WORLD HEALTH ORGANIZATION

Avian Influenza

By Jacky Kwong

Introduction

In 1997 the first human cases of H5N1, the deadly strain of avian influenza, surfaced. Ever since then, the World Health Organization (WHO), government officials and scientists throughout the world have responded to the avian influenza pandemic threat in many different ways, including reducing opportunities for human infection, vaccinating and **culling** animal populations, strengthening surveillance and detection systems, stockpiling antiviral drugs, developing vaccines, and creating public health plans and procedures in case of a possible pandemic. Although avian influenza has not yet become pandemic, the virus remains extremely deadly and scientists agree it is probably only a matter of time before it becomes pandemic. This fear is compounded by the fact that the world is in the midst of an H1N1 "swine flu" pandemic. Unlike H5N1, H1N1 is not particularly lethal, but it is highly transmissible from human to human. Experts fear that H1N1 and H5N1 could merge and produce a virus that is as transmissible as H1N1 and as deadly as H5N1. Though H1N1 has not yet turned into a pandemic, it is a reminder to the global community just how vulnerable we are. All of the actions mentioned earlier are crucial components of pandemic preparedness and have been taken in varying degrees by countries around the world. But what are the most effective steps in dealing with a deadly influenza pandemic? For example, stockpiling antiviral drugs is a very practical response to the threat, but this is very expensive and may ultimately be ineffective against the virus as the evolution of the virus is unpredictable. What actions should the WHO advise countries to take, particularly those with limited resources?

culling- *removing animals from a specific group to either get desired results or to remove an undesired characteristic*

Explanation of the Problem

Background

According to the Center for Disease Control (CDC), avian influenza, or bird flu, refers to the influenza A viruses that exist naturally in bird populations and primarily affect birds. The viruses are very contagious and spread easily among birds. Wild birds infected with avian influenza viruses usually do not get sick from them but domesticated birds are very vulnerable. The virus is highly pathogenic among poultry and can lead to death within 48 hours.

There are many different subtypes of influenza A viruses, distinguished by differences in the surface proteins of the virus, hemagglutinin [H] and neuraminidase [N]. Sixteen H subtypes and nine N subtypes have been identified thus far, with each combination representing influenza A subtype. This committee will focus on one specific subtype of avian influenza A virus, the H5N1 strain that has generated worldwide alarm because of the deadly outbreaks among poultry and wild birds and the hundreds of cases of human infections.

The H5N1 strain of avian influenza was first isolated from a farmed goose in Guangdong, China in 1996 but spread quickly throughout the world and is currently **epizootic** in Asia, Europe, the Middle East and Africa. The H5N1 virus has proven especially pathogenic and enduring, causing the largest and most severe outbreaks of avian influenza in poultry on record, causing the death or destruction of hundreds of millions of birds. The mortality rate for poultry has reached 90-100%. The H5N1 virus has also infected humans, with the first cases being reported in Hong Kong in 1997. Since then, 423 cases in 15 countries have been officially reported to the World Health Organization, with the actual number likely to be much higher due to underreporting. Symptoms of avian influenza have been varied, including eye infections and regular flu symptoms such as fever, cough, sore throat, and muscle aches, and even severe respiratory illness like pneumonia and acute respiratory distress. The mortality rate has been very high, with 258 deaths, or approximately 60% of the infected individuals dying. The vast majority of the people who have been infected with the virus had direct contact with infected birds or objects, either through handling dead infected poultry or visiting a live poultry market. There have also been some clusters of human H5N1 cases in which family members living within the same household as an infected person have been infected.

epizootic- *an outbreak of a disease affecting many animals of one kind at the same time*

Scientists are primarily concerned that H5N1 will develop into a pandemic flu, which has occurred periodically throughout human history. There were three influenza pandemics in the 20th century, in 1918, 1957 and 1968, causing millions of deaths worldwide. In 2008, a new pandemic emerged, the H1N1 influenza. To date, the H1N1 pandemic has caused far fewer deaths than the previous pandemics. However, the pandemic has not yet run its full course. The World Health Organization estimates that an avian influenza pandemic flu occurring today would cause an estimated 2-7.4 million deaths. The H5N1 virus already meets two of the three conditions required for a pandemic. First, it is a new subtype of influenza virus. This means that humans have practically no natural immunity to it and a global outbreak of the virus would cause high rates of illness and death. Second, the virus is infectious and can cause serious harm, which the virus has demonstrated in numerous countries. Only the third condition has not yet been met: the efficient and sustained human-to-human transmission of the virus. This commit-

tee will focus on how to prevent the emergence of this pandemic strain of the H5N1 virus.

The Biology of Avian Influenza Viruses

In order for the H5N1 virus to become pandemic, the virus must either gradually mutate and adapt to human cells through the process of **antigenic drift** or it must undergo an **antigenic shift,** in which a human influenza virus and an avian influenza virus exchange genetic information through re-assortment and produce a new subtype of influenza that has a combination of the surface proteins of the two original viruses.

The H5N1 virus is very capable at both mechanisms of improving its transmissibility among humans. Influenza A viruses are members of Orthomyxoviridae, a family of RNA viruses which also includes the Influenza B and Influenza C viruses. Essentially, if these mutations result in changes to the surface proteins of the virus, the virus could become better adapted to avoiding immune cells or binding to the cells of a new host species.

Influenza A viruses are also prime candidates for the genetic re-assortment needed for an antigenic shift to occur. Re-assortment occurs when two similar viruses exchange genetic information. First, influenza A viruses have a large host range, infecting humans, mammals and birds. This increases the possibility that two similar but different viruses will infect the same cell and allow for the exchange of genetic material. Second, influenza A viruses are also composed of eight separate segments of RNA, which each encode for individual specific viral proteins. This segmentation promotes "genetic mixing" because when new viruses are assembled in the host cell, they take a copy of each RNA segment, which could come from either influenza virus. Therefore, through re-assortment, a new virus with a mixture of human and avian influenza genes can arise. If that new virus has avian influenza antigens that humans have no immunity to and was easily transmitted from human to human, it would be a pandemic strain. Although influenza B and influenza C viruses can also infect humans, only influenza A viruses can cause pandemics because the other two mutate 2-3 times more slowly, are not very common, and have limited host ranges, which prevents antigenic shift.

It is currently unknown exactly what mutations need to take place in order for the H5N1 virus to be easily transmitted from human to human. However, due to its continuous evolution, the Avian Influenza A (H5N1) virus could one day be easily transmissible from human to human. Since humans cannot control this process of genetic change, it is crucial to limit animal-to-human transmission of the virus. The avian influenza virus is transmitted to humans in two main ways: through direct contact with infected birds and infected surfaces, and through intermediary hosts, like pigs. Therefore, the more contact there is between

antigenic drift- *a process that changes the antigens of a virus, thus making the host's immune system less effective in fighting the virus*

antigenic shift- *the process by which two different types of viruses combine to form a new type of virus. The new virus usually contains the antigens of the two previous viruses,*

humans and infected sources, the greater the chance is that an avian influenza virus will infect humans or come into contact with a human influenza virus, and this will lead to a greater chance of pandemic strain arising through antigenic drift or genetic re-assortment.

Avian Flu Transmission

The influenza virus is usually transmitted through coughing and sneezing by mammals and through feces and secretions by birds. Infections occur through contact with these substances or contaminated surfaces, most commonly through the fecal-oral route in humans and birds. Avian influenza viruses generally do not infect humans because of host range restrictions. Correspondingly, human and avian influenza viruses preferentially bind to their respective receptors. However animal-to-human transmission of influenza viruses can and has occurred. Strategies that target the transmission of influenza viruses would not only lower the chances of the avian influenza virus infecting and adapting to human hosts or exchanging genetic information with a human influenza virus, but would also inhibit the spread of new strains that arise naturally in birds or other hosts.

Recent Developments

Interestingly, there has been a decline in the number of human H5N1 cases in recent years, from a peak of 115 cases in 2006, to 88 cases in 2007, and 44 cases in 2008 (WHO, Cases 2009). However, this does not mean that the threat from avian influenza is subsiding or that the virus is stabilizing. On the contrary, the virus has spread widely throughout the world and is now considered **endemic** in many countries, including Indonesia, Vietnam, China, Cambodia, Laos, Thailand, Egypt, Nigeria, Bangladesh, India, Burma, and Pakistan (WHO, 2005). Mammalian species previously thought to be not susceptible to the virus have become infected. Significantly, scientists point to the fact that the virus has not decreased in **virulence** as it continues to spread among poultry as particularly alarming (McNeil, 2008). Human mortality has also not decreased (WHO, Cases 2009). Studies confirm that the avian influenza virus continues to evolve rapidly and now has hundreds of variants. It is developing into a highly virulent **genotype** with an increasing host range and poses a serious danger to human health (Pappaioanou, 2009).

endemic- *a disease that is constantly present*

virulence- *the degree to which an agent can cause disease*

genotype- *the genetic make-up of an organism*

H1N1

The latest twist in the threat of avian influenza is of course the current H1N1 pandemic. This is the first flu pandemic in 40 years and is causing general concern around the world. Many of the measures currently being used to fight this H1N1 strain were actually developed in response to the H5N1 threat. Therefore, the effectiveness of these measures is currently being tested as the H1N1 pandemic continues. Many

countries have increased attention on their public health systems and have heightened their preparedness levels in response to the current pandemic, which involves for example, greater monitoring of influenza symptoms in the general populace and increasing the supply of antiviral. Experts consider the current H1N1 pandemic mild because of its low mortality rate. If it continues at its current state, the effect of this pandemic would be similar to a bad season of the regular annual flu. However, the current pandemic can also become more serious. This is where avian influenza is relevant. Scientists say there is a real possibility that the H1N1 strain could obtain some genes and features of the H5N1 strain through contact. The H5N1 strain has a high mortality rate, which would make the current pandemic very devastating. The strain that caused the 1918 flu pandemic, with many millions of deaths worldwide, had such a combination of avian and swine influenza genes.

Focus of the Debate

Stockpiling Antiviral Drugs

Stockpiling antiviral drugs is a very common strategy governments pursue. The public is generally very supportive of stockpiling vaccines and other drugs as it is a visible and concrete method of pandemic preparedness. Unlike other strategies, the public understands the need for these drugs and often requests that governments stockpile greater quantities, particularly those countries that do not produce these drugs domestically. But this is not an entirely sound solution in the event of a pandemic. Many countries are vulnerable to drug shortages in case of a pandemic as only a few countries around the world are major drug producers. Even the United States, a leader in the global drug industry, is only capable of producing 20% of the vaccines it needs. This leaves many countries at risk because producer countries may not be willing to export drugs in a crisis, particularly if they are needed at home. While drugs are certainly a necessity for treating people who become sick with the virus, vaccines are expensive and may ultimately be ineffective against the virus as the evolution of it cannot be predicted. Similarly, an effective vaccine for the pandemic flu cannot be developed until the pandemic strain of the virus emerges, and at this point production of the vaccine will take several months. There are currently only two vaccines that treat avian influenza, which means there is much room for more drug and vaccine research and production.

stockpiling—*building up large amounts of a given good and storing them for future use*

Human-to-Animal Transmission

Limiting animal-to-human transmission of the virus is another action humans can take to prevent a pandemic. One way of limiting animal-to-human transmission of the virus is to eradicate the virus from poultry populations since most humans come into contact with the

H5N1 virus through infected poultry. However, this remains difficult for a large number of reasons. First, wild **aquatic** birds are the natural reservoir for influenza A viruses and are the primary source of infection for poultry populations. Birds spread H5N1 through their saliva, nasal secretions, and feces. Therefore, the virus can be spread from bird population to bird population through contact with contaminated aerosols**,** water, feed, surfaces, and other materials. Influenza A viruses have achieved stability in wild bird populations so viruses can continue to be transmitted from wild birds to poultry and other animals, causing outbreaks of avian influenza. Scientists generally agree that control of infection in wild birds is not a feasible option. Another difficulty in eradicating the virus from poultry populations is the decentralized nature of the traditional farming systems in many parts of the world where avian influenza is a problem. In Asia, for example, there are millions of small farms that contain poultry, complicating eradication efforts. Not only would eradication be difficult to achieve, but it would also be economically disastrous for the owners of these small farms who cannot easily afford more livestock.

aquatic organism- *an organism that lives in water*

NGO Perspectives

The Heritage Foundation

The Heritage Foundation is an American public policy research institution whose goal is to formulate and promote conservative public policies. The Heritage Foundation promotes a "common sense approach" to the pandemic threat. Rather than enacting measures like closing the border, the Heritage Foundation advocates a focus on good public health policies:

1. Treating those affected with the virus,
2. Continuing to collect useable and timely information about the flu, and
3. Educating Americans on the proper means of preventing transmission.

The Heritage Foundation also advocates a more open vaccine market. A reason for the vaccine shortage in the United States is because many drug companies have stopped manufacturing flu vaccines. Drug companies cite heavy losses because the government is the primary purchaser of flu vaccines and does not pay enough to cover the costs of making a vaccine every year.

Amnesty International

Amnesty International is a global organization and movement, which campaigns for internationally recognized human rights for everyone. Amnesty International is generally not involved in public heath crises, although it strongly believes in healthcare as a universal right and reports on abuses related to the healthcare industry. For example, in February 2006, health workers in Poland were accused of testing a bird flu vaccine on over 200 patients without their permission.

Possible Solutions

Poultry Culling

The two main methods of controlling the disease in bird populations, large-scale culling and vaccination campaigns, have had mixed results. Many countries turn quickly to massive culling campaigns when outbreaks of avian influenza occur, but these culling campaigns are rarely precise because of political pressures and cannot meet their objectives. Governments typically follow a circular area approach when culling. For example, all birds within 5 kilometers of a determined infection would be culled. But this approach ignores the physical reality of how viruses are spread. Viral infections do not follow a regular pattern, but rather a complex web of geographical barriers, migratory/ transport routes, trade links, and other factors. Therefore, this culling strategy can result in both the unnecessary destruction of scarce resources and the failure to control the spread of the disease. There is great resistance to culling campaigns wherever they occur as governments usually fail to pay fair **market value** for destroyed birds. In many areas of the world affected by avian influenza, farmers depend heavily on their poultry and many would kill and eat their flocks or transport them elsewhere before the government can destroy them. Culling can be very effective if implemented quickly and properly. The one-size-fits-all approach can be beneficial at times, eliminating a need for planning that may take some time.

market value- *the price at which an asset would be placed in a competitive free market*

Poultry Vaccination

The **vaccination** of poultry populations has also been a major method of control. Billions of doses of poultry vaccine have been administered worldwide to contain the spread of the avian influenza virus. However, the virus continues to spread in some areas because of continued contact with wild birds as well as secondary transmission of the virus between poultry populations as birds are sold and transported. There are also objections to widespread vaccination efforts as they may promote the evolution of a more virulent form of the virus that can evade the host's immune response. This would make any future pandemic even more deadly and less treatable.

vaccination—*an inoculation which renders the recipient immune to a given disease*

Exposure Reduction

Some scientists think the best way to limit animal-to-human transmission of the avian influenza virus is to reduce behaviors that expose humans to the virus. First of all, people who are particularly at-risk for possible infection should be targeted and trained to lower the risk of virus transmission. Studies show that poultry and swine professionals, and individuals with high poultry contact in areas affected by avian influenza H5N1, have significantly higher risks of becoming infected (Gray, 2007). Due to their prolonged and intense contact with animal populations, these workers serve as an important bridge for viruses, introducing human influenza viruses to animals and introducing avian influenza viruses to people. The World Health Organization has issued guidelines for individuals at risk of avian influenza virus infection, recommending that these individuals (WHO, Protection 2008):

Be registered with the animal health authority or by the public health authority.

Wear appropriate personal protective equipment (PPE).

Maintain diligence in personal hygiene, including frequent hand washing.

Receive adequate instruction on disinfection/disposal of contaminated articles.

Be monitored twice daily for fever (>38°C) and influenza-like illness after contact

However, these crucial and relatively simple guidelines are not mandatory. Regulations should be enacted to make these guidelines mandatory and heavily enforced. Studies have shown that many of these practices, such as wearing personal protective equipment significantly reduce exposure to potentially infected materials.

Strong regulations have also been proposed to govern animal markets and agricultural practices. The banning of live poultry markets has been proposed. Studies have shown that they are particularly high-risk public arenas of interaction that lead to not only human infection, but also to transmission between poultry populations. **Rural** farmers with small holdings of poultry should be given advice and aid on how to limit exposure. There can also be a greater focus on the possibility of virus transmission through intermediary host populations, especially pigs. Pigs are unique among animals in that their epithelial cells have both human and avian flu receptors, so both viruses can infect them at the same time. Genetic re-assortment occurs frequently in pigs and studies have linked them to the last two flu pandemics. Regulations can

rural—*referring to the countryside, areas outside of cities*

be enacted to prevent pigs from becoming infected, like those that contracted avian influenza after contact with contaminated bird feces in the Netherlands in 2003. Keeping pig and bird populations separate would help impede this critical historic mode of animal-to-human transmission and thus, the development of a pandemic virus. Given the current H1N1 pandemic, there are very likely going to be interactions between the H1N1 virus and the H5N1 virus. It is uncertain whether the two will combine to create a truly deadly virus. There is still too little known about the H1N1 pandemic, but the signs are disturbing many scientists. The virus mainly affects young healthy adults, like previous pandemics, and unlike the regular flu, which mainly affects the old, the very young and sick or weak individuals. The virus also seems to be following the course of previous pandemics, arriving late in the flu season and perhaps resurfacing in full force the following year.

Border Control

Many countries in the past have also tried to limit the spread of diseases by tightly controlling borders or closing public places like schools and government buildings. These drastic measures are usually criticized as unnecessary and disruptive. Although research shows that diseases cannot be contained forever by such measures, if implemented quickly and thoroughly, it could slow down infection by a few days. While a few days may not seem like a lot, it could provide health officials with some valuable time to enact other measures. Education of the public and awareness building are also crucial factors that need to be considered. Some countries are better equipped to engage in such activities, but regardless, they need to be implemented sooner rather than later. Encouraging the public to engage in **hygienic** behaviors like washing hands frequently can have a significant effect

hygienic—*practices associated with good health*

Questions for Policymakers

Policymakers must assess and understand the current threat of avian influenza in different parts of the world and take a close look at the measures that are currently in place to deal with that threat. While governments throughout the world are aware of the situation, some experts believe that there is much that remains to be done and that the world remains at serious risk. Questions that must be asked include: Is the world truly prepared for an avian influenza attack? What strategies are respective countries pursuing? To what extent have these strategies been implemented? Are these strategies the most effective at limiting the impact of an avian influenza pandemic? To what degree is the populace prepared for a pandemic? Regarding next steps in pandemic preparedness, what measures should be taken next? How long would it take for these measures to work? How much would these measures cost

and is there money to pay for these measures? What are some things that countries that lack time and resources can do?

Conclusion

Avian influenza A (H5N1) poses a very significant threat to human health due to its pandemic potential. The only condition preventing H5N1 from becoming a pandemic is that it has not yet developed the capacity for sustained human-to-human transmission. There are many different strategies to combat avian influenza, including limiting animal-to-human transmission of the avian influenza virus, culling and vaccination efforts, stockpiling drugs, targeting and training of at-risk individuals and strong regulations aimed at reducing human and animal exposure to the virus. Given the current situation regarding H1N1, it has become even more important to combat avian influenza, as a pandemic combining the two viruses would have severe consequences and be difficult to control. The strategies and plans that the WHO decides to promote would be critical in this fight. A close examination of the current strategies and policies is essential, as well as innovative new ideas.

Guide to Further Research

The World Health Organization closely monitors the avian influenza virus on its website and provides information on the programs and policies it currently recommends and what specific countries/regions are doing to combat the virus.

http://www.who.int/csr/disease/avian_influenza/en/

There are also the latest developments on the H1N1 pandemic on the WHO website.

http://www.who.int/csr/disease/swineflu/en/index.html

There is also a great deal of news coverage of the avian influenza and H1N1 pandemic, that provide a look into how people throughout the world are viewing and reacting to the crisis.

Bibliography

Avian Influenza A Virus Infections of Humans. Centers for Disease Control and Prevention, 2008. (Accessed May 2, 2009 at http://www.cdc.gov/flu/avian/gen-info/avian-flu-humans.htm.).

Avian influenza frequently asked questions. World Health Organization, 2005. (Accessed May 2, 2009 at http://www.who.int/csr/disease/avian_influenza/avian_faqs/en/index.html.).

Avian Influenza Protecting Poultry Workers at Risk- Safety and Health Information Bulletins. US Department of Labor, 2004) (Accessed May 2, 2009 at http://www.osha.gov/dts/shib/shib121304.html.).

Avian Influenza: Current H5N1 Situation. Centers for Disease Control and Prevention, 2008. (Accessed May 2, 2009 at http://www.cdc.gov/flu/avian/outbreaks/current.htm)

Can Pigs 'catch' Avian Influenza? Defra Response, UK. Department for Environment Food and Rural Affairs, 2006.

Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO. World Health Organization, 2009. (Accessed May 2, 2009 at http://www.who.int/csr/disease/avian_influenza/country/cases_table_2009_05_06/en/index).

De Jong MD, Hien TT. Avian Influenza A (H5N1). J Clin Virol. 2006 Jan; 35(1):2-13.
Drake J. Rates of spontaneous mutation among RNA viruses. Proc Natl Acad Sci USA 1993; 90(9): 4171–5.

Gray GC, Trampel DW, Roth JA. Pandemic influenza planning: shouldn't swine and poultry workers be included? Vaccine. 2007 May 30; 25 (22):4376-81.

H5N1 avian influenza: Timeline of major events. World Health Organization, 2009. (Accessed May 2, 2009 at http://www.who.int/csr/disease/avian_influenza/ai_timeline/en/index.html.).

Key Facts About Avian Influenza (Bird Flu) and Avian Influenza A (H5N1) Virus. Centers for Disease Control and Prevention, 2007. (Accessed May 2, 2009 at http://www.cdc.gov/flu/avian/gen-info/facts.htm.).

Kuiken T, Holmes EC, McCauley J, Rimmelzwaan GF, Williams CS, Grenfell BT. Host species barriers to influenza virus infections. Science 2006 Apr 21; 312(5772):394-7.

Landman WJ, Schrier CC. Avian influenza: eradication from commercial poultry is still not in sight. Tijdschr Diergeneeskd 2004 Dec 1; 129 (23):782-96.

Lee M, Bishop K, Medcalf L, Elton D, Digard P, Tileya L. Definition of the minimal viral components required for the initiation of unprimed

RNA synthesis by influenza virus RNA polymerase. Nucleic Acids Research 2002; 30(2): 429–438.

Liu JP. Avian influenza—a pandemic waiting to happen? Journal of Microbiology, Immunology and Infection 2006 Feb; 39(1):4-10.

McNeil, D. A Pandemic That Wasn't but Might Be. New York Times 2008.

Morgan O, Kuhne M, Nair P, Verlander NQ, Preece R, McDougal M, Zambon M, Reacher M. Personal protective equipment and risk for avian influenza (H7N3). Emerg Infect Dis. 2009 Jan; 15(1):59-62.

Nobusawa E, Sato K. Comparison of the mutation rates of human influenza A and B viruses. J Virol 2006; 80 (7): 3675–8.

Pappaioanou M. Highly pathogenic H5N1 avian influenza virus: cause of the next pandemic? Comp Immunol Microbiol Infect Dis. 2009 Jul; 32(4):287-300.

Protection of individuals with high poultry contact in areas affected by avian influenza H5N1: Consolidation of pre-existing guidance. World Health Organization, 2008. (Accessed May 2, 2009 at http://www.who.int/csr/disease/avian_influenza/guidelines/high_contact_protection/en/index.html.).

Responding to the avian influenza pandemic threat. World Health Organization, 2005.

Shinya K. Host adaptation mechanisms of Influenza A viruses. Uirusu 2008; 58: 69-72.

Spread of Avian Influenza Viruses among Birds. Centers for Disease Control and Prevention, 2008. (Accessed May 2, 2009 at http://www.cdc.gov/flu/avian/gen-info/spread.htm.).

Srikantiah S. Mass culling for avian influenza: rational strategy or needless destruction? Indian Journal of Medical Ethics 2008; 2.

Su Z, Xu H, Chen J. Avian influenza: should China be alarmed? Yonsei Med J. 2007 Aug 31; 48(4):586-94.

Thomas JK, Noppenberger J. Avian influenza: a review. Am J Health Syst Pharm. 2007 Jan 15; 64(2):149-65.

Transmission of Influenza A Viruses Between Animals and People. Centers for Disease Control and Prevention, 2005. (Accessed May 2, 2009 at http://www.cdc.gov/flu/avian/gen-info/transmission.htm.).

Van Reeth K. Avian influenza in swine: a threat for the human population? Verh K Acad Geneeskd Belg. 2006; 68(2):81-101.

Wagner R, Matrosovich M, Klenk H. Functional balance between haemagglutinin and neuraminidase in influenza virus infections. Rev Med Virol 2002; 12 (3): 159–66.

Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y. Evolution and ecology of influenza A viruses. Microbiol. Rev. 1992; 56 (1): 152–79.

What Is an Influenza Pandemic? United States Department of Health and Human Services, 2009. (Accessed April 24, 2009 http://www.pandemicflu.gov/general/index.html.).