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Editorial

Feathered fears: Could avian H5N1 influenza be the next pandemic threat of disease X?

H5N1 is a type of influenza virus that causes a highly infectious and severe respiratory disease in birds, commonly known as avian influenza or bird flu. While human cases of H5N1 avian influenza do occur occasionally, it is still challenging for this virus to transmit from person to person. Most cases of H5N1 infection in humans have been associated with close contact with infected live or dead birds or H5N1-contaminated environments [1].

The risk of H5N1 transmission from birds to humans is currently low. The virus primarily circulates among birds and has caused significant mortality in domestic and wild bird populations worldwide. However, occasional spillover events to mammals, including seals and bears, have been observed [2]. Such spillover to other species underlines the importance of monitoring wildlife for the developement of H5N1 infection in order to prevent potential outbreaks. The occurence of cross-species infection illustrates the broader ecological impacts of the virus beyond avian species.

Recent studies have demonstrated the genetic stability of H5N1 in wild bird populations even after significant die-off events, indicating the resilience and adaptability of the virus in natural reservoirs [3]. The US CDC continuously monitors H5N1viruses for genetic alterations that could enhance transmission among humans, increase illness severity, decrease antiviral effectiveness, affect diagnostic accuracy, or compromise vaccine efficacy. In addition, there had been an alarming reappearance of H5N1 avian influenza in Cambodia in 2024. This may result in infection of poultry and then humans [4]. The occurrence of H5N1 among U.S. cattle is of an additional concern [5]. The high--pathogenicity of the avian influenza H5N1 lineage 2.3.4.4b is of particular concern due to panzootic and the significant impact on poultry [6].

Humans can be infected by various zoonotic influenza viruses, including those from avian and swine sources, through direct interactions with infected animals in activities such as handling, culling, slaughtering, or processing, as well as indirectly through contaminated environments with bodily fluids from infected animals. Sporadic human H5N1 cases had been described sporadically because of direct contact with sick or dead poultry [7]. Although H5N1 avian influenza has primarily been transmitted to humans through direct contact with infected birds, the potential for human-to-human transmission exists, particularly through genetic reassortment when a person is co-infected with a human influenza virus and an avian influenza virus [8]. This could lead to the emergence of a new influenza virus capable of more sustained human-to-human transmission. Ongoing vigilance and surveillance are essential to monitor for genetic changes in the virus that could pose increased risks to human health (Fig. 1).

As avian influenza could spread rapidly, global surveillance efforts, the tracking and reporting of H5N1 cases in birds and mammals across different regions should emphasize the importance of international cooperation in managing avian influenza outbreaks or situational changes. The recent detection of H5N1 infection in a human in the United States is a further cause for concern. The WHO was notified about a laboratory-confirmed case of human infection with an influenza A (H5N1) virus on April 1, 2024. The patient developed symptoms on March 27 and had a history of exposure to dairy cattle presumed to be infected with the H5N1 virus [9]. The history of human H5N1 cases dates to 1997, when a poultry outbreak of highly virulent H5N1 influenza in live-bird markets in Hong Kong resulted in 18 human cases, marking the first known connection between avian influenza H5N1 and human respiratory disease [10,11]. Threefold increases in mortality (33

Fig. 1. Vigilance in the Flock: Monitoring Avian Influenza Amongst the Feathered Hosts. Of note, the text and symbols created in the figure are representative of keeping a close look at the unexpected, as variants in the Avian Influenza virus could change its infectivity and pathogenicity.
(Image created by OpenAI's DALL-E 3 on 13 April 2024 using the prompt: "Draw a picture representing the theme: Vigilance in the Flock: Monitoring Avian Flu in the Midst of Feathered Hosts" [19]).

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Table 1
Lessons and recommendations for the H5N1 avian influenza based on past pandemics in the past 100 years, helping to prepare more effectively for future outbreaks including the hypothetical "Disease X"

Pandemic	Lessons for HCWs	Lessons for Stakeholders	Lessons for Laypeople	Lessons for Communities
Spanish Flu	- Importance of personal protective equipment. - Need for rapid response capabilities. - Nursing shortage	- Coordination of resource distribution. - Effective public health policies needed.	- Awareness of hygiene practices. - Understanding public health directives.	- Community support systems crucial. - Importance of local health initiatives.
H1N1	Quick adaptation to new protocols. - Importance of vaccination for frontline workers.	- Quick decision-making in crisis. - Importance of transparent communication. - Global healthcare optimizations are needed to manage a long-term pandemic	- Necessity of staying informed about health issues. - Participation in vaccination programs.	- Rapid community response to contain spread. - Local health education campaigns.
SARS-CoV-2	- Critical role of timely information and training. - Use of technology in tracking and treatment.	- Global cooperation in health crises. - Funding and support for research and development.	- Compliance with health guidelines. - Social media is a blessing but misinformation is a curse	- Resilience in prolonged crises. - Adaptation to new normals (remote work, schooling).
Disease X	- Preparedness for unknown pathogens. - Flexibility in treatment approaches.	- Investment in R&D for broad-spectrum antivirals. - Strengthening health infrastructure.	- Understanding of potential rapid changes in health directives. - Readiness to adopt new health behaviors.	- Building robust systems for crisis management. - Fostering community resilience against unknown threats.

%), pneumonia incidence (61 %), and intensive care utilization (51 %) were linked to the outbreak. Since all of the virus's genes were avian in origin, it was shown that H5N1 crossed the species barrier without adapting [12]. Little indication of human-to-human transmission was found by serologic surveillance, and after the enormous killing of poultry, no new cases were identified.

H5N1 infections among humans range from mild, flu-like symptoms or eye inflammation to severe, acute respiratory diseases and even death. The severity of the disease depends on the specific virus and the characteristics of the infected host, whether human or another species. Upper respiratory tract symptoms such as rhinorrhea and sore throat may not be common in all patients, but the disease can progress rapidly. It is important to note that there is no evidence of sustained human-to-human transmission of the H5N1 virus. Properly prepared and thoroughly cooked food does not pose risk of H5N1 transmission to humans [1]. The mortality rate of H5N1 infection in humans is high, making it a cause for concern. However, it is crucial to understand that the likelihood of an H5N1 pandemic is currently low, but the potential impact on human health is significant. Efforts are being made to monitor and control the disease in both birds and humans through vaccination of humans or chickens and other preventive measures [1,13,14].

Table 1 shows historical pandemics—Spanish flu, H1N1, SARS-CoV-2—and the hypothetical "Disease X″ reflects a strategic approach to learning and applying vital lessons to different societal groups including healthcare workers, stakeholders, laypeople, and communities [15,16]. It emphasizes the need for ongoing preparedness for healthcare systems, dynamic and transparent decision-making for policy makers, informed and proactive participation for laypeople, and robust community support systems. This approach aligns with the World Health Organization's 2018 introduction of "Pathogen X″, a placeholder for an unknown pathogen with pandemic potential, highlighting the necessity for global readiness against unforeseen infectious agents that could pose severe health threats [16]. This concept underscores the importance of global vigilant surveillance, flexible healthcare policies that are based on the "best available evidence", and widespread educational initiatives to effectively manage potential future pandemics.

The integration of artificial intelligence technologies, particularly advancements seen with tools like ChatGPT-4 post-COVID-19, offers transformative potential for tailoring preventive and treatment strategies on an individual basis [17,18]. The recent developments in AI, exemplified by ChatGPT's ability to simulate complex medical discussions, underscore its utility in enhancing future pandemic responses. This technology could bridge the gap between generalized public health strategies and personalized patient care by leveraging data-driven insights from extensive studies like the Global Burden of Disease (GBD) [18]. By adopting AI tools in healthcare planning, professionals can customize approaches that cater to individual lifestyles and medical needs, ensuring a dynamic, accurate, and ethically compliant application of AI in medicine. This strategic application of AI could not only optimize resource utilization and improve patient outcomes but also set the stage for a broader adoption of precision medicine globally.

The importance of surveillance and international collaboration cannot be overstated, particularly with early notifications to the WHO about genetic sequencing of any novel virus capable of sustained human-to-human transmission. This proactive approach, combined with lessons learned from past pandemics, can significantly mitigate the adverse effects of widespread infections, both locally and internationally. Adhering to accurate information through social media and combating misinformation are crucial steps that can limit the speed of an outbreak until more specific measures, such as vaccine deployment and the dissemination of specific antiviral treatments, are widely available. Furthermore, emerging technologies like AI and ongoing R&D in rapid detection, vaccines' developments, and multimodal medications, could revolutionize how we personalize preventive and treatment modalities for each individual, enhancing our preparedness for the next pandemic threat.

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