Avian influenza: the threat of the 21st century*

Gripe aviária: a ameaça do século XXI

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Abstract

This study aimed to review the literature on infection with the H5N1 subtype of avian influenza A virus, taking into consideration the fact that, in the event of a pandemic, children might become a major risk group. Searches were limited to the past ten years and were carried out using the following electronic databases: Medline, MD Consult, HighWire and Medscape. Children and young adults account for a significant proportion of the susceptible population. We found that more than half of the individuals infected were under 20 years of age and that one quarter were under the age of 10. The incubation period ranged from 2 to 5 days. Initial clinical manifestations are nonspecific, which hinders the diagnosis. Most of the infected individuals presented severe pneumonia, which evolved to respiratory insufficiency within an average of 4 days. Chest X-rays can reveal diffuse multifocal/interstitial infiltrates or segmental/lobar consolidation with air bronchogram. The pathogenic potential is high, with mortality rates up to 63%, indicating that the pandemic virus might present high pathogenicity and high mortality. Knowledge of the risk of a pandemic and of the measures to be taken in suspect cases constitutes an important step toward controlling a potential pandemic.

Keywords: Influenza A virus; Disease vectors; Disease outbreaks; Influenza A virus, H5N1 subtype.

Resumo

Este estudo teve como objetivo fazer uma revisão da literatura a respeito da infecção pelo vírus influenza A subtipo H5N1, levando em conta a possibilidade de as crianças serem um dos grupos etários mais acometidos caso ocorra uma pandemia. A revisão bibliográfica foi realizada nos seguintes bancos de dados, restrita aos últimos 10 anos: Medline, MD Consult, HighWire e Medscape. As crianças e os adultos jovens representam uma fração importante da população susceptível. Mais da metade dos indivíduos infectados apresentavam menos de 20 anos de idade, e um quarto era menor do que 10 anos. O período de incubação variou de 2 a 5 dias. As manifestações clínicas iniciais são não específicas, o que dificulta o diagnóstico. A maioria dos casos apresentou um quadro de pneumonia grave, que evoluiu para insuficiência respiratória em 4 dias em média. A radiografia de tórax pode mostrar infiltrado intersticial difuso ou multifocal ou consolidação lobar ou segmentar com broncograma aéreo. A infecção tem alta patogenicidade, com 63% de letalidade, o que indica que o vírus pandêmico também pode apresentar alta patogenicidade com mortalidade elevada. O conhecimento sobre os riscos da pandemia e sobre as medidas que podem ser tomadas em casos suspeitos é um importante passo para o controle de uma possível pandemia.

Descritores: Vírus da influenza A; Vetores de doenças; Surtos de doenças; Vírus da influenza A subtipo H5N1.

Introduction

The first human epidemic of avian influenza, popularly known as bird flu, was reported in Hong Kong in 1997. At that time, 18 people were hospitalized and there were 6 deaths. In February of 2003, 2 more human cases of avian influenza, 1 of which resulted in death, were reported in Hong Kong, in a family who had recently travelled to continental China. In the period between 2003 and 2007, more than 20 countries in Asia, Africa and Europe reported cases of avian influenza in animals, and approximately 1.5 million birds were sacrificed to prevent dissemination of the virus.[1-4] However, from 2003 onward, infection in humans started to occur with greater frequency in many countries, being responsible for a high mortality rate. As of 10 September

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2008, the World Health Organization (WHO) had registered 387 confirmed cases in humans, with 245 deaths.[5] Unlike seasonal human influenza, which principally affects the elderly and suckling infants, avian influenza affects young adults and children. The mean age of the cases reported to date is 18 years, with 90% of the patients being ≤ 40 years of age. Although the mortality rate is 63.0%, individuals between 10 and 18 years of age present higher rates and those over the age of 50 present lower rates.[6] This study aimed to review the literature on avian influenza, taking into consideration the fact that, in the event of a pandemic, children might become a major risk group.

The influenza virus

The influenza virus is a RNA virus of the *Orthomyxoviridae* family and has three different types: A, B and C. It has two surface glycoproteins: hemagglutinin, which is the principal antigen and determines the ability of the virus to invade cells; and neuraminidase, whose activity is related to the release of new virions of the infected cells. To date, 16 hemagglutinins (H1-H16) and 9 neuraminidases (N1-N9) have been described.[6,7]

The influenza A virus can infect human beings, horses, pigs, birds and sea mammals. It has high morbidity and mortality, in addition to being responsible for all of the pandemics recorded in human history. The B virus infects exclusively human beings, causes a less severe clinical profile than does the A virus and can cause local epidemics. The C virus infects humans and swine, causes a mild form of upper respiratory tract infection and is not associated with epidemics or pandemics.[7] The influenza viruses have singular genetic characteristics. In addition to the possibility of exchange of genetic material among them, genetic mutations are frequent. Small genetic variations of surface antigens, collectively known as drift, can occur in all three types. The influenza A virus can also suffer specific large mutations in their surface antigens, collectively known as shift.[7]

Pandemics in history

The first flu epidemic was reported in 412 B.C. by Hippocrates, who described it as an outbreak of a respiratory disease that killed many people in a few weeks and later disappeared. Despite the lack of significant physical lesions, such as those resulting from smallpox, measles and the plague, some historic flu epidemics have been characterized by the way in which they rapidly affect the population, by the large number of patients and by the frequency of cough. There were reports of two major epidemics affecting Russia and Asia, in 1781 and 1830, respectively. The first recorded influenza pandemic, which occurred in 1889-90, resulted in approximately 300 thousand deaths, principally among the elderly, due to respiratory complications, such as bacterial pneumonia.[7] One of the most devastating pandemics in human history, known as the Spanish flu (1918-19), was caused by the influenza A H1N1 virus and resulted in 40-100 million deaths worldwide. In the 20th century, other influenza pandemics occurred: the Asian flu (1957-58), caused by the H2N2 virus; and the Hong Kong flu (1968-69), caused by the H3N2 virus. However, these last two pandemics were responsible for less mortality, with 2 million deaths in 1957 and 1 million in 1968. The lower number of deaths was likely related to the lower virulence of the viruses and to the greater availability of medical and hospital resources, including vaccines, intensive care and antimicrobial agents.[7] Only in 2005 was it possible to characterize the H1N1genome. The phylogenetic analysis indicated that it was a virus of avian origin and not swine, as it has been previously thought. Although there are no specimens of the avian virus that was circulating at the time, the most probable hypothesis is that the avian virus had suffered a significant mutation (shift) and has adapted itself to humans without intermediaries, such as swine, which would explained its high pathogenicity and mortality.[8-10] The H2N2 and H3N2 viruses, responsible for the other pandemics, were composed of a combination of human and avian influenza virus gene segments, which can explain the lower virulence.[10]

Influenza pandemics occur from three to four times each century.[11] The longest time between them was 42 years, and the last pandemic, that of the Hong Kong flu, occurred 40 years ago.[12] According to the WHO, there are three prerequisites for the occurrence of a pandemic: 1) the new virus must be one for which the human population has low or no immunity; 2) the virus must have the ability to replicate

in humans and cause severe disease; and 3) the virus must be easily transmitted from human to human.[13] The H5N1 virus meets the two first prerequisites. The analysis of cases occurring prior to 2008 indicated clustered transmission in at least 10 countries, corresponding to 25% of the cases. Most of these groups had two or three people affected in the same family (more than 90% of the cases), which suggests genetic susceptibility. The data show than these patients must have acquired the infection from a common source. However, in some situations, there is evidence that human-to-human transmission occurred following close contact with critically ill patients. However, even though human-to-human transmission had occurred, the virus was not transmitted to people outside the cluster.[4,14-16]

Epidemiology

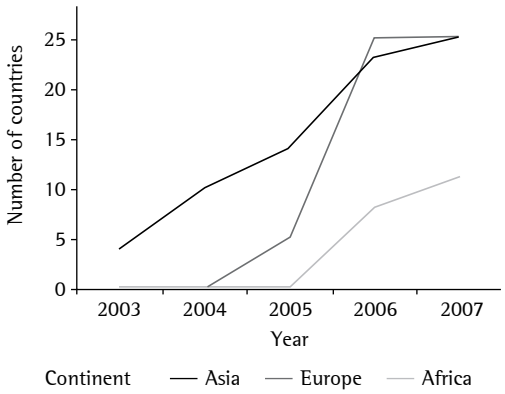
The highly pathogenic H5N1 virus was first isolated in geese, in 1996, in the province of Guangdong, located in the south of China. Following the outbreak recorded in Hong Kong in 1997, there were no reported cases in humans until February of 2003, when 2 new cases were identified in Hong Kong.[1]

At the end of 2003, an outbreak of avian influenza was identified in chicken in South Korea, lasting until September of 2004. From the beginning of 2004, the pandemic began to affect other countries: Thailand, Japan, Cambodia, Laos, Indonesia and Malaysia. In the following year, new cases were identified in Russia, Kazakhstan, Mongolia, Turkey and Kuwait. For the first time, cases in animals outside of Asia were also reported, having been described in Europe (England, Romania, Croatia and the Ukraine). In 2006, the pandemic affected other countries: in Asia and the Middle East (Iraq, Iran, India, Pakistan, Israel, Jordan and Afghanistan); in Europe (Bulgaria, Greece, Slovenia, Italy, Germany, France, Albania, Austria, Bosnia, Slovakia, Hungary, Azerbaijan, Georgia, Serbia and Montenegro, Switzerland, Poland, Denmark, Sweden, the Czech Republic and Spain); and Africa (Nigeria, Egypt, Cameroon, Sudan, Djibouti). In addition, between August and September of 2006, viral antigens were detected in swans and ducks in the United States. In 2007, Bangladesh, Saudi Arabia, Ghana, Myanmar and Benin also reported new cases in domestic birds. Infection with the H5N1 virus in chicken is already considered endemic in China, Cambodia, Thailand and Laos. It is estimated that it will take several years to control the disease in these regions.[1,2] Figure 1 shows the distribution of infection with H5N1 in animals.

The cases of avian influenza in humans followed the same course as that of those in birds. In 2004, 46 cases were reported in Vietnam and Thailand, with 32 deaths (69.6%). In 2005, there were 98 cases (43 fatal; 43.9% mortality), affecting China, Indonesia, Thailand, Vietnam, Cambodia and Indonesia. In 2006, 115 cases occurred, with 79 deaths (68.7%), the first cases being reported outside of Asia (in Azerbaijan, which is in Eastern Europe, as well as in Djibouti and Egypt, which are in Africa). In 2007, Nigeria, Myanmar, Pakistan and Laos confirmed the first cases in humans, the same occurring in Bangladesh in 2008. As of 10 September 2008, the WHO had confirmed 387 cases in humans, with 245 deaths, representing a mortality rate of 63.3%.[1,3,17] Figure 2 shows the number of cases of human infection with H5N1, by year and location.

Susceptible population

Many studies have shown that children and young adults represent a major portion of the population affected by avian influenza. Between December of 2003 and January of 2005, patients infected with H5N1 in Vietnam were, on average, 15 years of age.[11] In Indonesia and Turkey, the



Source: World Health Organization, 2008

Figure 1 - Number of countries that reported infection with H5N1 in animals.

median age was of 9 years. More of half of cases reported worldwide were in individuals below 20 years of age, a quarter being below the age of 10. The overall median age was 18.5 years.[18] Mortality also seems to be higher among children and young adults. The mean age at the time of death was 20 years.[10]

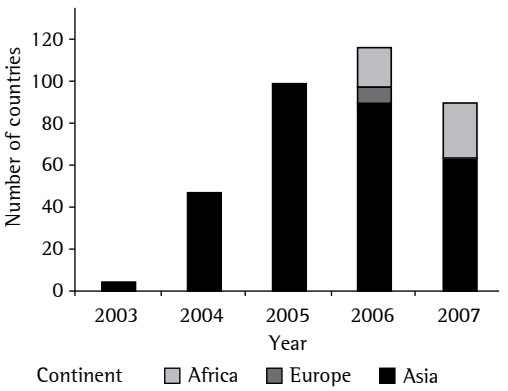
The three most recent pandemics presented age-specific differences in the patterns of mortality, although all resulted in high mortality among individuals in the first 10 years of life.[10] The greatest difference was in the Spanish flu, in which mortality was highest among individuals of approximately 30 years of age, below the mean age observed in other two pandemics. Taking into consideration the history of the most recent pandemics and the preliminary data on the first infections with H5N1, we can infer that children will likely represent one of the age brackets with higher morbidity and mortality in the case of a human pandemic of H5N1 infection.[6,10,18]

One author suggested that this greater impact on children can reflect an age-related difference in susceptibility.[18] Human infection is mediated by a receptor that is expressed principally in the terminal bronchioles and alveoli in adults. However, in the fetal lung, the same receptor is distributed homogeneously throughout the respiratory tract. In addition, there is evidence that its expression decreases with age. The same author suggested that, in children, this receptor is expressed in the upper airways, thereby increasing the risk of infection.[18] Other authors believe that the high incidence of the disease in children in Turkey was due to the common practices in the region, where there is greater exposure of children to domestic birds.[19] The mechanism of infection of human beings is not established and there is no consensus about the reason for the higher susceptibility of children, which warrants further studies on the theme.[6]

Forms of transmission

Avian influenza is transmitted easily between birds of different species. It can affect domestic birds and wild birds, which facilitates its dissemination to other continents and hinders its control. Transmission of the avian virus to humans is rare and typically occurs in cases of close, frequent contact with the sick animal, principally in the week prior to its death. Most of the patients acquired the virus through exposure to domestic birds at home or in the areas surrounding the home.[4,20] In approximately 25% of cases, the form of transmission was not totally clarified. Transmission might have occurred via fomites or via the environment (through contact with fertilizers containing bird feces or through inhalation of the aerosolized feces of contaminated animals).[6,7,13,20]

The H5N1 virus also can infect mammals, including domestic animals, such as dogs and cats. To date, there is no record of a human being infected by a mammal.[6] However, infection of mammals can be one of ways in which H5N1 adapts to human beings. Classically, it is believed that adaptation of the seasonal influenza virus to human occurs through adaptation of the avian virus to an intermediary species, often swine.[7] Another possibility is that H5N1 adapts to humans through the exchange of genetic material between the human and avian strains of the influenza virus in a person infected with both. The most widely accepted theory to explain the recent appearance of H1N1 is that adaptation is achieved due to the occurrence of an isolated genetic mutation (shift) in the avian virus.[7,8,13] It is important to emphasize that all of these possible forms of adaptation depend on genetic mutations, which are random phenomena. Therefore, it is not possible to predict whether or when any of them will occur. However, for them to occur, it is necessary that the avian virus be in constant contact with humans, which it has been since December of 2003.[7,8,13,20]



Source: World Health Organization, 2008

Figure 2 - Number of cases of human infection with H5N1 divided by continent and year of record.

Current data indicate the possibility of sporadic human-to-human transmission in isolated cases of close contact with critically ill patients. If this has truly occurred, the virus transmitted among humans has not established itself, no cases having been observed outside of the putative clusters.[6,14-16] For the purpose of prevention, the respiratory secretions, body fluids and feces of all patients with avian influenza should be considered potentially infective.[6]

Clinical manifestations

The H5N1 incubation period ranges from 2 to 5 days.[6] The initial manifestations are nonspecific, which hinders the diagnosis.[21] Fever, rhinorrhea, myalgia, headache, sore throat, cough, diarrhea, vomiting and abdominal pain can occur.[6,11] Most cases manifest as severe pneumonia that evolves rapidly to respiratory failure within an average of 4 days.[6,11] The radiological findings can include diffuse multifocal/interstitial infiltrates and segmental/lobar consolidation with air bronchogram. Multiple organ failure (of the heart and kidneys) can occur. Death occurs, on average, 9-10 days after the onset of symptoms. This pattern did not change since 2003.[6,11] From 2005 onward, a profile of upper respiratory tract infection, without pneumonia, has been observed with greater frequency in children, and this might be related to the increase of the early use of antiviral drugs.[6] Gastrointestinal symptoms have also decreased in frequency.[6] The most common biochemical abnormalities are leukopenia, lymphopenia, thrombocytopenia and increased transaminase levels. Lymphopenia and elevated lactate dehydrogenase are associated with a worse prognosis.[6] Due to the lack of specificity of initial symptoms and the different possible clinical presentations, infection with the influenza A virus (H5N1) must be considered in all patients with suggestive epidemiology and a clinical profile of atypical evolution, principally in the presence of rapidly progressing respiratory infections.[6] Chart 1 shows the principal clinical, radiological and biochemical manifestations of infection with H5N1.

Laboratory diagnosis

The biochemical diagnosis of infection with the influenza virus is typically carried out by indirect immunofluorescence in nasopharyngeal secretion samples, collected through nasopharyngeal aspiration or the combined swab technique (using two nasal swabs and one oropharyngeal swab).[22] However, this method does not differentiate among the subtypes of the influenza A virus and has low sensitivity for the diagnosis of H5N1 infection.[23] The gold standard is culture, which allows viral characterization. However, this method requires 2-10 days for viral growth and can only be carried out in laboratories with biosafety level 3 facilities.[23]

Chart 1 - Clinical, radiological and laboratory manifestations of human infection with H5N1.

Clinical manifestations	Radiological abnormalities	Laboratory test results
• Fever	• Diffuse interstitial infiltrate, often bilateral	• Leukopenia
• Rhinorrhea	• Segmental/lobar consolidation with air bronchogram	• Lymphopenia
• Myalgia		• Thrombocytopenia
• Headache		• Increased transaminase levels
• Sore throat		• Increased lactate dehydrogenase
• Cough		
• Diarrhea		
• Vomiting		
• Abdominal pain		
• Severe pneumonia		
• Respiratory failure		
• Multiple organ failure		
• Heart failure		
• Renal failure		

Although PCR has high sensitivity, it is a costly procedure, requiring specialized equipment and appropriate training. The serological diagnosis of influenza can be employed in the evaluation of postvaccination immune response and in retrospective seroepidemiological studies. However, serological testing is not indicated for the diagnosis of acute cases.[24] In Brazil, a plan for the epidemiological surveillance and the biochemical diagnosis of suspected cases (the Influenza Surveillance System) was developed in 2005. The plan outlines measures to be taken depending on the stage of pandemic. The objectives of the Influenza Surveillance System included expanding the network of laboratories and periodic technical training of professionals.[24]

Control measures

Many specialists believe that a pandemic of influenza A is inevitable. It is estimated that there will be at least one pandemic in this century, although it is more likely that, as in the last century, more than one will occur.[25] Therefore, preparation is crucial in order to minimize its devastating effects. The WHO developed an operational protocol to be followed in case of pandemic and recommends that all countries develop their own control plans.[26]

The principal measures suggested by the WHO are as follows: active surveillance for the identification of human cases of avian influenza; antiviral prophylaxis for contacts; application of anti-influenza A vaccine as soon as it becomes available (for H5N1 or for the new virus that appears following mutations); restriction of movement within affected areas; and other nonpharmacological interventions (isolation of the ill, voluntary quarantine of the exposed and social distancing measures, such as the closing of schools and public places). The WHO suggests that these measures be taken within the first three weeks following the identification of the index case and remain in effect for a minimum of 4-5 weeks, depending on the degree to which the outbreak is controlled.[26]

After the index case has been detected, areas of containment and protection should be defined. A containment area must retain all individuals known to be infected and most of their regular contacts. The following should be implemented: all individuals in whom infection is improbable should receive antiviral prophylaxis; all individuals should be vaccinated, if a vaccine is available; movement into and out of the containment zone should be restricted; and nonpharmacological measures should be taken.[26]

The protection zone should consist of the area in which it is more probable that new cases might appear, i.e., the zone surrounding the containment area. The measures to be taken in the protection zone include the following: the investigation, isolation and treatment of suspected cases (even prior to the receipt of the laboratory test results); the voluntary quarantine of contacts; and antiviral prophylaxis for contacts (following laboratory confirmation). Individuals in the protection zone should not be allowed to enter the containment zone but should be allowed to leave the protection zone. It is estimated that at least 4-5 weeks of containment will be needed before these measures can be discontinued. Even after discontinuation, the area must be carefully monitored for several months.[26]

In December of 2003, the Brazilian National Ministry of Health formally instituted a committee for the preparation of a contingency plan. The resulting plan implemented certain measures, strengthening the epidemiological surveillance of influenza, providing for the strategic stockpiling of the antiviral drug oseltamivir and equipping the Butantan Institute for the production of a vaccine against the pandemic strain.[27]

Antiviral prophylaxis

The WHO recommends that, in the case of a pandemic of influenza, antiviral drugs should be administered to the contacts and to all residents of the containment zone.[26] The prophylaxis should be initiated within the first 24-48 h following the exposure, preferably within the first 12 h. Neuraminidase inhibitors (oseltamivir, zanamivir or peramivir, the last two not being currently available in Brazil) are currently the agents of choice, due to the increase in resistance to amantadine and rimantadine. Oseltamivir is available in capsules and in liquid form.[28] Zanamivir is available only in aerosol form, and peramivir is administered intramuscularly. The WHO recommends that the prophylaxis with oseltamivir be given for 20 days, rather than the normal 10 days.[26] The recommendation

to extend the prophylaxis might be due to the lack of knowledge as to the nature of the H5N1 strain that would be the cause of the potential pandemic, which might present a longer incubation period than do seasonal strains, as well as to logistical concerns.[26,28]

Treatment

Treatment with oseltamivir is recommended for all suspected cases of human infection with avian influenza until 3 days following symptom onset. The initial observations suggest that the treatment reduces mortality and that the delay in its initiation is one of the principal risk factors for death. The dose and duration of the treatment are not yet well established. Studies show the persistence of the virus in the pharynx following treatment, which can indicate higher viral replication and lower elimination of the agent in the lower airways. Based on these findings, the use of higher doses and longer treatment duration might be necessary. In adult patients, a dose of 150 mg two times a day for 10 days can be used, principally in patients with severe pulmonary impairment or progressive disease. Although high doses are proven safe in adults, there have been no studies evaluating their safety in children.[6]

There are a number of drugs that are still in the research phase, and the results to date have been promising. One such drug is T-705, an inhibitor of viral RNA polymerase. In preclinical studies, the drug seems to be effective, even when applied in a single dose. In addition, it has the advantage of the possibility of being initiated at up to 96 h following the exposure.[29] Unfortunately, even if these favorable results are confirmed in clinical studies, T-705 will probably not be available for large scale use in the case of a pandemic.

Vaccines

A vaccine against H5N1 could minimize the effects of pandemic, delaying its progress and decreasing mortality.[30] Several vaccines against H5N1 are in different phases of development. However, since the pandemic virus will possibly present genetic and antigenic characteristics different from those of circulating strains, it remains unknown whether any of the vaccines in development will be efficacious in the control of pandemic. It is estimated that that the production of a new vaccine will take from 3 to 6 months following the isolation of the viral strain.[30]

There are several technical obstacles to the development of a vaccine against the avian influenza. Classically, the anti-influenza vaccine is produced in egg embryos. However, the H5N1 virus is so pathogenic that it is often lethal for the embryo or grows in very small amounts, hampering the production of vaccines by this method. Due to the pathogenicity of H5N1, the vaccine must be produced in laboratories with biosafety level 4 facilities, rather than biosafety level 2 facilities, as are used in the production of vaccines against seasonal influenza. This limits the number of potential producers of vaccine.[31] Another problem to be faced is a low immunogenicity of H5N1, which makes it necessary to use two doses or a higher quantity of antigen in a single dose in order to obtain effective protection; this can decrease the availability of vaccines and delay the control of the pandemic.[6,32] The use of adjuvants can reduce this problem, although clinical studies are needed in order to determine the formulation, as well as the concentration of the adjuvant and of the antigen, together with the dose of each potential vaccines, all of which can delay their approval for large scale use.[6]

Other technologies of production of vaccines are being researched for the influenza virus. One of them is the production by cell cultivation, which allows the virus to grow in living cell culture media rather than in fertilized eggs. This technique would allow the production of a higher amount of vaccines in a lower space of time, which can be important in case of a pandemic. Additional research has been carried out with recombinant vaccines, by genetic engineering. The gene of a given protein of the virus is isolated, cloned and put aside to grow in fungi or other cells in order to obtain a large amount of this protein. The protein is purified and used for producing vaccines. There are also studies underway to developing a universal vaccine, that would confer long-term protection against all known types of influenza.[33] However, these are in the initial phase, without the perspective of being solidified in the coming years.

Access to the vaccine is another important theme under discussion. Taking into consid-

eration the current limited capacity of vaccine production, which segments of the population should be prioritized? In an epidemic, it is necessary not only to try the prevent an outbreak, through vaccination of contacts and of patients at higher risk for complications, but also to ensure the functioning of support structures within the society, such as health care, the production chain, transport (of food and materials) and the police force. Another important issue is the access of developing countries to these vaccines. The limitations in health care infrastructure and treatment coverage in such countries could have a considerable negative impact on the control of a pandemic of avian influenza within their populations. An efficacious vaccine would minimize this impact in developing countries.[34] This concern led to several ethical discussions at the international level, culminating, in May of 2007, in a resolution by the WHO Assembly, which laid out an agreement for the international sharing of viral samples and collaboration in the production/distribution of vaccines.[35,36] However, there is still some concern regarding the limited availability of vaccines in developing countries. In 2005, the Brazilian Ministry of Health invested in the Butantan Institute in order to accelerate preparations for the construction of an emergency installation for the production of vaccines in case of a pandemic.[27]

Monoclonal antibodies

The use of monoclonal antibodies has been investigated as a potential strategy for the prophylaxis against and treatment of infection with H5N1. Some studies have shown that monoclonal antibodies confer protection against infection with H5N1 in animal models.[37,38] However, further studies are needed in order to confirm these results in humans.

Possible repercussions of the pandemic

The current distribution of the global population favors the rapid dissemination of a virus that is transmitted via respiratory secretions, given the epidemic of severe acute respiratory syndrome. The global population has nearly tripled since 1918; there has been a large increase of population urban, with the formation of large cities, that facilitate virus dissemination; and international air travel can speed transmission. Despite all the development of medical and hospital resources occurring in this period, there are currently fewer hospital beds per capita than there were in 1968.[12] Previous pandemics affected the whole world within 6 to 9 months, at a time when international voyages were made by ship. Currently, with large scale air trips, it is estimated that that entire world could be affected within approximately 3 months.[21] It is estimated that that half of the population worldwide would be infected within a year or more. In previous pandemics, between 25% and 35% of the population was affected. In Brazil, the Ministry of Health predicts the occurrence of 37 to 61 million of cases, with 18 million people requiring treatment due to complications in all of Brazil.[24]

Final considerations

There is a high potential for the occurrence of a new influenza pandemic, although it is not possible to predict when it will occur. The current avian influenza virus presents considerable pathogenic potential, with a mortality rate of 63.3%, suggesting that the pandemic virus could also present high pathogenicity and result in an excessive number of deaths, estimated between 2.4 and 7.0 million in worldwide. The measures of control of a potential pandemic are based on the active surveillance of cases, the isolation of cases (and of their contacts), the treatment of patients, the prophylactic treatment of contacts and immunization of the susceptible population. Taking into consideration the current limitations of production and supply of antiviral drugs and vaccines, active surveillance and isolation are the principal strategies available. Awareness of the risk of a pandemic and of the measures to be adopted when presented with suspected cases is important for the control of the epidemic. Health professionals should be attentive to the possibility of this new worldwide threat.

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