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Review Article

An overview of the recent outbreaks of the avian-origin influenza A (H7N9) virus in the human

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Abstract

Since the first human infection with influenza A (H7N9) viruses have been identified in Shanghai on March 31, 2013, the latest variant of the avian flu virus has spread across four Chinese provinces recently. Human infections with avian influenza are rare and this is the first time that human infection with a low pathogenic avian influenza A virus has been associated with fatal outcome. To date (May 5th, 2013), China had reported 128 confirmed H7N9 infections in human, among 27 died. Most reported cases have severe respiratory illness resulting in severe pneumonia and in some cases have died. No evidence of sustained human-to -humans at this time, however, there is one family cluster with two confirmed cases for which human-to-human transmission cannot be ruled out. Recent evidence showed that the gene sequences of this novel H7N9 virus is primarily zoonotic and may be better adapted than other avian influenza viruses to infect human. Effective global infection control is urgently needed, and further surveillance and analyses should be undertaken to identify the source and mode of transmission of these viruses.

Keywords: avian influenza virus (AIV); influenza A (H7N9)

1. Introduction

On March 31, 2013, a novel Avian-origin influenza A (H7N9) virus infection has been identified in Shanghai[1] and this is the first time that human infection with novel avian influenza A virus has been associated with a fatal outcome.[2] Influenza is an acute, usually self-limited, febrile illness caused by infection with influenza type A or B virus that occurs in outbreaks of varying severity almost every winter.[3] However, they always pose a pandemic threat, since the viruses may adapt to humans. The primary risk factor for human infection appears to be direct or indirect exposure to infected live or dead animals or contaminated environment. In 1997, the highly pathogenic H5N1 avian influenza virus (AIV) was first transmitted from birds to humans in Hong Kong.[4] This new H7N9 AIV (Fig.1)[5] is a subgroup among the larger group of H7 viruses, which normally circulate among birds.[6] Human infections with other subgroups of H7 influenza viruses (H7N2, H7N3, and H7N7) have previously been reported in the Netherlands, Italy, Canada, United States of America, Mexico and the United Kingdom.[7] While highly pathogenic H5N1 and H7 viruses may cause fatal disease in people, all human infections caused by low pathogenic H7 viruses so far have been mild. It is therefore our concern to see that how this new low pathogenic avian virus H7N9 virus can be lethal in humans.

2. Virology

Influenza A viruses are further divided into subtypes on the basis of their hemagglutinin (H1 to H17) and neuraminidase (N1 to N10) activity.[8] A third integral membrane protein, the M2 protein, is also present in small amount on the viral envelope[3] This novel avian influenza A virus (H7N9) differs genetically from A (H7) and A (N9) viruses that have been

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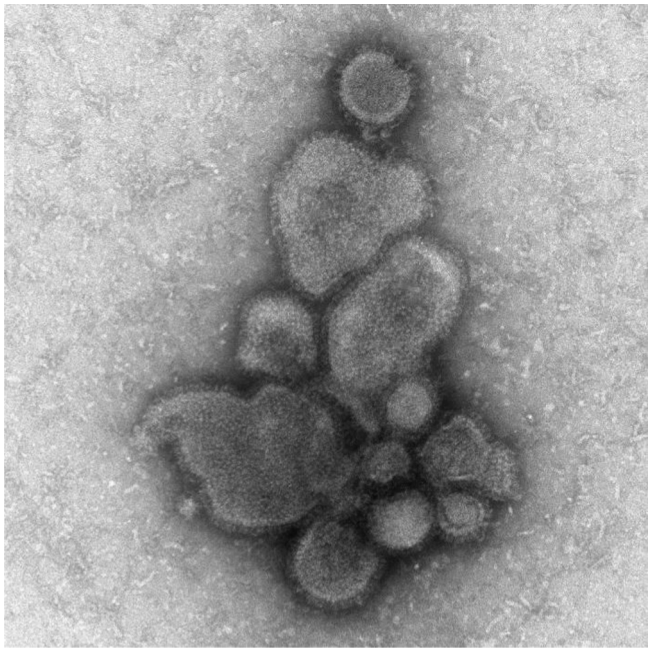

Fig.1. Electron micrograph of new influenza A (H7N9) virus from China. *Source: CDC USA Public Health Image Libery. ID#15673/ Cynthia S. Goldsmith and Thomas Rowe.*[5]

detected in Europe and elsewhere worldwide.[2] Gao and colleagues reported that the H7N9 viruses identified in the first three patients were of avian origin and all the internal gene segments were closely related to A/brambling/Beijing/16/2012-like viruses (H9N2). The neuraminidase (NA) gene was closely related to A/wild bird/Korea/A14/2011 (H7N9, subtype KO14) and the gene encoding hemagglutinin (HA) shared the highest identity with A/duck/ Zhejiang/12/2011(H7N3, subtype ZJ12).[9] The affinity of the influenza virus to different sialyl-sugar structures is an important determinant of range and pathogenicity in the viral host.[10,11] Q226L in the HA protein, which was first reported in H7 field viruses, as well as H5 subtypes, was expected to bind strongly to alpha 2-6 human like receptors.[9] Researchers reported that a laboratory-generated Q226L mutation at the 210-loop of HA could change the receptor binding of avian origin to a human-type receptor binding and might increase the ability of the virus to be transmitted by air.[12,13] Since human influenza viruses preferentially bind to alpha 2-6 receptors, they might have greater ability to infect mammalian species.[1]

3. Epidemiology

Human infections with avian influenza are rare and occurred most commonly after exposure to infected poultry. The novel rearranged H1N1 influenza virus (the swine-origin influenza virus) outbreak emerged from Mexico and the United stated in April 2009, then pandemic outbreak in all over the world.[14] Chan et al reported that there were certain risk groups of hospital personnel that may contract the disease. Their data showed that the seropositive rate (SPR) of antibodies against the pandemic (H1N1) 2009 virus in certain risk groups and most infected individuals probably only have mild or even subclinical symptoms.[14] H7 virus infection in humans is uncommon, however, this is the first time that this avian influenza subtype (H7N9) is found in people. To date (May 5th, 2013), China had reported 128 laboratory confirmed human cases from eight provinces: Anhui (4), Jiangsu (27), Zhejiang (46), Henan (4), Shandong (2), Jiangxi (5), Fujian (4), and Hunan (2), and two municipalities, Beijing (1) and Shanghai (33), including 27 fatal cases reported from Jiangsu (6), Zhejiang (6), Anhui (1), Jiangxi (1) and Shanghai (13).[15] In Taiwan, a cumulative total of 295 suspected H7N9 cases have been reported to Taiwan Centers for Disease Control (CDC) and infection with avian influenza A (H7N9) has been confirmed in one case, 3 cases are still pending results and the possibility of H7N9 infection has been ruled out in the remaining cases.[15] This virus is very different from other H7N9 viruses previously found in birds. Most H7 viruses identified worldwide in wild birds and poultry are low pathogenic avian influenza A (LPAI) viruses. The source of infection and the mode of transmission are currently unknown. Li Q et al reported that 77% of the first 82 H7N9 patients had some animal exposure, however, some cases have not had such contact.[16] Taiwan Central Epidemic Command Center (CECC) obtained that 139 people who have come into contact with the confirmed case, including 3 close contacts, 26 regular contacts (past the 10-day incubation period), and 110 healthcare workers. The public health authority conducted to all contacts for "Self-Health Management Advice for H7N9 Influenza" and will be following up with them closely until the period of voluntary contact tracing is lifted. When they develop influenza-like illness symptoms such as fever and cough, the public health authority will voluntarily assist the individual in seeking medical attention.[17] The possibility of animal-to-human or person-to-person transmission is being investigated. World Health Organization (WHO) issues first risk assessment on China's H7N9 outbreak on April 13, 2013, because two confirmed cases have been possibly associated with family clusters, in which one and two additional family members, respectively, developed severe pneumonia. Close contacts are being monitored but the agency said that no samples that have undergone polymerase chain reaction (PCR) testing have been found positive for the virus.[1,18]

4. Clinical characteristics

The main clinical feature among most patients is severe pneumonia. Symptoms include fever, cough and shortness of breath.[7] In humans, LPAI (H7N2, H7N3, H7N7) virus infections have caused mild to moderate illness (conjunctivitis and/or upper respiratory tract symptoms). However, high pathogenic avian influenza (HPAI) A (H7N3, H7N7) virus infections may cause mild to severe or even fatal illness.[19] Gao and colleagues reported that the clinical features in three patients with H7N9 virus infection were fulminant pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, multiorgan failure, rhabdomyolysis, and encephalopathy.[9] The first case (H7N9) reported in

Taiwan is a 53-year-old male patient who had fever for 3 days after returning from Suchow, Jiangsu Province, China on April 9, 2013. The patient still had high fever on April 16, 2013 and sought medical attention, two throat- swab specimens tested negative for H7N9 with real-time PCR on April 17 and April 20. He was then transferred to Medical Center on April 20 due to progressive dyspnea with progressive bilateral lower-lung consolidation on chest radiograph. Endotracheal intubation and mechanical ventilator support and extracorporeal membrane oxygenation were used due to respiratory failure. Then very high viral loads were found in the two sputum specimens and one throat-swab specimen collected on April 20 and April 22.[20] However, information of the full disease spectrum that influenza A (H7N9) virus infection might cause is still very limited.

4.1. Case Investigation and testing

In United states, Centers for Disease Control and Prevention (CDC) recommended that patients with illness compatible with influenza who recently travel to countries where human cases of novel influenza A (H7N9) virus infection have recently been detected, who with recent contact with confirmed human cases of infection with novel influenza A (H7N9) virus and who with recent direct or close contact with animals (such as wild birds, poultry, or pigs) or where influenza A (H7N9) viruses are known to be circulating in animals, should be candidates for reverse-transcription polymerase chain reaction (RT-PCR) testing for influenza. Decisions about diagnostic testing for influenza using RT-PCR should be made using available clinical and epidemiologic information, and additional suspected cases of influenza A (H7N9) virus infection should also be tested. Commercially available rapid influenza diagnostic tests (RIDTs) may not detect avian or variant influenza A viruses in respiratory specimens. Therefore, when RIDTs are positive for influenza A and there is concern for novel influenza A virus infection, respiratory specimens should be collected and sent for RT-PCR testing at a well equipped laboratory. All unsubtypeable influenza A virus specimens should be submitted to CDC immediately for additional diagnostic testing. At this time, confirmatory testing for avian influenza A (H7N9) will be conducted at CDC.[21]

CECC has continued to strengthen surveillance and fever screening of travelers arriving from China, especially areas with ongoing outbreaks of human infection with avian influenza A (H7N9), including Shanghai, Jiangsu, Zhejiang, Anhui, Beijing, Henan and Shandong. All the physicians are reminded to report suspected cases to the health authority within 24 hours of detection according to the relevant regulation as follow: before the infection is confirmed (1) isolate and hospitalized the suspect case-patient with severe respiratory infections, (2) asked the suspect case-patient with mild symptoms to conduct self-health management and put on a surgical mask and provided with thorough health education. In addition, specimens should collect from the patient for laboratory testing and administering of antiviral drugs if necessary. When human infection with avian influenza A (H7N9) is confirmed, an appropriate hospital for isolation and treatment will be determined by the Regional Commander of CECC.[17]

4.2. Treatment

No experience yet, however, laboratory testing conducted in China showed that influenza A (H7N9) viruses are sensitive to neuraminidase inhibitors (oseltamivir and zanamivir) but resistant to other antiviral drugs amantadine and rimantadine.[2,6,7] When these drugs are given early in the course of illness, they have been found to be effectively against seasonal influenza virus and influenza A (H5N1) virus infection.

5. Prevention

Currently, the best way to prevent infection with avian influenza A viruses is to avoid the sources of exposure. Advised people who work with poultry or who response to avian influenza outbreak to use of appropriate personal protective equipment and careful attention to hand hygiene.[22] There is no vaccine available for the prevention of influenza A (H7N9) infections at this time. Although both the source of infection and the mode of transmission are uncertain, it is prudent to follow basic hygienic practices to prevent infection. They include hand and respiratory hygiene and food safety measures.[7]

5.1. Hand hygiene

- Wash your hands before, during, and after you prepare food; before you eat; after you use the toilet; after handling animals or animal waste; when your hands are dirty; and when providing care when someone in your home is sick.[7]

5.2. Respiratory hygiene

- Cover your mouth and nose with a medical mask, tissue, or a sleeve or flexed elbow when coughing or sneezing; throw the used tissue into a closed bin immediately after use; perform hand hygiene after contact with respiratory secretions.[7]

5.3. Food safety measure

- Meat products can be safely consumed provided that these items are properly cooked and properly handled during food preparation. The consumption of raw meat and uncooked blood-based dishes is a high-risk practice and should be strongly discouraged.[7]

5.4. Vaccination

CDC and WHO recommended HPAI poultry outbreak responders should receive seasonal influenza vaccination annually and take prophylactic antiviral medication during response.

Although seasonal influenza vaccination will not prevent infection with avian influenza A viruses, they can reduce the risk of co-infection with human and avian influenza A virus.[22] Taiwan CDC also recommended that people who work in the inspection and quarantine sectors, medical and healthcare personnel and people who frequently visit areas at risk for H5N1 influenza infection to get vaccinated against H5N1.[23] When a critical portion of a community is immunized, most members of the community are protected , known as "herd" immunity.[24] The first step in development of a vaccine is the selection of candidate viruses that could go into vaccine production. WHO, in collaboration with partners, will continue to characterize available influenza A (H7N9) viruses to identify the best candidate viruses.[7] The influenza H7N9 A/Anhui/1/2013 strain has been proposed to be one of the candidate vaccine strains since it grows to a very high titer in eggs. Enhanced protective measures should be taken when dealing with these viruses, and increased surveillance and analyses of these viruses are needed.[9]

In conclusion, rapid detection and characterization of novel influenza viruses remain a critical component of national efforts to prevent H7N9 infection. Clinicians should consider the possibility of H7N9 virus infection in persons with respiratory illness and a travel or exposure history. All human infections with animal influenza viruses deserve close attention, not only because of the risk of death in individual people, but also because if these viruses become capable of spreading from human to human, they could spark a pandemic. However, whether the influenza A (H7N9) virus could actually cause a pandemic is still uncertain. First-line healthcare providers should be highly aware of appropriate infection prevention measures for patients under investigation.

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