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We need to keep an eye on avian influenza

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H5N1 avian influenza viruses of the A/goose/Guangdong/1/96 lineage have been circulating in wild birds for many years, have inflicted significant economic losses on the poultry industry and have caused zoonotic infections since 1997. However, the recent spread of avian H5N1 virus to the Americas and its detection in mammals have raised concerns about its pandemic potential.

Avian influenza viruses are typically relatively harmless for humans. Even in birds, infections are often mild or asymptomatic. However, these viruses can become of greater concern under certain circumstances. One problematic scenario is when avian influenza viruses become highly pathogenic for poultry. This typically happens when the haemagglutinin (HA), one of the two proteins on the surface of the virus (with neuraminidase (NA) being the second protein), acquires a polybasic cleavage site. This allows the HA to be activated not just by select proteases, which restricts the virus to certain tissues, but by furin-like proteases found in most tissues, allowing wider dissemination of the virus throughout the host. This polybasic cleavage site is the same element that is found in some coronaviruses, including SARS-CoV-2 and some human seasonal coronaviruses. Acquisition of a polybasic cleavage site can happen spontaneously, often when an avian influenza virus enters a poultry farm and replicates extensively in large concentrations of susceptible animals. Extensive replication increases the chance of insertions occurring in the viral genome, which can lead to the emergence of a polybasic cleavage site. In some cases, the source material of the insertion seems to be fragments of chicken ribosomal RNA[1]. This acquisition of a polybasic cleavage site by avian influenza viruses has been well documented in poultry farms across the United States; for example, it has occurred twice in the past few years, with an H7N8 virus in Indiana in 2016 (ref. 2) and with an H7N9 virus in Tennessee in 2017 (ref. 3). It has also been documented for H5 subtype HA. Avian H5 and H7 subtype influenza viruses with polybasic cleavage sites cause severe disease in poultry, result in economic losses including increased poultry and egg prices, and endanger wild birds. These viruses can also cause severe disease in humans if large amounts are inhaled deep into the lungs. When that occurs, the fatality rates can be high. However, these avian influenza viruses are not efficient in infecting humans or other mammals, do not replicate well in the human upper respiratory tract and, therefore, usually do not spread from human to human. Typically, they are problematic for individuals in direct contact with infected birds but they are unlikely to cause larger human outbreaks.

However, there are two other concerning scenarios for avian influenza viruses that can occur even in the absence of acquisition of a polybasic cleavage site. One, an avian influenza virus may infect a person who is at the same time infected with a human influenza virus. In that case, the two viruses may infect the same cell and re-assort their genomic segments, which could result in a virus that replicates well in human cells but has HA and NA glycoproteins to which humans are naive. Similar mixing can happen in other mammals including domestic pigs. This mechanism was likely involved in the emergence of at least three, if not all, of the four historic influenza pandemics. Two, an avian influenza virus may grow in a mammal and start to mutate in a way that would allow it to spread efficiently from mammal to mammal (and potentially to humans). A recent example is an outbreak of H10N7 infections in seals in Northern Europe, in which the virus mutated to become mammalian transmissible[4]. This virus did not have a polybasic cleavage site but still led to mass mortality among seals.

All of the current highly pathogenic avian H5N1 viruses that are endemic in many parts of the world trace back to A/goose/Guangdong/1/96 (ref. 5). This virus lineage caused its first zoonotic outbreak in 1997 in Hong Kong. After a short break, zoonotic infections were recorded again in 2003 through to present day, with the virus spreading across Eurasia and Africa in wild birds. According to the World Health Organization, 868 human cases of H5N1 infection with 457 fatalities were recorded between January 2003 and 23 January 2023 (ref. 6), with most of the cases occurring before 2016. This suggests a very high case fatality rate of 53%. However, many cases of asymptomatic or abortive infection may not have been recorded in areas where there is increased human contact with the virus[7].

The H5 viruses have diversified into different genetic clades. Clade 2.3.4.4 viruses emerged in China around 2010–2011 and showed a propensity to re-assort with other avian influenza viruses, acquiring NAs other than N1 in the process. These viruses, often H5N2, H5N6 and H5N8, are summarized under the term H5NX. H5NX viruses were introduced in North America through migrating birds in late 2014, causing economic issues in the poultry industry, but they had apparently mostly disappeared from the wild bird population by the end of 2015. A subclade of clade 2.3.4.4, namely 2.3.4.4b, now having an N1 NA again, started to spread extensively across Eurasia and Africa in 2020. Clade 2.3.4.4b viruses were then detected in North America early in 2022, where they arrived via migratory birds from Europe[8]; they have now spread across the Americas. Similar to the situation in Eurasia and Africa, the clade 2.3.4.4b H5N1 virus is causing much damage to the poultry industry in North America and has devastated wild bird populations. The virus has also infected many mammals that may feed on carcasses of dead birds, including foxes, raccoons and bears. These infections in mammals have caused severe disease, including neurological symptoms and often death. Most have been ‘dead end’ infections, meaning that the virus spread from birds to mammals but did not spread among mammals. Very few human cases have been reported, and only after close contact with infected birds. All but one of those cases presented with very mild disease. The exception was a young girl in Ecuador who seemed to have acquired the infection after interaction with infected chickens and who had to be hospitalized. Note that the lethal case of H5N1 infection that was recently reported in Cambodia was caused by a different virus from clade 2.3.2.1c (ref. 9). No human-to-human transmission has been recorded. Although these

findings suggest that we need to keep an eye on H5N1, none of these events is immediately concerning in terms of pandemic potential and public health.

However, recently reported events increase the concerns. According to a scientific report published in January 2023, mink in a fur farm in Spain started to die in October 2022 from H5N1 infection, and it seems that the virus may have acquired the ability to spread between these animals, which suggests that it has acquired mutations that facilitate transmission among mammals[10]. In addition, transmission among marine mammals is suspected in outbreaks in the Caspian Sea and along the Pacific coast of South America. If confirmed, this is concerning as the propensity to transmit among mammals is not typically seen with H5N1 viruses and it suggests that the 2.3.4.4b clade of H5N1 could perhaps also acquire the ability to transmit among humans.

Importantly, this is not a reason for panic. We have several antivirals such as neuraminidase inhibitors and cap-snatching inhibitors that efficiently target influenza viruses including H5N1. Also, there is likely at least partial immunity in the adult population to the N1 NA component of the virus as humans have been repeatedly exposed to the 2009 pandemic H1N1 virus through infection and vaccination. In addition, the virus strain that was able to spread among mink was likely eradicated when these animals were culled in November 2022. Nevertheless, we need to increase our awareness and preparedness. Physicians should be informed to be vigilant about non-seasonal influenza virus infections and a specific vaccine for clade 2.3.4.4b H5N1 should be produced and stockpiled, which is routine for avian influenza viruses with pandemic potential. In addition, the public needs to be aware of H5N1 and should not touch dead, sick or strangely behaving birds or mammals if they are not trained and equipped to handle these animals safely. It would also be advisable to keep pets, such as dogs, away from potentially infected animals. Importantly, this includes urban areas, which often have dense wild bird populations in parks and green spaces.

We also need to think about safe farming practices. As the case of the mink farm shows (as well as the examples from poultry farms in Indiana and Tennessee), influenza virus outbreaks in farms with large numbers of susceptible animals can lead to the emergence of novel and potentially dangerous viral strains that may have pandemic potential. There has recently been a lot of debate about revising regulations for experiments with viruses in laboratories, and this discussion is good to have. However, we should not forget that 'Mother Nature' is the biggest bioterrorist and that unsafe farming practices assist her in creating potentially dangerous viruses. Perhaps, while debating laboratory safety, we may also want to discuss the role of unsafe farming in the emergence of concerning pathogens such as mammalian transmissible avian influenza virus or antibiotic-resistant bacteria.

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Competing interests

F.K. has been consulting for Curevac, Seqirus and Merck and is currently consulting for Pfizer, Third Rock Ventures, Avimex and GSK. He is named on several patents regarding influenza virus and SARS-CoV-2 vaccines, influenza virus therapeutics and SARS-CoV-2 serological tests. Some of these technologies have been licensed to commercial entities and F.K. is receiving royalties from these entities. F.K. is also an advisory board member of Castlevax, a spin-off company formed by the Icahn School of Medicine at Mount Sinai to develop SARS-CoV-2 vaccines. The Krammer laboratory has received funding for research projects from Pfizer, GSK and Dynavax and three of F.K.'s mentees have recently joined Moderna. S.S.-C. declares no competing interests.