

Below is a summary assessment followed by more detailed analysis of virological, epidemiological, genomic, serologic and animal transmission studies to inform influenza A(H5N6) risk assessment.

SUMMARY ASSESSMENT:

Influenza A(H5N6) viruses are one of two A(H5) subtype viruses known to infect humans, the other being A(H5N1). Since 2014, there have been 29 sporadic human infections with A(H5N6) viruses, all of which have been reported from China, including 5 identified most recently in 2020. Average age of cases overall is about 35-40 years with range of 1-81 years. All but three human cases experienced severe illness and 11/29 (38%) are known to have died. All three of the non-severe cases were less than 6 years old, but one of four cases less than 6 years old also died. Nearly 90% of those for whom the investigation was concluded at time of reporting had documented history of exposure to avian species prior to illness onset. The human population is broadly susceptible and the virus has some features suggestive of mammalian adaptation. To date, however, the virus has shown limited ability to infect or transmit in mammalian species with no evidence thus far of human-to-human spread. Nevertheless, H5N6 viruses are an ongoing concern with respect to their pandemic potential. Monitoring of global reports and developments should continue, as should surveillance for unusual or severe presentations of acute respiratory illness in returning travelers notably those with history of poultry contact. Unsubtypeable influenza A viruses despite low Ct values should be investigated.

VIROLOGICAL CHARACTERISTICS

Clade 2.3.4 highly pathogenic avian influenza A(H5) viruses were first identified in China in 2008 and have since further evolved, including into a subgroup called clade 2.3.4.4 to which A(H5N6) and other A(H5Nx) viruses belong. The geographic spread of clade 2.3.4.4 viruses, notably through migratory birds, has been unprecedented. Dispersed clade 2.3.4.4 A(H5) viruses have reassorted with other avian influenza viruses that are enzootic in different regions, acquiring various neuraminidases including N1, N2, N5, N6, and N8. This has resulted in several novel subtypes, including most frequently H5N2, H5N6 and H5N8. Regional epizootics have ensued such as the H5N2 outbreak in poultry in British Columbia in 2014 that also caused widespread outbreaks in commercial poultry flocks mainly in the Pacific, Western and North Central regions of the United States [1,2].

While some clade 2.3.4.4 viruses spread globally (e.g. H5N8), other genetic subgroups of clade 2.3.4.4 have been more limited in their geographic range. Since 2013, influenza A(H5N6) viruses have mostly been maintained among avian species in China, Japan, Lao People's Democratic Republic, Republic of Korea and Vietnam [1,2].

Since 2014 there have been 29 known human cases of influenza A(H5N6) and all have been reported from China [3].

EPIDEMIOLOGICAL CHARACTERISTICS

Time

The first reported case of A(H5N6) had onset in mid-April 2014 (a 49 year old fatal case in a man from Sichuan) [3,4], although in scientific publication there is mention of an earlier case with onset in mid-February 2014 (a 5.5 year old girl from Hunan with mild illness identified through ILI surveillance) [5]. Thereafter, the largest number of human cases by year of illness onset was in 2016 (9 cases), with next largest tallies in 2015 (5 cases) and most recently in 2020 (5 cases). The remaining ten of 29 cases accrued as follows: 2014 (3 cases), 2017 (2 cases), 2018 (4 cases), 2019 (1 case). Most A(H5N6) cases occurred between November and April (22/29; 76%) [3].

Place

Most human cases of A(H5N6) have accrued in the southern part of China. Of the 17 cases between 2014 and 2016, most (7; 35%) were from Guangdong Province and next most from Hunan (4; 24%) with the remainder scattered in Sichuan, Yunnan, Hubei, Anhui and Guangxi Autonomous Region (AR). Of the 7 cases between 2017 and 2019, 3 (43%) were from Guangxi AR, with one each from Fujian, Guangdong and Jiangsu (one unknown region). The five cases in 2020 were scattered with one each in Jiangsu, Hunan, Guizhou, Anhui and Chongqing [3].

Person

Of the 29 known human A(H5N6) infections, sex and age information is available for 28 cases, of which 17 (61%) were female and mean/median age was 39/36 years (range 1-81 years). Of the 24 for which potential source was investigated and concluded at the time of reporting, 22 (88%) had some sort of exposure to avian species including poultry (live or meat), poultry market exposure, or exposure to dead wild birds. All five cases in 2020 are among those with prior poultry market exposure. All but three A(H5N6) cases overall experienced severe illness and 11/29 (38%) are known to have died. All three of the non-severe cases were less than 6 years old, but one of four cases less than 6 years old also died (from 2020) [3].

GENOMIC FEATURES

To date, no clear difference in genetic sequence data for the receptor binding site are found among A(H5N2), A(H5N6), and A(H5N8) viruses to explain why only A(H5N6) viruses are found in humans. Amino acid substitutions and other factors needed to cross the species barrier likely vary and require further investigation [1,2].

The H5N6 virus possesses multiple basic amino acids at the HA cleavage site resulting in its high pathogenicity for chickens. The virus is 226Q and 228G (H3 numbering), suggestive of preferential avian (Sia- α 2,3Gal) over human (Sia- α 2,6Gal) receptor binding; other mutations in the HA protein such as 128P, 137A and 160A may facilitate adaptation and potential infection in mammals. The 160A substitution constitutes a lack of glycosylation motif in combination with residues 158-160. Compared to other clade 2.3.4.4 H5 genes, influenza A(H5N6) possesses an additional single amino acid deletion at position 133 which alters the 3D structure potentially increasing α 2,6 binding affinity [1,2].

Among studies that examined receptor binding specificity of clade 2.3.4.4 A(H5) viruses, 13 isolates including two A(H5N2), seven A(H5N6) and four A(H5N8) viruses had specificity for both α 2,6 and α 2,3 receptors. In general, viruses that exhibited affinity for human type (α 2,6) receptors also maintained high affinity for avian-type (α 2,3) receptors. Most of the 13 viruses with dual receptor specificity had 128P, 137A, and 160A, but not all viruses possessing these amino acids had dual-receptor specificity [1,2].

Human A(H5N6) viruses also bear an 11 amino acid deletion in the neuraminidase stalk (positions 58-68) which is known to be an adaptation to terrestrial poultry and has been associated with enhanced virulence in mice. Amino acid substitutions that confer oseltamivir resistance (H274Y and N294S by N2 numbering) have not been found in human A(H5N6) viruses. Some strains of A(H5N6) from human cases did, however, have the M2 S31N mutation associated with adamantane resistance [1,2].

Various A(H5N6) genotypes contain varying internal genes originating from A(H5N1) and A(H9N2) viruses circulating in poultry as well as A(H3) viruses circulating in ducks. Multiple amino acid substitutions associated with mammalian adaptation have also been found in internal viral proteins [1,2].

TRANSMISSION STUDIES

Airborne or respiratory droplet transmission of clade 2.3.4.4 A(H5N2), A(H5N6) and A(H5N8) viruses has not been demonstrated in any animal model examined (including guinea pig, ferret, pigs or dogs), which is consistent with the epidemiology showing no evidence of human-to-human spread [1,2].

SERO-SUSCEPTIBILITY

In a study involving 523 farmers exposed to poultry during the 2016-2017 Republic of Korea A(H5N6) outbreaks, no evidence of infection (sero-positivity) was found based on micro-neutralization assay [6]. Conversely, hemagglutination inhibition titres greater than 20 against an A(H5N8) virus were found among 61 of 760 (8%) sera from poultry farmers in the Russian Federation [7]. No reactivity against A(H5N1) antigens was found before or after the A(H1N1)pdm09 pandemic in 6896 sera collected from 11 countries in Asia, Europe and North America using an HA protein microarray [8]. These data indicate broad population susceptibility in the event A(H5N6) viruses adapt to the human host.

REFERENCES

1. Yamaji R, Saad MD, Davis CT, et al. Pandemic potential of highly pathogenic avian influenza clade 2.3.4.4 A(H5) viruses. *Rev Med Virol* 2020;30:e2099
2. Bonilla-Aldana DK, Aguirre-Florez M, Villamizar-Pena R, et al. After SARS-CoV-2, will H5N6 and other influenza viruses follow the pandemic path? *Le Infezioni in Medicina* 2020;4:475-485
3. World Health Organization. Influenza. Monthly Risk Assessment Summary. Accessed: 4 February 2021. Available: https://www.who.int/influenza/human_animal_interface/HAI_Risk_Assessment/en/
4. Pan M, Gao R, Lv Q, et al. Human infection with a novel, highly pathogenic avian influenza A(H5N6) virus : virological and clinical findings. *J Infect* 2016;72:52-59.
5. Chen T, Zhang R. Symptoms seem to be mild in children infected with avian influenza A(H5N6) and other subtypes. *J Infect* 2015. Accessed 4 February 2021. Available: <http://dx.doi.org/10.1016/j.jinf.2015.09.004>
6. Ryu S, Kim CK, Kim K, et al. Serosurveillance of avian influenza A/H5N6 virus infection in poultry farmers. Gyeonggi Province, Republic of Korea, 2016-2017. *Int J Infect Dis* 2018;75:49-51.
7. Ilyicheva TN, Durymanov AG, Svyatchenko SV, et al. Humoral immunity to influenza in an at-risk population and severe influenza cases in Russia in 2016-2017. *Arch Virol* 2018;163:2675-85.
8. Freidl GS, van den Ham HJ, Boni MF, et al. Changes in heterosubtypic antibody responses during the first year of the 2009 A(H1N1) influenza pandemic. *Sci Rep* 2016;6:20385

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