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# The Resurgent Threat of Highly Pathogenic Avian Influenza HPAI A (H5N1) Virus: A Zoonotic Infectious Disease and Public Health Concern

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**ABSTRACT**

The highly pathogenic avian influenza (HPAI) A (H5N1) virus of clade 2.3.4.4b was identified among waterfowl (wild birds and geese) and domestic poultry across Southeast Asia, Europe, and Africa in 2021. By 2022, the HPAI virus was detected in North America, signifying further global dissemination. There is no human immunity to clade 2.3.4.4b A (H5N1). With the spread of the A (H5N1) virus throughout the United States and increasing viral infection in humans, resurgence of the A (H5N1) virus is of great public health concern that it could lead to the next infectious zoonotic pandemic after Covid-19. This paper describes the characteristics of HPAI A (H5N1) virus of clade 2.3.4.4b and recommendations for clinical treatment and prevention.

## Introduction

The 1918 influenza ("Spanish flu') pandemic was the most catastrophic event in infectious disease history on record [1,2]. The Spanish flu is the yardstick against all other pandemics in terms of a contagious infectious disease with high morbidity and mortality. The virulent influenza A (H1N1) virus spread rapidly throughout the world killing between 50 million and 100 million people [3]. After the 1918 pandemic, two epidemics occurred in 1957 (H2N2) and 1968 (H3N2), both originating in Asia and each killing approximately 1 million people [4]. Although the severity of the epidemics and the primary age groups affected varied, each was caused by a novel type A influenza virus of avian origin (Figure 1). The novel viruses had components of previous human and avian viruses. The genome of the influenza virus is made up of eight segments of RNA, and it was determined retrospectively that in both cases, there had been a reassortment of avian and human genes, due to coinfection of a host by two different viruses [5,6].

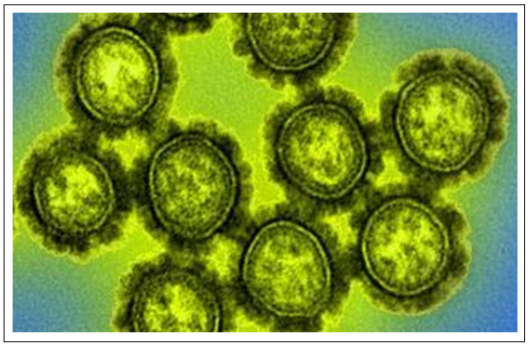

**Figure 1:** Electron Microscopic View of H1N1 Influenza Virus Particles. Photo Credit: Centers for Disease Control and Prevention.

However, compared to the influenza viruses of 1957 and 1968, the origin of the lethal 1918 virus is exclusively of avian origin (Figure 2). As waterfowl (ducks and geese) are the natural reservoir for avian influenza viruses, they are asymptomatic for the virus [7,8]. The goose precursor virus of the A (H5N1) strains that caused an avian influenza outbreak evolved into a dominant pathogenic genotype that is now endemic among terrestrial poultry and wild birds in Asia [9-11].

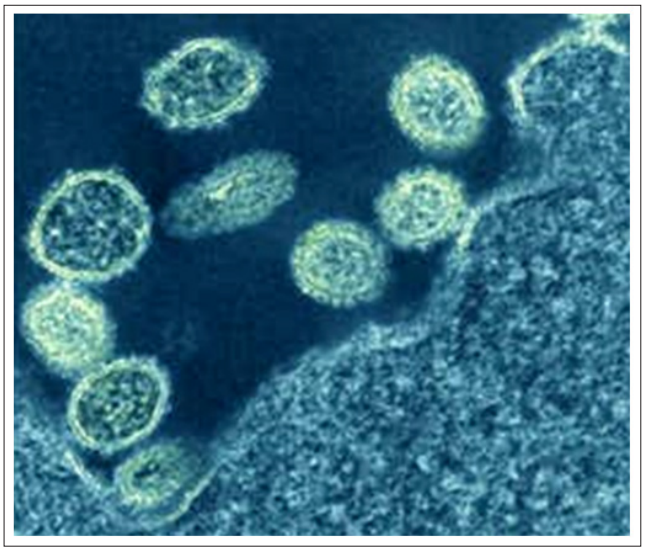

**Figure 2:** Electron micrograph of 1918 H1N1 influenza virus particles near a cell. Photo Credit: NIAID

## Timeline of Influenza A Virus

Similarities between the Spanish flu of 1918 and A(H5N1) virus raise public health concern [11]. Cross-species transmission of the circulating A (H5N1) virus may evolve into a pandemic strain by adapting to humans through genetic mutation or reassortment with human influenza strains. In the 1957 influenza epidemic novel influenza viruses emerged due to reassortment. In addition, dual infections occurred in a human (H1N1) and a bird (avian H2N2) resulting in mixing of genetic material and the emergence of a new influenza virus strain that began circulating in humans [12]. In 1968, it was replaced by another novel reassortment virus, the H3N2 Hong Kong virus created by replacement of the genetic material [13]. During an outbreak of the highly pathogenic influenza A (H5N1) virus among poultry in Hong Kong in 1997, 6 of 18 people with confirmed viral infection died [14]. In 2004, forty-five cases of influenza A (H5N1) were reported in humans with high mortality. Of the 45 cases, thirty-three people died. All patients presented with acute respiratory distress syndrome [15].

An additional fatal case of influenza A (H5N1) diagnosed in a boy who presented with severe diarrhea. Two weeks earlier, his sister died of a similar illness. Thus, pandemic influenza may originate through two distinct mechanisms; reassortment between an animal influenza virus and a human influenza virus that leads to a novel virus, and direct spread and adaptation of a virus from animals to humans [12].

As viral outbreaks have continued in 2024, it is of increasing global public health concern that it could eventually become the next 21st century pandemic after Covid-19 through genomic reassortment. Since 2022, five cases of human transmission have been reported in the United States. Of the five cases, 4 were reported after exposure to dairy cows [16,17]. The sole case in 2022 was due to exposure to poultry. All five persons recovered from the A(H5N1) virus.

At the time of this writing, there have been a total of 887 cases reported to the World Health Organization (WHO) of proven human A (H5N1) infections [18]. Of the total, 462 deaths have been reported. Of the twenty-three countries submitting data to the WHO, Egypt reported the greatest number of infectious cases (359), while Indonesia reported the most deaths (168). Avian H5N1 influenza viruses that are endemic in Egypt and Indonesia have a case fatality rate of approximately 60%. However, human-to-human transmission of influenza A (H5N1) virus has not been documented [18]. (Table 1).

**Table 1: Timeline and Global Dissemination of HPAI A(H5N1)**

| |
|---|
| 1959: HPAI isolated in Scotland |
| 1996: HPAI identified in wild geese in China |
| 1997: First recorded human infection in Hong Kong to HPAI |
| 2003-2005: HPAI spreads across the globe to China, Asia, Africa, Middle East, Europe |
| 2009-2016: Clade 2.2, 2.2.1.2; 2.3.2.1, 2.3.4.4b are detected globally. |
| 2011: China, Egypt, India, Indonesia, Vietnam |
| 2014: Canada |
| 2015: United States |
| 2020-2021: Clade 2.3.4.4b (Europe, Africa, Middle East, Asia) |
| 2022-2023: Clade 2.3.4.4b (United States, Canada, England, China, Peru. Brazil, Spain) |
| 2023: Netherlands, Estonia |

## HPAI A (H5N1) Virus Transmission

In February 2024, veterinarians were alerted to a syndrome occurring in lactating dairy cattle in Texas. Nonspecific illness with reduced feed intake and drop in milk production was observed [16]. In March 2024, similar clinical cases were reported in dairy cattle in Kansas and New Mexico [19]. Milk and tissue samples obtained from cattle and cats tested positive for influenza A virus (IAV) by screening with real-time polymerase chain reaction (RT-PCR) assays, which was confirmed and characterized as HPAI A (H5N1) virus by the US Department of Agriculture National Veterinary Services Laboratory [20]. In March 2024, HPAI A (H5N1) clade 2.3.4.4b was detected in mammalian live-stock, including dairy cattle in the United States (Figure 3). HPAI A (H5N1) has now been reported in twelve U.S. states and greater than 139 dairy herds [21].

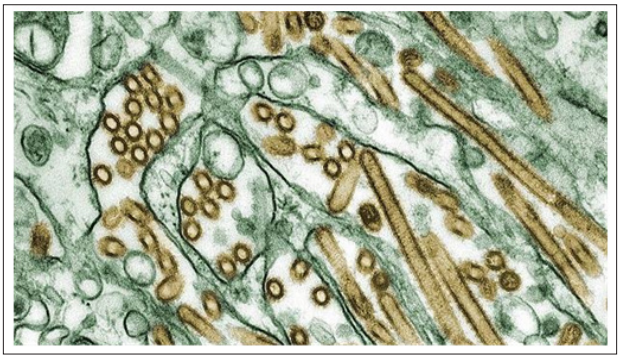

**Figure 3:** Transmission Electron Microscope of Avian Influenza A(H5N1) Virus (Gold Color Particles). Photo Credit: Cynthia Goldsmith, Jacqueline Katz, Sherif R. Zaki. Centers for Disease Control and Prevention

High titers of infectious virus and genome copies of HPAI A (H5N1) virus have been found in milk from these infected dairy cows [19]. Molecular testing revealed the presence of HPAI A(H5N1) genetic material in approximately 20% of the samples obtained from retail pasteurized milk products. Testing with real-time polymerase chain reaction (RT-PCR) assays in 96 commercially purchased milk products detected genetic traces of the A (H5N1) virus in 1 in 5 samples. This finding is significant as transmission of HPAI A (H5N1) is occurring from cow to cow, or from cows to humans through consumption of cow's milk. While the USDA and FDA have both stated that flash pasteurization effectively inactivates viruses and that the commercial milk supply is safe, limited data are available regarding the efficacy of pasteurization against H5N1 virus in raw milk [21].

## Clinical Symptoms

The clinical manifestations of A (H5N1) virus infection in humans range from asymptomatic infection to multiorgan failure (Table 2). Patients have reported the following clinical symptoms: fever (high fever > 38$^{o}$C), cough, fatigue, headache, rash, diarrhea, conjunctivitis, and myalgia [14,15]. These symptoms may be due to cytokine-induced tissue damage or acute-phase physiological changes. With the 1918 H1N1 influenza virus, the host resistance was hyperactive resulting in an excessive inflammatory response known as the cytokine storm phenomenon [23,24]. Such excessive inflammatory response is an overreaction of the body's immune system that can lead to multiorgan failure and death [25,26].

**Table 2: Clinical Symptoms of H5N1**

| | | | |
|---|---|---|---|
| Fever | Headache | Myalgia | Diarrhea |
| Vomiting | Cough | Sore Throat | Rhinorrhea |
| Abdominal Pain | Pneumonia | Multiorgan Failure | |

Lower respiratory tract symptoms develop early during HPAI A (H5N1) infection [27]. Respiratory distress, tachypnea, inspiratory crackles, pulmonary hemorrhage, and pneumothorax are frequently observed during clinical examination. A common radiographic finding is pneumonia [28]. Progression to respiratory failure and acute respiratory distress syndrome (ARDS) often result in death. Strikingly, the median time to ARDS was 6 days (range, 4 to 13 days).

**Antiviral Agents**

Avian (H5N1) influenza viruses target receptors of the human respiratory tract at the alveolar cell wall and junction of the respiratory bronchiole and alveolus. The virus causes severe disease as it attaches to type II pneumocytes, alveolar macrophages and non-ciliated bronchiolar cells [27]. As of this writing, vaccination is highly regulated and requires approval from each state's chief veterinary officer, or the secretary of agriculture [28]. However, the A(H5N1) virus, as well as other avian viruses A(H7N9) and A(H5N6) are susceptible to the neuraminidase inhibitors oseltamivir (Tamiflu, Roche) and zanamivir (Relenza, GlaxoSmithKline). By inhibiting viral replication and the release of newly formed virus particles, neuraminidase inhibitors prevent further spread of the virus in the body [29,30].

Neuraminidase inhibitors decrease viral infection within 1–3 days if administered early during infectivity. They also can reduce the severity of viral complications, especially pneumonia and bronchitis [31]. The approved dose of oseltamivir is 75 mg twice daily for five days for treating influenza A (H5N1. Resistance of influenza A (H5N1) virus to oseltamivir has recently been reported [32].

**Household Contacts**

Household contacts of persons with confirmed or suspected HPAI A (H5N1) viral infection should be monitored for signs and symptoms of illness for 10 days after viral exposure [17,21]. Although the risk of secondary transmission has appeared low, self-quarantine for a period of seven days after exposure to an infected person should be considered. If person-to-person transmission is occurring, quarantine is indicated to prevent community spread of the virus. Postexposure chemoprophylaxis should also be considered if there is exposure to infected persons or infected animals.

**Discussion**

The influenza pandemic of 1918 is estimated to have infected 500 million people and killed 50 to 100 million persons worldwide [1-3]. In a typical year of seasonal influenza, viral illness can result in over 5 million cases of severe illness and greater than 500,000 deaths [18]. Over the past decade, sporadic cases of severe influenza and deaths in humans have been caused by a number of avian influenza A viruses, including the H5N1 virus. The Asian H5N1 virus was first detected in Guangdong Province, China, in 1996, but received little attention until it spread through live-poultry markets in Hong Kong to humans in May 1997 killing 6 of 18 infected persons. From 1997 to May 2005, H5N1 viruses were circulating in Southeast Asia, rapidly spreading to the rest of the world with waterfowl the primary carriers of the virus. In anticipation of a pandemic before 2009, public health authorities focused on the threat of avian H5N1 influenza with a human mortality rate exceeding 50%. The most recent global pandemic was caused by the influenza A (H1N1) strain in North America in 2009 [33].

As of this writing, the A (H5N1) virus has not reached pandemic levels and there are no reported cases of human-to-human transmission. If human-to-human transmission occurs, transmission dynamics, modes of transmission, basic reproductive number, and incubation period must all be determined [18]. Therefore, public health interventions are critical to detect and mitigate influenza A (H5N1) viral infections to avert the morbidity and mortality experienced during the 1918 influenza pandemic [34,35]. Should A (H5N1) become the next pandemic strain, the resultant morbidity and mortality could rival the 1918 influenza pandemic when more than half of the deaths occurred among healthy young people between 18 and 40 years of age [36].

**Conclusion**

Pandemics will challenge every country. Preparation beyond planning with commitment from public health experts are critical. When the next influenza pandemic arrives, morbidity and mortality are the rule, rather than the exception. Lesson learned from the past pandemics will permit the international community to effectively plan and mitigate the influenza virus from advancing to a pandemic.

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