

Below is a summary assessment related to influenza A(H5N6), a highly pathogenic avian influenza (HPAI) virus that has caused sporadic but very severe infections in humans with a high per case fatality risk.

Following our last bulletin related to influenza A(H5N6) on February 5, 2021, there has been a further accumulation of cases, with the highest number of cases to date since 2014 now having accrued in 2021.

Summary assessment is followed by more detailed analyses of virological, epidemiological, genomic, serologic, and animal transmission studies.

SUMMARY ASSESSMENT, INFLUENZA A(H5N6):

- 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 53 sporadic human infections with A(H5N6) viruses, the majority (52; 98%) reported from China and one from Laos.
- Of the 53 detections in total, 23 (43%) accrued in 2021 alone, a tally that is two and a half times the next highest annual tally accrued in 2016 (n=9).
- Mean age of cases overall is 42 years (range: 1-81 years), with 8 pediatric cases <20 years of age. All but three human cases experienced severe illness and at least 26 (49%) are known to have died, three of whom were children.
- Exposure to avian species including poultry (live or meat), poultry market exposure, or exposure to dead wild birds was reported in 45 (85%) of cases, while the exposure of the remaining cases remained under investigation or was not yet clear at time of reporting.
- 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. Non-subtypeable influenza A viruses despite low Ct values should be investigated.

VIROLOGICAL CHARACTERISTICS

Clade 2.3.4 highly pathogenic avian influenza (HPAI) 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).

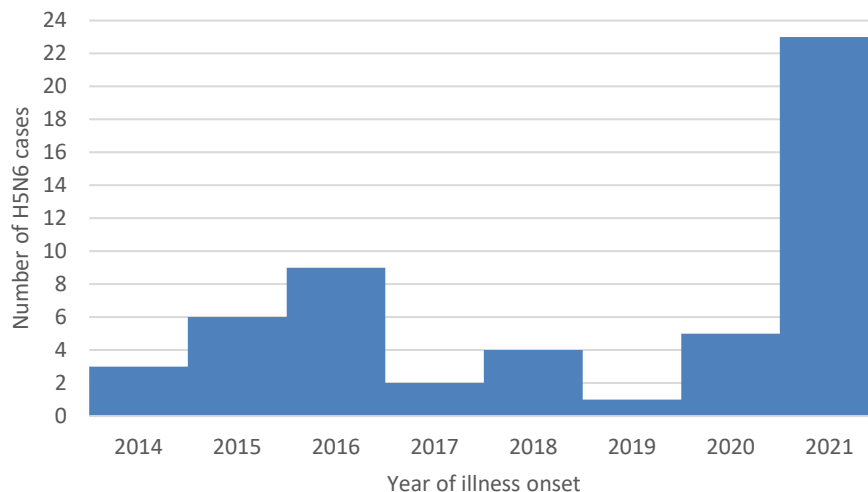
Since 2014 there have been 53 known human cases of influenza A(H5N6) and all have been reported from Asia (3–21).

EPIDEMIOLOGICAL CHARACTERISTICS

Time

Since 2014, a total of 53 human cases infected with influenza A(H5N6) have been reported through World Health Organization (WHO) bulletins, official statements, and news releases (5–8,10–21) or the scientific literature (3,4,9) (Figure 1). Of those, 23 (43%) had earliest illness onset dates in 2021 alone. Thereafter, the largest number of human cases based on year of illness onset was in 2016 (9 cases; 17%), with next largest tallies in 2015 (6 cases; 11%) and most recently in 2020 (5 cases; 9%). The remaining ten of the 53 cases accrued as follows: 2014 (3 cases), 2017 (2 cases), 2018 (4 cases), and 2019 (1 case). Whereas prior to the 2020/2021 COVID-19 pandemic, most A(H5N6) cases had onset dates during the typical November-April influenza season, reports to date inclusive of the 2021 tally show a slightly higher number of cases with onset dates between May and October (29/53; 55%), compared to November and April (24/53; 45%) (3–21).

Figure 1: Distribution of influenza A(H5N6) cases by year (n=53):



Place

All human cases of A(H5N6) were reported from China, except for one case that was reported from Laos in 2021 (Figure 2). Cases reported from China (n=52) mostly accrued in Southern China, with only one case reported from Beijing in 2019. The cases in Southern China (n=51) had onset of illness from Guangdong Province (12 cases; 23%), Hunan Province (11 cases; 21%), Guangxi Zhuang Autonomous Region (AR) (10 cases; 19%), Sichuan Province (6 cases; 12%), Chongqing Province (3 cases; 6%), two cases from each of Yunnan, Jiangsu, and Anhui Provinces (4% from each province), and one from each of Fujian, Guizhou, and Hubei Provinces (2% from each province). In 2021, cases in China (n=22) were mainly reported from Hunan Province (6 cases; 27%), Guangxi Zhuang AR (6 cases; 27%), Sichuan Province (5 cases; 23%), Guangdong Provinces (3 cases; 14%) and two cases from Chongqing Province (9%). No cases have been reported in Canadian residents to date (3–21).

Figure 2: Geographic distribution of influenza A(H5N6) cases (n=53):



Person

Of the 53 known human A(H5N6) infections, 29 (55%) were female and mean/median age was 42/49 years (range 1-81 years). A total of eight were pediatric cases <20 years of age, 5 (63%) of whom were hospitalized; in contrast, all adult cases reported (n=45) were hospitalized. At least 26 (49%) cases have died since 2014, involving all age groups, including three children. Exposure to avian species including poultry (live or meat), poultry market exposure, or exposure to dead wild birds was reported in 45 (85%) of cases, while the exposure of the remaining cases remained under investigation or was not yet clear at time of reporting. All cases in 2021 were among those with prior poultry exposure, with exception of one case where exposure was unclear (3–21).

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). More recent investigation of the tropism of five recent HPAI A(H5N6/H5N8) avian isolates of clades 2.3.4.4 in human airway organoids and human alveolar epithelial cells also suggests zoonotic potential but low transmissibility of these avian isolates among humans (22).

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 (23). 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 (24). 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 (25). These data indicate broad population susceptibility in the event A(H5N6) viruses adapt to the human host.

HIGHLY PATHOGENIC AVIAN INFLUENZA IN ANIMALS

Since late 2019, there has been a significant increase in HPAI avian events in Asia and Europe, and a small increase in HPAI reports from Africa. The most frequent subtypes of HPAI animal events in Asia between January 1, 2020, and June 30, 2021 were A(H5N8), A(H5N6) and A(H5N5). There has been an increase in HPAI events in domestic poultry in Vietnam (59 H5N6 events) and in wild birds in China (9 H5N6 events) between Oct 1, 2020, and Sept 29, 2021 (26). There were also 2 H5N6 wild swan events in Mongolia in April 2020 (27). Although Europe is experiencing the largest epidemic of HPAI on record, with the H5N8 subtype accounting for the large majority of detections, followed by H5N1, no H5N6 has been detected in Europe between Oct 1, 2019, to Sept 15, 2021 (28). A close relation of the HA gene found in three viral isolates from human cases of H5N6 in China has been found in the H5 viruses circulating in birds in Europe and Asia (28).

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