Review

Influenza A (H1N1) 2009: a pandemic alarm

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At this critical juncture when the world has not yet recovered from the threat of avian influenza, the virus has returned in the disguise of swine influenza, a lesser known illness common in pigs. It has reached pandemic proportions in a short time span with health personnel still devising ways to identify the novel H1N1 virus and develop vaccines against it. The H1N1 virus has caused a considerable number of deaths within the short duration since its emergence. Presently, there are no effective methods to contain this newly emerged virus. Therefore, a proper and clear insight is urgently required to prevent an outbreak in the future and make preparations that may be planned well in advance. This review is an attempt to discuss the historical perspective of the swine flu virus, its epidemiology and route of transmission to better understand the various control measures that may be taken to fight the danger of a global pandemic.

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1. Introduction

Influenza virus is a common human pathogen that has caused serious respiratory illness and death over the past century. It has the potential to cause widespread pandemics. A pandemic occurs when a new type of influenza strain appears in the human population and then spreads easily from person to person (Khanna *et al.* 2002; Khanna *et al.* 2006). Swine influenza has come into the limelight with its current occurrence in humans. It has affected a large number of countries globally, indicating that it is capable of causing large-scale pandemic destruction. Reports of widespread transmission of the swine flu (H1N1) virus in humans in Mexico, the United States and elsewhere have put the health authorities on a high alert (Myers *et al.* 2007). Swine flu virus, a respiratory virus initially known to cause infection in pigs, belongs to the Orthomyxoviridae family of viruses that include influenza A, influenza B, influenza C and thogotoviruses (Lamb *et al.* 1996; Voyles 2002). Swine flu virus generally circulates throughout the year, but the disease mostly occurs during the late fall and early winter season. It has a major economic impact on the swine industry in the United States as it causes high mortality and morbidity in pigs, resulting in financial losses (Kay *et al.* 1994). The most commonly circulating strains of swine flu virus isolated from pigs in the United States are H1N1, H1N2, H3N2 and H3N1, which belong to the influenza A subtype (Lekcharoensuk *et al.* 2006; Shin *et al.* 2006; Vincent *et al.* 2008). In the past, the Centers for Disease Control and Prevention (CDC) have received reports of approximately one human swine influenza virus infection every one to two years in the United States but a sustained pattern of human-to-human transmission has been seen to occur only recently, raising a pandemic alarm.

2. Epidemiology

The swine flu virus was first implicated as a human pathogen in 1918 when pigs and humans were infected simultaneously (Kilbourne 2006; Taubenberger and Morens 2006). The exact events leading to the origin of the 1918 strain remains elusive (Vana and Westover 2008). The pandemic virus was transmitted from humans to pigs, and branched off into two lineages; human and porcine, which exist even today. The classical swine influenza lineage has evolved continuously

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since 1918, while the human lineage has caused many episodes of pandemics and endemics of influenza from 1918 to 1956 (Kanegae *et al.* 1994). The human line apparently disappeared entirely around 1957 only to reappear in 1977, and has circulated endemically in humans recently (Nakajima *et al.* 1978; Taubenberger *et al.* 2001) (table 1). The influenza virus was established as a cause of disease in pigs in 1930 (Shope 1931).

In 1970, transmission of the influenza H1N1 virus was reported in the swine population of Asia (Shortridge *et al.* 1979). A new variant of the H1N1 virus appeared in 1976, which caused the deaths of many US army soldiers, and was found to be A/New Jersey/1976/H1N1 (Gaydos *et al.* 1977; Goldfield *et al.* 1977). Studies showed that the new strain was closely related to the 1918 pandemic strain. In 1988, appearance of a new triple reassortant swine flu virus HIN1 in Wisconsin killed many persons (Wells *et al.* 1991; Newman *et al.* 2008). In 1994, reassorted avian–human H1N2 influenza was isolated for the first time from the UK (Guo *et al.* 2000). Further, between 1997 and 2002, the emergence of new strains (H3N2 and H4N6) was reported as a cause of influenza among pigs in North America (Vincent *et al.* 2009). Between 1958 and 2005, 37 cases of swine influenza were reported among civilians, out of whom 6 people died and 16 had a history of exposure to pigs (Shinde *et al.* 2009) (table 1). Since then, only 12 cases of human infection with swine influenza virus have been documented.

3. Global outbreak in 2009

On 17 April 2009, CDC reported for the first time that a new strain of swine flu virus had infected two children in California, United States (CDC 2009a). The recent H1N1 virus strain has been found to be closely related to the swine flu virus but with a genetic composition that is quite different from the earlier known isolates (CFIA 2009). After that, 5 more cases with the same strain were reported from the United States. At the same time, the Public Health Agency of Canada confirmed 18 cases of respiratory illness in Mexico, with 12 of them being genetically identical to the Californian virus (CDC 2009b; CDC 2009c). Following the outbreak, on 2 May 2009, it was observed that there was a clear link of previous swine flu infections in the United States and Mexico (WHO 2009a). Genetic analysis suggested that a reassortment event was responsible for the appearance of the novel H1N1 strain of swine influenza originating from two strains, from swine in North America and Eurasia (MacKenzie 2009). As of 13 April 2009, Mexican authorities had reported around 2000 cases of respiratory illness mainly affecting healthy young adults. The most recent updates given by WHO confirm a total of 2,67,105 reported cases of swine influenza affecting 175 countries, with a total of 2,692 deaths (WHO 2009b).

4. Antigenic shift in the H1N1 virus

Pandemics are rare events that occur every 10–50 years and cause a colossal loss of human lives. Genetic reassortment, one of the major reasons for a pandemic outbreak, takes place between viruses from different hosts so that a new virus is produced, capable of infecting a third host (Cox and Bender 1994; Zhou *et al.* 1999; Gramer and Rossow 2004; Gramer 2006) (figure 1). The avian influenza virus has an affinity for NeuAc-<alpha>2,3 Gal sialic acids, while the human influenza virus binds to NeuAc-<alpha>2,6 Gal sialic acids. Pigs are considered logical candidates for reassortment because they can be infected by either avian or human viruses as they possess both NeuAc-<alpha>2,3Gal and NeuAc-<alpha>2,6Gal sialic acids on the cells of the respiratory system (Scholtissek 1990; Ito *et al.* 1998). In addition, pigs are known to be involved more frequently in interspecies transmission of influenza A viruses than other

Table 1. Timeline: evolution of the swine influenza A virus

1918–19	H1N1 influenza A appeared in pigs, affected 50 million people worldwide
1930	Isolation of H1N1 from pigs for the first time
1970	Transmission of H3N2 virus to swine in Asia
1976	New strain of swine flu variant of H1N1; A/New Jersey/1976, affected soldiers at Fort Dix in the US
1984	Reassortment between human H3N2 and avian H1N1 in swine
1988	Women exposed to pigs at county fair exhibition in Wisconsin died of H1N1 infection from swine
1994	H1N2, isolated from pigs in the UK. Example of human–avian reassortment
1998	H3N2 virus caused severe disease in North America. Triple reassorted (avian–human–swine) distinct from earlier strains
1958–2005	37 cases of swine influenza reported among humans
2005–2009	Triple reassortant swine flu virus in human, in United States
2009	New strain of swine influenza H1N1, reported from Mexico and the United States shows sustained human-to-human transmission

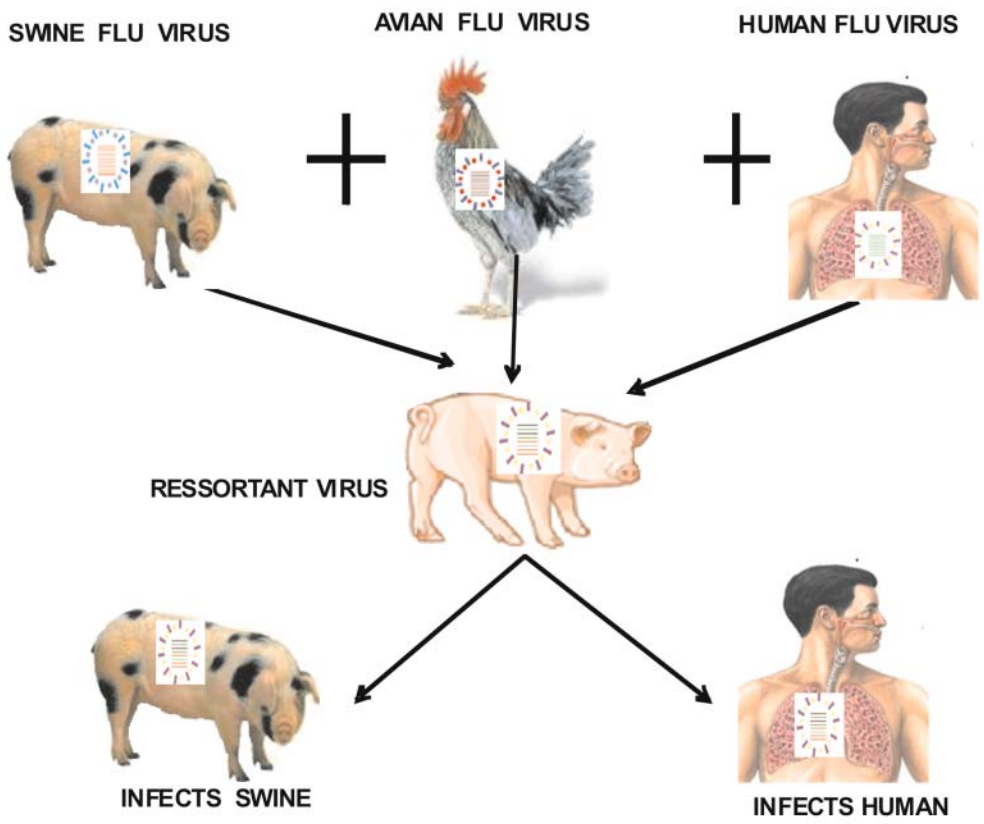

Figure 1. Genetic reassortment in influenza virus.

animals (Scholtissek *et al.* 1998). The same strains can infect and spread in both humans and pigs.

The novel H1N1 virus is a combination of the swine, human and avian flu genes drawn from different strains that infect pigs (MacKenzie 2009). The current H1N1 swine flu virus is a 'quadruple reassortant' virus, with six of its genes from flu viruses that were circulating in North American pigs and two genes of Eurasian origin (Vincent *et al.* 2008; Trifinov *et al.* 2009). CDC released the genomic sequences of viral RNAs from 6 swine flu isolates from California and Texas on 29 April 2009. The influenza viral genome consists of eight RNA segments, namely, PB1, PB2, PA, HA, NP, NA, MP and NS. The earliest reported swine flu cases from California were found to be epidemiologically unlinked yet genetically similar. The 2009 H1N1 virus contains a combination of gene segments that have previously not been reported in swine or human influenza viruses in the US or elsewhere. The NA and M gene segments are derived from the Eurasian swine genetic lineage. The HA, NP and NS gene segments are derived from the classical swine lineage, and the PB1, PB2 and PA gene segments from the swine triple reassortant lineage. The virus possesses the genetic marker (S31N in M2) for resistance to adamantane antivirals and is sensitive to oseltamivir and zanamivir in functional assays. There are no specific genetic markers found in the neuraminidase (NA) gene which are known to decrease the effect of NA inhibitors (Garten *et al.* 2009).

An evolutionary analysis of the critical NA protein produced by the 2009 virus showed that it has undergone extensive mutation as compared with other H1N1 strains. The NA of the 2009 H1N1 virus more closely resembles this protein from the H5N1 avian flu than the 1918 flu virus, and current mutations render the available vaccine less effective in case of this novel H1N1 virus. The commercial drugs Tamiflu and Relenza are less effective in treating the current virus than earlier viruses (MaurerStroh *et al.* 2009).

5. Virus transmission and clinical features

The mode of transmission of the virus may occur in three stages: (i) transmission between pigs, (ii) transmission from pigs to humans, and (iii) transmission within the human population. The main route of transmission in pigs is through direct contact between infected and uninfected animals (Kothalawala *et al.* 2006). These close contacts are common during animal transport. Intensive farming increases the risk of transmission, since pigs are raised in close proximity to each other (Gilchrist *et al.* 2007; Tim 2008). Direct transfer of the virus probably occurs either by pigs touching noses or

through dried mucus. Wild animals, such as wild boar, help in spreading the disease between farms (Vicente *et al.* 2002). Transmission of the virus from swine to human occurs when humans come in contact with an infected swine population. People working with poultry and swine are at increased risk for zoonotic infection and constitute a population of human hosts where zoonosis and reassortment can co-occur (Gray *et al.* 2007; Gray and Kayali 2009). Spread of the virus among human populations takes place commonly through sneezing and coughing via large-particle aerosols, as well as by contact with surfaces that have been contaminated with respiratory droplets (CDC 2009d).

Symptoms of infection in pigs include fever, anorexia leading to loss of weight, lethargy, inactivity, reluctance to move or even drink, prostration, paroxysmal coughing, sneezing, irregular abdominal breathing, and ocular and nasal discharge (Olsen 2004). Susceptible sows have very high temperatures leading to abortion and infertility. The precise incubation period of H1N1 infection ranges from 1 to 4 days. In human populations, frequently observed symptoms include sudden onset of fever (94%), cough (92%), sore throat (66%), running nose, bodyache, headache, chills and fatigue. A significant number have diarrhoea (25%) and vomiting (25%) (CDC 2009d) (table 2). Abortion and preterm birth have also been reported among pregnant women, especially those with pneumonia (McKinney *et al.* 1990). The chest X-ray shows a picture of pneumonia and mild fibrosis in severe patients. Studies have shown that, at the time of presentation, most patients have multifocal consolidation and develop pleural effusion and cavitation during the course of the disease. Additional features include pseudocavitation, pneumatocele formation, lymphadenopathy and centrilobular nodules (Qureshi *et al.* 2006; CDC 2009e).

6. Diagnosis

Diagnosis of the new reassortant virus needs to be updated accordingly. In response to the rise in H1N1 swine flu cases to alarming proportions, guidelines have been established by CDC for prompt diagnosis and effective management. Testing for H1N1 influenza A is required in individuals with acute febrile respiratory illness, or sepsis-like syndrome (CDC 2009f). Priority testing should be done of individuals requiring hospitalization, and those who are at high risk for severe complications (table 3). A nasopharyngeal aspirate or nasal wash should be collected. In intubated patients, an endotracheal aspirate should be used for diagnosis. Specimens should include all relevant information (USCDCP 2009a) and sent to laboratories that have P3 facilities.

Real-time polymerase chain reaction (RT-PCR) assay is currently the only technique available for confirmation of the novel swine H1N1 virus. Besides this, other methods may also be used. These include virus isolation from clinical samples of suspected cases and rapid diagnostic tests. The latter can help in the diagnosis and management of patients showing signs compatible with influenza.

Such tests detect seasonal influenza A and B. Direct or indirect immune-fluorescent antibody testing (DFA

Table 2. Clinical signs needing immediate medical intervention

In children	In adults
Influenza-like symptoms improve but then return with fever and cough	Influenza-like symptoms improve but return with fever and cough
Skin colour changes to blue or grey	Tightness in the chest or abdominal pain
Unable to take adequate fluids	Episodes of dizziness
Severe or continuous vomiting	Severe or continuous vomiting
Exhausted or not playing well	Marked tiredness and confusion
Increase in rate of breathing (tachypnoea) or dyspnoea	Troubled breathing or breathlessness

Table 3. Case definition recommended by the World Health Organization (WHO)

Confirmed case	An individual with laboratory-confirmed swine influenza A (H1N1) virus infection by one or more of the following tests: • real-time polymerase chain reaction (RT-PCR) • viral culture • Four-fold rise in swine influenza A (H1N1) virus-specific neutralizing antibodies
Probable case	An individual with an influenza test that is positive for influenza A, but is non-typable by reagents used to detect seasonal influenza virus infection OR A individual with a clinically compatible illness or who died of an unexplained acute respiratory illness who is considered to be epidemiologically linked to a probable or confirmed case

or IFA) can be employed in cases of suspected H1N1 swine influenza infection. However, information is not yet available on the use of rapid influenza diagnostic tests for novel H1N1 infection. A patient with a positive DFA or IFA may be considered a probable case if he/she meets the other criteria. A negative test does not rule out H1N1 influenza A infection since the antibodies used may not bind to targets on the virus and could result in false-negative results (USCDCP 2009b).

7. Prevention and treatment

Prevention of swine influenza depends on three key factors: prevention in swine, prevention of transmission to humans, and prevention of its spread among humans.

Methods for preventing the spread of influenza virus among swine include facility management, herd management and vaccination. Facility management includes the use of disinfectants and controlling the ambient temperature to limit the spread of virus in the environment. Herd management includes preventing the addition of infected pigs to the uninfected swine population (Gray *et al.* 2007). The potential candidates for vaccination against the H1N1 virus should include health-care workers, outbreak responders and swine breeders (Gray and Baker 2007).

Precautionary measures include the use of face masks and gloves by farmers and veterinarians when dealing with infected animals (Gray and Baker 2007). Studies show that swine flu cannot be spread by consuming pork products, since the virus is not transmitted through food (CDC 2009g). Recommendations to prevent spread of the virus among humans as recommended by CDC include washing the hands with soap and water or with alcohol-based hand sanitizers (Ryan *et al.* 2001). Social distancing is another tactic. It means staying away from people who might be infected and can include avoiding large gatherings, spreading out a little at work, or perhaps staying home and lying low if an infection is spreading in a community (Gray *et al.* 2007).

Swine influenza is rarely fatal in pigs; therefore, little treatment beyond rest and supportive care is required. Vaccination and animal management techniques play an indispensable role. Antibiotics are used to treat the disease; although they have no effect against the virus, they help prevent bacterial pneumonia and other secondary infections in influenza-weakened herds (VDPAM 2009). Antiviral therapy and vaccination represent the best protection against the current virus but an appropriate vaccine may take at least six months to develop (CFSPH 2009). CDC recommends that diagnosed cases of swine influenza should be treated with oseltamivir and zanamivir (CDC 2009h; Ramirez *et al.* 2006). Swine influenza virus has been shown to be resistant to standard antiviral drugs such as amantidine and rimantidine (CDC 2009h).

8. Containment

WHO has developed a framework of pandemic phases, revised in April 2005 and then in April 2009 (WHO 2009c). In late April, WHO raised the pandemic alert level for the novel H1N1 swine virus to phase 6 (figure 2).

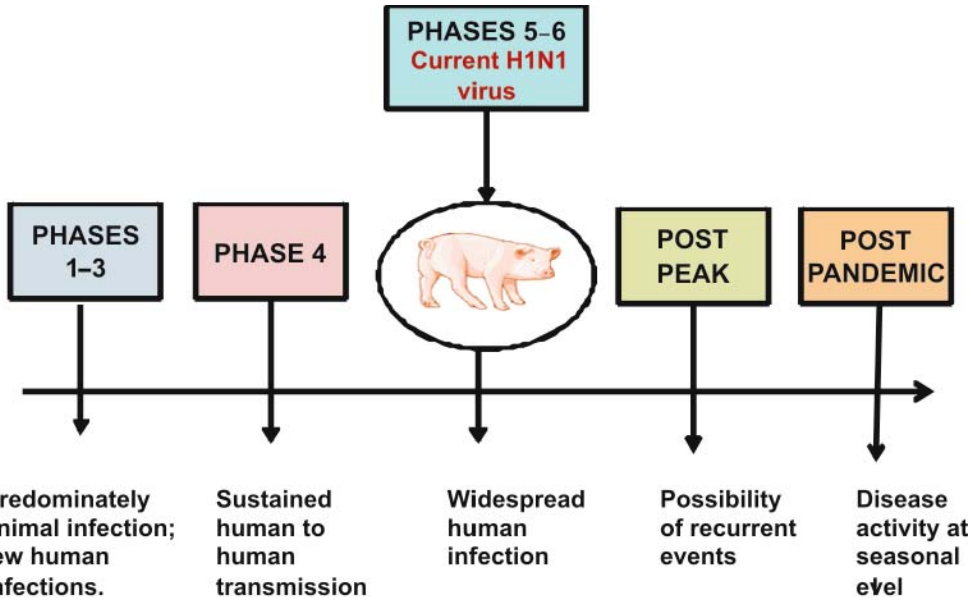

Figure 2. Stage-wise evolution of a pandemic

9. Response to an outbreak

Due to the global nature of influenza pandemics, there is a need for close international collaboration to develop sound prevention and control strategies. Enhancing global surveillance for influenza is crucial because an early warning of an impending pandemic might save thousands of lives. WHO is keeping a close eye on the current pandemic situation through the Global Alert and Response system, which is an integrated system for epidemics and other public health emergencies based on strong national public health systems and capacity, and an effective international system for a coordinated response. It has also emphasized the importance of epidemiological training and laboratory analysis as well as communication attributes (WHO 2009d).

In the wake of the current H1N1 pandemic, WHO and CDC are coordinating with laboratories worldwide to control the virus (CDC 2008). The activities undertaken so far as a part of global surveillance include: daily updates on newly diagnosed cases and deaths, laboratory guidelines for the collection of samples from suspected cases, guidelines for the safety of workers and personal hygiene, sequences of swine HINI virus and protocols for RT-PCR (WHO 2009e). To decrease the transmission of the virus in the community, strict vigilance is being carried out at airports, especially among passengers arriving from countries with reported cases of flu infection. Passengers are being screened for the symptoms of influenza and suspected cases are kept in isolation and treated with antiviral drugs until they show signs of improvement.

It is critically important to develop candidate pandemic influenza vaccine seeds now for influenza A subtypes that pose a pandemic threat. Initiatives are being taken by CDC to design a vaccine by reverse genetics and classical reassortment technology by propagating the reference swine flu virus strains in eggs. The best defence against the next pandemic will be to strengthen the global capacity to respond to yearly epidemics of influenza. By consolidating this capacity, thousands of lives could be saved and better preparedness would be established for the next pandemic.

10. Indian scenario

The first case of swine flu (H1N1) virus in India was reported on 13 May 2009. The second case was reported by the National Institute of Virology (NIV), Pune in a mother and son duo from Chennai, on 1 June 2009. A total of 14,777 persons have been tested so far out of which 2,772 have been reported positive for swine H1N1. The laboratory confirmed deaths reported by the States as on 23rd August 2009 are 60, with Maharashtra (36), Karnataka (12), Gujarat (6), Tamil Nadu (3), Delhi (2) and Kerala (1) as their individual death toll (MOHFW 2009). The Government of India has initiated a series of preventive actions approved by the Inter-Ministerial Task Force (IMTF) on Influenza at its meeting held on 28 April 2009 to carry out surveillance activities (WHO 2009f). All health-care facilities in states under the country's Integrated Disease Surveillance Project (IDSP) and medical colleges are being activated to report on influenza-like illnesses and pneumonia cases. The Government is required to communicate risks, personal protective measures and preventive guidelines through the mass media to the public. The Ministry of Health and Family Welfare has rolled out a structured media campaign on the prevention of flu infection.

In the wake of threat posed by the influenza A (HINI), the Government of India has authorized a number of hospitals across the country to test and treat cases of swine flu: among them are the National Institute of Virology (Pune), National Institute for Communicable Diseases (Delhi), All India Institute of Medical Sciences (Delhi), King Institute of Preventive Medicine (Chennai), and Vallabh Bhai Patel Chest Institute (Delhi). Haffkine Institute (Mumbai), National Institute of Cholera and Enteric Diseases (NICED, Kolkata), are among the authorized testing centers. Dr Ram Manohar Lohia Hospital (Delhi), Kasturba Gandhi Hospital, Sir J J Hospital (Mumbai), ID Hospital (Kolkata), Victoria Hospital, SDS Tuberculosis and Rajiv Gandhi Institute of Chest Diseases (Bangalore), Communicable Diseases Hospital are some of the screening centers.

The Indian pharmaceutical company Cipla is manufacturing a generic version of Tamiflu at lower than normal prices. India has made an effort to upscale the stock of antivirals to 10 million as compared to the earlier availability of 1 million, which is quite limited for the huge Indian population. CDC is working in collaboration with the Food and Drug Administration (FDA) and National Institutes of Health (NIH) to prepare a vaccine against the swine flu virus. A 'reference stock virus' will be made in fertilized hen eggs, and further distributed to laboratories (Schaffhausen 2009). CDC will provide its seed to the Serum Institute of India, Ltd., Pune to develop a vaccine against the presently circulating strain of swine flu (H1N1) virus (*The Hindu* 2009). Presently, the institute is seeking permission from the Drug Controller General of India for starting preclinical and clinical development of the HINI vaccine.

A vaccine that will prove effective against the new H1N1 swine influenza virus is still awaited. In India, two more pharmaceutical companies; Bharat Biotech, and Panacea Biotech have also started working on developing the vaccine along with Serum Institute of India against the novel H1N1 virus and have also submitted their plans to launch the vaccine by March 2010.The issue of development of a suitable vaccine has been addressed aggressively by the

sharing of updated information between different countries. The most urgent aspect required for preventing the spread of the virus is planning and coordination between various countries.

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