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H1N1 Influenza [Swineflue]

D. Madavateja*, Dr. C .Madhavilata, K. Lavanyalahari, P. Bhavana, P. Nagashirisha, SK. Maseehabaanu

Ratnam Institutue of Pharmacy, Pidathapolur, Nellore, Andhra Pradesh, India

A b s t r a c t

The 2009 flu outbreak in humans, known as "swine influenza" or H1N1 influenza A, refers to influenza A due to a new H1N1 strain called swine-origin influenza virus A (S-OIV). The new swine flu virus is actually a genetic mixture of two strains, both found in swine, of unknown origin. S-OIV can be transmitted from human to human and causes the normal symptoms of influenza. Prevention of swine influenza spread among humans includes use of standard infection control measures against influenza and constitutes the main scope of World Health Organization. For the treatment of S-OIV influenza oseltamivir and zanamivir are effective in most cases. Prophylaxis against this new flu strain is expected through a new vaccine, which is not available yet. Worldwide extension of S-OIV is a strong signal that a pandemic is imminent and indicates that response actions against S-OIV must be aggressive.

Keywords: swine influenza, H1N1 influenza virus A, infection control, oseltamivir, zanamivir

A r t i c l e I n f o

Corresponding Author
D. Madavateja
Ratnam Institutue of Pharmacy,
Pidathapolur, Nellore, Andhra Pradesh, India

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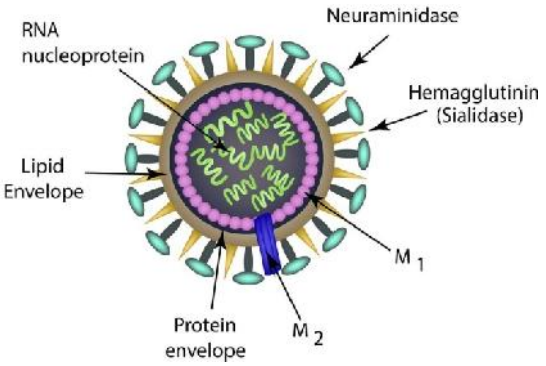
C o n t e n t s

1. Introduction

H1N1 influenza is a subtype of influenza A virus, a communicable viral illness which causes upper and in some cases lower respiratory tract infections in its host. This result in symptoms such as nasal secretions, chills, fever, decreased appetite, and in some cases, lower respiratory tract disease. This activity reviews the presentation, evaluation, and management of H1N1 influenza and stresses the role of an inter professional team approach to the care of affected patients. H1N1 Swine flu is a subtype of influenza A virus (a communicable viral disease), which causes upper, and potentially, lower respiratory tract infections in the host it infects, resulting in symptoms such as nasal secretions, chills, fever, decreased appetite, and possibly lower respiratory tract disease. H1N1 swine influenza is a common infection in pigs worldwide, and that is why it is also known as swine flu. H1N1 swine flu leads to respiratory disease that can potentially infect the respiratory tract of pigs. Sometimes, people who are

closely associated with pigs or in the proximity of pigs have developed swine flu (zoonotic swine flu). Swine influenza viruses can potentially cause infections in humans if antigenic characteristics of the virus change through reassortment. When this happens, transmission from person-to-person is usually inefficient. Influenza A pandemics such as the ones in 1918 and 2009 can occur if the transmission from person-to-person becomes efficient.



In 1918, a deadly influenza pandemic caused by H1N1 influenza virus, also known as the Spanish flu, infected approximately 500 million people around the world and resulted in the deaths of 50 to 100 million people (3% to 5% of the world population) worldwide, distinguishing it as one of the most deadly pandemics in human history. In 2009, a new strain H1N1 swine flu spread fast around the world among humans, and the World Health Organization (WHO) labeled it a pandemic. However, the 2009 H1N1 virus was not zoonotic swine flu because it was not transferred from pigs to humans. Instead, it spread through airborne droplets from human to human, and potentially, through human contact with inanimate objects contaminated with the virus and transferred to the eyes or nose. This virus caused similar symptoms to those seen in swine, possibly due to reassortment of the viral RNA structure, which allowed human-to-human transfer. Despite the name, an individual cannot acquire swine flu from eating pig products such as bacon, ham, and other pig products.

2. Etiology

The H1N1 influenza virus is an orthomyxovirus and produces virions that are 80 to 120 nm in diameter, with an RNA genome size of approximately 13.5 kb. The swine influenza genome has 8 different regions which are segmented and encode 11 different proteins:

- Envelope proteins hemagglutinin (HA) and neuraminidase (NA)
- Viral RNA polymerases which include PB2, PB1, PB1-F2, PA, and PB
- Matrix proteins M1 and M2
- Nonstructural proteins NS1 and NS2 (NEP), which are crucial for efficient pathogenesis and viral replication

The surface glycoproteins HA and NA are how the H1N1-strain is differentiated from other strains of influenza A (H1N1, H1N2) depending on the type of HA or NA antigens expressed with metabolic synergy. The function of hemagglutinin is to cause red blood cells to cluster together, and it attaches the virus to the infected cell. Neuraminidase helps move the virus particles through the infected cell and assists in budding from host cells.

The H1N1 swine influenza viruses can potentially cause infections in humans if antigenic characteristics of the virus change. In 2009, the pandemic which started in Mexico with the H1N1 strain displayed a combination of segments of 4 different influenza viruses (quadruple genetic reassortment): pig-origin flu North American avian (comprising 34.4%), bird-origin flu of the human influenza strain (comprising 17.5%), North American swine (comprising 30.6%), and Eurasian swine (comprising 17.5%). Due to this coinfection with influenza virus from diverse animal species, the viruses were able to interact, mutate, and form new strains that had variable immunity. Although it had originated in pigs, it was able to spread from human to human. When the flu spreads from human-to-human, instead of from animals to humans, there can be further mutations, making it harder to treat because people have no natural immunity.

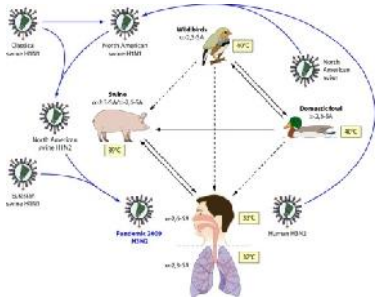
Epidemiology

Swine flu was first isolated from pigs in the 1930s by researchers in the United States and was subsequently recognized by pork producers and veterinarians as a cause of flu infections in pigs worldwide, and for the next 60 years, H1N1 was the predominant swine influenza strain. People who are closely associated with pigs have been known to develop an infection, and pigs have also been infected with human flu from these handlers. In the vast majority of cases, cross-species transmission of the virus had remained confined to the specific area and not caused national or global infections in either pigs or humans. Unfortunately, due to the potential for genetic variation in the swine flu virus, there is always a possibility for cross-species transmission with the influenza viruses to occur. Investigators concluded that the "2009 swine flu" strain, which originated in Mexico, was termed novel H1N1 flu since it was mainly found infecting humans and exhibits 2 main surface antigens, hemagglutinin type 1 and neuraminidase type 1. The 8 RNA strands in novel H1N1 flu have 1 strand from human flu strains, 2 derived from avian (bird) strains, and 5 that were derived from swine strains. During the 2009 pandemic, the Centers for Disease and Control and Prevention (CDC) estimated that there were 43 to 89 million cases of swine flu reported during a 1-year span, with 1799 deaths in 178 countries worldwide.

The 1918 deadly influenza pandemic caused by H1N1 influenza virus, infected approximately 500 million people

around the world and caused the death of roughly fifty to a hundred million people. The H1N1 variant of swine flu is the progeny of the strain that caused the 1918 swine flu pandemic. Although persisting in pigs, the descendant variants of the 1918 virus have also known to infect humans, contributing to the yearly seasonal epidemics of influenza. Direct transmission of the virus from pigs to humans is a rare occurrence, with only 12 documented cases in the United States since 2005. The potential retention of influenza virus strains in swine after these strains have disappeared in the human population, essentially make pigs a reservoir where swine influenza viruses could persist, and later emerge to reinfect humans once their immunity to these strains has waned. More recently in 2015, a mutant strain of H1N1 which caused the global pandemic in 2009, spread across India with over 10,000 reported cases and 774 deaths. People who have a higher risk of becoming seriously ill if infected include:

- Children younger than 5 years old
- Adults older than age 65, younger adults, and children under age 19 who are on long-term aspirin therapy
- People with compromised immune systems due to diseases such as AIDS
- Currently gestating females
- People suffering from chronic diseases such as asthma, heart disease, diabetes mellitus, or neuromuscular disease

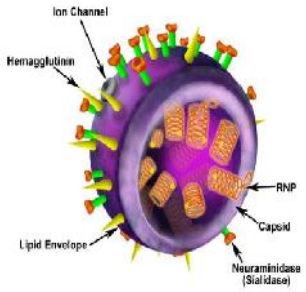


3. Pathophysiology

H1N1 swine flu is an acute disease that infects the upper respiratory tract and can cause inflammation of the upper respiratory passages, trachea, and possibly the lower respiratory tract. The known incubation period for H1N1 swine flu ranges from 1 to 4 days, with the average around 2 days in most individuals, but some individuals, it may be as long as 7 days. The contagious period for adults starts about 1 day before symptoms develop and lasts around 5 to 7 days after the person develops symptoms. The contagious period may be longer in individuals with weakened immune systems and children (e.g., 10 to 14 days). The acute symptoms of uncomplicated infections persist for three to seven days, and the disease is mostly self-limited in healthy individuals, but malaise and cough can persist for up to 2 weeks in some patients. Patients with more severe disease may require hospitalization, and this may increase the time of infection to around 9 to 10 days. The body's immune reaction to the virus and the interferon response are the causes of the viral syndrome which includes high fever, coryza, and myalgia. Patients with chronic lung diseases, cardiac disease and who are currently pregnant are at higher risk of severe complications such as viral pneumonia, superimposed bacterial pneumonia, hemorrhagic bronchitis, and possibly death. These complications can potentially develop within 48 hours from the onset of symptoms. The replication of the virus occurs primarily in the upper and lower respiratory tract passages from the time of inoculation and peaks around 48 hours in most patients. The recommended time of isolation of the infected patient is around 5 days.

Histopathology

Swine flu causes most symptoms in upper and lower respiratory tracts. Mild cases usually show a few pathologic changes in the respiratory tract, but severe cases can show clear pathologic changes of pneumonia. The pathological findings associated with swine flu include multifocal destruction and potential desquamation of the pseudo columnar and columnar epithelial cells, and possibly prominent hyperemia and edema in the submucosa. There may also be thrombus formation at the bronchiolar level. Sometimes, the acute inflammation could be severe and indicated by hemorrhagictracheo bronchitis and desquamative bronchiolitis, which could cause necrosis of the bronchiolar wall. Once necrosis occurs, polymorphs and mononuclear cells infiltrate into the affected area.



Histological changes in swine influenza pneumonia include: interstitial edema with possible inflammatory infiltrate, alveolar proteinaceous exudation associated with membrane formation, thrombosis of capillaries, necrosis of the alveolar septae, intra-alveolar hemorrhage, dislocation of desquamated pneumocytes with pyknotic nuclei into the surrounding alveolar spaces, diffuse alveolar damage with infiltration by the lymphocytes and histiocytes into the interstitium. During the late stage, the following changes have been reported in patients: diffuse alveolar damage, fibrosis, hyperplasia of the type II pneumocyte, epithelial regeneration, and squamous metaplasia have been found. These changes are characteristic of the fibro proliferative stage of acute respiratory distress syndrome and diffuse alveolar destruction. Bacterial coinfections were also identified in some autopsy cases. The most

common bacteria isolated included *Streptococcus*, methicillin-resistant *e*.

History and Physical

The history and clinical presentations of H1N1 swine influenza have ranged from mild flu symptoms to severe respiratory symptoms (and possibly death) depending on the age of the patient, co-morbidities, vaccination status, and natural immunity in patients to the virus. According to the CDC, the signs and symptoms in humans infected with the 2009 H1N1 swine flu were similar to those of influenza. These include a fever and chills, cough, sore throat, congested eyes, myalgia, shortness of breath, weight loss, chills, sneezing, headache, rhinorrhea, coughing, dizziness, abdominal pain, decreased appetite, and fatigue. The 2009 H1N1 strain also showed an increased number of people reporting vomiting and diarrhea as well. Because most of these symptoms are not exclusive to swine flu, a detailed history must also be taken to take into account the differential diagnosis of swine flu if the patient has directly contacted someone with confirmed swine flu or has been in an area that had documented cases of swine flu.

Respiratory failure was the most common cause of death in severe cases. Other causes included high fever (causing neurological problems), pneumonia (causing sepsis), dehydration and severe hypotension (from vomiting and diarrhea), electrolyte imbalance associated complications, and kidney failure. More severe cases and fatalities were more likely observed in children younger than 5 years of age and elderly patients older than 60 years. Other risk factors for severe disease include lung disorders such as chronic obstructive pulmonary disease (COPD), bronchial asthma, pneumonia, currently pregnant women, obesity, patients undergoing immunosuppressive therapy due to cancer or autoimmune disease, and underlying medical issues such as diabetes. Pregnant women acquired the infection during their third trimester were at greater risk for complications.

Evaluation

Influenza A (H1N1) virus infection could be encountered in a wide range of clinical settings and may result in variable pathologic findings. H1N1 should be one of the differential diagnosis in patients who present with unexplained flu-like symptoms or acute pneumonia in an area with known swine flu cases. Routine investigations should be performed for the patient who presents with these symptoms. These usually include hematological, microbiological, biochemical and radiologic tests. A respiratory sample (simple nose or throat swab) is required for a confirmed diagnosis of swine flu. In humans, these tests include the Reverse transcriptase-polymerase chain reaction test (RT-PCR), virus isolation test, and assays to detect a 4-fold increase in influenza virus antigens. The routine tests done to detect human influenza viruses, including the rapid test kits, do not always detect zoonotic viruses. An indication that a novel, possibly zoonotic swine influenza virus could be present, is a detection of the influenza A virus, but not of the hemagglutinins in the seasonal human influenza viruses. The zoonotic influenza virus infections can sometimes be diagnosed retrospectively by serology, but potential cross-reactivity with human influenza viruses can complicate this diagnosis. Another concern is that the neuraminidase (NA) and hemagglutinin (HA) of some swine influenza viruses (the main target of the antibodies) originated from human influenza viruses, to which people could have already been exposed. State, regional, and national public health laboratories do generally test for the novel influenza viruses.

4. Treatment

The initial and best step in management should be to prevent swine flu. Specifically, with the prevention of swine flu in swine, prevention of transmission of swine flu from swine-to-humans, and prevention of human-to-human spread. Prevention of swine flu in swine: Main methods to prevent swine flu in pigs involve facility management (using disinfectants and regulated temperature to control viruses in the environment), herd management (not adding pigs possibly carrying influenza to the herds that have not yet been exposed to the virus), and vaccination. As much of the morbidity and mortality observed with swine flu is due to secondary infection by other pathogens, strategies that solely rely on vaccination may be insufficient.

Prevention of swine to human viral transmission: Because swine can be infected with avian and human strains of H1N1 influenza, they are the primary hosts where antigenic shifts occur that can cause new strains of swine flu. Transmission of the influenza virus from swine to humans is usually seen in people who have a close association with pigs, such as farmers, pork handlers, and veterinarians. These individuals are strongly encouraged to wear face-masks when dealing with the animals to prevent transmission through respiratory droplets. The most important step of prevention is vaccination of the swine. Individuals with increased risk of acquiring swine flu through pigs are those who smoke and do not wear gloves or masks when dealing with infected animals, increasing the risk of possible hand-to-nose, hand-to-eye, or hand-to-mouth transmission.

Prevention of human to human transmission: The main route of swine flu virus spread between humans is exposure to the virus when someone infected sneezes or coughs, and the virus enters one of the potential mucous surfaces, or when a person touched something infected with the virus and subsequently touch their nose, mouth, and surrounding areas. Swine flu is most contagious in the

first 5 days of illness in most people, although this may increase in children and the elderly. Current CDC recommendations to prevent the spread of the virus include frequent hand washing with soap and water or alcohol-based sanitizers, and also disinfecting household, hospital and public settings by cleaning with a diluted bleach solution. Anyone who resides in an area where the disease is prevalent and suspects an infection or presents with flu-like symptoms, should stay away from work and public transportation and immediately see a doctor.

The best-known prevention method against swine flu is getting the H1N1 swine flu vaccine. In September 2009, the FDA permitted the new swine flu vaccine, and various studies by the National Institute of Health (NIH) showed that a single dose was enough to create sufficient antibodies to protect against the virus within 10 days. The vaccination is contraindicated in people who had a previous severe allergic reaction to the influenza vaccination. Those who are moderate to severely ill, including those with or without a fever, should take the vaccination when they recover or are asymptomatic.

The management for infected patients depends on the severity of symptoms of influenza, mild to moderate influenza can be treated at home with rest, oral hydration and symptomatic treatment with antipyretics like paracetamol, antihistaminic for nasal congestion and rhinitis and NSAIDS or Paracetamol for headaches and body aches. Patients with progressive or severe symptoms should be admitted to hospitals and preferably in intensive care units (ICU) if there are signs suggestive of impending respiratory failure or sepsis or multiorgan dysfunction. Aggressive supportive measures like intravenous (IV) hydration, correction of electrolyte imbalances, antibiotics for concomitant bacterial infections. Patients developing acute respiratory distress syndrome (ARDS) secondary to influenza should be treated with noninvasive or invasive mechanical ventilation. Severe cases of H1N1-induced ARDS have required the use of extracorporeal membrane oxygenation (ECMO).

The antiviral medications: zanamivir, oseltamivir, and peramivir have been documented to help reduce, or possibly prevent, the effects of swine flu if the medication is taken within 48 hours of the onset of symptoms. Known side effects of oseltamivir comprise skin conditions that are occasionally severe and sporadic transient neuropsychiatric events. These possible side effects are the reason the use of oseltamivir is cautioned in the elderly and individuals that have a higher risk of developing these side effects. An allergy to eggs is the only contraindication to zanamivir. Beginning October 1, 2008, the CDC tested 1146 seasonal influenza A (H1N1) collected viruses for resistance to the drugs oseltamivir and zanamivir. It concluded that 99.6% of the samples showed resistance to oseltamivir while none showed resistance to zanamivir. Of the 853 collected samples of the 2009 influenza A (H1N1) virus, only 4% demonstrated resistance to oseltamivir, while none of the 376 samples collected showed resistance to zanamivir.

Pregnant women who contract the H1N1, are at a greater risk of complications because of the body's hormonal changes, physical changes and changes to their immune system to accommodate the growing fetus. For these reasons, the CDC recommends that all pregnant women get vaccinated to prevent the swine influenza virus. Swine influenza in pregnant women can be treated using antiviral medications: oseltamivir and zanamivir (neuraminidase inhibitors). It has been demonstrated that these 2 drugs are most effective when taken within 2 days of becoming sick.

Differential Diagnosis

- Acute respiratory distress syndrome
- Adenovirus
- Arenaviruses
- Cytomegalovirus
- Dengue
- Echovirus infection
- Hantavirus pulmonary syndrome
- HIV infection and AIDS
- Human parainfluenza viruses and other parainfluenza viruses
- Legionnaires disease

Prognosis

Evaluation of data reveals that some patients admitted with swine flu are at risk for sepsis, ARDS and death. Predictors of death include chronic lung disease, obesity, underlying neurological diseases, delayed admission, and other co-morbidity.

Enhancing Healthcare Team Outcomes

Swine flu is very contagious and is easily spread from humans after contact with pigs. The infection rapidly leads to moderate to severe symptoms and deaths are not rare. The key is to prevent the infection in the first place. For best results, an interprofessional team should provide for the evaluation and care of patients with Swine flu. The team should be aware of patients at a high risk of becoming seriously ill if infected including you children, the elderly, those immune compromized, gestating females, and those suffering from chronic debilitating diseases.

Today, the primary care provider, pharmacist and nurse practitioner should recommend the H1N1 vaccine to children and adults at risk. In addition, all pregnant women should be urged to get vaccinated to prevent the high mortality of the infection. The school nurse should encourage closure of the school even if only one case of H1N1 is identified. Parents should be encouraged to get the children vaccinated and prevent them from interacting with others; pharmacists are empowered to perform this

function in many US states. In the hospital, the nurses should ensure that the patient is in a single isolation room with airborne precautions in place. Appropriate precautions have to be undertaken to prevent contact with body fluids and aerosols released in the air while coughing. Hand washing should be enforced and only a limited number of healthcare personnel should be allowed to come into contact with the infected person. Only through open communication among members of the interprofessional team can the morbidity and mortality of swine flu be reduced.

5. Conclusion

Response actions against S-OIV must be aggressive, although may vary across countries and communities depending on local circumstances. Communities, businesses, places of worship, schools and individuals can all take action to slow the spread of this outbreak. Information is insufficient to make recommendations on the use of the antivirals in prevention and treatment of S-OIV infection. In addition, until a new vaccine against S-OIV becomes available, avoidance of viral spreading is the most appropriate way to prevent a new pandemic.

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