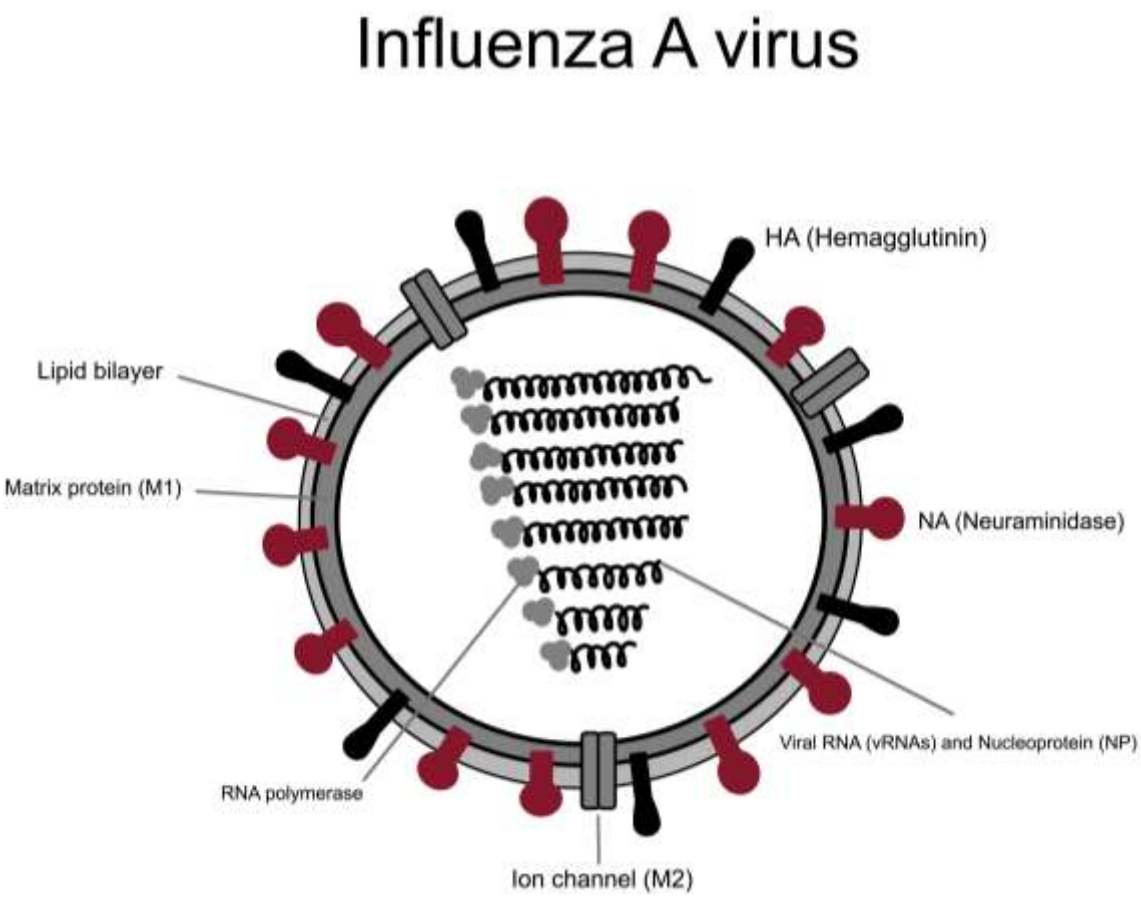
Episode 114 – Avian Influenza (Bird Flu) A(H5N1) August 9, 2024

Introduction

Influenza viruses are enveloped ribonucleic acid (RNA) viruses of the *Orthomyxoviridae* family. Influenza viruses can be classified based on their core proteins into influenza A, B, C, and D strains. Influenza A and B are the main influenza viruses that cause seasonal outbreaks in humans. Influenza C virus infections generally cause mild illness and are not thought to cause human epidemics. Influenza D is seen in animals, mainly cattle with spillover to other animals, and is not known to cause illness in humans. [1] [2]



Avian influenza, also known as avian flu or bird flu, is caused by the influenza A virus. Avian influenza primarily affects birds but can sometimes infect humans and other mammals, especially animals that hunt, scavenge, or consume infected birds, or are

exposed to virus contaminated environments. Animals that have been infected with avian influenza viruses include bears, cats, foxes, livestock (e.g., dairy cattle, goats), marine mammals, otters, raccoons, skunks, mink, and other farmed fur animals. [3] [4]

Influenza A viruses are further subdivided according to their antigenic surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA). To date, sixteen HA and nine NA influenza A subtypes have been detected in wild birds and poultry, which are the natural carriers of avian influenza viruses. [1] [5]

There are many subtypes of avian influenza that are caused by various strains of type A influenza virus (e.g., H5N1, H7N3, H9N2). Influenza A subtypes can be further broken down into different genetic clades and subclades. Currently, clade 2.3.4.4b is the most common avian influenza A(H5N1) virus circulating among birds worldwide. [2] [6] [7]

Avian influenza viruses are classified as low or high pathogenicity, based on the severity of the illness caused in birds:

- Low pathogenic avian influenza (LPAI) viruses cause mild illness in birds, typically causing little or no symptoms. Most avian influenza viruses are low pathogenic.
- Highly pathogenic avian influenza (HPAI) viruses cause serious illness in birds that can spread rapidly, resulting in high death rates in different bird species. [5] [8] [9]

There is no correlation between the pathogenicity of avian influenza viruses in birds and the infectious and pathogenic potential in humans. Both HPAI and LPAI viruses have caused mild to severe illness in infected humans. [1] [5]

Avian influenza A(H5N1)

Avian influenza A(H5N1) is classified as highly pathogenic avian influenza (HPAI). It is a zoonotic disease[1] that is less well-adapted to mammals. However, mammalian infections are increasing and mammal to mammal transmission has occurred. Mammals can be infected with the virus when they eat infected birds, poultry, or other animals, or if they are exposed to environments contaminated with the virus. [5] [10]

Globally, sporadic avian influenza A(H5N1) virus infections in mammals have been reported across Asia, North America, South America, Europe, and Antarctica. Specifically, recent avian influenza A(H5N1) infections in mammals have been detected in sea lions in Peru and Chile, sea elephants in Argentina, and foxes in Canada, France, and other countries. The most common way for the virus to enter a territory is through migratory wild birds. [3] [10]

Additionally, there have been reports of possible, limited, human to human transmission, but there has been no evidence of ongoing virus transmission between humans. [5]

Human infections of avian influenza A(H5N1) are reportable to the local medical officer of health. Provincial and territorial public health authorities are required to report

[1] Zoonotic diseases are infections that transmit from animals to humans.

confirmed and probable human cases of avian influenza A(H5N1), irrespective of illness symptoms or severity, to the Public Health Agency of Canada (PHAC) within 24 hours of their own notification. PHAC is required to report any human case detected in Canada to the World Health Organization (WHO). [1] [11]

Epidemiology of human infections

Global

In 1959, avian influenza A(H5N1) virus was first detected in a poultry outbreak in Scotland. In 1997, eighteen human infections were reported during a poultry outbreak in Hong Kong, China, resulting in six deaths. This was the first time avian influenza A(H5N1) infection was associated with human deaths. Since 2003, the virus has spread in bird populations from Asia to Europe and Africa, and to the Americas in 2021, and has become endemic in poultry populations in many countries. Outbreaks have resulted in millions of poultry infections. [12] [13] [14]

Since the emergence of avian influenza A(H5N1) in humans in 1997, just over 900 human cases of A(H5N1) have been reported globally, with a 51% death rate. Human cases have been reported mostly from countries in Asia, but also from countries in Africa, the Americas and Europe. Nonetheless, human infection with avian influenza A(H5N1) is rare. [3] [15]

Additionally, the number of human cases has decreased substantially since 2015. This decrease may be attributed to the use of poultry vaccinations, prevention and control initiatives, and potentially changes in the virus. [3]

The predominant avian influenza A(H5N1) viruses now circulating globally among birds and other animals are different from earlier A(H5N1) viruses. Avian influenza viruses continually change, which can affect how easily the virus spreads from birds to other mammals, including humans, and also illness severity. [3]

United States

A multistate outbreak of avian influenza A(H5N1) viruses in dairy cows was first reported on March 25, 2024. This was the first time these viruses were found in cows.

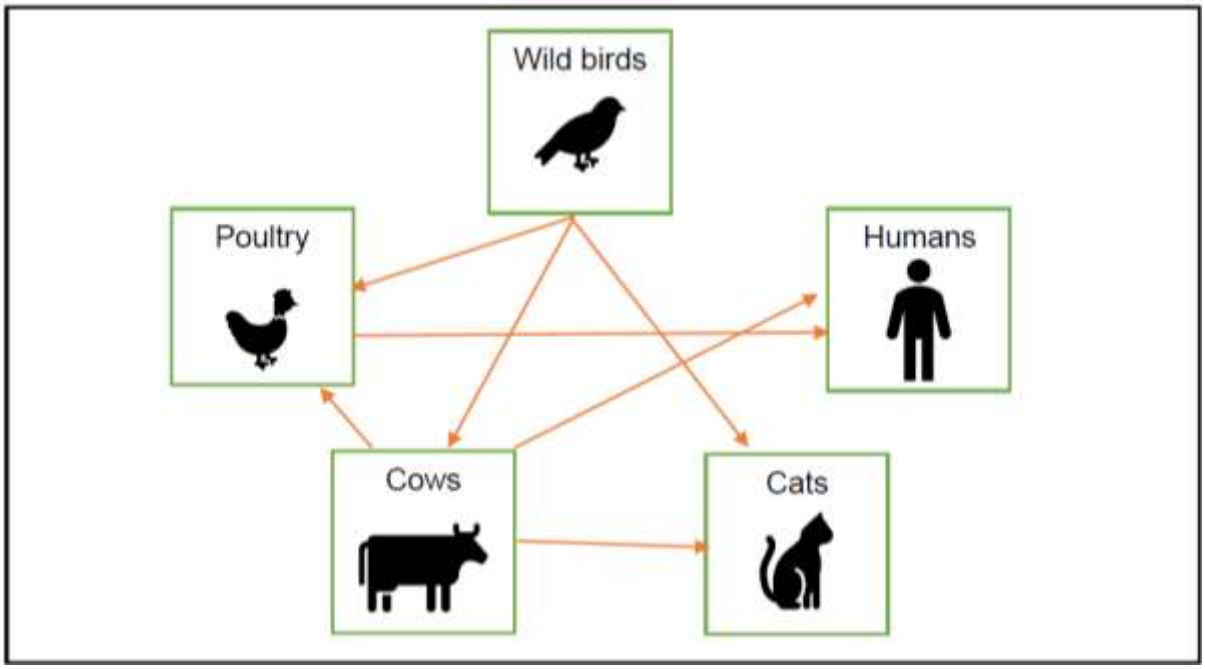
On April 1, 2024, the Centers for Disease Control and Prevention (CDC) confirmed one human avian influenza A(H5N1) infection in a person with exposure to dairy cows in Texas that were presumed to be infected with the virus. This is thought to be the first case of mammal to human transmission of avian influenza A(H5N1) virus. In May 2024, CDC began reporting additional, sporadic human cases in people who had exposure to infected dairy cows. [16] [17]

Since April 2024 (and as of July 26, 2024), thirteen human cases of avian influenza A(H5) infection have been reported in the United States. Four of these cases were associated with exposure to sick dairy cows and nine were associated with exposure to avian influenza A(H5N1)-infected poultry. The thirteen cases were all among farmworkers and all with mild symptoms (e.g., conjunctivitis and/or typical flu symptoms

of fever, chills, coughing, sore throat, runny nose). Based on the information available, CDC's current assessment is that the risk to the general public from avian influenza A(H5N1) remains low. [18] [19] [20]

During this 2024 outbreak, the virus has spread within and between cattle herds, including infections in poultry and cats and spillover into humans. To date, no human-to-human spread has been detected during this outbreak in dairy cows. [21]

How the avian influenza A(H5N1) virus is spreading in US [21]



Canada
In 2014, Canada reported a single fatal case of A(H5N1) in a resident of Alberta returning from travel in China where they were likely infected. However, to date, no domestically acquired human avian influenza A(H5N1) infections have ever been reported in Canada.

In late 2021, avian influenza A (H5N1) clade 2.3.4.4b was first detected in Canada in poultry, likely introduced through migratory wild bird populations from Europe. Avian influenza A(H5N1) detections associated with the current 2021-2024 A(H5N1) clade 2.3.4.4b have been reported in domestic, backyard, and wild bird populations, as well as in other animal species. To date, avian influenza A(H5N1) has not been detected in dairy cattle, other livestock, or raw milk in Canada. The risk of avian influenza A(H5N1) to the general population in Canada remains low. [4] [15] [22] [23]

Risk to humans
Avian influenza A(H5N1) viruses can cause severe disease in humans and have the potential for ongoing genetic mutation or viral reassortment. The wide geographic spread of avian influenza A(H5N1) viruses in wild birds, poultry, and other mammals could create additional opportunities for people to be exposed to these viruses.

Therefore, there could be an increase in sporadic human infections resulting from bird and animal exposures, even if the risk of these viruses spreading from birds to humans has not increased. [4] [10]

One Health
A coordinated and comprehensive 'One Health' response to the ongoing global outbreak of avian influenza A(H5N1) infections in dairy cattle, poultry, other animals, and humans is needed to identify and prepare for any developments that indicate an increase in the risk to public health. [24]

The World Health Organization (WHO) defines One Health as:

> *An integrated, unifying approach to balance and optimize the health of people, animals, and the environment. It recognizes that the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and interdependent.* [25]

By linking people, animals, and the environment, One Health can address all aspects of disease control, from prevention to detection, preparedness, response, and management, contributing to global health security. These efforts can contribute to the prevention of future pandemics and help build more resilient and equitable systems, environments, economies, and societies. [26] [27]

Transmission to humans
There are several ways avian influenza A(H5N1) can be transmitted to humans. Transmission can be divided into four categories according to the source of infection:
- Animal to human
- Environmental exposure
- Foodborne transmission
- Human to human [1]

Animal to human transmission
Virus transmission to humans occurs via inhalation or contact with mucus membranes (e.g., eyes, nose, mouth). This occurs if the virus is in the air in droplets, or possibly dust or feathers, or if the person touches a viral source and then touches their mouth, eyes, or nose. Virus exposure can occur through contact with various sources, including blood, secretions (e.g., mucus, saliva), or feces of infected birds or animals as the virus is shed in secretions and feces.

Transmission can occur during:
- Close contact with infected domestic animals, wildlife, and livestock.
- Plucking, handling infected poultry carcasses, and preparing poultry for consumption, especially in domestic settings.

Human infection has been reported after defeathering infected dead swans. It has been determined the virus can survive in feathers for several weeks in moderate temperatures, and over five months in cooler temperatures. [1] [7] [8]

Environmental exposure
Even though the majority of avian influenza A(H5N1) human cases have occurred after contact with infected poultry, some cases have been associated with exposure to highly contaminated environments (e.g., live animal markets, animal farms, poultry farms).

Foodborne transmission
Based on the limited available research, it is not known at this time if avian influenza A(H5N1) viruses can be transmitted through consuming raw or undercooked animal products. There have been anecdotal reports of human cases of avian influenza A(H5N1) possibly associated with consuming raw or undercooked contaminated poultry products (e.g., raw duck organs and blood). However, to date, there have been no confirmed cases of human infection with avian influenza A(H5N1) acquired through the food consumption. [1]

Additionally, there is no evidence to suggest consuming fully cooked poultry, beef, game meat, organs, or eggs can transmit the virus to humans. All evidence to date indicates thorough cooking will kill the virus. Pasteurized milk and pasteurized milk products remain safe to consume. Pasteurization eliminates harmful viruses and bacteria while retaining the nutritional properties of milk. [1] [3]

Research has confirmed pasteurization effectively inactivates avian influenza A(H5N1) virus in fluid milk and other dairy products made from pasteurized milk. Accordingly, people should avoid consuming raw milk or products produced from raw milk. [24] [28]

Research by Le Sage et al. (2024) found avian influenza A(H5N1) remained infectious on milking equipment for several hours, highlighting the risk for virus transmission to humans from contaminated surfaces during the milking process. Such infections could enable H5 viruses to adapt through viral evolution within humans and gain human to human transmission capability. To reduce H5N1 virus spillover from dairy cows to humans, farms should implement use of personal protective equipment (e.g., face shields, masks, eye protection) for workers during milking. In addition, sanitizing the equipment after milking each cow could reduce influenza virus spread between farm animals and help curb the current outbreak. [29]

Human to human transmission
Evidence of limited human to human transmission of avian influenza A(H5N1) through close physical contact (e.g., within a household) has been suggested in previous outbreaks. To date, sustained human to human viral transmission has never been observed globally. [1]

Clinical manifestations of avian influenza A(H5N1)
Signs and symptoms of avian influenza A(H5N1) have ranged from no symptoms to severe fatal illness. The virus mainly affects the respiratory tract, but can sometimes cause gastrointestinal or central nervous system symptoms (e.g., encephalopathy). Clinical illness is seen predominantly in children and young adults. The incubation period ranges from one to five days and up to nine days. [1] [5]

Symptoms often start with:
- Cough
- Shortness of breath
- Fever
- Muscle aches
- Headache

Other early symptoms may include:
- Diarrhea
- Rhinorrhea (runny nose)
- Sore throat
- Fatigue
- Conjunctivitis (eye redness)
- Bleeding gums

In rare cases, the infection may progress quickly to:
- Severe respiratory illness, which can include:
    - Difficulty breathing
    - Pneumonia
    - Acute respiratory distress syndrome
    - Pulmonary hemorrhage
    - Pneumothorax
- Neurological changes (e.g., altered mental state, seizures)

In severe cases, the infection may cause multiple organ failure, which can lead to death. Approximately, half of the over 900 human cases reported globally since 1997 have been fatal. However, this may be an overestimate given that mild infections may go undetected and under-reported. [5] [7]

Diagnosis
A laboratory test is required to diagnose avian influenza A(H5N1). Usually a nasal or throat swab is taken during the first few days of illness, which is sent for laboratory testing to identify the type of virus causing the infection. [7]

Treatment
Antiviral medications can be used to treat suspected, probable, or confirmed avian influenza A(H5N1) cases. The ideal time to begin antiviral treatment is within 48 hours of illness onset to maximize their benefit. Treatment should not be delayed and can be initiated while awaiting confirmatory test results. Antiviral options for treating avian influenza A(H5N1) include oseltamivir, zanamivir, and peramivir. Prophylactic use of influenza-specific antivirals (pre and post exposure) may prevent illness. [1]

Antiviral medications can:
- Reduce influenza symptoms
- Shorten duration of illness
- Potentially reduce serious complications and hospitalizations

Individuals with severe illness need to be hospitalized. [5] [7]

Observational studies of individuals infected with older and different clades of A(H5N1) viruses, (i.e., not the current clade 2.3.4.4b viruses currently identified) have found starting oseltamivir (Tamiflu®) treatment within 48 hours of symptom onset was significantly associated with survival benefit compared with no treatment or later initiation of oseltamivir treatment after symptom onset. [24]

Suspected avian influenza A(H5N1) case or contact
Individuals exposed to avian influenza A(H5N1), including those who used personal protective equipment (PPE), should monitor their health starting on the first day of exposure and for ten days after the last exposure. Any signs or symptoms of illness should be reported to their medical provider and the local public health department.

If a person is symptomatic after exposure or has a confirmed infection, they should isolate away from others and follow measures to reduce the spread of influenza and other respiratory viruses. These include respiratory etiquette (e.g., covering coughs and sneezes), physical distancing, wearing a mask when physical distancing is not possible, regular hand hygiene, improving indoor ventilation (e.g., opening windows), and regularly cleaning and disinfecting surfaces and objects. [5]

At risk activities
People with close contact to infected animals or birds are at increased risk of avian influenza A(H5N1) infection, and should take appropriate precautions. [3]

Examples of activities that may increase the risk of exposure and infection include:
- Working with infected poultry (e.g., chickens, turkeys, ducks) or livestock (e.g., cattle, goats) such as on commercial farms, small farms, or backyard poultry.
- Hunting, defeathering, field dressing, and butchering infected wild birds and animals.
- Working with wild birds for activities such as research, conservation, or rehabilitation.
- Working with wild animals, especially animals that commonly eat wild birds (e.g., foxes, skunks, raccoons, some marine mammals, and mink and other farmed fur animals).
- Visiting animal farms or live animal markets. [3]

Prevention
The risk of avian influenza A(H5N1) infection is low for the general public. However, basic preventive measures are advised to mitigate zoonotic disease transmission, including:
- Avoiding close contact with wild birds and animals (e.g., not touching, feeding, handling them).
- Avoiding contact with animals, including livestock that may be sick or infected.
- Avoiding exposure to blood, secretions, and feces from birds and animals. Wearing protective gloves or using a doubled plastic bag if contact is unavoidable.

- Removing gloves after use and washing hands thoroughly with soap and water, or using hand sanitizers containing at least 60% alcohol if soap and water are unavailable.
- Washing hands after visiting areas where birds and wildlife reside or nest (e.g., parks, zoos). Children should be supervised to ensure proper handwashing.
- Keeping pets away from birds, wildlife, and their feces. [3] [5]

Individuals who have close contact with poultry, livestock, wild birds, wildlife, or animals infected with the virus (suspected or confirmed) or work in environments contaminated by them, should take additional precautions (e.g., wearing masks, eye protection, protective clothing, etc.). [3]

Foodborne risks

To limit any potential foodborne risks:

- All poultry, beef, and other meat, organs and eggs should be thoroughly cooked to kill potential viruses, parasites, and bacteria.
- All milk and milk products should be pasteurized before consuming.
- Safe food handling practices should be followed, such as handwashing and keeping raw meat, organs, and eggs separate from other food products to avoid cross contamination. [1]

Vaccination

CDC regularly develops candidate vaccine viruses (i.e., viruses made for vaccine production) for novel avian influenza viruses with pandemic potential. Two existing avian influenza A(H5N1) candidate vaccine viruses are already available to manufacturers, and which could be used to make vaccine if needed. Currently, there is no avian influenza vaccine available in Canada for public use. [1] [5] [30]

Some countries have developed and licensed vaccines that could be used for avian influenza viruses, including H5N1, as part of their influenza pandemic preparedness work. Currently, human infections of avian influenza A(H5N1) are limited and vaccines are not recommended by the WHO. [31]

The National Advisory Committee on Immunization (NACI) recommends those likely to have significant exposure to avian influenza A(H5N1) through interactions with birds or mammals (e.g., poultry, livestock, slaughterhouse and processing plant workers, veterinarians, wildlife officers, researchers) receive the seasonal influenza vaccine.[2] Seasonal influenza vaccines do not protect against avian influenza viruses. However, they may reduce the risk of seasonal human and influenza A(H5N1) virus coinfection and possible viral reassortment leading to a human-transmissible virus with pandemic potential. Receiving the yearly seasonal influenza vaccine can also help reduce the spread of human influenza viruses between people and between people and animals. [3] [10] [32]

[2] Refer to Episode 97 for discussion on viral respiratory infections, including seasonal influenza.

Avian influenza A(H5N1) in birds
Avian influenza A(H5N1) can infect multiple species of domestic chickens, turkeys, quails, guinea fowl, etc., as well as wild birds and pet birds. Birds spread avian influenza viruses through their feces and secretions. Pet birds with outdoor access may become infected through direct or indirect contact with infected wild or domestic birds. Pet birds kept indoors may be exposed through contaminated surfaces such as clothing if proper precautions are not taken.

Signs of the virus in birds include:
- Lack of energy, movement, or appetite
- Decreased egg production
- Swelling around the head, neck, and eyes
- Coughing, gasping for air, or sneezing
- Nervous signs, tremors, or lack of coordination
- Diarrhea
- Sudden death

Clinical signs in pet birds are similar to those in other bird species. The severity of clinical signs may vary between species and individual birds. [33]

Avian influenza A(H5N1) in dairy cattle
Signs of avian influenza A(H5N1) in dairy cattle include:
- Sudden decrease in milk production (especially in older cows)
- Thicker consistency milk
- Decrease in feed consumption
- Dry manure or constipation (diarrhea has been observed occasionally)
- Fever (sometimes)
- History of dead wild birds on the property [33]

Avian influenza A(H5N1) in cats and dogs
Cats and dogs can be infected with the virus, especially those who hunt, scavenge, and consume infected birds.[3] Signs of avian influenza A(H5N1) in cats and dogs include:
- Fever
- Lethargy
- Conjunctivitis
- Lack of appetite
- Difficulty breathing
- Neurological signs (e.g., tremors, seizures)
- Death [33]

[3] Note: Sick or dead birds or other wildlife should be reported to the Ontario regional centre of the Canadian Wildlife Health Cooperative by calling 1-866-673-4781 or via their website: https://www.cwhc-rcsf.ca/report_and_submit.php [34]

Take home messages

- Avian influenza A(H5N1) viruses are a significant global challenge due to their widespread circulation and high mortality rates. The documented cases of human infection and recent outbreaks in various wildlife and domestic animals, underscore the ongoing concerns regarding transmission and potential human infections.
- The current global outbreak has brought urgent attention to the need to monitor and understand these viruses to assess their potential for increased transmissibility and pathogenicity.
- It is vital to pay attention to this virus since an expanded range of hosts increases the potential for the virus to persist, evolve, and potentially cross species barriers, posing a greater threat to animal and public health.
- The increasing reports of human infections underscores the need for vigilance and continuous research to understand the evolving nature of the virus to effectively respond to the ongoing outbreak among animals, mitigate its impacts, and prevent future outbreaks and transmission to humans.
- Public awareness of avian influenza A(H5N1) is crucial, including the importance of avoiding contact with dead or ill birds and animals unless individuals are properly trained and equipped to handle them safely.
- It is essential to exercise caution and keep pets (e.g., dogs, cats) away from potentially infected animals and birds. This precautionary measure applies to rural and urban environments, including parks and green spaces, which frequently harbour high concentrations of wild bird populations, amplifying the risk of exposure.

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Client Resources

Avian influenza A(H5N1): Symptoms and treatment, Government of Canada
https://www.canada.ca/en/public-health/services/diseases/avian-influenza-h5n1.html

Avian influenza A(H5N1): Prevention and risks, Government of Canada
https://www.canada.ca/en/public-health/services/diseases/avian-influenza-h5n1/prevention-risks.html

Avian influenza in wild birds, Government of Canada
https://www.canada.ca/en/environment-climate-change/services/migratory-game-bird-hunting/avian-influenza-wild-birds.html

Animals susceptible to H5N1 highly pathogenic avian influenza (HPAI), Government of Canada https://inspection.canada.ca/en/animal-health/terrestrial-animals/diseases/reportable/avian-influenza/animals-susceptible-h5n1-hpai

Canadian Wildlife Health Cooperative
Sick or dead birds or other wildlife should be reported to the Ontario regional centre of the Canadian Wildlife Health Cooperative by calling 1-866-673-4781 or via their website: https://www.cwhc-rcsf.ca/report_and_submit.php

Additional Resources

Avian influenza A(H5N1): For health professionals, Government of Canada, July 26, 2024 https://www.canada.ca/en/public-health/services/diseases/avian-influenza-h5n1/health-professionals.html

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https://nccid.ca/debrief/avian-influenza-h5n1/

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Highly pathogenic avian influenza A(H5N1) virus infection in a dairy farm worker, Uyeki, T; Milton, S; Webb, C; et al. *New England Journal of Medicine*, Volume 390, Issue 21, May 3, 2024, p 2028-2029 https://www.nejm.org/doi/full/10.1056/NEJMc2405371

Persistence of influenza H5N1 and H1N1 viruses in unpasteurized milk on milking unit surfaces, Le Sage, V; Campbell, A; Reed, D; et al. *Emerging Infectious Diseases*, Volume 30, Issue 8, August 2024, p 1721-1723 https://wwwnc.cdc.gov/eid/article/30/8/24-0775_article

Pathogenicity and transmissibility of bovine H5N1 influenza virus, Eisfeld, A; Biswas, A; Guan, L; et al. *Nature*, July 8, 2024 https://www.nature.com/articles/s41586-024-07766-6