Food and Agriculture Organization of the United Nations

WORLD ORGANISATION FOR ANIMAL HEALTH

World Health Organization

## Preliminary FAO/OIE/WHO Joint Rapid Risk Assessment

# Human infection with Influenza A(H3N8), China

18 May 2022

## 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.

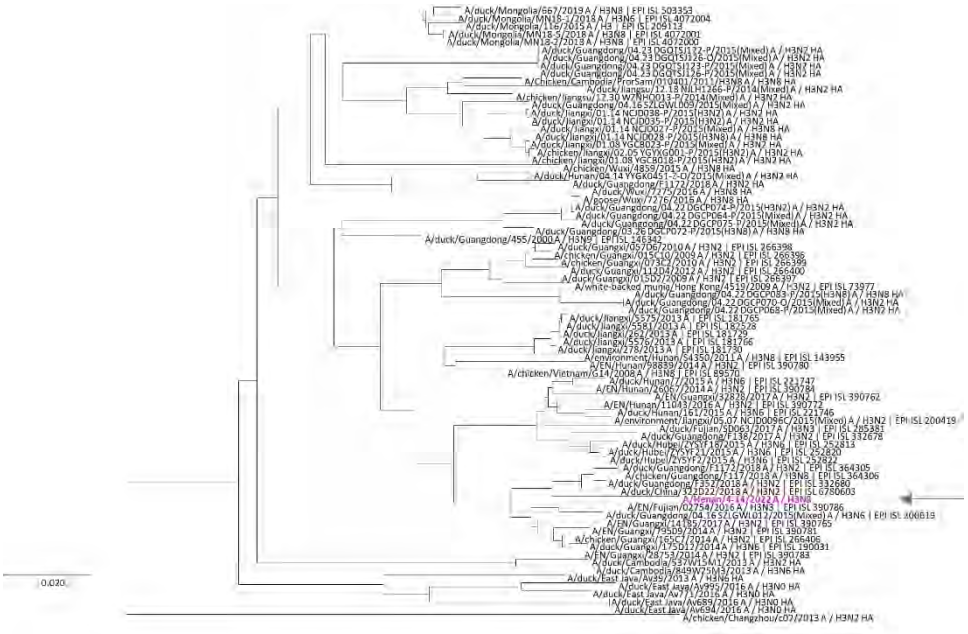
## Recommended actions

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 birds 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.

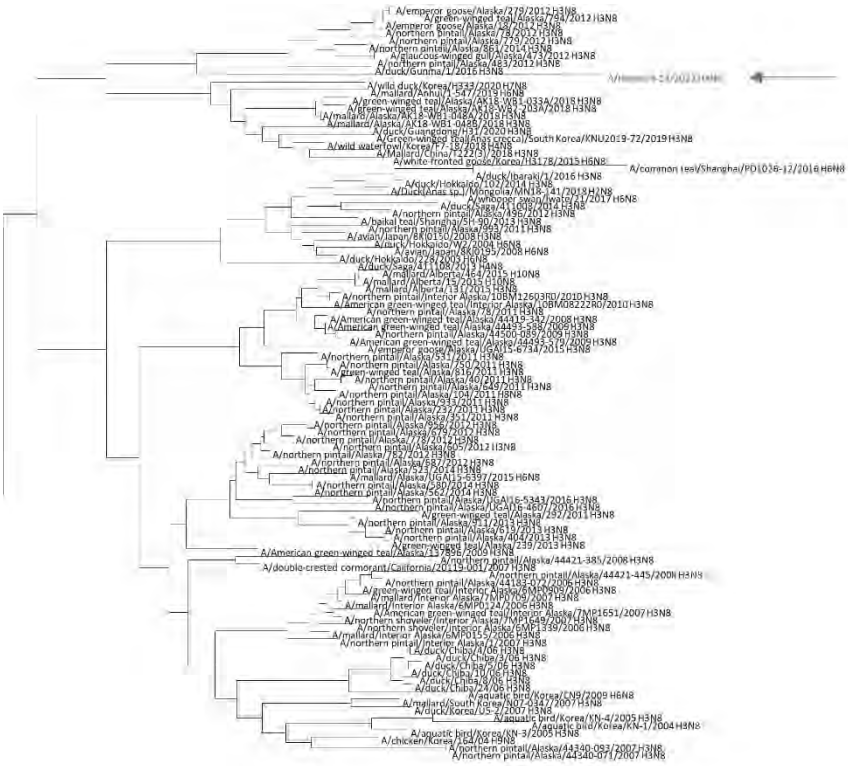
## Annex 1. Phylogenetic trees and genome-wide molecular marker analysis of A/Henan/4-14/2022 A(H3N8)

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.*

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