

**SWINE FLU
EMERGING THREAT****VIEW POINT****Emergence of Swine Origin Influenza (H1N1 Virus)****Sandeep Dogra**

In the new millennium, emergence of three novel Influenza A viruses; SARS virus (a novel Corona virus) in 2003, Influenza H5N1 ('Avian flu') in 2004 and the present new strain of Influenza virus 2009 A/H1N1 has demonstrated the collective vulnerability of humankind to pandemic spread of respiratory viruses. In April 2009, a novel influenza A virus, also called swine-origin influenza A (H1N1) virus (S-OIV), was identified in Mexico (1). After its discovery, S-OIV rapidly spread throughout the world within few weeks. This novel S-OIV is a hybrid virus containing a combination of swine, avian, and human influenza virus genes. In sharp contrast to SARS and Avian Influenza H5N1 viruses which emerged from the Asian continent, S-OIV virus emerged from North America. Indeed, one of the notable features of the current strain of S-OIV virus is the high efficiency of human-to-human transmission. This probably explains the alarming spread of the virus across the globe in a very short time and therefore poses a serious pandemic threat.

Influenza virus is an enveloped RNA virus of the Orthomyxoviridae family. It is divided into three serologically different types (A, B, and C) according to the antigenicity of conserved inner virus structures, i.e., the nucleoprotein (NP) and matrix proteins (M1 and M2) of the envelope. It is endowed with an inherent capacity for genetic variation and is based on the presence of a segmented genome, with eight RNA segments that are genetically independent of each other. Depending on the antigenicity of two envelope spikes, which first mediate virus adsorption to target cells in vivo or erythrocytes in vitro (hemagglutinin, H) and second the release of viral progeny from the infected cells (neuraminidase, N), influenza A viruses are divided into 16 H (H1-H16) and 9 N (N1-N9) groups resulting in theoretically 16×9 serologic subtypes. Influenza viruses harbor a negative-sense RNA genome, which is transcribed by its own polymerase. RNA transcription is associated with many point mutations persistently producing many changes in virus proteins including the surface proteins H and N

(2,3). The mutations in surface proteins result in antigen drift which helps the virus to escape the immunity of its host. Since the influenza virus genome is segmented into eight parts, two or more different virus variants infecting the same cell can produce progeny virus with a mixed genome, which supports the variability of viral structures. It may result in an antigenic shift, if two different subtypes of influenza A virus reassort their genomic segments. The emergence of H2N2 and H3N2 in mankind has been traced to such genomic reassortment (4). These unique molecular features coupled with the ability of the virus to cause infection in a wide host range of humans, domestic animals and birds render it a potential pandemic agent. Domestic pigs and birds because of their proximity to humans provide a great opportunity for the occurrence of mixed influenza infections. Consequently, pigs and birds act as 'melting pots' for re-assortment of viruses and play a crucial role in evolution of influenza pandemics. The current outbreak of S-OIV is a rare recombination of gene segments from swine with avian and human influenza strains. Genomic analysis of the 2009 S-OIV virus in humans indicates that it is closely related to common reassortant swine influenza A viruses isolated in North America, Europe, and Asia (*Fig-1*) (5-7). The segments coding for the polymerase complex, hemagglutinin, nuclear protein, and nonstructural proteins show high similarity with the swine H1N2 influenza A viruses isolated in North America in the late 1990s. H1N2 and other subtypes are descendants of the triple-reassortant swine H3N2 viruses isolated in North America. They have spread in swine hosts around the globe and have been found to infect humans (8). The segments coding for the neuraminidase and the matrix proteins of the new human H1N1 virus are, however, distantly related to swine viruses isolated in Europe in the early 1990s.

The outcome of influenza virus infection is influenced by the host's immune status and the virulence of the influenza strain (9). In an immunologically competent host, protective immune responses are mostly directed against

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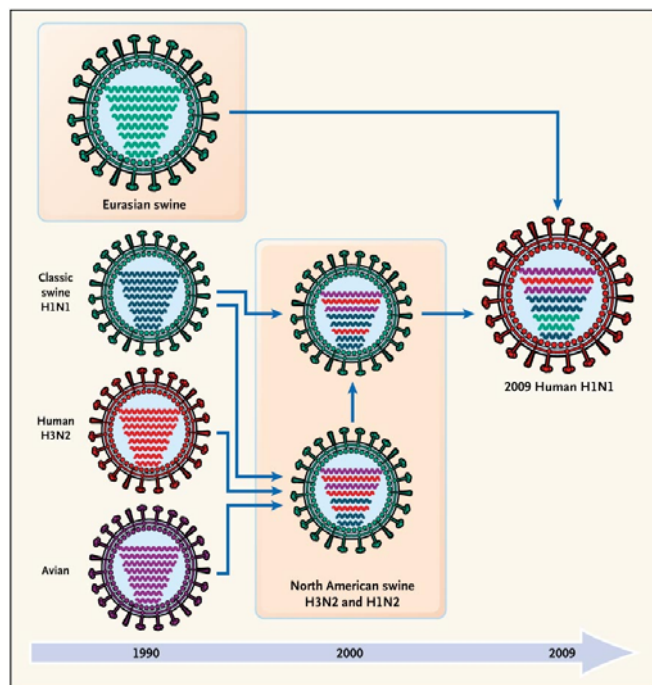


Fig.1 Showing History of Reassortment Events in the Evolution of the 2009 Influenza A (H1N1) Virus

the influenza virus major surface glycoproteins H and N. In case of a naïve host, virulence is mostly determined by the virus. The novel genetics of S-OIV reduce the probability of a substantial immunity in humans although some protection of humans that had been infected naturally with H1N1 viruses cannot be excluded. Antibodies to the matrix M2 protein, which is conserved within A-type influenza viruses, are cross-protective between different subtype-virus infections, although the level of protection is limited. Moreover, peptides generated from influenza endogenous antigens such as NP which are targets for cytotoxic lymphocytes may elicit immune responses that show cross-reactivity in their recognition of the different subtypes of human influenza A viruses(10,11). A preliminary analysis of S-OIV proteins involved in virus virulence and pathogenicity revealed that they are most similar to strains that cause mild symptoms in humans. The incubation time appears to range between 2 and 7 days for S-OIV(12). Based on seasonal influenza data, viral shedding might be expected from 1 day prior to disease onset until 5-7 days after first symptoms or until symptoms resolve. In certain patient groups including immunocompromised individuals, severely ill patients, and young children virus shedding time may be prolonged (13). Research on previous pandemic strains suggested that mortality can vary widely between different countries, with mortality being concentrated in the developing world

Table 1. Influenza Pandemics since the 20th Century

Year	Virus subtype	Deaths(estimated)	Reassortment
1918/1919	"Spanish Xu" H1N1	50 million	All segments of avian origin
1957-1963	"Asian Xu" H2N2	2-4 million	Five segments of H1N1 + PB1, HA, NA of avian origin
1968-1970	"Hong Kong Xu" H3N2	1-2 million	Six segments of H2N2 + PB1, HA of avian origin
1977-1979	"Russian Xu" H1N1	0.7 million	Identical with "Spanish Xu" virus
2009-?	Swine-origin inXuenza A virus H1N1	?	Three segments of clasis swine North America, two segments avian North america, one segment H3N2, two segments Eurasian swine lineage

(14). Nutritional status of the host can influence not only the host response to the pathogen, but can also influence the genetic make-up of the viral genome (15). Moreover, bacterial co-infections are also being considered as possible cause for differences in outcome of influenza infection in different locations. It has been suggested that the majority of deaths in 1918-1919 influenza pandemic likely resulted directly from secondary bacterial pneumonia caused by common upper respiratory-tract bacteria (largely streptococcal or pneumococcal bronchopneumonias) rather than from "primary" viral pneumonia (i.e., with little or no bacterial growth) (16). In the current S-OIV outbreak, the cause of first deaths was diagnosed as atypical pneumonia, a pneumonia which, helped by the influenza, becomes more dangerous. Such situation requires early and aggressive treatment, including antibiotic and intensive care which may be less available in some areas resulting in increased morbidity and mortality. This also suggests that antibiotic treatment should be included in any preparedness strategy. Notably, choice of adequate antibiotic therapy may be crucial. Some antibiotics may even heighten morbidity and mortality (17). Other antibiotics like some macrolide antibiotics were shown to inhibit replication of influenza A viruses in vitro (18) and exert inhibitory effects on influenza infection in vivo in animal models (19). Influenza A viruses including S-OIV are transmitted from infected individuals through air by coughs or sneezes, creating aerosols containing the virus (20,21). Influenza can also be transmitted by saliva, nasal secretions, feces, and blood. Infections occur through contact with these body fluids or with contaminated surfaces. Influenza viruses can remain infectious for about 1 week at human body temperature, over 30 days at 0°C, and indefinitely at very low temperatures. However, most influenza strains can be inactivated easily by disinfectants and detergents (22). Moreover, influenza A viruses are relatively sensitive to higher temperatures. Importantly, swine influenza virus are killed by cooking temperatures of 70°C, corresponding to the general guidance for the preparation of pork and other meat.



The recommended procedure for laboratory diagnosis of S-OIV virus infection is real-time reverse-transcriptase PCR or culture (19). To establish the diagnosis of S-OIV in the laboratory, an upper respiratory sample (nasopharyngeal swab, nasal swab, throat swab, combined oropharyngeal/nasopharyngeal swab, or nasal aspirate) should be collected (23). In intubated patients, an endotracheal aspirate should also be obtained. Swabs with a synthetic tip (e.g., polyester or Dacron) and an aluminium or plastic shaft should be used. Swabs with cotton tips and wooden shafts are not recommended. Swabs made of calcium alginate are not acceptable. The collection vial in which the swab is placed should contain one to three ml of viral transport media (VTM). Specimens should be placed in viral transport media and placed on ice (4°C) or refrigerated immediately for transportation to the laboratory (23). Once the samples arrive in the laboratory, they should be stored either in a refrigerator at 4°C or in a minus 70°C freezer. If a minus 70°C freezer is not available, they should be kept refrigerated, preferably for less than or equal to one week. Specimens should be shipped on dry ice to the designated laboratories in clearly labeled containers and should include all information requested by the state health laboratory (23).

The early phases of pandemic present decision makers with predictable challenges that have been evident as the current novel S-OIV virus has spread. No reasonable forecasts can be made about how this pandemic may evolve in future. Nevertheless, the only way to avoid an influenza pandemic is an effective vaccination program. Therefore, it is important to increase and coordinate preventive activities at a global level to slow virus transmission to provide enough time for the preparation and distribution of a well-matched vaccine. India should seize this opportunity to strengthen its capability to tackle the pandemic.

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