High-pathogenicity avian influenza in wildlife: a changing disease dynamic that is expanding in wild birds and having an increasing impact on a growing number of mammals

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ABSTRACT
While diverse strains of low-pathogenicity avian influenza have circulated in wild birds for a long period of time, there has previously been little pathology in wild birds, ducks have been the primary and largely asymptomatic wild reservoir, and spillover into mammals has been limited and rare. In recent years, a high-pathogenicity avian influenza (HPAI) virus has emerged on the global scene and shifted the previously established dogmas for influenza infection. High-pathogenicity avian influenza has expanded into wildlife in unprecedented numbers and species diversity, with unmatched disease severity for influenza in wildlife. As the disease ecology of influenza has shifted with this new variant, significant efforts are underway to understand disease course, pathology, and species susceptibility. Here we focus primarily on the impact that HPAI has had in wild mammals while framing these novel spillovers within the context of significantly expanding disease in avian species and geography. The clinical and pathology presentations of HPAI in these atypical hosts are discussed, as well as prognosis and risk for continued spillover. The companion Currents in One Health by Runstadler and Puryear, AJVR, May 2024, provides further context on viral reservoirs and possible routes of direct or environmental transmission and risk assessment of viral variants that are emerging within wildlife.

Keywords: influenza, HPAI, spillover, wildlife, One Health

Introduction
Influenza A virus (IAV) is a zoonotic pathogen that has had an impact on animal health since at least the late 1800s when it was first described in chickens as fowl plague. There have been 4 human pandemics associated with IAV since, with a small number of subtypes that established endemic infection in humans as seasonal influenza. The virus is well documented to infect numerous bird and mammal species, including domestic and wildlife. Wild birds, primarily waterfowl, are the primary natural reservoir where diverse strains of IAV are known to circulate and reassort. Influenza A virus consists of 2 surface glycoproteins, of which there are currently 16 known hemagglutinins (H) and 9 known neuraminidases (N) that have combined into at least 134 subtype combinations that have been observed in wild birds (eg, H1N1, H3N8, etc), with a large number of variants within each subtype (Figure 1).

Low-pathogenicity Avian Influenza
Despite the high degree of variation in both virus and host, the vast majority of IAV subtypes and variants are known as low-pathogenicity avian influenza (LPAI) and are generally associated with little to no documented clinical disease in the natural host. Although there have been spillover events observed in numerous species, most are dead-end events, sporadic, in small numbers, and associated with mild disease.

As with humans, most mammalian infection of immune-competent hosts of IAV is primarily a respiratory infection and is most frequently associated with asymptomatic or mild disease. When symptoms present, they may include fever, fatigue, loss of appetite, nasal discharge, coughing, sneezing, or wheezing. When symptomatic, most LPAI mammalian infections respond well to supportive care or resolve without intervention. The majority of mammalian infections are thought to be acquired through mucosal transmission, with virus transmitted through respiratory...
aerosol or droplets, saliva, or nasal discharge. Following the initial spillover event in a handful of species, some subtypes became endemic within the spillover species and adapted to that host such that transmission to additional species, including humans, is rare. In some cases, a spillover subtype that became endemic circulated within the species for years to decades, before becoming extinct again within that species. Influenza A virus in horse, dogs, and cats reflects each of these scenarios. In 2016, a novel form of H7N2 spilled into domestic cats from wild birds and was associated with the infection of approximately 500 cats and 1 veterinarian. The outbreak spanned 3 months and was confined to New York City. In horses, the subtype H7N7 was the first to be observed, spilling over from wild birds, adapting to the horse, and circulating endemically for several decades. It has since been replaced by another wild bird–derived spillover of the subtype H3N8, which can be transmitted from horse to horse and continues to circulate within the species on a global scale. In 1999, equine IAV H3N8 spilled over into domestic dogs within the US, where it further evolved to become canine specific and is now considered endemic. A second canine influenza A H3N2 variant arose from a likely direct avian spillover in South Korea in 2004 and is considered endemic within the US since its arrival in 2015. The H3N2 within canines is distinct from the seasonal H3N2 that circulates in humans. In addition to the endemic forms of IAV within some domestic animals, both cats and dogs have infrequently acquired seasonal influenza subtypes H1N1 and H3N2 from humans. Swine are susceptible to diverse forms of influenza acquired from both human and avian sources. Variants of H1N1, H1N2, and H3N2 have established endemic infection within agricultural pigs and continue to circulate, generally with mild associated clinical disease.

Also similar to human IAV infections, some nonhuman mammalian infections can present with severe disease and in some cases be associated with regional outbreaks or mortality events. These tend to be relatively narrow in scope and duration and are generally self-limiting, with documented cases primarily occurring in marine mammals. Low-pathogenicity avian influenza has been observed in marine mammals for over 50 years and has been previously associated with 5 unusual mortality events (UMEs) dating back to the late 1970s. The most recent UME associated with LPAI occurred in the North Sea in 2014 and 2015 and was attributed to the influenza subtype H10N7. In all cases documented to date, influenza observed in marine mammals has traced back to waterfowl and seabirds. Once in marine mammals, past outbreaks, such as that associated with H10N7, have demonstrated the ability of the virus to transmit within seal species, most notably in harbor seals. In addition, longitudinal active captures for health assessments of gray seals in the Gulf of Maine have demonstrated that influenza can circulate in a marine mammal population even outside of the documented mortality events, and over a dozen subtypes of LPAI have been identified in pinnipeds and cetaceans primarily in the North Atlantic and recently in the North Pacific. The majority of the

Figure 1—Each of the 16 influenza A virus hemagglutinin (H) 1 to 16 are shown on the top of the matrix. Each of the 9 influenza A virus neuraminidases (N) 1 to 9 are shown down the left side of the matrix. Each HxNx subtype that has been identified in wild birds is shaded in light blue. Each HxNx subtype that has been identified as a spillover into a nonhuman mammal is shaded dark blue. The spillover host is shown as S (swine), D (dog), P (pinniped), or C (cetacean). A subtype that became endemic within the spillover mammalian host is marked (asterisk). HPAI = High-pathogenicity avian influenza.
LPAI infections that have been detected in marine mammals have been asymptomatic or impacted a small number of animals.

**High-pathogenicity Avian Influenza**

In contrast to the generally mild strains of LPAI, a small subset of variants are classified as high-pathogenicity avian influenza (HPAI), defined by the ability to cause high morbidity and mortality in poultry. The impact of HPAI on farmed birds can be devastating and can lead to the loss or culling of entire flocks at both backyard and commercial levels. The current outbreak of HPAI that began in late 2021 and early 2022 in North America has affected over 81 million poultry in the US alone, impacting 459 commercial and 617 backyard flocks. This HPAI variant is classified as H5N1 2.3.4.4b, but the ancestral strain initially emerged in farmed poultry in Guangdong, China, in 1996. It underwent continuous evolution through genetic drift and reassortment while circulating within Eurasia and Africa for the past 2 decades. The dissemination by migratory birds of H5N1 2.3.4.4 across the Atlantic in late 2021 marked the beginning of a rapid and dramatic increase in the scope and impact of HPAI.

While the impact of the current HPAI outbreak to farmed poultry has been devastating, the impact on wildlife has been unprecedented. This virus has infected wild birds around the globe, hitting colonially nesting seabirds and birds of prey particularly hard, with tens of thousands of bird mortalities in multiple species such as gannets, great skua, vultures, terns, pelicans, and flamingos, with mortalities extending across the Atlantic in late 2021 marked the beginning of a rapid and dramatic increase in the scope and impact of HPAI.

As the prevalence of HPAI in wildlife and the diversity of impacted species has steadily increased over the past 2 years, the availability of easily captured or scavenged prey that is HPAI infected has likely been a significant contributing factor to the widespread spillover of HPAI that has occurred. Some of the first observations of mammalian spillover were documented in red fox and were generally confined to single animals or within a den of littermates.

In June 2022, the first large-scale outbreak in wild mammals occurred in harbor and gray seals along the US coast of Maine. The outbreak in Maine was declared a UME by the National Oceanic and Atmospheric Administration and included several hundred animals. There was a concurrent outbreak of HPAI in the St. Lawrence Estuary in Quebec. Viral sequences obtained from the seals and sympatric wild bird species suggested that spillover likely occurred from multiple sources including gulls, terns, and eiders. To date, all of the spillover cases involving large numbers of wild mammals have continued to be in pinnipeds. Since the initial UME in Maine, outbreaks of HPAI have occurred in marine mammals around the globe, including both pinnipeds and cetacean species. Many of the spillover events into marine mammals have been correlated with overlapping die-offs in coastal birds within the same region. In August 2023, a breeding colony for Caspian terns in Washington state experienced a devastating loss of over 1,600 birds and HPAI spilled into and caused mortality in dozens of harbor seals that occupied the same island. Similar reports of a single to a few dozen cases have occurred in Europe, and unconfirmed suspected cases involving hundreds of animals have been reported in Russia. Many of these spillover events in the Northern hemisphere continue to be attributed to direct contact with, or preying upon, infected birds. In the past year, HPAI has extended throughout South America for the first time and has now been associated with large die-offs of hundreds to thousands of sea lions in Peru, Argentina, Uruguay, and Brazil; fur seals in Chile and Brazil; and elephant seals in Argentina. As of early 2024, large-scale mortality from HPAI infection of southern elephant seals and fur seals have also been confirmed in the sub-Antarctic. The current data continue to be inconclusive regarding mechanism of transmission in these large die-offs. The relative contribution of direct contact between an infected and naïve host versus indirect contact through environmental transmission remains unclear. Equally unclear are how factors such as temperature, pH, and humidity may impact environmental persistence in a way that impacts the magnitude and species of spillover and reservoir hosts. These are important areas of research that are under active investigation and are also discussed in the Currents in One Health article by Runstadler and Puryear, AJVR, May 2024.

According to the Food and Agricultural Organization of the United Nations, at the end of 2023, HPAI had been confirmed in 502 wild birds and 60 mammal species, primarily carnivores. Since the emergence of the current strain of HPAI in 2021, this is a 2.8-fold expansion of mammalian species and 2.2-fold expansion of wild bird species, representing a significant increase in some families and the addition of some families with no prior evidence of HPAI infection (Figure 2).

**High-pathogenicity avian influenza diagnosis and presentation**

While the species diversity and geographic range of the current HPAI outbreak has itself been unprecedented, the clinical presentation of this current HPAI has been equally unusual, particularly in mammals. Recent reports on mammals with confirmed HPAI in 2022 to 2023 in North America detailed natural infections in 67 terrestrial wild mammals and 13 marine mammals in the US and 40 wild mammals in Canada. In addition, there is a growing body of information derived from smaller outbreaks and individual case reports. Infection has occurred in both adults and juveniles, with no apparent sex bias.

**CNS involvement**—In nearly all cases of mammalian infection where HPAI has been confirmed, the animal was either found deceased or observed...
with neurologic symptoms (Table 1). The strong neurologic presentation has also been observed in wild birds such as seabirds, shorebirds, and birds of prey, though some avian species such as wild ducks show less frequent neurology. Although neurologic symptoms are infrequently observed with prior forms of influenza, the current HPAI is significantly more neuropathogenic than other IAVs. The virus is able to gain access to the CNS through the cranial nerves, with the olfactory bulb and trigeminal nerves implicated as the likely primary routes on the basis of experimental infection in both mouse and ferret models.18 The neurotropism of HPAI has been dominant even over respiratory disease. Likewise, viral antigen has most reliably been recovered from brain, even when respiratory samples or mucosal swabs fail to detect virus.17

The CNS involvement has presented in numerous ways, though most frequently includes seizures or tremors and ataxia.10,13,14,16,17,19–24 Lethargy, torticollis, impaired mobility or circling, impaired vision, and unconsciousness have also been observed.13,14,16,21,22,24,25

Figure 2—The total number of species with confirmed HPAI infection within a family is shown. Detections of HPAI through 2020 are shown in blue. New species with HPAI detections from 2021 to present are shown in orange.
This range of CNS symptoms has been documented in red fox,16,19,25–27 striped skunk,16,25 mink,21,27 raccoon,16 bobcat,16 Virginia opossum,16 coyote,16 fisher,16 gray fox,16 black bear,26 polecat,26 otter,24,26 seals,10,22 and sea lions.13,14,21,24,28

Respiratory disease—The second most frequent presentation of HPAI in wild mammals has been respiratory disease, though this has been highly variable and often not present (Table 1). Dyspnea has been frequently observed in domestic cats,16,19,25–27 sea lions,14,21,32,33 with pneumonia confirmed in each of these species. Viral RNA has been detected in lung of seals,28 and viral antigen has been detected in lung of striped skunk16 and raccoon.16

Although the majority of mammalian species with confirmed HPAI infection exhibited limited signs of respiratory infection, most species examined have had some degree of associated lung pathology observed upon necropsy.16,25–27 Red fox,26,27 polecat,26 badger26 and otter26 have generally had no respiratory symptoms in addition to no evidence of virus within the respiratory tissue. Despite this, lung lesions have been observed in many of the animals examined17 and have included severe pneumonia or hemorrhage in red fox,16,17 river otter, lynx,14 mink,25 skunk,16 raccoon,16 bobcat,16 coyote,16 gray fox,16 and fisher.16

Additional symptoms of respiratory infection such as nasal and ocular discharge and hyper salivation have only been reported in a small number of species. Copious nasal discharge has been observed in both sea lions,14,21,24,32,33 and southern elephant seals,22 while mild ocular discharge has been observed in a small number of red fox.16 Hyper salivation was also observed in sea lions,14,21,24,32,33 red fox,16,19 and a large outbreak of HPAI in farmed mink in Spain.21

Change of iris color—There is mounting evidence that at least some avian species may be undergoing a change in eye color associated with HPAI infection, a phenomenon that has previously been observed in Marek disease26 and in raptors infected with West Nile Virus.36 An iris color change from blue to mottled or completely black was first reported in gannets in Scotland in June of 2022,37 in the midst of an HPAI outbreak within the colony. Subsequently, 17 seemingly healthy gannets were captured and tested negative for active infection, though 7 of 9 with darkened irises had antibodies to H5 and only 1 of 8 with unchanged iris color had antibodies to H5.37 In mammalian infections, visual impairment has been observed in some animals,16,20 though no lesions have been identified in the eyes.16

Involvement of other body systems—In addition to the primary CNS and respiratory presentation of HPAI infection, there has been infrequent and variable histopathology observed in additional body systems. A deceased lynx with HPAI had multifocal hemorrhaging in the heart; lesions, viral RNA, or viral antigen have been observed in a small number of red fox,16 raccoon,16 bobcat,16 and coyote16; and some domestic cats with HPAI infection have suffered cardiac arrest.30

Additional infrequent lesions have been observed in the pancreas of river otter,26 spleen of red fox,17 and liver of domestic cats.17,30 red fox,16,17 skunk,16 raccoon,16 opossum,16 bobcat,16 and fisher.16 In nearly all cases, no viral RNA or viral antigen was detected.

Prognosis—The onset of morbidity and mortality appears to be rapid in nearly all cases in which HPAI infections have been observed, with the impacted animals

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Table 1—Primary clinical symptoms observed with HPAI infection of mammals.

<table>
<thead>
<tr>
<th>Species</th>
<th>Neurologic symptomsa</th>
<th>Respiratory symptomsb</th>
<th>Lung pathologyc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seizures or tremors</td>
<td>Dyspnea</td>
<td>Nasal or ocular discharge</td>
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<tr>
<td>Red fox</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Skunk</td>
<td>Yes</td>
<td>No</td>
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<td>Mink</td>
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<td>Raccoon</td>
<td>Yes</td>
<td>No</td>
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<td>Bobcat</td>
<td>Yes</td>
<td>No</td>
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<td>Opossum</td>
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<td>Coyote</td>
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<td>Fisher</td>
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<td>Gray fox</td>
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<td>Black bear</td>
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<td>Polecat</td>
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<td>Badger</td>
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<td>Seal</td>
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<td>Yes</td>
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<td>No</td>
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<tr>
<td>Elephant seal</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Cat</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

aPrimary clinical symptoms are noted as having been observed (yes) or not yet observed (no) for each species listed.
bKey lung pathology findings are noted as having been observed (yes) or not yet observed (no) for each species listed.
generally reported as being in good body condition. From the handful of studies in which tissue and swabs have both been examined, many suspect cases have tested negative on swabs, yet had detectable viral RNA or antigen in tissue, with brain tissue reliably producing the strongest signal across species.\textsuperscript{16,17}

To date, there has been limited evidence of animals that were able to recover from infection, with a handful of unconfirmed putative cases and 1 documentation of 2 red fox that were brought into care and clinically normal prior to release.\textsuperscript{18}

There is growing evidence that some species are able to recover from HPAI infection and that there may be a greater level of undetected circulation in the wild than is currently appreciated. As part of unrelated animal control responses in the Netherlands, sera were obtained from 19 fox and 126 stone martens that showed no signs of HPAI infection and were captured and euthanized.\textsuperscript{19} Thirty-seven percent of the fox and 56% of the stone martens had antibodies directed against H5 influenza, suggesting a high frequency of prior exposure within these populations that was either asymptomatic or resolved by the host.\textsuperscript{20}

High-pathogenicity avian influenza risk to animals and human populations

Risk to wild animals continues to be significant. It is critically important that wildlife professionals are aware of how significantly HPAI has recently shifted the previous dogma of influenza infection as primarily impacting ducks, and that current disease involves diverse avian and mammalian species that are susceptible to infection and, in numerous cases, undergoing significant and devastating consequences. Of particular importance is how readily HPAI appears to move through the food web and its propensity to cross species barriers, even between avian and mammalian hosts and including wild and domestic species. As possible, mitigation steps to limit forward transmission can be pursued and may be effective in limiting spillover in areas of high interaction between species or when the number of carcasses within a region is high. Dependent upon local and state guidelines, carcasses can be composted or collected and triple bagged for disposal. Targeted vaccine campaigns of wildlife may be warranted in some instances. After HPAI killed 21 of the estimated 350 remaining free-roaming California condors in 2023, an emergency use authorization was granted for H5N1 vaccination of 20 captive-bred condors.\textsuperscript{21} These birds were released in November of 2023 and will provide the basis for possible future vaccination endeavors on endangered species.\textsuperscript{22}

High-pathogenicity avian influenza has already been devastating to both commercial and backyard poultry, and there continues to be substantial risk to these populations. The current outbreak has not followed traditional seasonal trends, and infections within poultry operations have largely been continuous throughout the US, even throughout warm summer months. It is critical that biosecurity measures are maintained to protect flocks from both direct and indirect interactions with wild birds, and diligent adherence to cleaning and disinfecting protocols is crucial for those interacting with poultry. The USDA’s Defend the Flock education program provides detailed guidelines on best practices as the outbreak continues to evolve.\textsuperscript{23}

Widespread vaccination of domestic poultry is a potential mitigation that is under investigation but remains controversial and is not currently approved in the US. China has utilized poultry vaccination as part of their management strategy for many years and has demonstrated success with this approach.\textsuperscript{24} France recently began a mass-vaccination campaign focused on duck flocks throughout the country. However, broad concerns about masking asymptomatic infection coupled with the significant financial burden of a large vaccine campaign and importation restrictions on vaccinated birds between countries have been some of the limiting factors in pursuing a more widespread poultry vaccination against HPAI in additional countries.

Fur farms are at significant risk for continued spillover and large outbreaks, as has been demonstrated in farms of mink and arctic fox. An outbreak of HPAI on a mink farm in Spain in October 2022 was the first example of spillover from wild birds to mammals with strong evidence of subsequent mammal-to-mammal transmission. After initial observation of increased mortality in 1 barn within the farm of 50,000 animals, HPAI was confirmed in the mink. The virus moved through neighboring barns, causing mortality in clusters within the barns. Ultimately, the entire farm was depopulated.\textsuperscript{25} A similar scenario occurred in fur farms in Finland beginning in July 2023, spanning over 20 individual farms consisting of mink, fox, and raccoon dogs. The epidemiology of the outbreak and phylogenetic analysis of recovered viral sequences are both consistent with possible mammal-to-mammal transmission, though the initial introduction is likely wild birds, possibly in close succession at multiple locations.\textsuperscript{26}

Spillover to domestic animals, particularly dogs and cats, is a significant concern. The first confirmed case of HPAI in a domestic cat occurred in France in December 2022, when a cat that lived in close proximity to a duck farm with a confirmed HPAI outbreak presented with clinical abnormalities. The cat’s condition declined until severe neurologic and respiratory symptoms led to humane euthanasia.\textsuperscript{27} Lethal HPAI infections have since occurred in domestic cats in Poland,\textsuperscript{28} Canada,\textsuperscript{29} and the US.\textsuperscript{30} One case of a fatal HPAI infection in a domestic dog was reported in Canada in 2023 and attributed to the dog chewing on wild goose presumed to be HPAI positive.\textsuperscript{31} While most of the reports have been in limited cases and largely associated with outdoor pets with likely exposure to infected birds, the outbreak in Poland involved over 30 domestic cats across the region and included both indoor and outdoor pets.\textsuperscript{32} Given what appears to be a low species barrier for the virus to move from infected birds to domestic dogs and cats that come into close contact with infected animals, it is important for veterinarians to be aware of the possibility for
HPAI infection in domestic animals, particularly those that present with neurologic symptoms. In addition, it will be advantageous for practitioners of domestic animals to remain vigilant for outbreaks of HPAI in wildlife within their region.

There has also been at least 1 documentation of asymptomatic infection in both domestic dogs and a cat. After an outbreak of HPAI occurred in backyard chickens in Italy, the 5 dogs and 1 cat that also resided on the farm were tested for evidence of infection. Despite the absence of any clinical presentation, antibodies to H5 were detected in all 6 animals.45 This suggests that spillover to domestic animals may also be asymptomatic and possibly occurring more frequently than currently recognized.

The risk to human health is still considered to be minimal, though it is of concern and caution should be taken. For both human and nonhuman animal health, it is important to follow current recommendations for handling animals with suspected or confirmed HPAI. From 2003 to 2023, the WHO has documented 882 human infections of H5N1 worldwide, with 1 confirmed case in the US.15 These have been single spillover events and almost exclusively within those in close contact with poultry. However, at approximately 52%, the case fatality rate has been extremely high and demands careful attention. Due to the high consequence of infection and the presence of mutations that enhance viral replication within mammalian hosts, the potential spillover of HPAI into humans is closely monitored for pandemic potential. The risk to human health coupled with the crippling risk to agriculture has led to the designation of HPAI as a select agent that is carefully regulated by both the USDA and CDC.

Conclusions

After the initial incursion of Eurasian-origin H5N1 2.3.4.4 virus into North America from trans-Atlantic migratory birds,46 there have continued to be additional incursions of new lineages.25,47,48 These have occurred primarily from Europe,47 across Iceland,49 and onto the North Atlantic seaboard.25 Incursions of HPAI have also been observed from the Pacific.25 In addition to an ongoing influx of new lineages, HPAI continues to reassort and evolve.36,48 The spillover into mink in Spain was associated with an H5N1 reassortment with a gull-associated LPAI H13 variant.23 A gull-adapted reassortment termed the BB genotype has become common in Europe and is responsible for the fur farm outbreaks in Finland43 but is as yet undetected in North America. The HPAI reassortment H5N5 has recently been detected in North America, entering along the trans-Atlantic route, and associated with mortality in raccoon, red fox, and striped skunk in Canada.15

The current HPAI outbreak is unique in global expansion and in the wildlife species diversity that it is impacting and the range of wild mammals in which it is being detected. In March of 2024, infection of several dairy herds in multiple states was diagnosed, with possible transmission to a second human case in the US.50–52 Though the risk to humans remains low, this unexpected outbreak well illustrates the continued need for vigilance and further study. As the range of HPAI expands and the frequency of mammalian infections increase, the risk of zoonotic transmission continues to increase. This is why it is critical that robust surveillance occurs and appropriate biosafety caution is exercised, particularly in novel and atypical hosts, so that evidence for mammalian adaptation and mammal-to-mammal spread can be captured as early as possible. This then allows for variants to undergo pandemic risk assessment and to help inform vaccine preparedness efforts, as detailed further in the companion Currents in One Health article by Runstadler and Puryear, AJVR, May 2024.

Acknowledgments

Partnerships and discussions with wildlife professionals at the Tufts Wildlife Clinic, Cape Cod Wildlife Center, New England Wildlife Center, Wild Care Inc, Marine Mammals of Maine, and Atlantic Marine Bird Cooperative have been invaluable in our understanding of high-pathogenicity avian influenza pathology in wildlife.

Disclosures

The authors have nothing to disclose. No AI-assisted technologies were used in the generation of this manuscript.

Funding

Dr. Puryear and Dr. Runstadler are partially supported by the Centers of Excellence for Influenza Research and Response network through contract No. 75N93021C00014.

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