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The Panzootic Spread of Highly Pathogenic Avian Influenza H5N1 Sublineage 2.3.4.4b: A Critical Appraisal of One Health Preparedness and Prevention --Manuscript Draft--

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Corresponding Author:	David Thomas Stuart Hayman, PhD Massey University Palmerston North, Manawatu NEW ZEALAND
First Author:	Marion P. G. Koopmans, PhD
Order of Authors:	Marion P. G. Koopmans, PhD Wiku B Adisasmito, PhD Salama Almuhairei, PhD Casey Barton Behravesh, DVM Pepe Bilivogui, MD Salome A Bukachi, PhD Natalia Casas, MSc Natalia Cediël Becerra, PhD Dominique F Charron, PhD Abhishek Chaudhary, PhD Janice R Ciacci Zanella, PhD Andrew A Cunningham, PhD Osman Dar, MD Nitish Debnath, PhD Baptiste Dungu, PhD Elmoubasher Farag, PhD George Gao, DPhil Margaret Khaitisa, PhD Catherine Machalaba, PhD John S MacKenzie, PhD Wanda Markotter, PhD Thomas C Mettenleiter, PhD Serge Morand, PhD Vyacheslav Smolenskiy, PhD Lei Zhou, MD David T. S. Hayman, PhD
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The Panzootic Spread of Highly Pathogenic Avian Influenza H5N1 Sublineage 2.3.4.4b: A Critical Appraisal of One Health Preparedness and Prevention

Authored by the members of the One Health High-Level Expert Panel (OHHLEP):

Marion P. G. Koopmans^{1*}, Casey Barton Behravesh², Andrew A. Cunningham³, Wiku B. Adisasmito⁴, Salama Almuhairei⁵, P  p   Bilivogui⁶, Salome A. Bukachi⁷, Natalia Casas⁸, Natalia Cedi  l Becerra⁹, Dominique F. Charron¹⁰, Abhishek Chaudhary¹¹, Janice R. Ciacci Zanella¹², Osman Dar¹³, Nitish Debnath¹⁴, Baptiste Dungu¹⁵, Elmoubasher Farag¹⁶, George F. Gao¹⁷, Margaret Khaitsa¹⁸, Catherine Machalaba¹⁹, John S. Mackenzie²⁰, Wanda Markotter²¹, Thomas C. Mettenleiter²², Serge Morand²³, Vyacheslav Smolenskiy²⁴, Lei Zhou²⁵, David T. S. Hayman^{26*}.

* Corresponding authors

Affiliations

¹Erasmus MC, Department of Viroscience, Rotterdam, The Netherlands

²Centers for Disease Control and Prevention, Atlanta, GA, USA.

³Institute of Zoology, Zoological Society of London, London, UK.

⁴Universitas Indonesia, Depok, West Java, Indonesia.

⁵National Emergency Crisis and Disasters Management Authority, Abu Dhabi, United Arab Emirates.

⁶World Health Organization, Guinea Country Of, Conakry, Guinea.

⁷Institute of Anthropology, Gender and African Studies, University of Nairobi, Nairobi, Kenya.

⁸National Ministry of Health, Autonomous City of Buenos Aires, Argentina.

⁹School of Agricultural Sciences, Universidad de la Salle, Bogot  , Colombia.

¹⁰Visiting scholar, One Health Institute, University of Guelph, Guelph, ON, Canada.

¹¹Indian Institute of Technology (IIT) Kanpur, Kanpur, India.

¹²Brazilian Agricultural Research Corporation, Embrapa Swine and Poultry, Conc  rdia, Santa Catarina, Brazil.

¹³Global Operations Division, United Kingdom Health Security Agency, London, UK.

¹⁴DAI Global, Dhaka, Bangladesh.

¹⁵Faculty of Veterinary Science, University of Kinshasa, Kinshasa, Democratic Republic of Congo.

¹⁶Ministry of Public Health, Health Protection & Communicable Diseases Division, Doha, Qatar.

¹⁷The D. H. Chen School of Universal Health, Zhejiang University, Hangzhou, People's Republic of China.

¹⁸Mississippi State University, Starkville, MS, USA.

¹⁹EcoHealth Alliance, New York, NY, USA.

²⁰Faculty of Health Sciences, Curtin University, Perth, Australia.

²¹Center for Viral Zoonoses, Department of Medical Virology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa.

²²Friedrich-Loefer-Institut, Bundesforschungsinstitut F  r Tiergesundheit, Federal Research Institute for Animal Health, S  dufer 10, Greifswald 17493, Insel Riems, Germany.

²³HealthDEEP, CNRS, Montpellier, France.

²⁴Federal Service for Surveillance on Consumer Rights Protection and Human Well-being (Rospotrebnadzor), Moscow, Russian Federation.

²⁵Chinese Center for Disease Control and Prevention, Beijing, People's Republic of China.

²⁶Molecular Epidemiology and Public Health Laboratory, Hopkirk Research Institute, Massey University, Palmerston North, New Zealand

ABSTRACT

The changes in H5N1 Highly Pathogenic Avian Influenza's (HPAI) epidemiology and ecology are devastating wild birds, poultry, farms and communities, and wild mammals worldwide. Originating in farmed poultry, these viruses are now globally spread by wild birds with transmission to many mammal and avian species, most recently leading to transmission among dairy cattle with associated human cases. These ecological changes pose challenges to mitigate the impacts on wildlife, ecosystems, domestic animals, food security, and humans. H5N1 HPAI highlights the need for One Health approaches for pandemic prevention and preparedness, emphasizing multisectoral collaborations among animal, environmental, and public health sectors. Action is needed to reduce future pandemic risks by preventing transmission among domestic and wild animals and people, focusing on upstream drivers of outbreaks, and ensuring rapid response and risk assessment for zoonotic outbreaks. Political commitment and sustainable funding are crucial to implementing and maintaining prevention programs, surveillance, and outbreak responses.

INTRODUCTION

With the world gradually recovering from the COVID-19 pandemic, it is important to prepare and plan to prevent future infectious disease outbreaks. There has been a huge body of work on the early detection and response to emerging disease outbreaks following the spillover of animal viruses to humans, but far 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. It requires a focus on understanding underlying principles of disease emergence, and the prevention of spillovers through a One Health approach across human, animal, and environmental health sectors¹. Therefore, in addition to the public health concerns that are currently already widely addressed, One Health requires a focus on biodiversity conservation and environmental impacts, wildlife health, livestock production and consumption (including impacts of food safety and security), and both wild and domestic animal health and welfare. The recent unprecedented emergence and spread of highly pathogenic avian influenza (HPAI) illustrates this need.

The current global shift in the ecology of H5N1 HPAI virus (HPAIV) is an important case study for the critical need for strengthening the One Health concept into pandemic prevention, preparedness, and response and to move away from anthropocentric thinking towards a more holistic approach to emerging diseases². H5N1 HPAIVs have caused zoonotic infections in humans in close contact with infected poultry, mostly in Asia and Africa, with occasional cases in Europe and recently in the Americas^{3,4}. Since the emergence of a new lineage of H5N1 HPAI in 1996, these viruses have evolved into multiple clades and genotypes through genetic mutations and antigenic drift, as well as a complex pattern of reassortments of gene segments (antigenic shift) during continued circulation in poultry farms with insufficient biosecurity and recycling of spillovers and spillbacks between poultry and wild bird populations⁵. While the East and Southeast Asia regions have been a source of H5 HPAIVs into poultry farms in other regions⁶, either directly through the movement of poultry or indirectly via carriage in wild birds, the global expansion that occurred in the past three years is unprecedented. H5 HPAIVs have spread globally in wild birds to previously

uninfected geographic areas⁷, infecting an increasing number of wildlife species, including aquatic and terrestrial wild mammals, as well as pets (dogs and cats) and animals in production settings like farmed mink and dairy cattle⁸⁻¹⁴. A suspected foodborne incident led to the infection of multiple domestic cats across Poland, including deaths, where cats had neurological and/or respiratory signs^{15,16}, which highlights the risk for other possible routes of exposure among felids, previously reported in captive wild tigers and lions^{17,18}, because some cats (5 of 25) had no access to the outdoors. A similar event was recorded from South Korea¹⁹ and similar clinical findings were seen in the USA following likely cattle to cat transmission, with cat viruses clustering together on analyses suggestive of cat-to-cat transmission^{20,21}. While the risk for infection of humans is still considered low, and there have been only few reported human infections with the current globally spreading H5 HPAIV clade from 2022^{4,22,23}, it is clear that these viruses have infected a wide range of mammalian species efficiently (e.g. seals, sea lions, cetaceans, otters, foxes, bobcats, mountain lions, skunks and mink), most likely attributable to the very high prevalence of the virus in multiple wild bird species^{18,24}. This high prevalence in animals could result in a higher risk for humans²⁵. Most recently, HPAIV H5N1 clade 2.3.4.4b viruses were identified in clinically ill goats, dairy cows and unpasteurized (raw) milk samples in multiple U.S. states^{8,9} and one dairy farm worker in Texas³ and two in Michigan as of 31 May 2024 (<https://www.cdc.gov/flu/avianflu/avian-flu-summary.htm>), with repeated spillback infections from cattle to other domestic animals (e.g., cats, poultry), and wild bird and mammal species^{9,20,21}.

One Health approaches have been applied to prevention and control of HPAIV since these viruses were first documented as a cause of severe zoonotic disease in humans²⁶. The inclusion of One Health concepts has also been promoted since the New Delhi intergovernmental meeting on avian influenza²⁷. For instance, circulation of H5 HPAIVs in the poultry production system in Asia has been suppressed through vaccination programs, although its effectiveness is impacted by the emergence of escape variants and the capacity to use vaccines sufficiently in or, ideally, before outbreaks²⁸. However, the current panzootic is driven by circulation among wild birds, for which vaccination is not an option, except for targeted protection of specific endangered species²⁹. Therefore, this novel scenario challenges our current ability to control HPAI³⁰.

BACKGROUND ON INFLUENZA

Influenza A viruses (IAV) are common pathogens known to infect humans and a wide range of animal species. They are characterized and named after the subtypes of two surface proteins on the virus particle, the hemagglutinin (H) and the 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. Wild birds are the natural reservoir of IAV specifying 16 H and 9 N subtypes. In addition, there is evidence for influenza A virus infection in bats, adding 2 H subtypes and 2 N subtypes (H17N10 and H18N11) to the diversity of IAV³¹.

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 thereof into the human population. Influenza viruses are – arguably – the best-known pandemic threats. Influenza pandemics have occurred regularly in human history, with the last example being the H1N1 ‘swine flu’ pandemic in 2009, resulting 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 reassortment of avian- and swine- or human influenza virus genes^{32,33}. In the last 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 low pathogenic avian influenza (LPAI) forms 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 localized infection and disease with high mortality in poultry (HPAI). H5 and H7 HPAI influenza outbreaks have devastated poultry farms, often causing major economic loss and negatively impacting human livelihoods and well-being. Sporadic zoonotic infections have occurred throughout the history of H5 HPAI infections, with low but varying risks to humans depending on the combination of genes and mutations present in specific virus variants. While some of the factors that determine higher risk for humans are known, it remains difficult to predict which viruses could trigger more widespread human disease outbreaks, and the ongoing process of viral evolution by genomic reassortment requires regular updates of risk assessment. Therefore, continuous surveillance in One Health setting is crucial.

The H5N1 HPAI virus originated in a commercial goose farm in China in 1996 and likely increased its pathogenicity within commercially farmed poultry in Asia where it spilled over into wild birds. The virus then evolved over the years causing epidemic outbreaks with subsequent intercontinental spread with multiple poultry-wild bird host switches in Asia, Africa, and Europe, leading to the current situation^{34,35}. This spread has had a significant impact on many wild species, with unprecedented numbers of species impacted. Infections have been confirmed mostly through detections of dead birds in over 400 bird species, including critically endangered species. Local epizootics have led to massive numbers of bird deaths, with significant proportions of some bird populations, such as 10% of the global Dalmatian Pelican (*Pelecanus crispus*) breeding population and 7% of the critically endangered California Condors (*Gymnogyps californianus*). Many long-lived species have been impacted, whose populations may face multiple threats and will take years to recover³⁶.

EARLY IDENTIFICATION OF ZONOTIC 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 characterization of the virus and contact tracing to assess the extent of spread in people and other animals. The World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) have developed risk assessment frameworks in which the pandemic potential of animal influenza viruses is ranked based on ten risk elements^{37,38}, using an Influenza Risk Assessment Tool (IRAT) describing:

- properties of the virus (receptor binding properties, genomic characteristics, transmission in animal models, susceptibility to antiviral treatment),
- attributes of viral infection in the human population (human infections, disease severity, population immunity), and
- virus ecology and epidemiology in non-human animal hosts (geographic distribution in animals, animal species infected).

Periodically, new candidate vaccine viruses are defined based on the work of the Global Influenza Surveillance and Response System (GISRS) network and the World Organization

for Animal Health (WOAH)/Food and Agriculture Organization of the United Nations (FAO) Network of Expertise on Animal Influenza (OFFLU). This 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 organizational support and why primary prevention² (discussed below) is preferable, by reducing the frequency of spillovers.

COMPARING THE CURRENT SITUATION WITH H5N1 HPAI POULTRY OUTBREAKS IN ASIA OVER TIME SINCE 1996

If we consider the risk for humans from the properties and attributes of H5N1 HPAIV in the current situation, including considering criteria used in the IRAT framework³⁹, the risk to the human population is not fundamentally different from events over the past decades, and one could argue that the current H5N1 HPAIV sublineages 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^{10,35,40}. This element of the risk assessment, however, has not been translated into action: while we know of the global geographic and taxonomic expansions of H5N1 HPAIV 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 efforts such as OFFLU and WOAH's World Animal Health Information System (WAHIS), 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 HPAIV in wild birds may come from human disease reporting and subsequent outbreak investigations. However, currently, an important missing component is the systematic collection of data from wild birds and mammals. While this is understandable in terms of costs and priorities for disease detection, OHHLEP strongly recommends exploring the potential of driver-based hot spot surveillance (analogous to ecological monitoring) to enhance the level of preparedness. Currently, when viewing this with a One Health lens, no fully integrated system in place allows the systematic monitoring of the evolving situation in a manner that could be used to assess changes in risk.

Frameworks exist for inter-agency collaboration between the FAO, WOAH, and WHO Tripartite, that allow the exchange of information. These include a Tool for Influenza Pandemic Risk Assessment (TIPRA)³⁸ undertaken after initial assessments, and the Global Early Warning System for transboundary animal diseases (GLEWS+) as a mechanism for sharing information rapidly and conducting risk assessments on threats at the animal environment interface⁴¹. These could form the basis for further development.

WEAKNESSES IN PANDEMIC PREPAREDNESS AND PREVENTION

With this, we note a weakness in pandemic preparedness, where public health action is typically triggered by human cases, and action on protecting animal health and associated consequences for biodiversity is mostly focused on the early detection and control of outbreaks in poultry involving culling and/or regional poultry vaccination. However, these actions impact food security and livelihoods and may have other environmental impacts, especially in lower income regions, and do not address the fundamentally different pandemic risk to humans and among wild animals in the current situation from previous HPAIV outbreaks arising from a panzootic wildlife infectious disease. Following spillover to mammals by H5N1 HPAIV, mutations are observed in these viruses associated with an increase in the risk of human infection as well as impacts on domestic and wild animal health⁴²⁻⁴⁴. Moreover,

although definitive proof is lacking, a recent outbreak on a mink farm in Spain indicated possible direct mink-to-mink transmission¹² and most recently there has been widespread transmission among dairy cattle in the USA with health impacts for farmed mink, cattle, and other domestic species^{8,9,20,21}. 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 the circulation among humans had been detected, the window of opportunity for containment had closed.

So, what is next? The fast expansions of H5 HPAIV and the resulting spillover infections in fur and 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 animals and humans in a sufficiently timely manner to allow for early containment? We now have a better understanding of what the global fur animal 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 prolonged circulation as was observed for SARS-CoV2⁴⁵. How are authorities set up to monitor and control H5 HPAIV, now that there is widespread dairy cattle infection in multiple USA states, a species previously not typically thought susceptible?^{8,9,46} Similarly, as we see an increasing list of spillover to mammals, what is being done to enhance surveillance in feral and domestic pigs? Initial experimental infections with H5 HPAIVs (e.g., H5N1, H5N2, and H5N8 clade 2.3.4.4 viruses) suggested pigs are not highly susceptible to viruses of sublineage 2.3.4.4⁴⁷⁻⁴⁹, but the ongoing genetic changes should be a warning sign that we cannot consider this “one virus” and we cannot be complacent about pandemic potential⁵⁰. The introduction of H5N1 in goats, cattle and alpaca’s took influenza virus experts by surprise, reaffirming that it is crucial to keep an open mind when observing large scale changes in the spread of a virus. There is also an unprecedented but difficult to quantify ecological impact of this virus. Populations of wild birds have been severely affected by introduction from poultry and subsequent cross- and trans-continental spread. The massive die-offs of wild sea birds and waterfowl in multiple continents, most recently in South America and endangering Antarctica (<https://scar.org/library-data/avian-flu>), has also affected birds of prey, and terrestrial and marine mammals⁵¹. Oceania is the only region with no infections recorded so far, likely due to the region’s isolation and the species of birds using migratory flyways in this region, though an H7 HPAIV was detected in May 2024 in a poultry farm, showing the region is susceptible (<https://www.outbreak.gov.au/current-outbreaks/avian-influenza>). However, the lack of systematic tracking of wildlife and broader ecological impacts from this major event underscores a massive global gap in surveillance for early spillover events as well as for equity for the wildlife health sector. There are major gaps in our understanding of the impact of this panzootic on wildlife and the environment on short and longer time scales.

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 transmission². Although extremely challenging, this preventative approach, including strong farm biosecurity, is essential in complementing the current focus on early detection and response in poultry, cattle, and in the human population^{29,52,53}, all with the necessary health and safety measures, including biosafety, where appropriate. Based on this, we suggest using this ongoing panzootic to further assess where H5N1 HPAIV surveillance and AIV surveillance more generally can be improved at all levels (international, regional, national, and local) using a One Health approach^{54,55}. This may address the other possible blind spots – the focus on specific viruses

and clades that have historically been an issue for animal, but not human health or vice versa. This includes exploring the potential expansion of the existing systems to driver-based surveillance to identify hot spots for increased spillover risk, including the role of large-scale farming of susceptible mammals and multi species animal holdings, of wild birds, and of pets^{24,36}. Given barriers to implementation of enhanced surveillance in general, which will be even more complex when expanding to One Health driver-based surveillance, innovative approaches are needed, for instance including environmental sampling (e.g., water, dust, food sources, slaughterhouse waste) and data collection involving citizen scientists⁵², perhaps promoted through efforts such as World Flu Day (1st November)⁵⁶, to raise awareness among all sectors of society. Information collected should be easily accessible internationally following good data governance principles and in compliance with relevant legal terms and agreements. This would include an agreed set of metadata using standards that have been developed in the field of big data analytics (for driver data), and for the current surveillance.

Important barriers for sharing of data include concerns about data privacy and security, intellectual property and data misuse, lack of incentives, lack of data quality standards, technical and capacity resource challenges, as well as concerns about priority and competition for publication. Other barriers could include mistrust, access to cases or human or other animal populations for viral or serosurveillance and fear of repercussions, including preemptive culling of wildlife, trade impacts, loss of income, and stigmatization. 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, as they can effectively mobilize resources and awareness, leveraging the critical role of the private sector in addressing outbreaks that impact the poultry industry, which is a major source of employment in many low- and middle-income countries. To promote global preparedness, we also suggest careful evaluation of current incidents (H5 HPAI infection of 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, it's important to consider stakeholder buy-in, a legal basis, appropriate funding⁵⁷ and a careful translation to possible actions⁵⁸⁻⁶². Recommendations include more immediate measures such as improved communication regarding risk (e.g. including feed sources like raw meat diet for domestic and farmed wild animals, roaming cats), farm biosecurity, risk-based surveillance and early warning systems involving poultry and potential bridging hosts (e.g., mink, pigs, domestic cats and now cattle)⁵⁴ 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 the illegal trade in domestic and wild birds and other animals^{2,63,64}, and the implementation of vaccination programs on farms and possibly for some wild species, coupled with AIV vaccine stewardship⁵⁸. Longer-term solutions likely 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^{1,63-67}. Measures may require appropriate compensatory mechanisms. Many of the approaches will require local community-level work, e.g., working with small producers such as local duck farmers for whom HPAI might not be seen as a threat, to help mitigate risk^{68,69}. These measures may need to parallel actions that directly mitigate human health risk and will help change behavior and social norms and reduce barriers that together are more effective and sustainable.

Measures that reduce short-, medium-, and long-term risks to wildlife species are also required. Reducing pressure on wildlife includes addressing direct drivers such as land/sea use change, direct exploitation, pollution, invasive species, and climate change, as well as indirect drivers which include demographic and sociocultural changes related to values and behaviors, and encompass economic, technical, institutional and governance changes⁷⁰, all of which are linked to changes required for infectious disease control. Immediate opportunities to explore include the placement of future poultry operations away from wetland ecosystems and enhanced biosecurity to avoid poultry-wild bird mixing³⁶. Given the human, domestic, and wild animal health issues and environmental impacts, all One Health sectors need to advocate for further funding and improved responses, including a focus on prevention.

IMPLICATIONS FOR THE PANDEMIC INSTRUMENT UNDER DEVELOPMENT

WHO Member States established an Intergovernmental Negotiating Body (INB) to “draft and negotiate a WHO convention, agreement, or other international instruments on pandemic prevention, preparedness and response”⁷¹, whose work is underway and expected to finish by May 2025. The One Health Joint Plan of Action⁷², a framework to guide the implementation of a prevention-focused, One Health approach, collaboratively developed by the FAO-UNEP-WHO-WOAH Quadripartite⁷³, is relevant in the ongoing negotiations for this new instrument, as it focuses on understanding the drivers of (re-)emerging zoonotic diseases and related processes and pathways, developing risk mitigation measures and upstream prevention, and enhancing sustainable and targeted coordinated, multisectoral surveillance using One Health principles, including equitable cross-sector responses^{1,2,54,74}. The current HPAI 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 HPAIV exerts a devastating impact on wild birds, affected 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 farming, and now are globally dispersed in wild birds and impacting multiple mammalian species, most recently dairy cattle in the USA. With this, 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. H5N1 HPAI panzootic and human spillover risk 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, coordinated outbreak response, and developing countermeasures to prevent disease emergence and to control its spread. To reduce future pandemic risk, urgent action is required. This should focus not only on current efforts to prevent zoonotic infection among people at highest risk of exposure (like farm workers), but also on improving efforts to prevent transmission between and among wild and domestic animal species and people, with emphasis on upstream drivers that foster conditions conducive to such outbreaks as well as 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 programs, coordinated, multisectoral surveillance, and timely and efficient coordinated and rapid response to outbreaks.

DISCLAIMERS

This publication was prepared by OHHLEP members who serve in their personal capacity. The opinions expressed in this article are the author's own and do not necessarily reflect the view of the employer or affiliated institution or agency.

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AUTHOR CONTRIBUTIONS

Conceptualization: Marion Koopmans; Thomas Mettenleiter; Wanda Markotter; David Hayman; Writing - original draft: Marion Koopmans; David Hayman; Writing - review & editing: all co-authors

CONFLICTS OF INTEREST

The authors declared no conflicts of interest.

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