Epidemiological Alert
Human infections caused by avian influenza A(H5N1) in the Americas Region

8 October 2024

The Pan American Health Organization / World Health Organization (PAHO/WHO) calls on Member States to work collaboratively and intersectorally to preserve animal health and protect public health. PAHO/WHO urges Member States to strengthen efforts to implement protocols for the timely detection, notification, and rapid response to outbreaks in animals, as well as for the detection of human cases of avian influenza A(H5N1). In addition, PAHO/WHO encourages the sharing of viruses with WHO Collaborating Centers in both sectors to strengthen risk analysis and to prepare candidate vaccine viruses.

Global Context

The avian influenza virus, which is typically transmitted among birds, has shown an increase in cases in mammals due to changes in its ecology and epidemiology *(1)*. The highly pathogenic avian influenza (HPAI) virus[1] (H5N1) currently circulating in the Americas belongs to a 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 spread *(2)*. Since 2020, the H5N1 subtype of clade 2.3.4.4b has caused an unprecedented number of deaths in wild birds and poultry in numerous countries in Africa, Asia, and Europe *(1)*. In 2021, the virus spread through waterfowl flyways to North America and, in 2022, to Central and South America *(1)*. By 2023, epidemic outbreaks in animals were reported in14 countries and territories, mainly among the Americas Region *(1, 3)*.

The risk of infection in mammals and humans increases when there is contact with infected birds or exposure to contaminated environments *(3)*. Since 2022, 18 countries on three continents have reported outbreaks in mammals to World Organization for Animal Health (WOAH), with both marine and terrestrial mammals affected, including cattle, goats, dogs, cats, farmed mink, seals, and sea lions *(4)*.

Between 2003 and 19 July 2024, a total of 896 cases and 463 deaths (51.7% fatality) in humans caused by the influenza A(H5N1) virus were reported to the World Health Organization (WHO) globally, affecting 24 countries *(5)*.

[1] Broadly speaking, the multiple strains of avian influenza virus can be classified into two categories according to the severity of disease presentation in poultry: low pathogenic avian influenza viruses (LPAIV) and highly pathogenic avian influenza viruses (HPAIV).

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Summary of the situation in the Americas Region

Between 2022 and epidemiological week (EW) 39 of 2024, a total of 19 countries and territories in the Americas Region reported 5,472 outbreaks of avian influenza in domestic and wild birds to WOAH: Argentina, the Plurinational State of Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Ecuador, , Honduras, the Falkland Islands, Mexico, Panama, Paraguay, Peru, the United States of America, Guatemala, Uruguay, and the Bolivarian Republic of Venezuela (**Table 1**) *(4)*. During this period, 693 outbreaks of HPAI A(H5N1) have been reported in mammals in Argentina, Brazil, Canada, Chile, Peru, the United States, and Uruguay (**Table 2**) *(4)*. Between EW 1 and EW 39 of 2024, eight countries and territories in the Americas Region have identified 373 avian influenza outbreaks in birds and 289 outbreaks in mammals (**Table 3**) (**Figure 1, Figure 2, Figure 3, Figure 4, and Figure 5**) *(4)*.

Between 2022 and EW 39 of 2024, 19 human infections caused by avian influenza A(H5) have been reported in the Americas. Of these, 17 were reported in the United States *(6);* one in Ecuador, reported on 9 January 2023 *(7);* and one in Chile, reported on 29 March 2023 *(8)*. During 2024, 16 human cases were reported, of which 15 have been reported in the last five months.

The following is a summary of the situation in countries and territories in the Americas Region in alphabetical order, that reported outbreaks of avian influenza A(H5N1) in birds and mammals during 2024, and the information on human cases reported in 2024.

In **Argentina**, between EW 1 and EW 39 of 2024, an outbreak of H5 avian influenza was reported to WOAH. The outbreak was identified in the province of Chubut in January affecting a South American sea lion; no new outbreaks have been reported since then. No human cases of avian influenza (H5N1) infection have been reported in the outbreaks identified to date *(4)*.

In **Brazil**, between EW 1 and EW 39 of 2024, 16 outbreaks of avian influenza A(H5) have been confirmed in wild birds in the states of Espírito Santo, Rio de Janeiro, Rio Grande do Sul, and São Paulo. The last reported outbreak was in May 2024. To date, no outbreaks in production birds or human cases of infection with avian influenza (H5N1) have been detected *(4)*.

In **Canada**, between EW 1 and EW 39 of 2024, multiple HPAI A(H5N1) outbreaks in poultry and wild birds have been reported to WOAH in nine Canadian provinces. The provinces of Alberta, Nova Scotia, Prince Edward Island, and Quebec have reported ten outbreaks in wild mammals. The last identified outbreak was reported in July 2024. No human cases of avian influenza (H5N1) infection have been reported in the outbreaks identified to date *(4)*.

In **Ecuador**, between EW 1 and EW 39 of 2024, an outbreak of H5N1 avian influenza in backyard poultry was reported to WOAH. The outbreak was identified in Pastaza province in February; no new outbreaks have been reported since. No human cases of avian influenza (H5N1) infection have been reported in the outbreaks identified to date *(4)*.

In the **Falkland Islands**, between EW 1 and EW 39 of 2024, WOAH was notified of eight outbreaks of avian influenza in birds, all related to wild birds *(4)*. The last outbreak was reported in September 2024. No human cases of avian influenza (H5N1) infection have been reported in the outbreaks identified to date (9).

In **Mexico**, between EW 1 and EW 39 of 2024, 15 outbreaks of avian influenza in wild and domestic birds were reported to WOAH. The outbreaks occurred in the states of Chihuahua, Guanajuato, Jalisco, Mexico, Michoacán, Oaxaca, Puebla and San Luis Potosí. The last outbreak was reported in July 2024. No human cases of avian influenza (H5N1) infection have been reported in the outbreaks identified to date *(4)*.

In **Peru**, between EW 1 and EW 39 of 2024, 57 outbreaks of HPAI A(H5) were reported to WOAH, mostly in backyard domestic poultry in the departments of Ancash, Arequipa, Cajamarca, Cusco, Ica, Junín, La Libertad, Lambayeque, Lima, and Moquegua. The last outbreak was reported in September 2024. No human cases of avian influenza (H5N1) infection have been reported in the outbreaks identified to date *(4)*.

In the **United States of America**, detections of HPAI A(H5) virus in wild birds, commercial poultry, and/or backyard poultry have been reported to WOAH since early 2024 in 26 states[2] in the country *(4)*. Outbreaks in wild mammals have also been reported in a variety of species, including bobcats, raccoons, cougars, minks, skunks and foxes in seven states (California, Kentucky, Missouri, Montana, New York, Vermont and Washington) (*4*). The first detection of influenza A(H5N1) in goats was reported in Minnesota on March 18. On 25 March 2024, the first detection of influenza A(H5N1) was reported in dairy cattle and in samples of unpasteurized milk obtained from dairy cattle in the states of Texas and Kansas *(3)*. Since then, detections of A(H5N1) have been reported in 254 herds of dairy cattle across 14 states, as of 4 October; 82% of the herds were in Colorado (n=64), California (n=56), Idaho (n=33), Michigan (n=29), and Texas (n=26) (*10)*. In the last 30 days, 82 affected herds were reported in the states of California (n=79) and Idaho (n=3) (*11*). Fatalities have also been observed among wild cats and birds within some affected farms *(12)*.

During 2024, as of 4 October, 16 human cases of influenza A(H5N1) were confirmed in the United States, nine of which followed exposure to poultry *(6)*. Of the 16 reported cases, 15 have been reported in the past 5 months. The 16 human cases were reported in California (n=2), Colorado (n=10), Michigan (n=2), Missouri (n=1), and Texas (n=1) (6).

On 1 April 2024, the United States reported the first human case of influenza A(H5N1) in a farm worker, being related to an event in dairy cattle in the State of Texas (*13*). This case represents the first instance of probable transmission of the avian influenza A(H5N1) virus from mammals to humans. Since then, and as of 4 October 2024, six human cases of influenza A(H5N1) involving cattle have been reported in the states of California (n=2), Colorado (n=1), Michigan (n=2), and Texas (n=1) (*14, 15*).

On 6 September 2024, the United States reported the first confirmed case of influenza A(H5N1) in which there is no known recent exposure to animals. The case was identified through the Missouri state seasonal influenza surveillance system (*16*). As of 27 September, five health care professionals who were exposed to the case and had presented mild symptoms were detected. As the polymerase chain reaction (PCR) technique would not be reliable in identifying these exposures, blood samples were collected for serology. As of 4 October, the results of the serological tests performed following the Missouri case are pending (*17*).

[2] California, Colorado, Florida, Idaho, Indiana, Iowa, Kansas, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Montana, Nebraska, New Mexico, New York, North Carolina, Ohio, Oregon, Pennsylvania, South Carolina, South Dakota, Texas, West Virginia, and Wisconsin.

Table 1. Number of outbreaks in birds and mammals in the Americas Region from 2022 to EW 39 of 2024.

Country/Territory	Birds	Mammals
Argentina	168	62
Bolivia	40	
Brazil	197	12
Canada	1.736	102
Chile	464	34
Colombia	73	
Costa Rica	10	
Cuba	11	
Ecuador	43	
Falkland Islands	12	
Guatemala	1	
Honduras	9	
Mexico	193	
Panama	14	
Paraguay	7	
Peru	469	3
United States of America	2.004	466
Uruguay	19	14
Venezuela	2	
Total	5.472	693

Source: Adapted from World Organization for Animal Health. Avian Influenza. Paris: WOAH; 2024 [cited 3 October 2024]. Available from: https://wahis.woah.org/#/event-management; and Falkland Islands Department of Agriculture. Avian Influenza Information. Stanley: IFAD; 2024 [cited 3 October 2024]. Available from: https://falklands.gov.fk/agriculture/avian-influenza

Table 2. Record of outbreaks in mammals in the Americas between 2022 and as of EW 39 of 2024.

Mammals	Argentina	Brazil	Canada	Chile	Peru	United States	Uruguay
Arctocephalus australis (two-hair fur seal)	Yes	Yes					Yes
Camelidae (alpaca)						Yes	
Canis latrans (Coyote)						Yes	
Canis lupus familiaris (domestic dog)			Yes				
Capra hircus (domestic goat)						Yes	
Dairy cattle						Yes	
Didelphis virginiana (Virginia opossum)						Yes	
Felis silvestris catus (domestic cat)			Yes			Yes	
Halichoerus grypus (gray seal)			Yes			Yes	
Lontra canadensis (northern river otter)						Yes	
Lontra felina (sea otter)				Yes			
Lontra provocax (huillin)				Yes			
Lynx rufus (Red lynx or bobcat)						Yes	
Martes americana (marta)						Yes	
Mephitis mephitis (Skunk)			Yes			Yes	
Microtus Ochrogaster (Prairie vole)						Yes	
Mirounga leonina (Southern Elephant Seal)	Yes						
Mus musculus (House mouse)						Yes	
Nasua nasua (Cochi or South American coati)							Yes
Neogale vison (American mink)			Yes			Yes	
Otaria flavescens (South American fur seal)	Yes	Yes		Yes	Yes		Yes
Panthera leo (Lion)					Yes		
Panthera pardus orientalis (Amur Leopard)						Yes	
Panthera tigris (Tiger)						Yes	
Pekania pennanti (Fisherman)						Yes	
Peromyscus sonoriensis (Western deer mouse)						Yes	
Phoca vitulina / Halichoerus grypus (Seal)			Yes			Yes	
Procyon lotor (Raccoon)			Yes			Yes	
Puma concolor (Puma)						Yes	
Sciurus aberti (Squirrel)						Yes	
Sylvilagus audubonii (Desert cottontail rabbit)						Yes	
Tursiops truncatus (Bottlenose dolphin)						Yes	
Ursus americanus / U. arctos horribilis (Bear)			Yes			Yes	
Ursus arctos (Brown bear)						Yes	
Ursus maritimus (Polar bear)						Yes	
Vulpes vulpes (Fox)			Yes			Yes	

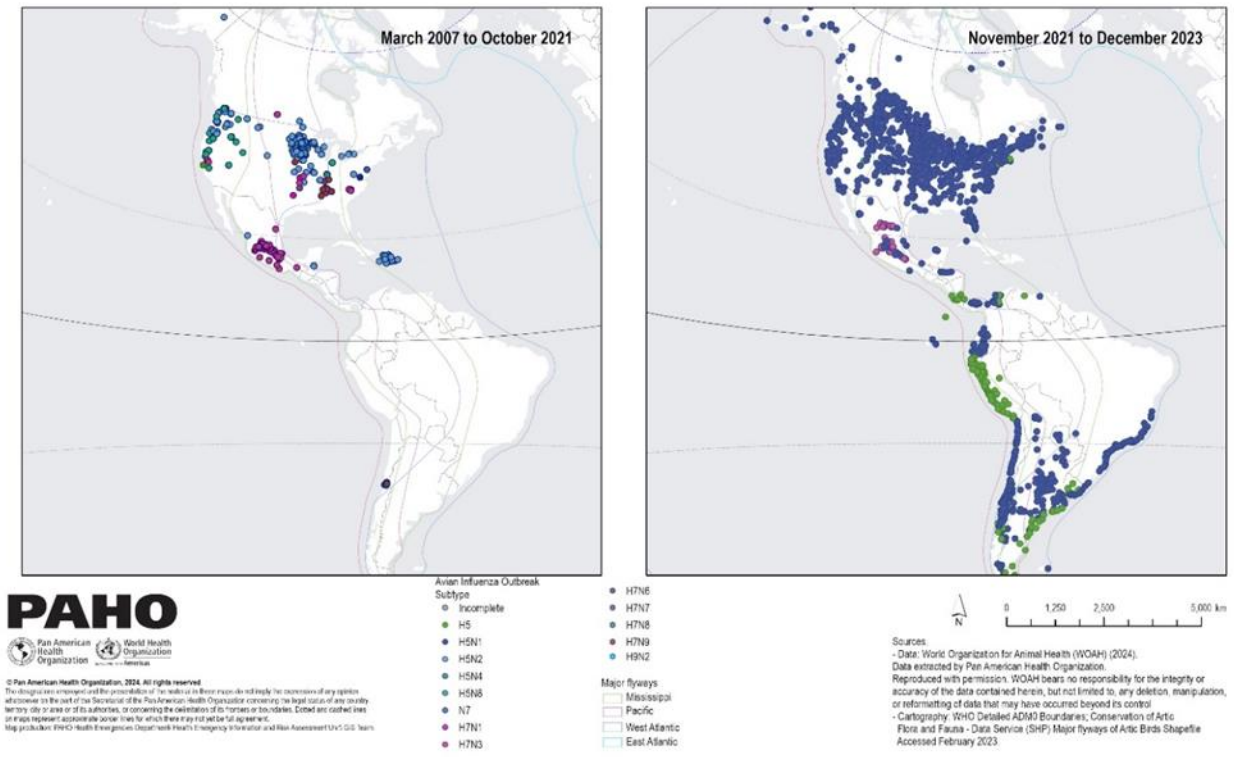
Source: Adapted from World Organization for Animal Health. Avian Influenza. Paris: WOAH; 2024 [cited 3 October 2024]. Available from: https://wahis.woah.org/#/event-management

Table 3. Avian influenza outbreaks in the Americas Region as of EW 39 of 2024.

Country	Outbreaks in birds	Outbreaks in mammals
Argentina		1
Brazil	16	
Canada	127	10
Ecuador	1	
Falkland Islands	8	
Mexico	15	
Peru	57	
United States	149	278
Total	**373**	**289**

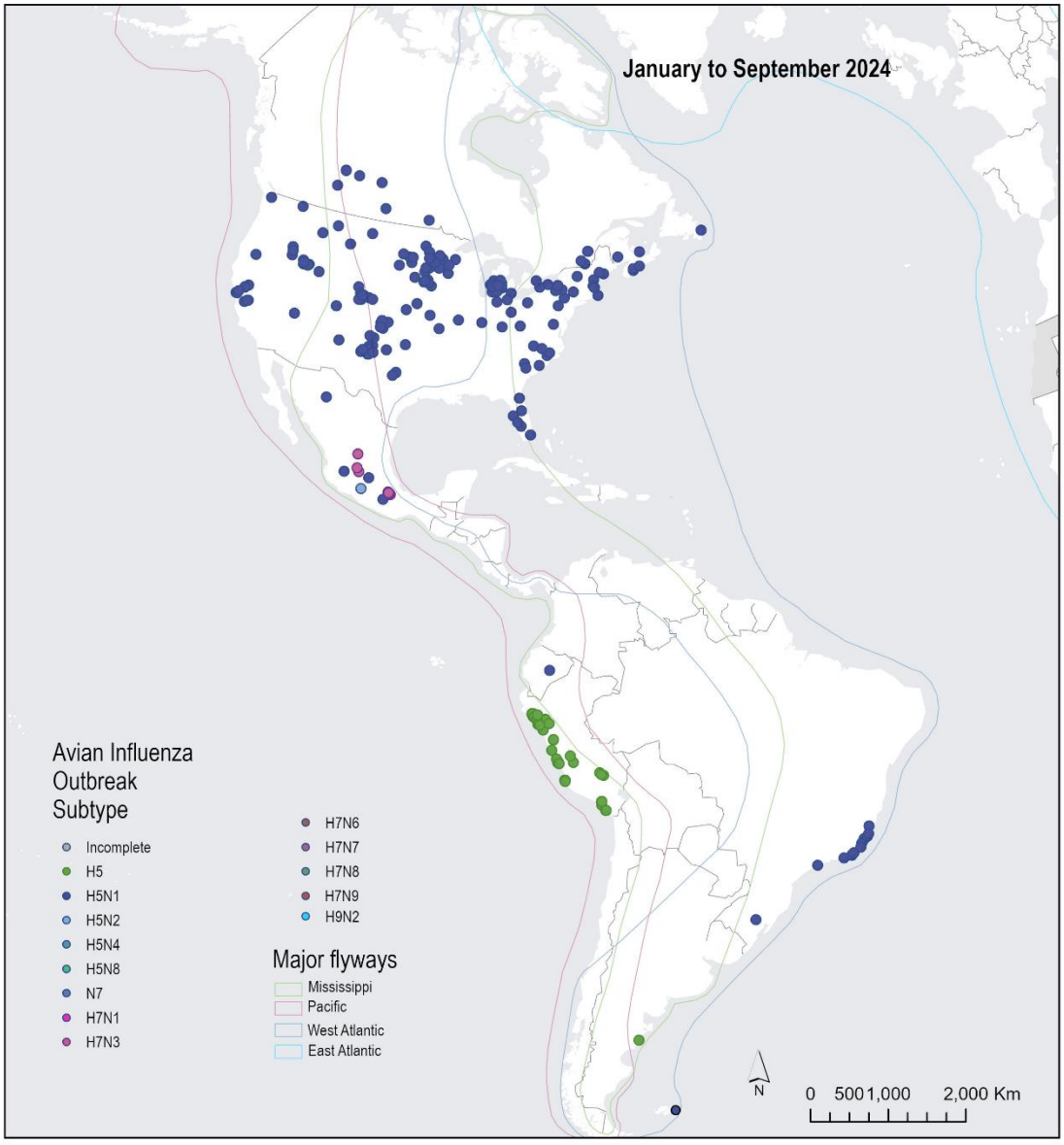
Source: Adapted from World Organization for Animal Health. Avian Influenza. Paris: WOAH; 2024 [cited 3 October 2024]. Available from: https://wahis.woah.org/#/event-management; and Falkland Islands Department of Agriculture. Avian Influenza Information. Stanley: IFAD; 2024 [cited 3 October 2024]. Available from: https://falklands.gov.fk/agriculture/avian-influenza

Figure 1. Historical avian influenza outbreaks by subtype and main migratory routes of wild birds between March 2007 to October 2021, and November 2021 to December 2023 in the Americas Region.



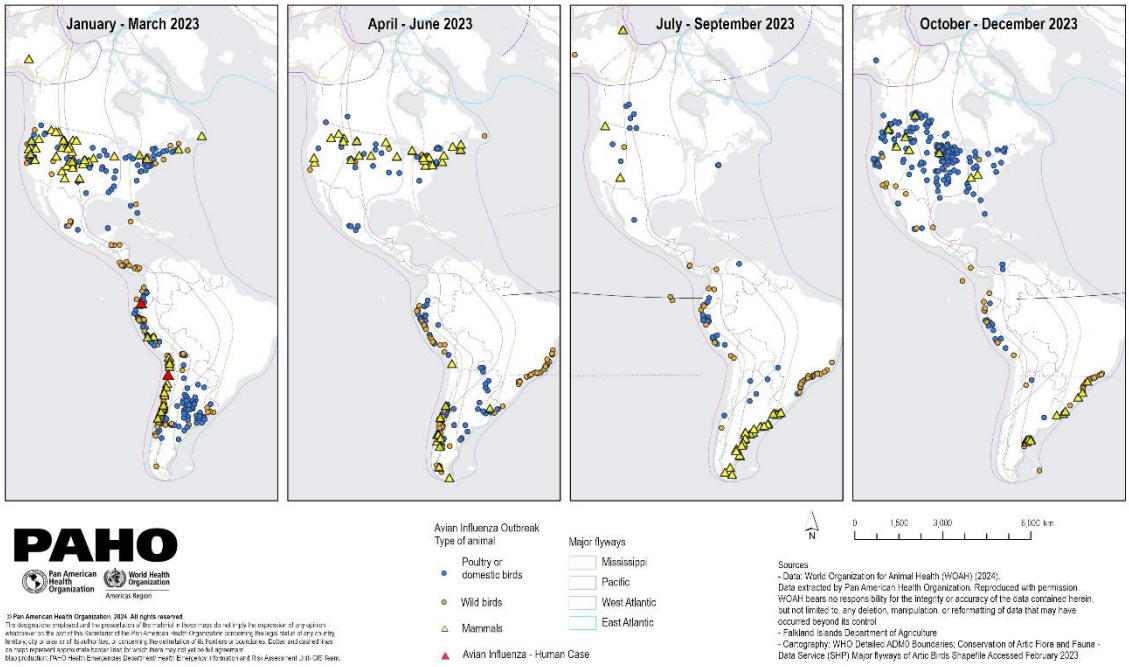
Source: Adapted from World Organization for Animal Health. Avian Influenza. Paris: WOAH; 2024 [cited 3 October 2024]. Available from: https://wahis.woah.org/#/event-management

Figure 2. Historical avian influenza outbreaks in 2024 as of EW 39 of 2024 by subtype and main migratory routes of wild birds in the Americas Region**.**



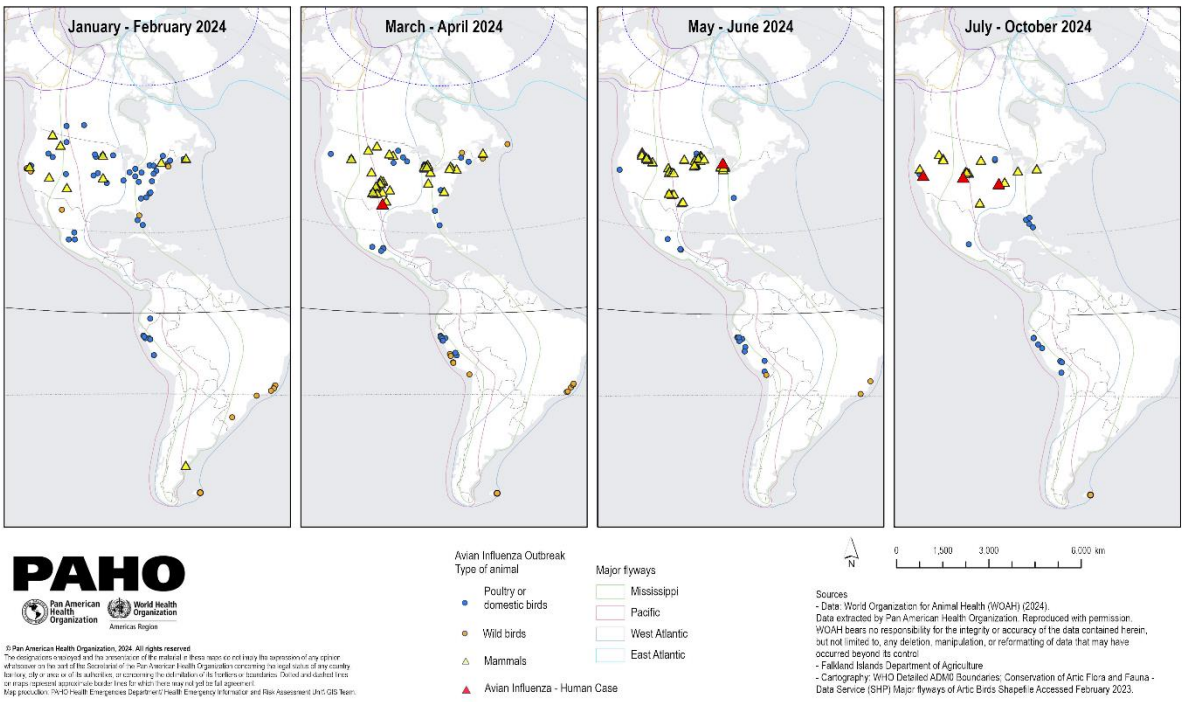
Source: Adapted from World Organization for Animal Health. Avian Influenza. Paris: WOAH; 2024 [cited 3 October 2024]. Available from: https://wahis.woah.org/#/event-management.

Figure 3. Historical avian influenza outbreaks and main migratory routes of wild birds by type of animal during 2023 in the Americas Region.



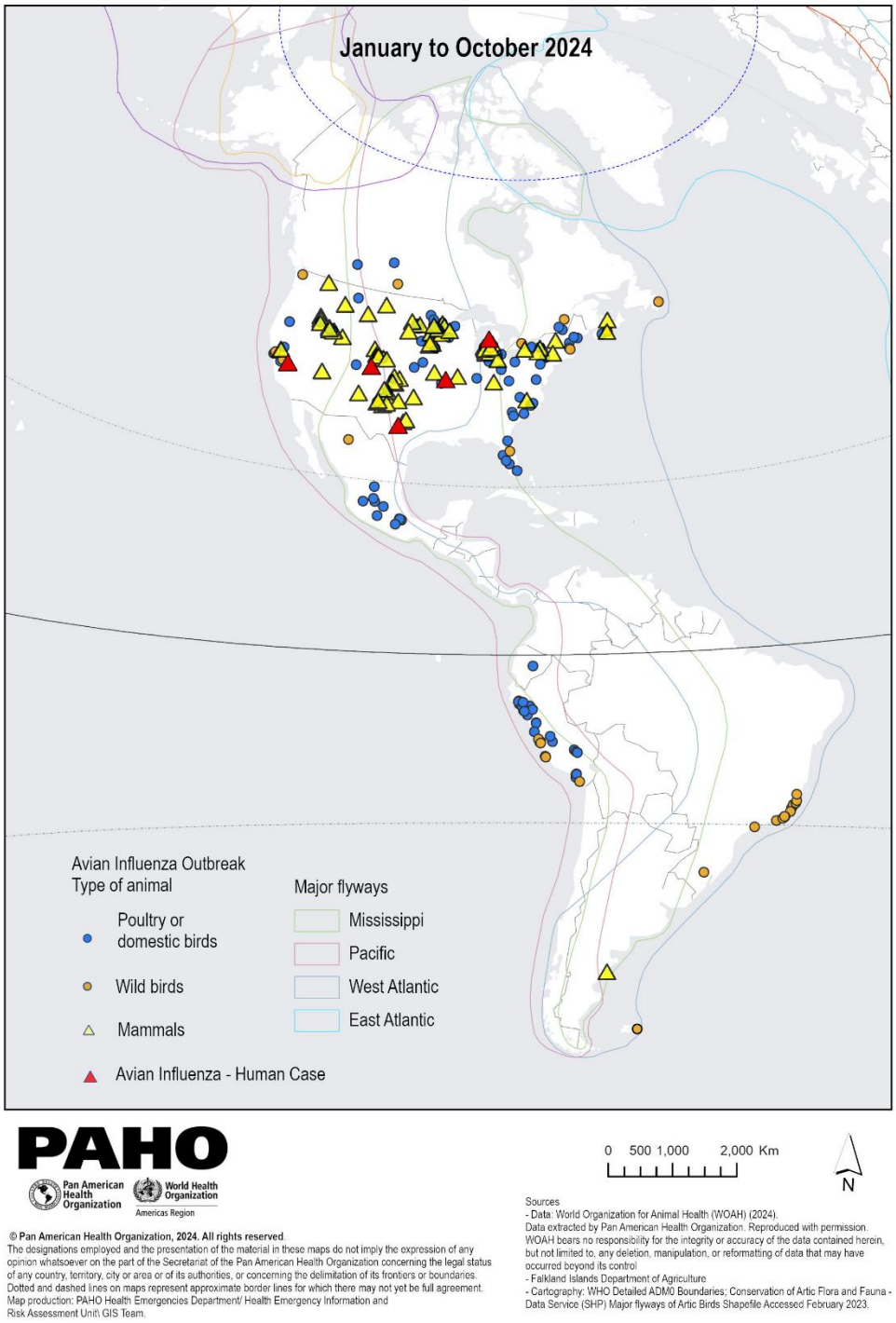
Source: Adapted from World Organization for Animal Health. Avian Influenza. Paris: WOAH; 2024 [cited 3 October 2024]. Available from: https://wahis.woah.org/#/event-management.

Figure 4. Monthly history of avian influenza outbreaks and main migratory routes of wild birds by type of animal during 2024 in the Americas Region.



Source: Adapted from World Organization for Animal Health. Avian Influenza. Paris: WOAH; 2024 [cited 3 October 2024]. Available from: https://wahis.woah.org/#/event-management.

Figure 5. Historical clustering of avian influenza outbreaks and major flyways of wild birds by type of animal during 2024 in the Americas Region**.**



Source: Adapted from World Organization for Animal Health. Avian Influenza. Paris: WOAH; 2024 [cited 3 October 2024]. Available from: https://wahis.woah.org/#/event-management.

Recommendations for Member States

While largely affecting animals, avian influenza outbreaks pose continuing risks to public health. Together, the Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO), and the World Organization for Animal Health (OIE) urge Member States to work collaboratively and intersectorally to preserve animal health and protect human health *(1, 3)*.

The detected sporadic cases of H5N1 2.3.4.4b clade virus in humans are mostly associated with direct contact with infected animals and contaminated environments. Current evidence reflects that the virus does not appear to be easily transmitted from one person to another. However, it is imperative to strengthen surveillance to detect any possible changes in this situation *(3)*.

WOAH has specific recommendations on the avian influenza situation and mammals. These recommendations advise countries to maintain intensified surveillance for the disease in domestic and wild birds, preventing the spread of the disease by implementing biosecurity measures *(18)*. WOAH recommends controlling the movement of susceptible domestic animals and their products and protecting people in close contact with sick animals. Monitoring of susceptible domestic and wild animals, investigating increases in mortality in wild animals, is crucial. In addition, timely reporting and sharing of avian influenza virus genetic sequences are essential for understanding the dynamics of the disease *(18)*.

The Pan American Health Organization / World Health Organization (PAHO / WHO) calls for action for Member States to work collaboratively and intersectorally to preserve animal health and protect public health. It is essential that avian influenza preventive measures are implemented at source, protocols for detection, notification and rapid response to outbreaks in animals are established, surveillance for both animal and human influenza is strengthened, epidemiological and virological investigations are carried out in relation to animal outbreaks and human infections, sharing of genetic information about viruses, fostering collaboration between animal and human health settings, effective risk communication, and ensuring preparedness for a potential influenza pandemic at all levels (*19, 20)*.

The following are the main lines of recommendation for Member States with a One Health approach, which include coordination for intersectoral surveillance and response, as well as prevention measures and risk communication.

Intersectoral coordination

Preparedness for detection and response to public health emergencies requires the adoption of a holistic intersectoral and multidisciplinary approach. Intersectoral actions such as the establishment of standardized protocols that are inclusive of all relevant sectors, with well-established roles that facilitate information sharing and analysis, the development of a One Health response strategy that includes both human and/or animal risk, and human resource training. A viable, culture-driven coordination and systemic approach to emergency preparedness and health systems strengthening is essential before it is necessary to respond to an event. Integration of the One Health perspective and stakeholder roles is essential and should be promoted *(21)*.

High-level political commitment, stakeholder mapping and analysis, joint needs assessment, and the establishment of communication channels are key elements of multisectoral coordination for health emergency preparedness. These pillars should be implemented through a transparent, reliable, and accountable framework *(21)*.

Surveillance of human cases *(20)*

In order to identify early cases or transmission events at the human-animal interface, surveillance and follow-up of exposed persons and their contacts is recommended.

Due to the constantly evolving nature of influenza viruses, PAHO/WHO continues to emphasize the importance of strengthening severe acute respiratory infection (SARI) and influenza syndrome (ILI) surveillance, as well as strengthening event-based surveillance.

This allows the detection of virological, epidemiological and clinical changes associated with circulating influenza viruses, which may impact human health. In addition to the active case-finding, contact identification and follow-up activities carried out during the epidemiological investigation of zoonotic events, it is advisable to alert and sensitize clinicians to consider the diagnosis of avian influenza and to strengthen existing surveillance systems in areas near poultry farms, areas where human cases and animal outbreaks have been reported, or where the source of infection is suspected. To complement surveillance for SARI and TIE, PAHO/WHO recommends establishing early warning systems to detect unusual events and to have a more complete picture of the situation and to conduct a joint and coordinated risk assessment between the human, animal and environmental sectors in a timely manner.

PAHO/WHO reiterates to Member States the need to maintain and strengthen seasonal and zoonotic influenza virus surveillance, including the immediate submission of human influenza samples caused by avian influenza to the WHO Collaborating Center at the U.S. Centers for Disease Control and Prevention (CDC).

Because information on the circulation of avian influenza A(H5N1) viruses is important for human influenza vaccine composition and to generate data for preparedness and response, countries are encouraged to share animal influenza samples with the WHO Collaborating Center at St. Jude Children's Hospital, which focuses exclusively on the threat posed to humans by zoonotic influenza viruses.

Laboratory diagnosis of human cases

Human sample collection

Samples should be collected by trained personnel in compliance with all biosafety standards, including the use of appropriate personal protective equipment (PPE) for respiratory viruses.

The recommended specimens are the same type of specimens used for routine influenza surveillance. The nasopharyngeal swab is the optimal specimen collection method for influenza diagnostic testing. However, a combined nasal and pharyngeal swab or aspirate specimen may be collected.

In the context of influenza A(H5) infection in humans recently described in the United States, it has been observed that it is possible to have a negative nasopharyngeal swab but a

positive conjunctival swab *(22, 23)*. Therefore, in suspected cases or in persons exposed to influenza A(H5) with symptoms of conjunctivitis, it is suggested, in addition to the nasopharyngeal swab, to consider taking a conjunctival swab. It is essential to follow the established protocols and collect both nasopharyngeal and ocular samples in patients with conjunctivitis, for a complete evaluation of possible infection by the A(H5N1) virus *(24, 25, 26, 27, 28)*.

A sterile dacron/nylon swab should be used for specimen collection. Cotton-tipped and wooden-tipped swabs are not recommended as they interfere with specimen processing and inhibit molecular diagnostic reactions. Swabs should be placed in a viral transport tube containing 3 ml of sterile viral transport medium and transported in the same tube with viral transport medium (VTM).

Collection of specimens within four days of symptom onset is recommended for highest yield of influenza virus and best detection. Sampling of asymptomatic contacts is not recommended unless deemed necessary according to national guidelines.

Samples should be kept refrigerated (4-8°C) and sent to the laboratory (central, national or reference laboratory) where they should be processed within 24-72 hours of collection. If samples cannot be shipped within this period, it is recommended to freeze at -70°C (or below) until samples are shipped (ensuring that the cold chain is maintained).

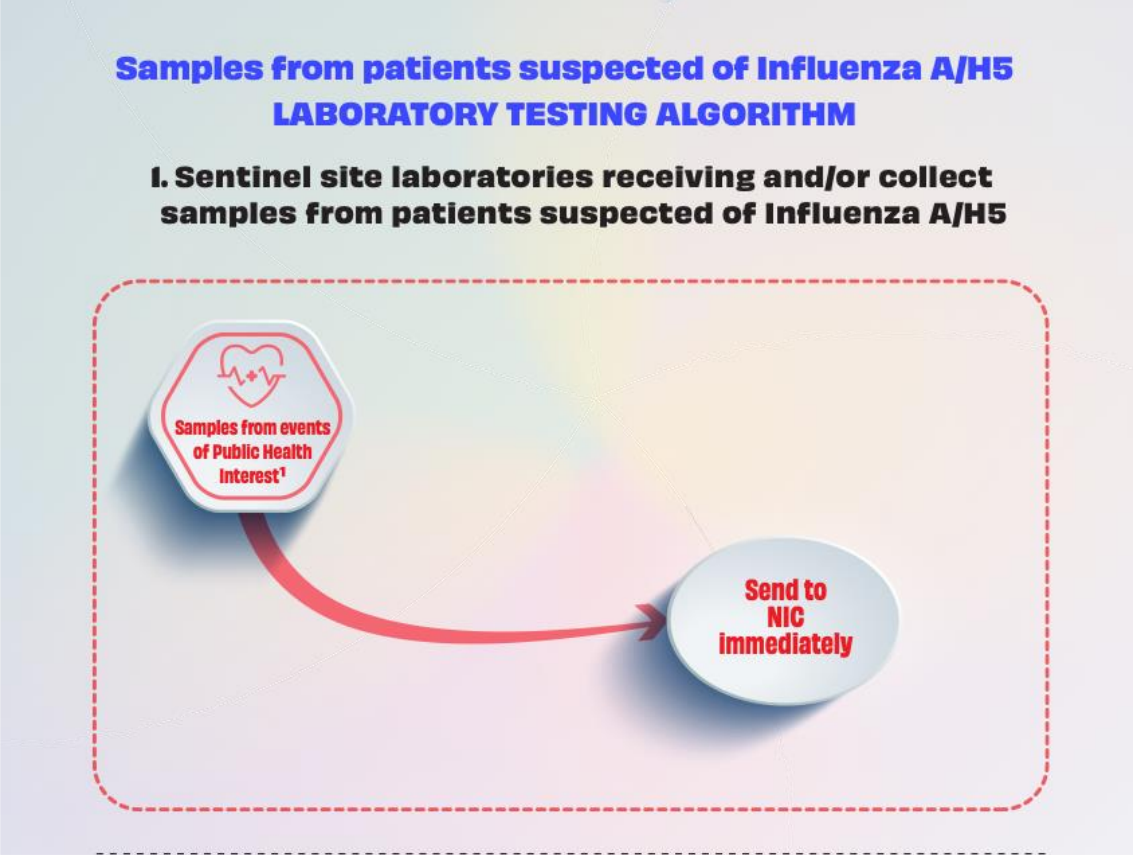
Sample flow and laboratory testing algorithm

In the Americas, all National Influenza Centers (NICs) and National Reference Laboratories (NRLs) for human influenza, as part of the WHO Global Influenza Surveillance and Response System (GISRS), use molecular diagnostic protocols and reagents developed and validated by the WHO Collaborating Center at the Centers for Disease Control and Prevention in the United States of America.

Upon identification of suspected cases of human infection with avian influenza A(H5), a respiratory specimen should be collected and submitted to the NIC or LNR for analysis (**Figure 6**) *(29) (29)*.

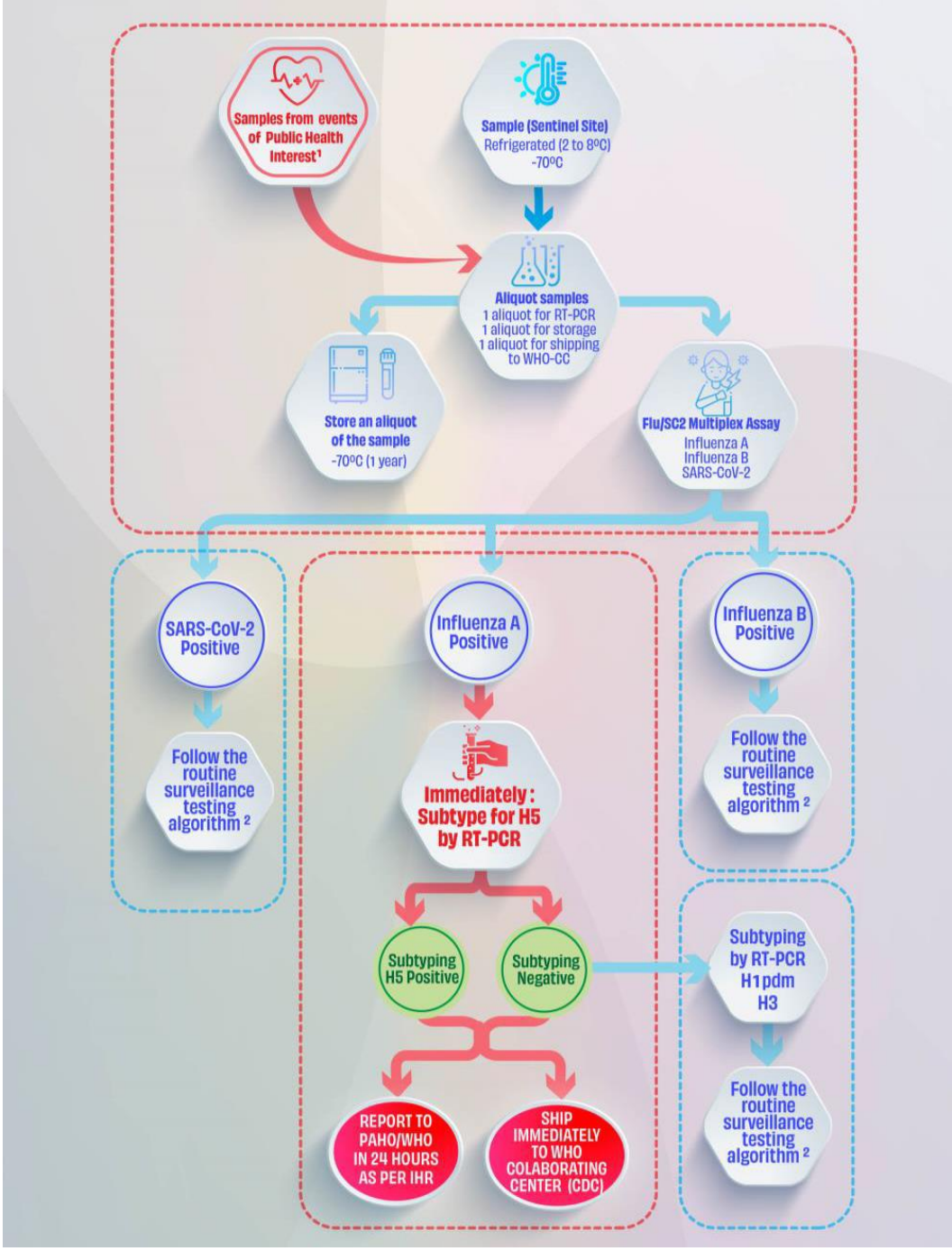
Specimens collected from suspected human cases exposed to birds or humans infected with avian influenza A(H5) should be tested for influenza. Influenza A positive specimens should be further subtyped for H5 **(Figure 7**) *(29, 30)*.

Figure 6. Sample flow for samples of suspected cases of Influenza A(H5) at sentinel sites and decentralized laboratories.



Source: Pan American Health Organization. Samples from patients suspected of Influenza A/H5 Laboratory Testing Algorithm. 2 December 2022. Washington, D.C.: PAHO; 2022. Available from: https://www.paho.org/en/documents/samples-patients-suspected-influenza-ah5-laboratory-testing-algorithm.

Figure 7. NIC analyzing samples of suspected cases of Influenza A(H5)



Source: Pan American Health Organization. Samples from suspected Influenza A(H5) patients - Laboratory testing algorithm. 2 December 2022. Washington, D.C.: PAHO; 2022. Available from: https://www.paho.org/es/documentos/muestras-pacientes-sospechosos-influenza-ah5-algoritmo-pruebas-laboratorio

Laboratory reagents

The U.S. CDC kits for real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) detection of influenza viruses are available through the International Reagent Resource (IRR).

For influenza detection and subtyping of influenza A(H5), the following kits and controls for molecular detection are available:

- Influenza SARS-CoV-2 Multiplex Assay (RUO) (500 reactions) (Catalog No. FluSC2PPB-RUO), dried primers and probes
- Influenza SARS-CoV-2 Multiplex Assay Positive Controls Kit (RUO) (500 reactions) (Catalog No. FluSC2PC-RUO)
- CDC Real-Time RT-PCR Influenza Virus A(H5) (Asian Lineage) Subtyping Panel (VER 4) (RUO) (Catalog No. FluRUO-13)
- CDC Influenza A(H5N1) (Asian Lineage) Real-Time RT-PCR Positive Control with Human Cell Material (RUO) (Catalog No. VA2715)

Interpretation of results

The CDC kit markers (targets) for detection of influenza A/H5 subtype are as follows: INFA (M), H5a (HA), H5b (HA) and RP.

When using the CDC influenza A(H5) subtyping kit:

- Samples positive for INFA, H5a and H5b markers are considered **positive for influenza A(H5).**
- Samples positive for a single H5 marker are considered **presumptive for influenza A(H5).**

In both cases, specimens should be submitted to a WHO Collaborating Center for further characterization or confirmation (in the case of presumptive results). However, a positive specimen for influenza A(H5) (both marker positive) should be reported immediately.

PAHO is currently working to support Member States in preparing for and responding to influenza A(H5). For additional assistance, contact laboratoryresponse@paho.org.

Shipment of samples

The U.S. Centers for Disease Control and Prevention (CDC) is the WHO Collaborating Center (WHO-CC) in the Americas Region to receive human specimens positive for avian influenza A(H5).

International air shipment of human specimens to the WHO-CC at the U.S. CDC must meet all international standards in accordance with the International Air Transport Association (IATA), with special documents required for transport to the United States that are different from those for routine shipment of seasonal influenza specimens.

It is important to note that specimens should **not** be submitted to the U.S. CDC as routine influenza specimens. PAHO should be contacted to coordinate shipment to the WHO Collaborating Centre at laboratoryresponse@paho.org.

Response to human cases

Upon detection of human infection, early notification is essential for investigation and implementation of appropriate measures including isolation and early treatment of the case, active search for other cases associated with the outbreak, and identification of close contacts for appropriate management and follow-up *(31)*.

It is recommended that the human health sectors, the animal health sector, and the environmental sector work together to analyze the risk at the human-animal-environment interface. It is recommended that, when avian influenza (HPAI or LPAI) is suspected in animals, the animal health and environmental sectors can alert and call health personnel in areas where transmission is occurring, and where there is a greater probability of infection in people exposed to these viruses, to be on alert for symptoms compatible with influenza syndrome and to participate in investigations in people exposed to infected animals. In addition, when avian influenza is suspected in humans, it is recommended that the health sector alert and call animal health and environmental personnel to investigate possible cases in domestic and wild animals so that they can detect possible sources of infection *(19)*.

Case research

In the presence of a confirmed or suspected human infection caused by influenza virus with pandemic potential, including an avian virus, the following is recommended:

- A thorough epidemiological investigation of the history of animal exposure, travel and ill contacts should be carried out. The investigation should not be delayed, even if confirmatory laboratory results are awaited.
- Epidemiological investigation should include early identification of unusual respiratory events, which could signal person-to-person transmission of the new virus.
- Clinical specimens collected at the time and place where the case occurred should be tested and sent to the WHO collaborating center for characterization within one week of detection.
- Standard infection prevention and control (IPC) procedures and standard precautions should always be applied, and appropriate personal protective equipment (PPE) should be used according to risk (based on the most likely modes of transmission) to protect the health of investigators. PPE should be used when in contact with symptomatic persons and in situations where person-to-person transmission is suspected.
- The epidemiological investigation should include information from official veterinary services and the private sector (animal production) on the origin of the animals and records of movements on and off the premises. This information will help define the scope (location) of investigations in humans exposed to infected animals.
- Information from official veterinary services could provide guidance on possible influenza events (both notifiable and non-notifiable) occurring in the area and farms related to the event.
- For more information regarding the investigation of non-seasonal influenza cases, the World Health Organization's "Protocol for Investigating Non-Seasonal Influenza and Other Emerging Acute Respiratory Diseases" is available at: https://apps.who.int/iris/handle/10665/329895.

Notification of human cases

- A **confirmed case** of human infection with avian influenza should be reported **immediately** through two channels: to the WHO Regional Contact Point for International Health Regulations (IHR) through the National IHR Liaison Center (NLC), and to the WHO Global Influenza Surveillance and Response System (GISRS) administered by PAHO and WHO (flu@paho.org). The report should include all available results of the epidemiological investigation of the case and the virological characteristics of the virus.

- A suspected case of human infection with avian influenza should be reported **immediately** to the GISRS (flu@paho.org), and information on the suspected case may be shared with the WHO Regional Contact Point for IHR, as this is an unusual event. The report should include all available results of the epidemiological investigation of the case and the characteristics of the virus.

Animal surveillance, diagnosis and response

FAO, WHO and WOAH urge countries to prevent avian influenza at its source to facilitate a rapid response. The implementation of a comprehensive surveillance program, including wild birds and poultry, both backyard and commercial, is essential for early detection. Targeted risk-based surveillance strategies should be combined with a strengthening of general surveillance. In this aspect, awareness-raising among trained actors and the community in general, particularly in rural areas, is key to promote prevention and health surveillance. The information collected can allow the modeling of spread and strengthen risk analyses to increase their accuracy *(3, 19, 20)*.

Avian influenza is included in the WOAH list of notifiable diseases by the competent authorities. This includes notification of infections with HPAI viruses, infections in birds other than poultry with highly pathogenic influenza A viruses, and infections in domestic and captive wild birds with low pathogenic avian influenza viruses, provided that natural transmission has been demonstrated in humans and is associated with severe consequences *(32)*.

At the regional level, there are veterinary laboratories with the capacity to detect and type the virus in both serological and molecular samples. A round of proficiency testing is currently being conducted by the WHO regional reference laboratory in Campinas, São Paulo, Brazil, with the support of PANAFTOSA-PAHO/WHO. Previously, the round conducted in 2021 demonstrated the good ability of the participating laboratories to perform serological (ELISA, HI and AGID) and molecular (RT-qPCR) diagnostic tests for the purpose of reaching a final diagnosis of avian influenza. This round included Argentina, Bolivia, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, Paraguay, Peru and Uruguay, in addition to Brazil as the coordinating laboratory. Other veterinary services laboratories participated in other proficiency tests in 2022 with excellent results, for example, those developed by the WOAH reference laboratory of the United States Department of Agriculture (USDA) Ames, Iowa, United States, in which the Vesicular Disease Diagnostic Laboratory of Panama participated or coordinated by GD Laboratory as in the case of the National Service of Health, Safety and Agrifood Quality of Mexico.

Surveillance strategies combine serological and molecular techniques to detect both previous exposure to the virus and the current presence of the virus, which is crucial for early

detection. In poultry, virus subtyping in birds focuses primarily on identifying Influenza A virus subtypes H5 or H7. These analyses, which allow differentiating the presence of highly pathogenic avian influenza, are sufficient to support field actions. The collection of nervous tissue samples from wild birds during the investigation of suspicious outbreaks is highlighted to optimize pathogen detection.

The regional reference laboratory in Campinas, Brazil, is assisting in diagnostic confirmation and sub-typing for South American countries. Full virus sequencing is being carried out with the support of other laboratories including the USDA WOAH reference laboratory in Ames, Iowa, USA.

Shipment of samples

It is recommended that samples of animals detected with the virus be sent for analysis, data generation, and reference material for the development of human vaccines for response to zoonotic influenza. For this purpose, animal samples should be sent to the WHO Collaborating Center at St. Jude Children's Hospital. Special documents are required for transport to the United States of America, and all international standards must be met.

For more information on logistics and shipping of human or avian influenza A(H5) samples, please contact PAHO/WHO at laboratoryresponse@paho.org.

Sequencing and genomic surveillance

Sequencing

The submission of animal or human influenza A(H5) positive samples to the appropriate WHO Collaborating Center **should be prioritized** for antigenic and genomic characterization of the sample.

For this reason, measures should be taken to avoid exhausting samples, such as reserving an aliquot of the sample for shipment to the WHO-CC before starting processing for virus sequencing.

For laboratories that have sequencing capabilities, in addition to sending the positive sample to the Collaborating Center, they are encouraged to sequence the virus to generate genomic data, and to share the sequences in a timely manner on the GISAID global platform.

The publication of sequences in GISAID requires the use of the nomenclature recommended by the WHO *(33)*:

- The format for humans is:
  [influenza type]/[region]/[internal reference number]/[year of collection].
  E.g.: A/Wisconsin/2145/2001

- For all other animal hosts:
  [type of influenza]/[host]/[region]/[internal reference number]/[year of collection].
  E.g.: A/chicken/Rostov/864/2007

Genomic Surveillance

Human influenza A(H5) virus: Since the beginning of 2020, the influenza A(H5) viruses reported to WHO as infecting humans are of gene group 2.3.4.4b. Virus sequences from these human cases} have not (to date) shown markers of mammalian adaptation or resistance to antivirals, including oseltamivir and baloxavir *(34)*. Results of analyses of available sequences for human cases in the United States confirmed avian influenza A(H5N1) virus of clade 2.3.4.4b, closely related to genotype B3.13 detected in dairy cattle, suggesting direct animal-to-human transmission *(3)*. Both the viruses detected in cows and in two human cases mainly retain genetic characteristics of avian influenza viruses, genetic changes that would make them more suitable for infecting or transmitting between humans *(35)*. No known markers for antiviral resistance against influenza were found in the available sequences of influenza A(H5N1) viruses from human cases *(36)*.

Animal influenza A(H5) virus: clade 2.3.4.4b that was introduced in late 2021 into North America by wild birds has spread across the continent throughout 2022 and 2023. Worldwide circulation of the virus has led to opportunities to generate multiple genotypes with varied clinical signs. Through routine monitoring and viral sequencing, few sequences with markers of mammalian adaptation were found. These mutations probably occurred after transmission to the mammalian host and do not appear to be transmitted forward *(37)*. The information currently available for avian influenza cases in dairy cattle in the United States of America show no new mutations possibly associated with further transmission to humans *(3)*. Available sequences for the 2.3.4.4b gene cluster of avian and mammalian viruses indicate that markers associated with reduced susceptibility to antivirals are rare *(38)*.

Vaccine candidate viruses for zoonotic influenza: WHO Global Influenza Surveillance and Response System (GISRS), in collaboration with the veterinary and animal health sector, including the WHO/FAO Animal Influenza Expert Network (OFFLU), regularly evaluates candidate vaccine viruses for pandemic preparedness purposes. Although most dairy cattle viruses from the 2.3.4.4b strain have amino acid substitutions at antigenic sites, they react antigenically well to at least one of the 2.3.4.4b candidate vaccine viruses (CVVs) *(36)*. CVVs for influenza A(H5) of the 2.3.4.4b genetic group are identified and available *(36)*. This includes one A(H5N8) candidate virus, in fact, A/Astrakhan/3212/2020, as well as one A(H5N1) virus, A/chicken/Ghana/AVL-76321VIR7050-39/2021 and the novel A(H5N1) clade 2.3.2.1c candidate virus, A/Cambodia/SVH240441/2024 *(36)*. The A/Astrakhan/3212/2020 vaccine virus is closely related to recently detected circulating influenza A(H5) strains *(37)*.

Risk communication and community participation *(39, 40)*

Risk communication is a fundamental component of preparedness and response to health emergencies, especially those with pandemic or epidemic potential. Early and transparent communication with populations, as well as clear messages about behaviors and preventive measures to be adopted by communities, is vital to reduce transmission. In addition, adequate risk communication will help to reduce rumors, myths and misinformation related to the outbreak and will allow populations to make the right decisions to reduce the risk of contagion.

FAO, WHO and WOAH urge countries to communicate the risk of avian influenza by alerting and training health care workers and persons occupationally exposed to the virus on how to

protect themselves. The general public, and those exposed to sick and/or dead animals, should also be informed to encourage prompt notification of the competent authorities. Guidance should be provided on how to seek medical attention in case of discomfort and to communicate any exposure to animals to their health care provider *(3)*. A differentiated communication strategy should be considered depending on the audience (e.g. livestock and backyard producers, rural communities, ordinary citizens, wildlife stakeholders, indigenous groups, etc.).

PAHO/WHO recommends that Member States take the following actions as part of their risk communication preparedness measures in the event of an outbreak of avian influenza:

- Delegate an individual or team responsible for risk communication to review existing risk communication plans or strategies in pandemic or epidemic contexts and make adjustments or updates necessary to strengthen preparedness and response to an eventual outbreak. WHO has guidelines for risk communication plans related to respiratory diseases.
- Gather existing information and/or conduct joint qualitative and/or rapid quantitative assessments between public health, animal health, and environmental sectors to understand the characteristics of the most at-risk communities, communication patterns and channels, language, religion, influencers. This information is vital in order to formulate appropriate preparedness and response actions for risk communication.
- Generate trust through early, transparent and timely communication, with dissemination through multiple platforms, methods and channels. To maintain public confidence, it is also key to communicate even in the midst of uncertainty, clarifying what is known and what is not.
- Identify communities with whom to work on risk communication actions and allow them to participate in their implementation, to ensure that interventions are collaborative, and that the community takes ownership of the communication processes. Community involvement will contribute to the adoption of preventive behaviors.
- Broadcast messages to the public on symptom identification and prevention, particularly to populations with greater potential for exposure to the virus: rural environments, farmers, farm workers, backyard poultry owners. Messages should be broadcast on the channels and through the platforms consulted by each type of audience.
- Activate social listening for rumors and misinformation through digital platforms and other relevant information exchange channels (hotlines, web portals, etc.), to respond to possible false messages circulating among the public and adapt messages according to the needs detected by this monitoring.

Prevention measures for birds and animals

According to WOAH, the implementation of strict biosecurity and hygiene measures are essential to prevent outbreaks of avian influenza in animals. These include ensuring that poultry and other domestic animals susceptible to avian influenza infection do not have contact with wild birds, ensuring sanitary conditions in production areas, clothing and personnel, and reporting bird diseases and deaths, and suspicions of avian influenza infection in other domestic animals, to animal health services. If infection in poultry or other domestic

animals is detected, the current regulations applied by the animal health authority should be followed to contain, control and rapidly eradicate the disease. These actions result in a significant decrease in environmental viral contamination. WOAH encourages national authorities to consider the development of compensation plans for farm owners and producers whose production was affected by the measures implemented by the authorities *(32)*. According to WOAH, the use of vaccination in poultry against HPAI is a decision of the national animal health authorities, in coordination with poultry producers, and should be adapted to the epidemiological and socioeconomic context of the countries *(41)*. Avian influenza vaccination alone should not be considered as a sustainable solution to control avian influenza and should be part of comprehensive disease control strategies *(32)*.

Prevention measures in humans

Persons at risk of infection are those directly or indirectly exposed to infected birds and other animals (domestic, wild or captive), for example, individuals who maintain close and regular contact with infected domestic animals, or during slaughter, or during the cleaning and disinfection of affected farms. For this reason, the use of appropriate personal protective equipment and other protective measures is recommended to avoid zoonotic transmission in these operators *(34)*.

Seasonal influenza vaccination in the context of avian influenza *(42, 43)*

Although the seasonal influenza vaccine is not designed to prevent zoonotic influenza in humans, vaccination would help reduce the risk of co-infection and possible genomic recombination of avian and human viruses, which could result in new strains with pandemic potential.

WHO recommends vaccination against seasonal influenza in persons at risk of influenza A (H5) virus infection, especially in areas with avian influenza circulation in animals. This recommendation applies to workers in the poultry and livestock industry, veterinary services personnel involved in surveillance and control tasks, as well as persons who may be in contact with wild birds, workers in wildlife care centers, and those people who perform tasks in the field that involve handling these animals.

Vaccination with seasonal influenza vaccines should be used in combination with other control measures, such as infection prevention and control measures and the use of personal protective equipment, to reduce the risk of zoonotic infection in these populations.

There are some licensed vaccines for **human use** against avian influenza A(H5), but their use is restricted. Since the risk of zoonotic infection remains low, WHO does not recommend vaccination of the population with these vaccines in the inter-pandemic period.

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