The panzootic spread of highly pathogenic avian influenza H5N1 sublineage 2.3.4.4b: a critical appraisal of One Health preparedness and prevention

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Changes in the epidemiology and ecology of H5N1 highly pathogenic avian influenza are devastating wild bird and poultry populations, farms and communities, and wild mammals worldwide. Having originated in farmed poultry, H5N1 viruses are now spread globally by wild birds, with transmission to many mammal and avian species, resulting in 2024 in transmission among dairy cattle with associated human cases. These ecological changes pose challenges to mitigating the impacts of H5N1 highly pathogenic avian influenza on wildlife, ecosystems, domestic animals, food security, and humans. H5N1 highly pathogenic avian influenza highlights the need for One Health approaches to pandemic prevention and preparedness, emphasising multisectoral collaborations among animal, environmental, and public health sectors. Action is needed to reduce future pandemic risks by preventing transmission of highly pathogenic avian influenza among domestic and wild animals and people, focusing on upstream drivers of outbreaks, and ensuring rapid responses and risk assessments for zoonotic outbreaks. Political commitment and sustainable funding are crucial to implementing and maintaining prevention programmes, surveillance, and outbreak responses.

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Introduction

With the world gradually recovering from the COVID-19 pandemic, preparing and planning to prevent future infectious disease outbreaks is important. A huge body of work has been generated on the early detection of and response to emerging disease outbreaks following spillovers of animal viruses to humans, but there has been much less focus on primary prevention. Primary prevention starts before the first cases of human illness occur, reducing the risk of transmission rather than responding to those cases, but its implementation is challenging. Primary prevention requires a focus on understanding the underlying principles of disease emergence, and the prevention of spillovers through a One Health approach across human, animal, and environmental health sectors.[1] Therefore, in addition to the public health concerns that are currently already widely addressed, One Health requires a focus on biodiversity conservation and the environment, livestock production and consumption (including impacts on food safety and security), and both wild and domestic animal health and welfare. Since 2020, the unprecedented emergence and spread of highly pathogenic avian influenza illustrates this need.

The global shift in the ecology of H5N1 highly pathogenic avian influenza virus is an important case study of the crucial need for strengthening the One Health concept in pandemic prevention, preparedness, and response and moving away from anthropocentric thinking towards a more holistic approach to emerging diseases.[2] H5N1 highly pathogenic avian influenza viruses have caused zoonotic infections in humans in close contact with infected poultry, mostly in Asia and Africa, with occasional cases in Europe and, since 2022, in the Americas.[3,4] Since the emergence of a new lineage of H5N1 highly pathogenic avian influenza in 1996, these viruses have evolved into multiple clades and genotypes through genetic mutations and antigenic drift, and through a complex pattern of reassortments of gene segments (antigenic shift) during their continued circulation in poultry farms with insufficient biosecurity and the recycling of spillovers and spillbacks between poultry and wild bird populations.[5] Although the east and southeast Asian regions have been sources of H5Nx highly pathogenic avian influenza viruses spreading into poultry farms in other regions,[6] either directly through the movement of poultry or indirectly via carriage of the viruses in wild birds, the global expansion that has occurred in the past 3 years is unprecedented. H5N1 2.3.4.4b clade highly pathogenic avian influenza viruses have spread globally among wild birds and reached previously unaffected geographical areas,[7] infecting an increasing number of wildlife species, including aquatic and terrestrial wild mammals, and pets (dogs and cats) and animals in production settings (eg, farmed mink and dairy cattle).[8–15] A suspected foodborne incident led to the sometimes fatal infection of multiple domestic cats across Poland, where cats showed neurological or respiratory symptoms or both,[16,17] highlighting the risk for other possible routes of exposure among felids, previously reported in captive wild tigers and lions,[18,19] as some of the cats (five of 25) had no access to the outdoors. A similar event was recorded in South Korea[20] and similar clinical findings were seen in the USA following probable cattle-to-cat transmission, with cat viruses clustering together in analyses suggestive of cat-to-cat

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For more on the **current H5N1 avian influenza situation in the USA** see https://www.cdc.gov/flu/avianflu/avian-flu-summary.htm

transmission.[15,21,22] Although the risk for human infection is still considered low and there have been only a few reported cases of human infection with the globally spreading H5N1 2.3.4.4b clade highly pathogenic avian influenza virus from 2022,[4,23,24] these viruses have efficiently infected a wide range of mammalian species (eg, seals, sea lions, cetaceans, otters, foxes, bobcats, mountain lions, skunks, and minks), most probably due to the high prevalence of the virus in multiple wild bird species.[15,25] This high prevalence in animals could result in a higher risk for humans.[26] Since March, 2024, a change in epidemiology has been the emergence of the highly pathogenic avian influenza virus H5N1 clade 2.3.4.4b viruses in non-carnivorous mammals, with infections identified in clinically ill goats, dairy cows, and unpasteurised (ie, raw) milk samples in multiple states in the USA[8,9] and, as of July 30, 2024, there have been 13 human cases, of which four have been linked to dairy farms in three states in the USA, with repeated spillback infections from cattle to other domestic animals (eg, cats and poultry) and wild bird and mammal species.[9,15,21,22]

One Health approaches have been applied to the prevention and control of highly pathogenic avian influenza since these viruses were first documented as a cause of severe zoonotic disease in humans.[27] The inclusion of One Health concepts has also been promoted since the New Delhi intergovernmental meeting on avian influenza in 2007.[28] For instance, circulation of H5Nx highly pathogenic avian influenza viruses in the poultry production system in Asia has been suppressed through vaccination programmes, although its effectiveness has been affected by the emergence of escape variants and the capacity to use vaccines sufficiently in or, ideally, before outbreaks.[29] However, the current panzootic is being driven by virus circulation among wild birds, for which vaccination is not an option (unless for the targeted protection of specific endangered species).[30] Therefore, this novel scenario challenges our ability to control highly pathogenic avian influenza.[31]

Background on influenza

Influenza A viruses are common pathogens known to infect humans and a wide range of animal species. They are characterised and named after the subtypes of two surface proteins on the virus particle, haemagglutinin (H) and neuraminidase (N). Current seasonal human influenza viruses have H1N1 or H3N2 surface protein subtypes. These surface proteins are key determinants for pathogenicity, host range, and transmissibility, and in combination with additional viral and host factors, determine the likelihood and impact of infections in humans. 16 H subtypes (H1–H16) and nine N subtypes (N1–N9) have been identified in wild birds, the natural reservoir of influenza A viruses. There is also evidence for influenza A virus infection in bats, adding two H subtypes and two N subtypes (H17N10 and H18N11) to the diversity of the influenza A virus.[32]

Epidemics, epizootics, and pandemics

For decades, pandemic preparedness planning has focused on the potential for influenza pandemics following zoonotic spillover of avian influenza viruses, swine influenza viruses, and reassortants of both into the human population. Influenza viruses are, arguably, the best known pandemic threats. Influenza pandemics have occurred regularly throughout human history, with the last example being the H1N1 pandemic (known as the swine flu pandemic) in 2009, which resulted from viruses that evolved through complex reassortment steps, mixing genes from human, avian, and swine influenza viruses. Other pandemics have resulted either from direct spillovers of avian influenza viruses or following the reassortment of avian and swine or human influenza viral genes.[33,34] In the past 100 years, there have been five well documented influenza pandemics, with greatly differing severity. Avian influenza viruses of subtypes H5 and H7 that circulate naturally in the form of low pathogenic avian influenza in wild birds can acquire mutations that introduce a modified activating proteolytic cleavage site (the notorious furin cleavage site) in the H protein resulting in systemic rather than localised infection and disease with a high mortality in poultry (highly pathogenic avian influenza). H5 and H7 highly pathogenic avian influenza outbreaks have devastated poultry farms, often causing major economic losses and negatively affecting human livelihoods and wellbeing. Sporadic zoonotic infections have occurred throughout the history of H5Nx highly pathogenic avian influenza infections, with low but varying risks to humans depending on the combination of genes and mutations present in specific variants. Although some of the factors that determine higher risk for humans are known, predicting which viruses could trigger more widespread human disease outbreaks remains difficult, and the ongoing process of viral evolution by genomic reassortment requires regular updates to risk assessment. Therefore, continuous surveillance in the One Health setting is crucial.

The H5N1 highly pathogenic avian influenza virus originated in a commercial goose farm in China in 1996 and probably increased in pathogenicity within commercially farmed poultry in Asia where it spilled over into wild birds. The virus then evolved, causing epidemic outbreaks with subsequent intercontinental spread and multiple poultry–wild bird host switches in Asia, Africa, and Europe, leading to the current situation.[35,36] This spread has had substantial impact on many wild species, with an unprecedented number of species affected. Infections have been confirmed mostly through detection of dead birds in over 400 bird species, including critically endangered species. Local epizootics have led to massive numbers of bird deaths, with substantial proportions of some bird populations affected, such as 10% of the global Dalmatian Pelican (*Pelecanus crispus*) breeding population and 7% of the critically endangered California Condor (*Gymnogyps californianus*) population. Many long-lived species have been affected, whose populations might face multiple threats and will take years to recover.[37]

Early identification of zoonotic influenza virus outbreaks and pandemic risk assessment

Given the risk of pandemics, spillover infections of animal influenza viruses to humans need to be tightly monitored in a One Health approach. Zoonotic influenza virus infections causing clinical illness in humans are rare but require careful evaluation with rapid characterisation of the virus and contact tracing to assess the extent of the spread in people and other animals. WHO and the US Centers for Disease Control and Prevention have developed risk assessment frameworks in which the pandemic potential of animal influenza viruses is ranked on the basis of ten risk elements[38,39] with an Influenza Risk Assessment Tool (IRAT) describing: the properties of the virus (eg, receptor binding properties, genomic characteristics, transmission in animal models, susceptibility to antiviral treatment, and antigenic relationship to vaccine candidates); the attributes of viral infection in the human population (eg, the presence of human infections, disease severity [in people and other animals], and population immunity); and the ecology and epidemiology of the virus in non-human animal hosts (eg, the geographical distribution of the virus in animals and the animal species infected).

Periodically, new candidate vaccine viruses are defined on the basis of work by the Global Influenza Surveillance and Response System network and the World Organisation for Animal Health (WOAH)–Food and Agriculture Organization of the UN (FAO) Network of Expertise on Animal Influenza (OFFLU). This work underscores the importance of a multisectoral One Health approach to inform sufficient understanding of the current and evolving scope of animal influenza viruses, but also highlights the need for continued financial and organisational support and why primary prevention[2] (by reducing the frequency of spillovers) is preferable.

Comparing the current panzootic with H5N1 highly pathogenic avian influenza poultry outbreaks in Asia since 1996

If we consider the current risk to the human population from the properties and attributes of the H5N1 highly pathogenic avian influenza virus, including considering criteria used in the IRAT framework,[40] it is not fundamentally different from the risk posed by events over the past few decades. One could argue that the H5N1 highly pathogenic avian influenza virus sublineages currently dominating globally (based on lineage 2.3.4.4b) are less worrisome than other, less widespread, sublineages associated with more frequent and more severe zoonotic infections. When looking at virus ecology and epidemiology, however, the situation is very different and the risk of zoonotic emergence has certainly increased.[10,36,41] This element of the risk assessment, however, has not been translated into action. Although we know of the global geographical and taxonomic expansions of H5N1 highly pathogenic avian influenza virus from reports of wild bird mortality incidents and related mortalities of seals, sea lions, cetaceans, otters, foxes, mink, and domestic cats (along with the occasional human case) and surveillance efforts, such as those of OFFLU and WOAH's World Animal Health Information System, there are gaps in international reporting of animal influenza viruses of pandemic potential and these need strengthening. For instance, in some countries, the first evidence of the circulation of H5 highly pathogenic avian influenza virus in wild birds could come from human disease reporting and subsequent outbreak investigations. An important missing component is the systematic collection of data from wild birds and mammals. Although this shortcoming is understandable in terms of costs and priorities for disease detection, the One Health High-Level Expert Panel strongly recommends exploring the potential of driver-based hotspot surveillance (analogous to ecological monitoring) to enhance our level of preparedness. When viewing the current surveillance systems through a One Health lens, no fully integrated system is currently in place to allow for the systematic monitoring of the evolving influenza situation in a manner that could be used to assess changes in risk.

Frameworks exist for interagency collaboration among the FAO, WOAH, and WHO Tripartite, which enable the exchange of information. These frameworks include a Tool for Influenza Pandemic Risk Assessment,[39] which is undertaken after initial assessments, and the Global Early Warning System for transboundary animal diseases, a mechanism for sharing information rapidly and conducting risk assessments on threats at the animal–environment interface.[42] These frameworks could form the basis for further development.

Weaknesses in pandemic preparedness and prevention

We note a weakness in pandemic preparedness in that public health action is typically triggered by human cases, and action on protecting animal health and the associated consequences for biodiversity is mostly focused on the early detection and control of outbreaks in poultry (which involves culling or regional poultry vaccination). However, these actions affect food security and livelihoods and can have other environmental impacts, especially in lower-income regions. These actions also do not address the fundamentally different pandemic risk to humans and wild animals in the current situation from previous highly pathogenic avian influenza virus outbreaks arising from a panzootic wildlife infectious disease. Following spillover to mammals by the H5N1 highly pathogenic avian influenza virus, mutations have been observed in these viruses associated with an increase in the risk of human infection and impacts on domestic and wild animal health.[43–45] Moreover, although definitive proof is lacking, an outbreak on a mink farm in Spain indicated possible direct mink-to-mink transmission[12] and there has been widespread transmission among dairy cattle in the USA, with health impacts for farmed mink, cattle, and other domestic species.[8,9,21,22] These events are not routinely captured by the existing surveillance systems in all countries, stressing the need for adaptiveness. The COVID-19 pandemic taught us that the world was far from optimally prepared, and that by the time viral circulation among humans had been detected, the window of opportunity for containment had closed.

For more on **highly pathogenic avian influenza in the sub-Antarctic** see https://scar.org/library-data/avian-flu

So, what is next? The fast expansions of H5N1 2.3.4.4b clade highly pathogenic avian influenza virus and the resulting spillover infections in fur-bearing and other agricultural or farmed animals and wild carnivores can be used as preparedness scenarios, asking for instance: are we able to detect emerging circulation among domestic species such as cattle, pigs, fur-bearing animals, and humans in a sufficiently timely manner to allow for early containment? We now have a better understanding of what the global fur industry looks like, but surveillance is still patchy, despite such farms being a potential pandemic threat, and control measures differ between countries, with the potential of extended circulation as was observed for SARS-CoV2.[46] How are authorities set up to monitor and control H5N1 2.3.4.4b clade highly pathogenic avian influenza virus, now that there is widespread infection of dairy cattle in multiple US states (a species not typically thought to be susceptible)?[8,9,15,47] Similarly, as we see an increasing list of spillover to mammals, what is being done to enhance surveillance in wild, feral, and domestic pigs? Initial experimental infections with H5 highly pathogenic avian influenza viruses (eg, H5N1, H5N2, and H5N8 clade 2.3.4.4 viruses) suggested that pigs are not highly susceptible to viruses of sublineage 2.3.4.4,[48–50] but the ongoing genetic changes should be a warning sign that we cannot consider this single virus and we cannot be complacent about pandemic potential.[51] The introduction of H5N1 in goats, cattle, and alpacas took influenza virus experts by surprise, reaffirming the crucial need to keep an open mind when observing large-scale changes in the spread of a virus. Highly pathogenic avian influenza viruses also have an unprecedented but difficult to quantify ecological impact. Populations of wild birds have been severely affected by viral introduction from poultry and subsequent cross-continental and trans-continental spread. The massive die-offs of wild sea birds and waterfowl on multiple continents, most recently occurring in South America and endangering Antarctica, has also affected birds of prey, and terrestrial and marine mammals.[52] Oceania is the only region with no infections recorded so far, probably due to its isolation and the species of birds that use migratory flyways in the region, although a series of H7 highly pathogenic avian influenza viruses have caused outbreaks in poultry farms in Australia since May, 2024, showing that the region is still susceptible. However, the absence of systematic tracking of the wildlife and broader ecological impacts of this major panzootic event underscores a massive global gap in surveillance for early spillover events and equity for the wildlife health sector. There are major gaps in our understanding of the impact of this panzootic on wildlife and the environment both on short-term and long-time scales.

For more on the **detection of H7 highly pathogenic avian influenza virus in Australia** see https://www.outbreak.gov.au/current-outbreaks/avian-influenza

Suggestions moving forward

Improving efforts to prevent transmission between and among wild and domestic animal species is one of the best ways to avoid animal-to-human transmission.[2] Although very challenging, this preventive approach, including a focus on strong farm biosecurity, is essential in complementing the current focus on early detection and response in poultry, cattle, and the human population,[30,53,54] all with the necessary health and safety measures (including biosafety) when appropriate. We suggest using this ongoing panzootic to further assess where H5N1 highly pathogenic avian influenza virus surveillance and avian influenza virus surveillance more generally can be improved at all levels (international, regional, national, and local) with a One Health approach.[55,56] This assessment might address the other possible blind spot—the focus on specific viruses and clades that have historically been an issue for animal rather than human health or vice versa. This work will include exploring the potential expansion of existing systems to driver-based surveillance to identify hotspots for increased spillover risk, including the role of large-scale farming of susceptible mammals and multispecies animal holdings both of wild birds and of pets.[25,37] Given the general barriers to the implementation of enhanced surveillance, which will be even more complex when expanding to One Health driver-based surveillance, innovative approaches are needed, including environmental sampling (eg, water, dust, food sources, and slaughterhouse waste) and data collection involving citizen scientists.[53] These initiatives could perhaps be promoted through efforts such as World Flu Day (on Nov 1),[57] to raise awareness among all sectors of society. Information collected should be easily accessible internationally, follow good data governance principles, and be in compliance with the relevant legal terms and agreements. This information would include an agreed set of metadata following standards that have been developed in the field of big data analytics (for driver data) and for current surveillance.

Important barriers for data sharing include concerns about data privacy and security, intellectual property and data misuse, poor incentives, poor data quality standards, technical and capacity resource challenges, and concerns about priority and competition for publication. Other barriers could include mistrust, poor access to cases or human or other animal populations for viral surveillance or serosurveillance, and fear of repercussions (including the pre-emptive culling of wildlife, trade impacts, loss of income, and stigmatisation). Public sector engagement by government authorities, including partnerships with industry, small farmers, and communities, are therefore essential for influenza control in poultry and other farmed species. Such partnerships can effectively mobilise resources and awareness, leveraging the crucial role of the private sector in addressing outbreaks that impact the poultry industry, which is a major source of employment in many low-income and middle-income countries. To promote global preparedness, we also suggest careful evaluation of current incidents (eg, H5 highly pathogenic avian influenza infections in different mammals) with regards to the timeliness of their detection and the completeness of the follow-up for scenario exercises.

If these measures are to be implemented successfully, considering stakeholder buy-in, a legal basis, appropriate funding,[58] and a careful translation to possible actions[59–63] will be important. Recommendations include more immediate measures, such as improved communication regarding risk (eg, including feed sources such as a raw meat diet for domestic and farmed wild animals, and roaming cats), farm biosecurity, risk-based surveillance, and early warning systems involving poultry and potential bridging hosts (eg, mink, pigs, domestic cats, and now cattle),[55] with more medium-term approaches, such as reducing farm sizes and stocking densities, strengthening biosecurity, carefully regulating, managing, and monitoring high-risk production systems in high-risk areas (such as the legal trade in and the farming of wildlife), reducing illegal trade in domestic and wild birds and other animals,[2,64,65] and implementing vaccination programmes on farms and possibly for some wild species, coupled with avian influenza vaccine stewardship.[59] Longer-term solutions will probably require understanding and reducing the broad, upstream drivers that foster conditions conducive to such outbreaks, such as the demand for poultry products, while considering the need for high-quality and safe food, produced in environmentally sustainable and ethical ways.[1,64–68] Measures might require appropriate compensatory mechanisms. Many of the approaches will require local community-level work (eg, working with small producers, such as local duck farmers for whom highly pathogenic avian influenza might not be seen as a threat, to help mitigate risk).[69,70] These measures might need to parallel actions that directly mitigate human health risk and will help change behaviour and social norms and reduce barriers to be more effective and sustainable.

Measures that reduce short-term, medium-term, and long-term risks to wildlife species are also required. Reducing pressure on wildlife includes addressing direct and indirect drivers of biodiversity loss, all of which are linked to changes required for infectious disease control. Direct drivers include land and sea use change, direct exploitation, pollution, invasive species, and climate change, and indirect drivers, which include demographic and sociocultural changes related to values and behaviours and encompass economic, technical, institutional, and governance changes.[71] Immediate opportunities to explore include the placement of future poultry operations away from wetland ecosystems and enhanced biosecurity to avoid mixing of poultry and wild birds.[37] Given the human, domestic, and wild animal health issues and environmental impacts of avian influenza, all One Health sectors need to advocate for further funding and improved responses, including a focus on prevention.

Implications for pandemic instruments under development

WHO member states established an Intergovernmental Negotiating Body in December, 2021, to “draft and negotiate a WHO convention, agreement, or other international instruments on pandemic prevention, preparedness and response”.[72] The Intergovernmental Negotiating Body’s work is underway and expected to finish by May, 2025. The One Health Joint Plan of Action,[73] a framework to guide the implementation of a prevention-focused One Health approach to improve human, domestic and wild animal, and environmental health that was collaboratively developed by the FAO–UN Environment Programme–WHO–WOAH Quadripartite,[74] is relevant to the ongoing Intergovernmental Negotiating Body negotiations. The One Health Joint Plan of Action focuses on understanding the drivers of emerging (and re-emerging) zoonotic diseases and related processes and pathways, developing risk mitigation measures and upstream prevention, and enhancing sustainable and targeted coordinated, multisectoral surveillance with One Health principles, including equitable cross-sector responses.[1,2,55,75] The current highly pathogenic avian influenza A (H5N1) global panzootic and associated increased risk of zoonotic spillover into humans highlight the urgency of including a One Health approach to pandemic prevention, preparedness, and response within this global agreement.

Conclusion

The unprecedented change in the epidemiology and ecology of H5N1 highly pathogenic avian influenza virus is having a devastating effect on wild birds, domesticated animals, farmers and their communities, and wild mammals globally and represents a clear and growing risk of zoonotic spillover to humans. These viruses evolved in poultry farms, and now are globally dispersed in wild birds and affecting multiple mammalian species, most recently dairy cattle in the USA. With this change, a global challenge is to understand and reduce the impact of this disease risk on wildlife health, ecosystems, domestic animals, and humans now and in the years to come. The risk of this H5N1 highly pathogenic avian influenza panzootic and potential human spillover also stresses the need for integrating One Health as the basis for pandemic prevention and preparedness planning, and thus the importance of multisectoral collaborations among the animal, environmental, and public health sectors in conducting risk assessments, addressing early prevention, coordinating outbreak responses, and developing countermeasures to prevent disease emergence and control its spread. To reduce future pandemic risk, urgent action is required. This action should focus not only on current efforts to prevent zoonotic infection among people at highest risk of exposure (eg, farm workers), but also on improving efforts to prevent transmission between and among wild and domestic animal species and people, with an emphasis on the upstream drivers that foster conditions conducive to such outbreaks and on rapid response and risk assessment of every zoonotic outbreak. Sustained support and commitment from a variety of stakeholders from multiple sectors are needed to implement and maintain One Health prevention programmes, coordinated, multisectoral surveillance, and timely and efficient coordinated and rapid responses to outbreaks.

Contributors

MPGK, TCM, WM, and DTSH contributed to the conceptualisation of this Personal View. MPGK and DTSH wrote the original draft. All authors contributed to the review and editing of the final version.

Declaration of interests

All authors declare no competing interests.

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