

2009 Pandemic Influenza in India

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Pandemic-09-H1N1 virus caused the pandemic starting in the second quarter of 2009. The world was prepared to face the pandemic since it was anticipated for over one decade. Most countries, including India, had made detailed pandemic preparedness plans well ahead of its actual occurrence. The infection rapidly spread to the whole country within 2-3 months. The national tactics were to slow down its importation through international air travelers and to slow down its spread in cities and major towns. More than 75% of all infected persons were urban dwellers, suggesting that efforts were concentrated in urban communities. In general the illness of pandemic influenza has been similar to endemic/seasonal influenza; however, there is insufficient epidemiological and clinical data on the latter. We hope that the unprecedented experience of managing the pandemic will encourage the Government of India to plan to confront endemic/seasonal influenza more systematically. The pandemic seems to have reached a peak in September/October and has been on the decline since then.

Keywords: Pandemic, Influenza, H1N1, India.

The 2009 global pandemic of influenza is currently active in 207 countries including India(1). India's central and state governments have taken the pandemic very seriously and have made several unprecedented and innovative interventions. In the past India had neglected to monitor endemic/seasonal influenza, but the pandemic has raised public awareness to a high level through print and electronic media. This perspective offers a review of information on global evolution of this pandemic.

INDIA'S PREPAREDNESS: ANTICIPATING PANDEMIC

For the first time in history, people were able to watch the pandemic approach, evolve and grow, with ample time available to prepare to face it(2,3). Human influenza viruses belong to 3 types, A, B and C. Only type A causes pandemics. It was the 'highly pathogenic avian influenza A/H5N1 virus' (HPAI-H5N1) that emerged as pan-zootic in 2003 that alerted the world of an impending pandemic(4,5). It infected humans only rarely(6). In February 2006, it affected poultry farms in the tri-junction region of Maharashtra,

Gujarat and Madhya Pradesh. During 2008 and 2009, it infected farm and backyard chicken in several districts in West Bengal, Assam, Tripura and Sikkim(7). Massive culling within 3 kilometers of infected birds and strict control of importation of chicks and feeds halted the outbreak. No human infection occurred in India(7). Globally, 442 human infections and 262 deaths (case-fatality 59%) were reported in 15 countries(7). It does not transmit between humans; hence it did not seed a pandemic. However, anticipating a pandemic, India's Ministry of Health and Family Welfare (MoHFW) drafted a Pandemic Preparedness and Response Plan (PPRP) in 2004(8).

What emerged in 2009 was another virus, Pandemic influenza A (H1N1) (P-09-H1N1), with opposite qualities – highly transmissible but of low virulence(9). It appeared in March in western coastal North America, and spread very rapidly in Mexico and California in April and then to other countries through May and June(10,11). The WHO formally declared the pandemic (Phase 6 on a scale of 1-6) on June 11(11). Promptly India revised PPRP in anticipation of its arrival in India(12).

ANTIGENIC DRIFT, SHIFT AND EMERGENCE OF PANDEMICS

The host range of influenza A viruses include water birds, domestic ducks, poultry, swine and humans. The protein spikes on the viral surface – hemagglutinin (H, for viral attachment to host cell) and neuraminidase (N, for viral release from cell after multiplication), are used to classify subtypes. Birds get infected with viruses carrying H1 to 16 and N 1 to 9; humans are infected by viruses carrying H1, H2 and H3 and N1 and N2 – rarely with H5 and H7.

The virus genome contains 8 single-stranded RNA molecules. During virus multiplication in host cells they may commonly undergo point mutations causing antigenic variations in daughter viruses – this is '*antigenic drift*'. A network of global laboratories conduct continuous surveillance of influenza-like illness (ILI) and isolated influenza viruses are analyzed to determine if any new drifted variants have begun circulating; in that case vaccine for the next season would be updated to include the new variant. Since influenza season is not synchronous in the north and south hemispheres, vaccine definition may be different for the two.

Simultaneous host infection with 2 subtypes can lead to the emergence of 'reassortant' viruses with different gene configuration from either parent virus. If the emergent virus carries surface antigens not present in earlier circulating strains, the phenomenon is called as '*antigenic shift*'. Since wild birds and swine are frequently infected with several H and N subtypes, antigenic shift is relatively frequent among avian and swine influenza viruses. Host-specificity and transmission efficiency are determined by cell-surface virus receptors. Swine's receptors accept swine, avian and human viruses and serve as 'mixing vessel' for antigenic shift. If shifted virus is capable of efficient human-to-human transmission, the stage is set for pandemic as humans would be immunologically naïve to it. Only a rare antigenic variant may be fit for human infection, thus seeding a pandemic.

The 20th century pandemics were in 1918 (H1N1), 1957 (H2N2) and 1968 (H3N2). The new virus tends to replace endemic/seasonal influenza viruses and post-pandemic, it continues to circulate as the new seasonal virus. Thereafter it would exhibit

antigenic drift; thus more than one drifted variant may co-circulate. H1N1 virus circulated globally from 1918 till 1957 and was replaced by H2N2 virus; in 1968, H3N2 virus replaced H2N2. The seasonal H3N2 viruses that continue to be isolated globally are descendants of the 1968 pandemic virus. In 1977 a descendant of the 1918 pandemic H1N1 virus reappeared in northern hemisphere; it might have been accidentally released from a laboratory(13). It slowly established circulation globally; subsequently endemic/seasonal viruses in both hemispheres are H3N2 and H1N1.

THE VIRUS OF 2009 PANDEMIC

The P-09-H1N1 virus was unanticipated(14). Although by definition H1N1, its antigens came from swine influenza viruses(14). Interestingly, in 1976 another novel swine-origin H1N1 had emerged in the United States but it did not easily transmit between humans(15). P-09-H1N1 is antigenically distinct from earlier human H1N1 viruses. Neither seasonal H1N1 nor vaccine containing it induces cross-reacting neutralizing antibodies against P-09-H1N1(16). It is a re-assortant with gene segments from viruses of swine (European, North American and Asian; 5 segments), birds (two segments) and humans (one segment)(17). Although swine-related, it has not been detected in nature in swine or birds(18). When exposed to infected humans, swine and turkeys have been infected by P-09-H1N1(19, 20). Under laboratory conditions turkeys do not develop clinical disease and transmission between birds is very inefficient(21).

Once the pandemic settles down, the virus is most likely to become the predominant agent of endemic/seasonal influenza. Antigenic changes in seasonal H3N2 occur by mutations and genetic recombination between co-circulating viruses of the same subtype (22). A similar phenomenon is likely to occur with P-09-H1N1 also, resulting in variants that escape natural or vaccine-induced immunity, to become future seasonal influenza. Reassortment with co-circulating viruses of a different subtype may also occur; the fear is that viruses with greater pathogenicity and efficient transmissibility may thus emerge. Of greatest concern is the possibility of re-assortment with HPAI-H5N1 in domestic poultry/

ducks. Continuous surveillance of influenza cases, particularly severe or atypical, is essential for the early detection of such variants.

PATHOGENESIS OF INFLUENZA (P-09-H1N1)

Influenza virus enters host cells through specific cell-surface virus receptors consisting of sialic acid (SA) linked to galactose such as SAa(2,3)Gal (avian) or SAa(2,6)Gal (human). In birds receptors are widely distributed in gastrointestinal and respiratory tracts, but in humans are mostly in upper respiratory tract (URT, nasal mucosa, paranasal sinuses, pharynx). Within this broad picture, specific subtypes may use receptors distributed differentially(23,24). The preferential binding leads to host specificity of viruses. Human viruses replicate efficiently in URT, hence transmit between humans via droplets of URT secretions. Virus replication in the lower respiratory tract contributes to greater pathogenicity. The absence of HPAI-H5N1 receptors in human URT is why it does not spread human-to-human. With heavy/repeated exposure it may reach the bronchioles carrying receptors, leading to severe disease with high case-fatality(2, 7). Since P-09-H1N1 binds to URT receptors, it circulates among humans. Receptors have also been detected in the lungs, offering an explanation why the pandemic influenza leads to primary viral pneumonia and acute respiratory distress syndrome (ARDS) with high case-fatality more frequently than endemic/seasonal influenza(25).

Pathology of influenza is due to direct cell/tissue damage, inflammation and innate immunity. Respiratory symptoms are due to cell death and inflammation. Innate immune responses lead to the release of chemokines/cytokines, mostly pro-inflammatory IL-6 and IFN- α (26). Viral damage is essentially confined to URT, trachea and bronchi. The systemic symptoms (see below) are attributed to cytokine excess or 'cytokine storm'(26). Primary viral pneumonia, pulmonary edema and ARDS are due to bronchiolar/alveolar viral cytopathology and cytokine storm. Secondary bacterial pneumonia is common. In severe cases, multi-organ failure may occur. Rarely influenza causes encephalopathy or encephalitis in children; the pathogenetic mechanism is unknown. Not unexpectedly they have been observed even during the current pandemic(27).

IMMUNE RESPONSES TO INFLUENZA

Adaptive immunity results in humoral and cell-mediated responses. Immunity offers long-term protection against disease when exposed to the homologous or closely related virus subtype. Thus, when H1N1 closely related to 1918 pandemic virus reappeared in 1977, persons born prior to 1955 had lower attack rates than younger individuals – in 1957 H1N1 had been replaced by the pandemic H2N2(28). However, unlike in the case of many other viral diseases, robust protection against re-infection and disease may not happen in many. This is due to a complex set of factors. Since the incubation period is very short and infection and disease are due to local infection in URT, adaptive immunity may not act fast enough to prevent symptoms. Antigenic drift results in virus subtypes that escape from immunity.

Rich nations in the temperate zones promote influenza vaccinations in selected population sections with high risk for severity. Using the surrogate of antibody response for protection, P-09-H1N1 vaccines have been made and are in current use in many countries.

EPIDEMIOLOGY AND CLINICAL SPECTRUM

In temperate climate countries, seasonal influenza incidence reaches epidemic proportions during winter months – October to December in the Northern and June to August in Southern Hemispheres. The seasonal epidemics cause excess mortality — mostly in the elderly (>65 y) and in the very young (<5 y). This pattern apparently results from complex factors of epidemiology and immunity. The very young tend to be immunity-naïve and the very old have co-morbidities, particularly chronic lung or heart disease.

In India, endemic/seasonal influenza had been generally ignored in public health and in healthcare. Etiology-specific diagnosis requires laboratory tests that are not widely available. Therefore what we know about epidemiology and clinical features are from research studies. Both pandemic H2N2 (1957) and H3N2 (1968) circulated in India(29). The National Institute of Virology (NIV) started influenza surveillance in Pune in 1976, where annual rainy season outbreaks occur, mostly due to H3N2

and B viruses(29). Seasonal H1N1 appeared in the 1990s(29). Since 1980s there were several studies on viruses in acute respiratory diseases in children, in Vellore, Chennai, Lucknow, Kolkata, Delhi and Pune(30). Influenza virus infection was documented in every study – with about 4-15% positive nasopharyngeal specimens(30). Recently a network of influenza virus surveillance laboratories have been established at Pune, Vellore, Chennai, Kolkata, Dibrugarh, Mumbai, Nagpur and Delhi, for virus isolation from Influenza like illness(ILI). Results are not yet available. India does not have a vaccination policy for Influenza.

The ILI begins suddenly with any of the following, in varying combination: fever, sore throat, cough, nasal congestion, malaise, headache, myalgia and loss of appetite. Occasionally nausea, vomiting and diarrhea may occur. The sensitivity and specificity of clinical diagnosis are low. In the majority, the illness is self-limited with recovery within a week.

The incubation period is 1-3 days (range 1-7 days). The clinical picture of P-09-H1N1 is usually a mild ILI. Detailed investigations in Peru showed that one-third infected persons were asymptomatic; one-third had short febrile illness without seeking medical care and one-third were ill enough to be hospitalized(31).

Some unexpected clinical features have been detected in the 2009 pandemic, with relatively higher frequency of severe disease and case-fatality in certain subjects – such as in otherwise healthy children and pregnant women (particularly third trimester)(32). The experience in other countries has shown higher risk of severe influenza (endemic/seasonal) disease in children below 2 years, and persons above 65 years and those with chronic respiratory (asthma, chronic obstructive pulmonary disease) and cardiac (congestive cardiac failure) diseases, diabetes or immunosuppression (HIV infection, malignancy, immunosuppressive medications). Obesity (BMI>30) is also associated with severe disease. Attack rate has been lower in senior citizens than in younger persons, possibly due to immune memory of H1N1 infection prior to 1957. About 10-30% of hospitalized persons during this

pandemic have required intensive care including ventilator support. Severe disease in the healthy and young has caused much fear among the public(33). Clinicians must be alert to secondary invasive bacterial infection and septic shock.

Shortness of breath, low blood pressure, cyanosis and labored breathing should alert the pediatrician of impending viral pneumonia or ARDS. Persistent high grade fever beyond 3 days is another signal of possible severe disease.

VACCINES

Two types of seasonal influenza vaccines are available – live attenuated and inactivated(34). The inactivated vaccine is ‘trivalent’ containing 2 recent circulating virus A subtype representatives and a B subtype(34). The vaccine formulation (of representative subtypes) is prescribed by the World Health Organization twice every year before the peak influenza season in the southern and northern hemispheres.

Some 30 different monovalent P-09-H1N1 vaccines have been licensed recently in many countries – using virus grown in eggs or cell culture(35-37). Inactivated vaccines may be whole virus or subunit (split) and with or without adjuvant. Over 150 million doses have already been administered. The current FDA-approved vaccine is non-adjuvanted(38). For children (6 months-10 years), 2 doses and for all above 10, a single dose has been recommended(38). Adjuvanted vaccines are in use in some European countries. The Global Advisory Committee on Vaccine Safety is currently reviewing safety data. In general the safety profile has been excellent; anaphylaxis may occur and the vaccine-provider should be fully prepared to detect early signs/symptoms and to treat immediately and appropriately. Since seasonal virus and pandemic virus are co-circulating in many countries, both vaccines are recommended for simultaneous vaccination in a few countries(39). There are various recommendations for prioritizing vaccination in different population groups(37, 39). The P-09-H1N1 virus will replace seasonal H1N1 virus for southern hemisphere winter of 2010(39).

In India, the processes for licensing pandemic

vaccine (for importation and for indigenous manufacture) are in progress(40). Unless a national policy is articulated on the control of endemic/seasonal influenza, including surveillance, laboratory diagnosis, case-reporting and vaccination, the pandemic vaccine may be viewed as a tool for crisis-management and not visionary.

ANTIVIRAL THERAPY

Neuraminidase inhibitors (NAI) – oseltamivir, zanamavir and peramivir can be used for treatment or prophylaxis. Detailed information is available on the web sites of WHO and CDC(41,42). Individuals with severe influenza or with high risk for the same, benefit from therapy, particularly when initiated within 48 hours of onset of symptoms – and may be beneficial even if delayed beyond 48 hours(43). Persons on intensive care may benefit from doubling the dosage and duration of treatment(43,44). Reports of resistance to oseltamivir are a cause for concern; zanamavir (by inhalation) or peramavir (IV) should be used in oseltamivir-resistant cases(43,44).

LABORATORY DIAGNOSIS

Laboratory diagnosis of infection with P-09-H1N1 is ideally made by direct detection methods – real time reverse transcriptase polymerase chain reaction (rRT-PCR), viral culture or antigen detection by immunochromatography. Respiratory secretion sampling is made by nasopharyngeal aspiration, deep nasal or throat swabbing, or a combination. Viral culture provides viral strains for further characterization, subtyping and genotyping. Serum antibody assays using haemagglutination-inhibition or virus neutralization methods are not useful for clinical care, but are excellent for epidemiology and for vaccine-response studies.

INDIA'S RESPONSE TO THE PANDEMIC

The interventions designed by the Government of India (GoI) are to prevent entry of P-09-H1N1, to retard its circulation in urban communities and to reduce case-fatality through diagnosis and antiviral treatment in designated hospitals(40). Starting from mid-April, all passengers arriving from overseas are screened at 18 international airports and anyone with ILI tested for infection. Infection was first detected

on 16 May; by 4 December 9,735,765 have been screened, 28,150 individuals tested virologically for infection and 315 (1.2%) found infected with P-09-H1N1(40). In the community, 91,945 symptomatic persons were tested and 19,632 (22%) were diagnosed infected and treated(40). Once infection is found spreading in the community, the usefulness of airport screening is open to question.

Among the total of 19,947 persons confirmed infected, 627 have died – for an overall case-fatality of 3.14%. This includes persons with and without co-morbidities and persons with primary viral and secondary bacterial pneumonias. Considering that hospitalization and testing would be skewed towards more severely ill, the case-fatality is likely to be an overestimate of what it is among all infected persons or ill persons. Highest case-fatality was in the age group 20-39 and next highest in <5 children.

India began with all virological tests conducted in just 2 national laboratories (in Delhi and Pune) and later expanded the laboratory network to include one per state. Thus the pandemic has acted as a spotlight on the paucity of diagnostic laboratories for the nation(45). GoI designated selected hospitals for admitting persons with P-09-H1N1 infection so that further transmission could be slowed. When severely ill persons were hospitalized, the lack of intensive care competence and equipment were found to be a serious problem in some of them, again illustrating the questions of quality and equity of healthcare in many hospitals(45).

There has been an earnest attempt by GoI to educate the public about the need to cover the mouth when sneezing or coughing (to prevent droplets in air) and for hand-washing after touching sick persons. Unfortunately, the MoHFW does not have an efficient communication channel to inform the medical personnel. Dedicated websites and television/newspaper advertising have attempted to bridge this gap(40,46).

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