Review

Human pandemic threat by H5N1 (avian influenza)

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Accepted 26 August, 2013

Influenza viruses infect a wide range of animal hosts and cause yearly wintertime epidemics among people living in temperate zones. Due to 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. The aim of this study was 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.

Key words: Influenza, pandemic, H5N1, vaccine, antiviral agents.

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. Influenza pandemics, defined as global outbreaks of the disease due to viruses with new antigenic subtypes, have exacted high death tolls from human populations (Horimoto and Kawaoka, 2001).

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 (Webster et al., 2006).

During March 2006-March 2009, a total of 6,355 suspected cases of avian influenza (H5N1) were reported to the Ministry of Health in Egypt. Sixty-three (1%) patients had confirmed infections; 24 (38%) died. Risk factors for death included female sex, age > or = 15 years, and receiving the first dose of oseltamivir >2 days after illness onset. All but 2 case-patients reported exposure to domestic poultry probably infected with avian influenza virus (H5N1). No cases of human-to-human transmission were found. Greatest risks for infection and death were reported among women > or = 15 years of age, who...
accounted for 38% of infections and 83% of deaths. The lower case-fatality rate in Egypt could be caused by a less virulent virus clade. However, the lower mortality rate seems to be caused by the large number of infected children who were identified early, received prompt treatment, and had less severe clinical disease (Kandeel et al., 2010). In Egypt, influenza types and subtypes are: H1N1, H1N2, H3N2 and B. One or two types are usually circulating in a season. In the last 2 years, influenza in Egypt has taken on special importance and attracted media attention since that season, also because the H5N1 strain attacked poultry in 2006 and was detected in some Egyptian human cases. In 2005 and 2006, both types A and B were circulating. The subtype A/H1N1 was circulating in 2006 (Awadalla et al., 2009).

**PANDEMIC PHASES**

In reviewing the public health implications of a pandemic, it is useful to understand the various phases that a pandemic will go through. World Health Organisation (WHO) has developed these phases that can be used by pandemic planners (WHO Influenza pandemic preparedness, 2005).

**Interpandemic period**

**Phase 1**

No new influenza virus subtypes have been detected in humans. As influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of human infection or disease is considered to be low.

**Phase 2**

No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease.

**Pandemic alert period**

**Phase 3**

Human infection(s) with a new subtype, but no human-to-human spread, or at most rare instances of spread to a close contact.

**Phase 4**

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**

Larger cluster(s) but human-to-human spread still localized, suggesting that the virus is becoming increasingly better adapted to humans, but may not yet be fully transmissible (substantial pandemic risk).

**Pandemic period**

**Phase 6**

Pandemic refers to increased and sustained transmission in general population.

**Evolutionary pathways of influenza viruses**

Studies on the ecology of influenza viruses have led to the hypothesis that all mammalian influenza viruses are derived from avian influenza reservoirs support for this theory comes from phylogenetic analyses of nucleic acid sequences of influenza A viruses from a variety of hosts, geographic regions, and virus subtypes (Webster et al., 1992).

A surprising discovery from phylogenetic analyses of amino acid changes was that avian influenza viruses, unlike mammalian strains, show low evolutionary rates (Gorman et al., 1990). In fact, influenza viruses in wild aquatic birds appear to be in evolutionary stasis, with no evidence of net evolution over the past 60 years. 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, wherein nucleotide changes provide no selective advantage. It also means that the source of genes for pandemic influenza viruses exists phenotypically unchanged in aquatic bird reservoir (Wright and 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. This benign equilibrium between the influenza virus and its host may have changed (Webster et al., 2006).

Overall, the most important implication of phylogenetic 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 and Webster, 2001). The startling observation of Taubenberger and Morens (2006) was 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 have infected humans and adapted 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, and direct spread and adaptation of a virus from animals to humans.

It is important to mention influenza A/H1N2 viruses, which emerged during 2001, are genetic reassortants between H1N1 and H3N2 subtype viruses which have cocirculated 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 to many regions of the world and have predominated over H1N1 viruses in several countries (for example, Egypt) (Gregory et al., 2002).

**Next pandemic**

Past influenza pandemics occurring during the 20th century apparently all 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 (Horimoto and Kawaoka, 2001). 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 and Kawaoka, 2001). However, the role of pigs in creation of pandemic strains is still not clear. It is also not clear if reassortment in another animal host is necessary or whether an avian strain could directly cause a global pandemic in humans (Webster, 1997).

The last two pandemic viruses were combinations of bird 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 human can become infected with a novel virus. Some-times, 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 interpandemic period. These plans must be flexible enough to respond to different levels of disease (Cox et al., 2003).

Influenza A (H1N1) virus emerged in 2009. It is a new reassortment that has never before circulated among humans. This virus is not closely related to previous or current human seasonal influenza viruses. Respiratory transmission occurs mainly by droplets disseminated by unprotected coughs and sneezes. Short-distance airborne transmission of influenza viruses may occur, particularly in crowded enclosed spaces. Hand contamination and direct inoculation of virus is another possible source of transmission (WHO, 2013b).

Influenza A (H7N9) is one of a subgroup of influenza viruses that normally circulate among birds. Until recently, this virus had not been seen in people. However, human infections have now been detected. As yet, there is limited information about the scope of the disease the virus causes and about the source of exposure. The disease is of concern because most patients have been severely ill. There is no indication thus far that it can be transmitted between people, but both animal-to-human and human-to-human routes of transmission are being actively investigated (WHO, 2013a).

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 and 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 and Hussein, 2006). The 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 and Maslow, 2006). Since 2003, there have been a total of 436 cases and 262 deaths due to H5N1 infections. The number of cases has decreased steadily since 2006 (Adams and Sandrock, 2010).

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:

1. 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).
2. 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 and Pringle, 2005).
3. 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).
4. 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).

The emergence of multiple genetically distinct sublineages of H5N1 has continued. These emerging sublineages display varying levels of drug resistance and in some cases an increased preference for binding to human α2,6-linked sialic acid cellular receptors. Though H5N1 has not shown efficient transmissibility between humans, the rapid evolution of the virus presents a concern for the emergence of a virus with this capability (Adams and Sandrock, 2010). 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 and Subbarao, 2006).

Inactivated vaccines against avian influenza subtypes require two 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 and 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 and Maslow, 2006).

Since 2005 it is recommended that people with occupational contact with wild or domestic birds should be vaccinated to reduce the risk of simultaneous infection with a human and an avian influenza virus (Eich, 2007). 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 or 15 mg 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 (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 and 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 (Ward, et al., 2005).

CONCLUSION

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. An influenza pandemic is a rare but recurrent event. Three pandemics occurred in the previous century: “Spanish influenza” in 1918, “Asian influenza” in 1957, and “Hong Kong influenza” in 1968. The 1950s pandemic influenza infection in Egypt during two consecutive seasons (J. Public Health. 17(3):195-203).

REFERENCE


