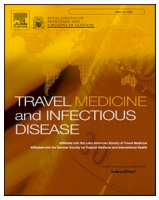
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Avian influenza spillover to humans: Are we prepared to deal with another potential pandemic?



Avian influenza, known as bird flu, is caused by influenza type-A viruses, primarily adapted to bird species, including domesticated and poultry. Bird flu can infect entire flocks within days and is transmitted through respiratory secretions, faeces and saliva [1–3]. The transmission can occur directly and through contaminated feed and water. Notably, bird flu viruses are extraordinarily resistant and can survive for prolonged periods, even in low temperatures [1–3]. Based on pathogenicity standards, avian flu strains are divided into high pathogenic and low pathogenic. The highly pathogenic avian influenza (HPAI), a highly transmissible variation of bird flu, is linked predominantly to the H5N1 and H7N9 strains of influenza type-A viruses. H5N1 is the most widespread of the HPAI strains and was first isolated in 1996 from farmed geese in China [1–5]. It is also considered to have the highest transmission rate (estimated R_0 1.69) and the shortest estimated generation time (4.8 days) compared to H5N8 and H5N6 subtypes [6].

The world is going through its largest-ever recorded outbreak of avian flu, tearing through the poultry and wild bird populations (Fig. 1). The endemic is the largest on record in Europe, North America and Japan and is driven mainly by the H5N1 avian flu virus, clade 2.3.4.4b. In 2022, HPAI infections with H5N1 viruses from clade 2.3.4.4b resulted in the loss of an excess of 131 million poultry across 67 countries. The disease has spread rapidly in 2023, and infections have been reported in 14 additional countries [1]. As of 12 July 2023, an excess of 58 million poultry birds are diagnosed with HPAI resulting from infections with H5N1 viruses from clade 2.3.4.4, in addition to a little more than 7000 wild birds, in the United States alone [2].

Further, the World Organization for Animal Health (WOAH, formerly OIE) reported that during the four weeks between 05 May to 01 June 2023, there were 82 and 198 outbreaks reported in poultry and non-poultry birds, respectively, with more than 860,000 deaths of poultry birds alone [3]. The 2.3.4.4b clade may have risen in the Netherlands in late 2020 and spread to Europe, Asia and Africa. Bird flu possibly arrived to the United States of America (USA) in late 2021's, resulting in massive outbreaks in multiple states and diverse fowl species. The current HPAI outbreak has affected more wild birds than ever before, with the World Health Organization (WHO) estimating that nearly 42 million domestic and wild birds may have been infected since the documented origin of the endemic in the Netherlands in October 2021. Indeed, HPAI has become a pandemic of significant global concern, and several countries like the United Kingdom (UK), USA and Japan have suffered disastrous poultry losses. WHO estimates indicate that at least 60 countries may have been exposed to the HPAI pandemic. More recently, Senegal reported an outbreak of HPAI in a poultry farm in Potou which resulted in the deaths of at least 500 birds [4]. In the second week of February 2023, Argentina and Uruguay declared a state of National Sanitary emergency after detecting the virus in wild birds [5], bringing the number of South American countries where the avian flu endemic has progressed to ten. The list includes Peru, which reported flu-related fatalities of an excess of 50,000 birds and over 500 seals. In the US, an estimated 43 million poultry birds have been either culled to prevent the spread of avian flu or died due to the infection since the spread of the endemic. The Economic Research Service of the US Department of Agriculture (USDA) has estimated that the losses amount to almost a third of the egg-laying hens, resulting in a 210% increase in egg prices from the end of 2020 to the end of 2021 [7]. These horrifying facts prove the uneasiness and relevance of avian/bird flu in the current scenario. Since late 2003 these highly pathogenic H5N1 avian influenza virus have spread throughout 48 countries and a relationship of the appearance of these outbreaks shortly after a drop in temperature in each affected Eurasian region has been described; furthermore, in China between 2005 and 2006 it is described that the dust storms that affected Qinghai Lake in May 2005 were related to greater dissemination of the outbreaks in that period, supposing a possible climatic role related to the outbreaks in these areas [8].

Experts believe that the high prevalence of the infection in wild birds may have fanned the rapid spread of HPAI across continents, allowing its transmission from Europe and Asia to North America. It should be noted that wild migratory birds, particularly waterfowls, are the natural vectors (hosts and reservoirs) of the avian flu viruses. High prevalence and prolonged incubation of the bird flu viruses in these birds' respiratory and intestinal tracts can result in their greater spread over long distances, even between continents, along the migratory tracts. The high prevalence of avian flu in wild birds can result in severe devastation of fowl populations and endanger the sustainability and biodiversity of the ecosystems. Thus, in the Scotland coast during the summer season of 2021-2022 the clade 2.3.4.4b was isolated from Greats skuas affected, an important wild bird species considered of epidemiological concern [9]. On the other hand, direct or indirect exposure of poultry birds to the infected wildfowl may be the reason behind the present HPAI pandemic. Of note, while the risk of avian flu infection was previously thought to be the highest during the active spring migration from autumn to summer, experts now believe that its presence in multiple wild bird species has elevated the risk levels through all the seasons. Unfortunately, this means that the outbreaks may not soon abate in poultry birds. In these last, density of birds was related with high risk of outbreak in Lombardy regions (Italy) when regions with higher bird density >10,000 birds/km^2 have high probability of outbreak event (67%), and outbreak were more frequent in provinces where had any previous outbreak [10]. Nevertheless, in a genetic analysis of the strains during 2021/2022 outbreaks in Asia and Europe, where H5N1 strains in northern Japan

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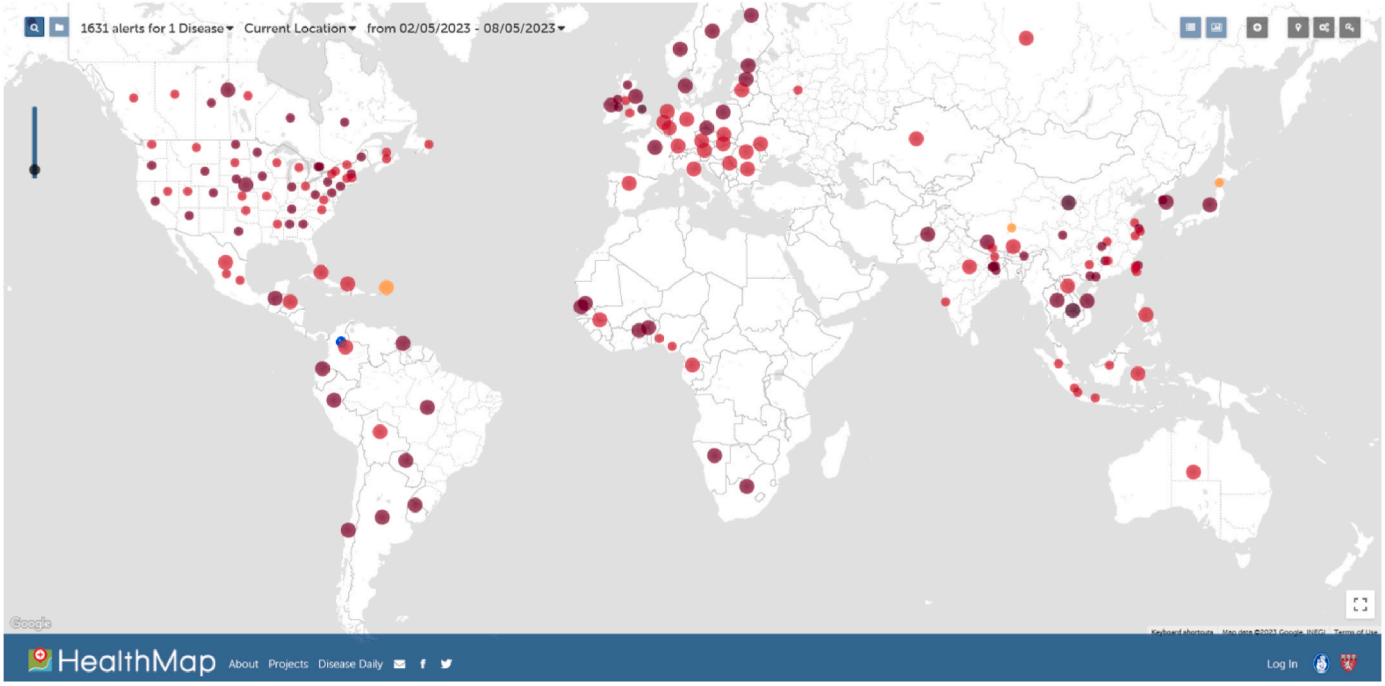


Fig. 1. Global alerts on avian influenza at HealthMap during the last six months (February–August, 2023).

and eastern Russia were evaluated to be of the same subgroup as the viruses prevalent in Europe in the same season but different from those circulating in Asia in winter of the same period, also suggesting the improbability of causing a genetic re-assortment between this type of H5 viruses and those circulating locally in Asia but related to a spread along these territories related to migration [11]. While this concerns the world's food supply, it also presents a grim picture of human disease spillover.

HPAI is primarily known to manifest in birds; however, in rare instances, the infections may elicit in animals, including humans. According to Gregorio Torres of the WOAH, the bird flu virus may be more likely to change into a more pathogenic and transmissible form. More worryingly, it may also elicit increased infectivity and pathogenicity in mammals. Indeed, the Director-General of WHO, Tedros Adhanom, has recently warned about a possible human-bird flu pandemic. The first cases of mammal-to-mammal infection of H5N1 were confirmed in a mink (*Neovison vison*) farm in Spain in October 2022 [12]. This outbreak was unnerving for two reasons; the first and apparent reason was the adaptation of the avian flu virus for mammalian pathogenicity, and the second reason was that minks are closely related to ferrets which elicit a similar pattern of flu progression as humans [13]. Since then, many reputed authorities have reported the spread of bird flu infections in many mammals [14]. More recently, spillover of the H1N5 strain, clade 2.3.4.4b, was confirmed in North-eastern US marine mammal species of *Pinnipedia* (seals) [15].

Similarly, grizzly bears (*Ursus arctos horribilis*) were, for the first time, reported to contract HPAI, possibly due to the consumption of the infected birds [16]. Worryingly, domesticated cats have recently been diagnosed with H5N1 bird flu (2.3.4.4b clade) in Poland, resulting in severe neurological symptoms and even death [17]. These recent discoveries of mammal-to-mammal transmission of avian flu do not bode well for the proponents of mammalian spillover of HPAI.

Avian influenza is known to cross the species barrier and infect diverse mammalian species, including humans. Human infections of bird flu viruses may follow an air-borne pattern, similar to SARS-CoV-2/COVID-19. The prolonged and unprotected interaction with domesticated birds is the primary reason for the increased likelihood of human bird flu inflexion. The flu-like symptoms in such cases may range from no noticeable or mild changes to severe disruptions and even death. The first documented spillover cases of human infection of H5N1 influenza A virus were reported in Hong Kong in 1997 and traced back to domestic and wild waterfowl in Guangdong, China [18]. While the number of human cases of avian flu in this outbreak was limited to 18, the infection resulted in the deaths of 6 of these subjects, a discouraging mortality rate of 33%. Since then, bird flu infections in humans have been sporadically reported. The WHO has reported that there have been more than 890 human cases of H5N1 infections in 22 countries since November 2003. Worryingly, there has been a whooping mortality rate of 53%. However, the data also indicates that the infectivity of H5N1 remained weak enough in humans to not trigger larger outbreaks, possibly because of the rarity of human-to-human transmission [19]. While the infection has been detected in wild and poultry birds during the last two decades, the recently detected spillover to mammalian species is disturbing. It is distressing to know that such transmissions might result in increased adaptive pathogenicity of the bird flu viruses in mammals, including humans [20]. During the past 12 months or so, only a handful of cases of HPAI have been confirmed in humans [21–23]. That includes the recent highly pathogenic H5N1 avian influenza in a 53-year-old Chilean man on 29 March 2023 [24]. From January 2022 to June 2023, 13 cases have been reported of H5N1 infections in eight countries, with six cases of high severity and two deaths [25]. In the US, only one reported human case of H5N1 infection was detected on 28 April 2022 [26]. Almost all human cases of H5N1 flu were found to be exposed to infected poultry; there has been no evidence yet that the virus has been able to jump from newly infected mammals to people. The public health risk of an avian flu outbreak remains low, but the fact that it was transmitted from birds to mammals and then spread among them indicates a disquieting trend. There is increase in the number of wild mammals contracting HPAI-like pathology in many countries. Global concern is growing and the situation has become quite serious, with the concerns that could it become a new pandemic.

The spread of the avian flu virus from birds to mammals has heightened the risk of its spillover into humans. The situation can become disastrous if the virus mutates into variants with increased capabilities of human infection and transmission [27]. Concerns about the recent surges in mammal-to-mammal transmission of bird flu are

worrying. Despite the prolonged Covid-19 pandemic from which we have not completely recovered, the world is poorly prepared for another outbreak. Positive steps need to be urgently initiated through various directives from the government and intergovernmental organizations in response to the HPAI pandemic. As per the WOAH guidelines, the first line of defense against bird flu is the early identification of the disease outbreak. An accurate warning system may aid in an effective and timely response to prevent and control the spread of the outbreak in the concerned geographical region and across near and far-off locations. Since avian influenza viruses are both resistant and contagious, strict biosecurity measures and good hygiene practices must be in place to limit the outbreak's spread.

It should be noted that vaccination of poultry birds may be recommended but may not represent a permanent stand-alone solution to prevent or control bird flu outbreaks. Fowl vaccination must be complemented with other disease control strategies. Some preventive measures include ensuring hygienic conditions in poultry enclosures, regular equipment disinfection, disallowing poultry contact with wild birds, and reporting any bird illnesses (or disease-related deaths) to the local and national veterinary services. At the international level, there is an urgent need for concerted community work across multiple sectors to contain the endemic. The close association of WOAH, WHO, and the Food and Agriculture Organization of the United Nations (FAO) for the OFFLU initiative (www.offlu.org) is an excellent example of monitoring and preventing the potential transformation of bird flu at the bird-animal-human-environment interfaces. Strategic frameworks such as the One World, One Health initiative by WHO and WOAH, among others, must be developed to contain and prevent the pandemic. Biosecurity arrangements against highly infective and pathogenic diseases may never be perfect, as we discovered during the COVID-19 pandemic; however, precautionary measures must be designed and implemented. Rapid responses, such as the changes in cattle-farming practices in the 1990s in response to the detection of Creutzfeldt-Jakob disease (caused by prions), the human variant of mad cow disease, are desired. The design of preventive measures, such as vaccination, additionally requires a thorough understanding of the epidemiology and pathophysiological mechanisms of the disease. More focused-research studies are hence warranted on an urgent basis on the global stage for avian influenza [28–31]. Bird farms should implement robust biosecurity protocols, including restricted access to the farm area, controlled movement of personnel, vehicles, and equipment, and regular disinfection of facilities. Governments and international bodies should regulate the trading of birds to ensure that they come from disease-free or controlled environments. Imported birds should undergo a quarantine period to monitor for any signs of illness before they are introduced to local populations. Tracking the origin of birds through proper documentation and identification can help contain outbreaks and identify potential sources of infection [32].

In conclusion, considering the probable risk of the pandemic impacting human life, we need to be vigilant and ensure that all preventive and precautionary measures are in place to ascertain that the spread of bird flu in newer mammalian species is contained [33,34]. Enhancing preparedness plans for surveillance and laboratory tests are needed, as well as infection control standards, PPE supplies, treatment supplies, and vaccination supplies to avoid detrimental consequences of another pandemic. Public education should be considered early on too through social media from the scientist community to the public to counter misinformation. The more the virus circulates in mammals, the higher the risk of generating a new variant adapted for human transmission. As with the COVID-19 pandemic, this could evolve even newer variants with increased pathogenicity, transmissibility and virulence in humans [35].

Conflicts of interest

The authors report no conflicts of interest.

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