The Public Health Company
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H5N1 Avian Influenza

Situation Update and Threat Overview for Business Continuity and Risk Management

THE PUBLIC HEALTH COMPANY

PHC Summary

H5N1 has received significant attention in mainstream media and the scientific community over the past three months, though it is not a new virus. Recent outbreaks in mink farms appear to be the first widespread transmission among mammals, raising concerns the virus could soon mutate to spread among humans. Though the odds of this happening are low, the outcome would be potentially catastrophic on a global scale. This low-probability/high-threat potential keeps the scientific community vigilant, particularly as the virus becomes better at spreading among mammals.

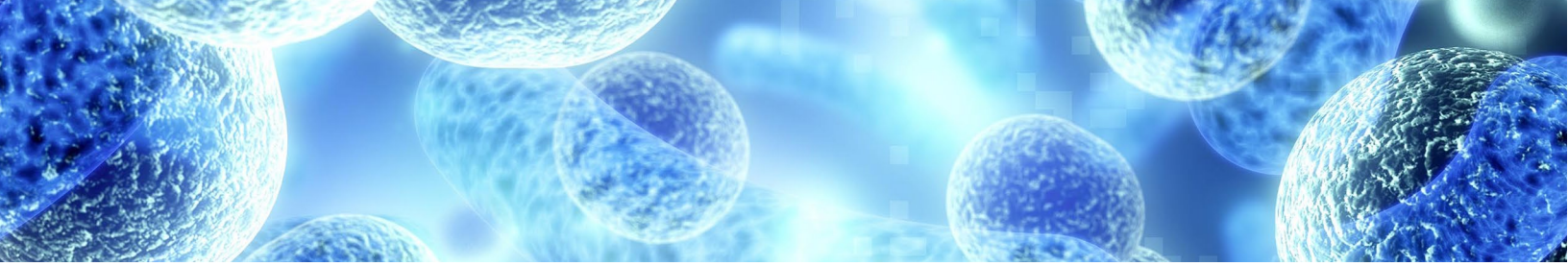
At this time, H5N1 poses little direct threat to most enterprise businesses. The main business impact is to specific sectors that rely on poultry or poultry products.

PHC Predicts

- H5N1 will remain a constant, low-level biorisk for enterprise business. (High Confidence)
- H5N1 will cause regular disruptions, largely confined to the agricultural sector and businesses that rely on poultry products, unless a novel mutation occurs that enables widespread human-to-human transmission. (Moderate-to-High Confidence)
- Though currently low, the risk of an H5N1 global human pandemic will continue to increase given the changing interface among animals, humans, and the environment. (Moderate-to-High Confidence)
- Access to vaccines against H5N1 would be limited in the event of a pandemic due to challenges of vaccine production at scale, despite the fact that approved formulations currently exist. (Moderate Confidence)

PHC Recommends

- Maintain policies that enable continuity of operations in the face of unpredictable biorisks. Should a circulating avian influenza virus become capable of sustained human to-human transmission, mitigation measures will be similar to those used during the COVID-19 pandemic. Masking and physical distancing would be even more essential as a pandemic strain of influenza could likely carry a higher mortality than COVID-19. Ensuring lessons learned from the pandemic are codified in policy builds business resilience. Turn-key mitigation measures should include work-from-home policies, in addition to masking, handwashing, ventilation/filtration optimization, and physical distancing.
- Avoid contact with wild birds and poultry. Most human cases of H5N1 are linked to direct contact with live poultry or bird carcasses. Properly cooked eggs and poultry are safe to eat.



What is Avian Influenza A/H5N1?

Influenza A virus subtype H5N1 is an animal disease that has recently grabbed public attention due to concern for its pandemic potential after it was documented to display widespread transmission among mammals for the first time[1], [2] and its ability to cause sporadic cases in humans.[3]

Avian influenza–or "bird flu"–encompasses numerous influenza A viruses that infect and circulate primarily in domestic and wild bird species. A minority of these viruses have been documented to be zoonotic pathogens, or viruses that can spillover from animals to humans. H5N1 is a subtype within this influenza A virus family. The first documented human cases of H5N1 occurred in the 1990s. Though such spillover events from animals to humans are rare, they can cause severe illness. Widespread human-to-human transmission has not occurred.

Avian influenza viruses are broken down into two broad categories, each based on the severity and speed at which they cause mortality in poultry in a laboratory setting: high pathogenicity (HPAI) and low pathogenicity (LPAI).[4] The vast majority of documented viruses are LPAI, meaning that they cause more limited illness even in poultry. The current HPAI H5N1 outbreak is concerning both due to its severity in birds and because its global scale provides more opportunities for the virus to gain the ability to infect humans. Avian influenza viruses are additionally named for the specific surface proteins that they harbor, hemagglutinin (H) and neuraminidase (N), with specific numbers corresponding to different versions of these proteins. These viruses range from causing mild or no disease in their natural hosts (wild birds) to causing severe disease and mortality once introduced into poultry flocks. The most concerning viruses for health security and economic security are HPAI H5N1 and H7N9.[5]

Avian influenza viruses have a global reach, as wild birds carry the viruses vast distances across trans-continental migratory routes. H5N1 is the subtype of influenza virus that has recently decimated domestic poultry populations in the United States (US) and Europe. Sustained and recurrent poultry epidemics provide spillover opportunities for sporadic human infections that could, in the worst case, lead to more significant human outbreaks. Additionally, the world is closely watching countries in Central and South America after countries in these regions experienced their first H5N1 outbreaks in over 20 years.[6]

H5N1 and other avian influenzas will continue to circulate and mutate in wild bird populations for the foreseeable future. Human infections are rare and typically occur in those with direct contact to live poultry or bird carcasses.[7]

[1] https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-disease-information/avian/avian-influenza/hpai-2022/2022-hpai-mammals
[2] https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2023.28.3.2300001
[3] https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON420
[4] https://apps.who.int/iris/bitstream/handle/10665/68985/WHO_CDS_2005.29.pdf;jsessionid=0B4C8B18135614FF7CD517C868DC916C?sequence=1
[5] https://www.who.int/news-room/fact-sheets/detail/influenza-(avian-and-other-zoonotic)?gclid=CjwKCAiA0JKfBhBIEiwAPhZXD0uxwl7O5uxTRUNZ1QTf1JdgzgGCjDBzcqRowJzjjp4aw9XC5cM-RRoC1D0QAvD_BwE
[6] https://www.woah.org/en/controlling-the-surge-of-avian-influenza-cases-in-central-and-south-america/
[7] https://www.cdc.gov/flu/avianflu/reported-human-infections.htm

Why is there Concern Now?

H5N1 burst onto the scene as a potential pandemic threat approximately 20 years ago.[8] Current concerns regarding H5N1 largely stem from the COVID-19 pandemic, which opened the world's eyes to risk management of pandemic potential pathogens. During this period, H5N1 has spread widely in bird populations (domestic and wild), creating opportunities for spillover in humans, and opportunities for viral mutation and evolution to forms that could more widely impact humans. H5N1 also has continued to spread to new animal hosts. A recent report suggested H5N1 has infected and spread widely among commercially farmed mink in Spain in October 2022.[9] This raised alarm bells as mink are closely related to ferrets, which in turn have served as a model for the study of human influenza viruses due to ferrets' ability to become infected and display symptoms similar to humans.[10], [11]

The current concern is valid, though the risk of an H5N1 global human pandemic remains relatively low.[12] Avian influenza, and the H5N1 subtype, will remain a constant, low-level biorisk for enterprise business. While the probability of H5N1 mutating to cause a major pandemic is low, it is increasing as humans come into closer and more frequent contact with wildlife and domestic animals, enabling potential spillover.[13] Though the vast majority of spillover events go undetected and do not lead to human disease outbreaks, with an increase in spillover opportunities comes an increase in the chances for a problematic mutation of the H5N1 virus.

What is the Threat to Humans?

Almost all human cases of H5N1 are linked to direct contact with infected poultry or wild birds. When people come into close contact with H5N1 infected birds (living or dead), or surfaces contaminated with infected bird saliva, mucous, or feces, there is a risk of transmission. The virus gains entry into the human body through the eyes, nose, mouth, mucous membranes, or by being inhaled into the lungs.[14] A handful of documented human cases have shown it takes less than a week for symptoms to appear after a person is infected.[15], [16] Human illness has varied from mild upper respiratory symptoms, conjunctivitis, gastrointestinal symptoms, to severe pneumonia and death.[17]

A total of 868 cases of H5N1 have been confirmed in humans since 2003, and 457 have resulted in death (case fatality rate (CFR) = 52.7%).[18] Only seven cases have been identified in humans since 2020, and only one to date in the US in 2022.[19] A second form of avian influenza, H7N9, is also active and being tracked now. Since its first documented human case in 2013, a total of 1,568 human cases of H7N9 have been confirmed in humans, and 616 have resulted in death (CFR = 39.3%).[20] Though there are likely many more undiagnosed, less severe cases leading to an overestimated CFR for each of these virus subtypes, it is clear that this virus family can have devastating outcomes.

[8] https://apps.who.int/iris/bitstream/handle/10665/68985/WHO_CDS_2005.29.pdf;jsessionid=0B4C8B18135614FF7CD517C868DC916C?sequence=1
[9] https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2023.28.3.2300001
[10] https://pubmed.ncbi.nlm.nih.gov/19412910/#:~:text=Ferrets%20are%20used%20as%20an,that%20are%20seen%20in%20humans
[11] Andrew Pavia, MD lecture, 49th Remington Winter ID Course, February 6, 2023.
[12] https://cdn.who.int/media/docs/default-source/influenza/human-animal-interface-risk-assessments/influenza-at-the-human-animal-interface-summary-and-assessment--from-12-november-to-5-january-2023.pdf?sfvrsn=8382d727_1&download=true
[13] https://www.nytimes.com/2022/10/31/opinion/viral-chatter-bird-flu.html
[14] https://www.science.org/doi/10.1126/science.1213362
[15] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2630744/
[16] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2660684/
[17] https://www.cdc.gov/flu/avianflu/avian-in-humans.htm
[18] https://www.who.int/publications/m/item/cumulative-number-of-confirmed-human-cases-for-avian-influenza-a(h5n1)-reported-to-who-2003-2022-27-june-2022
[19] https://www.cdc.gov/media/releases/2022/s0428-avian-flu.html
[20] https://www.who.int/docs/default-source/wpro---documents/emergency/surveillance/avian-influenza/ai_20230106.pdf?sfvrsn=5f006f99_108

Human-to-human transmission of H5N1 is notably rare, though a few cases have been documented. Those cases did not result in sustained human outbreaks.[21] Should H5N1 become efficient at human-to-human transmission, susceptibility to the virus will be extremely high because humans have virtually no natural immunity from prior infections. Reassuringly, viral genome sequencing of key codons (sections of RNA) in the current H5N1 virus receptor binding domain show it lacks the necessary mutations that facilitate human-to-human transmission.[22]

What would it take for H5N1 to become transmissible between and among humans? A necessary component would be mutations that enable the virus to bind to human receptors more easily, allowing efficient spread from one person to the next. Although such mutations have not been identified, scientists are on heightened alert and ongoing research is being conducted on the phylogenetic tree underlying the recent mink outbreak. Advancements in global capabilities for viral genome sequencing are being applied to monitor the evolution of H5N1.

An H5N1 virus with the capability to readily and repeatedly transmit between humans could be catastrophic, leading to fast global spread. Control measures including lockdowns, universal masking, and airborne spread mitigation would be similar to those the world has experienced during the COVID-19 pandemic. And with a CFR potentially orders-of-magnitude higher than COVID-19, the death toll would be significant. This is why experts scrutinize how and where H5N1 is spreading and mutating, even though in its current form the threat to humans remains low.

What Tools Exist for Prevention and Treatment in Humans?

Prevention and treatment countermeasures for avian influenza have been the subject of scientific and medical research efforts for decades. Progress has certainly been made, as outlined below. However, it is not realistically possible to eradicate H5N1 (or any avian influenza virus) given its global reach and circulation in wild bird populations.

Vaccines. Multiple countries (including the US, United Kingdom, China, Japan, and India) have already invested in developing candidate vaccines to counter different strains of avian influenza, including H5N1 and H7N9.2[3] The US Food and Drug Administration (FDA) has approved human vaccines with experimental efficacy against H5N1 avian influenza, and the US government maintains a stockpile for use if a pandemic arises.[24] These vaccines are not available to the public at this time. If urgently needed, these vaccines would still need to be assessed against any emerging pandemic subtype for efficacy, as influenza viruses are constantly mutating. In the event of a large-scale outbreak or pandemic, availability would be limited in the early stages as production scales up.

[21] https://www.cdc.gov/flu/avianflu/h5n1-human-infections.htm
[22] https://jamanetwork.com/journals/jama/fullarticle/2801499
[23] https://www.who.int/teams/global-influenza-programme/avian-influenza/vaccine-viruses/docs/default-source/influenza/cvvs/zoonotic-cvv/h5n1/summary_a_h5n1_cvv_nh2021_22_20210305
[24] https://www.fda.gov/vaccines-blood-biologics/vaccines/influenza-virus-vaccine-h5n1-national-stockpile

Traditional methods of large-scale influenza vaccine production rely on egg-based mechanisms, which take months. The process would be even more challenging if egg supplies were limited by a concomitant outbreak in poultry. Other egg-free methods of production exist (recombinant techniques and cell culture based), but they are expensive and less likely to scale at the speed required for addressing a global pandemic.

The annual flu vaccine does not protect against H5N1.

Therapeutics. Humans infected with avian influenza are recommended to receive supportive care and antiviral treatment at the earliest possible stage of disease.[25] Antiviral therapy is the gold standard of care, using the same drugs that would be indicated to treat the seasonal flu.[26] However, given the low number of human cases, data is limited regarding the effectiveness of these antiviral medications.

Non-pharmaceutical interventions. Given that these viruses have not caused sustained human-to-human transmission of H5N1, prevention of human cases is focused on addressing interactions with potentially infected birds. The general public should avoid contact with sick birds. Individuals with small, "backyard" flocks should take measures to reduce interaction between their poultry and wild birds. People who work with poultry should ensure that effective personal protective equipment and biosecure practices are employed if in contact with poultry, especially sick birds or carcasses.

In the event of sustained human-to-human transmission, the novel influenza outbreak would require measures similar to those used for COVID-19, including avoiding sick individuals and physical distancing where possible. Masking will help reduce transmission significantly, but not entirely. Hand washing and sanitizers help reduce seasonal influenza virus spread and should be effective. Optimized room ventilation and air filtration would be expected to reduce H5N1 transmission as well.

What is the Threat to Animals?

As a high pathogenicity virus in birds, H5N1 poses a significant threat to poultry farms, as well as small backyard flocks. When introduced into a flock, the virus can cause up to 100% mortality.[27] It is standard in many countries to depopulate flocks with documented outbreaks of H5N1–as well as healthy, neighboring flocks–in an effort to stamp out further spread. Last year in the US alone, 43 million egg-laying hens died as a result of H5N1 outbreaks and depopulation practices.[28] In addition to poultry, H5N1 has been detected in numerous bird species, where it can range from causing no signs of illness to severe illness and death. It has additionally been detected in an increasing number of mammals,[29] but has not yet emerged as a widespread threat in any animals aside from poultry.

[25] https://www.cdc.gov/flu/avianflu/prevention.htm
[26] https://www.cdc.gov/flu/treatment/whatyoushould.htm
[27] https://www.aphis.usda.gov/animal_health/emergency_management/downloads/hpai_response_plan.pdf
[28] https://www.ers.usda.gov/data-products/chart-gallery/gallery/chart-detail/?chartId=105576#:~:text=As%20a%20result%20of%20recurrent,outbreak%20began%20in%20February%202022
[29] https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-disease-information/avian/avian-influenza/hpai-2022/2022-hpai-mammals

Where Do Outbreaks Occur in Animals?

Outbreaks in animals follow a seasonal pattern, and the virus constantly circulates around the globe, mainly in wild bird populations.[30] Poultry are at risk of acquiring H5N1 from wild birds that carry it wherever they are farmed. Isolated cases in mammals have been detected in locations overlapping with those where outbreaks have occurred in birds, suggesting likely transmission between birds and mammals (see figure below).

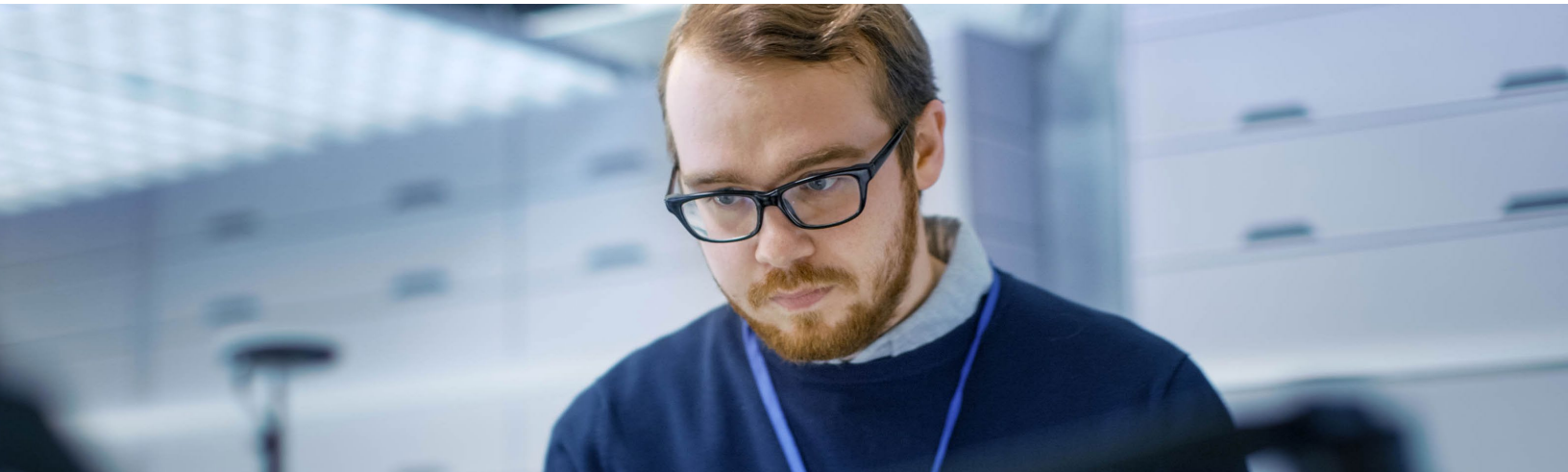
Avian influenza viruses are not unique to North America, however, and have been detected in animals on five continents since October 2022.[31] Definitive understanding of avian influenza's next movements is difficult given the variability of outbreak seasons, the complexity of wild and domestic animal interactions, reporting and detection biases, and differing surveillance system capacity around the world.

What Is Still Unknown?

There is still much we do not know, and cannot predict, about influenza A virus subtype H5N1. These unknowns include:

- If, or when, H5N1 will mutate to cause sustained human-to-human transmission;
- How well a stockpiled vaccine would work against current-day H5N1: Antigenic drift (accumulation of minor mutations in the viral RNA over time) has occurred since the vaccine stockpile was created;
- How extensively the H5N1 genome will mutate in any given season or year: This is an RNA virus, which constantly changes. A primary driver of mutation is ongoing spread among wild bird populations, domestic poultry flocks, and other mammals; and
- Locations where highly pathogenic outbreaks of H5N1 will occur next: H5N1 has caused outbreaks in poultry on all continents (except for Antarctica), though Asia, Europe, and North America have reported the most consistent number of events over the last decade.

[30] https://www.woah.org/en/disease/avian-influenza/
[31] https://www.fao.org/animal-health/situation-updates/global-aiv-with-zoonotic-potential/en -



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