## How Concerned Should We Be About the Recent Avian Influenza Outbreaks?

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nfluenza is mainly caused by influenza A and B viruses, which are responsible for annual outbreaks. The 1918 Spanish flu pandemic that killed nearly 50 million people was caused by influenza A/H1N1 virus.<sup>1,2</sup> In recent years, there has been a risk of influenza A virus causing another pandemic, thanks to the large pool of influenza viruses circulating in migratory birds.<sup>3</sup>

Migratory aquatic birds such as gulls, shorebirds, and wild waterfowl are the natural reservoir (host) of avian influenza viruses.<sup>4</sup> These viruses are occasionally transmitted to domestic birds resulting in catastrophic consequences to animal agriculture, particularly poultry farming. Infections have also been recorded in mammals including seals, foxes, skunks, raccoons, minks, and dolphins, as well as zoo animals like leopards and tigers.<sup>5</sup> Sporadic cases among humans have also been recorded and linked with exposure to infected animals.<sup>6</sup> Infections among humans and other mammals are of big concern as they may offer the virus an opportunity to select adaptive mutations that may allow it to replicate and spread more efficiently in this host, raising the risk of a pandemic.6

Wild birds can carry the virus without showing any symptoms, shedding it mainly in their fecal matter into their environment and water bodies where the virus can remain infectious for a prolonged period facilitating its transmission to other birds and mammals.<sup>7</sup> Infection in mammals can also occur upon eating infected birds. In mammals, the virus can spread systemically and can be found in various organs and body fluids including blood, milk, and respiratory secretions.<sup>8</sup> Human infections can occur through respiratory droplets or fine aerosols via the nostrils, mouth, or conjunctiva. Prolonged and unprotected exposure of humans to infected animals increases the risk of infection.<sup>9</sup> Nonetheless, humanto-human transmission is rare and not sustained.<sup>9</sup>

The highly pathogenic avian influenza (HPAI) A/H5N1 virus was first identified in domestic waterfowl in Guangdong, Southern China.<sup>10</sup> The virus caused several outbreaks with high mortality in chicken farms in Hong Kong in 1997.<sup>11</sup> In the same year, the first human infection was reported in a three-year-old boy.<sup>11</sup> Between 2003 and 1 April 2024, 889 cases with 463 fatalities (52%) were documented across 23 countries.<sup>12</sup>

In 2021, a new strain (clade 2.3.4.4b) of the HPAI H5N1 virus emerged. By the end of that year, the infection had spread in Asia, Africa, Europe, and the Middle East. By 2022, outbreaks were reported in poultry and wild birds in the USA and Canada.<sup>10</sup> Large-scale outbreaks in poultry necessitated the culling of hundreds of millions of birds.<sup>6</sup> Between 2022 and 2023, nearly 60 million birds were killed in the USA alone.<sup>13</sup>

Additionally, the clade 2.3.4.4b strain has been associated with spillover events and outbreaks in various mammals.<sup>9</sup> The US Department of Agriculture has recorded 200 cases of infection in mammals in the USA since 2022.<sup>10</sup> As of March 2024, a multistate outbreak of HPAI A/H5N1 virus in dairy cows in eight American states marked the first instance of avian influenza infection in cattle.<sup>10</sup> The first human case of A/H5N1 in the USA was reported in 2022, spread from infected birds, followed by a second one in Texas in March 2024 in a farm worker who was handling infected dairy cattle.<sup>14</sup> Cambodia has also reported four cases in 2024, bringing the total reported human cases in the country to 10 since 2023.<sup>15</sup> A recent study in five live bird markets in Egypt found that human seropositivity of clade 2.3.4.4b was several times higher than the estimates for older strains, suggesting that the currently circulating viruses are more infectious to humans.<sup>16</sup> The recent outbreaks of A/H5N1 in cattle and the recent case of mammalto-human transmission (despite being mild) in the USA<sup>17</sup> have heightened fears of a potential pandemic if the virus gets more opportunities to adapt to mammals.

Nonetheless, the Centers for Disease Control and Prevention has described the risk to humans as low while stressing on the need for vigilance including close monitoring of exposed workers and warned the public not to handle sick or dead animals without proper precautions. The Centers for Disease Control and Prevention has also advised the public to avoid consuming raw milk or products made from raw milk from animals with confirmed or suspected A/H5N1 infection.<sup>12</sup> Likewise, the World Health Organization has stated that the current outbreak of A/H5N1 poses a low to moderate risk to public health. It has advised enhanced surveillance and monitoring of any confirmed or suspected A/H5N1 human case. As influenza viruses can evolve quickly, there is a need to improve and strengthen surveillance especially among groups with higher occupational risk of exposure.12

Though current information about the recent A/H5N1 human cases is not alarming, and we have not seen any cases of human-to-human transmission, the expanding geographic spread and host range is concerning. The recent outbreaks in cattle have established A/H5N1 in a new mammalian host. As the biosecurity and biocontainment measures in cattle farms are not as strong as in poultry farms, cattle handlers may be at increased risk of infection.<sup>17</sup>

Historically, vaccination and culling have been used to control avian influenza in chickens.<sup>18</sup> According to the World Organization of Animal Health, since 2005, more than 500 million birds have been killed (culled or dead due to disease). That has put tremendous pressure on food supplies in Western countries, leading to a sharp rise in prices of poultry products. The World Organization of Animal Health has informed that the current avian influenza is more pathogenic and widespread in wild birds, making it difficult to protect commercial flocks, and has recommended vaccination of poultry.<sup>19</sup> Regarding the outbreaks in cattle farms, the US Department of Agriculture's Animal and Plant Health Inspection Service's current recommendations do not include culling, instead focuses on enhancing biosecurity, minimizing animal movements, testing animals before movement, and isolating recently moved animals.<sup>20</sup>

Moreover, although the risk of A/H5N1 viruses to public health remains low,<sup>6</sup> the economic burden and disruptions in the food supply chain cannot be underestimated. In the USA, economic losses due to avian influenza in poultry in 2023 were estimated to be around USD 3 billion.<sup>21</sup>

The COVID-19 pandemic has taught humanity a valuable lesson in that uncontrolled transmission could pave the way for the emergence of new variants that are potentially more pathogenic and more contagious. With global openness and collaboration, we can control the A/H5N1 outbreaks and prevent its potential to become a deadly and global pandemic. All countries need to be encouraged to enhance their surveillance efforts and biosecurity capacities with a One Health approach and report suspected and confirmed cases of avian influenza. Public health measures should not be punitive for countries to foster transparency and cooperation. Finally, countries should review their pandemic preparedness plans by incorporating learnings from the COVID-19 pandemic.

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