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Editorial

Avian 'Bird' Flu – undue media panic or genuine concern for pandemic potential requiring global preparedness action? ☆

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In 1996, highly pathogenic avian influenza (HPAI) A(H5N1) virus was first isolated from a domestic goose in Guangdong province, China [1]. Since then, it has been identified in other poultries and wild birds with spillover into humans in over 60 countries, including United States of America (US), United Kingdom and Canada. In May 1997, the first human case of A(H5N1) virus infection and an outbreak of a total of 18 cases and 6 deaths in Hong Kong were documented [2]. The high mortality rate was very concerning and attracted significant media attention and the disease was dubbed "bird flu". Five years later, two human cases with a history of travel to southern China were reported in February 2003 in Hong Kong [3]. First human infection reported in 2005 in China [4], A(H5N1) continued to spread and human cases with high mortality were reported from Asia (Southeast and West) and subsequently Africa [5].

Since the global incidence of human A(H5N1) cases has remained at low level, public health authorities' attention was diverted to other emerging and re-emerging zoonoses such as Ebola, Lassa fever in West Africa, MERS in Saudi Arabia, variant swine 'pig' influenza A(H3N2) in the US, novel avian influenza A(H7N9) in China, and other avian influenza A(H5) subtypes in Asia, Europe and North America. From January 1, 2003 to April 1, 2024, 889 human cases of HPAI A(H5N1) and 463 deaths (CFR, 52%) were reported from 23 countries worldwide [6]. While A(H5N1) currently does not transmit easily from human to human, its ability to cause severe illness, the high mortality rate, its potential to mutate to more contagious variants, the ongoing circulation in poultry and wild birds as well as the continuing reports of human cases is of concern for pandemic potential and critical for preparedness.

The current outbreak of the Eurasian origin HPAI A(H5N1), clade 2.3.4.4b began in 2020 and has proven its unique ability to

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infect many mammalian species. Outbreaks in mammals have been attributed to their close proximity to avian reservoirs or consumption of infected prey in scavenging species. While most outbreaks in free-ranging wildlife have remained small, some outbreaks such as those in seals and sea lions have devastated local populations [7–9]. In April 2022, the first human case of HPAI A(H5N1) infection in US was reported in Colorado, in a person who was involved in the culling of poultry with presumptive A(H5N1) infection [10]. In March 2024, A(H5N1) was detected in dairy cows from 16 herds in six different states in the US. On April 1, 2024 Texas public health authorities reported to the US CDC, the country's second human case of A(H5N1) infection in a person who had a history of exposure to dairy cows presumed to be infected with the A(H5N1) virus [6]. This first report of a cow-to-human spread of "bird flu" has created widespread media coverage and fear of an impending epidemic. While the US public health authorities have reassured the public that the safety risk to cattle, meat, and pasteurized milk is very low, concerns about potential impacts on prices and the livelihoods of farmers have however arisen. Nevertheless, the CDC has issued recommendations to avoid consumption of raw or undercooked food or related uncooked food products, such as unpasteurized (raw) milk or raw cheese, from animals with suspected or confirmed infection with HPAI A(H5N1) virus. Genetic sequencing has shown only minor mutations in the virus isolated from the cases [11]. According to WHO the virus seems not to have acquired mutations that may facilitate transmission among humans and the estimated public health risk is considered to be low for the general population, and low to moderate for occupationally exposed persons [6].

The report of the US human case brings forth several important issues including the question of whether this signals a global pandemic in the making? Foremost, how has transmission in cows and from cow to human occurred? Infected cows show symptoms such as decreased lactation, anorexia, lethargy, fever and dehydration, raising concerns of an increased risk of H5N1 viruses becoming better adapted to mammals with enhanced potential to spilling over to humans and other livestock [12]. It has been suggested that A(H5N1) might not be spreading among cows through the air [13]. The current thought is that the virus has spread via the use of contaminated milking equipment between infected and uninfected cows [14]. How a virus that causes respiratory tract disease ends up in cow udders, and is detectable in milk, and whether other organs are infected is important to elucidate. No infection in beef cattle has been detected yet, but this could be due to sub-clinical or mild symptoms and lack of active surveillance. Another question is how to prevent further spread from dairy farms. Taking reference from experiences with controlling HPAI associated with poultry, the strategies include culling of the entire herd, while vaccination is another option. Improving on farm biosecurity and establishing surveillance programs will be critical, including steps to protect personnel involved in the culling, by vaccination and antiviral prophylaxis.

HPAI had previously led to the culling of hundreds of millions of poultry around the globe in the past years and local outbreaks have been contained in this manner. However A(H5) is largely carried by migrating birds and continues to spread to new regions and new mammalian hosts including cats, tigers, seals, dolphins, goats and polar bears, constantly mutating and hence possibly increasing risk of spillover to humans [15–16]. Also, there has been a number of outbreaks on a mink farm in Spain in autumn 2022 [17] and in 2023 multiple outbreaks on fur farms in Finland [18]. So far, limited number of human cases have occurred after close contacts with infected wild birds or poultry, while the latest US case was the first that followed exposure to mammal; importantly, little human-to-human transmission has been observed. The European Food Safety Agency (EFSA) warned of a large-scale avian influenza pandemic if the virus becomes transmissible among people given that the human population has no immunity against the A(H5N1) virus and herd immunity is absent [19]. As a respiratory infection, transmission in human would require a shift in the preferred receptor on the cell surface from sialic acid alpha 2,3 found deep in the human lungs to the 2,6 receptor found in the human upper respiratory tract [20]. However, the US patient who was exposed to dairy cattle had presented with conjunctivitis as the only symptom, and mucosal transmission may have occurred. It is possible, however, that more human cases, sub-clinical, mild cases might have remained undetected and further investigation is needed, including serology studies of exposed humans.

A pertinent question is whether H5N1 vaccines based on the current circulating clade 2.3.4.4b should be developed and stockpiled, and also if dairy workers should be vaccinated using the human H5N1 vaccine stockpile? Currently only a limited stockpile of vaccines targeting early strains of H5N1 are available, and more specific vaccines for birds [21], animals and humans need to be developed since the threat of ongoing mutations and more human-to-human transmission is ever present. For cattle, no H5N1 vaccines exists. It is possible to develop a new cattle vaccine by modifying the ones based on the swine vaccine which is already used. On the other hand, poultry vaccines are used in China, with some successes [22]. Concerns about international trade restrictions limited the adoption of vaccination in poultry industry in many countries. Vaccinating birds is potentially concerning, due to the possibility of continued transmission of silent infections and the risk of breakthrough transmission leading to vaccine resistance [23]. Nevertheless, vaccination as a strategy has been recently endorsed as compatible with the pursuit of safe trade by the World Assembly of World Organization for Animal Health (WOAH) national delegates [24].

Current prevention and control programs rely on reactive surveillance, notifications, isolating farms or other places of captivity, and culling of infected birds and those in close contact. This policy may not be effective as it has missed early 2024 outbreaks heralded by dead cats on the farm [13]. The mechanisms have not taken into account the influences of climate and environment change as drivers of zoonotic diseases outbreaks. At this time there are a lot of uncertainties. Scaling up of the production of human vaccines against the new A(H5N1) variants seems imperative, primarily to protect high-risk individuals such as farm workers against infection, but also for stockpiling, and secondly to increase preparedness should the virus evolve to sustained human-to-human transmission. Culling of poultry has so far not resulted in controlling the zoonotic pandemic (enzootic) of A(H5N1); perhaps a shift towards prevention instead, by the vaccination of farm animals and farm workers needs to be considered.

Limiting exposure to and spread of avian influenza will require more comprehensive 'One Health' measures to mitigate risk of adaptation and spread from current bird reservoirs to mammals and humans [19,25], embracing the concept of shared risks and benefits. Extrinsic drivers that require investigation are wildlife and human activities, farming practices and the use of natural resources, climatic and environmental factors. They need to be addressed urgently through enhancing surveillance, and ensuring access to rapid diagnostics. Can new rapid diagnostic tests be manufactured quickly and distributed to all those involved in domestic animal husbandry? Effective engagement between veterinarian and human health virologists, epidemiologists and professionals of other expertise is important, so as to strengthen animal health programs, and the reduction of wildlife contact with domestic animals, especially at poultry and animal farms. More proactive surveillance for HPAI needs to be put in place alongside current proactive detection and surveillance programs.

The scale of the A(H5N1) pandemic in wild and domestic birds is enormous, and the spillover in mammals is a concern [26]. The recent incident of A(H5N1) in dairy cattle and the human infection is a wake-up call for action. Since 2020, A(H5N1) has caused over 50 million bird deaths worldwide, many migrating from Europe to the Middle East contracting the virus from domestic poultry. The hundreds of dead or dying sea lions in Peru indicate that the virus may be adapting for mammal-to-mammal transmission. The problem may even be related to climate changes, as migration of birds may be affected by drought, rising temperatures, increasing sea levels [27]. The potential for a leap to become a human pathogen that may lead to a pandemic must be monitored carefully. Given the evolving epidemiology of the A(H5N1) virus, and the obvious shared risk for domestic animals, wildlife and pandemic potential for humans worldwide, it is urgent to apply the notion of a 'shared benefit' approach, grounded in One Health [24], for enhancing preparedness and achieving effective control. Striking the right balance between the existing pandemic in birds with the pandemic potential for humans is the essence. Based on an inter-species immunity protection that could only be attained through mass vaccination of poultry with no further hesitancy, it is a real test case for the quadripartite organizations – FAO (Food and Agriculture Organization), UNEP (United Nations Environment Programme), WHO and WOAH.

Declaration of competing interest

The authors declare no conflict of interest.

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