Influenza (Flu)

Human Infection with highly pathogenic avian influenza A(H5N1) virus in Chile

Updated April 17, 2023

This addendum to Technical Report: Highly Pathogenic Avian Influenza A(H5N1) Viruses, originally published on March 17, 2023, provides a summary of the case and the genomic analysis of the virus from the first H5N1 infection reported in a human in Chile. The overall risk to human health associated with the ongoing A(H5N1) outbreaks in wild birds and poultry has not changed and remains low at this time.

On March 29, 2023, Chile reported its first human infection with HPAI A(H5N1) virus. This is the second human case of A(H5N1) ever reported in South America, which includes a January 2023 case reported by Ecuador (1).

The Chilean patient was a 53-year-old man with symptom onset on March 13. He was hospitalized with severe illness and remains in respiratory isolation under multidisciplinary management, with mechanical ventilation due to pneumonia.

After hospital admission on March 22, the patient received antiviral treatment with oseltamivir and antibiotic treatment. HPAI A(H5) was detected in wild birds and sea lions in the Antofagasta region of coastal northern Chile where the patient lived (2). Potential contact of the patient with wild birds, marine mammals and/or environmental exposures remains under investigation. Close contacts of the patient have been asymptomatic and have tested negative for influenza viruses, indicating that no known human-to-human transmission occurred (2).

Viral RNA obtained from a bronchoalveolar lavage specimen from the patient has been sequenced and genetically analyzed by the National Influenza Centre in Chile (Instituto de Salud Pública) and by the Influenza Division/CDC. The virus was identified as having a clade 2.3.4.4b HA and was determined to be the same genotype that has been detected in the majority of wild birds in South America, indicating no evidence for genetic reassortment compared to A(H5N1) viruses predominating in birds in South America. The virus was 99% identical to many viruses identified in A(H5N1) virus-infected wild birds in Chile. Overall, the genomic analysis of the virus in this specimen does not change CDC's risk assessment related to the avian A(H5) clade 2.3.4.4b viruses. The overall risk to human health associated with the ongoing A(H5) outbreaks in wild birds and poultry remains low.

The hemagglutinin (HA) gene codes for one of the two surface glycoproteins and is central to species specificity because it is responsible for virus attachment and fusion with host cells. Analysis of this HA gene shows that it is closely related to avian A(H5) viruses in HA clade 2.3.4.4b and lacked amino acid changes that improve recognition of mammalian receptors or fusion of the viral membrane with the host endosomal membranes. The HA is also the primary target of neutralizing antibodies elicited by infection or vaccination, and the HA of virus from this specimen is very closely related (99% identity) to the A/Astrakhan/3212/2020-like pre-pandemic candidate vaccine viruses (e.g., IDCDC-RG71A (3)) that is available to vaccine manufacturers. There are only three amino acid changes (i.e., L104M, L115Q, V210A) between the HA of the virus from the Chilean case and A/Astrakhan/3212/2020-like candidate vaccine, and they are not in major antigenic epitopes strongly suggesting that antibodies elicited by the A/Astrakhan/3212/2020-like vaccine would be expected to have good cross-reactivity – and therefore protection – against this virus.

The neuraminidase (NA) gene encodes the other surface protein of the virus. The major role of the NA is to release new progeny virions from an infected cell by enzymatically cleaving sialic acid receptors, which aids virus spread to uninfected cells within an infected host. The enzymatic activity of NA is inhibited by one class of antiviral drugs that are FDA-approved for treatment of influenza (i.e., NA inhibitors). Analysis of the N1 NA gene from the Chile specimen showed that it did not have any known or suspected markers of reduced susceptibility to this class of antivirals (i.e., oseltamivir). Furthermore, the NA has

a full-length stalk which is consistent with viruses that naturally circulate in wild birds. In previous A(H5N1) outbreaks and zoonosis the NA stalk region often had deletions (e.g., a 20 amino acid deletion at positions 49–68 relative to A/goose/Guangdong/1/1996) that enhances replication and/or pathogenesis in terrestrial poultry and mice (4-6).

Analysis of the other gene segments (PB2, PB1, PA, NP, M, NS) was also conducted. No known or suspected markers of reduced susceptibility to antiviral compounds that target the PA (i.e., baloxavir marboxil) or M2 (i.e., amantadine, rimantadine) were found.

In addition to the HA and NA, the RNA transcription and replication complex (PB2, PB1, PA, NP) also have species-specific determinants that impact efficient replication in humans and other mammals, particularly polymerase basic protein 2 (PB2). The PB1, PA and NP lacked markers of mammalian adaptation. The PB2 of this specimen had two changes compared to PB2 genes typically found in A(H5N1) viruses circulating in wild birds. A PB2-D701N substitution was found and this is understood to be associated with mammalian adaptation because it improves RNA polymerase activity and replication efficiency in mammalian cells; based on experimental studies in mice, guinea pigs and ferrets, it has the potential to impact pathogenesis or transmission in infected mammals (7-11). PB2 D701N substitution has previously been identified in human cases of A(H5N1) with no evidence of onward transmission among humans (12) as well as in human cases of clade 2.3.4.4b A(H5N6) (13). The other PB2 change was Q591K; this substitution has been less frequently identified and is also associated with enhanced replication efficiency in mammalian cells and increased pathogenesis in experimentally infected mice (14, 15). This change has also been identified in human cases of A(H5N1) in the past. The combination of PB2 substitutions of Q591K and D701N have previously been detected in zoonotic avian A(H7N9) viruses (16). It is important to note that these two substitutions are not typical of closely related PB2 genes in viruses circulating in wild birds or poultry in the surrounding area in Chile, strongly suggesting they were acquired in the patient during the course of illness. Viruses can undergo changes in a host as they replicate after infection, and it is not uncommon or surprising for A(H5N1) viruses to undergo these and other polymerase gene changes in patients who experience prolonged infection and severe illness.

The protein products from the M (M1 and M2) and NS (N1 and N2) genes lacked markers associated with mammalian adaptation. Collectively, epidemiologic, and viral genomic analyses found that this case represents a single zoonotic event and while the HA lacked changes likely to enhance transmission to mammals, it did acquire substitutions in PB2 likely to enhance replication in mammals, which illustrates that we have to remain vigilant and characterize zoonotic viruses.

References:

1. Bruno A, Alfaro-Nunez A, Mora D, Armas R, Olmedo M, Garces J, Munoz-Lopez G, Garcia-Bereguiain MA. 2023. First case of human infection with highly pathogenic H5 avian influenza a virus in South America: a new zoonotic pandemic threat for 2023? J Travel Med doi:10.1093/jtm/taad032.
2. World Health Organization. 2023. Human infection caused by Avian Influenza A (H5) – Chile. . https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON453 . Accessed
3. World Health Organization. 2023. Summary of status of development and availability of A(H5) non–A(H5N1) candidate vaccine viruses and potency testing reagents. https://www.who.int/publications/m/item/a(h5)-non-a(h5n1)—northern-hemisphere-2023-2024 . Accessed
4. Stech O, Veits J, Abdelwhab EM, Wessels U, Mettenleiter TC, Stech J. 2015. The Neuraminidase Stalk Deletion Serves as Major Virulence Determinant of H5N1 Highly Pathogenic Avian Influenza Viruses in Chicken. Sci Rep 5:13493.
5. Naguib MM, Arafa AS, El-Kady MF, Selim AA, Gunalan V, Maurer-Stroh S, Goller KV, Hassan MK, Beer M, Abdelwhab EM, Harder TC. 2015. Evolutionary trajectories and diagnostic challenges of potentially zoonotic avian influenza viruses H5N1 and H9N2 co-circulating in Egypt. Infect Genet Evol 34:278-91.
6. Zhou H, Yu Z, Hu Y, Tu J, Zou W, Peng Y, Zhu J, Li Y, Zhang A, Yu Z, Ye Z, Chen H, Jin M. 2009. The special neuraminidase stalk-motif responsible for increased virulence and pathogenesis of H5N1 influenza A virus. PLoS One 4:e6277.
7. Li Z, Chen H, Jiao P, Deng G, Tian G, Li Y, Hoffmann E, Webster RG, Matsuoka Y, Yu K. 2005. Molecular basis of replication of duck H5N1 influenza viruses in a mammalian mouse model. The Journal of Virology 79:12058-12064.
8. Gabriel G, Abram M, Keiner B, Wagner R, Klenk HD, Stech J. 2007. Differential polymerase activity in avian and mammalian cells determines host range of influenza virus. J Virol 81:9601-4.
9. Steel J, Lowen AC, Mubareka S, Palese P. 2009. Transmission of influenza virus in a mammalian host is increased by PB2 amino acids 627K or 627E/701N. PLoS Pathog 5:e1000252.
10. Gao Y, Zhang Y, Shinya K, Deng G, Jiang Y, Li Z, Guan Y, Tian G, Li Y, Shi J, Liu L, Zeng X, Bu Z, Xia X, Kawaoka Y, Chen H. 2009. Identification of amino acids in HA and PB2 critical for the transmission of H5N1 avian influenza viruses in a

mammalian host. PLoSPathog 5:e1000709.

11. Zhou B, Pearce MB, Li Y, Wang J, Mason RJ, Tumpey TM, Wentworth DE. 2013. Asparagine substitution at PB2 residue 701 enhances the replication, pathogenicity, and transmission of the 2009 pandemic H1N1 influenza A virus. PLoS ONE 8:e67616.
12. Le QM, Ito M, Muramoto Y, Hoang PV, Vuong CD, Sakai-Tagawa Y, Kiso M, Ozawa M, Takano R, Kawaoka Y. 2010. Pathogenicity of highly pathogenic avian H5N1 influenza A viruses isolated from humans between 2003 and 2008 in northern Vietnam. J Gen Virol 91:2485-90.
13. Zhu W, Li X, Dong J, Bo H, Liu J, Yang J, Zhang Y, Wei H, Huang W, Zhao X, Chen T, Yang J, Li Z, Zeng X, Li C, Tang J, Xin L, Gao R, Liu L, Tan M, Shu Y, Yang L, Wang D. 2022. Epidemiologic, Clinical, and Genetic Characteristics of Human Infections with Influenza A(H5N6) Viruses, China. Emerg Infect Dis 28:1332-1344.
14. Yamada S, Hatta M, Staker BL, Watanabe S, Imai M, Shinya K, Sakai-Tagawa Y, Ito M, Ozawa M, Watanabe T, Sakabe S, Li C, Kim JH, Myler PJ, Phan I, Raymond A, Smith E, Stacy R, Nidom CA, Lank SM, Wiseman RW, Bimber BN, O'Connor DH, Neumann G, Stewart LJ, Kawaoka Y. 2010. Biological and structural characterization of a host-adapting amino acid in influenza virus. PLoS Pathog 6:e1001034.
15. Mashaal D, Mahmoud SH, Muller C, Abo Shama NM, Kamer AA, Abdelaziz AA, Ali MA, Pleschka S, Mostafa A. 2022. Differential Impact of Specific Amino Acid Residues on the Characteristics of Avian Influenza Viruses in Mammalian Systems. Pathogens 11.
16. Chen GW, Kuo SM, Yang SL, Gong YN, Hsiao MR, Liu YC, Shih SR, Tsao KC. 2016. Genomic Signatures for Avian H7N9 Viruses Adapting to Humans. PLoS One 11:e0148432.

Acknowledgement:

We thank the National Influenza Center in Chile for their excellent work in identification, response, communication, and sharing of the genomic sequence data in a publicly accessible database.

Last Reviewed: April 17, 2023

Error processing SSI file