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Are we cultivating the perfect storm for a human avian influenza pandemic?

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Abstract

The emergence of highly pathogenic avian influenza (HPAI) A H5N1 virus in dairy cattle marks a troubling new chapter in the ongoing battle against zoonotic diseases. Since its initial detection in 1955, the H5N1 virus has primarily been associated with poultry, posing significant threats to both animal and human health. However, recent outbreaks in U.S. dairy herds across nine states have revealed an alarming expansion of the virus, with over 190 herds affected as of September 2024. This unprecedented spread in cattle has sparked intense concern among scientists and health officials, especially with reports indicating that up to 20% of dairy products may contain traces of the virus. The implications of the H5N1 virus establishing itself in cattle populations are profound. This potential endemic presence could transform dairy farms into reservoirs of the virus, facilitating its evolution and increasing the risk of human transmission. Mutations enhancing viral replication in mammals have already been identified, including the notorious PB2 E627K mutation linked to increased virulence. Moreover, the detection of the virus in the central nervous system of infected animals, including cats, underscores the broad tissue tropism and severe pathogenic potential of the H5N1 virus. Current containment efforts include stringent biosecurity measures and financial incentives for enhanced testing and personal protective equipment (PPE) for farmers. Yet, gaps in testing infrastructure and the resurgence of raw milk consumption pose significant challenges. The U.S. Department of Agriculture (USDA) and the Centers for Disease Control and Prevention (CDC) emphasize the critical need for comprehensive testing and pasteurization to mitigate the risk of human infection. As the scientific community races to adapt existing antiviral treatments and develop effective vaccines, the concept of a One Health approach becomes increasingly vital. This holistic strategy calls for coordinated actions across human, animal, and environmental health sectors to preemptively tackle emerging zoonotic threats. Strengthening surveillance, fostering international cooperation, and investing in research are essential steps to prevent the H5N1 virus from igniting the next global health crisis. The current avian influenza outbreak serves as a stark reminder of the delicate balance between human activities and viral evolution. Our collective ability to respond effectively and proactively will determine whether we can avert the perfect storm brewing on the horizon.

Keywords H5N1, HPAI, Dairy cattle, Pandemic

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Introduction

Dairy cattle infection with H5N1 virus: a new endemic disease?

Although the first human case was detected in a child in Hong Kong in 1997 [1], historical records of the disease, initially known as 'fowl plague', date back to 1878, being characterized as a severe and rapidly spreading disease affecting chickens [2]. Despite its earlier characterization, the etiological agent remained unknown until 1955, when it was identified as a Type A influenza virus (orthomyxovirus). The term 'highly pathogenic avian influenza (HPAI)' came into use until 1981 during the first International Symposium on avian influenza held in 1981 in Beltsville, Maryland, United States of America (U.S.) [2].

Since its first reported outbreak in 1959 (A/chicken/Scotland/59) [3], the HPAI H5N1 variant has emerged as a global threat, rapidly spreading across the world [4, 5]. To date, more than 900 zoonotic human infections have been reported in 23 countries [6]. The case fatality rate (CFR) of the HPAI H5N1 virus in humans is significantly high, ranging from 59% to 66%, underscoring its severe impact on human health [7–9].

Traditionally, the HPAI virus primarily affects birds [10] leading to the destruction of millions of poultry worldwide, significantly impacting food security and livelihoods [11]. However, since 2020, the H5N1 clade 2.3.4.4b [12] emerged as a predominant strain in wild birds and poultry across multiple continents, posing significant threats to both animal and human health due to its widespread dissemination and genetic diversity [13, 14]. These precedents are summarized in Fig. 1.

Recent reports of HPAI H5N1 virus infecting dairy cattle in the U.S. have sparked significant concern [15]. As shown in Fig. 2, as of September 2024, detections in over 190 dairy herds in 14 states-Texas, Kansas, Michigan, New Mexico, Idaho, Ohio, North Carolina, South Dakota, Colorado, Minnesota, Wyoming, Iowa, Oklahoma and California-based on the confirmation date, indicate widespread dispersion across the U.S. [16].

The U.S. Department of Agriculture (USDA) and the Centers for Disease Control and Prevention (CDC) have recommended the implementation of enhanced biosecurity measures to contain the outbreak [16]. These measures include restricting farm access, segregating infected animals, and ensuring that milk from sick cows does not enter the food supply [17]. Moreover, the USDA has recently introduced financial incentives to encourage testing and the use of personal protection elements (PPE) among farmers. These incentives include funding to enhance biosecurity measures

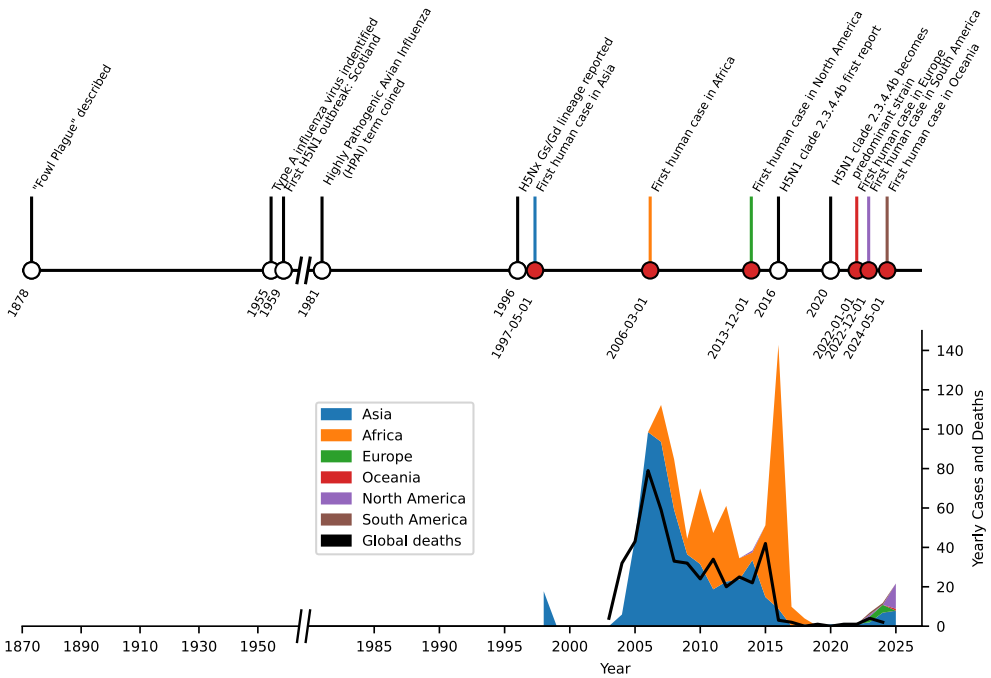

Fig. 1 Global timeline of highly pathogenic avian influenza (HPAI) outbreaks and key events. The timeline spans from the late 19th century to the present, highlighting as red dots the first identified human cases of avian influenza in various continents, as well as the evolution of the virus. The graph also tracks the yearly global human cases and deaths associated with H5N1 virus outbreaks. While cases in the current decade are still low, the recent increase in affected people is of concern

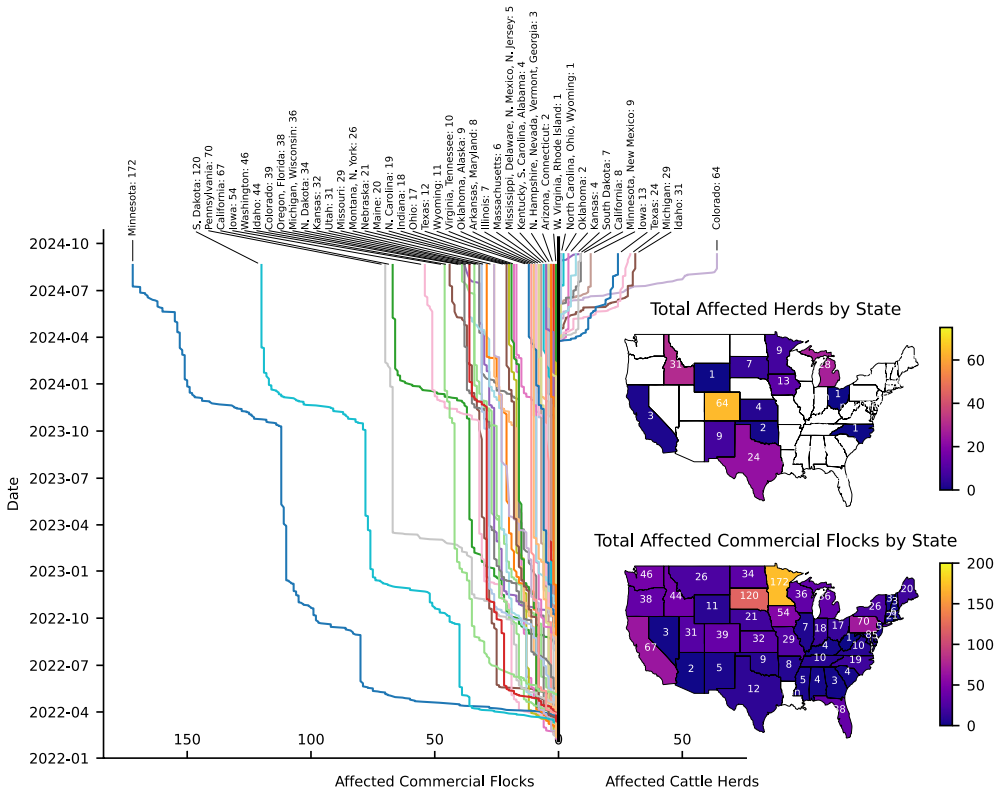

Fig. 2 Spatial distribution and temporal progression of affected commercial flocks and cattle herds by state from January 2022 to September 2024. The graph tracks the number of affected herds and flocks across various states, including notable peaks in states such as California, Iowa, Minnesota, and South Dakota. The data highlights the variability of outbreaks over time, with different states showing varying levels of impact. The color-coded bars represent the cummulative number of affected commercial flocks and cattle herds, for each state illustrating the widespread nature of the outbreaks across the United States. Even though spread in herds has begun only recently, the propagation has been faster than for flocks. The spatial distribution of affected farms is very different depending on the type of animals

and cover costs related to additional testing and PPE for employees [18].

In spite of these containment efforts, recent studies have revealed a concerning prevalence of H5N1 virus RNA in dairy products, with findings indicating that approximately one in five dairy products may contain remnants of the virus [19]. Further studies have shown that pasteurization effectively inactivates the H5N1 virus, leading to the U.S. Food and Drug Administration (FDA) to confirm that pasteurized milk and dairy products, including cheese, are safe for consumption [20]. Unexpectedly, a revival of raw milk consumption, particularly that coming from herds infected with H5N1 virus, has surged in the U.S. [21, 22]. Although no human cases have been directly linked to drinking raw milk, the FDA strongly advises against the consumption of raw milk and raw milk derived products from infected cows due to the presence of potentially harmful pathogens, including the H5N1 virus [20, 23]. This recommendation is supported by a recent study in which oral inoculation of raw milk from herds infected with the HPAI H5N1 virus caused systemic infections in mice [24].

Of note, while in the midst of these unprecedented massive outbreaks detected in more than 190 herds in the U.S., as of September 2024 (Fig. 2), significant gaps in the readiness to detect and manage avian influenza outbreaks still remain [25]. The scarcity of tests, which hinders timely identification of the virus, particularly in farmworker communities, and the role of health insurance constraints and FDA regulations in limiting testing availability are all components hindering a more accurate situational awareness. The current testing infrastructure seems insufficient to comprehensively monitor and control the spread of HPAI H5N1 virus [26]. While the USDA has mandated testing for interstate movement of dairy cattle, this measure does not extend to all herds or consistently include the totality of farm workers who may be exposed to the virus, nor does it include non-symptomatic dairy cows [27].

In a recent effort to overcome these limitations, the CDC is seeking to expand testing capacity for H5N1 virus in people by addressing current diagnostic infrastructure shortcomings and the challenges posed by regulatory requirements and funding constraints. The CDC's initiative aims to surmount these obstacles by increasing testing availability and enhancing outreach to high-risk populations, ensuring a more robust defense against potential avian influenza outbreaks in humans [28].

Since February 2022, the CDC, along with state and local health departments, has been monitoring individuals exposed to infected birds, poultry, or other animals for a 10-day period post-exposure. Over this span, more than 10,000 people have been monitored and up to 370 individuals have been tested for the HPAI H5N1 virus. In response to the ongoing HPAI outbreak in cattle, similar monitoring efforts have been applied to those exposed to infected cattle. From March 2024 to the present, at least 1300 individuals have been monitored. As of July 2024, 61 of these individuals have been tested for HPAI H5N1 virus [29].

The widespread of herds infection together with the presence of HPAI H5N1 virus RNA in dairy products, suggest that the infection in herds could be much larger than previously thought [30]. Thus, the possibility that the H5N1 virus could become endemic in dairy cattle in the U.S. is a growing concern [31, 32]. If the virus establishes itself in cattle populations, it could persist and circulate within herds, making it more challenging to eradicate. This scenario could lead to continuous low-level infections and sporadic outbreaks, or even worst, to create in vivo laboratories allowing the virus to evolve in mammals which are in very close contact to humans.

Viral evolution in real time: back to the Spanish flu

The H5N1 virus, which has been affecting dairy cattle and, as of July 2024, has infected four farm workers in the U.S. [33]-one from Texas, two from Michigan and one from Colorado-exhibits mutations that could potentially increase the risk of human-to-human transmission [34, 35]. A key mutation identified in the virus from the first case from Texas, A/Texas/37/2024, which is also present in one sequence report from cattle [36] is PB2 E627K [37]. This mutation is known to enhance the virus's ability to replicate efficiently in mammalian hosts [38]. Of note, PB2 E627K has been previously observed in other mammals infected with the H5N1 virus, indicating a significant adaptation to mammalian cells [39, 40].

The sequences from the H5N1 virus infecting the second human case, the first reported in Michigan, A/Michigan/90/2024, lacked the PB2 E627K mutation found in the Texas case but contained the PB2 M631L mutation, which is associated with viral adaptation in mammalian hosts. This mutation is present in 99% of dairy cow sequences but is only sporadically observed in birds [36, 41].

Fortunately, in both cases, the infection remained mild, characterized mainly by conjunctivitis, and responded well to antiviral treatment with oseltamivir [37].

Of note, the third human case, also from Michigan, exhibited more typical symptoms of acute respiratory illness associated with influenza virus infection. Among others, the patient reported upper respiratory tract symptoms including cough without fever and eye discomfort with watery discharge [42]. Despite the patient recovered after treatment with oseltamivir, the exhibition of upper respiratory tract symptoms is of concern due to the potential for virus spread via aerosols through coughing.

Another critical mutation present in the H5N1 virus is PB2 T271A, which has been reported in infected minks in Spain [43]. This mutation is particularly important because it was also present in the H1N1 virus responsible for the 2009 pandemic [44], suggesting it plays a role in enhancing the virus's transmissibility among mammals. The presence of this mutation in various mammal species infected with the H1N1 virus, especially those like minks and pigs that can act as mixing vessels for different influenza viruses, is of high concern [45, 46]. In the case of co-infection between H5N1, H1N1, and other influenza A variants in these animals, new viral strains capable of efficient human-to-human transmission could emerge through genetic reassortment events [47].

On March 29, 2023, Chile reported its first human infection of HPAI H5N1 virus, marking the second such case in South America after a January 2023 case in Ecuador [48, 49]. The PB2 D701N mutation was identified following the isolation and sequencing of the virus. This mutation, located in the C-terminal domain of PB2, is linked to increased virulence and transmissibility in mammals, as demonstrated by experiments in mice, guinea pigs, and ferrets [50–53]. It has also been previously found in human H5N1 HPAI virus infections in Asia, with no evidence of human-to-human transmission [54, 55].

Significantly, the PB2 D701N mutation, along with other amino acid substitutions (Q591K in the PB2 gene, R57Q in the PA gene, and V226T in the NS gene), was detected during recent outbreaks among sea lions in Brazil, Chile, and Peru [56, 57]. The widespread presence of this mutation in both terrestrial and aquatic mammals, including red foxes, lynx, black bears, and seals [58], and more recently in dairy cattle [36], underscores its role in mammalian adaptability and pathogenicity.

Other significant mutations observed in the HPAI H5N1 virus infecting dairy cattle include a set of

substitutions in the HA protein, such as 137A, 158N, and 160A (using H3 influenza subtype number) [59]. Denoting the ongoing viral adaptation occurring in cattle, these mutations have been documented to increase the affinity of avian influenza viruses for human-type receptors [60, 61].

Surprisingly, it has been found that both avian and mammalian receptors are present in the mammary glands of dairy cows [62]. This dual presence of receptors can facilitate the binding and replication of the virus in a way that promotes cross-species transmission.

The implication of these findings is profound. The potential for the virus to become endemic and the presence of multi-species receptors raises significant concerns about infected cattle becoming reservoirs for the HPAI H5N1 virus, facilitating human contagion [32].

During the 1918–1919 Spanish influenza pandemic, pigs may have played a notable role in the epidemiology of the disease, as the virus was a novel H1N1 strain with genetic material from avian and swine influenza viruses [63]. A similar phenomenon ocurred in Mexico in 2009, producing the 2009 swine flu pandemic [64]. Pigs, known as mixing vessels, can be infected by both avian and human influenza viruses, facilitating the reassortment and emergence of new influenza strains [47, 65].

As of June 2024, dairy cows, another mammal which lives in close contact with humans, may play a similar role to that of pigs during the Spanish flu pandemic.

More than a flu: a viral infection of the central nervous system

Recent cases of H5N1 virus infections in cats on dairy farms in the U.S. have raised significant concerns due to the Central Nervous System (CNS) tropism of the HPAI virus [66]. Post-mortem analyses of the cats exhibited severe systemic viral infections with notable CNS damage. This included severe subacute multifocal necrotizing and lymphocytic meningoencephalitis, vasculitis, and neuronal necrosis. Immunohistochemistry revealed positive influenza A virus antigen in brain tissues, particularly in neurons and retinal layers [66]. These findings highlight the significant CNS tropism of the H5N1 virus, demonstrating its ability to replicate in a wider array of mammalian tissues [67].

Evidence from other studies highlight the CNS tropism of the H5N1 virus. Infections in mammals such as mice, ferrets, and wild foxes have shown that the virus can invade and replicate in the CNS, causing neuroinflammation and neurodegeneration [68–71]. Viral antigens and RNA have been found in brain tissues, indicating that the H5N1 virus can cross the blood-brain barrier and infect neural cells [72].

The neurotropism of the H5N1 virus is influenced by a variety of mutations across different genes. Key mutations include those in the NS1 gene (F103L and M106I), PB2 (E158G and M631L), NA (K110E), and NP (K470R) [73–76]. These mutations enhance the virus's ability to infect and replicate in mammalian neural tissues, contributing to its neurovirulence and neurotoxicity.

Thus, in the eventuality of the HPAI H5N1 virus becoming a human pandemic, its burden could be exacerbated by generating unknown cognitive effects at the population level, leading us into uncharted territory.

Adapting to change: overcoming H5N1 antiviral resistance and vaccine challenges

The availability of effective treatments and vaccines is crucial in combating a potential HPAI H5N1 pandemic in humans. Antiviral drugs such as oseltamivir (Tamiflu®) and zanamivir (Relenza®) are currently the primary treatments for H5N1 virus infections and as a profilactic measure for people in close contact with the infected person [37, 77]. These NA (neuraminidase) inhibitors work by preventing the virus from exiting the cell and spreading within the body [78]. However, the effectiveness of these antivirals can be compromised by viral evolution. Mutations, such as H274Y in the NA gene, have been shown to confer resistance to oseltamivir, reducing the drug's efficacy [79, 80]. In cases of antiviral resistance or the appearance of symptoms after treatment with oseltamivir, as an interim measure the CDC has recommended the use of baloxavir [81], which has been reported as effective in treating infections with H5N6 virus [82].

Fortunately, no evidence for the presence of this mutation or any other mutations conferring antiviral resistance has been found in infected dairy cattle or in the infected farm workers.

As avian influenza (H5N1) cases increase among cattle in the United States, global efforts are ramping up to develop and distribute vaccines to prevent potential human transmission. Vaccines are a critical component of pandemic preparedness, and as of July 2024, both Europe and the U.S. have approved vaccines to protect humans against the H5N1 influenza virus [83–86].

In 2020, the FDA approved Audenz, an adjuvanted monovalent vaccine developed by Seqirus, intended for adults to prevent disease caused by the H5N1 influenza virus subtype [87]. In 2013, Glaxo-Smith Kline received approval for its adjuvanted pandemic Influenza A (H5N1) Virus Monovalent Vaccine, also known as Q-Pan H5N1 influenza vaccine, for immunization of adults 18 and older [88], although its efficiency against clade 2.3.4.4b is low [89].

In the European Union, the European Medicines Agency (EMA) has recommended several vaccines against H5N1 virus, including Celldemic and Incellipan, both developed by Seqirus Netherlands B.V. [90]. These vaccines are designed for active immunization against avian influenza and are part of the EU's pandemic preparedness strategy.

Recent actions include the European Commission securing 700,000 doses of an H5 strain vaccine, with the option to acquire 40 million more [86], and Finland starting to vaccinate high-risk workers. The U.S. Department of Health and Human Services (HHS) has moved forward with plans to produce 4.8 million doses of the H5N1 avian influenza vaccine to enhance pandemic preparedness [91]. Official estimations indicate that over 100 million doses could be distributed within three to four months. However, since two doses are required per person, this supply would be sufficient for only 50 million people [92], a very low threshold compared to the U.S. population of over 340 million. In clear contrast, by mid-2021, approximately three billion doses of COVID-19 vaccines had been administered globally, helping stop the spreading of the disease, but even that comparatively high number was insufficient due to significant inequity in the distribution, which focused mostly on high-income countries [93].

Additionally, researchers are developing mRNA vaccines, which can be produced more rapidly and updated quickly to address new strains. The U.S. Department of Health and Human Services has invested $176 million in Moderna for the development of an mRNA-based H5 vaccine. Ensuring fair global distribution is essential, with the Coalition for Epidemic Preparedness Innovations (CEPI) striving to make sure low- and middle-income countries are not neglected.

Vaccinating cattle to reduce transmission is also being explored, though there are challenges in effectively targeting the virus in cows. Research teams are in the early stages of developing both conventional and mRNA vaccines for livestock. Despite these preparedness efforts, the available vaccine supply is very scarce in the context of a worldwide health emergency.

Pandemic preparedness requires a One Health approach

Wastewater surveillance by the CDC has detected the presence of influenza A virus in several states and cities across the U.S. [94]. A virome sequencing study identified HPAI H5N1 clade 2.3.4.4b in wastewater from nine of the ten monitored cities in Texas, U.S. [95]. Although the variant analysis in this study indicates an avian or bovine origin, other potential sources, especially humans, cannot be ruled out; additionally, the CDC surveillance methods are not as specific as those used in this study, so it is not possible to identify subtypes at the national level.

The uncertainty surrounding the types of influenza viruses present in wastewater further complicates public health responses and underscores the need for ongoing monitoring and analysis.

Current measures focus on containment and mitigation, but a proactive approach is urgently needed. Strengthening surveillance systems, increasing testing capacity, investing in research for vaccines and treatments, and fostering international cooperation to exchange data and stockpile vaccines are critical steps. In the longer term, addressing underlying factors such as intensive farming practices and wildlife trade, which create environments conducive to viral mutations, is crucial in preventing the next pandemic.

As a whole, the outbreak in dairy cattle underscores the interconnectedness of human, animal, and environmental health. The "One Health" approach, which emphasizes the collaboration of multiple sectors to achieve optimal health outcomes, is particularly relevant in this context [96, 97]. Efforts to prevent and control HPAI H5N1 must involve a comprehensive approach that considers the health of all species and their environments.

Conclusion

The detection of the HPAI H5N1 virus in dairy cattle and the recent infections in humans and various mammalian species signal an urgent need for immediate and coordinated action. This evolving situation underscores the potential for the H5N1 virus to adapt and pose significant public health risks. The rapid evolution of the virus, coupled with its expanding host range, highlights the necessity for robust surveillance systems, increasing testing capacity, continuous research, and adaptive strategies for antiviral treatments and vaccines. Moreover, the potential for the virus to reassort and create new strains in both mixed-species environments and mixing vessels further complicates these efforts, necessitating a flexible and dynamic approach to vaccine and antiviral development.

Given the profound implications for global health, a proactive One Health approach is urgent. This approach must involve collaboration across human, animal, and environmental health sectors to implement comprehensive biosecurity measures, enhance surveillance, and ensure rapid response to outbreaks. Immediate actions should include increased surveillance and testing capacity, increased funding for research, stockpiling and development of next-generation vaccines and antivirals, and the establishment of a global network for real-time data sharing and coordination.

Are we cultivating the perfect storm for a human avian influenza pandemic? The likely answer is not "if" but "when". Our ability to respond effectively and proactively to these emerging threats will determine our preparedness for the next global health crisis. The current HPAI H5N1 outbreak serves as a stark reminder of the need for global preparedness and action. The scientific community, policymakers, and international health organizations must collaborate to address this threat, preventing HPAI H5N1 from becoming a pandemic and protecting public health worldwide.

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TPA designed, researched the bibliography and wrote and reviewed the manuscript. CR researched the bibliography, analyzed the data, made the figures, and wrote parts of the manuscript. MR wrote and reviewed the manuscript.

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Declarations

Ethics approval and consent to participate
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Consent for publication
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Competing interests
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