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Influenza Risk Assessment Tool (IRAT) - Virus Report

Prepared by the CDC Influenza Division

Highly pathogenic avian influenza A(H5N8) virus; clade 2.3.4.4b

Virus Strain: A/Astrakhan/3212/2020

Date of Evaluation: March 2021

Introduction

Human infections with influenza A viruses that commonly circulate in animals are rare and the risk of such infections to humans is generally low [1]. Sporadic human infections with animal influenza A viruses do occur, but typically in situations where individuals are exposed to infected animals through direct or indirect contact or to a virus-contaminated environment. The Influenza Risk Assessment Tool (IRAT) [2] is used to examine multiple attributes of influenza A viruses that circulate in animals but have not gained the ability to spread by human-to-human transmission, and to assess the potential of these viruses to acquire this ability and the consequent potential public health impact.

Situation

The first human infection with genetic clade 2.3.4.4b A(H5N8) highly pathogenic avian influenza viruses (AIV), was reported in the Russian Federation in February 2021. Of the seven persons detected with A(H5) virus, one infection was confirmed with AIV A(H5N8) clade 2.3.4.4b, and all had reported exposure to layer hens infected with the same subtype and clade during a poultry farm outbreak in December 2020 [3,4]. All A(H5N8) human cases remained asymptomatic. The virus was isolated from one of the human cases and its whole genome sequence was submitted to the GISAID database.

Avian influenza A(H5) viruses of the A/goose/Guangdong/1/96-lineage have spread from Asia to Europe through wild birds since 2004 [3]. Clade 2.3.4.4 A(H5) viruses have reassorted with other AIVs, resulting in multiple A(H5) virus subtypes and genotypes detected in Asia, the Middle East, Europe, and Africa [3,5,6]. AIV A(H5N8) clade 2.3.4.4 was identified in the Russian Federation for the first time in 2014, with clade 2.3.4.4b detected in wild birds as early as 2017.

The AIV A(H5N8) clade 2.3.4.4b virus isolated from the human case (A/Astrakhan/3212/2020) and those from the poultry outbreaks in the Russian Federation were closely related to other clade 2.3.4.4b viruses detected in poultry and wild birds in other parts of Eurasia from October 2020 to February 2021 [4]. Analyses indicate that AIV A(H5N8) clade 2.3.4.4b has maintained the characteristics typical of viruses adapted to avian species [7]. The hemagglutinin (HA) of A/Astrakhan/3212/2020 differed by no more than 3 amino acids from the A(H5N6) A/Fujian-Sanyuan/21099/2017 candidate vaccine virus (CVV) and the majority of viruses detected in birds in the Russian Federation during 2016, 2017, and 2018. These poultry viruses reacted well with post-infection ferret antisera raised against the A/Fujian-Sanyuan/21099/2017 CVV [4].

Using the IRAT, the Centers for Disease Control and Prevention (CDC) assessed the pandemic potential of HA clade 2.3.4.4b, AIV A(H5N8) and the representative virus, A/Astrakhan/3212/2020.

IRAT Evaluation

Influenza subject matter experts (SMEs) from CDC, Food and Drug Administration, Animal and Plant Health Inspection Service, Agricultural Research Service, and Department of Defense were asked to evaluate the clade 2.3.4.4b, AIV A(H5N8) representative virus, A/Astrakhan/3212/2020, using the ten risk elements defined in the IRAT. Each SME scored 1 to 3 elements based on their areas of expertise. The point estimate scores for each risk element, which can range from 1 to 10, were averaged, multiplied by predetermined weights, and summed to give an aggregate score for each of the two IRAT risk questions related to potential risk for emergence in humans and potential public health impact if the virus gained the ability to spread efficiently between humans [2].

The overall estimated IRAT scores placed this virus in the lower to middle range of the moderate risk category, (which ranges from 4.0 to 7.9). The average risk score for the estimated potential emergence of the virus to achieve sustained human-to-human transmission was 4.6, in the lower range of the moderate risk category (Table 1). The average risk score for the virus to potentially impact public health if it were to achieve sustained human-to-human transmission was 5.2, in the lower to middle range of the moderate risk category (Table 2). The impact refers to the severity and burden of disease.

The average confidence level in the available data of all 10 risk elements was 2.1 (range: 1.0,3.2). The scores for this virus for emergence and for public health impact were ranked twelfth when compared to the other twenty viruses scored with the IRAT to date.

Slight variability was seen among SME point estimate scores in the risk element of Transmission in Animal Models, where the scores ranged from low to moderate risk, indicating some differences in interpretation of the available data. A sensitivity analysis using the lowest and highest scores for Transmission in Animal Models from SMEs resulted in an adjusted range of 4.5 – 4.8 for the overall emergence risk and 5.2 – 5.2 for potential impact, indicating that the categorization of A/Astrakhan/3212/2020 as moderate risk was unchanged by the range of Transmission in Animal Models scores.

Table 1: Estimated Risk of Emergence

Risk Element	Weight (W)	Risk Score (RS)	W X RS
Human Infections	0.2929	4.40	1.29
Transmission in Animal Models	0.1929	3.00	0.58
Receptor Binding	0.1429	2.75	0.39
Population Immunity	0.1096	9.00	0.99
Infections in Animals	0.0846	5.40	0.46
Genomic Analysis	0.0646	4.40	0.28
Antigenic Relatedness	0.0479	5.00	0.24
Global Distribution in Animals	0.0336	8.20	0.28
Disease Severity and Pathogenesis	0.0211	5.00	0.11
Antiviral Treatment Options	0.0100	2.00	0.02
TOTAL	**1.0001**		**4.63**

Table 2: Estimated Potential Public Health Impact Risk

Risk Element	Weight (W)	Risk Score (RS)	W X RS
Disease Severity and Pathogenesis	0.2929	5.00	1.46
Population Immunity	0.1929	9.00	1.74
Human Infections	0.1429	4.40	0.63
Antiviral Treatment Options	0.1096	2.00	0.22
Antigenic Relatedness	0.0846	5.00	0.42
Receptor Binding	0.0646	2.75	0.18
Genomic Analysis	0.0479	4.40	0.21
Transmission in Animal Models	0.0336	3.00	0.10
Global Distribution in Animals	0.0211	8.20	0.17
Infections in Animals	0.0100	5.40	0.05
TOTAL	**1.0001**		**5.19**

Individual Risk Element Summaries

Human Infections: Isolated occurrence of human infections in the Russian Federation has been reported, all with epidemiologic links to a specific poultry exposure event. There are no reports of human-to-human transmission. Together, these criteria meet the definition of moderate risk to humans.

Transmission in Animal Models: There is limited and inconsistent evidence of transmission in accepted mammalian models of human transmissibility, such as the ferret. A representative clade 2.3.4.4b A(H5N8) virus exhibited inefficient direct contact transmission in co-housed animals with detection in 1 of 3 ferret pairs. Other studies have shown a similar lack of contact or respiratory droplet transmission in ferrets. Together, these data indicate low risk to humans.

Receptor Binding: A/Astrakhan/3212/2020 and other clade 2.3.4.4b avian influenza A(H5N8) viruses have avian-like receptor binding specificity (i.e., binding to α2,3 galactose-linked sialic acids) with no evidence of adaptation to mammals. Also, sequence analysis of A/Astrakhan/3212/2020 indicated the HA retained an avian-like receptor binding site. Together, these data indicate low risk to humans.

Population Immunity: Data suggest that the pre-existing human population immunity to this virus is low (<10%). Numerous serosurveys suggest a low level of pre-existing immunity in the general population to A(H5Nx) viruses, including A(H5N8) and other clade 2.3.4.4b viruses closely related to A/Astrakhan/3212/2020. Together, these data indicate high risk to humans.

Infections in Animals: Clade 2.3.4.4b A(H5N8) AIV has exhibited sustained transmission and disease in several wild bird species and infected and caused continuous disease outbreaks in poultry in numerous geographic regions globally. In addition, limited infections in wild mammals and in humans have been identified. There is increased risk potential due to greater transmission within and between multiple bird species, including species with close human contact. Together, these data indicate moderate risk to humans.

Genomic Analysis: The A(H5N8) clade 2.3.4.4b viruses include multiple lineages with internal genes from various avian influenza A viruses from similar hosts, indicating reassortment with similar subtypes. In

addition to having the highly pathogenic avian influenza A virus multibasic cleavage site, there were some molecular signatures noted in the neuraminidase (NA) and internal genes, which may impact mammalian adaptation and virulence. Together, these data indicate moderate risk to humans.

Antigenic Relatedness: Similar to other A(H5N8) AIVs, clade 2.3.4.4b showed a lack of antigenic relatedness to seasonal influenza viruses. However, the HA of A/Astrakhan/3212/2020 differed by no more than 3 amino acids from the A(H5N6) A/Fujian-Sanyuan/21099/2017 CVV. Genetically related poultry viruses reacted well with post-infection ferret antisera raised against the A/Fujian-Sanyuan/21099/2017 CVV. Despite HA similarity to this A(H5N6) CVV, the N8 NA is unique compared to this and other clade 2.3.4.4 CVVs. Together, these data indicate moderate risk to humans.

Global Distribution in Animals: Distribution of the A(H5N8) clade 2.3.4.4b virus is in multiple geographic regions and new areas including in Asia, the Middle East, Europe, and Africa, and without clearly defined boundaries. Movement may be partially explained by repeated introductions by wild bird migratory patterns and likely also by domestic poultry movement due to commerce. Control of the virus through management efforts in affected poultry populations does not appear to effectively contain the virus in all regions. Together, these data indicate a high risk to humans.

Disease Severity and Pathogenesis: Human infection with A/Astrakhan/3212/2020 was reported as asymptomatic. Related clade 2.3.4.4 HPAI A(H5N8) viruses cause disease in experimentally infected mice and ferrets. Together, these data indicate moderate risk to humans.

Antivirals and Treatment Options: For A/Astrakhan/3212/2020, there is no evidence of reduced susceptibility to any of the antiviral medications approved for human use. However, a few of the AIV A(H5N8) clade 2.3.4.4b virus sequences have a single marker of resistance to M2 blockers, and amino acid substitutions in the polymerase gene that may slightly reduce susceptibility to baloxavir. Together these data indicate low risk to humans.

Comparison to other Viruses Scored with IRAT

The scores for the emergence risk and potential public health impact risk for the A/Astrakhan/3212/2020 virus were plotted along with a selection of 11 other influenza viruses scored using the IRAT (Figure). The estimate for A/Astrakhan/3212/2020 virus was in the lower moderate risk range for both risk of emergence and potential impact. The scores for emergence and for public health impact for this virus ranked twelfth when compared to the other twenty viruses scored on the IRAT to date.

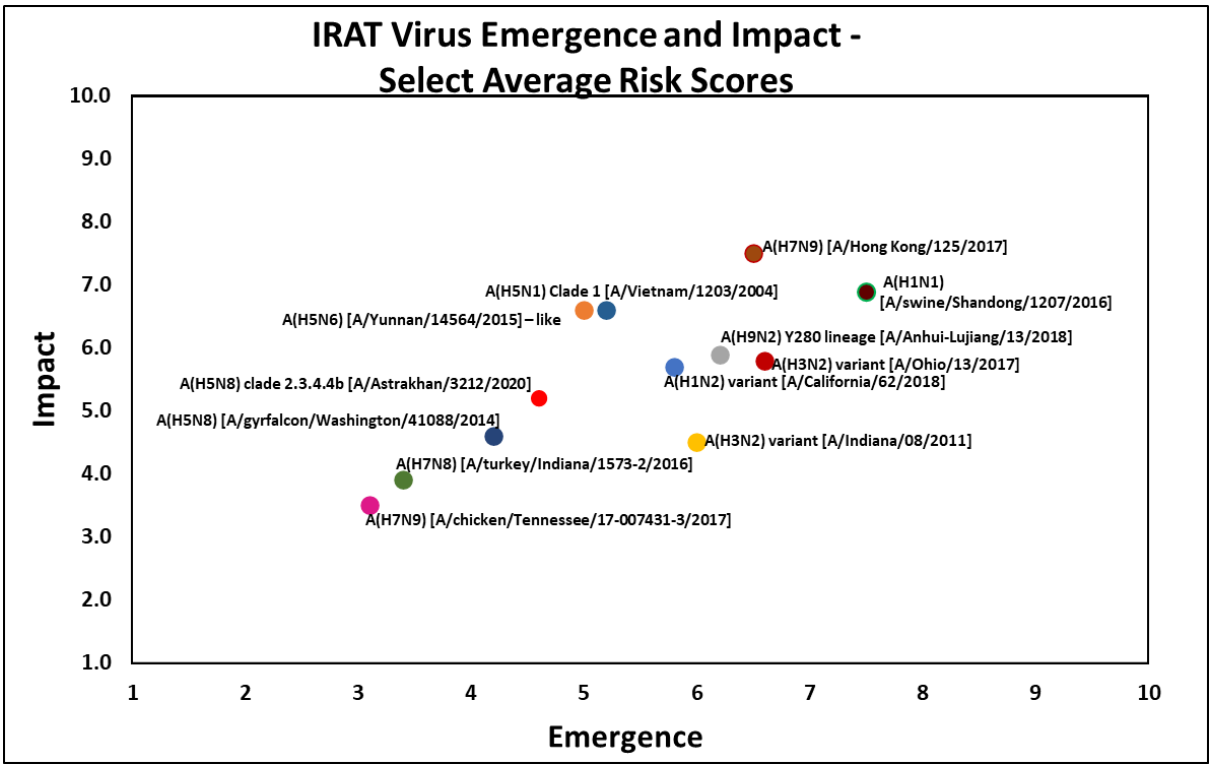

Figure: Average IRAT scores for the A/Astrakhan/3212/2020 virus plotted by emergence score and impact score. Additional select viruses scored using IRAT are displayed for comparison.

Note: IRAT results were generated using information and data known to influenza subject matter experts at the time of the evaluation. Subsequent findings may raise or lower the overall risk scores associated with the virus.

References

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