

2015 Resurgence of Influenza A (H1N1) 09: Smoldering Pandemic in India?

Influenza pandemic is commonly believed to sustain for a year or two. But history tells a different story describing several waves over multiple years causing high morbidity and mortality every time,^[1,2] meaning thereby, resurgence due to pandemic influenza virus is rather a norm than exception, even after the pandemic is over.

The latest influenza pandemic due to Influenza A (H1N1) 09 (pdm H1N1) began in May 2009, spread to all over the world and became global by July 11 2009. On 10th August 2010, the pandemic was declared to be an end with more than 18,449 deaths reported worldwide by end of the month.^[3,4]

In India the first positive case of pdm H1N1 was reported in May 2009 and by end of the year 2010, 20604 cases with 1763 deaths were reported.^[5] The country experienced three waves during the period of pandemic of 2009-2010, first one in 2009 September, followed by second wave in December, and the third peak in August 2010 when the end of pandemic was declared.

Circulation of Influenza A (H1N1) pdm09 during post pandemic years

Immediately after the emergence of pdm H1N1 in May 2009, the strain largely replaced the circulating seasonal Inf A (H1N1) and Inf A (H3N2) viruses. From 2010 onwards, the pandemic strain pdm H1N1 virus continued to circulate in India, but, along with the previously circulating influenza viruses; InfA (H3N2) and InfB, replacing completely the seasonal Inf A (H1N1). Circulation of these three influenza viruses continued with seasonal activity till resurgence of pdmH1N1 was observed in several Indian states in 2012-2013 winter months.^[6,7]

Post pandemic resurgence

After 2010, pdm H1N1 reappeared in several northern and western states of the country during the winter

months of 2012-2013. The presently ongoing resurgence since December 2014 however appears to be worse than the previous one, leading to over 30,000 cases and 2000 deaths countrywide (as of 28th March, 2015) as compared to 5044 cases and 405 deaths in 2012^[5] and 5250 cases and 692 deaths in 2013.^[8] The resurgent waves lead to more number of hospitalizations and deaths due to pdmH1N1 as compared to the rest part of the year and appear at an interval of 1.5-2 years.

The present article has focused on the plausible reasons of resurgence of pdm H1N1 in India.

Role of environmental temperature

Occurrence of both the resurgent waves in India during the winter months indicates the possible role of lower ambient temperature. Temperate regions of both northern and southern hemisphere demonstrate a synchronized seasonal influenza peak during their winter months. Whereas a year round activity is observed in tropical and sub-tropical regions with annual or bi-annual peak in different countries. India being a vast country with diverse climate demonstrates two seasonal activities, one during monsoon months which are observed in most part of the country with tropical climate and other in winter period which is observed in the temperate region of extreme northern part of the country.^[9-11]

Decrease ambient temperature has frequently been associated with the influenza seasonality. Ability of the viral particle for prolonged survival in colder temperature is also considered to play an important role.^[12] In addition to this, overcrowding during winter acts as a co-contributing factor in facilitating the spread of the virus. It also has been proposed that decrease in environmental temperature increases the physiological stress and energy loss due to thermal regulation, which in turn weakens the immune system and thereby increases the susceptibility of the host to infection.^[12]

Host immunity

Pandemic occurs with the emergence of a new virus which can affect severely the naïve population and spread worldwide. Immunity to the new virus is acquired either from exposure to infection or due to vaccination. Decrease rate of infection and severity is expected during

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the subsequent years due to building up of specific immunity against the new viral strain. Waning of host immunity has often been attributed as one of the possible cause of resurfacing of the influenza virus.^[10] Increased seroprevalence rate reported during the post pandemic years reflects the exposure to infection and vaccine coverage.^[13]

Increased vaccine coverage leading to high level of seropositivity before the influenza season has been shown to be correlated with decrease influenza activity.^[14] The rate of seroprevalence has often been found to be age stratified due to different rate of exposure in different age groups. This in turn reflects the age-group wise susceptibility for the coming season. Sero-epidemiologic study is in fact considered as the most reliable method for estimation of influenza attack rate, disease severity and population-level immunity and should be considered as one of the important parameter for vaccination policies.^[15] Seroprevalence in different age groups and from different parts of the country is essential for formulation of appropriate influenza vaccination policy. The centers under influenza surveillance network of Govt. of India are presently not engaged in sero-epidemiological study. The data on sero-prevalence from different regions representing east, west, north and south of country would have helped for a good vaccination policy.

Viral evolution

Influenza A virus is known for its high rate of mutation in hemagglutinin (HA) and neuraminidase (NA) antigenic epitopes. The rate of mutation has been estimated as 6.7×10^{-3} nucleotide substitution per site per year for HA. These mutations have the capability to prevent the binding of existing antibody against HA and NA with the virus, resulting in rapid turnover of mutant viral strains.^[12] The new pandemic virus pdm H1N1 has remained genetically stable since its emergence in 2009.^[16] However, the possibility of emergence of drift virus cannot be ruled out as the cause of present resurgence at this stage. Severe second pandemic season due to drift in neuraminidase antigen has been reported previously.^[17]

In a viral genomic study on Indian isolates circulating during the period of 2009-2012, selection pressure analysis has shown 18 positively selected sites in major surface proteins of Inf H1N1 which are important for attachment, assembly and release of virus. Therefore, substitutions at these sites can play important role in making these isolates more transmissible.^[16] Studies on genetic characterization

of the pdm H1N1 strain responsible for current resurgence will reveal the role of drift virus if any.

The emergence of a new pandemic influenza virus is expected to affect the naïve population with more severity worldwide. However, smoldering pattern has been reported with previous pandemics in several countries of Asia and Europe including England, characterized by a more severe second pandemic session as compared to the first one.^[17] The latest pandemic virus Inf A (H1N1) pdm 09 also has shown a more severe pattern in year 2010-2011 than the pandemic year 2009 in some of the European countries including England.^[2] Until the resurgence of current epidemic, a lesser or similar degree of disease severity was however observed in major parts of the world including India.^[2,18]

In contrast, the death toll in a span of three months during the current resurgence has already crossed the number of deaths occurred during the first 6 months of pandemic year in 2009 (>2000 Vs 981) which included two of the three pandemic waves. The high mortality of the current epidemic is of grave concern and necessitates a thorough dissection in order to avert such severe resurgence in future. Detailed epidemiological studies can only answer the real smoldering pattern of the current wave.

The detection of D222G mutation in HA gene of Indian isolates by Mullick *et al.*, is a cause of concern.^[19] These mutant strains have the capability of binding to both $\alpha 2-3/$ $\alpha 2-6$ - sialic acid linkage and thus can lead to more severe disease.^[20] The absence of D222G mutant strain in other Indian studies indicates it's minor contribution towards the burden of severe disease.^[21] The role of D222G strain in current resurgence however cannot be commented at this stage.

Role of vaccination

Herd immunity plays an important role in constraining the subsequent waves of pandemic. Several countries had adapted the strategy of mass vaccination for pandemic Inf A H1N1 2009 across the age groups which has resulted in high seropositivity and in turn lower rate of infection during the subsequent pandemic wave.^[13,14,22]

No definite evidence exists so far, regarding the critical level of herd immunity required for population protection, however the same has been proposed as 33% based on a mathematical model assuming equal population mixing and susceptibility.^[23]

In India vaccine for pdm H1N1 virus became available since September 2010. In the initial phase, there was a vaccination drive by Govt. of India when the vaccine was offered to the health care workers in most of the states, public awareness and education was created through media. However, with passage of time the vaccination campaign became slower and virtually stopped. Even after the resurgence of pdm 09 during 2012-13, neither any major vaccination drive was held nor annual influenza vaccination was implemented. CDC had released a “Flu vaccination pledge for 2014-2015”^[24] and on February 26th 2015 Advisory Committee on Immunization Practices (ACIP) has recommended for annual influenza vaccination for everyone above 6 months of age for the year 2015-2016.^[25] Annual flu vaccination as recommended by CDC could possibly have restricted the severity of this resurgent wave.

As reported by Mytton *et al.*,^[2] lack of vaccination drive for children, public awareness and education as contributing factors for severe second session of pandemic in England, the role of similar components for present resurgence in India cannot be ruled out.

Action taken by Govt. of India

During the current resurgence, Ministry of Health and Family Welfare, Government of India, restarted the process of public awareness and education through various modes of mass media to prevent transmission. Due to the lack of information regarding actual disease burden of influenza and its impact on all high risk groups, evidence based vaccination for all high risk groups was not possible for Ministry of Health and Family Welfare (MoHFW, GOI). Vaccination was only recommended for health care workers and staff who have the possibility of coming contact with influenza patients, laboratory personnel who are involved with influenza testing and members of “Rapid response team” who carryout investigation of influenza outbreak.^[26]

CONCLUSION

The present resurgence of pandemic virus cannot be attributed to any single factor at this stage. The prolong cold and dry weather, possibility of drift virus, absence of annual flu vaccination could have played an integrated role in resurfacing of pandemic virus. The role of sero-epidemiology should be given its due importance for vaccination policy along with the molecular surveillance of the influenza virus circulating strains which is already ongoing in India through an established influenza surveillance network. Vaccination campaign, public awareness and education measures should continue in an

optimum mode, even during the inter resurgence interval period, balancing the necessity vis-a-vis public panic. Lastly, considering the ecology, epidemiology, molecular biology of the pandemic virus, a modeling system should be developed to predict such resurgence in future and building up of herd immunity against all the circulating influenza viruses along with pdm H1N1 is essential to fight the battle with the virus.

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