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SWINE FLU - A DESCRIPTIVE REVIEW

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ABSTRACT
Swine influenza, also called pig influenza, swine flu, hog flu and pig flu, is an infection by any one of several types of swine influenza virus. Swine influenza virus (SIV) or S-OIV (swine-origin influenza virus) is any strain of the influenza family of viruses that is endemic in pigs. In H1N1, the 'H' refers to the hemagglutinin protein, and the 'N' refers to the neuraminidase protein. While at present the virus is causing a mild disease, the next wave may be more severe. Influenza is a simple virus, with just eight genes, but it makes poor copies of itself, leading to constant mutation. Influenza viruses are by nature unstable and unpredictable and have the unique capability of changing their antigenic characteristics by mutation. Occasionally, novel strains also emerge, often through re-assortment or exchange of genetic material among influenza viruses from different animal, human or bird sources. Such genetic restructuring occurs regularly in nature and, at times, provides the virus with the capability of causing widespread disease in immunologically naïve populations.
KEYWORDS: influenza virus, H1N1, Hemagglutinin (HA) and neuraminidase (NA)

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INTRODUCTION

Swine Influenza (swine flu) is a respiratory disease of pigs caused by type A influenza viruses (H1N1 subtype) that causes regular outbreaks in pigs. People do not normally get swine flu, but human infections can and do happen. Swine flu viruses have been reported to spread from person-to-person, but in the past, this transmission was limited and not sustained beyond three people[1]. Swine flu viruses cause high levels of illness and low death rates in pigs. Swine influenza viruses may circulate among swine throughout the year, but most outbreaks occur during the late fall and winter months similar to outbreaks in humans. The classical swine flu virus (an influenza type A H1N1 virus) was first isolated from a pig in 1930[2,3]. In April 2009 a new type began to infect people, probably starting with people who worked with pigs in Mexico and the US. It has been passed from person to person around the world. It causes an illness very much like seasonal flu. The virus passes around in the way normal seasonal flu, or colds, pass around – in airborne droplets when people cough or sneeze, and by people touching surfaces that have been infected by these droplets. Doctors classify viruses using numbers and letters. The type of flu we're talking about here is being called influenza type A, H1N1 2009. The reason people worry about a new strain is that people won't have built up immunity to fight it off, and it's hard to tell at first how widely it will spread, or how badly it will affect people[4]. Swine flu is an infection caused by a virus. This virus is contagious and can spread from human to human. In 2009 the media labeled as "swine flu", the flu caused the 2009's new strain of swine -origin A/H1N1 pandemic virus just as it had earlier dubbed as "avian flu" flu caused by the recent Asian- linage HPAI (High Pathogenic Avian Influenza).

Type of swine flu viruses

Like all influenza viruses, swine flu viruses change constantly. Pigs can be infected by avian influenza and human influenza viruses as well as swine influenza viruses. When influenza viruses from different species infect pigs, the viruses can reassert (i.e. swap genes i.e. can include more genes) and new viruses that are a mix of swine, human and/or avian influenza viruses can emerge. Over the years, different variations of swine flu viruses have emerged. At this time, there are four main influenza type A virus subtypes that have been isolated in pigs: H1N1, H1N2, H3N2, and H3N1. However, most

of the recently isolated influenza viruses from pigs have been H1N1 viruses[2,3].

Structure, properties, and subtype nomenclature

Influenza viruses A, B and C are very similar in overall structure[5]. The virus particle is 80–120 nanometers in diameter and usually roughly spherical, although filamentous forms can occur[5,6]. These filamentous forms are more common in influenza C, which can form cordlike structures up to 500 micrometers long on the surfaces of infected cells. However, despite these varied shapes, the viral particles of all influenza viruses are similar in composition[7]. These are made of a viral envelope containing two main types of glycoprotein's, wrapped around a central core. The central core contains the viral RNA genome and other viral proteins that package and protect this RNA. RNA tends to be single stranded but in special cases it is double[6]. Unusually for a virus, its genome is not a single piece of nucleic acid; instead, it contains seven or eight pieces of segmented negative-sense RNA, each piece of RNA containing either one or two genes[7]. For example, the influenza A genome contains 11 genes on eight pieces of RNA, encoding for 11 proteins: hemagglutinin(HA), neuraminidase(NA), nucleoprotein (NP), M1, M2, NS1, NS2(Nucleo Export Protein), PA, PB1, PB1-F2 and PB2[8].

Hemagglutinin (HA) and neuraminidase (NA) are the two large glycoprotein's on the outside of the viral particles. HA is a lectin that mediates binding of the virus to target cells and entry of the viral genome into the target cell, while NA is involved in the release of progeny virus from infected cells, by cleaving sugars that bind the mature viral particles[9]. Thus, these proteins are targets for antiviral drugs[10]. Furthermore, they are antigens to which antibodies can be raised. Influenza A viruses are classified into subtypes based on antibody responses to HA and NA. These different types of HA and NA form the basis of the H and N distinctions in, for example, H5N1[11]. There are 16 H and 9 N subtypes known, but only H 1, 2 and 3, and N 1 and 2 are commonly found in humans[12].

Different from ordinary flu

Swine flu is a respiratory disease and has some elements of a virus found in pigs. There is no evidence of this disease circulating in pigs in the UK and scientists are investigating its origins. Swine flu has been confirmed in a number of countries and it is spreading from human to human, which could lead to what is referred to as a pandemic flu outbreak. Pandemic flu is different from ordinary flu because it's a new flu virus that appears in humans and spreads very quickly from person to person worldwide. The World Health Organization (WHO) is closely monitoring cases of swine flu globally to see whether this virus develops into a pandemic. Because it's a new virus, no one will have immunity to it and everyone could be at risk of catching it. This includes healthy adults as well as older people, young children and those with existing medical conditions[13,14].

Transmission of swine flu

Influenza viruses can be directly transmitted from pigs to people and from people to pigs. Human infection with flu viruses from pigs are most likely to occur when people are in close proximity to infected pigs, such as in pig barns and livestock exhibits housing pigs at fairs. Human-to-human transmission of swine flu can also occur. Flu viruses are made up of tiny particles that can be spread through the droplets that come out of nose and mouth when someone cough or sneeze. When anybody cough or sneeze without covering their nose and mouth with a tissue, those droplets can spread and others will be at risk of breathing them in. If someone cough or sneeze into one's hand, those droplets and the germs in them are then easily spread from his hand to any hard surfaces that that person touch, and they can live on those surfaces for some time. Everyday items such as door handles, computer keyboards, mobile and ordinary phones and the TV remote control are all common surfaces where flu viruses can be found. If other people touch these surfaces and then touch their faces, the germs can enter their systems and they can become infected. That's how all cold and flu viruses, including swine flu, are passed on from person to person. Swine influenza viruses are not transmitted by food. One can not get swine influenza from eating pork or pork products. Eating properly handled and cooked pork and pork products is safe. Cooking pork to an internal temperature of 160°F kills the swine flu virus as it does other bacteria and viruses[13,15]. **(Figure 1)**

Replication of influenza- A virus

Viruses can only replicate in living cells[16]. Influenza infection and replication is a multi-step process:

Firstly, the virus has to bind to and enter the cell, then deliver its genome to a site where it can produce new copies of viral proteins and RNA, assemble these components into new viral particles and finally exit the host cell[7].

- Influenza viruses bind through hemagglutinin onto the surfaces of epithelial cells; typically in the nose, throat and lungs of mammals. After the hemagglutinin is cleaved by a protease, the cell imports the virus by endocytosis.(Stage 1)[17,18].

- Once inside the cell, the acidic conditions in the viral endosome cause two events to happen: first part of the hemagglutinin protein fuses the viral envelope with the vacuole's membrane, then the M2 ion channel allows protons to move through the viral envelope and acidify the core of the virus[19], which causes the core to dissemble and release the viral RNA and core proteins[20]. The viral RNA (vRNA) molecules, accessory proteins and RNA-dependent RNA polymerase are then released into the cytoplasm (Stage 2)[21].
- These core proteins and vRNA form a complex that is transported into the cell nucleus, where the RNA-dependent RNA polymerase begins transcribing complementary positive-sense vRNA (Steps 3a and b)[22].
- The vRNA is either exported into the cytoplasm and translated (step 4), or remains in the nucleus.
- Newly synthesized viral proteins are either secreted through the Golgi apparatus onto the cell surface (Step 5b) or transported back into the nucleus to bind vRNA and form new viral genome particles (step 5a).

Other viral proteins have multiple actions in the host cell, including degrading cellular mRNA and using the released nucleotides for vRNA synthesis and also inhibiting translation of host-cell mRNAs[23]. Negative-sense vRNAs that form the genomes of future viruses, RNA-dependent RNA polymerase, and other viral proteins are assembled into a virion.

- The vRNA and viral core proteins leave the nucleus and enter this membrane protrusion (step 6).
- The mature virus buds off from the cell in a sphere of host phospholipid membrane, acquiring hemagglutinin with this membrane coat (step 7)[24].

After the release of new influenza viruses, the host cell dies. **(Figure 2)**

Phases of swine flu

Phase 1- In this no viruses circulating among animals has been reported to cause infections in humans.

Phase 2- an animal influenza virus circulating among animals is known to have caused infection in humans, and is therefore considered a potential pandemic threat.

Phase 3- an animal or human-animal influenza virus has caused sporadic cases or small clusters of disease in people, but has not resulted in human-to-human transmission sufficient to sustain community-level outbreaks.

Phase 4- It is characterized by verified human-to-human transmission of an animal or human-animals influenza virus able to cause "community-level outbreaks." The ability to cause sustained disease outbreaks in a community marks a significant upwards shift in the risk for a pandemic. Phase 4 indicates a significant increase in risk of a pandemic but does not necessarily mean that a pandemic is a foregone conclusion.

Phase 5- It is characterized by human-to-human spread of the virus into at least two countries in one WHO region .While most of the countries will not be affected at this stage.

Phase 6- The pandemic phase, is characterized by community level outbreaks in at least one other country in a different WHO region in addition to the criteria defined in Phase 5. Designation of this phase will indicate that a global pandemic is under way.

In the post-pandemic period, influenza disease activity will have returned to levels normally seen for seasonal influenza. It is expected that the pandemic virus will behave as a seasonal influenza-A virus. At this stage, it is important to maintain surveillance and update pandemic preparedness and plans accordingly[25].

SWINE FLU IN PIGS

Swine flu viruses are thought to be spread mostly through close contact among pigs and possibly from contaminated objects moving between infected and uninfected pigs. Herds with continuous swine flu infections and herds that are vaccinated against swine flu may have sporadic disease, or may show only mild or no symptoms of infection.

H1N1 and H3N2 swine flu viruses are endemic among pig populations in the United States and something that the industry deals with routinely. Outbreaks among pigs normally occur in colder weather months (late fall and winter) and sometimes with the introduction of new pigs into susceptible herds. Studies have shown that the swine flu H1N1 is common throughout pig populations worldwide, with 25 percent of animals showing antibody evidence of infection. In the U.S. studies have shown that 30 percent of the pig population has antibody evidence of having had H1N1 infection. More specifically, 51 percent of pigs in the north-central U.S. have been shown to have antibody evidence of infection with swine H1N1. Human infections with swine flu H1N1 viruses are rare. There is currently no way to differentiate antibody produced in response to flu vaccination in pigs from antibody made in response to pig infections with swine H1N1 influenza[2,3].

Signs and Symptoms

Signs of swine flu in pigs can include sudden onset of fever, depression, coughing (barking), discharge from the nose or eyes, sneezing, breathing difficulties, eye redness or inflammation, and going off feed[2,3,4].

SWINE FLU IN HUMANS

Swine flu viruses do not normally infect humans. However, sporadic human infections with swine flu

have occurred. Most commonly, these cases occur in persons with direct exposure to pigs (e.g. children near pigs at a fair or workers in the swine industry). In addition, there have been documented cases of one person spreading swine flu to others. For example, an outbreak of apparent swine flu infection in pigs in Wisconsin in 1988 resulted in multiple human infections, and, although no community outbreak resulted, there was antibody evidence of virus transmission from the patient to health care workers who had close contact with the patient.

In the past, CDC received reports of approximately one human swine influenza virus infection every one to two years in the U.S., but from December 2005 through February 2009, 12 cases of human infection with swine influenza have been reported[2,3,4].

Pathophysiology

The mechanisms by which influenza infection causes symptoms in humans have been studied intensively. One of the mechanisms is believed to be the inhibition of adrenocorticotropic hormone (ACTH) resulting in lowered cortisol levels[26].

For instance, part of the process that allows influenza viruses to invade cells is the cleavage of the viral hemagglutinin protein by any one of several human proteases[17]. In mild and avirulent viruses, the structure of the hemagglutinin means that it can only be cleaved by proteases found in the throat and lungs, so these viruses cannot infect other tissues. However, in highly virulent strains, such as H5N1, the hemagglutinin can be cleaved by a wide variety of proteases, allowing the virus to spread throughout the body [27].

The viral hemagglutinin protein is responsible for determining both which species a strain can infect and where in the human respiratory tract a strain of influenza will bind[20]. Strains that are easily transmitted between people have hemagglutinin proteins that bind to receptors in the upper part of the respiratory tract, such as in the nose, throat and mouth. In contrast, the highly lethal H5N1 strain binds to receptors that are mostly found deep in the lungs[28]. This difference in the site of infection may be part of the reason why the H5N1 strain causes severe viral pneumonia in the lungs, but is not easily transmitted by people coughing and sneezing[29,30].

Signs and symptoms

The symptoms of swine flu in people are similar to the symptoms of seasonal flu in humans and may include[31]

Fever (greater than 100°F or 37.8°C), Sore throat, Cough, Stuffy nose, Chills, Headache and body aches and Fatigue.

In Addition

Breathlessness, chest pain, drowsiness, fall in blood pressure, sputum mixed with blood, bluish discoloration of nails, Irritability among small children and refusal to accept feed[32].

Safety precautions

Avoid live animal markets, poultry and pig farms in affected countries

Always maintain high levels of personal hygiene, especially before and after food preparation and in-out of toilets.

Regular wash your hands

Cook pork thoroughly

Do not consume half-done pork

While in an affected region, seek immediate medical attention if you develop influenza-like symptoms. (High Fever, body pain, coughing and red nose[1].

Diagnosis

To diagnose swine influenza A infection, a respiratory specimen would generally need to be collected within the first 4 to 5 days of illness (when an infected person is most likely to be shedding virus). However, some persons, especially children, may shed virus for 10 days or longer. Identification as a swine flu influenza A virus requires sending the specimen to CDC for laboratory testing.

Laboratory Tests

- Molecular diagnostics
- Virus isolation and typing by haem-agglutination inhibition or immunofluorescence
- Serology
- Rapid tests or immunofluorescence[18,33].

Pharmacotherapy

Human vaccine for swine influenza

There are no vaccines that contain the current swine influenza virus causing illness in humans. It is not known whether current human seasonal influenza vaccines can provide any protection. Influenza viruses change very quickly. It is important to develop a vaccine against the currently circulating virus strain for it to provide maximum protection to the vaccinated people. This is why WHO needs access to as many viruses as possible in order to select the most appropriate candidate vaccine virus[1].

Drugs available for treatment

Antiviral drugs for seasonal influenza are available in some countries and effectively prevent and treat the illness. There are two classes of such medicines -

1) Adamantanes (amantadine and remantadine), and

2) Inhibitors of influenza neuraminidase (oseltamivir and zanamivir)[1].

Because this is a new strain of flu (H1N1), it's hard to say what treatments definitely work. There hasn't been time for big, good-quality studies of medicines against this type of flu.

However, this is what we know from the research:

• Laboratory tests show that this type of flu virus is sensitive to two types of antiviral medicine: oseltamivir (Tamiflu) and zanamivir (Relenza)

• Both medicines may reduce the chances of getting complications from normal flu, such as pneumonia or bronchitis, although the evidence about this is not clear

• Studies show both these medicines reduce the chances of getting flu from a close contact.

Oseltamivir is a capsule, and zanamivir comes as a spray which can be breathe in. These can be taken them for five days (to treat flu symptoms) or 10 days (to protect against catching flu). Both may have side effects. Some people taking oseltamivir feel sick or vomit. Zanamivir can cause diarrhoea. Other types of antiviral drugs, including amantadine and rimantadine, don't work against this type of swine flu. It's important to know that taking these medicines will not stop the spread of swine flu. One will probably still be infectious while taking antiviral medicines. So everyone is also need to take good hygiene measures, such as avoiding direct contact with people, regularly washing your hands, covering your mouth and nose with a tissue when you cough or sneeze, and throwing tissues away[4]. **(Table: 1)**

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Table 1: Swine flu as compared to some other fatal diseases

Rank	Disease Case	% Fatalitiy
1	AIDS(untreated)	85
2	Bird Flu	60
3	Tubercolosis	45.5
4	AIDS(treated)	20
5	MRSA (Methicillin resistant staphylococcus aureus)	19.8
6	SARS (Severe acquired respiratory syndrome)	9.6
7	Bubonic Plague	5
8	Swine Flu	0.5
9	Malaria	0.3
10	Seasonal Flu	0.1

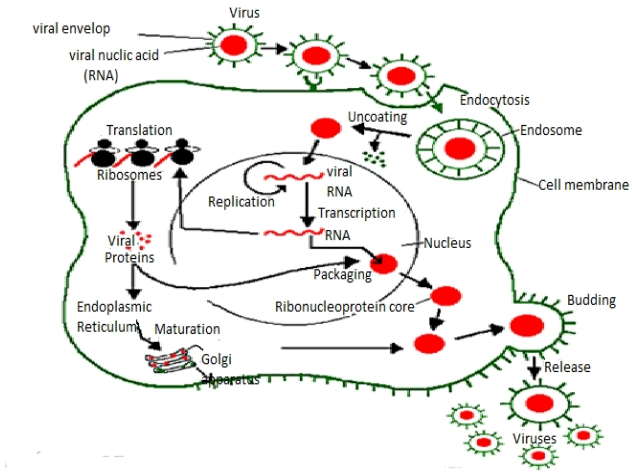

Figure 2: Replication of influenza virus

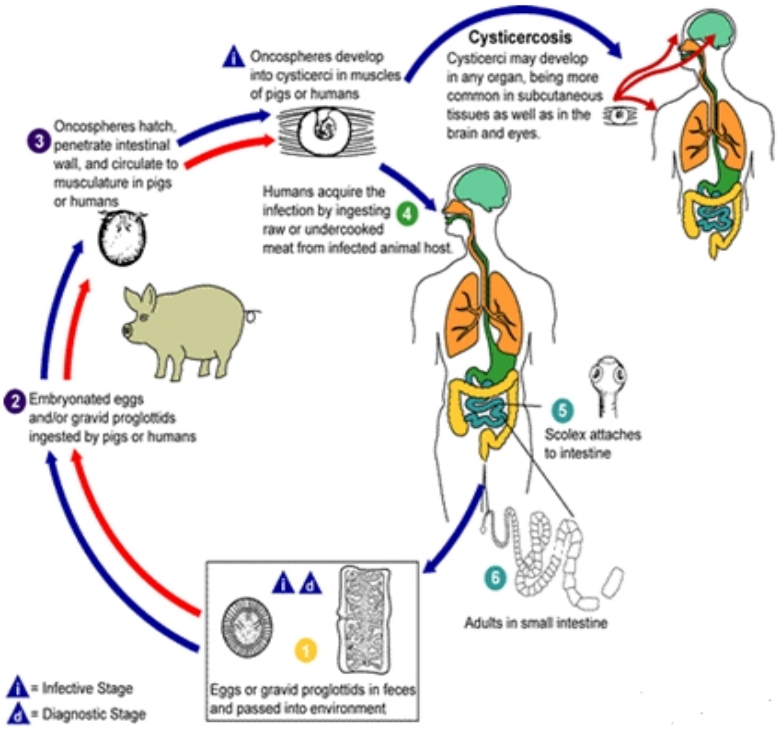

Figure 1: **Spread of swine influenza**