Rapid Risk Assessment Update: Avian Influenza A(H5N1) Clade 2.3.4.4b in Livestock- Public Health Implications for Canada

Date of this assessment: April 19, 2024; Version: 3.3
Date of previous risk assessment: June 21, 2023
Reason for the assessment: Finding of avian influenza A(H5N1) clade 2.3.4.4b in cattle and goats in the United States (US).

Risk Questions

1. **Risk Question:** What is the likelihood and impact of human infection with avian influenza A (H5N1) clade 2.3.4.4b due to exposure to livestock (e.g., cattle, goats, swine)[i] in Canada in the next 3 months?
2. **Additional Question on Future Risk:** How does the current situation affect potential future public health risk in Canada?

Risk Statement

1. For the **general population in Canada,** the likelihood of human infection with avian influenza A(H5N1) clade 2.3.4.4b acquired from livestock (e.g., cattle, goats, swine) in the next 3 months **is very low** due to a very low likelihood and level of exposure to infectious virus. Given the small number of human cases reported to date globally despite frequent high-dose exposures in certain populations, the virus appears to have a limited capacity to infect humans. Therefore, the likelihood is at most **low** for people **with higher level of exposure to infectious livestock.** There is high uncertainty in these estimates due to limited surveillance and testing of mammalian species, and limited information on the proportion of livestock infected, nature of infection and transmission dynamics in these species, and the potential for transmission of this clade from infected mammals to humans.

   There has been no change in the estimated magnitude of impact from the previous assessment on infected individuals or the Canadian population. There is no evidence that the virus has acquired the capacity for sustained transmission among humans.

2. It is unknown how the current situation will affect the potential future public health risk in Canada. However, continued transmission of avian influenza A(H5N1) clade 2.3.4.4b viruses in wild and domestic bird populations, and repeated spill-over into diverse wild and domestic mammalian species, increase the likelihood of viral reassortment and/or adaptation that could enable sustained transmission in mammalian species, including humans, as stated in the previous rapid risk assessment and the pandemic risk scenario analysis. Spillover into livestock increases opportunity for genetic change that could result in a virus with greater fitness in mammalian hosts, especially if the infections are mild or asymptomatic in cattle and go unnoticed with minimal infection precautions.

   While transmission of this clade is highly suspected to be occurring globally between mammals with sufficient contact, the degree of transmission is currently unclear. Contact between pigs and any animals that are infected, including livestock, may lead to an increased likelihood of significant genetic changes in the virus, since pigs are known to be a mixing vessel for influenza A viruses.[1]

   It is very hard to predict how this virus will evolve, but this uncertainty emphasizes the **importance of surveillance and preparedness activities** in both human and animal sectors.

Proposed Actions for Public Health Authorities and One Health Partners

One Health coordination on this issue remains vital. The proposed actions from the previous assessment continue to be important. PHAC will continue to engage One Health partners (federal, provincial, territorial,

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[i] Health Canada is assessing food safety risk associated with animal products.

Indigenous and other non-government organizations) domestically and collaborate with international partners to assess public health risks associated with current and future avian influenza A strains.

The recommendations proposed below are based on the knowledge gaps identified during this update.

Surveillance and reporting
- Continue efforts to further enhance and integrate surveillance activities for avian influenza across the One Health spectrum to:
    - monitor changes in virus evolution and species adaptation as well as antiviral resistance in any infected mammalian species,
    - rapidly detect and respond to a potential human infection, including in those exposed to infected livestock. Develop protocols *a priori* to aid in investigation, including for sero-incidence, and
    - understand infection risk in humans with exposure to livestock, such as with sero-epidemiological studies in animals and humans.

Risk Communication
- Continue regular communication on the current avian influenza A(H5N1) clade 2.3.4.4b with the public and those working with livestock, including people who have poultry and livestock on the same premises. Share Wildlife and avian influenza – Handling guidelines to protect your health guidance.
- Continue to build awareness among health professionals on early detection and management of avian influenza A(H5N1) clade 2.3.4.4b virus infection in people showing signs or symptoms of acute respiratory illness or conjunctivitis and who have relevant exposure history. Share Guidance on human health issues related to avian influenza in Canada (HHAI).

Research
- Consider pursuing research activities as identified in the knowledge gaps (2.4).

Disclaimer: The qualitative and expert-opinion-based methodology is intended to be used in situations where policy decisions need to be made in the face of high uncertainty. The assessment was primarily informed by the team's collective professional knowledge on such topics as infectious diseases, virology, epidemiology, the health system, industry practices, and human-animal interactions. Where appropriate, some references have been provided, but this is not intended as a literature review. The estimates represent the consensual, but not necessarily unanimous, opinions of the participants, and should not be interpreted as representing the views of all participants and their respective organizations.

1. Rapid Risk Assessment Background

1.1 Event Background

Current Situation (as of April 11, 2024)

Livestock (goats and dairy cattle)

At the beginning of March 2024, unusual deaths in newly kidded goats were reported on a farm in Minnesota where a backyard poultry flock was depopulated in February due to avian influenza A(H5N1) clade 2.3.4.4b.[2] The goats and poultry on the farm had access to the same spaces and shared water sources. Ten goats died, ranging from 5 to 9 days old. Of the ten goats that died, five have tested positive on brain and tissue samples for the virus; and genomic sequencing showed that viruses in samples from the kids and poultry on the farm were highly related.[3] As of March 11, no additional illnesses have been reported.

On March 11, 2024, illness of unknown aetiology was reported in dairy cattle in Texas, US.[4] Initial signs of low dry matter intake had been observed on March 9, 2024. Two days later, 17 cows showed various signs of illness including decreased milk yield, milk with thicker consistency and abnormal colour that was similar to colostrum, dry and tacky feces and anorexia.[5] Some of the cattle had secondary illnesses such as mastitis and pneumonia. On March 25, oropharyngeal and milk samples from cows in Texas and Kansas were confirmed as positive for avian influenza A(H5N1) clade 2.3.4.4b by PCR and immunohistochemistry. As of April 8, 2024, avian influenza A(H5N1) clade 2.3.4.4b has been confirmed in dairy cattle from 16 herds in 7 U.S. states: Texas (9), Kansas (3), Michigan (1), New Mexico (2), Idaho (1), Ohio (1), and North Carolina (1).[6] Morbidity has been seen in approximately 10% of animals in affected herds. Affected cattle have been recovering and there have been no deaths to date. Wild migratory birds are believed to be the source of infection for the initial implicated farms, as dead wild birds were found around the farms.[7]

The affected herd in Michigan had received cows from an affected farm in Texas. Affected herds in Idaho and Ohio had also received dairy cows from Texas, but it is unknown whether other herds have as well. Evidence of cattle-to-cattle transmission cannot be ruled out, possibly through contaminated milking equipment, as high levels of virus have been found in milk from infected cows with no or lower levels in nasal swabs and feces. Early pathogenic observations indicate apparent tissue tropism for mammary gland in lactating domestic cattle.[8] However, there has so far been no evidence of mammalian adaptations in the viruses detected in animals.[9] Dead pigeons and grackles, which have not been recognized as carriers or susceptible to highly pathogenic avian influenza (HPAI), and a barn cat from the initial cattle farm in Texas were tested and avian influenza A(H5N1) clade 2.3.4.4b was isolated. [10]

Humans

Since December 2021 (as of April 10, 2024), detections of avian influenza A(H5N1) clade 2.3.4.4b viruses in humans have been reported from China (n=2)[11,12], the United Kingdom (n=5)[13,14,15], the US (n=2)[16,17], Spain (n=2)[18], Viet Nam (n=2; clade not confirmed at time of writing for either case)[12,19,20], Ecuador (n=1)[11] and Chile (n=1)[21]. The most recent case was detected in the US on April 1, 2024. This individual had exposure to infected dairy cattle on one of the aforementioned farms. Eye redness (conjunctivitis) was the only clinical sign. Respiratory and conjunctival specimens tested positive. The individual was treated with oseltamivir and was in isolation while recovering. The case did not require hospitalization. Genomic analysis confirmed the virus sequence was avian influenza A(H5N1) clade 2.3.4.4b with each individual gene segment determined to be closely related to the viruses detected in dairy cattle in Texas. Unlike the viruses found in the infected cattle and that detected in wild birds in the region, the virus detected in the human had the PB2 E627K mutation.[22] This mutation may have occurred after infection through viral replication within the human case. It is one of the genetic changes known to be associated with mammalian adaptation, but there has been no known onward spread from people infected with a virus with this mutation.[23,24]

Birds

The avian influenza A(H5N1) clade 2.3.4.4b virus has resulted in unprecedented global transmission in birds, with a significant number of detections in domestic poultry (both backyard and commercial) and wild bird populations. Since 2021, avian influenza A(H5N1) clade 2.3.4.4b has been detected in 11,030,500 poultry birds (as of March 5, 2024)[25] and 2,824 wild birds (as of April 8, 2024)[26] in Canada. Overall, detections have occurred in more than 80 species of wild birds (these can be found on the CFIA Wild Positives Dash), many of which are migratory species that spend at least part of their annual cycles in Canada, migrating north in the spring to breeding areas, and south in the fall to overwintering areas.

Non-Human Mammals

In North America, avian influenza A(H5N1) clade 2.3.4.4b infections have occurred across a broad range of wild mammals, including mesocarnivores, large carnivores, marine mammals, marsupials, and rodents.[27] In South America, widespread infections have occurred in marine mammals, including a mass mortality event in South American sea lions involving thousands of individuals where mammal-to-mammal transmission has not been ruled out.[28,29] In addition, until recently, detections in domestic mammals in North America have only been reported in cats and a dog.

1.2 Definitions

Exposure definitions are the same as in the previous assessment, with the addition of:
- The exposure experienced by the **general (human) population** is assumed to be either negligible or lower level exposure to livestock.

Additions to the list of occupational and recreational groups with potentially relevant exposures in the previous assessment (appendix B) include:

- Livestock farm worker/small herd owner
- Meat/milk processing plant worker

2   Detailed Risk Assessment Results for Question 1

2.1 Risk Pathway

Risk pathway depicting exposure to infected livestock leading to human infection with avian influenza A(H5N1) clade 2.3.4.4b in Canada in the next 3 months. Human-to-human spread (Question 4) and human health impacts (Questions 5 & 6) were assessed previously.

Figure 1. Risk Pathway
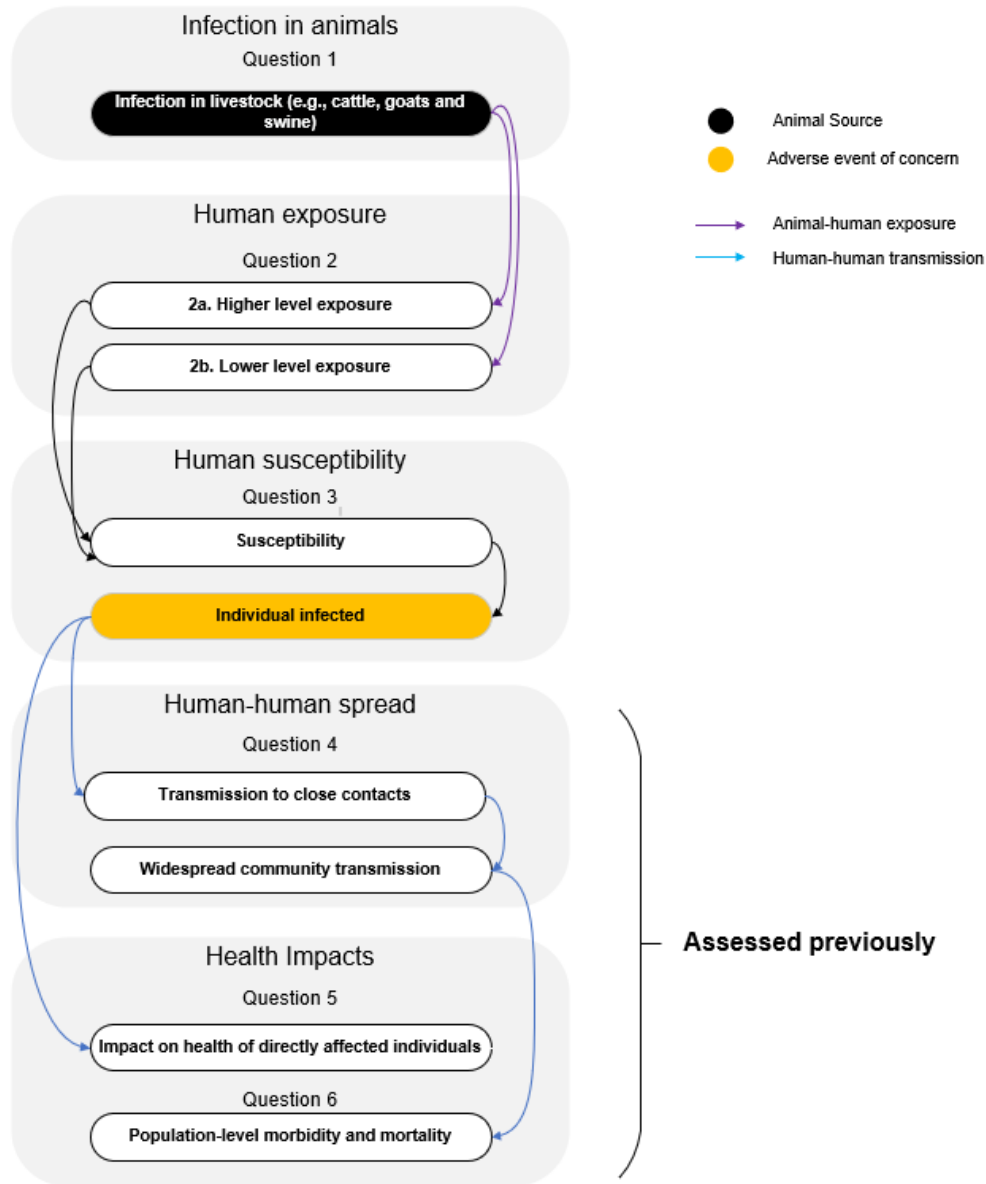
2.2 Likelihood estimate sub-questions

1. What is the likelihood that a random individual animal from a livestock herd in Canada is infected with avian influenza A(H5N1) clade 2.3.4.4b during the assessment period?	
Likelihood (Uncertainty)	Too uncertain to assess

Historically, cattle have largely been unaffected by influenza A. However, past research suggests that cattle are susceptible to the human influenza A viruses H1N1 and H3N2 and that these viruses play a role in causing respiratory disease and milk drop syndrome in cattle.[30,31,32] Experimentally, cattle have also been found to be susceptible to a HPAI H5N1 subtype (Asian lineage) and infectious virus was detected in nasal swabs of sub-clinically infected animals.[33] There had been no reports of infected cattle or goats with the current clade of the H5N1 subtype, despite it circulating extensively in birds around the world, until the recent findings in the US. Swine are known to be susceptible to avian influenza viruses, with a recent study in Italy reporting evidence of seroconversion of a swine herd to an H5N1 virus similar to the strain detected in laying hens on the same farm.[34]

Given the current findings in cattle and goats in the US, it is reasonable to assume that livestock with direct contact with infected birds and/or their contaminated environments (such as food and water sources) may become infected; however, the extent of these infections that may have already occurred or that may occur in the future is unknown. Surveillance for subclinical or mild infection with avian influenza A(H5N1) clade 2.3.4.4b in livestock mammals has not been conducted in Canada. There have been no reports of suspected infection with influenza A(H5N1) clade 2.3.4.4b (due to clinical signs) in cattle or other livestock in Canada to date. However, there is the possibility that infection could be introduced to Canadian cattle from movement of infected dairy cattle from the US.

Dairy cattle in Canada likely have less contact with wild birds than dairy cattle in the southern US, since their housing may be more enclosed. However, there is a lower level of biosecurity (e.g., more potential for humans to bring in contaminated soil) with dairy barns than with poultry barns. Beef cattle and other small ruminants spend more time outside and have a higher likelihood of contact with wild birds than dairy cattle. Compared to infections in dairy cattle, which require daily manipulations (e.g. milking), infections in livestock raised for meat production, like beef cattle, could be harder to detect since they are not monitored as closely.

Some species of wild birds, particularly waterfowl, begin to display spring migratory behavior in Canada in February, with core migratory periods for most species occurring between April and June. In Canada, seasonal patterns of infection prevalence coincide with periods of increased wild bird congregations during spring and fall seasons.[35,36] Sporadic infections in livestock in Canada could occur during the assessment period as observed in the US; however, the extent is uncertain. There may be geographic variation in infection prevalence, depending on the local avian influenza A(H5N1) clade 2.3.4.4b epidemiology, and density of wild bird and livestock populations.

The uncertainty is too high to allow an estimate of livestock infection at this time due to limited surveillance in livestock, limited information on susceptibility of livestock and the possibility of asymptomatic/mild infections.

2a. What is the likelihood that a higher level exposure involves a sufficient amount of virus to potentially cause an infection (for the average person)?	
Likelihood (Uncertainty)	Too uncertain to assess

The detection of this virus in a human with exposure to infected dairy cattle in the US suggests that transmission to those in close contact with infected livestock or highly contaminated environments may be possible. However, the extent and route of virus shedding by livestock and the route of transmission to the human case is uncertain, making it difficult to assess the likelihood of this occurrence over time. The US patient reported mild eye redness as the only clinical sign; therefore, even if this was the result of transmission from cattle or the contaminated environment, it is uncertain whether the amount of virus shed by cattle would be sufficient to elicit more severe infection. In addition, current information about infection in cattle from the US indicates high detection of the virus in milk, low or negligible detection in nasal swabs and no detection in blood samples; suggesting a non-systemic disease. As stated in the previous assessment, most human cases reported to date have involved higher level exposure with infected poultry and/or highly contaminated environments.

The uncertainty is too high to allow an estimate of the likelihood due to limited information about incubation period and shedding in livestock, and associated mode of transmission.

2b. What is the likelihood that a lower level exposure involves a sufficient amount of virus to potentially cause an infection (for the average person)?	
Likelihood estimate	Very low
Uncertainty estimate	High

This estimate is the same as the one made in the previous assessment in relation to people exposed to other (non-livestock) animals. Globally, there are no known human cases associated with lower level exposure of the general public. Due to the high volume of infections with this virus that have occurred in wild animals and poultry in Canada, there have likely been numerous low dose contacts that have not resulted in exposure to sufficient amount of the virus to cause significant disease in a person.

The uncertainty estimate is high based on lack of information concerning potential infectious dose in lower level exposure situations, and potential for under-detection of asymptomatic or mild infections in humans following lower level exposures.

3. What is the likelihood that a person who had exposure to sufficient amount of virus will develop an infection?	
Likelihood estimate	Low
Uncertainty estimate	Moderate

This estimate is the same as the previous assessment in relation to people exposed to other (non-livestock) animals. Although human populations are expected to have very little immunological protection against avian influenza A(H5N1) clade 2.3.4.4b viruses, there have been only a small number of human cases reported to date globally despite frequent high-dose exposures in certain populations, particularly those in contact with poultry. Genetic analysis from the virus isolated in cattle has not found any major changes to the virus from what has been found previously.[37]

The uncertainty estimate is moderate based on lack of information on this specific clade, the small number of detections in humans and limited surveillance activities in populations exposed to infected animals.

2.3 Combined likelihood estimates

What is the likelihood of human infection with avian influenza A(H5N1) clade 2.3.4.4b due to exposure to livestock in Canada in the next 3 months?	

Likelihood (Uncertainty)	1. Infection in livestock -> Too uncertain to assess
	2. Sufficient amount of virus from exposure
	      a. <u>Higher level</u> exposure -> Too uncertain to assess
	      b. <u>Lower level</u> exposure -> Very low (high uncertainty)
	3. Infection following exposure to sufficient amount of virus -> Low (moderate uncertainty)
	
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	• Combined likelihood for general population (1 AND 2b AND 3)*
	      ○ **Very low** (high uncertainty)
	• Combined likelihood for populations with higher level exposure (1 AND 2a AND 3)*
	      ○ **Low** (high uncertainty)

* Since the likelihood of each step in the risk pathway is conditional on the likelihood of preceding steps, the likelihood for the combined question is therefore determined by the lowest likelihood estimated along the given steps in the pathway (i.e., those separated by "AND" statements).

The likelihood of infection with avian influenza A(H5N1) clade 2.3.4.4b is **very low** for the **general population** that have negligible or lower level exposure to livestock (e.g., cattle, goats, swine), driven by very low likelihood of exposure to the virus. There is high uncertainty with this estimate due to the lack of information on potential infectious dose for lower level exposures.

The likelihood of infection with avian influenza A(H5N1) clade 2.3.4.4b for **populations that have higher level exposure to livestock** (e.g., cattle, goats, swine) is at most **low** due to the limited capacity of the virus to infect humans. The uncertainty is high for this estimate due to lack of information on the infectivity of this clade for humans, the small number of infections in humans, and limited surveillance and testing in livestock and human populations exposed to livestock.

2.4 Knowledge gaps

Many of the key scientific uncertainties and knowledge gaps from the <u>previous assessment</u> remain. Those specific to this assessment are included below (see Table 1).

Table 1. Knowledge gaps

Risk pathway sub-section	**Unknown/More information needed**
Infection in animals e.g., routes of introduction	• There is a scarcity of information on infection and shedding in livestock, and limited understanding of the clinical presentation in these species (including how much the epidemiological situation has changed recently versus a change in diagnosis and detection). • There is uncertainty regarding the extent of livestock-to-livestock transmission. • Lack of information on degree of virus shedding by infected cows (symptomatic and asymptomatic) in milk, mucus and manure, duration of shedding, and incubation and infection period. • Lack of understanding of infection risk in other species on affected livestock farms (e.g. cats, wildlife) due to potential transmission from livestock.

Risk pathway sub-section	Unknown/More information needed
Exposure and infection in humans e.g., incidence, prevalence	• There is a lack of evidence regarding the infectious dose in humans and the types of exposures necessary (intensity, duration) to induce infection in humans following contact with infected livestock and contaminated environments. • Current surveillance strategies may lead to under-detection of mild and subclinical human infections, limiting our understanding of livestock exposures associated with these mild infections. • There is uncertainty regarding the best testing strategies for patients presenting with non respiratory symptoms (e.g., conjunctival versus nasopharyngeal swabs). • There are many uncertainties associated with the transmission of the virus through the ingestion of raw animal products (e.g., raw milk and cheese). • There is limited understanding of the effectiveness of biosecurity measures to prevent spillover to people in cattle/dairy industry

Appendix A: Acknowledgements

Avian Influenza A(H5N1) clade 2.3.4.4b Rapid Risk Assessment Team

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