



Rapid Risk Assessment

Assessment of risk associated with recent influenza A(H5N1) clade 2.3.4.4b viruses

Background

During 2020, highly pathogenic avian influenza (HPAI) A(H5N1) clade 2.3.4.4b viruses arose from previously circulating 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 the autumn of 2022. Additionally, there has been an increased spill over to non-avian species including wild terrestrial and marine mammals and, more recently, the detection of an outbreak in a mink farm in Spain. From 2020 to date, six human cases of influenza A(H5N1) belonging to the 2.3.4.4b clade were reported to WHO.

The majority of the influenza A(H5N1) HPAI characterized genetically since 2020 related to these outbreaks are belonging to the 2.3.4.4b clade. This risk assessment focuses on the most recent A(H5N1) viruses belonging to the 2.3.4.4b clade.

Understanding of the virus

Human infections with influenza A(H5N1) 2.3.4.4b viruses

Since the beginning of 2020, detections in humans of influenza A(H5N1) clade 2.3.4.4b viruses have been reported to WHO from the following countries¹: China (one case)[1], Spain (two cases)[2], the United Kingdom of Great Britain and Northern Ireland (one case)[3], the United States of America (USA) (one case)[4], and Viet Nam (one case)[1]. All four human cases reported in Europe and North America were asymptomatic or mild, with only fatigue reported for the case detected in the USA. The case detected in China resulted in a fatality while the case in Viet Nam had severe symptoms but recovered. All human cases had exposure to infected poultry either through participation in response activities to poultry outbreaks or direct exposure to infected poultry in backyard holdings or live bird markets.

Virus sequences from these human cases, where available, did not show markers for mammalian adaptation nor for resistance to neuraminidase inhibitors (such as oseltamivir) or endonuclease inhibitors (such as baloxavir).

Based on the available information for A(H5), although based on limited seroprevalence information available on other A(H5) virus subtypes and clades, human population immunity against the A(H5) clade 2.3.4.4b virus haemagglutinin is expected to be minimal.

Infections in animals

Avian influenza A(H5N1) viruses, especially those in clade 2.3.4.4b, continue to diversify genetically and spread geographically. From 2021 to 2022, Europe and North America have observed their largest and most extended epidemic of avian influenza with unusual persistence of the virus in wild bird populations. A broader range of wild

¹ These cases listed here are those for which A(H5) clade information was available. Additional cases may have been reported but for which the A(H5) clade was determined not to be 2.3.4.4b or where clade information is unavailable.

bird species continue to be infected globally which has significant ecological consequences and has caused mass die offs in some species. Additionally, continuous infection in wild and migratory birds has led to multiple separate incursions in domestic species. These circumstances have led to increased opportunities to generate multiple genotypes with varied clinical signs. Some of the recent viruses have caused severe infections with neurological signs in mammals.[5]

There have been limited reports of transmission between mammals despite the increase in mammalian infections. Affected mammals include badger, black bear, bobcat, coyote, dolphin, ferret, fisher cat, fox, lynx, mink (mink-to-mink in Spanish farm), opossum, otter, pig, polecat, porpoise, raccoon, raccoon dogs, seal (seal-to-seal in USA) and skunk.

Regular monitoring and screening of viral sequences found few sequences with markers of mammalian adaptation. These mutations likely occurred after transmission to the mammalian host and do not seem to transmit onwards. 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 transmission studies, transmission between ferrets did not occur, however some genotypes resulted in severe disease in infected ferrets.[6, 7]

Candidate vaccine viruses

The WHO Global Influenza Surveillance and Response System (GISRS), in collaboration with animal health and veterinary sector colleagues, regularly evaluate candidate vaccine viruses. Clade 2.3.4.4b A(H5) candidate vaccine viruses (CVV) have been developed. This includes a A(H5N8) clade 2.3.4.4b CVV made from A/Astrakhan/3212/2020 as well as a newly recommended A(H5N1) A/chicken/Ghana/AVL-76321VIR7050-39/2021-like virus which is under development. The HA of A/Astrakhan/3212/2020 is closely related to the circulating strains.

Summary of the assessment of current risk to humans posed by influenza A(H5N1) clade 2.3.4.4b viruses

Despite the high number of poultry outbreaks and likely human exposures to the virus at the human-animal-environment interface since 2020, only six A(H5N1) clade 2.3.4.4b virus detections in samples from people directly exposed to infected poultry have been reported. In the four human cases from Europe and North America, the individuals had no symptoms or only mild clinical signs, however the two cases from Asia had severe and fatal outcome. The use of antivirals as part of the treatment of the severe and fatal cases is unknown. Recently, there was an increase in reports of spill over from wild birds to some mammalian species in different countries in Europe and North America. This is likely a result of high prevalence of the virus in avian populations in these regions. There is still limited evidence for mutations associated with adaptation to mammals and humans even when transmission in mammals has been reported. At this juncture, the risk of infection for humans remains low and no sustained human-to-human transmission has been reported.

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.

Recommended actions

As these viruses are constantly evolving and spreading in animal populations, and with an increased risk of exposure for humans, there is an urgent need for increased vigilance and public health actions.

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. Clinicians should also

be alerted to potential zoonotic infection in patients with an exposure history to wild birds or domestic poultry suspected of avian influenza infection.

Rapid sharing of information and sequence data is critical for rapid risk assessment, and 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.

Further antigenic characterization of A(H5N1) viruses, notably in relation to similarities with 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.

Procedures to reduce human exposure to birds and mammals potentially infected with avian influenza viruses should be implemented to minimize the risk of zoonotic infections. This includes warning the public not to touch or collect dead or sick wild animals, but to report them to the local competent authorities. People involved in culling and disposing of infected birds or mammals should be trained on the proper use of appropriate personal protective equipment. All persons involved in these tasks should be registered and monitored closely by local health authorities for seven days following the last day of contact. Where possible, testing of all asymptomatic individuals who had significant contact with infected poultry/mammals or potentially infected environments when unprotected with PPE should be considered. Those who develop respiratory symptoms should be rapidly sampled and precautionary infection control measures should be put in place to prevent further spread among humans. If test results are delayed more than 24 hours, treat with antivirals if there are signs of complications or severe disease, or if the patient belongs to a high-risk group. For detailed guidance on treatment, refer to relevant global and national guidance.[8]

WHO, FAO, WOA and OFFLU (Joint WOA-FAO Scientific Network on Animal Influenza) are working closely together to 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.

References

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