Epidemiological Alert
Human Cases of Avian Influenza A(H5N1) in the Americas Region

3 December 2024

Human cases of avian influenza A(H5) have been reported in the Americas Region since 2022, with an increase in the last two months, including some cases for which the source of infection is unknown. Given this, the Pan American Health Organization / World Health Organization (PAHO / WHO) urges Member States to continue strengthening their capacities for detection, epidemiological investigation, notification, and timely response to human cases of avian influenza A(H5). In addition, PAHO/WHO invites Member States to share virus samples with WHO Collaborating Centers to support risk analysis and candidate vaccine viruses.

Global Context

The avian influenza virus, which is usually transmitted between birds, has led to an increase in infections in mammals due to changes in its ecology and epidemiology *(1)*. Since 2020, an unprecedented number of deaths in wild birds and poultry have been detected in numerous countries in Africa, the Americas, Asia, and Europe *(1)*, most of which are related to the detection of the influenza A(H5N1) clade 2.3.4.4b. Since 2022, 19 countries on three continents have reported outbreaks in mammals to the World Organization for Animal Health (WOAH) *(2)*.

Since the beginning of 2003 until 1 November 2024, 939 human cases of avian influenza A(H5N1), including 464 deaths (49.4% case-fatality rate), have been reported to the World Health Organization (WHO) in 24 countries globally *(3)*.

Human cases of influenza A(H5N1)[1] in the Americas Region

Between 2022 and as of 2 December 2024, 61 human infections caused by avian influenza A(H5N1) have been reported in four countries in the Americas Region: 58 cases in the United States of America *(4)*, one case in Canada confirmed on 13 November 2024 *(5)*, one case in Chile reported on 29 March 2023 *(6)*, and one case in Ecuador reported on 9 January 2023 *(7)*.

During 2024, 58 human cases have been reported, one in Canada and 57 in the United States *(4, 5)*. Seventy-four percent (n=43) of the cases reported this year were reported between October and November 2024 *(4, 5, 8, 9)*; 59% of the cases were associated with exposure to dairy cattle and among 5% of cases (n=3), the source of exposure could not be established *(4, 5, 8, 9)*. Ninety-six percent (n= 56) of the cases reported in 2024 have corresponded to

[1] These include cases that are either confirmed as influenza A(H5N1) or as influenza A(H5) with exposure to birds or cattle in facilities where highly pathogenic avian influenza (HPAI) A(H5N1) virus had been detected.

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persons over 18 years of age. Two cases have been reported among children under 18 years of age, one in Canada and one in the United States *(8, 9)*.

Regarding the data on the subtype identified from the total number of cases, for 21% (n= 12 cases) the H5N1 subtype was confirmed, and for 21% (n= 12 cases) the clade 2.3.4.4b was identified; for three of these cases, the genotype was B3.13 *(8, 9)*.

Summary of human cases of influenza A(H5N1) by country during 2024

In **Canada,** on 14 November 2024, the Public Health Agency of Canada (PHAC) reported the confirmation of a human case of influenza A(H5N1), the first domestically acquired human case of influenza A(H5) reported in the country. The case was an adolescent who developed symptoms on 2 November 2024 and was later hospitalized and identified by laboratory testing as a presumptive positive for avian influenza A(H5) by PCR testing. On 13 November, the PHAC National Microbiology Laboratory (NML) in Winnipeg confirmed the identification of influenza A(H5N1). Genomic sequencing from both the British Columbia Centre for Disease Control and NML indicated that the virus is related to the highly pathogenic avian influenza (HPAI) A(H5N1) viruses detected in wild/domestic birds during the current HPAI outbreak in British Columbia (influenza A(H5N1), clade 2.3.4.4b, genotype D1.1) *(5, 9)*.

Analyses conducted showed that the genome has an E627K mutation in the PB2 gene associated with mammalian adaptation and enhanced replication. This mutation has previously been observed in other human and mammalian infections. The HA gene also contained mixed bases, at positions 190 (E190D) and 226 (Q226H) (H3 numbering) in the mature HA protein. Mutations at these positions have been known to affect host specificity. To date, the investigation carried out by the regional health authority has not determined the source of infection of the case. This case has no known exposure to affected poultry farms in the province of British Columbia. The case has received medical treatment including antivirals and remains hospitalized in critical condition. This case was identified through laboratory-based influenza surveillance in British Columbia. No additional human cases have been identified at the time of writing this alert *(5, 9)*.

In the **United States**, between 1 January 2024 and 2 December 2024, 57 human cases of influenza A(H5N1) have been confirmed in 7 states: California (n= 31), Colorado (n= 10), Michigan (n= 2), Missouri (n=1), Texas (n= 1), Oregon (n= 1), and Washington (n=11). Ninety-eight percent (n= 56) of the cases were among persons >18 years of age. One case has been reported in a minor <18 years of age in the state of California, which is the first case in a minor to be reported in the United States *(4, 8)*. Reported cases associated with exposure to dairy cattle and poultry have been primarily reported from the Central Valley in California, Weld County in Colorado, and Franklin County in Washington *(4, 8)*.

Among 51 cases with available information on symptom, 90% (n= 46 cases) had conjunctivitis, 29% (n= 15 cases) had fever, and 20% (n= 10 cases) reported headache *(8)*.

Of the overall total in the United States, 60% (n= 34 cases) have been linked to exposure to sick or infected dairy cattle, while 37% (n= 21 cases) are linked to exposure to poultry, and for two of the cases, the source of exposure could not be determined (**Table 1**). Detailed information on these two cases is described below *(4, 8)*:

On 6 September 2024, the United States reported the first confirmed case of influenza A(H5N1) for which there is no known recent exposure to animals. The identified case is a Missouri

resident, 18 years of age or older, with a history of severe underlying clinical illness. Onset of symptoms was on 20 August 2024, consisting of chest pain, nausea, vomiting, diarrhea, and weakness. The case was hospitalized, treated with oseltamivir, and recovered from the illness. The case reported no contact with animals in the 10 days prior to symptom onset. A nasopharyngeal swab specimen was collected and tested by multiplex PCR respiratory panel at the hospital laboratory, which was positive for influenza A virus and negative for influenza A(H1) and A(H3). The specimen was sent to the Missouri State Public Health Laboratory (MSPHL), where the specimen underwent additional testing. Testing at MSPHL indicated a presumptive positive result for influenza A(H5) using the U.S. Centers for Disease Control and Prevention (U.S. CDC) Human Influenza Virus Real-Time RT-PCR Diagnostic Panel Influenza A(H5) subtyping assay *(8, 10)*.

The specimen was received at U.S. CDC on 4 September 2024 and on 5 September 2024 confirmed positive for influenza A(H5). On 13 September 2024, the HA gene sequence confirmed that the virus belongs to clade 2.3.4.4b and the NA gene sequence was confirmed as N1. The case was identified through the Missouri state seasonal influenza surveillance system *(8,10)*. During the investigation of this case, five healthcare professionals who were exposed to the case and had mild symptoms were identified and blood specimens were collected for serology testing. These were negative *(8,11)*. The source of exposure for this case could not be determined and having concluded the investigation, possible human-to-human transmission was ruled out *(8, 11)*.

On 23 November 2024, the United States reported a confirmed human case of avian influenza A(H5) virus infection for which the source of exposure was unknown *(12)*. The case was a minor residing in the state of California who had no comorbidities and no history of travel. The case had onset of symptoms on 11 November 2024, with nasal congestion, sore throat, cough, and fatigue. The case received medical attention at an emergency center on 12 November 2024, at which time a nasopharyngeal swab specimen was collected for laboratory analysis. On 13 November 2024, the specimen yielded positive results for influenza A by an influenza/VRS/SARS-CoV-2 rapid PCR test and the case was treated with oseltamivir *(8)*. The case did not require hospitalization and is recovering from their illness. According to available information, the case had not had any contact with animals infected with influenza A(H5N1) virus within the 10 days prior to the onset of symptoms. Investigation of possible sources of exposure is ongoing *(8)*.

The specimen was sent to an affiliated academic laboratory, where additional testing for influenza A(H5) virus was performed by RT-PCR. Testing indicated a possible influenza A(H5) virus on 15 November 2024. The specimen was sent to the California Department of Public Health's Viral and Rickettsial Disease Laboratory (VRDL) for additional testing. On 17 November 2024, the VRDL reported a presumptive positive result for influenza A(H5) virus using the U.S. CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel Influenza A(H5) subtyping assay. The specimen was sent to U.S. CDC for confirmatory testing where it was confirmed to be positive for influenza A(H5N1), clade 2.3.4.4b through partial genetic sequencing. Additional sequencing and viral cultures are currently underway *(8)*.

The investigation conducted by the California Department of Public Health identified that three contacts of the case developed respiratory symptoms the day before or within 10 days of symptom onset of the confirmed case. On 16 November 2024, specimens were collected from all three contacts and a new specimen was collected from the case. The results of these specimens were negative for influenza virus, but positive for other seasonal respiratory viruses.

Contact tracing continues, including monitoring of identified contacts of the case *(8)*. This is the second case identified through national influenza surveillance in the country *(12)*.

Between 24 March and 2 December 2024, dedicated surveillance efforts specific for avian influenza A(H5) have monitored more than 7,900 people for exposure to infected animals, and more than 390 of them have had laboratory testing conducted for avian influenza A(H5) *(4)*.

As of 2 December 2024, **no human-to-human transmission of avian influenza A(H5N1) virus has been reported** *(4)*.

Table 1. Cases of avian influenza A(H5N1) infections in the United States during 2024 and as of 2 December 2024.

State	Linked to livestock	Linked to poultry	Origin Unknown	Total by State
California	30	0	1	31
Colorado	1	9	0	10
Michigan	2	0	0	2
Missouri	0	0	1	1
Oregon	0	1	0	1
Texas	1	0	0	1
Washington	0	11	0	11
Total	**34**	**21**	**2**	**57**

Source: United States Centers for Disease Control and Prevention. Avian Influenza H5. Atlanta: U.S. CDC; 2024. [accessed 2 December 2024]. Available from: https://www.cdc.gov/bird-flu/situation-summary/index.html

Recommendations for Member States

To date, reported human cases of influenza A(H5N1) clade 2.3.4.4b are mostly associated with direct contact with infected animals and contaminated environments. Current evidence indicates that the virus does not appear to be easily transmitted from one person to another. However, it is imperative to strengthen intersectoral surveillance to detect any possible changes in this situation *(13)*.

PAHO/WHO urges Member States to work collaboratively and intersectorally to preserve animal health and protect public health. It is essential that avian influenza preventive measures be implemented at the source, protocols for detection, notification and rapid response to outbreaks in animals be established, and surveillance for both animal and human influenza be strengthened. It will be equally important to conduct epidemiological and virological investigations of animal outbreaks and human infections, share genetic information on viruses, foster collaboration between animal and human health fields, and effectively communicate risk to the public, as well as **ensure preparedness for a potential influenza pandemic at all levels** *(14, 15)*.

The following is a summary of the key guidance for Member States regarding the new clinical management guidelines for human cases and reiterates the recommendations for surveillance, laboratory diagnosis, sequencing and genomic surveillance of avian influenza

A(H5) as well as vaccination against seasonal influenza in the context of avian influenza transmission.

Clinical management

Timely, evidence-based clinical management, prevention and control of infection, and prevention of complications in patients with zoonotic influenza infection are critical elements. PAHO/WHO recommends that Member States update their treatment guidelines based on the updated WHO guidelines, which include the management of severe influenza caused by zoonotic influenza *(16)*. When infections caused by avian influenza A(H5) are suspected, PAHO/WHO recommends *(17)*:

Perform initial triage of patients

- Upon the first contact with the healthcare system, patients with signs of Severe Acute Respiratory Infection (SARI) should be promptly identified.
- It is crucial to prioritize immediate attention to severe cases and avoid any delay in emergency care.

Apply infection prevention and control precautions

- Implement standard precautions in all cases.
- Use contact and droplet precautions in suspected cases of severe influenza.
- If aerosol-generating procedures are performed, add airborne precautions in addition to contact and droplet precautions.

Classify patients according to the severity of their condition

- Patients should be placed in designated areas according to the severity of their illness and acute care needs.
- Those with complications such as severe pneumonia, sepsis, organ dysfunction or co-infections should be hospitalized in intensive or critical care areas, as appropriate.

Hospital care and management of complications

- Severe patients with SARI usually require hospitalization to manage complications such as pneumonia, sepsis or exacerbations of chronic diseases.
- In case of acute organ failure, admission to the intensive care unit (ICU) should be immediate for close monitoring and advanced care. ICU admission of these patients should not be delayed.

Continuous monitoring and follow-up

- Provide continuous follow-up in the ICU to assess the patient's evolution and adjust treatment as needed.

Regarding antiviral treatment and prevention among persons with exposure to zoonotic influenza virus, PAHO/WHO recommends *(16)*:

Treatment should be administered as soon as possible and within 2 days after the onset of symptoms.

- Antiviral treatment of patients with severe influenza (including novel influenza A infection associated with high mortality or unknown risk of severe disease):
  - conditional recommendation for the use of oseltamivir in treatment,
  - conditional recommendation against the use of peramivir,
  - conditional recommendation against the use of zanamivir.

- Antiviral treatment of patients with non-severe influenza:

  - Conditional recommendation for the use of baloxavir in patients with non-severe influenza and high risk of progression to severe disease;

- Person exposed to zoonotic influenza virus associated with high mortality or unknown risk of severe disease:

  - For asymptomatic persons exposed to zoonotic influenza viruses associated with high mortality in humans or with unknown risk of causing severe disease, illness in the previous 2 days, baloxavir, laninamivir, oseltamivir, or zanamivir is suggested (conditional recommendation).

Full recommendations regarding clinical management are available in the "WHO clinical practice guidelines for influenza", Available from: https://iris.who.int/bitstream/handle/10665/378872/9789240097759-eng.pdf?sequence=1 *(18)*.

Surveillance of human cases

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 *(19)*. Because of the constantly evolving nature of influenza viruses, PAHO/WHO continues to emphasize the importance of strengthening SARI and influenza like illness (ILI) surveillance, as well as strengthening event-based surveillance *(1)*.

This allows the detection of virological, epidemiological and clinical changes associated with circulating influenza viruses that 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 *(20)*. To complement surveillance for SARI and ILI, 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. 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 of influenza A(H5N1)

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 *(21, 22)*. 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 *(23-27)*.

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).

Key guidance for the collection, storage, and transport of respiratory specimens for the diagnosis of zoonotic influenza, such as influenza A(H5) virus, is available for easy reference in the infographic on "Collection of respiratory specimens for the diagnosis of zoonotic influenza (Influenza A/H5 and other zoonotic influenza viruses)," Available from: https://www.paho.org/en/documents/respiratory-sample-collection-zoonotic-influenza-diagnosis-influenza-ah5-and-other *(28)*.

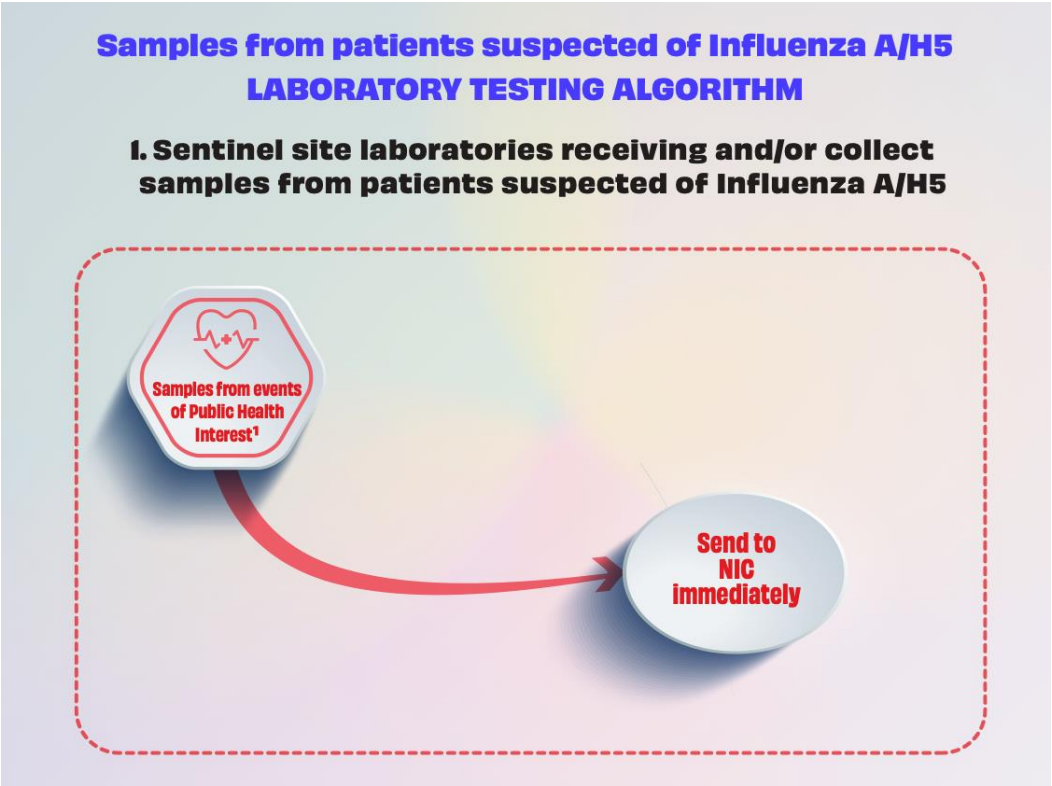
Sample flow and laboratory testing algorithm

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 U.S. CDC.

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 1**) *(29)*.

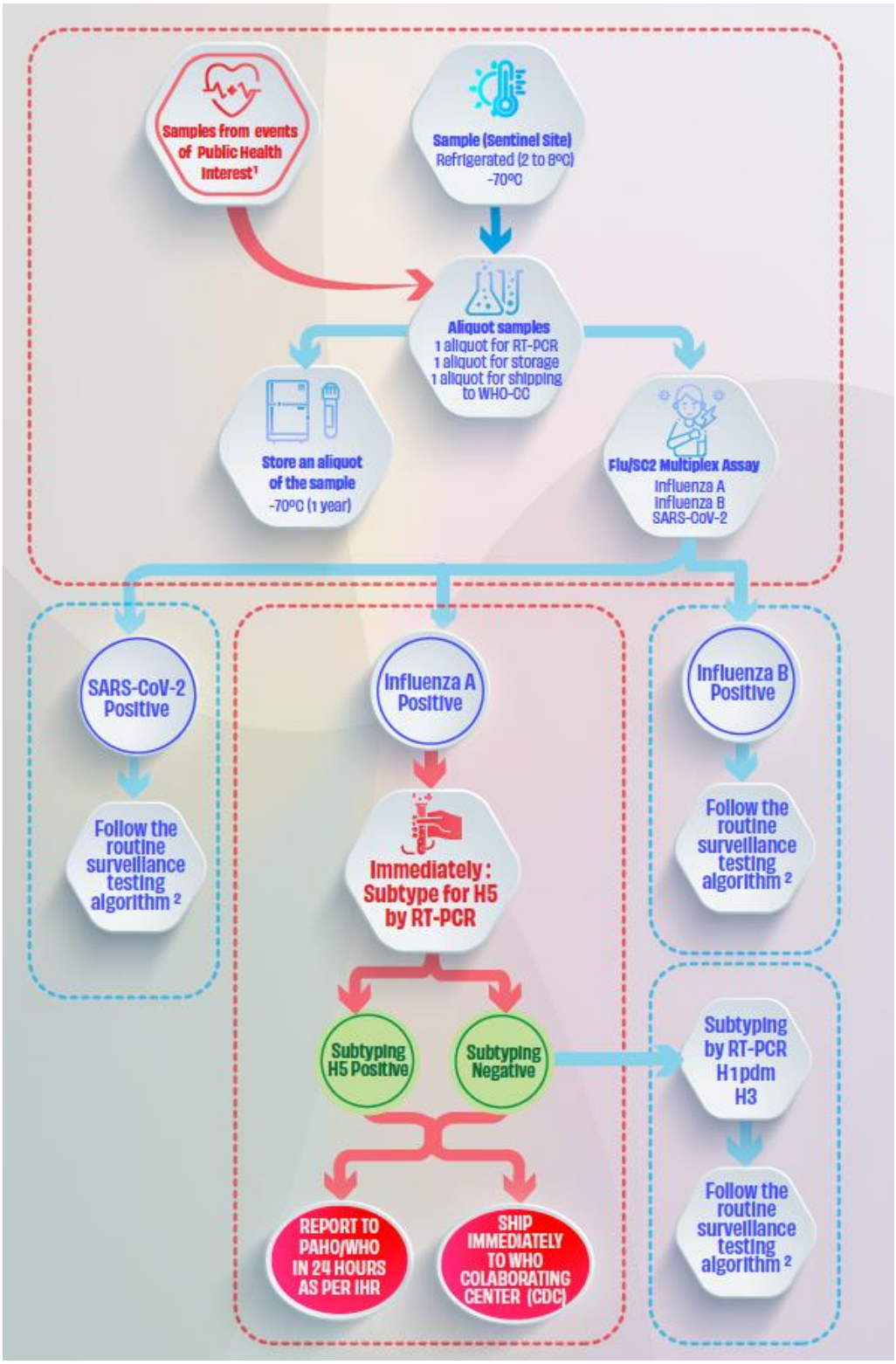
Specimens collected from suspected human cases exposed to birds or humans infected with avian influenza A(H5) should be tested for influenza. Influenza A-positive specimens should be further subtyped for H5 **(Figure 2**) *(29, 30)*.

Figure 1. Sample flow for samples of suspected cases of Influenza A(H5) at sentinel sites and decentralized laboratories.



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

Figure 2. 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, DC: PAHO; 2022. Available from: https://www.paho.org/en/documents/samples-patients-suspected-influenza-ah5-laboratory-testing-algorithm.

Laboratory reagents

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)
- U.S. CDC Real-Time RT-PCR Influenza Virus A(H5) (Asian Lineage) Subtyping Panel (VER 4) (RUO) (Catalog No. FluRUO-13)
- U.S. CDC Influenza A(H5N1) (Asian Lineage) Real-Time RT-PCR Positive Control with Human Cell Material (RUO) (Catalog No. VA2715)

Interpretation of results

The U.S. 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 U.S. 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. CDC is the WHO Collaborating Center in the Americas Region to receive human samples positive for avian influenza A(H5).

International and air shipment of human specimens to the WHO Collaborating Center 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 the documents for routine shipment of seasonal influenza specimens.

It is important to note that specimens should **not be** sent to the U.S. CDC as routine influenza specimens. PAHO should be contacted to coordinate shipment to the WHO Collaborating Center 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 *(19)*.

It is recommended that the human health sector, the animal health sector and the environmental sector work together on risk analysis at the human-animal-environment interface. It is recommended that, upon detection of suspected avian influenza (HPAI or LPAI) in animals, the animal health and environmental sectors should alert and summon health personnel in areas where transmission is occurring, and where there is a greater probability of infection in persons exposed to these viruses, to be attentive to symptoms compatible with influenza syndrome and to participate in investigations of persons exposed to infected animals. In addition, when avian influenza is suspected in humans, it is recommended that the health sector alert and summon animal health and environmental personnel to investigate possible cases in domestic and wild animals to detect possible sources of infection *(31)*.

Member States are encouraged to promote awareness messages to the general public to avoid contact with sick or dead animals, contact with animals at farms and animal markets, entering areas where animals may be slaughtered, contact with any surface that appears to be contaminated with animal feces, and slaughtering or eating sick animals. As well as messages for anyone exposed to animals infected, or possibly infected, with avian influenza A(H5N1) virus to seek immediate medical attention if they develop symptoms and to report such exposure. In addition, it is important to alert clinicians to the risk of zoonotic infection in patients exposed to birds or animals, especially in areas with confirmed or suspected circulation of the influenza A(H5N1) virus, in areas with limited animal surveillance, and in any type of occupational exposure *(32)*.

Case investigation

In the presence of a confirmed or suspected human infection caused by an influenza virus with pandemic potential, including an avian virus, it 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 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 from: https://apps.who.int/iris/handle/10665/329895 *(19)*.

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 IHR National Focal Point (NFP), 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 about 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.

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 running out of samples, such as reserving an aliquot of the sample for shipment to the WHO Collaborating Center prior to initiating virus sequencing processes.

For laboratories that have sequencing capabilities, in addition to sending the positive sample to the WHO Collaborating Center, they are encouraged to sequence the viruses 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 the 2.3.4.4b genetic group. Virus sequences from these human cases have (to date) shown no markers of mammalian adaptation or resistance to antivirals, including oseltamivir and baloxavir *(38)*. The results of sequence analyses available for human cases in the United States confirmed avian influenza A(H5N1) virus clade 2.3.4.4b, closely related to the B3.13 genotype detected in dairy cattle, suggesting direct animal-to-human transmission *(34)*. Both the viruses detected in cows and in two human cases maintain mainly genetic characteristics of avian influenza viruses, genetic changes that would make them more apt to infect or transmit between humans *(33)*. No known markers for antiviral resistance against influenza were found in the available sequences of influenza A(H5N1) viruses from human cases *(34)*.

Zoonotic influenza vaccine candidate viruses: The WHO Global Influenza Surveillance and Response System (GISRS), in collaboration with the veterinary and animal health sector, including the WAHIS/FAO Network of Expertise on Animal Influenza (OFFLU), periodically evaluates candidate vaccine viruses for pandemic preparedness purposes. The list of candidate zoonotic influenza vaccine viruses, including A(H5N1) viruses and potency test reagents, is updated on the WHO website *(32)*. Although most of the dairy cattle viruses in the 2.3.4.4b broth have amino acid substitutions at antigenic sites, they react well antigenically to at least one of the 2.3.4.4b candidate vaccine viruses (CVVs) *(35)*. CVVs for influenza A(H5) of the 2.3.4.4b gene pool are determined and available *(34)*.

Regular genetic and antigenic characterization of contemporary zoonotic influenza viruses is also published on the WHO website.

This includes a candidate A(H5N8) virus, in fact, A/Astrakhan/3212/2020, as well as an A(H5N1) virus, A/chicken/Ghana/AVL-76321VIR7050-39/2021 and the novel candidate A(H5N1) virus clade 2.3.2.1c, A/Cambodia/SVH240441/2024 *(34)*. The vaccine virus A/Astrakhan/3212/2020 is closely related to the recently detected circulating influenza A(H5) strains *(35)*.

Prevention measures in humans

People at risk of contracting infections 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 implementation of good animal husbandry and hygiene practices is recommended when handling animal products, such as the use of adequate PPE and other protective measures to avoid zoonotic transmission in these operators *(32, 36)*.

Since people exposed to the virus in work environments or who have contact with infected or potentially infected animals are at increased risk, it is recommended that the necessary preventive and personal protective measures be taken to prevent possible infection. PPE should be properly donned, worn and removed, and disposed of or decontaminated in a safe manner. Individuals who need to use PPE should be trained in their proper use in various environmental conditions *(32, 37)*.

Research continues to determine the risk to humans of consuming raw or unpasteurized milk contaminated with influenza A(H5N1) virus. FAO and WHO recommend consuming pasteurized milk because of the potential health risks associated with various zoonotic pathogens *(32)*.

Vaccination against in the context of avian influenza

Some vaccines for **human use** against avian influenza A(H5) are licensed, 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 interpandemic period *(38)*.

The **seasonal influenza vaccine** is not designed for the prevention of zoonotic influenza in humans; however, it would contribute to decrease the risk of co-infection and possible genomic recombination of avian and human viruses, which could result in new strains with pandemic potential *(38, 39)*.

WHO recommends vaccination against seasonal influenza in persons at risk of influenza A(H5) virus infection, especially in areas with confirmed cases of avian influenza in animals. This recommendation applies to workers in the poultry and livestock industry, veterinary services personnel involved in surveillance and disease control, as well as to people who may be in contact with birds, workers in wildlife care centers, and those in the field handling these animals *(38)*.

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 *(38)*.

Detailed recommendations related to surveillance, diagnosis and response in animals, as well as those related to risk communication and community participation can be found in the Epidemiological Update: Avian Influenza A(H5N1) in the Americas Region, dated November 15, 2024 published by PAHO/WHO and Available from: https://www.paho.org/sites/default/files/2024-11/2024-nov-15-phe-alert-avian-influenza-eng-finalpublicacion.pdf *(40)*.

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