

Public Health Risk Assessment associated with the spread of zoonotic avian influenza A(H5N1) clade 2.3.4.4b in the Region of the Americas

12 July 2024

Date of risk assessment: 9 July 2024

Overall risk and confidence human health (based on information available at the time of assessment)

Overall risk to the general population	Confidence in available information ¹
Regional	Regional
Low	Moderate

Risk statement

The purpose of this regional rapid risk assessment (RRA) is to assess the current public health risk to human health associated with the introduction and expansion of zoonotic avian influenza A(H5N1) clade 2.3.4.4b in mammals species in the Region of the Americas.

The RRA has been conducted taking into account the following criteria: **(i)** the risk of virus dissemination, specifically the potential occurrence in further countries in North America, Central America, South America, and in the Caribbean of events in dairy cattle and related spillovers to other mammals; **(ii)** the risk to human health including the risk of human exposure to infected animals and contaminated environments, the potential worsening of clinical and epidemiological characteristics of the disease if the virus further adapts to humans and/or other mammals, the potential for increased mammalian susceptibility from genomic mutations and viral reassortment, as well as risk factors for the occurrence of human infections and determinants related to outbreaks in animals; and **(iii)** the risk to public health based on the varying levels of capacities for early detection, prevention, and response with a One Health approach within the region, as well as the challenges in the implementation and adaptation of control measures (encompassing response capabilities, surveillance, diagnostic techniques, health and animal service preparedness, and medical supplies with available resources).

The overall risk in the general population of this event for the Region of the Americas to human health is classified as “Low” with a level of confidence in the available information of “**Moderate**”, for the following reasons:

Epidemiological and virological factors: Current epidemiological data indicate localized occurrences of avian influenza A(H5N1) clade 2.3.4.4b in dairy cattle herds within the United States of America, with spillover into humans and other mammals in direct contact. Virologically, the virus remains predominantly bound to avian-type receptors, limiting its transmissibility to humans via respiratory droplets or fomites, as demonstrated by recent studies. A substantial component of the risk of spread throughout the Region of Americas has, and will continue to be, predominantly from wild birds however, after introduction in cattle, the continuous transmission between the different states in the United States has evidenced other mechanisms of transmission (e.g., movement of cattle). Even with no further change in the virus there are likely to be additional outbreaks in mammals, and sporadic cases reported in humans. The recent global risk, given the same parameters, has been considered to be low by the World Health Organization (WHO), but requiring vigilance and ongoing monitoring (1-3).

Capacity for surveillance and response: The Region of the Americas benefits from robust pandemic preparedness initiatives led by Pan American Health Organization (PAHO), including the WHO Pandemic Influenza Preparedness (PIP) Framework and Preparedness and Resilience for Emerging Threats (PRET) initiative. PIP and PRET strengthens regional capacities for early detection, surveillance, vaccine deployment and response to zoonotic influenza outbreaks thereby mitigating the potential impact of localized influenza outbreaks and enhancing the region’s readiness to manage any potential spread (4). However, it is prudent for countries to enhance event-based surveillance mechanisms at the

¹ As of 9 July 2024



animal-human interface and continue to monitor influenza through its network of influenza-like illness (ILI) and severe acute respiratory infections (SARI) surveillance sites.

The available evidence supports a coordinated regional risk assessment of “**low**” for the general population and “low-to-moderate” for occupationally exposed individuals.

The rapid risk assessment will be reviewed should further epidemiological or virological information become available.

Criteria	Evaluation		Risk	Rationale
	Likelihood	Consequences		
Potential risk for human health in general population linked to animal exposure in the Region of the Americas?	Unlikely	Minor	Low	<ul style="list-style-type: none"> The detection of avian influenza virus infection, which is usually transmitted among birds, has emerged in new mammalian species and demonstrated a steady increase in such species. Whenever avian influenza viruses are circulating in birds, there is a risk for sporadic infections in mammals and humans due to exposure to infected animals (including livestock), or contaminated environments. Prolonged exposures to infected animals, products and contaminated environments may lead to potential additional human infections (5-7). <u>Global spread dynamics:</u> Since 2022, ten countries on three continents have reported outbreaks of avian influenza A(H5N1) in mammals to the World Organization for Animal Health (WOAH) (5, 7). In October 2022, an outbreak of influenza A(H5N1) clade 2.3.4.4b in farmed mink in Spain showed evidence of mink-to-mink transmission, although the mode of transmission was not identified (8, 9). A similar outbreak occurred in Finland in July 2023, affecting mink, foxes and raccoon dogs on 20 farms. Genetic analysis suggests that the virus was introduced by wild birds, and direct transmission between animals was evident (10). Despite these outbreaks, the primary mode of transmission remains from birds to mammals, not sustained human-to-human transmission. <u>Detection of avian influenza in mammals:</u> The detection of avian influenza virus infection in new mammalian species highlights the ongoing risk of sporadic infections in mammals and humans due to exposure to infected animals, products or contaminated environments. Eight countries in the Region of the Americas have reported events, in both marine and terrestrial mammals, including dairy cattle, alpacas, house mice, dogs, cats, farmed mink, seals and sea lions (7, 11, 12). Previously, there have been human infections with other avian influenza subtypes following exposure to infected mammals. Since the detection of highly pathogenic avian influenza HPAI A(H5N1) clade 2.3.4.4b outbreaks in dairy cattle, with its new genotype B3.13, four human cases with no epidemiological connection to each other have been associated to the cattle outbreak in the United States: one in the Texas, two in Michigan and one in Colorado. Three cases had mild symptoms (conjunctivitis) and one had mild respiratory symptoms. None required hospitalization, all recovered, and no further human cases have been detected associated with these events. (3, 11, 12). As of 9 July 2024, the severity and case fatality rates (CFR) associated with the four human cases in the United States remain



Criteria	Evaluation		Risk	Rationale
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				<p>consistent with previous WHO risk assessments. The mild nature of these cases and the lack of further transmission support a low-risk assessment for the general population.</p> <ul style="list-style-type: none"> Virological evidence: The detection of human cases of HPAI A(H5N1), clade 2.3.4.4b, associated with the exposure to cattle is thought to be the first instance of likely mammal to human transmission of the virus. Sequencing of the HPAI A(H5N1) virus from the Michigan dairy farm worker case did not identify the PB2 627 marker, which is associated with increased transmissibility. The presence of PB2 M631L, associated with viral adaptation to mammals, has been detected primarily in dairy cow sequences and only sporadically in birds. The overall genetic profile of the virus suggests cow-to-human transmission, not sustained human-to-human spread. Ongoing exposure to livestock remains a known concern. The risk in occupationally exposed persons in the latest WHO risk assessments is low-moderate. But this does not translate to a higher risk in the general population. In most cases, symptoms in humans may be mild or subclinical forms, or not even respiratory, which can lead to under-reporting of the event and difficulties in diagnosis (6).
Risk of virus spreading in new geographic areas?	Likely	Minor	Moderate	<ul style="list-style-type: none"> There is evidence concerning the capacity of the virus to spread and infect other mammalian and bird species. Since 2020, influenza A(H5N1) clade 2.3.4.4b variant has caused outbreaks in wild birds and poultry in Africa, Asia, and Europe, reaching North America in 2021 and Central and South America in 2022. Influenza A(H5N1) clade 2.3.4.4b has been detected in North and South America. Infections among various domestic and wild animal species in different countries suggest that influenza A(H5N1) clade 2.3.4.4b has the potential to continue to spread to new geographic areas. Given the characteristics of the current virus there are likely to be additional animal events (including introduction and endemicity in cattle) and possible sporadic human cases in previously unaffected regions (12). Although cases of the avian influenza virus A(H5N1) clade 2.3.4.4b, genotype B3.13, have so far been reported in only one country within the region of the Americas, the historical rapid spread of this genotype suggests a potential for it to disseminate into other currently unaffected areas. However, ferret studies of genotype B3.13 current suggest the A(H5N1) virus from the human case in Texas spread efficiently between ferrets in direct contact but did not spread efficiently between ferrets via respiratory droplets (1 in 3, or 33% were infected). This is different from what is seen with seasonal flu, which infects 100% of ferrets via respiratory droplets. The virus currently circulates within dairy cow herds in the United States leading to occasional exposures in mammals and humans through contact with infected animals or premises. The dominant mechanism of global spread through wild bird migrations (which has been ongoing for several years). There have not been recent changes in transmission patterns or virus characteristics that

Criteria	Evaluation		Risk	Rationale
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				would significantly increase the risk of widespread geographic expansion beyond what has been observed globally and previously characterised as low risk to general populations.
Risk of insufficient early detection, prevention, response and control capacities with available resources?	Unlikely	Minor	Low	<ul style="list-style-type: none"> • Early case detection and response capacities for animal and public health differ across Member States (MS) in the Region of the Americas. Reported and recorded challenges for some MS include the shipping of related samples to WHO Collaborating Centres and WOA Reference Centres. • Depopulation of infected animals is not a feasible strategy for dairy cattle infected with avian influenza. Lack of implementation of alternative appropriate control and prevention measures relevant for local and national contexts could facilitate the spread of the virus. • In general, countries of the Region of the Americas have systems in place to detect avian influenza A(H5N1) in poultry and wild birds. Surveillance systems that are in place to monitor diseases in cattle would need to be adapted to detect avian influenza, based on local context and risk. • Across the Region of the Americas, there are different levels of capacity to implement control measures including compensation packages to avoid the commercialization of dairy and animal products from infected animals including livestock. • There are gaps in the understanding of the impact on the spread of the virus among dairy farms and other animal production sites and how it might be facilitated by the movements of animals, humans and supplies. • The strengthening of biosecurity and hygiene measures among farmers, rural agricultural workers, and possibly local farming communities might require a human behavioural change, particularly in small-scale and rural farming operations. • Countries and territories in the Americas have different levels of capacity to perform integrated surveillance for zoonotic avian influenza. PAHO has consistently led in pandemic preparedness.

Background information

Hazard Assessment

Avian Influenza A(H5N1) clade 2.3.4.4b

Avian influenza (AI) is caused by infection with a virus of the family *Orthomyxoviridae*, included in the genus *Alphainfluenzavirus* (influenza A virus). Influenza A viruses have antigenically related nucleoproteins and matrix proteins but are classified into subtypes based on their hemagglutinin (H) and neuraminidase (N) antigens. Currently, 16H (H1-H16) and 9N (N1-N9) subtypes have been identified (13). AI is a highly contagious viral disease that affects both domestic and wild birds (14).

Birds are the natural hosts of avian influenza viruses. However, avian influenza viruses have also been isolated from mammalian species, both terrestrial and marine, as well as from humans (14). Some strains of avian influenza virus have caused sporadic zoonotic infections, mainly of the H5, H7, and H9 subtypes, and these three subtypes have been highlighted as potential pandemic risks in the event of additional mutations favoring sustained human-to-human transmission (13).

Avian influenza viruses are distinct from human seasonal influenza viruses and are not readily transmitted between humans. However, avian influenza viruses can occasionally infect humans through direct or indirect contact with infected animals or contaminated environments. Human infections can range from mild respiratory symptoms to severe pneumonia, acute respiratory distress syndrome, shock, and death. Gastrointestinal symptoms such as nausea, vomiting, and diarrhoea have also been reported in H5N1 infections (14). Four recent human cases in the United States associated with outbreaks of influenza A(H5N1) in dairy cattle have been reported: three presented mild ocular symptoms and only one had mild respiratory symptoms (15-19).

Frequent transmission of highly pathogenic avian influenza clade 2.3.4.4b between avian and mammalian species has led to genetic adaptations favoring mammalian hosts. Genomic analyses have documented that approximately half of the mammalian sequences globally within the AI A(H5N1) 2.3.4.4b clade have amino acid signatures in basic protein polymerase 2 (PB2) that enhance viral replication, host-specific polymerase activity, and temperature sensitivity (25). Outbreaks in farmed mink in Europe in 2022 have shown the virus can mutate to recognize human receptors, further increasing the risk of zoonotic transmission (20).

Exposure Assessment

The detection of avian influenza virus infection, which is typically transmitted among birds, has been increasingly observed in mammals. This increase in mammalian cases in recent years is attributed to changes in the ecology and epidemiology of the virus. Indeed, influenza A(H5N1) viruses, especially clade 2.3.4.4b, continue to diversify genetically and spread geographically. Since 2020, the clade 2.3.4.4b variant has caused an unprecedented number of deaths in wild birds and poultry in numerous countries in Africa, Asia, and Europe. In 2021, the virus spread to North America and, in 2022, to Central and South America. That same year, outbreaks of highly pathogenic avian influenza (HPAI) A (H5N1) in poultry and wild birds were reported to the World Organization for Animal Health (WOAH) from 67 countries on all continents. By 2023, epidemic outbreaks in animals were reported by 14 countries and territories, mainly in the Americas (12).

Whenever birds infected with avian influenza virus are detected, there is a risk of sporadic infections in mammals and humans due to exposure to infected animals or contaminated environments. Since 2022, ten countries on three continents have reported outbreaks in mammals to WOA, with both marine and terrestrial mammals affected, including cattle, dogs, cats, farmed mink, seals, and sea lions (7, 11, 12). Regarding clade 2.3.4.4b, in October 2022, an outbreak of HPAI H5N1 of clade 2.3.4.4b was reported in farmed mink in Spain, with evidence of mink-to-mink transmission, but the mode of transmission was not identified (8, 9). In July 2023, an outbreak by the same clade affected a mink breeding farm for commercial fur production in Finland. Infection was confirmed in foxes, American mink, and raccoon dogs from 20 farms. Genetic analysis suggested the introduction from wild birds foraging in agricultural areas. Investigations pointed to direct animal-to-animal transmission (10). Since 2003 and up to 3 May 2024, there had been 889 human cases and 463 deaths (52% case fatality) caused by influenza A(H5N1) virus reported to WHO, affecting 23 countries globally (12).

The avian influenza A(H5N1) virus, particularly clade 2.3.4.4b currently circulating in the Region of the Americas belongs to a high pathogenic AI (HPAI) genotype resulting from a recombination that occurred in wild birds in Europe and low pathogenic strains in wild and domestic birds during its global dissemination (21). This genotype has rapidly spread from Europe to North America, Africa, and Western Asia through waterfowl migratory routes. Since its detection in the Americas in 2021, the virus continues to spread throughout the continent (22-24).

Since 2022 to epidemiological week (EW) 20 (ending on 18 May) of 2024, 19 countries and territories in the Region of the Americas reported to WOA 5,261 AI A(H5N1) outbreaks in domestic and wild birds: Argentina, the Plurinational State of Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Ecuador, Guatemala, Honduras, Falkland Islands, Mexico, Panama, Paraguay, Peru, the United States of America, Uruguay, and the Bolivarian Republic of Venezuela (12). During this same period, 457 outbreaks of AI A(H5N1) in mammals were recorded in eight countries in the Region: Argentina, Brazil, Canada, Chile, Mexico, Peru, the United States, and Uruguay (12). Six countries reported 210 bird outbreaks and 78 mammal outbreaks between EW 1 and EW 20 of 2024 (12). Seven human infections caused by avian influenza A(H5N1) have been reported since 2022 in the Americas. Five were reported in the United States, on 29 April 2022, 1 April 2024, 22 May 2024, 30 May 2024, and 3 July 2024; one in Ecuador, reported on 9 January 2023; and one in Chile, reported on 29 March 2023 (6, 12, 18).

In the United States, since the beginning of 2024, detections of HPAI A(H5) virus in wild birds, commercial poultry, and/or backyard poultry have been reported in 28 states to WOA. On 25 March 2024, the first detection of HPAI H5N1 was reported in dairy cattle and in samples of unpasteurized milk obtained from dairy cattle. Since then and as of 9 July, detections of A(H5N1) have been reported in dairy cattle and other animals, affecting 145 dairy herds and one site with Alpacas in twelve states. Deaths have also been observed among wild cats and birds within some affected farms (12, 25).

Since 1 April 2024, there have been four unrelated confirmed human cases of influenza A(H5N1): one in Texas, two in Michigan, and one in Colorado that are related to the dairy cattle event in the country. These cases are suspected to represent the first instance of transmission of HPAI A(H5N1) avian influenza virus from mammals to humans. The four cases are in dairy workers who had direct contact with sick animals: three presented mild symptoms particularly with conjunctivitis, and one presented with upper respiratory tract symptoms, including cough without fever. Between March and June 2024, local, state, and national authorities in the United States have monitored persons exposed to infected cattle for a period of ten days post-exposure; at least 1,390 individuals were monitored, with 60 samples collected and three confirmed human cases of influenza A(H5N1) (6, 12, 18, 26). Studies to date indicate that pasteurization is effective in inactivating the virus in milk (27).

Context Evaluation

The transmission of HPAI A(H5N1) from cattle to humans is unprecedented. Although animal-to-human transmission remains sporadic, the possibility of more human cases increases with recent animal events.

Infections in various species in different countries suggest potential spread of the virus to new areas, increasing the risk of outbreaks in previously unaffected regions. In humans, symptoms are usually mild or subclinical, which can make diagnosis difficult and lead to underreporting. Sustained human-to-human transmission could generate a high demand for resources and challenge the response capacity of some countries. No vaccine has been approved for human infection with the influenza A(H5) virus, although candidate vaccines have been developed to prepare for a possible pandemic.



Table 3: Strengths and vulnerabilities of countries and territories in the Region of the Americas related to highly pathogenic avian influenza A(H5N1), June 2024

Strengths	Vulnerabilities
<ul style="list-style-type: none"> • Member States have strengthened influenza surveillance in both animal and human populations. • Enhanced coordination between animal, agricultural, and human health sectors for information exchange and control actions. • Improved information systems for monitoring avian influenza outbreaks in birds and other mammal species. • Regular alerts and regional epidemiological updates from PAHO. • Robust public health systems in many Member States allowing early case detection and response to disease outbreaks, including avian influenza. • Several countries in the region have advanced laboratories capable of diagnosing and characterizing viral strains, which is crucial for identifying the presence of highly pathogenic avian influenza (HPAI). • Most Member States have epidemiological surveillance systems in place that monitor diseases in humans and animals, helping to detect any unusual changes in the virus or clinical disease patterns. • At the animal laboratory level, a large number of countries have participated in inter-laboratory performance rounds, generally obtaining good results. • Enhanced collaboration among countries in the region through organizations like PAHO, facilitating the exchange of information and coordination in case of outbreaks. • Some Member States have faced similar disease outbreaks in the past, providing them with valuable experience in responding quickly and effectively to such situations. • Many countries have trained animal health authorities and resources to monitor animal health, which is essential to prevent and control the spread of the disease from its origin. • Member States have improved their risk communication and community engagement over the years, which is essential for informing the public and taking appropriate measures in emergency situations. 	<ul style="list-style-type: none"> • Surveillance in wild animals and mammals in some countries is poorly structured, reducing early detection capabilities. • Timely detection of avian influenza outbreaks is challenging in geographically dispersed or hard-to-reach access areas, particularly in rural and small animal production sites. • Surveillance systems for monitoring disease in dairy cattle need adaptation to detect avian influenza. • Challenges to timely identify appropriate prevention and control measures tailored for national and local contexts for infected animal production sites, in lieu of routinary control measures not applicable to dairy cattle (culling of infected animals). • Asymptomatic animals complicate timely detection and notification. As do nonspecific clinical signs that resemble other diseases in dairy cattle. • Outbreaks in domestic animals, as well as infections in wild birds and certain wild mammals, could put some groups of people at higher risk of infection due to occupational or recreational exposure. Clinical symptoms and current case definition for avian influenza infections in humans might limit the prompt detection of cases with minor or unusual symptoms, as well as severe cases. • Laboratory diagnostic capacity for animal events is limited in some countries, as well as challenges to send samples to the WHO Collaborating Centers in both animal and human sectors. Milk testing for avian influenza needs to be implemented by veterinary laboratories. Although veterinary laboratories generally have good baseline capacity, the emergency response has shown high susceptibility to saturation due to processing large volumes of samples, shortages of reagents and tests, and limitations in available human resources. • Most countries must strengthen the laboratory capacity for genetic sequencing of animal samples to determine how avian influenza virus is evolving and, potentially, adapting to non-avian species. • Countries' import protocols for live cattle, particularly dairy cattle, must be adapted to avoid the introduction of infected



Strengths	Vulnerabilities
<ul style="list-style-type: none"> • Member States are updating their pandemic influenza response plans based on lessons from COVID-19 and the current A(H5N1) outbreak. • Support and strengthening activities by PAHO/WHO, primarily through the team at the Pan American Foot-and-Mouth Disease Center and Veterinary Public Health (PANAFTOSA) and the Influenza team directed at Member States: <ul style="list-style-type: none"> ○ Workshop on “Management of High Mortality in Animals during Avian Influenza Emergencies,” held at the Pan American Foot-and-Mouth Disease Center and Veterinary Public Health (PANAFTOSA). ○ Regional consultation for strengthening intersectoral work at the human-animal influenza interface. Representatives from the Ministries of Health and Agriculture of Argentina, Brazil, Canada, Chile, Colombia, Ecuador, Guatemala, Mexico, and the United States, as well as from PAHO and partners, developed a series of guidelines to mitigate the risk of avian influenza transmission. These guidelines will complement PAHO’s recommendations and can be adopted by countries in the region. ○ Specifically in the animal component, PAHO has worked on strengthening surveillance through a review of strategies and personnel training, supporting decision-making in emergency response, epidemiological monitoring, risk characterization, and building diagnostic capacity in veterinary laboratories in collaboration with the regional WOA reference laboratory in Campinas, Brazil. 	<p>animals with avian influenza virus; for example, incorporating specifications to ensure that the original source farm was free from the virus. Limitations in staff of the official veterinary services in some countries, compromising emergency response capacity during peak saturation periods when responding to different tasks (handling suspected cases, monitoring contacts, implementing control measures, etc.).</p> <ul style="list-style-type: none"> • Contingency plans and capacity in many countries are not updated according to new methodologies on control alternatives, which are more efficient and respectful of animal welfare, ensuring appropriate waste disposal, optimizing pathogen inactivation and reducing the risk of environmental contamination. • There are challenges in real-time emergency information management, hindering evidence-based decision-making processes for emergency response. • Heterogeneity in the implementation of biosecurity measures on animal production sites across the Region of the Americas, potentially facilitating the spread of the virus. • Challenges for risk communication and community participation in prevention and control activities. • Limited capacity in some Member States to conduct joint risk assessments among sectors involved in the response. • Challenges for the integration of surveillance systems, exchanges of information, joint analysis among different sectors for the monitoring of animal events and human cases. • Failure to comply with farm biosafety protocols can propagate the spread of the virus among different animal species and potentially to humans, thereby increasing the risk of widespread outbreaks.

Immediate Actions

- Continue to closely monitor the situation. Enhance event-based surveillance at the animal human interface, routine influenza monitoring systems, nationally notifiable disease surveillance systems, and animal-human sector coordination at national and subnational levels in the region.
- Enhance laboratory capacity in human and animals including genomic surveillance, risk communication, and community engagement.
- Assure availability of appropriate personal protective equipment (PPE) in those with exposure to potentially infected animals.

Besides PIP and PRET, PAHO activities to respond to the outbreak includes:

- Strengthening routine and event surveillance on the human-animal interface with WHO Collaborating Centers and strategic partners.
- Regular risk assessment for transmissibility and severity for zoonotic viruses.
- Update of guidelines on influenza surveillance and response at the human-animal interface.
- Revision of experiences in response and lessons learned from countries that experienced zoonotic influenza outbreaks.
- Technical strengthening of risk communication capacities for events at the human-animal interface.
- Clinical management training on zoonotic influenza treatment, infection prevention and control (IPC), and reorganization of health services.
- Animal carcass handling training, including IPC technical aspects.
- PAHO published recommendations to strengthen intersectoral work in surveillance, early detection, and research at the human animal interface.
- Establishment of a regional commission for the preparedness, prevention and control of zoonotic influenza

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