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THE AVIAN INFLUENZA OUTBREAK

ECOLOGICAL AND BIOLOGICAL SECURITY IMPLICATIONS

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OVERVIEW

The United States and Europe are currently experiencing the most severe outbreaks of avian influenza in their respective histories.[1] On a global scale, this outbreak of the H5N1 avian flu is unprecedented in the variety of mammals impacted, ease of spread, and number of countries impacted. Fueled by a new and especially dangerous clade of H5N1 (a form of highly-pathogenic avian influenza, known as HPAI),[2] this outbreak has been devastating to ecosystems and poultry farms, and has led to the deaths of over 58 million birds in the United States over the past year. More recently, Cambodia reported two human cases of H5N1, including the death of a young girl, who may have been exposed to several sick birds in her family home.[3] Further analysis on the virus isolated from these two human cases by the Cambodian Centers for Disease Control (CDC) revealed that it is from Clade 2.3.2.1c, which is endemic in Cambodia, and not Clade 2.3.4.4b, which is causing so many infections around the world in poultry, wild birds, and mammals.

1 Will Sullivan, "As Bird Flu Spreads to Mammals, Health Officials Urge Caution," *Smithsonian Magazine,* February 10, 2023.

2 U.S. Centers for Disease Control and Prevention, "Ask the Expert: Highly Pathogenic Avian Influenza A(H5N1) Viruses," February 24, 2023.

3 Jennifer Rigby, "Bird Flu Situation 'Worrying'; WHO Working with Cambodia," *Reuters,* February 24, 2023.

While most recent coverage of H5N1 is focused on concerning trends over the past few months, the concerning clade (2.3.4.4b) first began circulating in Africa, Asia, and Europe in 2020, and has gradually snowballed into a major biological and ecological threat.[4] H5N1 has the capacity to infect and easily spread through a wide range of avian species, including domestic and wild birds (including migratory species). This makes the outbreak exceptionally difficult to control—any wild bird that comes into contact with an affected poultry farm has the potential to spread H5N1 widely. For example, researchers suspect that H5N1 was first introduced to North America in winter 2021 by a gull migrating from Europe to Canada.[5]

While H5N1 is generally only transmissible in birds, mammals (including humans) may become infected upon direct exposure to an infected bird. However, infected mammals typically cannot transmit or maintain sustained spread of the disease to other mammals. While human infections are rare, they are deadly—the mortality rate is about 56%.[6] The lack of sustained human-to-human transmission has reduced the general threat to humans, but often translates to inadequate risk awareness given the ease at which influenza viruses mutate and evolve.

A concerning shift in the global burden of avian influenza came in October 2022, when an outbreak of H5N1 occurred on a mink farm in Spain.[7] Scientists believe that the circulating variant was being transmitted between mink, an alarming observation that highlights the capability of H5N1 to adapt to mammalian hosts. While all of the 50,000 mink on the affected farm were culled and no workers were infected, the borders of the farm were porous, meaning that contact between mink and free-roaming mammals like cats and dogs may have occurred.[8]

Sequencing of samples from infected mink shows evidence of genetic changes known to enhance the capability of influenza to reproduce in mammals. These same mutations have also been observed in samples from other mammals infected with H5N1 over the past several months.

As of this writing, the Animal and Plant Health Inspection Service in the U.S. Department of Agriculture (USDA) has reported 144 cases of H5N1 in mammals across 22 states, and this is almost certainly an underestimate.[9] Infected mammals include foxes, raccoons, and opossums. H5N1 is causing major issues outside the United States as well—across Peru's Pacific coastline, nearly 3,500 sea lions have died of H5N1 since November 2022, along with at least 63,000 seabirds.[10] Scientists are concerned that the virus may be spreading in the sea lion population, meaning that this may be another instance of mammal-mammal transmission.[11]

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4 World Health Organization, "Assessment of Risk Associated With Recent Influenza A(H5N1) Clade 2.3.4.4b viruses," December 21, 2022.

5 Jim Robbins, "A Gull Flaps Its Wings and a Deadly Virus Explodes," *The New York Times,* June 17, 2022.

6 World Health Organization, "Avian Influenza Weekly Update Number 884," February 24, 2023.

7 Montserrat Agüero, "Highly Pathogenic Avian Influenza A(H5N1) Virus Infection in Farmed Minks, Spain, October 2022," *Eurosurveillance* 28 (January 2023).

8 Emily Anthes, "What a Bird Flu Outbreak Among Mink Could Mean for Humans," *The New York Times,* February 8, 2023.

9 Animal and Plant Health Inspection Agency, "2022-2023 Detections of Highly Pathogenic Avian Influenza in Mammals," *U.S. Department of Agriculture,* February 27, 2023.

10 Carlos Robles, "Nearly 3,500 Sea Lions in Peru Die of H5N1 Bird Flu," *BNO News,* March 2, 2023.

11 Madeleine Cuff, "Researchers 'Cannot Rule Out' Bird Flu Spreading Between Sea Lions," *NewScientist,* February 14, 2023.

As H5N1 infects more mammals, the risk to humans grows. More infections increase the risk for H5N1 to adapt to mammalian hosts, and creates more chances for a virus to hit the suite of mutations required to become transmissible among mammals—potentially including humans. Mammals being co-infected with H5N1 and another strain of influenza increases this risk, as viral recombination may occur—meaning a daughter virus could potentially have the pathogenicity of H5N1 along with the ability to transmit among mammals. Moreover, infections in mammals and a growing outbreak increase the risk for a spillover event during farming, veterinary care, hunting, and a number of other interactions between species.

Regardless of whether H5N1 evolves to be transmissible among humans, it's crucial to consider the immense ecological toll it has already taken. North American birds are already facing staggering population decline[12]—and some experts are concerned that the H5N1 outbreak could be a death knell for some avian species. Population decline in birds will have myriad downstream effects—fewer birds may mean reduced seed dispersal, declining populations of animals that prey on birds, and rapid growth in the insects, rodents, and fish that birds prey on.[13] These impacts will also have knock-on effects as ecological phenomena are complex and interdependent, so a mass die-off of birds may have long-lasting and unforeseeable consequences. Furthermore, the surveillance and control efforts required to address this outbreak will place new strain on the already limited resources of public health and ecological services.

VACCINES—AN OPPORTUNITY FOR IMPROVEMENT

H5N1 was first detected in 1996. Since then, there have been several serious outbreaks, and the virus has had a major detrimental impact on the poultry and egg industries. Despite the long history of H5N1, there are few tools available to address it.

While there are some H5N1 vaccines approved for potential use in poultry, it is not yet clear whether existing vaccine designs will be effective against the circulating variant. Officials within the Biden administration recently said that the USDA will be initiating the first round of H5N1 vaccine testing in poultry in years, though further details on this testing are not yet publicly available.[14]

If an effective vaccine emerges from the upcoming trials, it is unclear at what point the United States will move forward with vaccinating flocks of commercial birds. Some officials have cited concerns that vaccinating poultry may make it more difficult to export poultry and poultry products, given that vaccinations could potentially mask H5N1 infections and allow further spread—some countries have placed restrictions on importing H5N1-vaccinated birds for this reason.[15] However, other experts believe that a well-run vaccination campaign

12 Kenneth V. Rosenberg et al, "Decline of the North American Avifauna," *Science* 366, No.6461 (September 2019).

13 Katherine J. Wu, "Eagles Are Falling, Bears Are Going Blind," *The Atlantic,* February 15, 2023.

14 Alexander Tin, "U.S. to Test Shots Against Bird Flu Outbreak, as Biden Administration Weighs Poultry Vaccinations," *CBS News,* February 9, 2023.

15 Sybille De La Hamaide, "Bird Flu Alarm Drives World Towards Once-Shunned Vaccines," *Reuters,* February 17, 2023.

poses minimal risks.[16] U.S. poultry are routinely vaccinated for other diseases, such as infectious bronchitis and fowlpox. China, which does not have a major poultry export market, has been vaccinating farmed birds against H5N1 for nearly 20 years, and has significantly reduced outbreaks.[17] In response to the recent outbreak, Mexico and Ecuador have launched vaccination campaigns, and the European Union is on track to do so as well. A vaccine for poultry would be a gamechanger in reducing the burden and risk of avian influenza, and ultimately should be prioritized.

There are several H5N1 vaccines approved for use in humans, though again it is unclear whether they will be effective against the circulating variant.[18] While the World Health Organization (WHO) has emphasized that the risk to humans is low at this time,[19] it is important to consider capacity for scaling up vaccine production should the situation take a turn for the worse. A recent study of an mRNA vaccine against all known influenza subtypes showed promising results in mice and ferrets.[20] Prioritizing vaccines that are effective against entire viral families or subfamilies is a smart direction—this way, it will not be necessary to reinvent the wheel for new variants.

THE NEED FOR SAFE FARMING PRACTICES & ENHANCED SURVEILLANCE

The H5N1 outbreak highlights the critical need to adjust commercialized agricultural practices to be safer, more secure, and better surveilled. Avian influenza is not a novel disease and the risks have been well documented for years, but progress in preparedness and response is lagging and lacks a sense of urgency. Combatting H5N1 will require numerous complementary efforts that address early identification and surveillance, as well as response through testing and mass vaccination efforts.

While there has been a great deal of media attention to activities that increase risk for spillover undertaken in the Global South (e.g., wet markets), less attention has been paid to the unsafe practices occurring in the Global North. It is essential that in pandemic prevention efforts, the Global North addresses its own shortcomings rather than placing the blame solely on others.

First and foremost, **mink farms**, like the one in Spain which experienced an H5N1 outbreak in 2022, pose an immense risk with regard to infectious disease spread.[21] These farms tend to be extremely dense, with mink caged in close proximity to each other, facilitating disease spread. Mink farms also generally do not have

16 Sheryl Gay Stolberg and Emily Anthes, "U.S. Considers Vaccinating Chickens as Bird Flu Kills Millions of Them," *New York Times,* March 6, 2023.

17 Ibid.

18 U.S. Food and Drug Administration, "Vaccines Licensed for Use in the United States."

19 Jennifer Rigby and Gabrielle Tétrault-Farber, "Risk to Humans from H5N1 Bird Flu Remains Low But We Must Prepare - WHO," *Reuters,* February 8, 2023.

20 Claudia Arevalo et al, "A Multivalent Nucleoside-modified mRNA Vaccine Against All Known Influenza Virus Subtypes," *Science* 378, No. 6622 (November 2022).

21 Emily Anthes, "What a Bird Flu Outbreak Among Mink Could Mean for Humans," *New York Times,* February 8, 2023.

sufficient security—mink sometimes escape the farms, and previous studies have indicated that cats living on mink farms roam widely.[22] The porous nature of mink farms is not only a concern to human and pet health, but also poses risks to the wellbeing of surrounding ecosystems. The diet of farmed mink is also cause for concern—many farmers, including those on the farm in Spain, feed mink raw poultry, which has the potential to pass H5N1 to mink if the poultry is infected. Addressing these issues will be an essential step for improving the safety of mink farms.

Some experts even believe it is necessary to entirely ban mink farms, citing both infectious disease risks and animal cruelty concerns. Several nations have already banned or begun phasing out mink farms, including Italy, Ireland, and France.[23] In 2022, the U.S. House of Representatives passed a bill including a ban on mink farming, but this provision has been struck from the Senate version of the bill, indicating that a mink farming ban in the U.S. is unlikely to take place any time soon.[24]

Overly dense **pig farms** also pose a risk. Pigs can be infected by avian, swine, and human influenza strains, creating potential for a new recombined strain to emerge and infect workers. Overcrowding on pig farms allows infectious disease to spread more easily and can also lead to a stress-induced suppression of pigs' immune systems, making outbreaks more devastating on the pigs and potentially increasing viral shedding, thus increasing risks to workers.[25] Reducing the density of pigs on industrial farms is essential, as is investing in stronger sanitation practices and personal protective equipment (PPE) for workers.

Poultry farms, which have been forced to contend with major economic losses due to the outbreak, have the potential to operate in a much more secure manner. Improving standards of safety—including more frequent disinfection of vehicles, reducing contact with wild bird populations, reducing the density of poultry, and enhancing the use of PPE among workers are necessary measures. Some U.S. poultry producers have begun amping up biosecurity on farms, which is a promising sign.[26] However, security measures must be in place at all times, not just during crises. While investing in better practices will come with a price tag, it will likely only be a fraction of the financial cost incurred by culls and massive poultry die-offs. Poultry farms have been a source of growing concern as they represent a vulnerability for avian influenza and antimicrobial resistance, underscoring the relationship between human, animal, and environmental health.

22 Brian R. Amman et al, "GPS Tracking of Free-Roaming Cats (Felis catus) on SARS-CoV-2-Infected Mink Farms in Utah," *Viruses* 14 No. 10 (September 2022).

23 See: Human Society International, "In an Historic Vote, Italy to Ban Fur Farming and Shut Down All Mink Farms Within Six Months," December 21, 2021; Fur Free Alliance, "Republic of Ireland Bans Fur Farming," March 30, 2022; Nicole Pallotta, "France to End Mink Farming, Use of Wild Animals in Traveling Circuses, and Captivity of Orcas and Dolphins in Marine Parks," Animal Legal Defense Fund, December 28, 2020.

24 U.S. Congress, House, United States Innovation and Competition Act of 2021, H.R.4521, 117th Congress, introduced in House July 19, 2021.

25 Hamish A. Salvesen and C. Bruce A. Whitelaw, "Current and Prospective Control Strategies of Influenza A Virus in Swine," *Porcine Health Management* 7 (2021).

26 Tom Polansek, "U.S. Poultry Producers Harden Safety Measures as Bird Flu Spreads," *Reuters,* February 11, 2022.

In addition to improving agricultural safety, one of the most important tools currently available is intensive surveillance of wild bird populations. In the United States, there are several strategies that are undertaken to perform surveillance in wild birds across the country for avian influenza. The most notable is the U.S. Interagency Strategic Plan for Early Detection and Monitoring for Avian Influenzas of Significance in Wild Birds, which is facilitated by the Interagency Steering Committee for Avian Influenza Surveillance in Wild Migratory Birds, currently chaired by the U.S. Fish and Wildlife Service. This plan enhances avian influenza surveillance of wild birds across the country,[27] and is just one of many efforts that underscore the importance of routine surveillance efforts, which also include ensuring biosecurity and biosafety in managed lands and waters, as well as reporting guidance for bird mortalities. Hoye *et al*. acknowledged the logistical and financial hurdles that these surveillance efforts may face, suggesting that they should be expanded outside of existing convenience sampling and away from methods which are susceptible to sampling bias.[28] More effective and pragmatic surveillance efforts include global collection of wild bird HPAI data and pooling of expertise to develop more strategic initiatives to focus on specific aims, such as ecological and epidemiological goals or those focused on diversity and evolution.

CONTEXT & THE PATH FORWARD

A great deal of pandemic prevention work focuses on preventing spillover in specific, high-risk regions through identifying and characterizing viruses that have the potential to impact human populations. This work is important, but in order to be effective it needs to be accompanied with countermeasure development, robust surveillance programs, and focused prevention efforts.[29] H5N1 has been on our radar for decades; yet despite this knowledge we are still underprepared for the threat. Without establishing systems to respond once a viral threat has been identified, even the most robust identification and characterization efforts will not be able to effectively prevent spillover.

In addition to having been aware of H5N1 for many years, it is also well-understood that the virus has the potential to be transmitted between mammals. In 2012, a controversial study involving direct genetic modifications as well as serial passage of H5N1 through ferrets revealed that just a few mutations enabled airborne transmission of the virus among mammals.[30] However, due to concerns around biosafety and biosecurity practices, the study triggered a moratorium on similar federally-funded research, meaning that researchers

27 United States Department of Agriculture, United States Geological Society, U.S. Fish & Wildlife Service, National Wildlife Refuge System, "Early Detection and Monitoring for Avian Influenzas of Significance in Wild Birds, A U.S. Interagency Strategic Plan", June 2015.

28 Hoye et al, "Surveillance of Wild Birds for Avian Influenza Virus", *Emerg Infect Dis*., 16(12):1827–34. doi: 10.3201/eid1612.100589. (December 2010)

29 See: Natasha Bajema, Bill Beaver, and Christine Parthemore, "Toward a Global Pathogen Early Warning System: Building on the Landscape of Biosurveillance Today," Edited by Francesco Femia and Christine Pathemore, *Janne E. Nolan Center on Strategic Weapons, an institute of The Council on Strategic Risks*, July 2021; Rhys Dubin, Rassin Lababidi, John Moulton, Harshini Mukundan, Lillian Parr, Christine Parthemore, Saskia Popescu, and Daniel P. Regan. "Pathogen Early Warning: A Progress Report & Path Forward," Edited by Francesco Femia, *Janne E. Nolan Center on Strategic Weapons, an institute of The Council on Strategic Risks*, December 2022.

30 Herfst, Sander, Eefje J. A. Schrauwen, Martin Linster, Salin Chutinimitkul, Emmie de Wit, Vincent J. Munster, Erin M. Sorrell, et al. "Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets" *Science* 336, no. 6088 (June 22, 2012): 1534–41. https://doi.org/10.1126/science.1213362.

were unable to make further progress in this area until 2017, when a framework was developed to enable some potentially risky studies to be carried out, as long as appropriate safety measures are in place.[31] That framework, as well as other U.S. regulations on dual-use research, are currently being reviewed and updated to keep pace with changes in life sciences capabilities and risks.[32]

Unfortunately, the situation with H5N1 is all too familiar, and is emblematic of the issues within the U.S. biosecurity enterprise. As we have seen with previous public health threats, there is a tendency to delay action until the threat has an immediate effect on those in the United States, which is not cost-effective and does not improve the odds of effectively responding to threats which know no borders. Despite being discovered in 1976, the healthcare and public health infrastructure of the United States was left scrambling in 2014 to respond to a single imported case of Ebola virus disease identified in Dallas, Texas. It is an all-too-common trend to ignore or dismiss the biothreat potential of emerging infectious diseases that do not typically occur within the United States. The reality of ill-preparedness and delayed action can be devastating in both lives lost and economic impact. In the United States in 2014, the initial cost for healthcare response within just 45 Ebola treatment centers was roughly $53 million.[33] There are 6,093 hospitals across the United States, in which readiness for a high-consequence disease was likely not a major priority and Ebola response became deeply expensive.[34] The boom-and-bust nature of biopreparedness and biodefense has been a trend that often translates to inadequate and costly response.[35]

Lessons like those learned from the 2014-2016 Ebola outbreak and more recently, the COVID-19 pandemic, should reinforce the additive nature of biodefense and biopreparedness, and appreciation that no single initiative is enough to combat the spectrum of biological threats. In truth, this current outbreak of H5N1 serves as a brutally honest representation of U.S. biodefense. H5N1 is not a novel threat and we have the capacity to address it, but the question remains whether U.S. policymakers will be able to summon the political will needed to adequately respond.

Given the devastation the world has experienced from COVID-19, which has a significantly lower death rate than H5N1, it is difficult to imagine the scale of destruction that a H5N1 pandemic would have. While the H5N1 outbreak has already had immense ecological and economic consequences, the United States and global community still have the opportunity to prevent the outbreak from becoming an even greater threat. Taking steps now to enhance surveillance, accelerate vaccine testing and development, and improve the security of farms, will help prevent H5N1 from becoming the next pandemic. It is not too late to tackle this threat, but it is ultimately up to us to take action.

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31 Jocelyn Kaiser. "NIH Lifts 3-year Ban on Funding Risky Virus Studies", Science News, (Dec 2017).

32 See: Lillian Parr, "The Ongoing Review of Dual-use Research Policy," *Council on Strategic Risks,* August 11, 2022; Lillian Parr, "National Science Advisory Board for Biosecurity Votes to Support Stricter Regulations for Risky Research," *Council on Strategic Risks,* February 6, 2023.

33 Al, J. J. Herstein et. "Initial Costs of Ebola Treatment Centers in the United States", *Emerging Infectious Disease Journal - CDC*, 22(2), February 2016, https://doi.org/10.3201/eid2202.151431.

34 American Hospital Association, "Fast Facts on U.S. Hospitals, 2022", 2022.

35 Jenn Abelson, Dana Priest, John Sullivan and Nicole Dungca, "Boom-and-bust Federal Funding after 9/11 Undercut Hospitals' Preparedness for Pandemics," *Washington Post,* May 2, 2020.

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