Medical News & Perspectives

Bird Flu Has Begun to Spread in Mammals—Here's What's Important to Know

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As bird flu continues to circle the globe, a recent report suggests that the highly pathogenic avian influenza (HPAI) A(H5N1) virus spread between farmed mink in Spain last October. The virus also may have been transmitted between seals in coastal New England last summer.

The events mark the first large H5N1 outbreaks potentially driven by mammal-to-mammal transmission. The outbreaks, along with the virus' ongoing transmission in wild birds and poultry and increasing infections in wild mammals, have renewed concerns that H5N1, first identified in the mid-1990s, could be poised for spillover into humans.

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The ongoing avian influenza outbreak is now the largest on record in Europe and North America, according to the World Health Organization (WHO). The outbreak is being driven by H5N1 clade 2.3.4.4b viruses, which emerged in the Netherlands in October 2020 before spreading through Europe, Asia, and Africa. A recent report by the European Food Safety Authority and other agencies found that since October 2021, more than 58 million birds have died or been culled in H5N1-affected poultry establishments in 37 European countries.

By December 2021, bird flu had arrived in North America. Within a year, wild bird outbreaks were confirmed in 47 US states, according to a recent epidemiological alert from the Pan American Health Organization. Nearly 60 million birds in commercial and backyard flocks in 47 US states have died or been culled, the US Department of Agriculture reported in early February.

The virus has been detected in ducks, geese, gulls, pelicans, swans, vultures, crows, owls, eagles, and many other species of wild birds. With so many birds affected, the opportunities for exposure to other animals have been high. In addition to minks and seals, the list of mammals with confirmed infections in Europe and the Americas now includes badger, black bear, bobcat, coyote, dolphin, ferret, fisher cat, fox, leopard, lynx, opossum, otter, pig, polecat, porpoise, raccoon, raccoon dog, and skunk.

Martin Beer, DVM, who heads the Institute of Diagnostic Virology within the Friedrich-Loeffler-Institut, the Federal Research Institute for Animal Health, in Germany, said the mink farm outbreak requires special attention and awareness. "[T]he likely animal-to-animal spread connected with clinical signs and mortality is significant, since spread between mammals might allow for further adaptation to the mammalian host," he wrote in an email to *JAMA*.

Although no human infections were reported on the mink facility, the incident indicates that the virus has the potential to spread in this intensively farmed species, said Isabella Monne, DVM, PhD, head of the viral genomics and transcriptomics laboratory at the Istituto Zooprofilattico Sperimentale delle Venezie, the Italian public health institute that characterized the viruses identified in the outbreak, described in *Eurosurveillance*. Monne warned in an email that the "increasing genetic diversity and geographical distribution of HPAI H5N1 viruses may result in more spillover events in mammals posing great risks not only to the poultry industry but also to wildlife conservation and to human health."

Raising the Stakes

Avian influenza viruses are classified as "highly pathogenic" or "low pathogenicity" based on their effects in birds, not necessarily in other animals. Although the highly pathogenic H5N1 virus has caused sporadic human infections since it was first detected in waterfowl in China in 1996, it doesn't spread easily between people and other mammals.

Increasing mammalian infections raise the stakes, said Amesh Adalja, MD, a senior scholar at the Johns Hopkins Center for Health Security. "Lots of flu viruses circulate in birds but never pose major threats to humans," Adalja said in an interview. "When you think about the steps that are related to the emergence of a new human influenza threat, the ability to infect mammalian species is one of those steps."

For the most part, mammals probably have become infected with H5N1 while eating sick or dead birds with high virus loads, said Jonathan Runstadler, DVM, PhD, professor and chair of the Department of Infectious Disease and Global Health at Tufts University's Cummings School of Veterinary Medicine.

Runstadler's research team identified the outbreak in harbor and gray seals in New England last summer. Their findings, currently posted as a preprint to *BioRxiv*, will be published in *Emerging Infectious Diseases* in April. In an interview, Runstadler said some sort of respiratory transmission likely occurred in the mink outbreak and possibly in the seal outbreak, but whether it was airborne isn't known for certain.

"It's certainly plausible that those animals are spreading virus by droplet or aerosol to each other," Runstadler said of the seals. "They're having interactions at close range, and a lot of vocalizations....But there's other routes in that scenario that we can't rule out."

Some infected mammals have exhibited neurological symptoms. This January, Montana Fish, Wildlife & Parks reported that 3 sick grizzly bears euthanized last fall subsequently tested positive for H5N1. The bears, found in different regions of the state, were disoriented and partially blind.

Monne said researchers are now evaluating the zoonotic and virulence potential of the virus identified in minks using in vitro and animal models. She noted that the most relevant changes in the influenza virus receptor binding site, which are known to switch the receptor specificity from avian to human receptors, have been not identified. "According to the information currently available, these mutations are necessary for an H5N1 avian virus to become human-to-human transmissible," she said.

During the past 20 years, fewer than 900 confirmed human cases of H5N1 have been reported to the WHO. The historic case-fatality rate for human H5N1 infection has been high—more than 50%. But some experts say that's likely an overestimation because many mild or asymptomatic infections may go unreported.

Human cases have generally been "dead-end" infections. Although there's been some evidence of human-to-human transmission between close contacts in previous H5N1 outbreaks, those cases were extremely rare.

Only a handful of human infections have been reported in the current outbreak, all among people who had direct contact with infected poultry. Through last December, the WHO received 6 reports of human infections with H5N1 clade 2.3.4.4b viruses, one of which was fatal. Bird flu reached Central and South America late last year, and this January Ecuador reported a severe H5N1 infection in a child who had been in contact with backyard birds. Virus sequencing was available from some of the infected individuals, and it did not turn up mutations associated with mammalian adaptation or resistance to antivirals such as oseltamivir.

A bird flu pandemic would require sustained human-to-human transmission, which has yet to be reported with H5N1. In a recent assessment, the WHO said the risk of infection remains low for humans. But the WHO cautioned, "As these viruses are constantly evolving and spreading in animal populations, and with an increased risk of exposure for humans, there is an urgent need for increased vigilance and public health actions."

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>
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Of the infected seals that were found alive, Runstadler said, some appeared unable to orient themselves in the water and swim properly.

Assessing Human Risk

In both the minks and the seals, viral genome sequencing identified mutations known to improve virus replication in mammals. But according to the WHO, genetic markers of adaptation to mammals are still rare in sequenced H5N1 samples.

"In a next step," Beer said, "the virus has to be further characterized to analyze the zoonotic potential in more detail."

Preparing for the Worst

Despite the mink farm outbreak, Bruce Gellin, MD, MPH, chief of global public health strategy for The Rockefeller Foundation's pandemic prevention institute, cautioned against assuming an H5N1 pandemic is a now foregone conclusion. "I would be a little bit careful about thinking this is a step, and that will be followed by the next step that gets increasingly dangerous, because you never know," he said in an interview. "I think it's another reminder that while we've been focusing on COVID for three years, that doesn't mean flu has been squeezed out, and we need to continue to worry about it."

Gellin pointed out that universal influenza vaccine development has continued to advance. The hope is that the effort might one day lead to a vaccine that protects against all seasonal flu viruses and existing or emerging zoonotic viruses that have the potential to cause a pandemic.

In the meantime, the US has bulk H5N1 vaccine antigen and adjuvant, developed in the mid-2000s, stored in its National Pandemic Influenza Vaccine Stockpile.

In an emailed response to *JAMA*, a spokesperson for the US Administration for Strategic Preparedness and Response (ASPR) said that stockpiling of hundreds of millions of doses of vaccine against each circulating influenza strain with pandemic potential is impractical because influenza strains change over time and new strains circulate in animals every year without leading to sustained human-to-human transmission. Instead, the US government has a preparedness program that enables a rapid response to influenza strains as they evolve.

"As part of this program," the ASPR spokesperson said, "the Biomedical Advanced Research and Development Authority (BARDA) works with private industry partners to make and test small quantities of updated vaccines that match new strains of influenza viruses with pandemic potential as they emerge in case any of them drive sustained human-to-human transmission, while at the same time, supporting manufacturing capacity

to allow for large-scale vaccine production when needed."

Beyond vaccine development, Monne and others underscored the importance of better zoonotic disease surveillance in humans and other mammals. She urged more intensive surveillance for people in close contact with animals, particularly those working in intensive poultry, pig, and fur farming, in live animal markets and trade, or in wildlife rescue centers.

Runstadler said more funding is needed for wild animal surveillance. "We don't understand enough about what is circulating out there in these animals that may pass it to us," he said. "And that's part of the equation that often gets left out, I think, when we're talking about human disease and infectious disease." ■

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Note: Source references are available through embedded hyperlinks in the article text online.