

Assessment of risk associated with highly pathogenic avian influenza A(H5N6) virus

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Background

Highly pathogenic avian influenza (HPAI) A(H5N6) viruses belonging to the 2.3.4.4b haemagglutinin (HA) genetic lineage have spread in birds in China and some neighbouring countries since at least late 2020. There have been 26 A(H5N6) human infections reported in 2021, 20 of which had illness onset dates after 21 June 2021.

Summary of the assessment of current risk to humans posed by HPAI A(H5N6) virus

The rise in numbers of reported human cases of A(H5N6) infection may reflect the spread of these viruses in poultry, an increased diagnostic capacity and awareness for respiratory illness etiology amongst human health systems. The increased sensitivity of diagnostic systems is a direct outcome from the response to the COVID-19 pandemic. If there is continued circulation of the virus in birds, human infections will continue. It is unclear if the clade 2.3.4.4b A(H5N6) viruses, which were previously identified in a single human case in Fujian Province, China in 2017, have enhanced intrinsic zoonotic potential in comparison to other HPAI A(H5) subtypes and clades that caused human infections in previous years. Although genetic markers known to be associated with mammalian adaptation have been identified sporadically in individual cases following infection, these changes were not present in environmental or poultry viruses and likely reflect intra-host mutations. While the zoonotic threat remains elevated due to possible spread of the viruses in birds, based on evidence available so far, the overall pandemic risk is considered not significantly changed in comparison to previous years. Alleviating the risk to humans largely depends on reducing virus circulation in poultry, minimizing the amount of virus in environments at the human-animal interface (i.e., live bird markets and farms) and mitigating exposure to potentially infected birds.

Understanding of the virus

Human infections

Twenty-six human infections with HPAI A(H5N6) viruses have been reported to WHO in accordance with the International Health Regulation in 2021 (three cases had illness onset dates in 2020). Of the 26 reported cases, 25 by China and 1 by Lao People's Democratic Republic (Lao PDR), 10 were reported as fatal with three individuals still hospitalized at the time of writing. Cases were reported from 6 provinces and 1 municipality in China (1 in Anhui, 3 in Chongqing, 3 in Guangdong, 6 in Guangxi, 1 in Guizhou, 6 in Hunan, 5 in Sichuan) and occurred mainly in adults with a median age of 55 years. The greatest number of cases (6) were reported during August 2021. The single case reported by Lao PDR was in a child <18

years of age; no sequence data are available for the virus. Almost all confirmed cases reported exposure to poultry. Two cases reported in China in August 2021, with approximately 1 week difference in onset date, were in a husband and wife both of whom reported poultry exposure. Although exposure to poultry is the most likely cause, human-to-human transmission cannot be excluded.

Virology

All A(H5N6) viruses sequenced from human cases in China with illness onset after February 2021 were HPAI viruses belonging to HA genetic clade 2.3.4.4b. One case that occurred in February 2021 belonged to clade 2.3.4.4h, which had been commonly detected in birds up to that time. Genetic sequencing of viruses from 11 cases indicated all gene segments to be derived from avian virus lineages, with some gene segments related to previously identified HPAI A(H5N1) and A(H5N8) viruses. Amino acid residues associated with mammalian adaptation were detected in the PB2 genes (E627K and D701D/N) of 2 viruses and 1 virus had an HA1 substitution of Q226L (H3 numbering), which is associated with increased human cell receptor binding. These molecular markers were not identified in viruses collected from environmental surfaces or poultry indicating that these amino acid substitutions occurred sporadically during human infection.

Geographic distribution in animals

The human A(H5N6) viruses from China belong to a sublineage of viruses falling within HA genetic clade 2.3.4.4b. Clade 2.3.4.4b viruses (including A(H5N8) and A(H5N1)) have been found in birds throughout Europe and in some countries of Africa and Asia and they have been associated with human infections in the Russian Federation and Nigeria, although not all viruses from these cases could be sequenced. The HA of recent human A(H5N6) viruses from China are closely related to viruses circulating across Eurasia during the autumn and winter of 2020-21 that were first detected in China in wild birds in late 2020. The clade 2.3.4.4b viruses have become more prevalent in birds in China and neighbouring countries over the past year. Although the extent of clade 2.3.4.4b A(H5N6) virus circulation in birds is unclear, the viruses have been found on environmental surfaces in live poultry markets in China in recent months.

Candidate vaccine viruses

Clade 2.3.4.4b A(H5) [candidate vaccine viruses](#) (CVV) have been developed. This includes [a recommended A\(H5N8\) clade 2.3.4.4b CVV](#) made from A/Astrakhan/3212/2020. The HA of this virus is closely related to the 2021 A(H5N6) human viruses with at most 4 amino acid differences. Antigenic characterization of these and related viruses will be needed to confirm the predicted cross-reactivity of antisera raised against the CVV and the potential impact of a mismatched neuraminidase (NA) between N8 and N6 viruses.

Antiviral susceptibility

No genetic markers known to be associated with reduced susceptibility to clinically relevant antiviral drugs, including those targeting neuraminidase or polymerase, were identified in the recent A(H5N6) viruses causing zoonoses.

Recommended actions

It is recommended that countries, particularly National Influenza Centers 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.,

unsubtypable viruses), together with any that are confirmed as zoonotic events, should be [expedited](#) for shipment to a [WHO Collaborating Center](#) or [H5 Reference Laboratory](#) of GISRS. Further antigenic characterization of A(H5N6) viruses, notably in relation to similarities with existing 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(H5N6) viruses in birds and other animals are of particular importance. Procedures to reduce human exposure to potentially infected birds should be considered and implemented to minimize the risk of additional zoonotic infections.

WHO will continue to work closely with [FAO](#), [OIE](#) and [OFFLU](#) to monitor the avian influenza situation and A(H5) virus evolution and provide timely updated risk assessments.

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