Public health risk assessment associated with the potential occurrence of zoonotic avian influenza A(H5N1) clade 2.3.4.4b in Latin-American and the Caribbean

6 November 2024

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

Overall risk[1]
Regional
Moderate

Confidence in available information
Regional
Moderate

Risk statement

The purpose of this regional rapid risk assessment (RRA) is to assess the current public health risk associated with the introduction and expansion of zoonotic avian influenza A(H5N1) clade 2.3.4.4b in birds and mammal species, in Latin-American and the Caribbean and it complements the Americas Region RRA published on 13 July 2024 *(1)*.

This RRA has been conducted considering the following criteria: (i) the risk of virus dissemination, particularly the potential spread to additional countries in North America, Central America, South America, and the Caribbean, involving outbreaks in birds, dairy cattle, and spillovers to other mammals; (ii) the risk to human health based on the increasing trend of confirmation of human infections in the United States of America (U.S.A.), uncertainties surrounding the exposure source of a case confirmed in the U.S.A., the emergence of occupational risk exposures or incidental human-animal interfaces that facilitate contact between infected animals and humans such as dairy cattle or marine mammals infected with the virus, the continued exposure to contaminated environments, as well as risk factors and determinants related to animal outbreaks which are present in Latin-America and the Caribbean; and (iii) the public health risk based on varying capacities for early detection, prevention, response and containment within the region, as well as challenges in implementing and adapting control measures at intersectoral level (encompassing response capabilities, surveillance, diagnostic techniques, preparedness of health and animal services, and medical supplies with available resources). This assessment also considers that **the virus currently remains purely avian and that to date, human-to-human transmission of influenza A(H5) virus has not been identified**. It also considers that the risk of infection in agricultural workers exposed to infected animals ranges from low, moderate to high, depending on the type of exposures and the application of infection prevention and control measures.

The overall risk to this event in the Americas Region, especially in Latin-American and the Caribbean is classified as "Moderate," with a "Moderate" level of confidence in the available information, for the following reasons:

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

Epidemiological and virological factors:

Since 2021 and up to 24 October 2024, 19 countries and territories in the Americas Region had reported to the World Organisation for Animal Health (WOAH) 2,950 influenza A(H5N1) outbreaks in domestic and wild birds: Argentina, the Plurinational State of Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Ecuador, Falkland Islands, Guatemala, Honduras, Mexico, Panama, Paraguay, Peru, the United States of America, Uruguay, and the Bolivarian Republic of Venezuela *(2)*. During this same period, 640 outbreaks of avian influenza A(H5N1) in mammals caused morbidity and mortality in over 60 mammalian species, mostly carnivores, were recorded in seven countries in the Region: Argentina,

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[1] This assessment has been conducted considering a combination of hazards (animal, environmental and human), including potential exposures and diversity in response capacities in the Latin-American and the Caribbean.

Brazil, Canada, Chile, Peru, the United States, and Uruguay *(2)*. In 2024 up to 24 October, six countries had reported 242 outbreaks in birds (Brazil, Canada, Ecuador, Mexico, Peru, and the United States), and three countries had reported 340 mammal outbreaks (Argentina, Canada, and the United States) *(2)*.

Clade 2.3.4.4b of H5N1 avian influenza was initially detected in North America in 2021 and later reached South America in 2022. Studies confirm infections across birds and mammals, suggesting migratory birds play a key role in its transmission. Phylogenetic analysis shows South American strains are closely related to those from North America, supporting the hypothesis of a north-to-south transmission route across continents *(3, 4)*.

The clade 2.3.4.4b is associated with massive deaths of wild aquatic birds and wild mammals, and cases in poultry reported in countries along the Pacific Americas flyway, such as Peru and Chile. H5 HPAI clade 2.3.4.4b infections have also been reported in countries on the east side of the Andes Mountains, with large outbreaks in poultry, wild birds, and wild mammals in Brazil, Argentina, and Uruguay, occurring during 2023 *(2, 3, 4)*.

Since 2022, and as of 28 October 2024, avian influenza A(H5N1) clade 2.3.4.4b has been detected in 37 human cases in the United States, one case was reported in 2022 and 36 cases in have been reported in multiple states in 2024 *(5, 6).* In addition, two human cases have also been reported in Latin America, the first in early 2023 in the Bolívar province of Ecuador, and the second in the Antofagasta region of Chile in March 2023 *(1)*. The case in Ecuador was a nine-year-old female from a rural area who had contact with backyard birds, while the case in Chile was reported in March 2023, in a 53-year-old male from the Antofagasta region, near the seashore where seabirds infected with H5N1 had previously been detected *(1, 7)*.

Since March 2024, infection with avian influenza A(H5N1) clade 2.3.4.4b in dairy cattle has been reported, and ongoing multistate outbreak in dairy cattle, poultry and other animals in the U.S., has been ongoing *(2*, *8)*. During 2024, as of 28 October, 36 A(H5) human cases have been reported in the U.S., with all but one case associated with occupational exposure to infected animals *(5, 6)*. The source of exposure of the case detected in the state of Missouri through routine surveillance in August 2024 remains unknown; the detection occurred in a patient who was hospitalized and had underlying medical conditions, and no immediate animal exposure was identified *(9)*.

Capacity for surveillance and response: The Americas Region benefits from pandemic preparedness initiatives by the Pan American Health Organization (PAHO), including the World Health Organization (WHO) Pandemic Influenza Preparedness Framework (PIP Framework) and Preparedness and Resilience for Emerging Threats initiative (PRET). These programs enhance regional capacities for early detection, surveillance, vaccine deployment, and response to zoonotic influenza outbreaks, improving readiness to manage potential spread *(10)*. Nevertheless, intersectoral capacities *(11)* vary among countries, and within a country. Current uncertainties about the source of exposure for the most recent case highlight potential difficulties in monitoring the virus's circulation in animal populations or contaminated environments. This could elevate the risk of absence or delay in detection in humans in countries with limited detection capabilities at intersectoral level. In the Americas, GISRS network *(12)* is the foundation for public health surveillance in humans and the experience of the network can be used by other sectors to strengthen early detection.

Criteria	Evaluation		Risk	Rationale
	Likelihood	Consequences		
Potential risk for human health in general population linked to animal	Likely	Minor	Moderate	• <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

Criteria	Evaluation		Risk	Rationale
	Likelihood	Consequences		
exposure in the Americas Region?				environments. Eight countries in the Americas Region have reported outbreaks in both marine and terrestrial mammals, including dairy cattle, alpacas, house, mice, dogs, cats, farmed mink, seals, sea lions, and most recently in swine *(2, 8, 9, 13, 14)*. Previously, there have been human infections with other avian influenza subtypes following exposure to infected mammals. • Detection of avian influenza in swine: On 30 October, the U.S. Department of Agriculture (USDA) and Oregon state veterinary officials reported the first case of avian influenza A(H5N1) in swine in the U.S.; the case was detected in one pig from a mixed-species backyard farm, which includes poultry and swine. The swine showed no clinical signs *(14)*. • Human cases of avian influenza: In the U.S., as of 28 October, 36 avian influenza A(H5) human cases had been detected in 2024 of which 20 have been linked to infected dairy cattle, 15 to infected poultry, and the source of the exposure in one case remains unknown; uncertainty persists about potential undetected circulation of the virus in animal species or among humans *(5, 6)*. Thirty-five cases recovered without hospitalization; while one case, with unknown exposure had presented with acute symptoms (chest pain, nausea, vomiting, diarrhea, and weakness) requiring hospitalization, and recovered following treatment with oseltamivir *(15-20)*. Among the cases for which genetic sequencing was performed, including the case in 2022, 19 are avian influenza A(H5N1) clade 2.3.4.4b *(5, 6)*. • To date, human-to-human transmission of influenza A(H5) virus has not been identified. • Among 20 laboratory-confirmed human cases of avian influenza A(H5N1) after exposure to infected dairy cattle, there were 17 human cases detected in the U.S. in states bordering Mexico, the State of California (n=16) and Texas (n=1); all occurred on different farms. Genetic sequencing of nine of the 16 cases in California confirms that all are H5N1 viruses clade 2.3.4.4b and that all are closely related genetically to the virus causing infections in domestic dairy cattle *(5)*. Continued outbreaks may increase the likelihood of additional human infections. • Cross-species adaptation of influenza A(H5N1): Specific genetic changes have been identified in the human case reported in Missouri. These changes are not known to affect virus transmissibility or its ability to infect and spread among humans. However, these may lead to antigenic changes, potentially impacting the cross-reactivity of clade 2.3.4.4b candidate vaccine viruses. Such changes have been rarely observed in dairy cattle sequences *(18)*. Nevertheless, further testing for antigen detection is ongoing.

Criteria	Evaluation		Risk	Rationale
	Likelihood	Consequences		
				• Genomic sequencing efforts have linked human cases to viruses detected in poultry outbreaks and dairy cattle herds, indicating circulation of the same avian influenza A(H5N1) clade 2.3.4.4b virus among birds, cattle, and humans *(5, 6, 18)*. The presence of markers (PB2 M631L—typically found in mammals—) suggests adaptation to cattle and likely cow-to-human transmission *(18)*. This adaptation raises concerns, particularly for those occupationally exposed to livestock. No markers for increased transmissibility among mammals have been identified. • The H5 virus has evolved continuously since 1996, but it has never infected so many bird species nor been able to transmit to and replicate in cattle and marine mammals *(2, 21)*. The current epizootic outbreak involves adaptations and ongoing transmission of avian Influenza A(H5N1) clade 2.3.4.4b to non-avian species, resulting in a notable increase in human cases, a change from 2022 when only one human infection was reported in the Americas Region. Despite a limited number of sporadic human cases with varying severity since then, the genetic evolution and reassortment of the virus among wild birds and some mammals raise concerns about the potential for increased infectivity and spread among humans *(22)*. • The potential risk for human health is based on the ongoing detection of avian influenza A(H5N1) clade 2.3.4.4b in wild and domesticated birds in several countries within the Americas Region, the current outbreak among dairy cattle in the U.S., the first H5N1 detection in swine *(14)*, and the rising number of human cases with confirmed exposure to poultry and dairy cattle in the U.S. • The detection of an avian influenza A(H5N1) clade 2.3.4.4b case in the state of Missouri, where no livestock infections have been reported and the patient had no known exposure to infected animals or their products and the rapid increase of human cases in California (16 cases in under one month) support the concern that as the virus is increasingly found in mammal species, the potential risk of spread to humans increases *(15-20, 23)*.
Risk of virus spreading in new geographic areas?	Likely	Moderate	Moderate	• Regional spread dynamics: Since 2020, influenza A(H5N1) clade 2.3.4.4b variant has caused outbreaks in wild birds and poultry in Africa, Asia, and Europe *(1)*. In 2021, the virus spread through waterfowl flyways to North America and to Central and South America in 2022. From 2022 and until 24 October 2024, 19 countries and territories in the Americas Region had reported to WOAH 2,950 influenza A(H5N1) outbreaks in domestic and wild birds *(2, 24)*. During this same period, 640 outbreaks of avian influenza A(H5N1) in mammals were recorded in seven countries in the Region. In 2024 alone, up to 24 October, six countries had reported 242 outbreaks in birds (Brazil, Canada, Ecuador, Mexico, Peru, and the United States), and three countries reported 340

Criteria	Evaluation		Risk	Rationale
	Likelihood	Consequences		
				mammal outbreaks (Argentina, Canada, and the United States) *(2)*. - The dominant mechanism of global spread is through wild bird migrations (which has been ongoing for several years). However, the virus currently circulates among mammals (dairy cow herds), commercial and backyard flocks and wild birds in the United States. This circulation has led to increasing exposure in domestic and wild mammals and birds, as well as humans. - Migratory birds, especially waterfowl, serve as natural reservoirs of avian influenza viruses and play a key role in spreading the virus across large geographical areas *(13)*. Infected birds can shed the virus through their feces and respiratory secretions, contaminating water sources and raising the risk of transmission to wild and domestic animals, as well as humans, who may come into contact with these contaminated sources. - Spread in wild animals in the Americas Region: During 2022, 314 outbreaks in wild birds were registered in 10 countries and notified to WOAH. Until September 2022, only Canada and USA registered affected birds. During 2023, 8 additional countries and territories, for a total of 18, registered 371 outbreaks in wild birds. During 2024, the same 18 countries and territories notified 59 outbreaks in wild birds to WOAH *(2)*. Additionally, during 2022, 124 outbreaks in wild mammals in 2 countries were notified to WOAH (Canada and USA). During 2023, those 2 countries and 4 additional ones from South America, notified 159 outbreaks in wild mammals. During 2024, 45 outbreaks were notified in 5 countries *(2).* - While transmission of influenza A(H5N1) viruses from cattle into other local wild and domestic mammalian and avian species has also been detected, the frequency and transmission route(s) remain poorly understood at this time *(25)*. Between 15 September and October 26, avian influenza virus (H5) has been detected in wastewater in the United States in six sites, including California and Idaho *(26)*. - Spread in domestic animals in the Americas Region: During 2022, 1,089 outbreaks in domestic birds were registered in 7 countries and notified to WOAH. Until September 2022, only Canada, Mexico and USA registered affected birds. During 2023, 10 additional countries and territories, for a total of 17, registered 960 outbreaks in domestic birds. During 2024, the same 17 countries and territories notified 189 outbreaks in domestic birds to WOAH *(2)*. Additionally, during 2022 and 2023, only the USA notified two cases in domestic mammals (pets). In 2023, Canada and USA notified to WOAH 6 outbreaks in domestic mammals, mainly pets. During 2024, 248 outbreaks were notified to WOAH by two countries (Canada and USA) in domestic mammals. Most of them were in the USA related to dairy cattle *(2)*.

Criteria	Evaluation		Risk	Rationale
	Likelihood	Consequences		
				- Multiple outbreaks have been reported in cattle, which may indicate that avian H5 virus has continuous circulation among cattle populations. With the return of migratory birds this fall, there is an associated increase in the potential introduction of avian influenza viruses, including highly pathogenic avian influenza (HPAI). Migration events contribute to the global dispersal of HPAI H5, as seasonal movements can facilitate the virus's spread to new geographic areas within the Region *(27).* This process may incrementally elevate exposure risks among local wildlife and domestic animal populations. 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), spillovers into birds from mammalian species (cattle) and possible sporadic human cases in previously unaffected regions *(9)*.
Risk of insufficient early detection, prevention, response and control capacities with available resources?	Likely	Moderate	Moderate	- Countries and territories in the Latin America and the Caribbean have different levels of intersectoral capacity to perform integrated surveillance and response activities for zoonotic avian influenza. Many countries lack structured plans to conduct intersectoral surveillance strategies effectively, resulting in fragmented efforts. - Some countries face challenges in implementing the One Heath approach, coordinating response efforts and sharing of viruses to WHO Collaborating Centers for risk assessment purposes among different sectors, including animal, human, environmental, food safety sectors among others. While some initiatives exist, overall regional collaboration remains weak, hindering collective action against zoonotic threats. Limited allocation of public health resources for animal health surveillance affects overall health outcomes and response capabilities *(28)*. - Early case detection of zoonotic influenza differs across countries and territories in the Americas Region. The only two human infections caused by Influenza A(H5) in Latin America were identified through routine Severe Acute Respiratory Infection (SARI) sentinel surveillance. To complement sentinel surveillance, outpatient surveillance and event base surveillance should be strengthened to detect mild cases or different epidemiological situations that trigger a response. - Reported and recorded challenges for some countries and territories include the shipping of related samples (human and animal) to WHO Collaborating centers and WOAH Reference centers.

Criteria	Evaluation		Risk	Rationale
	Likelihood	Consequences		
			🟨	• There is a lack of effective mechanisms for monitoring and evaluating the impact of intersectoral collaborations and surveillance efforts. Surveillance systems that are in place to monitor diseases in cattle in case of a potential introduction in Latin America and the Caribbean would need to be adapted to detect avian influenza, based on local context and risk. • The absence of standardized protocols for sampling and testing in the animal sector limits the efficiency of surveillance activities at intersectoral level. There is an opportunity to strengthen technical guidelines on best practices for managing zoonotic influenza at intersectoral level, including strategies for vaccination and clinical management and readiness *(29)*. • Surveillance in wild birds is generally limited, typically relying solely on passive detection of unusual mortalities. Surveillance of backyard birds poses an additional challenge, as these small-scale, often self-sustaining production units are typically unregistered and, therefore, fall outside the scope of official veterinary services. Furthermore, since these operations are usually low-tech and focused on self-consumption, animal owners often have limited knowledge about identifying and reporting diseases. Compounding this issue, in most countries, swine influenza surveillance does not fall under the jurisdiction of official veterinary services *(11)*. • Depopulation of infected animals is not a feasible strategy for dairy cattle infected with avian influenza. Lack or challenge in the implementation of alternative appropriate control and prevention measures (e.g., quarantine and movement restrictions) relevant for local and national contexts could facilitate the spread of the virus. • According to what has been observed in the current outbreak in cattle, the risk of occupational infection is high in the absence of use and application of adequate personal protective measures. Occupational exposure, both for workers in poultry or pig production units and for healthcare workers, is a consistent concern across the region, underscoring the need for an established protocol. There is no precise definition of an "exposed person" in most countries in the Region; instead, there are general guidelines for testing individuals. While all countries recommend monitoring individuals with exposure, not all have formal protocols in place *(11)*. • Engagement of local communities in community surveillance and prevention efforts is often inadequate, missing an opportunity for grassroots mobilization.

Background information

Hazard Assessment

Avian Influenza A(H5N1) clade 2.3.4.4b

Avian influenza is caused by an 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 *(29)*. Avian influenza is a highly contagious viral disease primarily affecting avian species *(30)*.

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 *(29)*. 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 *(29)*. There is a risk that the virus could return to humans with pandemic characteristics due to genomic reassortment in co-infections (spillover and spillback). The evolution of the H5 virus in cattle populations and possible reassortments is currently unknown *(31)*.

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 illness to deaths *(30).*

Frequent transmission of highly pathogenic avian influenza (HPAI) A(H5N1) clade 2.3.4.4b between avian and mammalian species has led to genetic adaptations favoring infection of mammalian hosts. The current outbreak in dairy cattle in the United States evidences a successful adaptation and viral replication in mammalian tissues *(32)*. Genomic analyses have documented that approximately half of the mammalian sequences globally within the avian influenza A(H5N1) clade 2.3.4.4b have amino acid signatures in basic protein polymerase 2 (PB2) that enhance viral replication in mammalian cells, host-specific polymerase activity, and temperature sensitivity. 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 *(33)*. The severity of the expected clinical presentation of H5 virus, in contrast to seasonal influenza viruses, is still unknown.

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 has been 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 *(2, 13)*.

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, 27 countries and territories worldwide reported outbreaks in mammals to WOAH, with both marine and terrestrial mammals affected, including animals in the family of *Artiodactyla, Carnivora, Cetacea*, and *Didelphimorphia* (cattle, pigs, dogs, cats, farmed minks, foxes, seals, sea lions, opossum, etc.) *(8, 9, 13).* Regarding clade 2.3.4.4b, in October 2022, an outbreak of HPAI H5N1 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 *(33, 34)*. 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 *(35)*. Since 2003 and up to 27 September 2024, there had been 904 human cases and 463 deaths (51% case fatality) caused by influenza A(H5N1) virus reported to WHO, affecting 23 countries globally *(36)*.

The avian influenza A(H5N1) virus, particularly clade 2.3.4.4b currently circulating in the Americas Region, belongs to a high pathogenic avian influenza (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 *(37)*. 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 *(38-40)*.

In 2021, the virus spread through waterfowl flyways to North America and, in 2022, to Central and South America. Since 2021 and up to 24 October 2024, 2,950 avian influenza A(H5N1) outbreaks in domestic and wild birds in 19 countries and territories in the Americas (Argentina, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Ecuador, Falkland Islands, Guatemala, Honduras, Mexico, Panama, Paraguay, Peru, the United States, Uruguay, and Venezuela) and 640 outbreaks of avian influenza A(H5N1) in mammals in seven countries (Argentina, Brazil, Canada, Chile, Peru, the United States, and Uruguay) were reported to WOAH *(2)*.

On 25 March 2024, the first detection of avian influenza A(H5N1) was reported in dairy cattle and in samples of unpasteurized milk obtained from dairy cattle *(8)*. Since March 2024 up to 24 October, the United States Department of Agriculture (USDA) reported that 380 livestock herds across 14 U.S. states have confirmed cases of avian influenza A(H5N1) virus infections in dairy cattle, with the number of infected herds continuing to rise *(8)*. Detections of A(H5N1) have been reported in dairy cattle and other animals, affecting 238 dairy herds and one site with Alpacas in 14 states. Deaths have also been observed among wild cats and birds within some affected farms. Studies to date indicate that pasteurization is effective in inactivating the virus in milk *(34, 41)*.

With relation to human infections caused by avian influenza A(H5N1), 39 human infections have been reported in the Americas Region, one in the U.S. in 2022, one in Ecuador in January 2023, one in Chile in March 2023, and 36 in the U.S. in 2024, with the last 20 cases having been reported between 4 and 28 October 2024 *(5, 6, 9)*. Of the 36 cases reported in the U.S., 20 were following exposure to dairy cattle, and 16 cases have been linked to poultry exposure, including the case in 2022. Additionally, one case, reported on 6 September 2024, involved no immediately known animal exposure in the state of Missouri *(5, 6)*.

The case in Missouri has been confirmed influenza A(H5) clade 2.3.4.4b, with unknown source of exposure was detected through routine surveillance and involved a patient who was hospitalized on 20 August 2024 after developing acute symptoms and had underlying medical conditions; they were treated with oseltamivir and since recovered. Despite low viral RNA levels, partial sequencing identified two unique amino acid differences in the HA gene, potentially affecting vaccine cross-reactivity. No markers for mammalian adaptation or reduced susceptibility to neuraminidase inhibitors were found *(20)*. While this is the first case with no occupational exposure to infected animals, the available gene sequences are closely related to H5 sequences found in domestic animals in the country *(15-20)*.

Of the 36 laboratory confirmed human cases of H5 avian influenza detected in the U.S. in 2024, there were 17 human cases detected in the U.S. in two states bordering Mexico, the State of California (n=16) and Texas (n=1) *(5)*.

Among the 36 human cases in the U.S. in 2024, genetic sequencing results indicate 17 are avian influenza A(H5N1) clade 2.3.4.4b and efforts to sequence additional cases are in progress; in addition, the case detected in 2022 was also confirmed as avian influenza A(H5N1) clade 2.3.4.4b *(5, 6)*.

Given the start of the seasonal influenza period in the northern hemisphere, the possibility of human co-infection with seasonal influenza and H5 viruses cannot be excluded, particularly through occupational exposure. It is unknown what is the risk of dissemination of the avian influenza A(H5N1) clade 2.3.4.4b in South America, especially related to the migration of birds in autumn.

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. Likewise, the epizootic is unprecedented in the region, not only because of the large number of cases but also due to the diversity of affected animal species and changes in pathogenic behavior. Of particular concern is the increasing number of mammal species susceptible to the virus, leading to significant mortality events, especially among marine mammals, with mammal-to-mammal transmission likely playing a crucial role. Currently unknown is the role of pigs and other mammals as "mixing vessels." Moreover, the first detection of the H5N1 in a pig that was asymptomatic implies challenges in the early detection of the virus in this species.

Chronologically, in recent years, we can identify at least three scenarios marked by a progressive increase in risk.: (i) the occurrence of influenza in poultry and sporadically in wild bird, with no human cases; (ii) an increase in the magnitude of influenza in birds (both wild and poultry) and sporadic cases in humans; and (iii) continued transmission in birds and extended to mammals showing adaptation to non-avian species, with an increase in human cases due to direct contact and low biosecurity measures.

In addition, 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.

The impact on Latin American and Caribbean countries of a situation similar to that currently recorded in the United States could be moderate considering the variability of the surveillance and response capacities of countries in the region *(11)*.

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

Strengths	Vulnerabilities
• Member States have strengthened influenza surveillance in both animal and human populations. • Coordination between animal, agricultural, and human health sectors, in some countries, for information exchange and control actions. ○ The U.S., Food Safety and Inspection Services (FSIS) strengthened surveillance sampling in slaughter facilities,	• Surveillance for avian influenza 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 and backyard units. • Surveillance systems for monitoring disease in dairy cattle need adaptation to detect avian influenza. Likewise,

Strengths	Vulnerabilities
to ensure continued assurances on the safety of the beef supply destined for human consumption. ○ Countries in America tightened import requirements on dairy cattle from the U.S. • 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 some countries 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. • WOAH Reference laboratories for Avian influenza in the U.S., Brazil, and Canada to carry out and organize inter-laboratory proficiency testing with laboratories other than WOAH Reference Laboratories for the same pathogens and diseases to ensure equivalence of 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. • Some Member States are updating their pandemic influenza response plans based on lessons from COVID-19 and the current A(H5N1) outbreak.	systematic presence in swine could pose challenges in the early detection and surveillance for this species. • 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 protocol for avian influenza needs to be implemented by veterinary laboratories to expand surveillance approach. 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 generate genetic data 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 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.). • 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

Strengths	Vulnerabilities
• 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: ○ Information dissemination. ○ 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 WOAH reference laboratory in Campinas, Brazil.	including carcasses, 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 Americas Region, potentially facilitating the spread of the virus. • Insufficiency of infection prevention and control (IPC) measures, and the use of personal protective equipment (PPE) based on risk of exposure among the healthcare workers assisting suspected cases, regardless of the severity of the presentation. • Challenges for risk communication and community participation in prevention and control activities. • Limited capacity in some countries 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.
- Improve One Heath approach in coordination mechanism and platform among different sectors, health, animal, environmental among others.

Besides PIP and PRET, PAHO activities to respond to the outbreak at the intersectoral component include:

- Contingency plans and team preparation with drills and Sim-Ex;
- Surveillance strategies in wild animals, backyard and commercial poultry, and other potential relevant species;

- Laboratory capacity development together with the reference laboratory (e.g., Campinas) with proficiency rounds and trainings;
- Work at the human-animal interface with Infectious Hazard Management, Health Emergencies Department PAHO/WHO;
- Epidemiological monitoring, management and analysis of data during the emergency;
- Capacity building in the appropriate strategies for animal depopulation, carcasses elimination and cleaning and disinfection.
- Design and implement strategies for post-vaccination monitoring in vaccinated poultry and enhance surveillance measures to rule out the presence of undetected viral circulation in these populations. 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
- PAHO published recommendations to strengthen intersectoral work in surveillance, early detection, and research at the human animal interface *(11)*.

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