

A Review of Swine Influenza: An Emerging Pandemic

Fowotade Adeola, Agbede Olajide, Nwabuisi Charles, and Fadeyi Abayomi

Department of Microbiology and Parasitology University of Ilorin Teaching Hospital, Ilorin Kwara State, Nigeria.

Correspondence to: Fowotade Adeola, E-mail- temilabike@yahoo.com

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Summary

An unprecedented epizootic swine Influenza A (H1N1) virus that is highly pathogenic has crossed the species barrier in Mexico to cause many human fatalities and poses an increasing pandemic threat. This summary describes the aetiopathogenesis of human infection with Influenza A (H1N1) and reviews recommendations for prevention and clinical management.

Keywords- Review, Swine Flu, Pandemic

Introduction

Infectious viral disease of pigs, causing considerable economic impact. The latest Swine Influenza has been attributed to H1N1 strain of Influenza virus, a descendant of the Spanish flu that caused a devastating pandemic in humans in 1918-1919.^{2,3} Annual Influenza epidemics have been estimated to affect 5-15% of the global population. In addition, it has caused 3 major global pandemics during the 20th century: the Spanish flu of 1918, Asian flu of 1957 and the Hong Kong flu of 1968-1969.⁴ This influenza virus has also caused several pandemic threats over the past century, including the pseudo pandemic of 1947, the 1976 swine flu outbreak and the 1977 Russian flu, all caused by H1N1 swine flu virus.⁵

Scientists all over the world have been at an increased level of alert since the Severe Acute Respiratory Syndrome (SARS) epidemic in South East Asia. The level of preparedness was sustained with the advent of the H5N1 bird flu outbreak because of its high fatality rate.^{5,6}

Since the first case of swine flu was reported on 27th of April 2009 in Mexico,⁶ the number of affected countries has continued to increase. As at 5th May 2009, 21 countries had officially reported 1124 cases of H1N1 Swine flu.⁷

In view of the rapid spread of the swine flu, there is an urgent need to sensitize the public, especially health care workers on the safety measures aimed at limiting the scourge of this infection.

Aetiology

The Swine Influenza virus belongs to the genus Orthomyxovirus in the family Orthomyxoviridae. They are single stranded, negative sensed RNA viruses with eight segments. There are three genera of influenza virus; Influenza A, B and C. The type A group continually undergoes antigenic shift and drift unlike the types B and

C which are relatively stable.^{8,9} Swine Influenza is caused by Influenza A subtypes; H1N1, H1N2, H3N1, H3N2 and H2N3¹⁰⁻¹² and rarely Influenza C. Influenza B has not been reported in swine.

Type A Influenza has a spherical or filamentous morphology and is medium-sized, with a diameter of 80 to 120 nm. The virus is enveloped, and the lipid membrane of the virion is derived from the host cell in which the virus replicated. There are two surface transmembrane glycoproteins, Haemagglutinin (HA) and Neuraminidase (NA), which are commonly called 'spikes'. A third transmembrane protein, matrix protein (M2), also exists but only 20-60 molecules per virion are present. The matrix protein (M1), forms a layer beneath the envelope and gives structure to the virus and encapsulates the ribonucleoprotein (RNP) complexes. RNP complexes consist of ribonucleic acid (RNA) associated with nucleoprotein (NP) as well as the polymerases PA, PB1 and PB2 that are responsible for RNA replication and transcription.¹³ Two non-structural proteins are also associated with the virus: NS2 is found in the virion while NS1 is found only in infected cells. The influenza virus genome consists of eight unique segments of single-stranded RNA which have negative polarity. Each RNA strand encodes only one protein, except strands 7 and 8 which encode two.

Epidemiology of Swine Flu

Swine flu has often been reported as a zoonotic infection in pigs but can cross species barriers to infect humans.¹⁴

The new strain of Swine Influenza A (H1N1) implicated in the 2009 flu outbreak is a re-assortment of several strains of Influenza A virus subtype H1N1, endemic in humans, birds and swine. Preliminary genetic characterization found that the HA gene was similar to that of swine flu viruses present in the United States pigs since 1999 but

the NA and M genes resemble versions present in European swine flu isolates.¹⁵ Scientists elsewhere have however stated that analysis of the 2009 swine flu (A/H1N1) viral genome suggests that all RNA segments are of swine origin.¹⁶ Pigs are naturally infected with H1N1, H3N2, and H1N2 viruses and serve as a reservoir for the Influenza virus, intermittently causing infection in man when the level of herd immunity decreases.¹⁵

The epidemiologic pattern reflects the changing nature of the antigenic properties of influenza viruses, and their subsequent spread depends upon the susceptibility of the population. Influenza A viruses, in particular, have a remarkable ability to undergo periodic changes in the antigenic characteristics of their envelope glycoprotein; the hemagglutinin and the neuraminidase.¹⁷

Swine flu is common in swine in the mid western United States, Mexico, Canada, South America, Europe, Kenya, China, Japan, Taiwan and other parts of Eastern Asia.¹³ In late March and early April, 2009, an outbreak of H1N1 Influenza A virus infection was detected in Mexico, with subsequent cases observed in several other countries including the United States.¹⁴ The swine flu epidemic has since continued to spread across continental Europe and Latin America with at least 5 countries reporting new cases on the 2nd of May, 2009. By the 5th of May, 2009, 21 countries had officially reported 1124 cases of H1N1 swine flu.¹⁵

The swine flu has so far spread to 18 countries worldwide. The number of infections confirmed in Mexico has jumped from 25 to 473 cases with a fatality of 19.¹⁷ The Spanish Health Ministry announced that the country had 40 confirmed cases of swine flu making it the European nation hardest hit by the virus. Britain, Italy and Germany have also reported new cases.¹⁸ For unclear reasons, African countries including Nigeria seem to have been spared from the swine flu. The Federal Ministry of Health in Nigeria is however on the alert.

People working with poultry and swine, especially people with intense exposures, are at increased risk of zoonotic infection with influenza virus endemic in these animals, and constitute a population of human hosts in which zoonosis and reassortment can co-exist.¹⁹

The high humidity of summer and the increased exposure to ultraviolet light typically marks the end of the flu season as the virus becomes less likely to spread.²⁰

In Mexico city, May marks the end of the dry season, and experts speculate that the spread of the swine flu may slow down.²¹ Transmission of Influenza from swine to humans who work with swine was documented in a small surveillance study performed in 2004.²⁰ This study among others formed the basis of a recommendation that people whose jobs involve handling poultry and swine should be the focus of increased public health surveillance.

At a press briefing on April 27, the CDC stated that the median age of infected people was 16 years with age

range from 7 to 54 years.²² The WHO however, expressed some concern over the unusual age profile of fatal cases as early death was found to be commoner among those aged 25-50 years. More recent cases have a younger age profile, with more than half of Mexico's confirmed cases occurring in people under the age of 20 years.²³

Pathogenesis

Influenza spreads between humans through coughing, sneezing or via fomites.²¹ Swine flu cannot be spread by ingestion of pork or pork products, since the virus is not transmitted through food.²¹ The incubation period following exposure is between 2 to 7 days.

The swine flu is most contagious during the first five days of the illness although some people, most commonly children, can remain contagious for up to 10 days.

Clinical Presentation

According to CDC, the symptoms of swine flu in humans are similar to those of Influenza and Influenza-like illnesses in general. These include: fever, cough, sore throat, body aches, headache, chills and fatigue.²²⁻²⁴ The 2009 outbreak has however shown an increased percentage of patients with diarrhea and vomiting. Although acutely debilitating, Influenza, is a self limiting infection in the general population secondary bacterial infections can increase the severity of illness and may result in complications such as pneumonia. Morbidity may be up to 100% but the mortality rate is low and recovery is rapid, usually 5 to 7 days after the onset of clinical signs.²⁵

The disease caused by Influenza in pig is essentially similar to that in man, though milder. It is an acute febrile respiratory disease characterized by fever, usually in the range, 40.5-41.7 °C, apathy, anorexia, and laboured breathing.²⁶ Cough may be apparent during the later stages of disease. Clinical signs seen less frequently include: sneezing, nasal discharge and conjunctivitis.²⁷

Pathology

The gross lesions found in uncomplicated swine influenza are mainly those of viral pneumonia and are most often limited to the apical and cardiac lobes of the lungs, although in severe cases more than half of the lung may be affected. The altered lung areas are depressed and consolidated, they appear purplish, contrasting sharply with normal tissue. The airways are dilated and filled with blood-tinged fibrinous exudates. The associated bronchial and mediastinal lymph nodes are usually enlarged.²⁸

Swine flu associated gross lung lesions observed in pigs are characterized by multi-focal well demarcated purplish red lesions in the cranio-ventral areas of lung lobes, known as checker-board lung.^{29,30}

Laboratory Diagnosis

The success of viral diagnosis largely depends on the quality of the specimen and the conditions for storage and transport. Specimens for virus isolation should be kept chilled in an ice pack immediately after collection and inoculated into susceptible cell cultures and eggs as soon as possible. If sample can not be processed within 48 - 72 hours, the specimen should be kept frozen at or below -70 °C. Samples for influenza isolation should not be stored or shipped in dry ice (CO₂) unless the samples are sealed in glass. Specimens should be collected and transported in a suitable transport medium with antibiotics in ice or in liquid nitrogen.³¹ Suitable transport media are commercially available and includes: Hanks balanced salt solution, tryptose phosphate broth, veal infusion broth and cell culture medium.

Specimens for diagnosis of Influenza viral infection include: nasal swab, broncho-alveolar lavage fluid, airway broncho swab, fresh or formalin fixed lung tissue biopsy³². Available methods for laboratory diagnosis of swine flu includes: culture, serology, antigen detection and Reverse Transcriptase PCR (RT-PCR).

Specimens for isolation of Influenza virus in cell culture or embryonated chicken eggs should generally be taken during the first 3 days after onset of clinical symptoms. Madin Darby Canine Kidney Cells (MDCK) are the preferred host for Influenza. Virus isolation is a highly sensitive and very useful technique for diagnosis of swine flu. One important advantage of virus isolation is that the virus is available for further antigenic and genetic characterization and also for vaccine preparation or susceptibility testing.

Serologic methods such as the: Haemagglutination Inhibition (HAI), Neutralization, Neuraminidase assay and Neuraminidase assay inhibition are useful in epidemiologic and immunologic studies as well as in the evaluation of vaccine immunogenicity. The HAI is extremely reliable, provided reference antisera are available to all subtypes. Disadvantages of the HAI test include the need to remove nonspecific inhibitors which naturally occur in the sera. The HAI assay remains the test of choice for WHO global Influenza surveillance.³¹

RT-PCR is a powerful technique for the identification of influenza virus genomes even when they are present at very low levels. Since the genome of an influenza virus is single-stranded RNA, a DNA copy (cDNA) must be synthesized prior to the PCR reaction.³³

Centers for Disease Control and Prevention recommends the use of Tamiflu (oseltamivir) or Relenza (zanamivir) for the treatment and/or prevention of infection with swine influenza viruses, however, the majority of people infected with the virus make a full recovery without requiring medical attention or antiviral drugs.³³ The virus

isolated in the 2009 outbreak has been found resistant to Amantadine and Rimantadine.³⁴

In the U.S., on April 27, 2009, the FDA issued Emergency Drug Authorizations to make available Relenza and Tamiflu antiviral drugs to treat the swine influenza virus in cases for which they are currently unapproved.

Other supportive therapy include; antipyretics, fluid and electrolyte maintenance and oxygenation, as indicated. Bacterial super infection should be promptly treated with appropriate antimicrobials but prophylactic antibiotics to prevent super infection are of no known value.

Prevention and Control

The United Nations, World Health Organization (WHO), along with the Centers for Disease Control and Prevention (CDC), expressed concern that the Influenza A(H1N1) could become a worldwide flu pandemic, and WHO then raised its pandemic alert level to "Phase 5" out of the six maximum, as a "signal that a pandemic is imminent".³⁵

Although virologists have noted that the outbreak has proven relatively mild and less fatal than historic pandemics,³⁵ other health officials, including the CDC Director worry about what might happen later in the year, stating that "we are not seeing any sign of this tapering out, we are still on the upswing of the epidemic curve".³⁶ The number of cases is expected to rise as the new flu spreads across the country.³⁶

Recommendations to prevent spread of the virus among humans include using standard infection control practices. This includes frequent washing of hands with soap and water or with alcohol-based hand sanitizers, especially after being out in public.² Although the current trivalent Influenza vaccine is unlikely to provide protection against the new 2009 H1N1 strain, vaccines against the new strain have been developed and are already available.^{37,38}

Experts agree that hand-washing can help prevent viral infections, including Influenza virus. Individuals with flu-like symptoms such as a sudden fever, cough or muscle aches should stay away from work or public transportation and should see a doctor to be tested.⁵

Social distancing is another tactics. It means staying away from other 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 the community.

Several efforts have also been made to control swine flu in pigs. Although the Food and Agricultural Organization (FAO), WHO, and Office International des Epizooties (OIE) have re-affirmed that Influenza viruses are not transmissible to people through eating processed pork, nevertheless some countries, including ; Serbia, China and Russia have banned the importation and sales of pork product as a precaution against swine flu.^{21,41} On

April, 29, the Egyptian Government decided to kill all 300,000 pigs in Egypt, despite lack of evidence that the pigs had the disease or not. This led to clashes between pig owners and the police in Cairo.⁴²

Conclusion

Infected pigs have been the primary source of Influenza A (H1N1) infections in humans. Swine influenza in humans differs in multiple ways from influenza due to human viruses, including the routes of transmission, clinical severity, pathogenesis and response to treatment. Commercial rapid antigen tests are insensitive and confirmatory diagnosis requires sophisticated laboratory support. Despite recent progress, knowledge of the epidemiology, natural history, and management of Influenza A (H1N1) disease in humans is incomplete. There is an urgent need for more coordination in clinical and epidemiologic research among institutions in countries with cases of swine flu and internationally.

References

1. Swine Influenza: The Merck Veterinary Manual. 2008. <http://www.merckvetmanual.com/mvm/index.jsp?cfile=hum/bc/121407.htm>. Retrieved on April 30, 2009.
2. Taubenberger, JK, Morens, DM. "1918 Influenza: the mother of all pandemics" *Emerg Infect Dis*. 2006;12: 15-22. PMID 16494711.
3. Smith, W., Andrewes, C.H., and Laidlaw P.P. A virus obtained from influenza patients. *Lancet*, 1993; 2, 66-68.
4. US Pork groups urge hog farmers to reduce flu risk. *Reuters*. 26 April 2009. <http://www.reuters.com/article/latestcrisis/idUSN26488473>.
5. Swine Influenza; the free encyclopedia. Updated May 1 2009. Accessed May 1 2009.
6. Zampaglione, M. Press release; A/H1N1 Influenza like human illness in Mexico and the USA: OIE statement. World Organization for Animal Health. <http://www.oie.int/eng/press/en090427.htm>. Retrieved on April 29, 2009.
7. Avian Influenza Fact Sheet. World Health Organization. *Wkly Epidemiol Rec*. 2006;81:129.
8. Brooks, GF, Carroll, KC, Butel, JS, Morse, SA. Orthomyxoviruses (Influenza viruses) In: Jawetz, Melnick & Adelberg's Medical Microbiology. 2007. 24th ed. 39:533-544. McGraw Hill. New York.
9. Easterday, B.C. Animal Influenza. In: The influenza viruses and influenza (Ed. Kilbourne. E.D.) Academic Press, Orlando. 1975: 449-481.
10. "Swine Influenza". Swine Diseases (chest) Iowa State University. College of Veterinary Medicine.
11. Shin, JY, Song, MS, Lee, EH, Lee, YM, Kim, SY, Kim, HK et al. Isolation and characterization of novel H3N1 Swine Influenza viruses from pigs with respiratory distress diseases in Korea. *J Clin Microbiol*. 2006;44: 3923-7
12. Ma, W, Vincent, AL, Grammer, MA, Brookwell, CB, Lager, KM, Janke, BH, Gauger, PC, Patnayak, DP. Identification of H2N3 Influenza A viruses from swine in the United States. *Proc Natl Acad Sci USA*. 104:20949-54.
13. Yassine, HM, Al Natour, MQ, Lee, CW, Saif, YM. Interspecies and Intraspecies Transmission of triple reassortment H3N2 Influenza A virus. *J Virol*. 2007;28:129. doi:10.1186/11743-422x-4-129.
14. Schlotissek C, Henshaw, VS and Olsen, CW. Influenza in pigs and their role as the intermediate host In; *Textbook of Influenza*. (ed) Nicholson, KC, Webster, RG, Hay, AJ Blackwell Science. 1998. Oxford. 137-145.
15. Heinen, P. Swine Influenza: a zoonosis. *Veterinary Science Tomorrow*. 2003. c:/Doc and /user/my documents/Swine influenza:a zoonosis-@ Veterinary Science Tomorrow.htm.
16. Rabadan, R. Influenza A (H1N1) "Swineflu" worldwide (04). 2009. ProMED-mail. International Society for Infectious Diseases. Retrieved May 4 2009.
17. Hsieh, Yu-Chia, et al. "Influenza Pandemics: Past, Present and Future". *Journal of Fomosan Medical Association* 2006;105:1-6. <http://ajws.elsevier.com/ajws archive/200611051A1086.pdf>
18. Gray GC, Kayali G. "Facing pandemic influenza threats: the importance of including poultry and swine workers in preparedness plans". *Poultry Science*. 2009; 88: 880-4.
19. Loeffen, W.L., Kamp, E.M., Stockhofe-Zurwieden, N., van Nieuwstadt, A.P., Bongers, J.H., Hunneman, W.A., Elbers, A.R., Baars, J., Nell, T. and van Zijderveld, F.G. Survey of infectious agents involved in acute respiratory disease in finishing pigs. *Vet. Rec.*, 1999; 145, 123-129.
20. "A Primer in the UV-C Light". 2009. 5-2
21. Gray GC, McCarthy T, Capuano AW, Setterquist SF, Olsen CW, Alavanja MC. "Swine workers and swine influenza virus infections". *Emerging Infectious Diseases*. 2009; 13: 1871-8.
22. World Organization for Animal Health. OIE position on safety of international trade of pigs and products of pig origin. 2009. Press Release. <http://oie.int/eng/press/en090507bis.htm>. Retrieved May 8 2009.
23. Oppman, P. "Expert on flu's spread says new strain here to stay" *CNN*. April 28, 2009. Retrieved April 29, 2009.
24. "CDC media availability on human swine influenza cases". Centers for Disease Control and Prevention. April, 27, 2009. <http://www.cdc.gov/>

- media/transcripts/2009/t090427.htm. Retrieved on April 27, 2009.
25. "Swine flu and you". http://www.cdc.gov/swineflu/swineflu_you.htm. Retrieved on 2009-04-26
 26. Kay, R.M., Done, S.H. and Paton, D.J. Effect of sequential porcine reproductive and respiratory syndrome and swine influenza on the growth and performance of finishing pigs. *Vet. Rec.*, 1994; 135, 199- 204.
 27. Novel swine flu-origin A (H1N1) Virus investigation Team (May 2009). "Emergence of a Novel swine-origin Influenza A (H1N1) virus in humans". *N Eng J Med*. <http://content/abstract/NEJMoa09038> <http://www.cdc.gov/media/transcripts/2009/t090427.htm>. Retrieved on April 27, 2009.
 28. Novel swine flu-origin A (H1N1) Virus investigation Team (May 2009). "Emergence of a Novel swine-origin Influenza A (H1N1) virus in humans". *N Eng J Med* <http://content/abstract/NEJMoa09038>
 29. Hilleman, M. "Realities and enigmas of human viral influenza: pathogenesis, epidemiology and control" *Vaccine*. 2002; 20:3068-87.
 30. Lennette, D.E. 1995. Collection and preparation of specimens for virological examination, p. 868- 75. In Murray, P. R., E. J. Baron, M. A. Pfaller, F. C. Tenover, and R. H. Tenover (eds.) *Manual of clinical microbiology*, 6th edition. ASM Press. Wash
 31. WHO Manual Animal Influenza diagnosis and Surveillance. WHO/CDS/CSR/NCS.2002.5 Rev1.
 32. Harmon M.W., Rota, P.A., Walls H.H., and Kendal, A.P. 1988. Antibody responses in humans to influenza virus type B host-cell- derived variants after vaccination with standard (egg-derived) vaccine or natural infection. *J. Clin. Microbiol.* 26:333-37
 33. Ellis, J.S., Sadler, C.J., Laidler, P. De Andrade, H.R. and Zambon, M.C. 1997. Analysis of Influenza A H3N2 strains isolated from England during 1995-1996 using polymerase chain reaction. *J. Med. Virol.* 51:234-41. Mullis, K.B. 1990. The unusual origin of the polymerase chain
 34. Swine flu responds to Tamiflu." *NASDAQ*. 25 April 2009. 2009-04-25.
 35. WHO elevates pandemic threat level. *CNN*. 29 April 2009. <http://www.cnn.com/2009/HEALTH/04/29/swine.flu/index.html>.
 36. "Antiviral Drugs and Swine Influenza". Centers for Disease Control. http://www.cdc.gov/swineflu/antiviral_swine.htm. Retrieved on 2009-04-27.
 37. Scientists see this flu strain as relatively mild. *Los Angeles Times*. April 30, 2009.
 38. Swine flu spreads, fall flu season looms. *WebMD.com*. May 7, 2009.
 39. "Q & A: Key Facts about Swine Influenza (Swine flu) –virus strain" *CDC and P*. 24 April 2009. <http://www.cdc.gov/swineflu/keyfacts.htm>. Retrieved on 2009-5- 26.
 40. Lauren, P. Swine flu vaccine could be ready in 6 weeks. *NBC Connecticut.com/news/local/CT-Company making swine-flu- vaccine.html*. Retrieved on April 28, 2009.
 41. Lynn J. Russia, China ban pork imports from Mexico, US. *Reuters*. Geneva. <http://www.news.com.au/story/027574,25397431- 23109,00.html>.
 42. Clashes erupt over Egypt pig cull. *BBC News*. 2009-05-03. <http://news.bbc.co.uk/1/hi/world/middle east/8031490.stm>. Retrieved on 2009-05-03.