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Current Status & Future Perspectives of Swine Influenza

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Introduction

The word "Influenza" is derived from an Italian word influence meaning thought to be caused by influence of stars. Swine Influenza is a highly contagious acute respiratory disease of pigs caused by one of the several strains of swine influenza A. The main modes of transmission of the disease includes: aerosols, direct and indirect contact and asymptomatic carrier pigs. However, it is not acquired by eating pig products. The morbidity is usually high and the case fatality rate is low. Occasionally it affects other species i.e., turkeys, mink, ferrets and humans.

Most infections are limited to the person who had contact with pigs, although it can occasionally spread to family members or others in close contact. Humans transmit the virus to herds of pigs, and it reassorts with various swine influenza viruses. One of the major reservoirs for influenza A viruses are the aquatic birds.Pigs play an important role in the transmission of novel viruses to humans. Since human, avian and SIVs can replicate in pigs they are popularly termed as the "mixing vessel".

According to the report by CDC, during the 2009 pandemic 43 to 89 million cases of swine flu were reported during a 1-year span, with 1799 deaths in 178 countries worldwide.

Epidemiology

It is seen predominantly in the Mid-western United States, Mexico, Canada, South America, Europe (including UK, Sweden, and Italy), Kenya, Mainland China, Taiwan, Japan, and parts of eastern Asia and in various parts of India. The genetic reassortment between

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North American and Eurasian swine influenza viruses led to the 2009-2010 pandemic. The reassortment of the viral RNA structure is responsible for its human to human transfer.

Etiology

The virus of Swine flu belongs to the Orthomyxovirus (Single stranded RNA virus) which is roughly spherical having a diameter of 80 to 120 nm and RNA genome size of 13.5 kb (approx.)The virus has 8 different genomic region which are segmented and encode for 11 different proteins. Hemagglutinin (HA) and neuraminidase (NA) are the envelope proteins. Viral RNA polymerases are PB2, PB1, PB1-F2, PA, and PB. The matrix proteins are M1 and M2 and non structural proteins are NS1 and NS2 (NEP).Both the matrix and non structural proteins are crucial for efficient pathogenesis and viral replication.

Major targets for the immune response are HA and to a lesser extent NA. There is little or no cross-protection between different HA or NA types. High variability of the virus is due to mutation and genetic reassortment whereas mutations are mainly responsible for the antigenic drift. Once these proteins have changed sufficiently, immune responses against the former HA and NA may no longer be protective. Genetic reassortment leads to more rapid changes and can generate viruses containing either a new HA, a new NA, or both. 'antigenic shifts,'

Pig's flu is classified as : Influenza A, B, C.

There are 3 genera of influenza viruses: one cause human flu, two also cause influenza in pigs, with influenza virus A being common in pigs and influenza virus C being rare.

Influenza B: not reported in pigs.

Within influenza virus A and C, the strains found in pigs and humans are largely distinct, although due to reassortment there have been transfers of genes among strains crossing swine, avian, and human species boundaries.

PATHOGENESIS

The exact mode of transmission is not known. The main transmission is thought to occur mainly through the dissemination of large droplets and possibly small-particle droplet nuclei. Contact with fomites contaminated with respiratory or gastrointestinal material is another mode of transmission.The potential for fecal viral shedding and subsequent feco–oral transmission should be considered and investigated. Incubation period of the virus is 2 to 7

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days. However, in young children and in immunocompromised or severely ill patients the infectious period is longer.

Once established in swine, influenza viruses of human or avian origin pose a substantial threat to swine population's health and may spread to other geographically segregated populations.Threat of introduction or re-introduction into the human is associated with outbreak and pandemic risks. This risk was exemplified by the re-introduction of the H3N2v (variant) virus with surface glycoprotein genes of human origin to over 300 people in 2011–12 from an H3N2 virus that had been endemic in swines in the U.S. since the late 1990s.

Clinical signs

Illness may be seen only in certain age groups, while other animals remain asymptomatic. The clinical signs may include: fever, lethargy, anorexia, weight loss, coughing, sneezing, nasal and ocular discharge, conjunctivitis, labored breathing (expiratory dyspnea or "thumping"). All of these signs do not occur in all infected animals.

The cough usually develops after a few days, at time when fever starts to diminish. Abortion may be seen in some herds. Secondary or concurrent bacterial or viral infections, other illnesses and stressors such as transport can exacerbate the clinical signs. Severe, potentially fatal bronchopneumonia is also occasionally seen. The virus can also circulate among pigs with few or no clinical signs.

In humans, the symptoms of swine flu are similar to those of influenza namely chills, fever, sore throat, muscle pains, severe headache, coughing, weakness, and general discomfort. The clinical spectrum of novel swine influenza infection are both self-limited illness or in severe outcomes. It can lead to respiratory failure and death. Deaths associated with seasonal influenza epidemics largely comprise as the result of secondary complications, including

1. Primary viral pneumonia
2. Secondary bacterial pneumonia (particularly with group *Streptococcus, Staphylococcus aureus*, and *Strep. pneumoniae*)
3. Exacerbations of underlying chronic conditions

Diagnostic tests

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Virus isolation: This test is useful for the characterization of influenza viruses. The virus are grown in embryonated chicken eggs or cell cultures (e.g., Madin–Darby canine kidney cells). For this the lung tissues at necropsy, and from nasal swabs (and some other respiratory or oral fluid samples) are collected from acutely ill pigs. Samples are ideally collected within 24-72 hours after the onset of clinical signs.

Isolated viruses can be subtyped with hemagglutination inhibition and neuraminidase inhibition tests or RT-PCR, as well as by sequence analysis of the viral HA and NA genes.

Detection of viral antigens or nucleic acids

Serology

RT-PCR assays: It detects viral RNA in tissue samples and respiratory or oral fluids. Immunohistochemistry or immunofluorescence:It identifies antigens in lung tissue samples, nasal epithelial cells or bronchoalveolar lavage fluids.

ELISAs are also used to detect the antigens

The hemagglutination inhibition test: The HI test is subtype specific and is used most often but it may not detect new viruses.

Other serological assays (e.g., virus neutralization, indirect fluorescent antibody test, agar gel immunodiffusion) have been described in swine, but are not commonly used.

The major issue with serological tests is the cross reactivity. Although the extent of its interference can differ with the viruses present in an area, as well as the test.

Laboratory Diagnosis

A diagnosis of confirmed swine flu requires laboratory testing of a respiratory sample (a simple nose and throat swab). The CDC has developed a Swine Influenza Virus Real-Time PCR Detection Panel. Among the various diagnostic tests used are-

Real-Time PCR:

- Detect seasonal influenza A, B, H1, H3, and avian H5 serotypes
- Primers and probes specific for swine influenza A (H1 and H3 subtypes) were recently developed and tested for use in a modified version of this assay for the detection of human infection with swine influenza viruses.

Nucleotide Sequencing

- Amplicons for gene sequencing : Reverse transcription

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- Followed by PCR amplification to generate overlapping double-stranded DNA amplicons covering each of eight segments of the influenza virus genome.

Phylogenetic analysis

- Phylogenetic analysis of sequences contained six gene segments (PB2, PB1, PA, HA, NP, and NS) which were found in triple-reassortant swine influenza viruses circulating in pigs. The genes encoding neuraminidase (NA) and M protein (M) were most closely related to those in influenza A viruses circulating in swine populations.

Treatment

Treatment is not specific. Supportive care along with the antibiotic is commonly used to control the secondary infections. Antiviral drugs used to treat human influenza are not generally administered to swine.

Swine-origin influenza antiviral medication dosing recommendations (FDA, 2009)

Agent, group		Treatment	Chemoprophylaxis
Oseltamivir			
Adults		75 mg capsule twice/day for 5 days	75 mg capsule once/day
Children (age 12 months/older)	15 kg or less	60 mg per/day divided into two doses	30 mg once/day
	15-23 kg	90 mg/day divided into two doses	45 mg once/day
	24-40 kg	120 mg/day divided into two doses	60 mg once/day
	More than 40 kg	150 mg/day divided into two doses	75 mg once/day
Zanamivir			
Adults	Two 5 mg inhalations (10 mg total) twice/day		Two 5 mg inhalations (10 mg total) once/day

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Children	Two 5 mg inhalations (10 mg total) twice/day, age 7 years or older)	Two 5 mg inhalations (10 mg total) once/day (age 5 years or older).

The drug of choice in case of humans is Tamiflu. Human influenza A is susceptible to both oseltamivir and zanamivir.Two classes of antiviral medication are available for the treatment of seasonal human influenza: Neuraminidase inhibitors (oseltamivir and zanamivir)and Adamantanes (rimantadine and amantadine).

As per the CDC report, during the 2008–2009 pandemic, almost all circulating human influenza A (H1N1) viruses in the United States were resistant to oseltamivir. However, genetic and phenotypic analyses showed that the virus was susceptible to oseltamivir and zanamivir but resistant to the adamantanes.

The emergency-use authorization of oseltamivir to treat influenza in infants under the age of 1 year (treatment that is normally approved for those 1 year of age or older) and for chemoprophylaxis in infants older than 3 months of age (chemoprophylaxis that is normally approved for children 1 year of age or older) was given by the FDA in 2009

Prevention and Control

Management measures such as

- All-in/all-out production
- Isolating newly acquired pigs (or animals returning to a facility) and testing before release also reduces the risk of transmission to the rest of the herd.
- Biosecurity plans include avoiding contact with wild and feral pigs, wild birds (especially waterfowl and other birds from aquatic habitats), poultry, people, unsafe water sources that may contain viruses, and possibly even other species such as horses.
- Sanitation and routine hygiene help prevent transmission of fomites and mechanical vectors.
- To prevent human influenza viruses (including 2009 pandemic H1N1 virus) from entering a herd, swine workers and others who have influenza-like illnesses should avoid contact with pigs, and the public should be restricted from entering swine pens.

Prevention of pig to human transmission

- Transmission is believed to occur mainly in swine farms where farmers are in close contact with live pigs.

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- Major method of limiting swine to human transmission is swine vaccination.
- Risk factors include smoking and not wearing gloves when working with sick animals.

CDC recommendations for health care workers who provide direct care for patients with known or suspected swine influenza infection is that they should keep a check on contact and droplet precautions, including the use of gowns, gloves, eye protection, face masks, and fit-tested, disposable N95 respirators. If a patient is confirmed or suspected for swine influenza then a single-patient room with the closed door and airborne-infection isolation rooms with negative-pressure handling should be prepared.

Swine influenza vaccines

Pigs are susceptible to infection with many subtypes of influenza A virus. Only three subtypes (H1N1, H1N2 and H3N2) are consistently isolated from swine herds worldwide and antigenic shift and drift of SIVs are constantly reported. Only inactivated whole-virus vaccines are commercially available and widely used for swine influenza worldwide. Three major difficulties with the use of current commercially available inactivated SIV vaccines are:

1. SIV is antigenically changing faster than traditional inactivated vaccines can be developed.
2. The commercially available inactivated SIV vaccines do not provide good cross-protection among different SIV isolates, especially against heterovariant and heterosubtypic viruses.
3. Passively acquired immunity (MDA) can interfere with vaccine immunity in piglets.

Other vaccines available are: live attenuated, live-attenuated swine influenza vaccine with modified NS1 protein, Elastase-dependent live attenuated, Cold-adapted live attenuated vaccine, Baculovirus-derived influenza subunit vaccine, Vectored vaccines (Adenovirus-based SIV vaccine, Alphavirus-based SIV vaccines, Pseudorabies virus (PRV)-based SIV vaccines, Vaccinia virus based vaccine, Virus-like particle (VLP) vaccines, Plasmid DNA-based vaccines).

Vaxiflu-S, (0.5ml i.m) is the first indigenous influenza vaccine in India since Independence (Inactivated Influenza vaccine). Its side effects, experts say, are minor which include fever, aches, and mild soreness.Guillain Barre Syndrome is another side effect which

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is rarely observed in one in a million cases. It is recommended to humans above the age of 18 years.

'Nasovac' is first intra-nasal vaccine for swine flu, produced in Pune, India (live attenuated) and can be used for adults and children above three years.At present no side effects of the vaccine are known, but it is contraindicated in pregnant woman and lactating mothers.

Future Aspects

In comparison to humans and mice, there is a big knowledge gap in swine immunology. Therefore, the cell mediated and humoral immune responses at the systemic and mucosal levels need to be analyzed in future pig studies in order to develop better vaccines for the swine industry. A priority for novel SIV vaccine development i.e., improvement of heterovariant and heterosubtypic immunity and the selection of currently circulating SIV isolates as vaccine seeds is the need of the hour. Since MDA can be used to express the HA from influenza A viruses, it might be a promising future influenza vaccine.

Conclusion

Swine flu is an emerging viral infection and present global public health concern. Lessons from the outbreaks of H1N1 virus pandemic teach us that influenza viruses are important zoonotic pathogens and surveillance for SIVs in pigs is necessary to prevent and control future pandemics.Hence, there is need to develop more efficient delivery strategies that allow administration of DNA to easily accessible sites on the pig's body and overcome the difficulties encountered by traditional killed vaccines.

Procedures for new vaccine licensure are required to be updated to keep pace with the fast changes in influenza virus genetics along with the improvement of heterovariant and heterosubtypic immunity. National and international government agencies need to adjust policies on influenza surveillance and vaccine licensing in order to protect the public health and the swine industry.