Rapid Risk Assessment: Avian Influenza A(H5N1) Clade 2.3.4.4b

Date of this assessment: June 21, 2023; Version: 2.0
Date of initial risk assessment: June 9, 2022
Reason for the assessment: Continued circulation of avian influenza A(H5N1) clade 2.3.4.4b in wild and domestic bird populations, reported infections with this clade among an increasing range of mammalian species, and periodic reports of isolated human cases in other countries.
Completed by: Public Health Agency of Canada (PHAC)-Corporate Data and Surveillance Branch (CDSB)-Centre for Integrated Risk Assessment (CIRA) in collaboration with a multi-sectoral team

Risk Question:

What is the likelihood and impact of at least one human infection with avian influenza A (H5N1) clade 2.3.4.4b due to exposure to either birds or mammals in Canada up to the end of the 2023 fall bird migratory season?

Overall Risk Statement:

The **overall risk to the general population in Canada** from avian influenza A(H5N1) clade 2.3.4.4b is **low**. Those with **higher level exposure** to domestic or wild birds or wild mammals are at **increased risk** of infection.

For the **general population in Canada with low level of exposure to birds,** human infection with avian influenza A(H5N1) clade 2.3.4.4b acquired from birds (wild birds or commercial or backyard poultry) **is very unlikely**. For the **population with higher level of exposure to birds**, infection is **unlikely** due to the low proportion of birds infected as well as the limited capacity of the virus to infect humans. The uncertainty associated with these estimates varies widely, due to limited information on the infectivity of this clade for humans, limited surveillance and testing in human populations exposed to birds as well as backyard poultry, and gaps in information regarding backyard poultry flocks in Canada.

Infection with avian influenza A(H5N1) clade 2.3.4.4b from mammals is **very unlikely for the general population with higher level exposure to domestic mammals** (e.g., dogs and cats) but **lower level exposure to wild mammals**. For the **population with higher level exposure to wild mammals** (e.g., wild carnivores and scavengers), infection is **unlikely** due to the low proportion of wild mammals infected and the limited capacity of the virus to infect humans. There is moderate to high uncertainty in these estimates due to limited surveillance and testing of mammalian species and the limited information on the infectivity of this clade for humans.

The impact on the **first infected individual(s)** in Canada is estimated to be **major,** considering the severe clinical manifestations seen in some cases globally, as well as the expected burden from control measures, such as isolation and quarantine, on affected individuals and their close contacts. Notably, early detection and prompt treatment in Canada will likely reduce disease severity. Uncertainty in this estimate is high, because of the variability in clinical presentations, ranging from asymptomatic infection to death, among the limited number of reported human detections from other countries to date.

Since there is no evidence that the virus has acquired the capacity for sustained transmission among humans, further **human-to-human transmission is not expected**. Therefore, the **overall impact to the Canadian population** would be **minor**, with low uncertainty.

Risk Assessment Summary

Table 1. Likelihood and impact estimates of a human infection of avian influenza A(H5N1) clade 2.3.4.4b in Canada during the assessment period

	Description	Estimate	Uncertainty
Likelihood of infection from birds	Likelihood of infection for general population with lower/negligible exposure to domestic or wild birds	Very unlikely	High
	Likelihood of infection for population with higher exposure to domestic or wild birds	Unlikely	Very low to High*
Likelihood of infection from mammals	Likelihood of infection for general population with higher exposure to domestic mammals (e.g., dogs and cats) but negligible/lower exposure wild mammals	Very unlikely	Moderate to High*
	Likelihood of infection for population with higher exposure to wild mammals (e.g., wild carnivores and scavengers, as well as free-ranging cats and dogs)	Unlikely	Moderate to High*
Impact on individuals	Impact on infected individuals, including effects on mental health, disease morbidity/mortality, and general welfare	Major	High
Impact on the population	Overall impact on the general population given that no further spread beyond initial zoonotic infection is expected	Minor	Low

*The overall uncertainty comes from the uncertainties of the likelihood estimates that combine together to form the overall likelihood estimate and is therefore presented as a range where these estimates differ

Future risk in Canada

Continued transmission of avian influenza A(H5N1) clade 2.3.4.4b viruses in wild and domestic bird populations, and repeated spill-over into mammalian species, increases the likelihood of viral reassortment and/or adaptation that could enable sustained transmission in wild and/or domestic mammalian species. This may result in increased opportunities for human exposure to these viruses. Although human infections, including fatalities, have been documented in other countries among individuals with exposure to animals infected with avian influenza A(H5N1) clade 2.3.4.4b viruses and possibly virus-contaminated environments, human-to-human transmission has not been reported to date. There is high uncertainty regarding the likelihood of these viruses acquiring mutations that enable sustained human-to-human transmission. A recent multisectoral Pandemic Risk Scenario Analysis led by the Agency determined that the most likely scenario by March 2024 is sustained transmission in non-human mammals, according to majority expert opinion. Sustained human-to-human transmission leading to a pandemic was considered a scientifically credible but less likely scenario.

If sustained human-to-human transmission does occur, the human health impacts will depend on virus transmissibility (the reproduction number); the speed of transmission (epidemic doubling time); the role of asymptomatic and pre-symptomatic virus shedding in transmission; illness severity; individual, health system and societal vulnerabilities; and the effectiveness and availability of countermeasures. There is high uncertainty regarding all of these factors. The course of a human epidemic, were it to occur, is therefore highly uncertain at present, emphasizing the importance of surveillance and preparedness activities in both human and animal sectors.

Even in the absence of widespread community transmission, clusters of disease in high-risk settings such as healthcare institutions could put strain on medical and public health resources for diagnostics, medical treatment and outbreak management, and result in staff shortages through absenteeism if healthcare staff are affected.

Wider transmission in animal populations could also have indirect impacts on human wellbeing and wider society. Increasing outbreaks in farmed animals could have large-scale economic impacts in the agricultural sector from direct losses due to illness as well as outbreak containment measures and international trade implications. The wellbeing of producers and farm employees could also be affected due to animal welfare impacts, loss of livelihood, and disruption of the agricultural sector. Outbreak containment measures could also

affect the wellbeing of personnel involved in outbreak response and clean-up and disposal on farms. Shortages in food animal commodities could affect food security in certain sectors of the population. Widespread virus transmission in wildlife populations could also have food security implications in Indigenous communities that rely on wildlife for food. Wildlife population numbers, particularly for at-risk or endangered species, could be impacted, and there could also be impacts on the wellbeing of personnel involved in response and clean-up of wildlife die-offs. Impacts on human wellbeing could also occur from reduced interaction with natural ecosystems, resulting from fear of exposure to infected animals.

Proposed Actions for Public Health Authorities and One Health Partners

Recommendations proposed below are based on the knowledge gaps identified during this risk assessment. It is important that the public health response be proportionate to the risk, taking into consideration available public health resources and capacity.

PHAC will continue to engage One Health partners (federal, provincial, territorial 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 to guide public health actions in the following areas:

Surveillance and reporting

- Continue efforts to further enhance and integrate surveillance activities for avian influenza across the One Health spectrum to,
    - improve understanding of infection and disease burden due to avian influenza A(H5Nx) clade 2.3.4.4b in different animal species, particularly understudied mammalian species;
    - monitor changes in virus evolution and species adaptation as well as antiviral resistance;
    - understand infection risk in human population groups with higher exposure (e.g., backyard poultry, agriculture workers); and
    - rapidly detect and respond to a potential human infection, especially where human-to-human transmission may be occurring.
- Establish enabling mechanisms and structures between animal and human health surveillance systems in Canada for rapid information sharing of case detections, exposure data, genomic analysis including timely clade identification, and other relevant intelligence that can inform the global avian influenza knowledge base.

Communication and Coordination

- Continue to foster timely coordinated communication and actively build trust among One Health stakeholders, including counterparts in human, environmental and animal health sectors at local, provincial, regional and federal levels, such that established relationships may be leveraged for harmonized inter-agency pandemic preparedness and outbreak prevention and response activities, including response planning for the first human case(s).
- Continue regular communication with the public on the current avian influenza A(H5N1) clade 2.3.4.4b and share associated guidance related to preventive measures[1], specifically, for those at potentially higher risk of exposure and infection, including but not limited to farmers/producers and farm workers; hunters/trappers; and those who work with wildlife, stray and feral animals; etc.). When necessary, correct and counter mis- or disinformation.

Research

- Consider discussing and pursuing potential research activities as identified in the Knowledge gaps (Table 5).

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 and Methods

1.1 Event Background

Current Situation (as of May 30, 2023)

Birds

The avian influenza A(H5N1) clade 2.3.4.4b virus emerged in 2020, spreading across Europe, Asia, and Africa, in both wild birds and domestic poultry, and replaced the previously circulating avian influenza A(H5N8) clade 2.3.4.4b virus in Europe by spring 2021.

The Canadian Food Inspection Agency (CFIA)'s National Centre for Foreign Animal Diseases (NCFAD) first confirmed the avian influenza A(H5N1) clade 2.3.4.4b virus in Canada in December 2021, in a fancy chicken at a small mixed animal exhibition farm in Newfoundland and Labrador.[2] Since then, over 7 million birds from commercial and non-commercial flocks in Canada have been culled as a result of virus containment measures or have died from infection with the virus.[3]

Avian influenza A(H5N1) clade 2.3.4.4b viral activity is unprecedented in terms of the number of wild bird species infected, the extensive geographic spread, and duration of the epizootic.[4] Detection of avian influenza A(H5N1) clade 2.3.4.4b viruses containing the polymerase basic protein 2 (PB2) E627K amino acid substitution, a known marker of mammalian adaptation, has been reported since April 2023 in viruses from some infected poultry farms in Canada (12 in Québec, 1 in Ontario). While this adaptation has been detected in wild birds and birds of prey previously, this is the first time PB2 has been seen in Canadian domestic poultry.[5,6]

Non-Human Mammals

Since October 2020, sporadic avian influenza A(H5N1) and avian influenza A(H5) infections in several wild mammalian species have been reported in Europe and the Americas affecting at least 24 species of carnivores and 4 species of cetaceans.[7] In March 2023, 10 South American bush dogs in a captive breeding program in England tested positive for avian influenza A(H5N1). All were either dead or euthanized over a 9-day period.[8] They were tested as part of a routine investigation into an unusual mammal die-off in November 2022 and had minimal clinical signs before death.[8] There was no clear evidence suggesting mammal-to-mammal transmission and it is very likely all animals were exposed to the same source of infected wild birds.[8] In Canada, wild mammal species reported to have been infected with avian influenza A(H5N1) clade 2.3.4.4b include, but are not limited to, foxes, skunks, bears, raccoons, seals and dolphins.[4] Avian influenza A(H5N1) has recently been reported in a domestic dog and in feral cats in Ontario. The dog and one cat have been confirmed infected with avian influenza A(H5N1) clade 2.3.4.4b. Additional results are pending.

In an analysis of tissue samples collected from dead or euthanized mesocarnivores in Canada between April to July in 2022,[9] histologic lesions associated with avian influenza A(H5N1) clade 2.3.4.4b viruses were found in several red foxes, indicating extensive meningoencephalitis and pneumonia, as well as abundant virus antigen in the brain sections.[9] Ferret experiments conducted in Canada demonstrated efficient transmission by direct contact of an avian influenza A(H5N1) clade 2.3.4.4 virus (A/Red Tailed Hawk/ON/FAV-0473-4/2022), resulting in lethal outcomes.[10] These ferrets succumbed to infection within one week and showed detectable infectious virus in the brain, consistent with the neurotropism seen in infected foxes.[10]

Following detection of avian influenza A(H5N1) clade 2.3.4.4b in a free-ranging poultry farm in Rome virological and serological investigations were conducted in pigs with no clinical signs on the same premises. Serological samples were positive for avian influenza A(H5N1) and phylogenetic analysis confirmed the virus detected belonged to clade 2.3.4.4b.[11] There are limited reports of potential direct mammal-to-mammal transmission with avian influenza A(H5N1) clade 2.3.4.4b virus. In October 2022, an outbreak occurred on a farm of over 52,000 mink in Spain.[12] Of 15 mink tested, 14 were positive for avian influenza A(H5N1) clade 2.3.4.4b by RT-PCR and the mortality rate on the farm started at 0.8% the first week of October and by the third week reached a peak mortality rate of 4.3%.[12] Based on epidemiological evidence, onward transmission of the virus from mink-to-mink may have taken place on the affected farm.[12]

Large numbers of marine mammals have been infected with avian influenza A(H5N1) clade 2.3.4.4b viruses during the current global epizootic.[13] In an outbreak among New England seals in the United States, transmission is likely to have occurred from wild birds to seals via environmental transmission of shed virus.[14] In January and February 2023, a large sea lion die-off in Peru coincided with an outbreak of avian influenza A(H5N1) clade 2.3.4.4b in seabirds. A report of this event concluded that transmission likely occurred due to close contact with or consumption of infected birds, but direct transmission between sea lions could not be ruled out.[15]

Humans

Since December 2021, detections of avian influenza A(H5N1) clade 2.3.4.4b viruses in humans have been reported from China (n=2)[16,17], the United Kingdom (n=3)[18,19], the United States (n=1)[20], Spain (n=2)[21], Viet Nam (n=1; clade not confirmed at time of writing)[17,22], Ecuador (n=1)[16] and Chile (n=1)[23]. Human-to-human transmission has not been reported. Clinical severity has varied widely; the avian influenza A (H5N1) cases reported in humans from Europe and North America were asymptomatic or mild, while those in Asia and South America were severe or fatal. Almost all cases had known exposure to infected poultry. Exposure information was limited for the Chilean case, although highly pathogenic avian influenza A(H5) was detected in wild birds and sea lions in the area in which the case resided.[24] This case was notable because the virus identified from the Chilean patient had two mutations in the polymerase basic protein 2 (PB2) that have been shown to contribute to mammalian adaptation in experimental animal models.[25] In May 2023, avian influenza A(H5N1) clade 2.3.4.4b virus was detected in nasal swab specimens from two asymptomatic poultry farm workers in the UK as part of a voluntary testing program for individuals exposed to infected birds.[19] Virus detection in one of these two individuals is thought to have resulted from contamination of the nasal passages through inhalation of virus, rather than true infection.[19]

It is possible that human infections are under-detected, due to reliance on passive surveillance and limited testing of individuals exposed to infected animals. Mild and subclinical cases are likely to be detected only as part of special investigations during animal outbreaks or contact tracing for a confirmed human case.

In June 2022, the Public Health Agency of Canada (PHAC) analyzed the risk to humans from avian influenza A(H5N1) in Canada. At that time, the risk of infection with avian influenza A(H5N1) for the general population with limited contact with infected animals was considered to be low. The assessment is being updated due to continued widespread circulation of avian influenza A(H5N1) clade 2.3.4.4b in wild and domestic bird populations, the increasing range of mammalian species in which infection with this virus has been reported, and additional reports of isolated human cases in other countries.

1.2 Methods

This assessment was led by CDSB-CIRA, within the Public Health Agency of Canada (PHAC) in May and June 2023, and conducted in collaboration with a multi-sectoral team. The rapid risk assessment (RRA) methodology used by CDSB-CIRA has been adapted from the Joint Risk Assessment Operational Tool (JRA OT) to assess the risk posed by zoonotic disease hazards[26], developed jointly by the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), and the World Organization for Animal Health (WOAH). PHAC has adapted the JRA OT by modifying the likelihood and impact scales and associated definitions to incorporate elements from other RRA frameworks that are relevant to the Canadian context.[27,28]

Detailed methodology outlined in Appendix A.

1.3 Definitions

This risk assessment focuses on the risk of human infection with avian influenza A(H5N1) clade 2.3.4.4b virus in Canada from zoonotic or environmental exposures (due to animal contamination). Exposure risks related to contact with a human case are not included. If human-to-human transmission were to occur with this virus, a separate risk assessment would be conducted that includes such exposure risks, e.g., those experienced by close contacts of cases and healthcare workers.

See Appendix B for a list of occupational and recreational groups with potentially relevant exposures.

Table 2. Exposure definitions

Higher level exposure	High intensity (within 2 meters and/or prolonged) contact with animals infected with avian influenza A(H5N1) clade 2.3.4.4b virus* (i.e., wild birds, poultry, or mammals), or infected materials from these animals (e.g., feces, blood, secretions, or tissues), or an environment highly contaminated by infected animals. Exposures can include, but are not limited to the following without the use of appropriate PPE**: • Being in a closed airspace, touching, handling, culling animals • Preparation of birds/other animals for consumption (e.g., harvesting, slaughtering, defeathering, butchering) • Being in an area with mass animal mortality or live animal market • Consuming under- or un-cooked meat or egg products *Note: higher dose contact combined with appropriate use of PPE and hand hygiene could be considered lower or negligible exposure depending on circumstances.*
Lower level exposure	Low intensity (greater than 2 meters and/or transient) contact with animals infected with avian influenza A(H5N1) clade 2.3.4.4b virus* (i.e., wild birds, poultry, or mammals), or infected materials from these animals (e.g., feces, blood, secretions, or tissues), or an environment not highly contaminated by infected animals (e.g., diluted recreational bodies of water, open-air environment). Exposures can include, but are not limited to the following: • Contact with bird feeders frequented by corvids (e.g., blue jays, crows) • Drinking untreated surface water or swimming in recreational bodies of water (e.g., lakes, rivers, ponds) contaminated with feces or other secretions from infected birds/other animals (considered lower level exposure due to the significant dilution of virus in water)
Negligible exposure	The following are considered negligible exposures (i.e., not considered plausible exposure pathways): • Indirect contact with an environment minimally contaminated with avian influenza A(H5N1) clade 2.3.4.4b virus (e.g., feces, blood, or secretions from infected birds or mammals) including visiting a park with wild bird / other wild animal populations and/or living in the vicinity of wild birds/wild animals or farms with poultry • Preparing or consuming under- or uncooked meat or egg products from infected large/regulated poultry operations (considered a negligible source of exposure given that meat/poultry from infected regulated poultry operations are unlikely to enter the food chain) • Contact with bird feeders frequented by non-corvid passerines (i.e., songbirds) (considered negligible given that these birds are rarely infected based on available wild bird surveillance data for the current avian influenza A(H5N1) clade 2.3.4.4b virus in Canada, and reviews of the relevant literature)[29]

General population exposure	The exposure experienced by the general (human) population is assumed to be: • Either negligible or lower level exposure to wild birds, commercial poultry, backyard poultry, or wild mammals • Any of negligible, lower level exposure, or higher level exposure to domestic mammals (i.e., dogs and cats)***

*If the influenza status of the animal is unknown, the following considerations are used to help decide whether the animal should be considered infected for an individual-level risk assessment: is there known avian influenza activity in the area, is the animal a bird or a mammal, what species is the bird (e.g., certain species are less likely to exhibit clinical signs of illness), if a mammal is it likely to have scavenged or come in contact with other infected wild birds/mammals, is/was the animal sick, dead, or alive and well.

**Personal protective equipment (PPE) are items worn to provide a barrier to help prevent potential exposure to infectious disease. These items may include the following depending on the situation: gloves, gowns, surgical masks, respirators, face shields, and eye protection (e.g., goggles).

***Domestic mammals exclude unmonitored, free-ranging animals such as feral cats and stray dogs, which are considered wild mammals for the purposes of this risk assessment

1.4 Key Assumptions

- Relatively little is known about the epidemiological or viral characteristics of avian influenza A(H5N1) clade 2.3.4.4b viruses and this assessment assumes some similarities with other highly pathogenic avian influenza (HPAI) viruses.
- This assessment assumes that there will be no significant genetic changes to the currently circulating avian influenza A(H5N1) clade 2.3.4.4b viruses during the assessment period that would influence infectivity, transmissibility, or clinical severity in humans.
    - This assessment considers all avian influenza A(H5N1) viruses belonging to clade 2.3.4.4b currently in circulation at the time of this assessment.
- Pathway assumptions:
    - Infection routes for humans are primarily through respiratory and/or mucous membrane contact irrespective of animal source and/or human exposure groups (occupational/recreational), but it is assumed that, where applicable, prevention and control guidance will recommend measures to avoid all possible infection routes, which may include handling and consumption of raw or undercooked, contaminated animal products.
    - There is limited information regarding the susceptibility to and prevalence of infection in many of the different bird and animal species. To provide more precautionary estimates of the likelihood of infection (i.e., representing the worst-case scenario), the following guidance was used for estimating the likelihood of infection in different animal groups:
        - Wild birds: birds known to be susceptible to infection based on current evidence (e.g., Anseriformes and Charadriiformes).
        - Domestic mammals: mammals known to be susceptible to infection to some degree based on current evidence (e.g., cats and dogs); note that farmed mammals were not expressly included in this assessment as part of domestic mammals, although farmed mink are known to be susceptible, and a recent study found serological evidence of infection in swine.[12,11]
        - Wild mammals: mammals known to be susceptible to infection based on the current evidence (e.g., terrestrial and marine mammals).

2 Detailed Risk Assessment Results

2.1 Risk Pathway

See Appendix A for explanation of the use of the risk pathway to develop risk sub-questions.

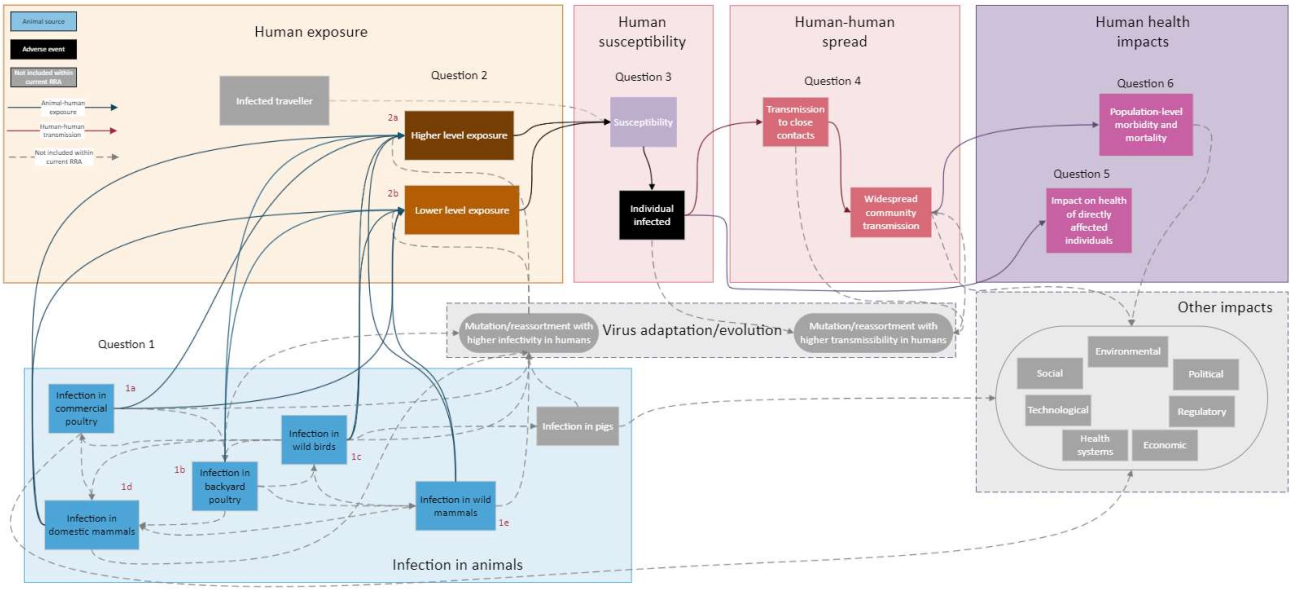

Figure 1. Risk pathway depicting sources and exposures leading to, and impacts of, a human infection with avian influenza A(H5N1) clade 2.3.4.4b in Canada by the end of the 2023 fall bird migratory season (generally ranging from October to December in Canada).

2.2 Likelihood and impact estimates

Estimates of the likelihood of a human infection with avian influenza A(H5N1) clade 2.3.4.4b in Canada resulting from exposure to infected birds or mammals by the end of the 2023 fall bird migratory season are presented in Table 3, together with associated rationales and uncertainty estimates. The likelihood of such an infection is dependent on the prevalence of infection in different groups of animals (Questions 1a-1e), combined with the likelihood of exposure to a sufficient amount of virus to potentially cause infection following different types of animal contact (Questions 2a-2b), and then combined with the likelihood that an individual exposed to a sufficient amount of virus actually develops infection (Question 3). The likelihood scale used in this assessment is described in Table A2.

The impact estimates presented in Table 4 include consideration of the most likely spread scenario were a human case to occur in Canada (Question 4), together with the magnitude of effects on infected individuals (Question 5) and the overall impact for the Canadian population (Question 6). The magnitude of effects and impact scales used in this assessment are described in Tables A3 and A4.

Table 3. Rationale for likelihood and uncertainty estimates.

Pathway Sub-Question		Estimate	Rationale	Uncertainty
1a	What is the likelihood that a random individual animal* from a commercial poultry flock in Canada is infected with avian influenza A(H5N1) clade 2.3.4.4b during the assessment period?	Unlikely	There continues to be outbreaks of avian influenza A(H5N1) clade 2.3.4.4b in commercial poultry flocks across Canada as biosecurity measures cannot entirely prevent transmission between wild birds and commercial poultry, however, the proportion of flocks infected remains small at <3%: from May to December 2022 (same date range as this assessment but last year), there were 141 commercial infected premises reported, with 4775 commercial poultry producers in Canada (in 2021).[3,30] Geographic variation in infection prevalence is expected, depending on the local avian influenza A(H5N1) clade 2.3.4.4b epidemiology, density of commercial operations and wild bird populations.	Very low to Low Based on existing surveillance information from poultry farms in Canada.
1b	What is the likelihood that a random individual animal* from a backyard poultry flock in Canada is infected with avian influenza A(H5N1) clade 2.3.4.4b during the assessment period?	Unlikely	Given continuing circulation of avian influenza A(H5N1) clade 2.3.4.4b in wild migratory birds, the lower level of biosecurity for backyard compared with commercial flocks, as well as the high susceptibility of poultry to infection, further sporadic infections in backyard poultry are expected in the assessment period and there is no indication that the rate of new infected premises will change during the next migratory season. During May-December 2022 (same date range as this assessment but last year), there were 66 backyard infected premises reported; although the total number of backyard premises in Canada is unknown, estimates from one province alone are >10 000 backyard flocks, resulting in a proportion of <1%.[31]	High Based on limited surveillance in and limited information on the number, size, and geographic distribution of backyard flocks in Canada, and high variability in implementation of biosecurity measures.

Pathway Sub-Question		Estimate	Rationale	Uncertainty
1c	What is the likelihood that a random individual wild bird* in Canada is infected with avian influenza A(H5N1) clade 2.3.4.4b during the assessment period?	Unlikely	The avian influenza A(H5N1) clade 2.3.4.4b virus is detected in wild birds on an ongoing basis, with approximately 4% positivity in apparently healthy wild birds (mostly waterfowl) during this time last year: of 9,900 samples tested between May and December, 2022, 386 have resulted in confirmed or suspected avian influenza A(H5N1) clade 2.3.4.4b detections (3.9%), with the majority identified in September. Increases in infection prevalence are observed during spring and fall migration seasons, and there is geographic variation in infection prevalence, depending on the local avian influenza A(H5N1) clade 2.3.4.4b epidemiology.[4]	Very low to Low Based on existing surveillance and other evidence demonstrating ongoing transmission in this population despite gaps in knowledge, underestimation of prevalence, and suspected variation in susceptibility between species.
1d	What is the likelihood that a random individual domestic mammal* in Canada is infected with avian influenza A(H5N1) clade 2.3.4.4b during the assessment period?	Very unlikely	Given continuing circulation of avian influenza A(H5N1) clade 2.3.4.4b in wild migratory birds, domestic mammals with direct contact to these birds may become infected; however, the number of detections in domestic mammals to date has been very small, in Canada and elsewhere.[32],[33]	Moderate Based on limited surveillance in domestic mammals in Canada
1e	What is the likelihood that a random individual wild mammal* in Canada is infected with avian influenza A(H5N1) clade 2.3.4.4b during the assessment period?	Unlikely	Reports in wild mammals continue and are increasing,[34] however, numbers are still limited in Canada, the USA and elsewhere. [13,14,35,36,37,38]	High Based on very limited surveillance in wild mammals in Canada and suspected variation in susceptibility between species.
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)?	Highly likely	Infected birds are known to shed high quantities of virus into the air and surrounding environment.[39,40,41] Most human cases reported to date have involved higher level exposure with infected poultry and/or highly contaminated environments.[16,17,18,19,20,21,22,23] Sero-epidemiological studies of other avian influenza A(H5N1) viruses	Low Based on current knowledge of the route of exposure in confirmed cases to date

Pathway Sub-Question		Estimate	Rationale	Uncertainty
			from numerous settings demonstrate the potential for infection in humans highly exposed to infected birds.[42]	
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)?	Very unlikely	Globally, there are no known cases associated with this type of exposure.[16,17,18,19,20,21,22,23] 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 virus.[43]	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 following lower level exposures.
3	What is the likelihood that a person who had exposure to sufficient amount of virus*** will develop an infection?	Unlikely	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. This is despite frequent high-dose exposures in certain populations, particularly those in contact with poultry. Although data specific to avian influenza A(H5N1) clade 2.3.4.4b are lacking, a recent US study reported 1 PCR detection of highly pathogenic avian influenza A(H5) virus in a respiratory sample, among more than 4000 humans exposed to avian influenza A(H5N1)-infected birds.[44] Previous meta-analyses of serosurveys have reported seroprevalence of avian influenza A(H5N1) antibodies of 1%-2% among poultry workers and those exposed to infected poultry.[45,46]	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

Pathway Sub-Question		Estimate	Rationale	Uncertainty

	What is the likelihood of at least one human infection with avian influenza A(H5N1) clade 2.3.4.4b due to exposure to **birds** in Canada up to the end of the 2023 fall bird migratory season?	Infection with avian influenza A(H5N1) clade 2.3.4.4b is **very unlikely** for the **general population** that have negligible or lower level exposure to birds (wild birds, or commercial or backyard poultry), driven by 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.
		
		Logic to derive the overall likelihood**** = [1a OR 1b OR 1c] AND 2b AND 3:
		• Infection in commercial poultry OR backyard poultry OR wild birds -> Unlikely
		• Sufficient amount virus from lower level exposure -> **Very unlikely (high uncertainty)**
		• Infection following exposure to sufficient amount of virus -> Unlikely
		  • Combined likelihood -> **Very unlikely**
		
		Infection with avian influenza A(H5N1) clade 2.3.4.4b is higher but still **unlikely** for **populations that have higher level exposure to birds** (wild birds, or commercial or backyard poultry) due to the limited capacity of the virus to infect humans as well as the low level of infection in birds. The uncertainty ranges from very low to high for this estimate due to large number of drivers: lack of information on the infectivity of this clade, the small number of infections in humans, limited surveillance and testing in human populations exposed to birds as well as backyard poultry, the lack of surveillance in backyard poultry and information regarding the number of backyard poultry flocks in Canada.
		
		Logic to derive the overall likelihood**** = [1a OR 1b OR 1c] AND 2a AND 3:
		• Infection in commercial poultry OR backyard poultry OR wild birds -> **Unlikely (very low to high uncertainty)**
		• Sufficient amount virus from **higher level** exposure -> Highly likely
		• Infection following exposure to sufficient amount of virus -> **Unlikely (moderate uncertainty)**
		  • Combined likelihood -> **Unlikely (very low to high uncertainty)**	

	What is the likelihood of at least one human infection with avian influenza A(H5N1) clade 2.3.4.4b due to exposure to **mammals in Canada** up	Infection with avian influenza A(H5N1) clade 2.3.4.4b is **very unlikely** for **the general population** that has higher exposure to domestic mammals (e.g., dogs and cats) but not wild mammals, due to the very low likelihood that domestic mammals are infected. There is a moderate to high level of uncertainty due to limited surveillance in domestic mammals and the lack of information on potential infectious dose for lower level exposures to wild mammals.		

Pathway Sub-Question		Estimate	Rationale	Uncertainty
	to the end of the 2023 fall bird migratory season?	Logic to derive the overall likelihood**** = [1d AND 2a] OR [1e AND 2b]) AND 3: • Infection in domestic mammals -> **Very unlikely (moderate uncertainty)** • Sufficient amount virus from **higher level** exposure -> Highly likely • Infection following exposure to sufficient amount of virus -> Unlikely **+** • Infection in wild mammals -> Unlikely • Sufficient amount virus from **lower level** exposure -> **Very unlikely (high uncertainty)** • Infection following exposure to sufficient amount of virus -> Unlikely • Combined likelihood -> **Very unlikely (moderate to high uncertainty)** Infection with avian influenza A(H5N1) clade 2.3.4.4b is **unlikely** for the **population that has higher level exposure to wild mammals** (e.g., wild carnivores and scavengers) despite their higher likelihood of exposure to the virus, due to the low likelihood of infection in wild mammals and the limited capacity of the virus to infect humans. There is a moderate to high level of uncertainty estimates due to limited surveillance and testing of wild mammals and limited information on the infectivity of this clade for humans. Logic to derive the overall likelihood **** = 1e AND 2a AND 3: • Infection in wild mammals -> **Unlikely (high uncertainty)** • Sufficient amount virus from **higher level** exposure -> Highly likely • Infection following exposure to sufficient amount of virus -> **Unlikely (moderate uncertainty)** • Combined likelihood -> **Unlikely (moderate to high uncertainty)**	

*for the purposes of these risk sub-questions, 'random individual' refers to an animal hypothetically selected at random from the corresponding animal population in Canada. The likelihood of such an animal being infected is dependent on the point prevalence of infection in the animal population.
**see Definitions

*** considering the dose of a human-adapted influenza virus that is thought to result in infection

**** 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). Where here there is an "OR" statement, the highest likelihood is chosen for use in the overall determination. Estimates for likelihood and uncertainty that are bolded are those that determine the final estimate.

Table 4. Considerations for estimation of overall impact

Pathway Sub-Questions		Estimate	Rationale	Uncertainty
4	In the event that human infection occurs, what would be the most likely spread scenario?	No further transmission	The most likely spread scenario is that of **zoonotic infection with no further transmission**, given that there is no evidence that the virus has acquired the capacity for sustained transmission among humans.	Low Based on the small number of detections of this virus in humans to date and the absence of evidence for human-to-human transmission of this virus. However, this assessment would change if evidence emerges of virus mutations or adaptations leading to efficient transmission in humans.
5	What would be the impact on an individual infected person (the magnitude of effects, including impact on mental health, disease morbidity/mortality, and/or welfare)?	Major	Detection of initial human cases would likely involve infection control measures such as isolation and quarantine, with impacts on the physical and mental health as well as financial wellbeing of affected individuals, their families, and other close contacts. Although clinical severity in Canada is likely to be reduced with prompt diagnostic testing and administration of antivirals (that remain effective against avian influenza A(H5N1) clade 2.3.4.4b viruses), among the small number of human cases reported globally to date, a high proportion have had severe clinical presentations (4 of 10 confirmed detections, including 1 fatality).[15,16,17,18,19,20,21,23]	High Due to variability in clinical presentation seen in the limited number of human cases so far (ranging from asymptomatic to death), and lack of data on the frequency of asymptomatic and mild infection.
6	What would be the impact on the Canadian population during the assessment period (based on the response to the most likely spread scenario in Question 4)?	Minor	Based on most likely spread scenario (Sub-question 4 above), human-to-human transmission is not expected to occur; health impacts will likely be limited to isolated	Low There is a lack of evidence of human-to-human transmission for currently circulating viruses.

			zoonotic cases. Some indirect impacts could occur, such as the potential for public anxiety from media coverage of human cases.	

2.3 Risk Estimate Summary

Based on the available data at this point in time, up to the end of the 2023 fall bird migratory season (generally ranging from October to December in Canada):

- The overall risk to the general population from lower or negligible exposure to either birds or mammals (#2 in Figure 2 in darker green area) is low.
- The risk for those with higher exposure to either birds or wild mammals is “increased” compared to the risk experienced by the general population (#1 in Figure 2 in the lighter green-yellow area)

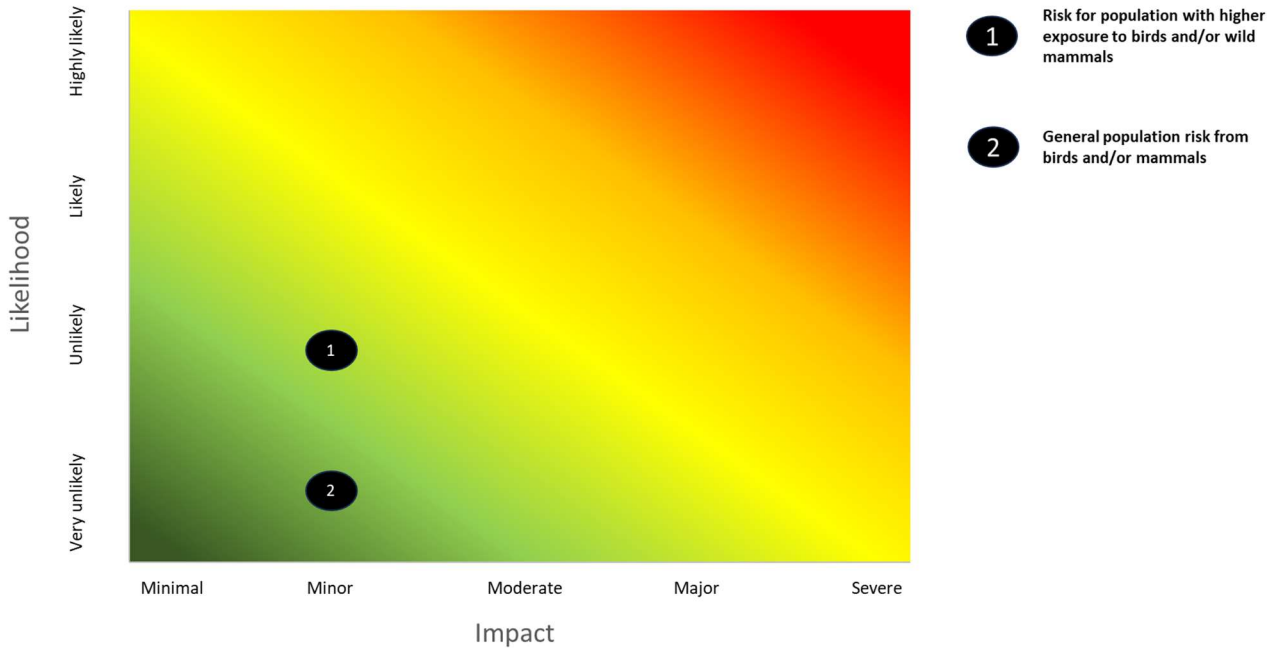

Figure 2. Risk-ranking matrix

2.4 Limitations

This assessment does not explicitly consider the frequency of human interactions with different types of animals; the size of different animal populations; or geographic variations in the distribution of animal populations, infection prevalence in animal species and human-animal contacts.

The qualitative method used for the likelihood estimation leads to an over-inflation of likelihood since the cumulative effect of probabilities less than 100% along the pathway will reduce the likelihood in a way that cannot be captured without quantitative data. This bias is in line with the use of the precautionary principle.

There was substantial variation in initial estimates provided by multi-sectoral experts to pathway sub-questions related to the likelihood of infection in different animal groups. Analysis of rationales provided by experts for their estimates indicated that the question had been interpreted in two different ways by Technical Team members, resulting in a divergence of estimates. The intended interpretation of the questions was subsequently clarified and revised likelihood estimates derived after discussion with Technical Team members and review of relevant evidence.

The wording of questions 2a and 2b (and associated naming of exposure levels) were changed during the review process to improve clarity. In the poll the questions were worded as follows: “What is the likelihood of at least one person getting exposed to sufficient amount of virus to potentially cause an infection for the average person following a higher/lower dose contact”.

2.5 Knowledge gaps

The key scientific uncertainties and knowledge gaps in this assessment are included below (see Table 5).

Table 5. 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 in domestic animals, such as cats and dogs, and wild mammals, due to limited testing and reliance on passive surveillance, and limited understanding of the clinical presentation in some species • Information on infection prevalence in wild birds is currently based on opportunistic testing and existing field programs, although initiatives are underway to optimize surveillance in wild birds, including an Interagency Wild Bird Avian Influenza Virus Surveillance Program • The role of immunity in wild migratory bird populations and its influence on infection prevalence and virus transmission to other bird and mammal species is not sufficiently understood • Publicly available data on the number, geographic distribution and density of commercial poultry premises and non-commercial poultry flocks in Canada is incomplete, which limits our understanding of risk “hot spots” in this poultry population
Exposure 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 birds and mammals • Current surveillance strategies may lead to under-detection of mild and subclinical human infections, limiting our understanding of exposures associated with these mild infections • More information is needed on the potential for between-mammal transmission in specific animal groups (e.g., feral cat colonies)

Risk pathway sub-section	Unknown/More information needed
Human susceptibility	• There are gaps in knowledge related to specific virus mutations conferring human adaptation, and the likelihood of such mutations • There is limited information on the risk factors for human infection • The role of pre-existing and cross-protective immunity to avian influenza A(H5N1) clade 2.3.4.4b viruses, overall and in different birth cohorts, is poorly understood
Immediate/direct impacts e.g., mental health, morbidity/mortality, welfare	• Limited virological and serological testing of individuals exposed to infected animals, and reliance on passive surveillance for human case detection, means that the frequency of infection in these populations is unclear. If there is substantial under-detection of mild and subclinical infection, cases with severe clinical presentations could be over-represented in human detections reported to date, potentially leading to an overestimation of the magnitude of effects on infected individuals • The small number of human cases reported globally to date means that data are scarce on the range of clinical presentations and risk factors for illness in humans
Interventions e.g., availability of effective medical countermeasures, public health measures	• There is a need to better understand the effectiveness of different interventions to limit the spread of the virus and reduce virus exposure both in animal species and humans, including biosecurity measures, PPE, vaccines and therapeutics • There is limited information regarding the extent to which prevention measures are implemented in backyard flocks

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Appendix A: Methods

The Centre for Integrated Risk Assessment at PHAC convened a Canadian One Health multi-sectoral team that formed two committees: the Rapid Risk Assessment (RRA) Steering Committee and the RRA Technical Team. The Steering Committee (largely comprised of senior managers and decision makers) defined the hazard, agreed on the purpose and key objectives for the assessment, outlined the scope, drafted the risk question, and reviewed the recommendations. The Technical Team (largely comprised of those with expertise and/or information related to the assessment) characterized the risk by providing qualitative estimates of likelihood, impact and uncertainty in relation to the risk questions being assessed, based on the available evidence and expert opinion. The Canadian One Health multi-sectoral team consisted of federal, provincial and academic experts from human, animal, and ecosystem health sectors, representing a variety of disciplines such as epidemiologists, virologists, wildlife biologists, veterinarians, and physicians.

The risk question being assessed was visualized using a risk pathway (Figure 1), a diagrammatic representation of the key components of the sequence of the hazard from its source to its infection of the host of interest. Each step in the risk pathway is associated with a likelihood or impact sub-question that was then addressed as part of the risk assessment. The risk pathway and sub-questions also included the animal and exposure sub-groups listed in Table 2.

The Technical Team were introduced to the risk pathway and associated questions in a meeting. Subsequently, a poll was used to obtain initial, independently assessed qualitative estimates from Technical Team members on the likelihood or impact associated with each risk pathway sub-question, using standardized qualitative scales (Tables A1-A4 below). The risk pathway, a slide deck explaining exposure groups, definitions for likelihood and impact and an evidence table were provided to assist each expert in making their best-considered estimation of risk. For each estimate, members were also asked to provide a rationale, indicate the level of uncertainty associated with their estimate and give a short explanation of the factors influencing this uncertainty. Lastly, members were given the option to not answer specific questions if they lacked sufficient expertise.

The poll results were used as a basis for discussion; final estimates were based on discussion with the Technical Team and review of the draft report by Technical Team and Steering Committee. A summary of poll responses was presented to Technical Team members in a meeting following the poll, highlighting where estimates and rationales clearly converged, and areas where poll results suggested differing interpretations of the questions or divergent estimates or rationales. Estimates and rationales that aligned with a common understanding of the rapid risk assessment questions were finalized based on subsequent discussions, as well as feedback through draft document review by the Technical Team and final review and feedback by the Steering Committee. In addition, Technical Team members were asked to identify key uncertainties and knowledge gaps that influenced their level of uncertainty in likelihood and impact estimates during the poll and in meetings. These were consolidated into a list of key uncertainties and knowledge gaps related to this risk assessment (Table 5).

Definitions of likelihood (Table A2), impact (Tables A3 and A4), and uncertainty (Table A1) are provided below. Since the risk pathway describes the sequence of events leading up to the undesired outcome, the likelihood of each event is conditional on the likelihood of preceding steps in the risk pathway, as assessed in the estimation process for each risk pathway sub-question. The likelihood for the overall risk question is therefore determined by the lowest likelihood estimated along the risk pathway. A risk matrix, adapted from WHO (2012), is used to integrate the likelihood and impact estimates into a summary risk estimate to support risk communication. Summary risk estimates are presented in context with the likelihood and impact estimates, given the known limitations of risk matrices.[47]

The findings and conclusions represent the consensual, but not necessarily unanimous, opinions of experts contributing to this risk assessment, and should not be interpreted as representing the views of all participants and their respective organizations. Evidence was gathered by scientific experts using a rapid, non-systematic literature search and includes published articles and pre-print manuscripts, reports on the current outbreak including surveillance reports, and communication from multi-sectoral experts. Where appropriate, some

references have been included; where references are not included this evidence was informed by input from the subject matter experts.

Table A1. Criteria for estimating level of uncertainty[1]

Uncertainty	Criteria
Very High	Lack of data or reliable information; results based on crude speculation only
High	Limited data or reliable information available; results based on educated guess
Moderate	Some gaps in availability or reliability of data and information, or conflicting data; results based on limited consensus
Low	Reliable data and information available but may be limited in quantity, or be variable; results based on expert consensus
Very low	Reliable data and information are available in sufficient quantity; results strongly anchored in empiric data or concrete information

Table A2. Criteria to estimate likelihood

Likelihood estimate	Criteria
Highly likely	The situation described in the risk assessment question is highly likely to occur (*i.e. is expected to occur in most circumstances*)
Likely	The situation described in the risk assessment question is likely occur
Unlikely	The situation described in the risk assessment question is unlikely to occur
Very unlikely	The situation described in the risk assessment question is very unlikely to occur (*i.e. is expected to occur only under exceptional circumstances*)

Table A3. Criteria for estimating magnitude of effect for individuals/population sub-groups if the situation described in the risk assessment question occurs*

Estimate	Criteria
Severe	Severe impact on mental health and/or disease morbidity/mortality, and/or welfare (e.g., loss of income)
Major	Major impact on mental health and/or disease morbidity/mortality, and/or welfare (e.g., loss of income)
Moderate	Moderate impact on mental health and/or disease morbidity/mortality, and/or welfare (e.g., loss of income)
Minor	Minor impact on mental health and/or disease morbidity/mortality, and/or welfare (e.g., loss of income)
Minimal	Minimal or no impact on mental health and/or disease morbidity/mortality, and/or welfare (e.g., loss of income)

*new scale and definitions for magnitude of effect is under development

Table A4. Criteria for estimating population-level impact in Canada if the situation described in the risk assessment question occurs**

Estimate	Criteria	Population Impact Criteria
Severe	The situation described in the risk assessment question will have severe negative consequences on the population under assessment	Potential pandemic in the general population or large numbers of case reports, with significant impact on the well-being of the population • Severe impact on mental health and/or disease morbidity/mortality, and/or welfare (e.g. loss of income) • Effect extremely serious and/or irreversible
Major	The situation described in the risk assessment question will have major negative consequences on the population under assessment	Case reports with moderate to significant impact on the well-being of the population • Moderate to significant impact on mental health and/or disease morbidity/mortality, and/or welfare (e.g. loss of income) affecting a larger proportion of the population and/or several regions • Effect serious with substantive consequences, but usually reversible
Moderate	The situation described in the risk assessment question will have moderate negative consequences on the population under assessment	Case reports with low to moderate impact on the well-being of the population • Low to moderate impact on mental health and/or disease morbidity/mortality, and/or welfare (e.g. loss of income) affecting a larger proportion of the population and/or several regions • Effect noticeable with important consequences, but usually reversible
Minor	The situation described in the risk assessment question will have minor negative consequences on the population under assessment	Rare case reports, mainly in small at-risk groups, with moderate to significant impact on the well-being of the population • Moderate to significant impact on mental health and/or disease morbidity/mortality, and/or welfare (e.g. loss of income) on a small proportion of the population and/or small areas (regional level or below) • Effect marginal, but insignificant and/or reversible
Minimal	The situation described in the risk assessment question will have minimal or no negative consequences on the population under assessment	No or very rare case reports with low to moderate impact on the well-being of the population • Negligible or no impact on mental health and/or disease morbidity/mortality, and/or welfare (e.g. loss of income) • Effect not usually indistinguishable from normal day-to-day variation

**new scale and definitions for impact is under development

Appendix B: Occupational and recreational groups with potentially relevant exposures

The population* with either occupational or recreational exposure to potentially infected wild birds, poultry, or mammals, their carcasses or highly contaminated environments includes the following:

- Poultry farm worker
- Backyard/small poultry flock owner
- Poultry processing plant worker
- Poultry culler (catching, bagging, transporting, or disposing of dead birds)
- Dealer, breeder, or handler of pet and other birds (e.g., exotics, falconry, racing pigeons)
- Butcher or person working with live or recently killed poultry or other potentially affected animals
- Person working in live animal market
- Veterinarian or other animal health worker
- Wildlife officer or biologist collecting specimens or euthanizing birds or mammals
- Wildlife rehabilitator
- Person performing permitted activities with wildlife (e.g., bird banding, capturing, sampling, removal, restoration, etc.)
- Person involved in hunting and trapping including Indigenous harvester
- Laboratory worker or researcher working with wild birds and/or mammals
- Caretaker of animals (e.g., pets, guardian dogs, hunting dogs) that regularly interact with wild birds or other potentially affected stray, or wild animals
- Person with other significant occupational or recreational exposure to wild birds and other potentially affected animals (e.g., mink farmer, biologist)

*If human-to-human transmission starts occurring for this virus, then healthcare workers and other contacts of cases would also need to be included.

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