members	1. Home isolation required 2. Oseltamivir treatment required	1. Immediate hospitalization required with symptomatic and Oseltamivir treatment

Categorization of Cases and Management of Epidemics

Severity of pandemic (H1N1) 2009 influenza varies from case to case and depends on several factors like age, health/ immune status of the infected person (persons suffering from diabetes, cardiac diseases, obesity, asthma and pregnant women are categorized under high risk groups) and environmental conditions which may determine the viral load (NIH 2013) [26]. As per the WHO guidelines, depending on the severity of the disease, patients are categorized into three groups viz. Group A, B & C (Table 1). The patients under critical conditions are categorized in group C and are immediately hospitalized followed by diagnosis of H1N1 infection and given treatment with Oseltamivir (Tamiflu) [27]. However, in specific cases where the virus seems to be resistant to Oseltamivir, Zanamivir (Relenza) may also be prescribed [28,29].

Since influenza virus can be transmitted through aerosols, irrespective of the disease severity, patients are kept isolated from healthy individuals who not displaying any flu like symptoms. The health care workers are also advised to take utmost precautions to avoid contracting and spreading the disease. The Govt. of India and health authorities across India

have been trying hard to minimize the number of casualties due to viral infection, however the number of cases doesn't seem to show a downward trend, which may be attributed to the climatic conditions prevailing in the country.

For timely management of the epidemic situation, it is necessary that a proper surveillance system exists in the country which not only keeps track of the circulating influenza strains, but also analyses the attack rates of the viral pathogen. Further, in developing countries like India, where people are very reluctant in taking vaccines against pathogens like influenza, the government needs to formulate a policy on immunization against the virus wherein the high risk categories that include pregnant women, diabetic persons, obese patients, asthmatic patients, heart disease patient and healthcare workers must be vaccinated on yearly basis [30]. The family physicians must play an important role in distinguishing the influenza from common cold and other Influenza-Like Illnesses (ILI) based on the intensity, severity and frequency of the symptoms. The diagnosis of influenza becomes easier when the physicians are aware of the epidemic scenario in their region which can be easily obtained from the local or state health departments and from the websites that post periodic status of the disease. Apart from these the 'Centres for Disease Control and Prevention' provides the surveillance data and creates awareness about the types and subtypes of influenza viruses that are circulating locally and nationally. This information can be very helpful to patients who may be travelling to or from high risk areas.

There are many factors that can help manage a pandemic situation effectively. For example social distancing is known to be an effective measure to prevent the spread of virus in many pandemic scenarios [31]. Events like concerts and movies may be cancelled in order to minimize public gathering and clustering at one place. Social networking sites like Facebook, Twitter and YouTube are yet another means to disseminate epidemiological data to the general public. It was recently reported in China that social networking sites can be potentially used for disease surveillance and public awareness during the influenza outbreak scenario [32]. Besides scientific community, the world at large access these social networking sites as than scientific journals, hence a faster way to calibrate response policies and for risk communications during influenza pandemics. Awareness of standard symptoms, obtaining correct diagnosis, prompt treatment, and further alertness to potential outbreak threats can help achieve better public health and manage this age-old disease efficiently. Public awareness in general should be increased by means of audio-visuals including television, newspapers and local announcements in the locality to spread the awareness and educate people to adopt good public health practices. India is currently facing the challenges from three different viruses simultaneously, the Influenza A (H1N1), Dengue and Chikungunya, all of which can be managed with appropriate knowledge, precautionary measures and potential policies of preparedness by health authorities.

A pandemic subtype of influenza A at times replaces but may also coexist with the previous seasonal subtype. For example, the pandemic subtype H2N2 (1957) replaced the seasonal subtype H1N1; whereas after 1977 subtypes H1N1 (from the pandemic) and H3N2 continue to coexist. To understand this, a hybrid model for the dynamics of influenza A was formulated by Sarder Mohammed Asaduzzaman et al. This model takes into account cross-immunity of strains depending on the most recent seasonal infection. Theoretical and numerical analyses were appointed to reach the conclusion that for very strong cross-immunity, the pandemic cannot invade, while for intermediate levels of cross-immunity the pandemic may replace the seasonal subtype and for strong and weak cross-immunity there is coexistencein the season following the pandemic [33].

A novel method for predicting which strain of influenza may be responsible for next season's epidemic, and provide conclusive suggestions for the composition of the seasonal vaccine has been developed by Sarder Mohammed Asaduzzaman et al. The theoretical model developed also connects susceptibility distribution with the evolutionary tree of antigens. Also established is a variant of our model which can be used to study the evolution of influenza after any pandemic. Again, cross-immunity between influenza strains can be used to compute the basic reproduction number (fitness) of the challenging strain [34].

DISCUSSION

Influenza A virus is one of world's major uncontrolled pathogen and has been responsible for explosive pandemics over

several decades. This was evidenced by the advent and continued prevalence of 2009 swine origin pandemic H1N1 Influenza A virus. The ability of the 2009 H1N1 virus to cause increased disease severity in humans arose due to thenumerous mutations and many unidentified molecular determinants assimilated by the virus throughout its evolution.

The presence of a segmented genome along with viral polymerase lacking proofreading activity of has bolstered the occurrence of multiple mutations which has been correlated to increased infectivity and severity of symptoms, especially the mutations in the haemagglutinin gene of the circulating strains of the virus. The novel influenza A (H1N1) 2009 virus strain was a fourth generation descendent of the 1918 H1N1 virus that spread worldwide with unparalleled speed. The Indian strains displayed two mutations in the HA gene - T200A and D225N. T200A accounted for its enhanced glycan receptor binding ability while greater severity of symptoms could be ascribed to D225N mutation. Another strain has been recognized to be harbouring K166Q mutations accounting for enhanced virulence with faster spread.

Risk groups include pregnant women, infants, senile groups, immuno-compromised or people with diabetes, cardiac diseases, obesity or asthma. Such patients are given first preference and due to aerosol transmission of this virus, patients are kept secluded to prevent further spread. Mitigating its disastrous effects through public awareness of its spread and symptoms, proper diagnosis and timely treatment via audio-visuals, printed materials or even social media has great potential.

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REFERENCES

1. Taubenberger JK, Morens DM. (2006). 1918 Influenza: The mother of all pandemics. Emerg Infect Dis. 12: 15–22.
2. Glezen WP. (1996). Emerging infections: pandemic influenza. Epidemiol Rev. 18: 64-76.
3. Khanna M, Saxena L, Gupta A, Binod Kumar, Roopali Rajput. (2013). Influenza pandemics of 1918 and 2009: a comparative account. Future Virol. 8: 1–8.
4. Khanna M, Gupta N, Gupta A, Vijayan VK. (2009). Influenza A (H1N1) 2009: a pandemic alarm. J Biosci. 34: 481–489.
5. Khanna M, Kumar B, Gupta N, Kumar P, Gupta A, et al. (2009). Pandemic swine influenza virus (H1N1): a threatening evolution. Indian J Microbiol. 49: 365-369.
6. CDC. (2009). Swine influenza A (H1N1) infection in two children--Southern California, March-April 2009. MMWR Morb Mortal Wkly Rep. 58: 400–402.
7. WHO. (2010). Pandemic (H1N1) 2009 - update 112.
8. Press Information Bureau, Government of India, Ministry of Health and Family welfare. (2015). Preventive measures on swine flu.
9. Khanna M, Kumar B, Gupta A, Kumar P. (2012). Pandemic Influenza A H1N1 (2009) Virus: Lessons from the Past and Implications for the Future. Indian J Virol. 23: 12–17.
10. Dangi T, Jain B, Singh AK, Mohan M, Dwivedi M, et al. (2014). Influenza virus genotypes circulating in and around Lucknow, Uttar Pradesh, India, during post pandemic period, August 2010--September 2012. Indian J Med Res. 139: 418–426.
11. Chudasama RK, Patel UV, Verma PB, Banerjee A, Buch P, et al. (2013). A Two Wave Analysis of Hospitalizations and Mortality from Seasonal and Pandemic 2009 A (H1N1) Influenza in Saurashtra, India: 2009-2011. Ann Med Health Sci Res. 3: 334–340.
12. Cousins S. (2015). Death toll from swine flu in India exceeds 2500. Br Med J. 351: h4966.
13. Mukherjee A, Nayak MK, Dutta S, Panda S, Satpathi BR, et al. (2016). Genetic Characterization of Circulating 2015 A(H1N1)pdm09 Influenza Viruses from Eastern India. PLoS One. 11: e0168464.
14. Parida M, Dash PK, Kumar JS, Joshi G, Tandel K, et al. (2016). Emergence of influenza A (H1N1)pdm09 genogroup 6B and drug resistant virus, India, January to May 2015. Euro Surveill. 21: 6-11.
15. Government of India; Ministry of Health and Family Welfare. Integrated Disease Surveillance Project. (2018). Influenza A (H1N1)– State/UT- wise, Year- wise number of cases and death from 2010 to 2018 (till 9th December 2018).

16. News Releases. (2013). NIH study sheds light on role of climate in influenza transmission.
17. Lowen AC, Steel J. (2014). Roles of Humidity and Temperature in Shaping Influenza Seasonality. J Viro. 88: 7692–7695.
18. Kumar B, Pati DR, Khanna M, Kumar P, Daga MK, et al. (2012). Age-sex distribution and seasonality pattern among influenza virus infected patients in Delhi, 2009-2010. Ind J Com Med. 37: 57-58.
19. Khanna M, Kumar P, Chaudhary K, Kumar B, Vijayan VK. (2008). Emerging influenza virus: a global threat. J Biosci. 33: 475-482.
20. Ruggiero T, De Rosa F, Cerutti F, Pagani N, Allice T, et al. (2013). A(H1N1)pdm09 hemagglutinin D222G and D222N variants are frequently harboured by patients requiring extracorporeal membrane oxygenation and advanced respiratory assistance for severe A(H1N1)pdm09 infection. Influenza Other Respi Viruses. 7: 1416-1426.
21. Xu R, Zhu X, McBride R, Nycholat CM, Yu W, et al. (2012). Functional Balance of the Hemagglutinin and Neuraminidase Activities Accompanies the Emergence of the 2009 H1N1 Influenza Pandemic. J Virol. 86: 9221-9232.
22. Linderman SL, Chambers BS, Zost SJ, Parkhouse K, Li Y, et al. (2014). Potential antigenic explanation for atypical H1N1 infections among middle-aged adults during the 2013-2014 influenza seasons. Proc Natl Acad Sci USA. 111: 15798-15803.
23. Tharakaraman K, Sasisekharan R. (2015). Influenza Surveillance: 2014–2015 H1N1 "Swine"-Derived Influenza Viruses from India. Cell Host & Microbe. 17: 279-282.
24. Pulla P. (2017). The Threat of Flu Pandemics is Real and India Needs a Vaccination Policy in Place Soon. The Wire.
25. Khanna M, Sharma S, Kumar B, Rajput R. Protective immunity based on the conserved hemagglutinin stalk domain and its prospects for universal influenza vaccine development. BioMed Research International. 2014: Article ID 546274.
26. Van Kerkhove MD, Vandemaele KAH, Shinde V, Jaramillo-Gutierrez G, Koukounari A, et al. (2011). Risk factors for severe outcomes following 2009 Influenza A (H1N1) infection: A Global Pooled Analysis. PLoS Med. 8: e1001053.
27. Government of India; Ministry of Health and Family Welfare. (2016). Guidelines on categorization of Seasonal Influenza cases during screening for home isolation, testing, treatment and hospitalization.
28. Gaur AH, Bagga B, Barman S, Hayden R, Lamptey A, et al. (2010). Intravenous zanamivir for oseltamivir-resistant 2009 H1N1 influenza. N Engl J Med. 362: 88–89.
29. Khanna M, Saxena L, Rajput R, Kumar B, Prasad R. (2015). Gene silencing: a therapeutic approach to combat influenza virus infections. Future Microbiol. 10: 131–140.
30. Khanna M, Gupta A. (2010). Vaccines for Pandemic Influenza A H1N1 (2009): Where Do We Stand? Indian J Virol. 21: 90-91.
31. Glass RJ, Glass LM, Beyeler WE, Min HJ. (2006). Targeted social distancing design for pandemic influenza. Emerg Infect Dis. 12: 1671-1681.
32. Zhang EX, Yang Y, Di Shang R, Simons JJP, Quek BK, et al. (2015). Leveraging social networking sites for disease surveillance and public sensing: the case of the 2013 avian influenza A (H7N9) outbreak in China. Western Pacific Surveillance and Response Journal. 6: 66-72.
33. Asaduzzaman SM, Ma J, van den Driessche P. (2015). The coexistence or replacement of two subtypes of influenza. Mathematical Biosciences. 270: 1-9.
34. Asaduzzaman SM, Ma J, van den Driessche P. (2018). Estimation of Cross-Immunity Between Drifted Strains of Influenza A/H3N2. Bull Math Biol. 80: 657-669.