



## Preliminary FAO/OIE/WHO Joint Rapid Risk Assessment Human infection with Influenza A(H3N8), China

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### Background

The Chinese health authority reported an influenza A(H3N8) infection in a 4-year-old boy from Henan Province on 25 April 2022 to the World Health Organization (WHO). No human infection with influenza A(H3N8) virus had been recorded before this case. Genetic analysis of the virus confirmed it is of avian origin. Avian influenza A(H3N8) viruses are commonly found - but not associated with disease - in wild birds [1]; such viruses have also been detected in live poultry markets in Asia [2, 3]. Occasionally, A(H3N8) viruses have been associated with disease in dogs [4], horses [5-7], pigs [8], donkeys [9], and most recently seals [10, 11]. However, the genetic composition of A(H3N8) viruses detected in animals to date is different from that detected in the patient.

### Summary of the assessment of current risk to humans posed by A(H3N8) virus

This is the first reported human infection with avian influenza A(H3N8). The virus detected in the human case is an A(H3N8) avian-origin reassortant that has the PB1, PB2, PA, NP, M, and NS gene segments from Eurasian lineage A(H9N2) poultry viruses. The presence of molecular changes associated with mammalian adaptation in the hemagglutinin (HA) and PB2 warrants close monitoring for other avian-origin reassortant A(H3N8) viruses. Further investigation on the source of the virus, contacts of the patient and environmental sampling is being conducted by China's health authority. While further human infections with A(H3N8) viruses cannot be excluded, the risk is low. The likelihood of sustained human-to-human transmission is also low. Based on the limited information obtained to date, FAO, OIE and WHO will re-assess the risk associated with the virus when more information becomes available.

### Understanding of the virus

#### The human infection

The case involved a 4-year-old boy from Henan Province [12]. He developed fever on 5 April 2022, cough and shortness of breath in the following days and was admitted to the hospital in critical condition on 10 April 2022 with severe pneumonia. On 20 April 2022, the National Influenza Center of the Chinese Center for Disease Control and Prevention tested the specimen sent from Henan province and confirmed the sample contained an influenza A(H3N8) virus with all genes being of avian origin. No other viruses were detected in the respiratory specimen and blood stream bacterial cultures were negative. The case had exposure to chickens kept at home before onset of disease. Clinical observation and sampling of the patient's close contacts were conducted and neither infection nor symptoms of illness were found. Preliminary investigations into the source of exposure of this case have yielded A(H3N8)-positive samples from the chicken coops in the patient's backyard and from live poultry markets in the area.

#### Virology

In the preliminary genetic analysis of the A/Henan/4-14/2022 virus sequence data available in [GISAID](#) showed that in the HA, there is an amino acid (AA) mixture at HA position 228 (G/S) that was found in all three sequences submitted to GISAID (two clinical specimens from 10 April and 14 April and the cell culture isolate from the case). HA 228S is conserved in seasonal A(H3N2) viruses; 228G is conserved in avian A(H3) viruses. In the absence of genetic sequence data from the avian source of the infection, it is unknown if the mutation causing the HA 228G/S

mixture was present in the source or if it emerged during replication in the child. An increase in the proportion of 228S detected between the samples collected on 10 April and 14 April (from 37% to 64%) suggests the causative mutation occurred during the infection potentially resulting in more efficient binding of the virus hemagglutinin to human cellular receptors.

As well as this notable HA residue mixture, there are many other differences between this virus and other mammalian A(H3) viruses; most differences were identified in putative antigenic sites indicating that this virus would be antigenically different from other A(H3) viruses detected in mammals (e.g., humans, swine, equines, dogs and marine mammals).

Phylogenetic relationships of the HA and NA genes to other viruses are shown in **Annex 1, A and B**, respectively and analyses of internal gene identities to closest BLAST hits in GISAID to assess their origin/lineages and presence of molecular markers of mammalian adaptation and drug resistance are shown in **Annex 1, C**.

Virus isolation from the A(H3N8)-positive samples collected in the case's backyard was unsuccessful. Further characterization of A(H3N8)-positive samples from live poultry markets is underway.

### **Geographic distribution in animals**

Wild birds form a large gene pool for influenza type A viruses in nature, such that 16 hemagglutinin (HA or H) [13] and 9 neuraminidase (NA or N) subtypes can be found in this reservoir. During the period 2011 to 2019 Low Pathogenic Avian Influenza (LPAI) A(H3N8) detections in animals (mainly in mallards) have been reported to the OIE by Belgium, Czech Republic, Finland and Hungary. This information has been reported through the OIE Voluntary Report on non-OIE listed diseases in wildlife. While influenza A(H3N8) viruses are occurring widely in wild birds, they can also cause outbreaks in equines, canine and other animal species [4-11, 14-16]. However, no genetic similarity was observed between the human case isolate and previously reported animal A(H3N8) viruses. Nevertheless, novel reassortant A(H3N8) influenza viruses were isolated from drinking water for ducks on a farm and from wild and domestic birds in China [17-22]. Influenza A(H3N8) was also detected in environmental samples from live poultry markets in China in January 2022, although the genetic compositions of these viruses were different from that detected in this human case.

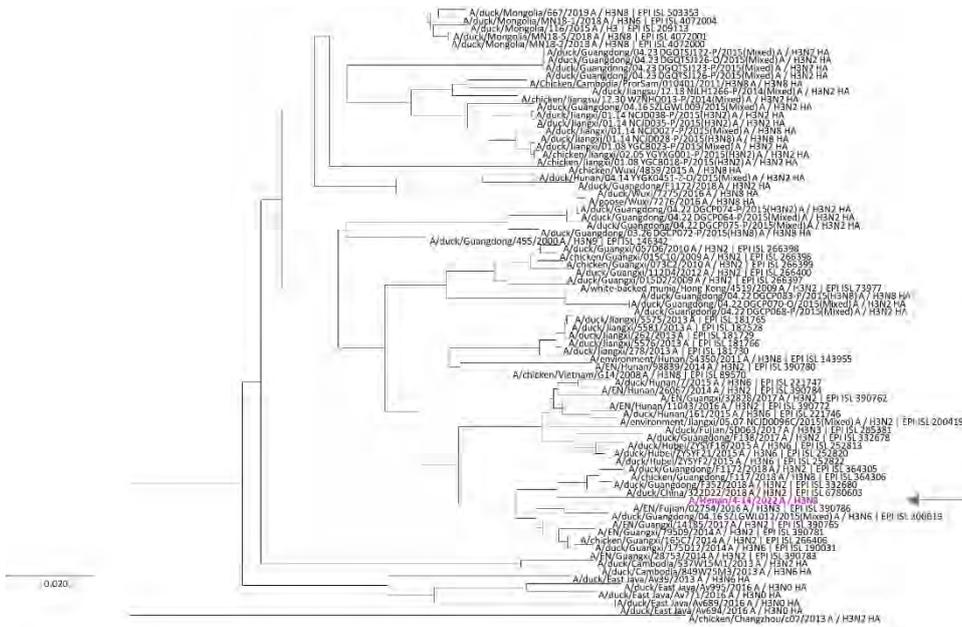
### **Recommended actions**

It is recommended that countries, particularly through National Influenza Centers (NICs) and other influenza laboratories associated with the Global Influenza Surveillance and Response System (GISRS), remain vigilant for the possibility of zoonotic infections. All human samples that are confirmed influenza A-positive but negative for the HAs of seasonal viruses and the HAs of any other subtypes that the laboratory tests for (i.e., un-subtypeable viruses), together with any additional information, should be expedited for shipment to a WHO Collaborating Center or H5 Reference Laboratory of GISRS. Further antigenic characterization of A(H3N8) viruses, notably in relation to similarities with existing Candidate Vaccine Viruses (CVVs), and generation of specific reagents is being prioritized at WHO Collaborating Centers in collaboration with veterinary sector colleagues. Additional data on the prevalence and genetic and antigenic characteristics of A(H3N8) viruses in birds and other animals are of particular importance; see guidance for field research and sampling from FAO [23]. Procedures to reduce human exposure to birds potentially infected with avian influenza viruses should be considered and implemented to minimize the risk of zoonotic infections. [FAO](#), [OIE](#) WHO and [OFFLU](#) are closely working together to monitor the avian influenza situation, including the detection and geographic spread of avian influenza viruses, including A(H3) viruses, and their evolution, and to provide timely updated risk assessments.

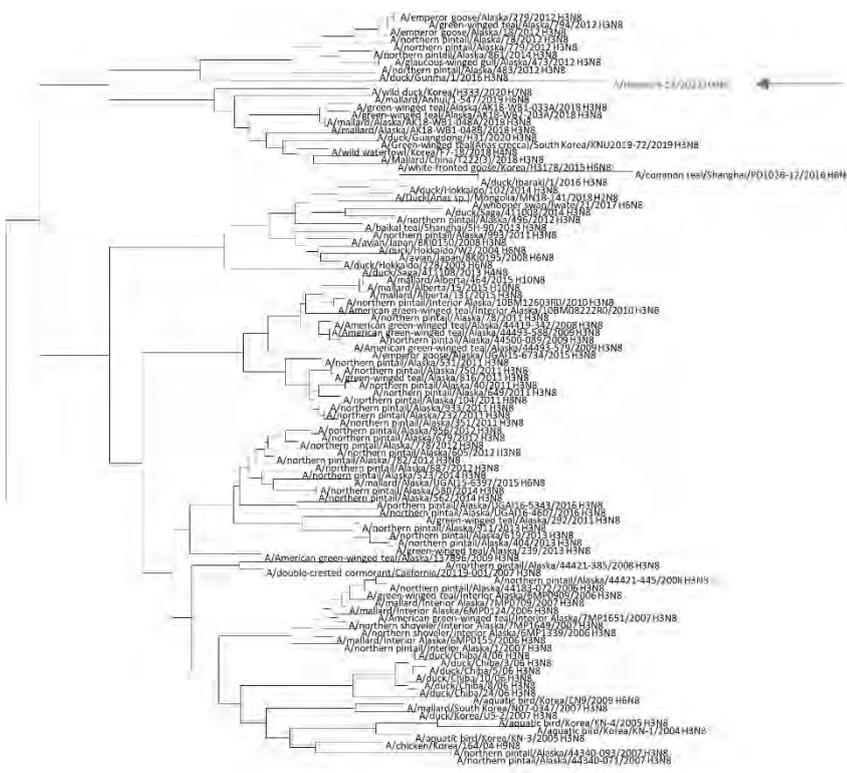
# Annex 1. Phylogenetic trees and genome-wide molecular marker analysis of A/Henan/4-14/2022 A(H3N8)

Phylogenetic trees of the genes encoding influenza surface protein are shown: **A)** Hemagglutinin (H3) from a range of A(H3Nx) viruses; **B)** Neuraminidase (N8) from a range of A(HxN8) viruses. **C)** For all gene products an analysis of amino acid substitutions that may be significant in terms of adaptation to replication in mammals and potential resistance to antivirals is shown.

**A.**



**B.**



**C. Mutation analysis of whole genome**

Protein	Closest sequence in database (Subtype) (% nucleotide identity)	Lineage	AA substitutions to monitor	Previously reported phenotypic effect
HA	A/duck/China/322D22/2018 (H3N2) (99%)	Eurasian avian-lineage found in domestic waterfowl/poultry	228S/G*	228S, increased binding to mammalian alpha 2,6 receptors (and mammalian adaptation)
NA	A/duck/Gunma/1/2016 (H3N8) (98%)	West Pacific/Pacific America Flyway wild bird lineage	Stalk length	Full length stalk (wild bird adapted)
			n/a	No antiviral resistance markers identified, but phenotypic testing to be conducted
PB2	A/Guangdong/00470/2021 (A/H9N2) (98%)	H9N2 Eurasian lineage poultry virus	A588V	Promotes the mammalian adaptation of H10N8, H7N9 and H9N2 avian influenza viruses
			627K	Associated with mammalian adaptation, increased virulence and transmissibility in mammalian animal models
PB1	A/Guangdong/00470/2021 (A/H9N2) (98%)	H9N2 Eurasian lineage poultry virus	n/a	None identified
PA	A/Environment/Jiangsu/zj1055/2021 (H9N2) (99%)	H9N2 Eurasian lineage poultry virus	n/a	No antiviral resistance markers identified, but phenotypic testing to be conducted
NP	A/Fujian-siming/19/2021 (H9N2) (99%)	H9N2 Eurasian lineage poultry virus	n/a	None identified
M1	A/Fujian-siming/19/2021 (H9N2) (99%)	H9N2 Eurasian lineage poultry virus	n/a	None identified
M2			S31N	Adamantane resistance marker identified
NS1	A/Guangdong/00470/2021 (H9N2) (98%)	H9N2 Eurasian lineage poultry virus	P42S	Increased virulence in mice
NS2			n/a	None identified

\*See findings on the mixture at this AA position under the Virology section above.

## References

1. Yoon, S.W., R.J. Webby, and R.G. Webster, *Evolution and ecology of influenza A viruses*. Curr Top Microbiol Immunol, 2014. **385**: p. 359-75.
2. Cui, H., et al., *Phylogenetic analysis and pathogenicity of H3 subtype avian influenza viruses isolated from live poultry markets in China*. Sci Rep, 2016. **6**: p. 27360.
3. Turner, J.C.M., et al., *Distinct but connected avian influenza virus activities in wetlands and live poultry markets in Bangladesh, 2018-2019*. Transbound Emerg Dis, 2022.
4. Crawford, P.C., et al., *Transmission of equine influenza virus to dogs*. Science, 2005. **310**(5747): p. 482-5.
5. Waddell, G.H., M.B. Teigland, and M.M. Sigel, *A NEW INFLUENZA VIRUS ASSOCIATED WITH EQUINE RESPIRATORY DISEASE*. J Am Vet Med Assoc, 1963. **143**: p. 587-90.
6. Baz, M., et al., *A live attenuated equine H3N8 influenza vaccine is highly immunogenic and efficacious in mice and ferrets*. J Virol, 2015. **89**(3): p. 1652-9.
7. Baz, M., et al., *Replication and immunogenicity of swine, equine, and avian h3 subtype influenza viruses in mice and ferrets*. J Virol, 2013. **87**(12): p. 6901-10.
8. Tu, J., et al., *Isolation and molecular characterization of equine H3N8 influenza viruses from pigs in China*. Arch Virol, 2009. **154**(5): p. 887-90.
9. Qi, T., et al., *Isolation and genetic characterization of H3N8 equine influenza virus from donkeys in China*. Vet Microbiol, 2010. **144**(3-4): p. 455-60.
10. Karlsson, E.A., et al., *Respiratory transmission of an avian H3N8 influenza virus isolated from a harbour seal*. Nat Commun, 2014. **5**: p. 4791.
11. Anthony, S.J., et al., *Emergence of fatal avian influenza in New England harbor seals*. mBio, 2012. **3**(4): p. e00166-12.
12. NHC, C. *Occurrence of one H3N8 Avian Influenza human infection case in Henan Province*. <http://www.nhc.gov.cn/yjb/s3578/202204/8dbeadf0efed45b0b2ea22928523e289.shtml>. [Webpage] 2022.
13. Fouchier, R.A., et al., *Characterization of a novel influenza A virus hemagglutinin subtype (H16) obtained from black-headed gulls*. J Virol, 2005. **79**(5): p. 2814-22.
14. Baz, M., et al., *A Single Dose of an Avian H3N8 Influenza Virus Vaccine Is Highly Immunogenic and Efficacious against a Recently Emerged Seal Influenza Virus in Mice and Ferrets*. J Virol, 2015. **89**(13): p. 6907-17.
15. CDC. *Spread of Bird Flu Viruses Between Animals and People*. 2015; Available from: <https://www.cdc.gov/flu/avianflu/virus-transmission.htm>.
16. Solórzano, A., et al., *Cross-Species Infectivity of H3N8 Influenza Virus in an Experimental Infection in Swine*. J Virol, 2015. **89**(22): p. 11190-202.
17. Dong, B.B., et al., *A novel reassortant H3N8 influenza virus isolated from drinking water for duck in a domestic duck farm in Poyang Lake area*. Biomed Environ Sci, 2013. **26**(7): p. 546-51.
18. Li, X., et al., *Co-circulation of H5N6, H3N2, H3N8, and Emergence of Novel Reassortant H3N6 in a Local Community in Hunan Province in China*. Sci Rep, 2016. **6**: p. 25549.
19. Li, Y., et al., *Wild bird-origin H3N8 avian influenza virus exhibit well adaptation in mammalian host*. J Infect, 2022. **84**(4): p. 579-613.
20. Yang, J., et al., *Epidemiological and Genetic Characteristics of the H3 Subtype Avian Influenza Viruses in China*. China CDC Wkly, 2021. **3**(44): p. 929-936.
21. Liu, T., et al., *Genetic Characterization of a Natural Reassortant H3N8 Avian Influenza Virus Isolated from Domestic Geese in Guangxi, Southern China*. Genome Announcements, 2014. **2**(4): p. e00747-14.
22. Pu, J., et al., *Pathogenicity of H3N8 influenza viruses isolated from domestic ducks in chickens with or without Escherichia coli coinfections*. Avian Dis, 2012. **56**(3): p. 597-600.
23. FAO. 2007. Wild Birds and Avian Influenza: an introduction to applied field research and disease sampling techniques. Edited by D. Whitworth, S.H. Newman, T. Mundkur and P. Harris. FAO Animal Production and Health Manual, No. 5. Rome