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Editorial: Global Surveillance of Highly Pathogenic Avian Influenza Viruses in Poultry, Wild Birds, and Mammals to Prevent a Human Influenza Pandemic

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Abstract Strains of avian influenza A, believed to have originated in poultry with transmission to wild birds, have been associated with epidemics and four major pandemics in humans in the past century. The 1918 influenza pandemic was caused by an avian strain of the influenza A(H1N1) virus that initially adapted to infect humans and then rapidly spread between humans. Since 2021, highly pathogenic avian influenza (HPAI) virus subtypes have been identified in poultry and wild birds. In October 2022, the HPAI virus variant A(H5N1) was isolated from intensively farmed American mink. The World Health Organization (WHO), the US Centers for Disease Control and Prevention (CDC), and the European Union Reference Laboratory for Avian Influenza (EURL) have stated that the risk of human infection from birds and mammals and human-to-human transmission from known HPAI viruses is currently low. However, they recommend increased infection surveillance and preparedness. This editorial aims to present the status of HPAI virus transmission in poultry, wild birds, and mammals to highlight the importance of international infection surveillance, control, and preparedness to prevent the next human influenza pandemic.

Keywords: **Highly Pathogenic Avian Influenza • H5N1 • Influenza A • Zoonosis • Editorial**

For over a century, strains of avian influenza A, believed to have originated in poultry with transmission to wild birds, have been associated with epidemics and four major pandemics in humans [1]. Influenza A is classified by hemagglutinin (H) and neuraminidase subtypes, with 16 H virus subtypes in the natural bird reservoir and nine N virus subtypes [2]. Three hemagglutinin subtypes have resulted in human respiratory infection, including H1, H2, and H3 [2]. The 1918 influenza pandemic was caused by the avian strain of the A(H1N1) virus that initially adapted to infect humans and then rapidly spread between humans [1,2]. Two further influenza pandemics involved the human–avian strains A(H2N2) in 1957 and A(H3N2) in 1968 [2]. In 2009 and 2010, another pandemic resulted from the combined swine, human, and avian influenza strains, A(H1N1) [2].

From 2020 and during the COVID-19 pandemic, several important epidemiological trends in influenza A infections have occurred. Between the influenza seasons from October 2020 to July 2021 in both the northern and southern hemispheres, mortality rates from influenza fell dramatically [3,4]. During the COVID-19 pandemic, resources were directed toward monitoring and disease surveillance for SARS-CoV-2 infections, which raised concerns that undetected strains of influenza, including

highly pathogenic avian influenza (HPAI), might result in an influenza pandemic [4,5].

Global surveillance of cases of influenza A showed that since May 2021, most reported human cases of A(H5) influenza were in poultry workers, with isolated influenza A(H5N6) virus infections in humans, including seven cases from the Russian Federation [3,6]. In June 2021, two cases of human infection with influenza A(H9N2) were reported in China, and a case of infection with the influenza A(H1N2) variant was reported in Canada [3,6]. The latest report from the World Health Organization (WHO) identified that between 12 November to 5 January 2023, there was one human case of infection with influenza A(H5N6), three human cases of infection with A(H9N2) viruses, and one case of infection with an A(H1N2) variant virus [7]. The WHO risk assessment for human infection from birds and mammals and human-to-human transmission from currently identified influenza viruses is low [7]. Also, at this time, all human infections caused by new influenza subtypes should be reported under the International Health Regulations (IHR, 2005) [8]. In the US, the Centers for Disease Control and Prevention (CDC) latest update on cases of avian influenza as of 15 February 2023 identified 58,386,983 cases of infected poultry in 47 states, 6,192 confirmed cases

of infection in wild birds, and one reported human case [9]. The CDC has advised that human infections with novel influenza A viruses should be reported [9]. Novel influenza viruses include influenza A virus subtypes H2, H5, H7, and H9, and H1 and H3 subtypes originating from non-human species or genetic re-assortment between animal and human viruses [9]. The CDC supports the recommendations of the WHO and the European Centre for Disease Prevention and Control (ECDC) that the risk of transmission to humans of novel influenza A viruses is low [7,9,10]. Since A(H5N1) was first identified in 1996, there have been few reports of transmission to humans and between humans. The WHO reported that between January 2003 and 25 November 2022, 868 cases of human infection with the avian influenza A(H5N1) virus were reported from 21 countries [6]. However, of concern is that of these 868 reported human cases, 457 have been fatal, which means that the mortality rate of A(H5N1) influenza in humans is >50% [6].

For more than a century, global outbreaks, epidemics, and avian influenza pandemics have been limited mainly to poultry, and the culling of affected poultry flocks has prevented the spread to wild birds [6,7]. However, since 2000, wild birds have been increasingly affected by HPAI viruses. Between 2014 and 2016, wild birds spread avian flu from Eurasia to Alaska, resulting in more than 50 million domestic bird deaths in the US [10]. In December 2021, the highly pathogenic A(H5N1) strain of avian flu was identified in eastern North America in wild birds [7,10]. There have been several theories to explain why the spread of this virus has continued. Mutations in the virus may have increased the ability to replicate and infect a broader range of species of birds [10]. A recent concern is that this strain has begun to infect mammals, including mink [11]. Currently, there is no evidence that A(H5N1) spreads between mammals, but this scenario is possible. Therefore, in 2022, new biosafety measures were announced in Europe and North America to control the spread of bird flu caused by A(H5N1) [9,10].

In January 2023, the latest scientific report was published by the European Food Safety Authority (EFSA), the ECDC, and the European Union Reference Laboratory for Avian Influenza (EURL) [10]. The report aimed to provide epidemiological data on the status of HPAI, including influenza A(H5N1), A(H5N6), and A(H9N2) in poultry and humans in Europe between October 2021 and September 2022 [10]. During these 12 months, 37 countries in Europe experienced an epidemic of HPAI, with 2,520 outbreaks in poultry, 3,867 infections detected in wild birds, and 227 outbreaks in captive birds [10]. The prevalence of viral infection resulted in the culling of 50 million birds believed to have been in contact with identified cases [10]. Also, the EFSA, ECDC, and EURL have reported that between 10 September and 2 December 2022, 27 countries in Europe reported 1,163 HPAI virus outbreaks, with 398 outbreaks in

poultry, 613 infections detected in wild birds, and 151 outbreaks in captive birds [10].

It has been proposed that, in the wild, waterfowl might be more involved in the transmission of the HPAI virus into poultry than seabirds [10]. The viruses detected since September 2022 (clade 2.3.4.4b) have been identified as belonging to 11 genotypes, of which three of which have been in circulation in European birds during the summer months, with eight being identified as new genotypes that have arisen since summer 2022 [10]. The risk of infection has been assessed as low for the general population in the EU/EEA and as low to medium for those occupationally exposed to poultry [10]. Within the past month, Horwood and colleagues have reported that live bird markets in Cambodia have been identified as a source of airborne spread of avian influenza viruses [11]. The authors have identified viral spread and persistence in market workers during a period of high viral circulation, which supports the possibility of the evolution of avian influenza viruses in live bird markets [11].

There is now increasing concern that HPAI viruses detected in farmed and wild mammal species in Europe and North America in late 2022 showed molecular adaptation markers for the ability to replicate in mammals [10,12]. Since December 2022, there have been reports of cases of influenza A in humans, including two cases of A(H5N1) in Spain, one case of A(H5N1), one case of A(H5N6), and one case of A(H9N2) in China, as well as one case of influenza A(H5) infection, without NA-type result, in Vietnam [10]. As of February 2023, the risk of infection was assessed as low to medium for occupationally exposed individuals, such as poultry workers, and low for the general population in the European Union (EU) and in the European Economic Area (EEA), which includes countries in the EU and Iceland, Liechtenstein, and Norway [10,12].

Recently, concerns have been raised regarding the transmission to mammals of the HPAI virus variant A(H5N1) following reports in October 2022 of infection in intensively farmed American mink (*Neovison vison*) at a single site in Galicia, northwest Spain [13,14]. It is not clear how the virus spreads from birds to mink, but it is known that farmed mink are often fed raw poultry [13]. Initially, two mink died from hemorrhagic pneumonia, with the HPAI virus variant A(H5N1) detected by real-time reverse transcription polymerase chain reaction (RT-PCR) from oropharyngeal swabs taken post-mortem [13]. Within weeks, the infection spread within the mink farm, and several cases of HPAI A(H5N1) infection were identified in wild birds, including 25 common gannets (*Morus bassanus*) and two seagulls (*Larus michaelis*) [13]. Further analysis of the hemagglutinin (HA) gene segment showed that the HPAI A(H5N1) viruses isolated from the infected mink belonged to clade 2.3.4.4b and belonged to a genotype that has

previously been described in wild bird species and outbreaks of infection in poultry in northern Europe [13,14]

In 1918, one-third of the world's population, or 500 million people, were infected by the H1N1 virus with avian origin genes, resulting in at least 50 million deaths [1]. The 1918 H1N1 virus also spread between wild birds and poultry before infecting humans [1]. There may be lessons still to learn from history regarding preparedness for future influenza A pandemics.

Conclusions

Current risk assessments by the WHO, CDC, and ECDC have recommended low risk to humans from increased infections in poultry and wild birds from avian influenza. However, lessons from history support that novel HPAI virus subtypes H1, H2, H3, H5, H7, and H9 should be under continued surveillance by international monitoring agencies due to possible transmission from non-human species or genetic re-assortment between animal, avian, and human influenza A.

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