Avian Flu: A possible pandemic threat

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Abstract

Background: Influenza viruses infect a wide range of animal hosts and cause yearly wintertime epidemics among people living in temperate zones. Because of their ability to mutate, re-assort gene segments, and cross species, influenza viruses can also lead to pandemics in which immunologically naive people are exposed to a new, highly contagious subtype. In the last century, these pandemics were caused by influenza viruses whose surface attachment proteins, or hemagglutinins, were derived from birds, the natural reservoir of influenza virus. Vaccines are the primary means to provide protection for people at risk for inter-pandemic influenza, and new vaccines, directed against avian-potentially pandemic-strains are now being tested.

Aim: The aim of this study is to examine available information on influenza pandemic in order to create awareness of preventive measures against influenza pandemic and to suggest future research areas in developing control strategies.

Method: Data sources: Review of literature via Internet, articles and journals. Data extraction: Abstracts and articles identified were accessed, read to establish relevance to this review. Data synthesis: Important points were prioritized and then included as subtitles; below each subtitle, published works were included.

Introduction

Influenza pandemics, defined as global outbreaks of the disease due to viruses with new antigenic subtypes, have exacted high death tolls from human populations. The last two pandemics were caused by hybrid viruses, or reassortants, that harbored a combination of avian and human viral genes. Avian influenza viruses are therefore key contributors to the emergence of human influenza pandemics. (Horimoto, and Kawaoka 2001).

Influenza develops in both pandemic and interpandemic forms. Fortunately, pandemics occur infrequently. Interpandemic influenza, although less extensive in its impact, happens virtually every year (Dolin, 2005). An influenza pandemic occurs when an influenza strain with a novel HA subtype (with or without a novel NA subtype) appears and spreads in the human population, which has little or no immunity to this novel HA. In the 20th century, three pandemics were reported: in 1918, 1957, and 1968 and were associated with substantial illness and death (Luke & Subbarao, 2006). Influenza A viruses are perpetuated in the wild birds of the world, predominantly in waterfowl, in which the 16 subtypes coexist in perfect harmony with their hosts. Currently, influenza epidemics in the winter are caused by H3N2 and H1N1 influenza A and influenza B viruses. (Webster et al., 2006).

Discussion

Pandemic Phases: In the 2009 revision of the phase descriptions, WHO has retained the use of a six-phased approach for easy incorporation of new recommendations and approaches into existing national preparedness and response plans. (WHO. Influenza pandemic preparedness, 2005).

Interpandemic period

Phase 1, no viruses circulating among animals have been reported to cause infections in human.

Phase 2, no new influenza virus subtypes have been detected in humans. As influenza virus subtype circulating in animals is known to have caused infection in human, and is therefore considered potential pandemic threat.

Pandemic alert period

Phase 3, Human infection(s) with a new subtype has caused sporadic cases but no human-to-human transmission sufficient to sustain community level outbreaks; this may occur under some circumstances.

Phase 4 is characterized by Small cluster(s) with limited human-to-human transmission but spread is highly localized, suggesting that the virus is not well adapted to humans.

Phase 5 is characterized by Larger cluster(s) but human-to-human spread still localized (two countries in one WHO region), suggesting that the virus is becoming increasingly better adapted to humans,
may not yet be fully transmissible (substantial pandemic risk).

**Pandemic period**

Phase 6 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.

post-peak period, during this period pandemic disease levels will have dropped below peak observed levels, it will be of uncertain if additional waves will occur and countries will need to be prepared for a second wave. At this stage, it is important to maintain surveillance and update pandemic preparedness and response plans accordingly.

Fig 1: The current WHO phase of pandemic alert (WHO, 2009)

**Evolutionary pathways of influenza viruses:**

Webster et al., (1992) described the ecology of influenza viruses, they suggested that all mammalian influenza viruses are derived from avian influenza reservoirs, support for this theory results from phenogenetic analyses of nucleic acid sequences of influenza A viruses from a variety of hosts, geographic regions, and virus subtypes

Influenza viruses in wild aquatic birds appear to be in evolutionary stasis, with no evidence of net evolution over the past 60 years. phenogenetic analyses of amino acid showed that avian influenza viruses, unlike mammalian strains, had low evolutionary rates (Gorman et al, 1990).

Nucleotide changes have continued to occur at a similar rate in avian and mammalian influenza viruses, but these changes no longer result in amino acid changes in the avian viruses, whereas all eight mammalian influenza gene segments continue to accumulate changes in amino acids. The high level of genetic conservation suggests that avian influenza viruses in their natural reservoirs are approaching or have reached an adaptive optimum, where in nucleotide changes provide no selective advantage. This means that the source of genes for pandemic influenza viruses exists phenotypically unchanged in aquatic bird reservoir (Wright & Webster, 2001).

This lack of change is surprising because influenza viruses are segmented, negative - stranded RNA viruses that have no quality control mechanisms during replication and are highly prone to variation. However, all 16 HA subtypes, including H5N1, have until recently been considered to be benign in their natural hosts, however this benign equilibrium between the influenza virus and its host may have changed (Webster et al, 2006).

The most important implication of phenogenetic studies is that the ancestral viruses that caused Spanish influenza in 1918, as well as the viruses that provided gene segments for the Asian/1957 (H2N2) and Hong Kong /1968 (H3N2) pandemics, are still circulating in wild birds, with few or no mutational changes (Wright & Webster, 2001).

Taubenberger et al. (2006) reported that the 1918 virus did not originate through a reassortment event involving a human influenza virus: all eight genes of the H1N1 virus are more closely related to avian influenza viruses than to influenza from any other species, indicating that an avian virus must first infect humans and then adapt to them in order to spread from person to person. Thus, pandemic influenza may originate through at least two mechanisms: reassortment between an animal influenza virus and a human influenza virus that yields a new virus strain, and direct spread and adaptation of a virus from animals to humans.

It is important to mention that influenza A/ H1N2 viruses, which emerged during 2001 are genetic reassortants between H1N1 and H3N2 subtype viruses which have circulated in the human population since 1977. They possess a H1 hemagglutinin antigenically and genetically similar to contemporary A/New Caledonia/20/99 (H1N1)-like viruses and seven genes closely related to those of recent A/Moscow/10/99 (H3N2)-like viruses. The viruses have spread into many regions of the world and have predominated over H1N1 viruses in several countries, (e.g.Egypt) (Gregory et al, 2002).

Fig. 2: Cumulative Number of Confirmed Human Cases of H5N1 (WHO, 2009)

**Next pandemic:**

All past influenza pandemics occurring during the 20th century apparently arose from the Eurasian avian lineage of viruses. Over the past several years, a great deal of attention has been focused on the role of avian influenza viruses as the source of the next pandemic strain.

Avian influenza was first identified in Italy more than
100 years ago. Pigs have receptors for avian and human influenza viruses and are susceptible to both; therefore, pigs have been considered logical intermediary hosts for viral reassortment between avian and human influenza strains (Horimoto & Kawaoka, 2001). However, the role of pigs in creation of pandemic strains is still under investigation. It is not clear whether avian strain could directly cause a global pandemic in humans or reassortment in another animal host is a necessary step (Webster, 1997).

The last two pandemic viruses resulted from combinations of avian and human influenza viruses (wild birds are considered the reservoir for type A influenza viruses). Many persons believe that these new viruses emerged when an intermediate host, such as pig, was infected by both human and bird influenza A viruses at the same time. A new virus was created. Events in Hong Kong in 1997, however, showed that this is not the only way that a new disease can become infected with a novel virus. Sometimes; an avian influenza virus can jump the species barrier and move directly from chickens to humans and cause the disease. So the direct contact with infected poultry is the route of transmission (Chotpitayasunondh, et al, 2006). In addition to a growing list of avian species that can be infected with H5N1 virus, the virus has infected several mammalian species, including tigers, leopards and pigs (Fauci, 2006).

Influenza viruses are impossible to eradicate, as there is a large reservoir of all subtypes of influenza A viruses in wild aquatic birds. In agricultural – based communities with high human population density such as are found in China, conditions exist for the emergence and spread of pandemic viruses. It is also impossible to predict when the next pandemic will occur. Moreover, the severity of illness is also unpredictable, so contingency plans must be put in place now during the inter–pandemic period. These plans must be flexible enough to respond to different levels of disease (Cox, et al, 2003).

We cannot predict when the next influenza pandemic will occur, or which influenza virus subtype will cause it. Forecasts of the severity of the next influenza pandemic differ in their predictions of deaths based on the models used. Modeling based on the pandemic of 1968 projects 2 million - 7.4 million excess deaths worldwide (Luke & Subbarao, 2006).

The H5N1 virus has infected birds in more than 30 countries in Asia, Europe and Africa, while further geographical spread remains likely. Human infections are still rare and the virus does not spread easily from birds to humans or readily from person to person (Saeed & Hussein, 2006).

The current epidemic of H5N1 highly pathogenic avian influenza in Southeast Asia raises serious concerns that genetic reassortment will result in the next influenza pandemic. There have been 164 confirmed cases of human infection with avian influenza since 1996. In 2004 alone, there were 45 cases of human H5N1 in Vietnam and Thailand, with a mortality rate over 70%. In addition to the potential public health hazard, the current zoonotic epidemic has caused severe economic losses. (Zeitlin & Maslow, 2006)

In six countries this virus has also caused fatal human infections. This has sparked fears that this agent may be the progenitor of a new pandemic influenza virus. During summer 2005 the disease has slowly spread westward. Isolated outbreaks have been reported from Kazakhstan, Russia, Romania, Turkey, Croatia and Ukraine. Migratory birds have been tentatively accused for spreading the infection along their flyways. (Werner, 2006)

This rapid rate of spread of virus along with notoriety of the virus for frequent genetic re-assortment, which might enable H5N1 to infect human beings, threatens of possible influenza pandemic since the last pandemic in 1968. The human influenza caused by this subtype of the virus (H5N1) has high case fatality of 54% and majority of affected humans are between the ages of 5 to 23 years. (Lahariya, et al, 2006)

Human infection with avian influenza virus:

Influenza A viruses causes natural infections of humans, some other mammals and birds. Few of the 16 haemagglutinin and nine neuraminidase subtype combinations have been isolated from mammals, but all subtypes have been isolated from birds (Alexander, 2006), of the 16 avian influenza virus subtypes, H5N1 is of particular concern for several reasons.

H5N1 mutates rapidly and has a documented propensity to acquire genes from viruses infecting other animal species. Its ability to cause severe disease in humans has now been documented (WHO: Avian influenza, fact sheet, 2004).

The virus has spread rapidly throughout poultry flocks in Asia over the past 2 years and now appears to be endemic in eastern Asia (Kaye & Pringle, 2005).
It has shown a propensity to acquire genes from viruses infecting other animal species. It causes severe disease in humans, with a high case-fatality rate (reportedly at about 70%, although adequate surveillance data are lacking to accurately define the rate).

The potential of exposure and infection of humans is likely to be ongoing in rural Asia, where many households keep free-ranging poultry flocks for income. (Stohr, 2005).

Vaccination is the best option by which spread of a pandemic virus could be prevented and severity of disease reduced. Production of live attenuated and inactivated vaccine seed viruses against avian influenza viruses, which have the potential to cause pandemics, and their testing in preclinical studies and clinical trials will establish the principles and ensure manufacturing experience that will be critical in the event of the emergence of such a virus into the human population. (Luke & Subbarao, 2006).

Inactivated vaccines against avian influenza subtypes require 2 doses and administration with adjuvant to achieve the desired level of the neutralizing antibody. The precise antigenic properties of a nascent pandemic strain cannot be predicted, so available vaccines may be poorly antigenically matched to the pandemic virus. Manufacturing capacity, the ability of candidate vaccine strains to grow well in eggs, and biological safety containment of parent strains for vaccine development are all problems to be addressed. Efforts are under way to develop and evaluate live, attenuated vaccines against potential pandemic strains of influenza along a track that parallels the development and evaluation of inactivated virus vaccines (Luke & Subbarao, 2006).

To date, vaccines have been shown to be safe and well tolerated, but have required multiple doses and dosage levels higher than traditionally needed for seasonal influenza vaccines in order to generate immune responses thought to be protective, (Campbell, 2006). If the emerging avian influenza or another new virus creates a pandemic, severely limited supplies of vaccines and antiviral medications are likely (Temte, 2006). Efforts must be concentrated on early detection of bird outbreaks with aggressive culling, quarantines, and disinfection. To prepare for and prevent increased human cases, it is essential to improve detection methods and stockpile effective antiviral. (Zeitlin & Maslow, 2006).

Development of effective vaccines against highly pathogenic avian influenza H5N1 viruses with the potential to cause a pandemic is a public health priority (Hoelscher et al., 2008). A two-dose vaccine regimen of either 7.5 microg or 15 microg of hemagglutinin antigen without adjuvant induced neutralizing antibodies against diverse H5N1 virus strains in a high percentage of subjects, suggesting that this may be a useful H5N1 vaccine. (ClinicalTrials.gov number, NCT00349141.) 2008 Massachusetts Medical Society (Ehrlich et al., 2008) Another randomised, dose comparison, parallel assignment, multicentre trials conducted in Australia, healthy adult volunteers received two doses of vaccine (phase I trial; N=400, phase II trial; N=400) (Nolan et al., 2008)

Antiviral agents can be used to treat influenza infection and can be taken as chemoprophylaxis during influenza outbreaks (Stephenson & Democratis, 2006). Oseltamivir (Tamiflu®) has been shown to be effective in the treatment and prevention of epidemic influenza infection in adults, adolescents and children (1 year). Although oseltamivir has not been approved for prophylactic use in children, it has been shown to be effective. Oseltamivir is also active against avian influenza virus strains. Evidence suggests that lower doses or shorter durations of treatment/chemoprophylaxis other than those approved may not be effective and may contribute to emergence of viral resistance. (Ward1, et al, 2005)

Conclusion(s)

Avian influenza refers to a large group of different influenza viruses that primarily affect birds. On rare occasions, these bird viruses can infect other species, including pigs and humans. The vast majority of avian influenza viruses do not infect humans. An influenza pandemic happens when a new subtype emerges that has not previously circulated in humans.


The keystone of influenza prevention is vaccination; vaccine preparation should be by genetic reassortment of high-yield seed viruses of all hemagglutinin subtypes. The recommendation assumes that the next pandemic virus is unpredictable, but it will come from one of the 16 hemagglutinin subtypes of avian or mammalian strains of influenza A.
References

28. WHO (2009) Cumulative Number of Confirmed Human Cases of avian influenza (H5N1) confirmed to WHO http://cumulative%20number%20of%20confirmed%20human%20cases%20of%20avian%20influenza%20a(H5N1)%20Reported%20to%20WHO. [Cited 2009 July].
29. Wright PF & Webster RG.(2001)


Illustrations

Illustration 1

The current WHO phase of pandemic alert (WHO, 2009)

The current WHO phase of pandemic alert (WHO, 2009)
Illustration 2

Cumulative Number of Confirmed Human Cases of H5N1 (WHO, 2009)

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