



# Updated joint FAO/WHO/WOAH assessment of recent influenza A(H5N1) virus events in animals and people

Assessment based on data as of 18 July 2024

14 August 2024

## Key points

At the present time, based on available information, FAO-WHO-WOAH assess the global public health risk of influenza A(H5N1) viruses to be low, while the risk of infection for occupationally exposed persons is low to moderate depending on the risk mitigation measures in place. Transmission between animals continues to occur and, to date, a limited number of human infections have been reported. Although additional human infections associated with exposure to infected animals or contaminated environments are likely to continue to occur, the overall public health impact of such infections at a global level is minor.

## Background

During 2020, high pathogenicity 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. This epizootic event has led to unprecedented numbers of deaths in wild birds and caused outbreaks in poultry. In late 2021, these viruses crossed the Atlantic Ocean to North America and subsequently reached South America in October 2022. Over the past few years, there have been increased detections of A(H5N1) viruses in non-avian species globally including wild and domestic (companion and farmed) terrestrial and marine mammals, with recent cases in livestock in the United States of America (USA). The majority of A(H5N1) viruses characterized genetically since 2020 belong to the haemagglutinin (HA) H5 clade 2.3.4.4b, with some regional exceptions. Other circulating A(H5N1) viruses belong to clade 2.3.2.1a or 2.3.2.1c or fall within clades that are reported less frequently. Since the beginning of 2021, 35 detections of A(H5N1) virus in humans have been reported to WHO, along with five cases of A(H5) virus detection in persons exposed to A(H5N1) infected animals, presumably A(H5N1) viruses, although the neuraminidase (NA) subtype was unable to be determined due to low viral ribonucleic acid (RNA) loads. Of these human cases where the A(H5) clade is known (n = 31), 17 have been caused by clade 2.3.4.4b viruses.

Considering additional information made available since the previous [assessment of 23 April 2024](#), FAO, WHO, and WOAH jointly updated their assessment here. This update focuses on A(H5N1) viruses characterized since 2021 and covers the risk of zoonotic transmission. Due to the potential risk to human health and the far-reaching implications of the disease on the health of wild bird and other animal populations, using a [One Health approach](#) is essential to tackle avian influenza effectively.

## 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 bird species.

Additionally, the ongoing virus circulation in wild and migratory birds and poultry has led to multiple separate infections of wild carnivorous and scavenging mammals, domestic cats and dogs, marine mammals, and seabirds in a number of countries. Clade 2.3.4.4b virus infections in mammals in the Americas, Asia and Europe has often resulted in severe disease with neurological signs in some species.<sup>1</sup> In 2024, A(H5N1) viruses have been detected in neonatal goats on a single premises shared with poultry<sup>2</sup>, and in alpacas from a premises where HPAI-affected poultry were depopulated.<sup>3,4</sup> In March 2024, A(H5N1) virus was detected in unpasteurized milk samples and an oropharyngeal swab from dairy cattle in the USA.<sup>5</sup> Detections of A(H5N1) continued to be reported through testing of dairy cattle showing clinical signs, though detections have also been reported in cattle with no apparent disease.<sup>6,7</sup> Analyses of sequence data of viruses from infected dairy cows has suggested a single bird-to-dairy cow transmission event of a B3.13 genotype A(H5N1) virus that occurred in late 2023 or early 2024.<sup>8</sup> Thus far, this genotype has not been detected in dairy cattle outside of the USA.<sup>9</sup>

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<sup>1</sup> Plaza PI, Gamarra-Toledo V, Euguí J, Lambertucci SA. Recent Changes in Patterns of Mammal Infection with Highly Pathogenic Avian Influenza A(H5N1) Virus Worldwide. *Emerg Infect Dis.* 2024;30(3):444-452. <https://doi.org/10.3201/eid3003.231098>.

<sup>2</sup> United States of America - Influenza A viruses of high pathogenicity (Inf. with) (non-poultry including wild birds) (2017-) - Follow up report 43. World Animal Health Information System. <https://wahis.woah.org/#/in-review/4451?reportId=166488>.

<sup>3</sup> United States Department of Agriculture. Highly Pathogenic Avian Influenza (HPAI) Detections in Mammals. Highly Pathogenic Avian Influenza (HPAI) H5N1 Detections in Alpacas <https://www.aphis.usda.gov/livestock-poultry-disease/avian/avian-influenza/hpai-detections/mammals/highly-pathogenic-avian>

<sup>4</sup> 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>

<sup>5</sup> United States Department of Agriculture. Federal and State Veterinary, Public Health Agencies Share Update on HPAI Detection in Kansas, Texas Dairy Herds. 25 March 2024. Available at: <https://www.aphis.usda.gov/news/agency-announcements/federal-state-veterinary-public-health-agencies-share-update-hpai>.

<sup>6</sup> United States Department of Agriculture. Case Definition - Avian Influenza, May 2024. Available at: <https://www.aphis.usda.gov/sites/default/files/hpai-livestock-case-definition.pdf>.

<sup>7</sup> United States Department of Agriculture. Highly Pathogenic Avian Influenza H5N1 Genotype B3.13 in Dairy Cattle: National Epidemiologic Brief, 8 June 2024. Available at: <https://www.aphis.usda.gov/sites/default/files/hpai-dairy-national-epi-brief.pdf>

<sup>8</sup> Nguyen T-Q, Hutter C, Markin A, Thomas M, Lantz K, Killian ML et al. Emergence and interstate spread of highly pathogenic avian influenza A(H5N1) in dairy cattle. *bioRxiv* 2024.05.01.591751; <https://doi.org/10.1101/2024.05.01.591751>.

<sup>9</sup> FAO. 2024. A(H5N1) influenza in dairy cattle in the United States of America. *EMPRES Watch*, Vol. 38, July 2024. Rome, FAO.

As of 18 July 2024, 162 dairy cattle herds in 13 states of the USA tested positive for A(H5N1).<sup>10</sup> Approximately 10 to 15% of the dairy cows in affected herds showed clinical signs including decreased feed intake, altered faecal consistency, respiratory distress, and decreased milk production with abnormal milk.<sup>11,12</sup> High infectious viral loads have been detected in raw milk from infected cows,<sup>13</sup> and examination of post-mortem tissues showed influenza virus antigen was present in the mammary gland and associated lymph nodes. Virus has only been sporadically found in the respiratory tract of infected cattle. Cats that were fed raw colostrum and milk from infected cows showed about 50% mortality on affected premises in two states in March 2024; those that died had severe systemic viral disease, including severe meningoencephalitis.<sup>14</sup> Studies have shown the commercial milk pasteurization process inactivates the virus, however raw milk may contain live virus.<sup>15,16</sup>

The routes and modes of transmission between cattle and the duration of infectious virus shedding in cows are to be defined. Studies of ongoing mammal to mammal transmission between farms seems to be linked to cattle movement although contaminated fomites (e.g., milking equipment, shared transportation vehicles, manure or handling equipment, or on the clothing or footwear of people working or visiting farms) and other mechanical means are other possible routes are currently being investigated.<sup>17</sup>

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<sup>10</sup> 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>.

<sup>11</sup> Burrough ER, Magstadt DR, Petersen B, Timmermans SJ, Gauger PC, Zhang J, Siepker C, Mainenti M, Li G, Thompson AC, Gorden PJ, Plummer PJ, Main R. Highly Pathogenic Avian Influenza A(H5N1) Clade 2.3.4.4b Virus Infection in Domestic Dairy Cattle and Cats, United States, 2024. *Emerg Infect Dis.* 2024 Jul;30(7):1335-1343. doi: 10.3201/eid3007.240508.

<sup>12</sup> Caserta et al. Caserta LC, Frye EA, Butt SL, Laverack M, Nooruzzaman M, Covaleda LM et al. From birds to mammals: spillover of highly pathogenic avian influenza H5N1 virus to dairy cattle led to efficient intra- and interspecies transmission. *bioRxiv* 2024.05.22.595317; doi: <https://doi.org/10.1101/2024.05.22.595317>.

<sup>13</sup> Caserta et al. Caserta LC, Frye EA, Butt SL, Laverack M, Nooruzzaman M, Covaleda LM et al. From birds to mammals: spillover of highly pathogenic avian influenza H5N1 virus to dairy cattle led to efficient intra- and interspecies transmission. *bioRxiv* 2024.05.22.595317; doi: <https://doi.org/10.1101/2024.05.22.595317>.

<sup>14</sup> Burrough ER, Magstadt DR, Petersen B, Timmermans SJ, Gauger PC, Zhang J, Siepker C, Mainenti M, Li G, Thompson AC, Gorden PJ, Plummer PJ, Main R. Highly Pathogenic Avian Influenza A(H5N1) Clade 2.3.4.4b Virus Infection in Domestic Dairy Cattle and Cats, United States, 2024. *Emerg Infect Dis.* 2024 Jul;30(7):1335-1343. doi: 10.3201/eid3007.240508.

<sup>15</sup> United States Food and Drug Administration. Updates on Highly Pathogenic Avian Influenza (HPAI). Ongoing Work to Ensure Continued Effectiveness of the Federal-State Milk Safety System. 28 June 2024. Available at: [https://www.fda.gov/food/alerts-advisories-safety-information/updates-highly-pathogenic-avian-influenza-hpai?utm\\_medium=email&utm\\_source=govdelivery](https://www.fda.gov/food/alerts-advisories-safety-information/updates-highly-pathogenic-avian-influenza-hpai?utm_medium=email&utm_source=govdelivery).

<sup>16</sup> Spackman E, Jones DR, McCoig AM, Colonius TJ, Goraichuk I, Suarez DL. Characterization of highly pathogenic avian influenza virus in retail dairy products in the US. *medRxiv* 2024.05.21.24307706; doi: <https://doi.org/10.1101/2024.05.21.24307706>.

<sup>17</sup> 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>.

Experimental infection studies of lactating dairy cattle and non-lactating heifers have been initiated and have provided some insight into viral replication kinetics and infection routes.<sup>18</sup> Studies have indicated that alpha 2,3 sialic acid receptors (avian virus-type) are abundant in certain parts of dairy cattle mammary tissue, consistent with the observation of high viral load in raw milk, as well as in the respiratory tract of dairy cattle.<sup>19,20</sup>

Transmission of A(H5N1) viruses from cattle into other local mammalian and avian species has also been detected, although the frequency and transmission route(s) remain poorly understood at this time.<sup>21</sup> The A(H5N1) virus has been detected in cats found dead on or near some of the affected dairy farms and found to be the same virus as detected in cattle.<sup>22, 23, 24, 25, 26</sup> Additional information can be found in the recently published [FAO EMPRES Watch addressing A\(H5N1\) influenza in dairy cattle in the United States of America](#).<sup>27</sup>

Regular monitoring and screening of viral sequences has rarely found markers of mammalian adaptation in clade 2.3.4.4b viruses, mainly in the polymerase proteins of the virus. As of 18 July 2024, there are no virus sequences from dairy cattle in the USA that have well-recognized markers in the HA gene associated with a switch in receptor preference despite continued circulation of the virus. Despite this, a recent receptor binding assay study suggest that a A(H5N1) virus from dairy cattle in the USA may be more likely to bind to the type of receptors distributed in the upper

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<sup>18</sup> Baker AL, Arruda B, Palmer MV, Boggiatto P, Davila KS, Buckley et al. Experimental reproduction of viral replication and disease in dairy calves and lactating cows inoculated with highly pathogenic avian influenza H5N1 clade 2.3.4.4b. bioRxiv 2024.07.12.603337; doi: <https://doi.org/10.1101/2024.07.12.603337>.

<sup>19</sup> Nelli RK, Harm TA, Siepker C, Groeltz-Thrush JM, Jones B, Twu N, et al. Sialic Acid Receptor Specificity in Mammary Gland of Dairy Cattle Infected with Highly Pathogenic Avian Influenza A(H5N1) Virus. *Emerg Infect Dis.* 2024;30(7):1361-1373. <https://doi.org/10.3201/eid3007.240689>.

<sup>20</sup> Kristensen C, Jensen HE, Trebbien R, Webby RJ, Larsen LE. The avian and human influenza A virus receptors sialic acid (SA)- $\alpha$ 2,3 and SA- $\alpha$ 2,6 are widely expressed in the bovine mammary gland bioRxiv 2024.05.03.592326; doi: <https://doi.org/10.1101/2024.05.03.592326>.

<sup>21</sup> 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>.

<sup>22</sup> 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.

<sup>23</sup> Caserta et al. Caserta LC, Frye EA, Butt SL, Laverack M, Nooruzzaman M, Covalada LM et al. From birds to mammals: spillover of highly pathogenic avian influenza H5N1 virus to dairy cattle led to efficient intra- and interspecies transmission. bioRxiv 2024.05.22.595317; doi: <https://doi.org/10.1101/2024.05.22.595317>.

<sup>24</sup> United States Department of Agriculture. 2024 Highly Pathogenic Avian Influenza (H5N1) - Michigan Dairy Herd and Poultry Flock Summary. 9 June 2024. Available at: <https://www.aphis.usda.gov/sites/default/files/hpai-h5n1-dairy-cattle-mi-epi-invest.pdf>.

<sup>25</sup> Nguyen T-Q, Hutter C, Markin A, Thomas M, Lantz K, Killian ML et al. Emergence and interstate spread of highly pathogenic avian influenza A(H5N1) in dairy cattle. bioRxiv 2024.05.01.591751; <https://doi.org/10.1101/2024.05.01.591751>.

<sup>26</sup> Burrough ER, Magstadt DR, Petersen B, Timmermans SJ, Gauger PC, Zhang J, Siepker C, Mainenti M, Li G, Thompson AC, Gorden PJ, Plummer PJ, Main R. Highly Pathogenic Avian Influenza A(H5N1) Clade 2.3.4.4b Virus Infection in Domestic Dairy Cattle and Cats, United States, 2024. *Emerg Infect Dis.* 2024 Jul;30(7):1335-1343. doi: 10.3201/eid3007.240508.

<sup>27</sup> FAO. 2024. A(H5N1) influenza in dairy cattle in the United States of America. EMPRES Watch, Vol. 38, July 2024. Rome, FAO.

respiratory tract of humans (alpha 2,6-linked sialic acids) compared to a A(H5N1) virus from 2004.<sup>28</sup> However, these findings have not been replicated by others using different A(H5N1) viruses from dairy cattle or human cases associated with dairy cattle exposure. For example, a separate preliminary study did not find the A(H5N1) virus from the first human case associated with dairy cattle exposure had any binding to alpha 2,6-linked sialic acids<sup>29</sup> and studies with other A(H5N1) viruses from dairy cattle have not observed this trait.

In one human infection associated with exposure to infected dairy cattle, the PB2 E627K mutation was identified which is known to be associated with increased replication in mammalian hosts. Similar markers in polymerase proteins have previously been reported in clade 2.3.4.4b viruses, particularly those isolated from mammals.<sup>30</sup> Constant monitoring is warranted to understand if these changes continue to occur or accumulate over time. Analysis of 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.

Other A(H5) virus clades such as 2.3.2.1c and 2.3.2.1a viruses continue to circulate and evolve in poultry in geographically restricted regions. For example, a novel reassortant influenza A(H5N1) virus has been detected in poultry in Cambodia and Viet Nam and was also detected in the human cases reported from Cambodia since late 2023 and Viet Nam in 2024. This reassortant virus has HA and NA genes from clade 2.3.2.1c viruses, while its internal genes belong to clade 2.3.4.4b viruses.<sup>31</sup> Furthermore, clade 2.3.2.1a viruses have been detected in poultry in Bangladesh, Bhutan, India and Nepal since their emergence and introduction into South Asia in 2011.

To date, there have been limited reports of transmission of clade 2.3.4.4b viruses between mammals other than the ongoing situation with viral transmission between dairy cattle. Large A(H5N1) virus driven die-offs of marine mammals<sup>32</sup> and infections in multiple fur animal farms (mink, foxes) in

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<sup>28</sup> Eisfeld AJ, Biswas A, Guan L, Gu C, Maemura T, Trifkovic S et al. Pathogenicity and transmissibility of bovine H5N1 influenza virus. *Nature* (2024). <https://doi.org/10.1038/s41586-024-07766-6>.

<sup>29</sup> Good MR, Ji W, Fernández-Quintero ML, Ward AB, Guthmiller JJ. A single mutation in dairy cow-associated H5N1 viruses increases receptor binding breadth. *bioRxiv* 2024.06.22.600211; doi: <https://doi.org/10.1101/2024.06.22.600211>.

<sup>30</sup> Hossain MG, Akter S, Dhole P, Saha S, Kazi T, Majbauddin A et al. Analysis of the Genetic Diversity Associated With the Drug Resistance and Pathogenicity of Influenza A Virus Isolated in Bangladesh From 2002 to 2019. *Front. Microbiol.* 2021. doi: 10.3389/fmicb.2021.735305.

<sup>31</sup> 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/>.

<sup>32</sup> Plaza PI, Gamarra-Toledo V, Euguí J, Lambertucci SA. Recent Changes in Patterns of Mammal Infection with Highly Pathogenic Avian Influenza A(H5N1) Virus Worldwide. *Emerg Infect Dis.* 2024;30(3):444-452. <https://doi.org/10.3201/eid3003.231098>.

Finland<sup>33</sup> and mink in Spain<sup>34,35</sup> are consistent with likely mammal-to-mammal spread in these instances, although further evidence and research studies are needed.

Experimental studies with A(H5N1) clade 2.3.4.4b viruses have shown variable transmission between ferrets by direct contact, but no or inefficient transmission via respiratory droplets.<sup>36,37, 38, 39</sup> Ferrets infected with an A(H5N1) clade 2.3.4.4b virus via the ocular route did experience severe disease and were able to transmit the virus to other ferrets via direct contact; these contact animals also developed severe disease.<sup>40</sup> Current A(H5N1) viruses would need to undergo further genetic changes to spread efficiently among humans via respiratory droplets, consistent with the current level of risk to public health, which is low.<sup>41</sup>

### Detections in humans

Since the beginning of 2021, 35 detections of A(H5N1) virus in humans have been reported to WHO, along with five cases of A(H5) virus detection in persons exposed to A(H5N1) infected animals in the USA and which are likely to be A(H5N1) viruses, although the neuraminidase (NA) subtype was unable to be determined due to low viral RNA levels. Where the HA clade is known (31 cases), 17 have been associated with clade 2.3.4.4b viruses. These 2.3.4.4b 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 USA (one in 2022 and five in 2024). Since February 2023, 13 human infections with HPAI A(H5N1) viruses have been reported from Cambodia, viruses from ten of these cases were confirmed to belong to clade 2.3.2.1c. Viet Nam also reported one fatal human infection with a A(H5N1) clade

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<sup>33</sup> 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..

<sup>34</sup> Agüero M, Monne I, Sánchez A, Zecchin B, Fusaro A, Ruano MJ et al. Highly pathogenic avian influenza A(H5N1) virus infection in farmed minks, Spain, October 2022. *Euro Surveill.* 2023 Jan;28(3):2300001. doi: 10.2807/1560-7917.

<sup>35</sup> Chen JM, Tan SM, Chen RX, Gong HY, Wang X, Lu SS. Distribution and risks of the infections of humans and other mammals with H5 subtype highly pathogenic avian influenza viruses in 2020-2023. *J Infect.* 2023 Dec;87(6):574-575. doi: 10.1016/j.jinf.2023.09.003.

<sup>36</sup> United States Centers for Disease Control and Prevention. CDC Reports A(H5N1) Ferret Study Results. 7 June 2024. Available at: <https://www.cdc.gov/bird-flu/spotlights/ferret-study-results.html>.

<sup>37</sup> Pulit-Penalzo 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.

<sup>38</sup> Eisfeld AJ, Biswas A, Guan L, Gu C, Maemura T, Trifkovic S et al. Pathogenicity and transmissibility of bovine H5N1 influenza virus. *Nature* (2024). <https://doi.org/10.1038/s41586-024-07766-6>.

<sup>39</sup> Restori KH, Septer KM, Field CJ, Patel DR, VanInsberghe D, Raghunathan V et al. Risk assessment of a highly pathogenic H5N1 influenza virus from mink. *Nat Commun* 15, 4112 (2024). <https://doi.org/10.1038/s41467-024-48475-y>.

<sup>40</sup> Belser JA, Sun X, Pulit-Penalzo JA, Maines TR. Fatal Infection in Ferrets after Ocular Inoculation with Highly Pathogenic Avian Influenza A(H5N1) Virus. *Emerg Infect Dis.* 2024;30(7):1484-1487. Available at: <https://doi.org/10.3201/eid3007.240520>.

<sup>41</sup> United States Centers for Disease Control and Prevention. CDC Reports A(H5N1) Ferret Study Results, 7 June 2024. Available at: [https://www.cdc.gov/bird-flu/spotlights/ferret-study-results.html?CDC\\_AAref\\_Val=https://www.cdc.gov/flu/avianflu/spotlights/2023-2024/ferret-study-results.htm](https://www.cdc.gov/bird-flu/spotlights/ferret-study-results.html?CDC_AAref_Val=https://www.cdc.gov/flu/avianflu/spotlights/2023-2024/ferret-study-results.htm).



2.3.2.1c virus in 2024. A travel-associated human infection with a clade 2.3.2.1a virus was reported in Australia in early 2024.

Since the last joint assessment of April 2024, an additional nine human cases of infection with A(H5) viruses have been reported from the USA in 2024: three in persons with exposure to A(H5N1)-infected dairy cattle and six in persons with exposure while involved in the depopulation of a A(H5N1)-infected commercial poultry farm. Samples from two of the six cases related to poultry depopulation yielded full or partial genomes to confirm A(H5N1) with HA clade 2.3.4.4b. Investigation of the six cases as a point-source outbreak related to this poultry depopulation is underway.

All above-mentioned A(H5N1) human cases reported in Europe and North America, including A(H5) with N1 laboratory-unconfirmed, were either asymptomatic or had mild symptoms ranging from fatigue or conjunctivitis to mild respiratory symptoms.<sup>42</sup> Asymptomatic detections may represent contamination of the respiratory tract or a true infection. One human case detected in China died while the other case was hospitalized with severe pneumonia. The human cases in Chile, Ecuador and Australia (the latter caused by a clade 2.3.2.1a virus) had severe symptoms and recovered. All human cases, except for those reported by Australia and Chile, had known 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.<sup>43</sup> The case reported by Australia<sup>44</sup>, which was in an individual with recent travel history to India, had no known exposure to animals at the time of reporting but exposure to animals was likely when the patient travelled; furthermore, virus genetic sequence obtained from the patient's samples indicated that the HA belonged to clade 2.3.2.1a, which is a clade of viruses circulating in birds in South Asia, but not Australia, and has been detected in previous human infections.

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

Of the 13 human infections with A(H5N1) viruses reported since February 2023 from Cambodia, two had no symptoms and were detected as part of contact tracing, two were mild and the others had more severe disease or were fatal. All reported cases from Cambodia had exposure to infected/sick

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<sup>42</sup> 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>.

<sup>43</sup> 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>.

<sup>44</sup> World Health Organization (21 April 2023). Disease Outbreak News; Avian Influenza A (H5N1) - Australia. Available at : <https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON519>.

poultry and the case reported from Viet Nam had exposure to wild birds.<sup>45</sup> There was no person-to-person transmission.

### **Virus characteristics of human A(H5N1) cases**

Virus sequences from the human cases have not shown markers for reduced susceptibility to neuraminidase inhibitors (antiviral medicines such as oseltamivir) or endonuclease inhibitors (such as baloxavir marboxil). Some of the virus sequences, as seen in other mammalian infections detailed above, have had genetic markers associated with mammalian adaptation, including a variety of substitutions in the PB2 gene segment. These included the sequences of 2.3.4.4b viruses from the human case in Chile in 2023 (PB2 Q591 K and D701N<sup>46</sup>) and the first human case in the USA associated with dairy cattle exposure in 2024 (PB2 E627K<sup>47</sup>). PB2 E627K mutations were 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.

A seroprevalence study was performed in people with exposures to A(H5N1) infected dairy cattle in Michigan, USA. None of the 35 individuals had detectable neutralizing or HI antibodies against the HA of the A(H5N1) clade 2.3.4.4b. virus.<sup>48</sup> Currently, we are aware that other studies are underway, however, it is unclear how many human serologic studies are underway to understand the extent of infection of 2.3.4.4b H5N1 viruses. 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 yet to be understood.

### **Candidate vaccine viruses (CVV)**

The WHO Global Influenza Surveillance and Response System (GISRS), in collaboration with animal health partners (FAO, WOA, OFFLU (Joint WOA-FAO network of expertise on animal influenza) and others), continue to 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 which include A(H5N1) viruses and potency testing reagents is updated on the WHO [website](#). Regular genetic and antigenic characterization of contemporary zoonotic influenza viruses are published [here](#) and an update on clade 2.3.4.4b A(H5N1) viruses identified in dairy cattle in the USA was published [here](#).

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<sup>45</sup> 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>.

<sup>46</sup> 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>.

<sup>47</sup> 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>.

<sup>48</sup> United States Centers for Disease Control and Prevention (2 April 2024). CDC A(H5N1) Bird Flu Response Update, July 19, 2024. Available at: <https://www.cdc.gov/bird-flu/spotlights/h5n1-response-07192024.html>.



## Assessment of current public health risk posed by influenza A(H5N1) viruses<sup>49</sup>

### 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 35 human cases of A(H5N1) detections reported since the beginning of 2021 and five human cases of A(H5) in 2024, 36 were infections in people exposed to A(H5N1) viruses through direct or indirect contact with infected birds, or contaminated environments, such as live poultry markets or other premises with infected birds. The remaining four cases were infections in people exposed to A(H5N1) virus through direct or indirect contact with infected dairy cattle in the USA. Thus far, among these cases, there has been no reported human-to-human transmission.

Current virologic and epidemiologic information indicate that these viruses remain avian influenza viruses without established adaptations to mammalian hosts and have not acquired the capacity for sustained transmission between humans.

The epidemiological situation has changed with the incursion and ongoing spread of A(H5N1) virus in the USA dairy cattle population. Persons exposed to affected dairy cattle may be in prolonged and close contact with potentially contaminated surfaces and animal products. As long as A(H5N1) viruses continue to be detected in animals and related environments, including unpasteurized/raw milk, further human cases are expected, particularly amongst exposed individuals not wearing appropriate personal protective equipment and/or in environments where mitigation measures are not in place.

Based on currently available information, FAO-WHO-WOAH assesses the global public health risk of influenza A(H5N1) viruses as low. Although additional human infections associated with exposure to infected animals or contaminated environments are likely to occur, the overall current public health impact of such infections at a global level is minor, considering the response, mitigation and control measures. However, while the risk of infection to the general public is low, among persons with exposure to infected birds or mammals or contaminated environments, the risk of infection can range from low to moderate, depending on nature of the exposure, the duration of exposure, the consistent and appropriate use of personal protective equipment, and the use of other response, mitigation and control measures particularly in environments where animals are kept. The risk posed by these viruses requires vigilance and close monitoring. It remains essential that occupationally exposed persons are provided with and trained in the use of personal protective equipment and that mitigation measures to reduce

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<sup>49</sup> World Health Organization. (2012). Rapid risk assessment of acute public health events. World Health Organization. Available at: <https://iris.who.int/handle/10665/70810>.

animal to animal transmission, animal to human transmission and environmental contamination are in place in affected settings.

## 2. 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. In 2007 and the years prior, small clusters of A(H5) virus infections in humans were reported, including some involving health care workers, where limited human-to-human transmission could have occurred; however, sustained human-to-human transmission was not reported.<sup>50</sup>

The A(H5N1) viruses currently 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.<sup>51</sup> No changes in receptor binding tropism have been consistently observed that would increase binding to receptors in the human upper respiratory tract which would increase transmission to and among people. Therefore, human-to-human transmission of the currently circulating A(H5N1) viruses is considered unlikely without further genetic changes in the virus. This is actively being assessed by FAO, WHO, WOAHA and partners.

WHO, together with FAO and WOAHA, continues to evaluate A(H5N1) viruses closely 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 public health, animal health, and veterinary sector colleagues.

## **Recommended actions**

Countries are recommended to:

- increase surveillance efforts for the early detection of A(H5) influenza viruses in domestic and wild birds;
- include infection with an A(H5) influenza virus as a differential diagnosis, in non-avian species, including cattle and other livestock and farmed domestic and wild animal populations, with high risk of exposure to A(H5) viruses;

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<sup>50</sup> 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>.

<sup>51</sup> 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>.

- report promptly HPAI events in all animal species, including unusual hosts, to WOAHA and other international organizations such as FAO;
- share genetic sequences of avian influenza viruses and associated metadata in publicly available databases;
- prevent the introduction and spread of the disease in animals by implementing biosecurity in livestock holdings/premises and along the value chain; and
- employ good production and hygiene practices when handling animal products, and protect persons in contact with suspected/infected animals.

Additional sets of recommendations related to avian influenza viruses with zoonotic potential can be found in:

- [WOAHA Statement on High Pathogenicity Avian Influenza in Cattle](#), 8 June 2024.
- [FAO recommendations for Global Avian Influenza Viruses with Zoonotic Potential](#).
- FAO EMPRES Watch entitled '[A\(H5N1\) influenza in dairy cattle in the United States of America](#)'.

Additional studies/surveillance, applying One Health principles are warranted, which could provide information to enhance confidence in the risk assessment. These may include serological studies in high-risk animal populations, in high-risk human populations, and epidemiological investigations in interfaces.

It is recommended that Member States, particularly through National Influenza Centres (NICs) and other influenza laboratories associated with GISRS, increase vigilance for the possibility of zoonotic infections. National authorities are recommended to assess the risk among occupationally exposed persons using methods e.g., active case finding and serologic methods, and as well as work with national agencies to understand the exposure to and risk from raw/unpasteurized milk and milk products.

Anyone who may have been exposed to infected or potentially infected animals should be advised to promptly seek health care if they feel unwell, and to inform their health care provider of their possible exposure. Following prompt testing, early and appropriate clinical management should be initiated, and precautionary measures put in place to assess and prevent potential further spread among humans and animals.

Clinicians should also be alerted to potential zoonotic infection in patients with an exposure history to birds or animals especially in areas where A(H5N1) viruses are known or suspected to be circulating in animals but also in areas where surveillance in animals may be limited.

Routine epidemiologic and virologic surveillance for influenza should be conducted ideally year-round using a standard case definition in healthcare facilities according to WHO guidance. Active case finding around suspected and confirmed human cases is critical to determine if there are additional cases or indications of human-to-human transmission.

Timely sharing of information and sequence data from both the human and animal health sectors from all regions should be improved and continues to be strongly recommended and is critical for rapid joint 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 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.<sup>52</sup> Data pertaining to the risk elements within TIPRA should be generated and shared with WHO.

Procedures to reduce human exposure to birds, livestock, and other mammals infected with or potentially infected with avian and other animal influenza viruses should be implemented to minimize the risk of zoonotic infections. 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.<sup>53</sup>

Those who are exposed to potentially infected animals should have access to, be trained in their use under different environmental conditions, and wear personal protective equipment including eye protection.<sup>54</sup> If they develop respiratory symptoms or conjunctivitis, they should be rapidly tested, 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.<sup>55</sup>

Some manufacturers have initiated production of an A(H5) vaccine that matches current circulating strains. Although a few countries are procuring vaccine to vaccinate occupationally exposed persons, this is not currently being recommended as a global strategy considering the limited number of human infections with A(H5N1) 2.3.4.4b viruses.

Investigations are ongoing to understand the risk to humans from consuming raw/unpasteurized milk contaminated with A(H5N1) virus. Due to the potential health risks from many dangerous zoonotic pathogens, raw/unpasteurized milk consumption should be avoided. FAO and WHO advise

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<sup>52</sup> 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)).

<sup>53</sup> 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>.

<sup>54</sup> 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>.

<sup>55</sup> 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).

consuming pasteurized milk. If pasteurized milk is not available, heating raw milk until it boils makes it safer for consumption.<sup>56</sup>

More information will be available as investigations are actively ongoing in the USA and elsewhere. WHO and GISRS, jointly with FAO, WOAHA and OFFLU 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 joint risk assessments.

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<sup>56</sup> 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](https://www.fao.org/fileadmin/user_upload/livestockgov/documents/CXP_057e.pdf).

