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Joint FAO/WHO/WOAH preliminary assessment of recent influenza A(H5N1) viruses

23 April 2024

Background

During 2020, highly pathogenic avian influenza (HPAI) A(H5N1) clade 2.3.4.4b viruses arose from previously circulating influenza A(H5Nx) viruses and spread predominantly via migratory birds to many parts of Africa, Asia and Europe. The epizootic has led to unprecedented numbers of deaths in wild birds and caused outbreaks in domestic poultry. In late 2021, these viruses crossed to North America and subsequently South America in October 2022. Additionally, globally, there have been increased detections of A(H5N1) viruses in non-avian species including wild and domestic (including companion and farmed) terrestrial and marine mammals and, more recently in goats and dairy cattle in the United States of America. The majority, with some regional exceptions, of the HPAI A(H5N1) viruses characterized genetically since 2020 belong to the 2.3.4.4b clade. Since the beginning of 2021, 28 detections of A(H5N1) in humans have been reported to WHO, including a case who had exposure to dairy cattle presumed to be infected with A(H5N1) virus. Of these human cases, where the haemagglutinin (HA) H5 clade is known, 13 have been caused by clade 2.3.4.4b viruses. This joint FAO/WHO/WOAH risk assessment focuses on A(H5N1) viruses characterized since 2021 and assesses the public health risk as well as the risk of the virus spread among animals.

Infections in animals

Avian influenza A(H5N1) viruses, especially those of clade 2.3.4.4b, continue to diversify genetically and spread geographically. Since 2022, a broader range of wild bird species has been infected globally which has had deleterious ecological consequences and caused mass die-offs in some species. The situation with wild mammals is also worrying, with some species suffering significant mortality events.

Additionally, ongoing circulation in wild and migratory birds and poultry has led to multiple separate incursions into wild carnivorous and scavenging mammals, domestic cats and dogs, and aquatic mammals in a number of countries. Spillover of clade 2.3.4.4b viruses from birds to mammals in the Americas and Europe have often resulted in severe infections with neurological signs in some mammals.¹ In 2024, A(H5N1) viruses have been detected in neonatal goats on a single premises shared with poultry, and in dairy cattle in the USA.

These circumstances have led to increased opportunities for viral reassortment generating new genotypes with varied clinical signs. For example, a novel reassortant influenza A(H5N1) virus has been detected in poultry in Cambodia (since 2023), Lao People's Democratic Republic and Viet Nam

¹ Rijks JM, Hesselink H, Lollinga P, Wesselman R, Prins P, Weesendorp E et al. Highly Pathogenic Avian Influenza A(H5N1) Virus in Wild Red Foxes, the Netherlands, 2021. *Emerg Infect Dis.* 2021;27:2960-2.

(since 2022) and was also detected in the human cases reported from Cambodia since late 2023 and Viet Nam in 2024. This virus contains the surface proteins from clade 2.3.2.1c that has circulated locally, but internal genes from a more recent clade 2.3.4.4b virus.²

To date, there have been limited reports of transmission between mammals despite the increase in mammalian infections. Although direct evidence is lacking, large A(H5N1) virus driven die-offs of sea mammals, infection in multiple fur animal farms in Finland³ and minks in Spain⁴ is consistent with mammal-to-mammal spread in these instances.

Since March 2024, A(H5N1) detections in dairy cattle herds have been reported in the USA, in 33 herds in eight states as of 23 April 2024.⁵ While the initial virus spill-over was likely of wild bird origin based on available information, some later affected herds received cows from other affected herds. Current evidence from the USA indicates that lateral transmission among cattle likely occurred. Thus far, the routes and modes of transmission and duration of viral shedding in cows remain under investigation.⁶ High concentrations of virus have been detected in milk from infected dairy cattle at levels greater than that seen in respiratory samples. The implications of this in terms of transmission is currently being investigated, as is the role of pasteurization in inactivation of the virus. Virus transmission via contaminated fomites or mechanical means are other possible routes being investigated.⁷

There have been reports that A(H5N1) virus has spread from dairy cattle premises back into nearby poultry premises, although the exact transmission route(s) remain currently unknown.⁸ At the present time, the frequency of cattle-to-bird transmission is also unknown. Poultry remain at risk from the continued circulation and spillover of A(H5N1) viruses from wild birds. The A(H5N1) virus has been detected in cats found dead at or near some of the affected dairy herds and found to be the same A(H5N1) virus detected in cattle.⁹

² Food and Agriculture Organization of the United Nations (FAO) Viet Nam (5 April 2024). Stay vigilant with Highly Pathogenic Avian Influenza A(H5N1). Available at <https://www.fao.org/vietnam/news/detail-events/ru/c/1680337/>.

³ Lindh E, Lounela H, Ikonen N, Kantala T, Savolainen-Kopra C, Kauppinen A et al. Highly pathogenic avian influenza A(H5N1) virus infection on multiple fur farms in the South and Central Ostrobothnia regions of Finland, July 2023. *Euro Surveill.* 2023;28(31):pii=2300400.

⁴ Agüero M, Monne I, Sánchez A, Zecchin B, Fusaro A, Ruano M et al. Highly pathogenic avian influenza A(H5N1) virus infection in farmed minks, Spain, October 2022. *Euro Surveill.* 2023;28(3):pii=2300001.

⁵ Animal and Plant Health Inspection Service, United States Department of Agriculture. Highly Pathogenic Avian Influenza (HPAI) Detections in Livestock. Available at <https://www.aphis.usda.gov/livestock-poultry-disease/avian/avian-influenza/hpai-detections/livestock>.

⁶ Animal and Plant Health Inspection Service, United States Department of Agriculture (16 April 2024). Detection of Highly Pathogenic Avian Influenza (H5N1) in dairy Herds: Frequently asked questions. Available at <https://www.aphis.usda.gov/sites/default/files/hpai-dairy-faqs.pdf>.

⁷ Animal and Plant Health Inspection Service, United States Department of Agriculture (12 April 2024). APHIS Recommendations for Highly Pathogenic Avian Influenza (HPAI) H5N1 Virus in Livestock For State Animal Health Officials, Accredited Veterinarians and Producers. Available at <https://www.aphis.usda.gov/sites/default/files/recommendations-hpai-livestock.pdf>.

⁸ Animal and Plant Health Inspection Service, United States Department of Agriculture (16 April 2024). Detection of Highly Pathogenic Avian Influenza (H5N1) in dairy Herds: Frequently asked questions. Available at <https://www.aphis.usda.gov/sites/default/files/hpai-dairy-faqs.pdf>.

⁹ Hu X, Saxena A, Magstadt DR, Gauger PC, Burrough E, Zhang J et al. Highly Pathogenic Avian Influenza A (H5N1) clade 2.3.4.4b Virus detected in dairy cattle bioRxiv 2024.04.16.588916.

Regular monitoring and screening of viral sequences found few sequences with markers of mammalian adaptation. As of 20 April 2024, there are no virus sequences from dairy cattle in the USA that have well-recognized markers of mammalian adaptation. In other mammals where markers of mammalian adaptation have been detected, they have most often been associated with changes in polymerase proteins and in association with infection of mammals. These mutations likely occurred rapidly after transmission to the mammalian host and currently there is no evidence of their further transmission. Continuous monitoring is warranted to understand if these changes continue to occur or accumulate over time. Available A(H5N1) clade 2.3.4.4b virus sequences from avian and mammalian hosts indicate that markers associated with reduced susceptibility to neuraminidase or endonuclease inhibitors are rare.

From published animal studies, transmission of A(H5N1) viruses between ferrets has not occurred, however some viruses resulted in severe disease in infected ferrets.^{10,11} More recent studies with clade 2.3.4.4b viruses have shown some transmission between ferrets by direct contact, but not via airborne routes.¹² Analysis of available sequence data suggest that these viruses are primarily avian viruses and no changes in the virus receptor binding tropism have been observed that would increase binding to receptors in the human upper respiratory tract, which would increase transmission to and among people.

Detections in humans

Since the beginning of 2021, 28 detections of A(H5N1) in humans have been reported to WHO. Of these, where the HA clade is known (24 cases), 13 have been associated with clade 2.3.4.4b viruses. These cases have been reported to WHO from: China (one in 2022 and one in 2023), Chile (one in 2023), Ecuador (one in 2022), Spain (two in 2022), the United Kingdom of Great Britain and Northern Ireland (one in 2021 and four in 2023), and the United States of America (USA) (one in 2022 and one in 2024).

All A(H5N1) human cases reported in Europe and North America were asymptomatic or mild, with fatigue reported for the case detected in the USA in 2022 following exposure to infected poultry, and conjunctivitis for the case detected in 2024 following exposure to dairy cattle presumed infected with A(H5N1).¹³ Asymptomatic detections may represent contamination of the respiratory tract or infection. One case detected in China died while the other case was hospitalized with severe pneumonia. The cases in Chile and Ecuador had severe symptoms and recovered. All human cases,

¹⁰ Kandeil, A., Patton, C., Jones, J.C. *et al.* Rapid evolution of A(H5N1) influenza viruses after intercontinental spread to North America. *Nat Commun* **14**, 3082 (2023).

¹¹ Pulit-Penalosa JA, Belser JA, Brock N, Thakur PB, Tumpey TM, Maines TR. Pathogenesis and Transmissibility of North American Highly Pathogenic Avian Influenza A(H5N1) Virus in Ferrets. *Emerg Infect Dis.* 2022;28:1913-5.

¹² Pulit-Penalosa JA, Brock N, Belser JA, Sun X, Pappas C, Kieran TJ, Thakur PB, Zeng H, Cui D, Frederick J, Fasce R, Tumpey TM, Maines TR. Highly pathogenic avian influenza A(H5N1) virus of clade 2.3.4.4b isolated from a human case in Chile causes fatal disease and transmits between co-housed ferrets. *Emerg Microbes Infect.* 2024 Mar 17:2332667.

¹³ World Health Organization (9 April 2024). Disease Outbreak News; Avian Influenza A (H5N1) – the United States of America. Available at <https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON512>.

except for that in Chile, had exposure to infected animals either through participation in outbreak response activities or direct exposure to infected animals in farm, backyard holdings or live bird market environments. The most plausible route of transmission of the case from Chile was through environmental exposure, given the large number of deaths in marine mammals and wild birds that were found in the area close to the patient's residence.¹⁴

The variation in disease outcome of H5N1 patients is likely due to a number of factors, including, virus genotype, viral load in the infectious material they were exposed to, underlying health conditions, duration of exposure, personal protective equipment used at the time of exposure and route of transmission.

Since February 2023, 11 human infections with HPAI A(H5N1) viruses have been reported from Cambodia, two of whom were epidemiologically linked (family members and with a common source of exposure to the virus in sick/dead chickens). Of these, ten viruses belonged to clade 2.3.2.1c. Viet Nam also reported one fatal human infection with a A(H5N1) clade 2.3.2.1c virus in 2024. All reported cases from Cambodia had exposure to infected/sick poultry and the case reported from Viet Nam had exposure to wild birds.¹⁵

Virus characteristics of human A(H5N1) cases

Virus sequences from the human cases, where available, have not shown markers for reduced susceptibility to neuraminidase inhibitors (antiviral medicines such as oseltamivir) or endonuclease inhibitors (such as baloxavir). The sequences of 2.3.4.4b viruses from the human case in Chile in 2023 and the human case in the USA in 2024 had markers associated with mammalian adaptation in the PB2 gene segment. This finding in the PB2 gene segment was also present in sequences from 2.3.2.1c viruses from four cases reported from Cambodia in October and November 2023 and the recent Viet Nam case in 2024. The virus from Chile had two substitutions (PB2-D701N and PB2-Q591K),¹⁶ while the virus from the USA had one substitution (PB2-E627K).¹⁷ Virus isolates from the human cases detected in Cambodia and Viet Nam have the PB2-E627K substitution as well.

Based on limited seroprevalence information available on other A(H5) virus subtypes and clades, human population immunity against the HA of H5 clade 2.3.4.4b and clade 2.3.2.1c viruses is expected to be minimal; human population immunity targeting the N1 neuraminidase is expected to be present although the impact of this immunity is relatively poorly defined.

¹⁴ World Health Organization (21 April 2023). Disease Outbreak News; Avian Influenza A (H5N1) - Chile. Available at <https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON461>.

¹⁵ World Health Organization (2 April 2024). Disease Outbreak News; Avian Influenza A(H5N1) – Viet Nam. Available at <https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON511>.

¹⁶ United States Centers for Disease Control and Prevention (17 April 2023). Human Infection with highly pathogenic avian influenza A(H5N1) virus in Chile. Available at <https://www.cdc.gov/flu/avianflu/spotlights/2022-2023/chile-first-case-h5n1-addendum.htm>.

¹⁷ United States Centers for Disease Control and Prevention (2 April 2024). Technical Update: Summary Analysis of Genetic Sequences of Highly Pathogenic Avian Influenza A(H5N1) Viruses in Texas. Available at <https://www.cdc.gov/flu/avianflu/spotlights/2023-2024/h5n1-analysis-texas.htm>.

Candidate vaccine viruses (CVV)

The WHO Global Influenza Surveillance and Response System (GISRS), in collaboration with animal health partners (FAO, WOAHA and others), evaluate candidate vaccine viruses for pandemic preparedness purposes both bi-annually and on an *ad hoc* basis. The list of available zoonotic influenza candidate vaccine viruses and potency testing reagents is updated on the WHO [website](#). Regular genetic and antigenic characterization of contemporary zoonotic influenza viruses are published [here](#).

Assessment of current risk to humans posed by influenza A(H5N1) viruses

1. What is the global public health risk of additional human cases of infection with avian influenza A(H5N1) viruses?

Despite the high number of A(H5N1) clade 2.3.4.4b outbreaks and detections in animals, and human exposures to the virus at the human-animal-environment interface, relatively few human infections have been reported to date.

Of the 28 human cases of A(H5N1) detections reported since the beginning of 2021, all were sporadic infections in people exposed to A(H5N1) viruses through direct or indirect contact with infected birds, infected mammals or contaminated environments, such as live poultry markets or other premises with infected animals. Among these cases, there has been no reported human-to-human transmission.

While the viruses continue to be detected in animals and related environments, including milk, further sporadic human cases among exposed individuals are expected. Active case finding around reported human cases has been ongoing, and should continue, to determine if there is any human-to-human transmission.

Individuals with activities that involve exposure to infected animals and/or contaminated environments are at higher risk and should take necessary precautions to prevent infection.¹⁸

At the present time, based on available information, WHO assesses the overall public health risk posed by A(H5N1) to be low, and for those with exposure to infected birds or animals or contaminated environments, the risk of infection is considered low-to-moderate. This risk requires close monitoring and WHO and partners will continue to regularly assess and publish public health risk assessments for avian influenza.

¹⁸ United States Centers for Disease Control and Prevention. Highly Pathogenic Avian Influenza A(H5N1) Virus in Animals: Interim Recommendations for Prevention, Monitoring, and Public Health Investigations. Available at <https://www.cdc.gov/flu/avianflu/hpai/hpai-interim-recommendations.html>.

2. What is the likelihood of cattle-to-human transmission of influenza A(H5N1) viruses?

Human cases have followed exposure to avian influenza-infected mammals for other influenza A subtypes, including A(H7N2)¹⁹ and A(H7N7)²⁰, but only in a few instances. To date, there has been one reported case of infection with an influenza A(H5N1) virus in the USA in a person who worked at a dairy farm where cattle were presumed to be infected with A(H5N1) viruses. This case presented with conjunctivitis as the only symptom and has since recovered.

Infected lactating cattle have been reported to have high viral loads in their milk and thus could be a source of exposure to persons in close contact with them.²¹ The potential role of consumption and handling of milk and milk products in transmission, and the role of pasteurization in mitigating the potential risk, is currently being investigated.

As long as people are in contact with infected cattle without appropriate personal protective equipment, there is a risk for human infections. The risk can be mitigated by measures to reduce exposure to the virus, such as the use of recommended personal protective equipment, appropriate personal hygiene and other risk-based biosecurity measures.

3. What is the likelihood of human-to-human transmission of avian influenza A(H5N1) viruses?

There has been no reported human-to-human transmission of A(H5N1) viruses since 2007, although there may be gaps in investigations. Prior to 2007, small clusters of A(H5) virus infections in humans were reported, including some involving health care workers, where limited human-to-human transmission could not be excluded; however, sustained human-to-human transmission was not reported.²²

The A(H5N1) viruses detected in mammals, including in human cases, largely retain genomic and biological characteristics of avian influenza viruses and remain well-adapted to spread among birds. Except for in-host obtained amino acid mutations in polymerase proteins, there is still limited evidence for adaptation to mammals and humans even when transmission in mammals has been suspected.²³ No changes in receptor binding tropism have been observed that would increase binding to receptors in the human upper respiratory tract which would increase transmission to and

¹⁹ Belser JA, Pulit-Penalzo JA, Sun X, Brock N, Pappas C, Creager HM et al. A Novel A(H7N2) Influenza Virus Isolated from a Veterinarian Caring for Cats in a New York City Animal Shelter Causes Mild Disease and Transmits Poorly in the Ferret Model. *J Virol*. 2017 Jul 12;91(15):e00672-17.

²⁰ Webster RG, Geraci J, Petursson G, Skirnisson K. Conjunctivitis in human beings caused by influenza A virus of seals. *N Engl J Med*. 1981 Apr 9;304(15):911.

²¹ Animal and Plant Health Inspection Service, United States Department of Agriculture (12 April 2024). APHIS Recommendations for Highly Pathogenic Avian Influenza (HPAI) H5N1 Virus in Livestock For Workers. Available at <https://www.aphis.usda.gov/sites/default/files/recommendations-workers-hpai-livestock.pdf>.

²² United States Centers for Disease Control and Prevention. Past Examples of Probable Limited, Non-Sustained, Person-to-Person Spread of Avian Influenza A Viruses. Available at: <https://www.cdc.gov/flu/avianflu/h5n1-human-infections.htm>.

²³ United States Centers for Disease Control and Prevention (2 April 2024). Technical Update: Summary Analysis of Genetic Sequences of Highly Pathogenic Avian Influenza A(H5N1) Viruses in Texas. Available at <https://www.cdc.gov/flu/avianflu/spotlights/2023-2024/h5n1-analysis-texas.htm>.

among people. Therefore, human-to-human transmission of the currently circulating A(H5N1) viruses is considered unlikely without further genetic changes in the virus.

WHO, together with the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (WOAH), continues to monitor these viruses and will re-assess the risk associated with the currently spreading A(H5N1) viruses as more information becomes available.

Further antigenic characterization of A(H5N1) viruses, including in relation to the existing CVVs, and development of specific reagents are being prioritized at the WHO Collaborating Centres and Essential Regulatory Laboratories of GISRS in collaboration with animal health and veterinary sector colleagues.

Recommended actions

As these viruses are constantly evolving and spreading in animal populations, and with an increased risk of exposure for humans, there is a continuous need to re-assess the risks as the situation evolves and when more information becomes available. FAO, WHO and WOAH will continue to conduct and publish risk assessments for avian influenza viruses.

Countries should maintain surveillance in birds, monitor and investigate cases in non-avian species, including livestock, report cases of HPAI in all animal species to WOAH and other international organizations, prevent spread in animals through strict biosecurity measures and protect persons in contact with suspected/infected animals.²⁴

It is recommended that countries, particularly through National Influenza Centres (NICs) and other influenza laboratories associated with GISRS, remain vigilant for the possibility of zoonotic infections. It is recommended that national authorities fully assess the risk among occupationally exposed persons using active case finding and serologic methods, as well as work with national agencies to understand the exposure and risk from milk and milk products.

Clinicians should also be alerted to potential zoonotic infection in patients with an exposure history to birds or animals in areas where avian influenza viruses are known to be circulating in animals. Epidemiologic and virologic surveillance and the follow-up of suspected and confirmed human cases should be conducted systematically.

Rapid sharing of information and sequence data from both the human and animal health sectors continues to be strongly recommended and is critical for rapid risk assessment. The rapid sharing of virus material with WHO Collaborating Centres of GISRS is essential to conduct a thorough risk assessment and develop or adjust targeted response measures. The Tool for Influenza Pandemic Risk Assessment (TIPRA) provides an in-depth assessment of risk associated with some zoonotic influenza

²⁴ World Organisation for Animal Health. Statement on High Pathogenicity Avian Influenza in Cattle, 5 April 2024. Available at: <https://www.woah.org/en/high-pathogenicity-avian-influenza-in-cattle/#:~:text=The%20recently%20reported%20detections%20of,H5N1%20viruses%20becoming%20better%20adapted.>

viruses – notably the likelihood of the virus gaining human-to-human transmissibility, and the impact should the virus gain such transmissibility. TIPRA maps relative risk amongst viruses assessed using multiple elements.²⁵

Procedures to reduce human exposure to birds and mammals potentially infected with avian and other animal influenza viruses should be implemented to minimize the risk of zoonotic infections. Those who are exposed to potentially infected animals should wear personal protective equipment including eye protection.²⁶ If they develop respiratory symptoms or conjunctivitis, they should be rapidly sampled, and precautionary infection control measures should be put in place to prevent potential further spread among humans and to animals. For detailed guidance on treatment, refer to relevant global and national guidance.²⁷

Investigations are ongoing to understand the risk to humans from consuming milk contaminated with A(H5N1) virus. It is important for people to continue to follow safe food practices.²⁸ Many dangerous zoonotic pathogens can be transmitted through unpasteurized milk, and FAO and WHO strongly advise the consumption of only pasteurized milk and to avoid consuming raw milk.²⁹

More information will be available in the coming days and weeks as investigations are actively ongoing in the United States and elsewhere. WHO and GISRS, jointly with FAO, WOAHA and OFFLU (Joint WOAHA-FAO Scientific Network on Animal Influenza) are working closely together to continuously assess the avian influenza situation. This includes increased surveillance and testing to monitor the evolution and geographic spread of avian influenza viruses, including A(H5N1) viruses, to provide timely and updated risk assessments.

²⁵ World Health Organization, Tool for influenza pandemic risk assessment. Available at [http://www.who.int/teams/global-influenza-programme/avian-influenza/tool-for-influenza-pandemic-risk-assessment-\(tipra\)](http://www.who.int/teams/global-influenza-programme/avian-influenza/tool-for-influenza-pandemic-risk-assessment-(tipra)).

²⁶ Animal and Plant Health Inspection Service, United States Department of Agriculture (12 April 2024). APHIS Recommendations for Highly Pathogenic Avian Influenza (HPAI) H5N1 Virus in Livestock For Workers. Available at <https://www.aphis.usda.gov/sites/default/files/recommendations-workers-hpai-livestock.pdf>.

²⁷ Guidelines for the clinical management of severe illness from influenza virus infections. Geneva: World Health Organization; 2022 (<https://apps.who.int/iris/handle/10665/352453>, accessed 2 Dec 2022).

²⁸ United States Food and Drug Administration (23 April 2024). Updates on Highly Pathogenic Avian Influenza (HPAI). Available at <https://www.fda.gov/food/alerts-advisories-safety-information/updates-highly-pathogenic-avian-influenza-hpai>.

²⁹ Joint FAO/WHO Codex Alimentarius Commission. Codex Alimentarius: Code of hygienic practice for milk and milk products. Available at: https://www.fao.org/fileadmin/user_upload/livestockgov/documents/CXP_057e.pdf.