

Avian H5N1 Flu Deaths are Marching Forward (The Beat Goes On)

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Before the year 2015, avian H5N1 killed over 52% of poultry workers and others who had close contact with infected poultry. Fortunately, the virus was [rarely transmissible among humans](#). From 2015 to 2020 [avian H5N1 fatalities in humans had almost disappeared](#), since the strains from nature that appeared in poultry markets were no longer deadly to humans. They were, so to speak, “defanged.” We thought we were finished with H5N1 avian flu virus. We thought we were in a good place.

The June 8, 2023 Bulletin of the Atomic Scientists article [“Once ‘defanged,’ H5N1 bird flu is gaining teeth again”](#) reported a new threat to birds and mammals, a deadly and highly transmissible avian H5N1 flu virus (the new avian flu virus, NAFV). Worldwide, this virus is responsible for the death of and purposeful culling of nearly a billion poultry birds; and according to one estimate, the deaths of 10 million wild birds. Recent deaths of large numbers of birds and mammals who otherwise would be alive is alarming and sad.

The focus of the just cited Bulletin article is 2021, 2022, and early-2023. We are now in the mid to later months of 2023. This new article subtitled “The Beat Goes On” is an attempt to bring us up to date for the rapidly changing situation surrounding the NAFV.

Could birds become extinct?

[As reported in the Guardian](#) in a March 2023 article, Peru scientists have “counted the deaths of at least 63,000 sea birds...many more can be seen strewn along the country’s coastline...Scientists estimate the true number of bird flu deaths is probably much higher.” Observed wild-bird deaths are expected to be vast underestimates since most wild birds will die unobserved and uncouned. Worldwide, the number of NAFV deaths of birds is expected to be very large.

One very interesting source of wild-bird deaths comes [from another Guardian article](#) where scientists attempt to take underestimates into account. This source provides the only quantitative data for the magnitude of underestimates. The data comes from the Netherlands and for one species, sandwich terns. The Netherlands scientists calculated a 200-fold difference between reported numbers and observed numbers of deaths. Below are quotes from the Guardian article that point to the difficulty of estimating the deaths of wild birds.

[“The World Organisation for Animal Health](#) estimates that more than 50,000 wild birds have died of the highly pathogenic avian influenza H5N1 since October 2021, mainly in Europe and America. But experts say this is likely to be a huge underestimate... conservationists say the true impact is still unknown, and most are unwilling to speculate...For

example, of the approximate 8,000 sandwich terns that died in the Netherlands, only a handful are included in [the official numbers](#) – in this case a more than 200x difference between reported numbers and observed deaths. The lack of appreciation for the scale of wild bird mortality is concerning as there may be species/population level ramifications.”

However, I will speculate by applying this single quantitative number, 200x, to the minimum worldwide estimate of 50,000 wild-bird deaths yielding $200 \times 5 \times 10^4 = 1 \times 10^7$ or 10 million or 0.010 billion deaths worldwide.

[According to the National Geographic](#), there are between 50 billion and 430 billion birds on Earth. For a calculation, using the least favorable denominator number, 50 billion, the likelihood of extinction of all wild birds is $0.010 \text{ billion} / 50 \text{ billion} = 1 \times 10^{-2} / 5 \times 10^1 = 0.2 \times 10^{-3}$ or 0.2%. Experts believe this could still be a huge underestimate. While 0.2% is low enough to make it unlikely that all birds would become extinct, we should think more about what species of birds might be at risk of extinction.

Many inland birds eat foods like seeds and worms where it would seem to be difficult to be infected with avian H5N1. However, meat eating birds such as condors, eagles, hawks, and vultures are at risk of contracting the new avian flu virus. Unfortunately, some bird species may be at risk of extinction. For example, there is now an [effort to vaccinate California condors](#) to protect them from extinction. It was tested in black vultures; a species related to California condors. [It is now being tested in condors](#).

“The U.S. Fish and Wildlife Service’s Incident Command Team, in collaboration with partner agencies, continues to develop and implement conservation strategies to help California condors in light of Highly Pathogenic Avian Influenza (HPAI). Strategies include implementation of vaccine trials, field monitoring... Titers (concentration of antibodies) present in the birds [black vultures] are still being evaluated by USDA’s Southeast Poultry Research Laboratory... Vaccination of condors in managed care continued this week. Blood samples from the birds will be collected at 21-days and 42-days following vaccination to evaluate the immune response from two different vaccination approaches. The first sample will be collected on August 8... The Peregrine Fund is preparing to release three of birds that received treatment for HPAI at Liberty Wildlife. All have some level of immunity to HPAI based on Hemagglutination Inhibition tests performed on their blood samples by USDA’s National Veterinary Services Laboratory. This week, the birds were transferred from Liberty Wildlife back to the release site in Arizona to reacclimate to their home. A release date will be determined based on their behavior and weather. The fourth bird that survived also has immunity to HPAI and will be released at a later time as he is currently re-growing molted flight feathers. The California Condor Recovery Program continues to implement standard operations and we are hopeful this will include the release of juveniles this year.”

The U.S. Fish and Wildlife Service will determine how long the antibodies last. It is possible the condors might need to be re-vaccinated every year or so, a daunting task.

We can compare the World Organisation for Animal Health’s (WOAH) latest and a previous Situation Report, [Situation Report 07/13/2023](#) and [Situation Report 03/09/2023](#), to determine if numbers of outbreaks and losses of both poultry, wild birds and wild mammals are increasing or decreasing. For the three-week period covered in the latest Situation Report, 07/13/2023, there were 100 reported outbreaks in non-poultry animals. From the previous [Situation Report 03/09/2023](#), for the three-week period there were 161 outbreaks in non-poultry birds. Note that while a period of three weeks is the same in both reports, the older report does not mention animals, only wild birds. Yet the newer report has many less outbreaks reported, 100 vs. 161, perhaps an encouraging sign.

These reports do not list the number of losses (deaths) in non-poultry outbreaks as losses in wild birds and wild animals occurred largely unobserved and uncounted.

[The World Organisation for Animal Health](#) discusses the “devastating consequences” of the NAFV and their rules for mandatory reporting:

“With devastating consequences for the poultry industry, farmer’s livelihoods, international trade, and the health of wild birds, avian influenza, most commonly known as ‘bird flu’, has captured the attention of the international community over the years. Where outbreaks occur, it is often the policy to cull all poultry, whether infected or healthy, to contain the spread of avian influenza. This represents heavy economic losses for farmers and a long-lasting impact on their livelihoods.

But poultry is not the only impacted. While they play a major role in the spread of the disease, wild birds also become victims of bird flu viruses.

Avian influenza is also a major concern for public health. Whenever avian influenza viruses circulate in poultry, sporadic cases of avian influenza in humans are sometimes identified... The first line of defense against avian influenza is the early detection and reporting of disease outbreaks to allow a rapid response. Putting in place accurate warning systems is thus essential to efficiently prevent and control the disease.

Because of its capacity to rapidly spread across regions, timely reporting of cases is key to enable countries to anticipate and get prepared for potential new outbreaks of avian influenza.

[The new avian flu virus] is an WOA-listed disease. As such, national Veterinary Authorities must report:

- all high pathogenicity avian influenza viruses, irrespective of their subtypes, detected in birds (domestic and wild)
- all low pathogenicity viruses, in domestic or captive wild birds, that have proven natural transmission to humans with severe consequences.
- When LPAI viruses are detected in wild birds, countries can voluntarily report them through the voluntary report on non WOA-listed diseases in wildlife. In addition, countries may self-declare the absence of high pathogenicity avian influenza from their territory on a voluntary basis.”

Deaths of mammals

[According to the CDC](#), in a June 30, 2023 updated report the estimates of the number of land mammals infected with the new avian flu virus has risen from 30 different species to 196 different species in 26 U.S. states or territories.

The new avian flu virus had infected small numbers of over 30 species of land mammals and has sparked outbreaks with thousands of deaths of mammals such as seals that reside at times at the edge of sea and land. In April 2023, a many-authored [Emerging Infectious Diseases article](#) reported the deaths of seals along the New England coast. The lead author, Wendy Puryear, is a virologist at The Cummings School of Veterinary Medicine at Tufts University in the Department of Infectious Disease and Global Health. Her research interests focus on epidemiology, evolution, and adaptation of wildlife diseases.

“As of January 2023, H5N1 infections in mammals have been primarily attributed to consuming infected prey, without evidence of further transmission among mammals. We report an HPAI A(H5N1) virus outbreak among New England harbor and gray seals that was concurrent with a wave of avian infections in the region, resulting in a seal unusual mortality event (UME); evidence of mammal adaptation existed in a small subset of seals. Harbor (*Phoca vitulina*) and gray (*Halichoerus grypus*) seals in the North Atlantic are known to be affected by avian influenza A virus and have experienced previous outbreaks involving seal-to-seal transmission. Those seal species represent a pathway for adaptation of avian influenza A virus to mammal hosts that is a recurring event in nature and has implications for human health...Transmission from wild birds to seals was evident for distinct HPAI H5N1 lineages in this investigation and likely occurred through environmental transmission of shed virus. Viruses were not likely acquired by seals

through predation or scavenging of infected animals, because birds are not a typical food source for harbor or gray seals. Data does not support seal-to-seal transmission as a primary route of infection. If individual bird–seal spillover events represent the primary transmission route, the associated seal UME suggests that transmission occurred frequently and had a low seal species barrier.”

More than 300 seals died (see the Yale School of the Environment article below).

In [an interview](#) with the *Journal of the American Medical Association*. Jonathan Runstadler suggests another way that seals may be transmitting virus “It’s certainly plausible that [seals] are spreading virus by droplet or aerosol to each other...They’re having interactions at close range, and a lot of vocalizations.” Runstadler is also at The Cummings School of Veterinary Medicine at Tufts University in the Department of Infectious Disease and Global Health.

In May 4, 2023 article by Andrew S. Lewis published by the Yale School of the Environment titled [Avian Flu Outbreaks in Marine Mammals Mark New Era for Deadly Virus](#) expands the discussion of the seal unusual mortality event.

“By the end of July, more than 330 harbor and gray seals had died from the virus — enough that the National Marine Fisheries Service immediately declared an “unusual mortality event” ...Deborah Fauquier, a veterinary medical officer with the National Marine Mammal Health and Stranding Response Program, says that, as of now, it appears that last summer’s outbreak of H5N1 in Maine resulted from bird-to-seal transmission, not mammal to mammal. “We’ve been continually testing, and we haven’t seen a positive since July 15 [2022],” Fauquier adds, “If no new cases emerge during this year’s pupping season, which is underway, Fauquier and her colleagues...recommend closing the unusual mortality event (UME) declaration, which would stop active investigation by the program’s working group, as well as some federal funding.” But, Fauquier says, “we’ll continue to monitor even if the UME closes, because we want to make sure that, if it becomes seal-to-seal, we’ll know that right away.”

Importantly, Fauquier observes “that there have not been any positive H5N1 infections in Maine seals so far this year.” The last new avian flu virus infections of seals were seen in July 2022. However, she ends with words of caution “we’ll continue to monitor even if the UME closes, because we want to make sure that, if it becomes seal-to-seal, we’ll know that right away.” The fact that no large number of new virus seal deaths have occurred is an extremely positive development, but an explanation was not given in the Yale article. Let’s hope the observation of no new avian flu virus seal deaths continues, and hope we can find out why.

We are now in the mid to later months of 2023. [According to the CDC](#), in a June 30, 2023 updated report the estimates of the number of land mammals infected with the new avian flu virus has risen from 30 different species to 196 different species in 26 states or territories.

“Sporadic HPAI A(H5N1) virus infections of mammals have been reported since 2003 during HPAI A(H5N1) virus outbreaks in poultry or wild birds. HPAI A(H5) viruses are known to occasionally infect mammals that eat (presumably infected) birds or poultry and mammals that are exposed to environments with a high concentration of virus.

In the United States, from May 2022 to June 27, 2023, [USDA APHIS reported](#) HPAI A(H5N1) virus detections in 196 mammals of different species in 26 states or territories. Globally, sporadic HPAI A(H5N1) virus infections have been reported in multiple mammalian species in many countries; for example, in farmed mink in [Spain](#), [harbor and gray seals in the United States](#), sea lions in Peru and [Chile](#), a [cat in France](#) and other countries, and foxes in North America and Europe. The reports of HPAI A(H5N1) virus infections in mammals are not surprising given the widespread outbreaks of HPAI A(H5N1) virus infections in wild birds...

Genetic data have revealed that when some mammals are infected with HPAI A(H5N1) virus, the virus may undergo intra-host evolution resulting in genetic changes that allow the virus to replicate more efficiently in the lower respiratory tract.

Although these genetic changes may impact mammalian disease outcome, they have not been associated with changes to receptor binding specificity or enhanced transmissibility of the virus to humans. HPAI A(H5N1) viruses do not currently have an ability to easily infect and bind to α 2,6-linked sialic acid receptors that are in the human upper respiratory tract, which would be needed to increase the risk of transmission to people.”

In its [Advice to countries from FAO, WHO, WOAHA on avian influenza outbreaks in animals](#) the species of mammals that have been infected with NAFV are listed.

“The Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO), and the World Organisation for Animal Health (WOAH) are urging countries to work together across sectors to save as many animals as possible and to protect people. Avian influenza viruses normally spread among birds, but the increasing number of H5N1 avian influenza detections among mammals—which are biologically closer to humans than birds are—raises concern that the virus might adapt to infect humans more easily...

Recently, there have been increasing reports of deadly outbreaks among mammals also caused by influenza A(H5)—including influenza A(H5N1)—viruses. 10 countries across three continents have reported outbreaks in mammals to WOAHA since 2022...

Species of mammals known to be infected with A(H5N1) clade 2.3.4.4b viruses to date: ferret, mink, European otter, North American river otter, marine otter, European badger, skunk, Virginia opossum, Amur leopard, Amur tiger, mountain lion, fisher, European polecat, lynx, bobcat, domestic cat, red fox, coyote, raccoon, raccoon dog, South American bush dog, American black bear, brown Bear, grizzly bear, Kodiak bear, domestic pig (serology only), grey seal, harbour seal, fur seal, sea lion, porpoise, bottlenose dolphin, short-beaked common dolphin, white sided dolphin, dogs, Japanese raccoon dogs, Beech marten, Caspian seals, Asiatic black bear, Chilean dolphin, Burmeister’s porpoise.”

As summarized on August 9, 2023 by [The Center for Infectious Disease Research and Policy](#) (CIDRAP) there have been 200 reported NAFV infections in the United States, the latest being a mountain lion in the state of Montana detected on August 4 2023. But Montana is not alone the edge of sea and land (the seacoast), how did the mountain lion become infected? Was it infected from eating infected birds who have travelled inland from the seacoast? Or has this mountain lion become infected by mammals eating mammals in a chain of mammals eating mammals or close associations between mammals in chain links that started on a seacoast. For whatever reason, infected mammals are found far inland.

For the list of 200 infections of NAFV mammals dating back to the year 2022, see the [Animal and Plant Health Inspection Service \(APHIS\) list](#).

Twenty-eight [domestic cats in Poland](#) have tested positive for NAFV.

“Since 19 June 2023 the General Veterinary Inspectorate has begun to receive the first unofficial information from different parts of the country about cat infections with an agent of unknown aetiology. The infections had a high mortality rate.”

Since these are domestic cats living in “different parts of the country,” it is likely they were infected from eating NAFV infected food purchased by the cat owners.

Do U.S. pet owners need to worry about feeding their pets canned or dried dog and cat food? From the article titled [An Inside Look at How Canned Dog Food is Made](#) by Nancy Kerns in Whole Foods Journal, the ingredients and the final canned food is heat sterilized several times, which would kill viruses and bacteria. Kerns visited three cat and dog food canning facilities in the U.S. It is unlikely that dried food can contain live virus since it is baked and dried, and likely sterilized previously as well.

Uncooked foods that are becoming popular to feed dogs in the U. S. is another story. There needs to be very careful selection of food sources to ensure that they are NAFV free.

What is the danger to humans?

Will the new avian flu virus kill us as well? So far, there have been almost no human fatalities. [A June 28 2023 study published in Nature](#) identifies a single protein called BTN3A3 that protects humans and some other primates from the deadly and highly transmissible avian H5N1 flu virus. The study is authored by more than a dozen scientists mostly from Scotland. BTN3A3 was [discovered originally](#) as a potential therapeutic target for breast cancer.

From the Nature article, below is a highly redacted version of the **DISCUSSION** section that outlines the protective properties of the BTN3A3 protein and how the H5N1 virus might evade BTN3A3 to infect humans. We will not be infected with avian flu unless there is a so-called “spillover” event. Spillover is the word used to indicate that an avian flu virus could now infect humans, where it previously could not. Spillover events are what we must prevent.

“Our study reveals that human BTN3A3 is a powerful barrier for the replication of avian IAVs [influenza A viruses] but not human IAVs. Through data obtained *in vitro* in cell culture assays and *in vivo* in experimental animal models, in addition to comprehensive evolutionary analyses, we showed that evasion of human BTN3A3 is one of the risk factors for the zoonotic potential of IAVs...The anti-avian IAV properties of BTN3A3 arose in primates. Hence, humans are the only species maintaining endemic infections with influenza viruses that restrict avian IAV replication...We showed that BTN3A3 interferes mostly with avian IAV vRNA replication, at the early stages of the virus life cycle...

The exception to the rule of BTN3A3 representing a key barrier to avian IAV spillover into humans is represented by highly pathogenic H5N1. HPAI viruses are defined by the presence of a polybasic cleavage sites in their haemagglutinin protein that may allow the virus a wider cellular tropism, potentially providing the ability to infect BTN3A3 low-expressing cells, or a more efficient replication fitness leading to a higher chance of a successful infection and therefore overriding the antiviral effects of BTN3A3...

HPAI H5N1 viruses appear to be able to infect humans in the absence of either a BTN3A3-resistant genotype or PB2 human adapting mutations. These observations suggest that this virus may possess distinctive features that allow it to spill over in humans more effectively than other avian viruses.

In recent years, the GsGd lineage of HPAI H5 virus that originally emerged in Asia, has caused an increasing number of outbreaks in wild birds, poultry and wild mammals across several continents. This lineage shows a high frequency of the BTN3A3-resistant genotype. Of note, is a particularly concerning recent outbreak of H5N1 in a farm housing roughly 50,000 mink in Spain. Viruses isolated from this outbreak showed both an ANP32A-linked PB2 T271A mutation, associated with enhanced polymerase activity in mammalian cells, and a NP 52N mutation conferring a BTN3A3-resistant genotype that was acquired in an avian host before emergence of the H5N1 virus in mink.

Transmission of these viruses within farmed animal populations provide them with the opportunity to further adapt to the mammalian host, in addition to provide further opportunities for onwards transmission to humans. Hence, H5N1 viruses with a BTN3A3-resistant genotype may be better posed in the future to adapt to humans.

Global efforts during the SARS-CoV-2 pandemic and over the years for IAV infections have shown that surveillance based on virus genomic sequences can be a useful tool not only to provide insight into disease spread and

epidemiology, but also for the early identification of viruses with undesirable phenotypic traits from a public health perspective. The BTN3A3-resistant genotype is one of the determinants associated with avian IAV spillover in humans that should be considered in risk-assessment frameworks.”

The following quote from the Nature article in the **BTN3A3 evolution** section illustrates the effort by the authors who carried out to study to find the origin of the BTN3A3 gene in various primate species.

“We then examined the origin of anti-avian IAV activity in the BTN3 gene family. Phylogenetic analysis of the BTN3A genes of the *Haplorrhini* suborder (tarsier, monkeys, apes and humans) indicated that BTN3A1–3 originated through two successive duplications after the split between the new world monkey lineage (*Platyrrhini*) and the old world monkey and ape lineage (*Catarrhini*) around 40–44 million years ago...Humans, chimpanzees (*Pan troglodytes*), gorillas (*Gorilla gorilla gorilla*), orangutans (*Pongo abelii*), macaques (*Macaca mulatta*) and green monkeys (*Chlorocebus sabaeus*) all have at least one BTN3A1 or BTN3A3 gene capable of inhibiting Mallard viral replication...The other primate group does not make the protein. The evolutionary history of these genes could explain the many gains and/or losses of antiviral function.”

So, an accident of genome evolution that occurred millions of years ago, an extraordinary bit of luck, protects us from the new avian flu virus, at least for now.

[In a June 2023 article published online](#) by Laura Graf and Peter Staeheli largely confirms the study by the Scottish group but progress is being made. Two proteins, BTN3A3 and another protein MX1. Both proteins interfere with an early step of the viral replication cycle. The Graf and Staeheli article also cautions us about spillover events, “Only by understanding the diversity of adaptive mutations that viruses must acquire for successful transmission into the human population will we be able to identify, in a timely manner, zoonotic IAVs that have pandemic potential.”

From January 2022 to June 29, 2023, [thirteen cases of NAFV in people including two deaths](#), have been reported globally, according to the US Centers for Disease Control and Prevention (CDC). Clearly, the pandemic in birds and mammals is not over, even though the number of non-poultry outbreaks has decreased substantially, which may be highly encouraging even though we don’t yet understand the cause or consequences of the reduction. Data trends are the most that we can do to look at the reemergence of deadly, highly transmissible avian H5N1 virus in wild birds and mammals.

We urge those of you who live along coastlines to observe shore birds to see if they are behaving normally going about their daily business.