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Influenza Risk Assessment Tool (IRAT) - Virus Report

Prepared by the CDC Influenza Division

Highly pathogenic avian influenza A(H5N1) virus; clade 2.3.4.4b

Virus Strain: A/American wigeon/South Carolina/AH0195145/2021

Date of Evaluation: March 2022

Introduction

Human infections with influenza A viruses that commonly circulate among animals are rare, and the likelihood of sustained human-to-human transmission of these viruses remains low [1,2]. Sporadic human infections with animal influenza A viruses do occur but typically in situations where individuals are exposed to infected animals through direct or close indirect contact or to a virus-contaminated environment. The Influenza Risk Assessment Tool (IRAT) [3] is used to examine multiple attributes of influenza A viruses that circulate among 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

Since January 2022, highly pathogenic avian influenza A(H5N1) virus (AIV) clade 2.3.4.4b has been detected in the United States in numerous wild bird species, including aquatic birds such as ducks, and in commercial and backyard domestic poultry in numerous states [4].

The A(H5N1) clade 2.3.4.4b virus emerged in 2020, spreading across Europe, Asia, and Africa, in both wild aquatic birds and domestic poultry, and replacing the previously circulating A(H5N8) clade 2.3.4.4b viruses by 2021 [5]. In 2022, the virus has been detected in more than 50 countries in these three regions, and was first reported in migrating wild aquatic birds in the Americas in December 2021. First detections in the United States also were from migratory wild aquatic birds [6,7].

In January 2022, one asymptomatic human infection with this virus, with known repeated exposure to infected ducks in England, was reported to the World Health Organization [8,9].

Phylogenetic analysis of A(H5N1) clade 2.3.4.4b viruses show high levels of genetic similarity to previously circulating A(H5Nx) clade 2.3.4.4b viruses, with little to no evidence of mammalian adaptation [10]. The hemagglutinin (HA) genes of circulating wild bird and poultry viruses show a high level of genetic similarity, with some genetic variability noted among the neuraminidase (NA) gene, which is wild bird adapted [5,7].

Previously recommended A(H5) candidate vaccine viruses (CVVs) are expected to be effective against A(H5N1) viruses currently circulating among wild birds and poultry. In addition, A(H5N1) virus genetic and phenotypic analysis suggests that they remain susceptible to available influenza antiviral medications [11,12].

Using the IRAT, the Centers for Disease Control and Prevention (CDC) assessed the pandemic potential of HA clade 2.3.4.4b, AIV A(H5N1) viruses using A/American wigeon/South Carolina/AH0195145/2021 as the prototype strain.

IRAT Evaluation

Influenza subject matter experts (SMEs) from CDC, the Food and Drug Administration, and Agricultural Research Service were asked to evaluate these A(H5N1) clade 2.3.4.4b viruses including the prototype virus, A/American wigeon/South Carolina/AH0195145/2021, 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 totaled to give an aggregate weighted score for each of the two IRAT risk questions related to 1) potential risk for emergence of the virus to achieve sustained human-to-human transmission and 2) potential public health impact if the virus gained the ability to spread efficiently between humans [3]. The impact refers to the severity and burden of disease.

The overall estimated IRAT scores placed this virus in the moderate risk category, which ranges from 4.0 to 7.9. The average risk score for the estimated potential emergence of the virus was 4.4, in the lower range of the moderate risk category (Table 1). The average risk score for the virus to potentially impact public health was 5.1, also in the lower range of the moderate risk category (Table 2). The average SME confidence level in the available data of all 10 risk elements was 2.4 (range: 1.0-3.0) out of a possible confidence level of 0-4.

Some variation was seen among SME point estimate scores in the risk element Disease Severity and Pathogenesis, where the scores ranged from low to high risk, indicating some uncertainties in interpretation and confidence of the limited available data.

A sensitivity analysis using the lowest and highest scores for this risk element resulted in adjusted ranges for the overall emergence risk and for the potential impact risk that continued to place this virus in the low range of the moderate risk category, indicating that the categorization of A(H5N1) clade 2.3.4.4b virus including A/American wigeon/South Carolina/AH0195145/2021 as moderate risk was unchanged by the range of scores within the Disease Severity and Pathogenesis risk element exhibiting variability.

Table 1: Estimated Weighted Risk of Potential Emergence[1]

Risk Element	Weight (W)	Risk Score (RS)	W X RS
Human Infections	0.2929	4.20	1.23
Transmission in Animal Models	0.1929	1.80	0.35
Receptor Binding	0.1429	3.00	0.43
Population Immunity	0.1096	9.25	1.01
Infections in Animals	0.0846	6.00	0.51
Genomic Analysis	0.0646	4.20	0.27
Antigenic Relatedness	0.0479	4.80	0.23
Global Distribution in Animals	0.0336	8.60	0.29
Disease Severity and Pathogenesis	0.0211	4.67	0.10
Antiviral Treatment Options	0.0100	2.00	0.02
TOTAL	**1.0001**		**4.44**

Table 2: Estimated Weighted Risk of Potential Public Health Impact[1]

Risk Element	Weight (W)	Risk Score (RS)	W X RS
Disease Severity and Pathogenesis	0.2929	4.67	1.37
Population Immunity	0.1929	9.25	1.78
Human Infections	0.1429	4.20	0.60
Antiviral Treatment Options	0.1096	2.00	0.22
Antigenic Relatedness	0.0846	4.80	0.41
Receptor Binding	0.0646	3.00	0.19
Genomic Analysis	0.0479	4.20	0.20
Transmission in Animal Models	0.0336	1.80	0.06
Global Distribution in Animals	0.0211	8.60	0.18
Infections in Animals	0.0100	6.00	0.06
TOTAL	**1.0001**		**5.07**

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Individual Risk Element Summaries

Human Infections: A single asymptomatic human infection with A(H5N1) clade 2.3.4.4b virus from the United Kingdom was reported in 2022, having direct and prolonged exposure to A(H5N1) clade 2.3.4.4b virus infected ducks. There were no reports of human-to-human transmission.

Transmission in Animal Models: In the ferret model, the A/American wigeon/South Carolina/AH0195145/2021 A(H5N1) virus exhibited no transmission in either the direct contact or respiratory droplet transmission models. Multiple studies on A(H5Nx) clade 2.3.4.4 viruses have reported inconsistent evidence of direct contact transmission and no respiratory droplet transmission among ferret, mice, and guinea pig models.

Receptor Binding: The sequence analysis of this A/American wigeon/South Carolina/AH0195145/2021 A(H5N1) virus indicates the hemagglutinin to possess an avian-like receptor binding site. With no hemagglutinin substitutions conferring predominant α2,6–linked sialic acid binding; that is, very little binding to human-like receptors. This indicates these A(H5N1) viruses have the typical avian-like pocket in the receptor binding site and predominantly bind α2,3-linked sialic acid.

Population Immunity: There is little evidence for population immunity against A(H5N1) clade 2.3.4.4b viruses. Numerous seroprevalence surveys for A(H5Nx) viruses have consistently shown very low levels of humoral immunity, suggesting that most of the population is susceptible to infection with these viruses if they were to gain the ability to infect humans.

Infections in Animals: There is sustained transmission and endemicity of A(H5N1) clade 2.3.4.4b viruses in many species of wild waterfowl globally, with virus transmission to domestic poultry reported along migratory flyways and causing sporadic to sustained infections in domestic poultry in Asia, Europe, Africa, and North America. Transmission among domestic poultry is controlled through depopulation and other mitigation efforts in countries with resources. There are reports of limited infections in mostly carnivorous wild mammals in Europe.

Genomic Analysis: All gene segments of A/American wigeon/South Carolina/AH0195145/2021 A(H5N1) virus have >99% identity to avian influenza A(H5N1) viruses circulating in European wild birds. Several internal gene segments are similar to avian influenza A(H5N5) or A(H5N8) viruses but there is little evidence of recent reassortment with other lineages. The neuraminidase is typical of wild bird viruses. Since these are highly pathogenic avian influenza A viruses, the hemagglutinin has a molecular signature of importance for mammalian hosts, the polybasic cleavage site.

Antigenic Relatedness: The A/American wigeon/South Carolina/AH0195145/2021 A(H5N1) virus antigen shows a lack of reactivity in hemagglutination inhibition assay to sera raised against some avian influenza A(H5) virus strains, suggesting that these A(H5N1) viruses are expected to show a lack of antigenic relatedness to human seasonal influenza vaccines. Data show a 4-fold reduction for the A/American Wigeon/South Carolina/22-000345-001/2021 A(H5N1) virus against ferret antisera raised to the CVV-A/Astrakhan/3212/2020-like. Also, A/American wigeon/South Carolina/AH0195145/2021 A(H5N1) virus has two hemagglutinin substitutions relative to the CVV-A/Astrakhan/3212/2020 2.3.4.4b CVV antigenic sites.

Global Distribution in Animals: The A(H5N1) clade 2.3.4.4b virus has wide geographic distribution in multiple countries within Asia, Europe, Africa, and North America, spread primarily by multiple species of

migratory aquatic birds and some predatory birds. Outbreaks in commercial and backyard poultry in all global regions are common and, in some countries, widespread. Sporadic non-sustained infections in wild carnivorous mammals, such as foxes and an otter, have been reported in a few countries in Europe.

Disease Severity and Pathogenesis: A single asymptomatic human infection with A(H5N1) clade 2.3.4.4b virus was reported in 2022. Information on severe or fatal disease with A(H5Nx) virus infections in experimental animal models such as ferrets or primates is limited and inconsistent.

Antivirals and Treatment Options: There are no published reports of resistant markers in these A(H5N1) clade 2.3.4.4b viruses. Analysis of the M2, NA, and PA sequences from the A/American wigeon/South Carolina/AH0195145/2021 A(H5N1) virus, as well as sequences from other viruses from the current wild bird and poultry outbreaks, revealed no known markers indicating a decrease in drug susceptibility. The NA inhibition assay showed this virus to be susceptible to the NA inhibitors oseltamivir, zanamivir and peramivir. Cell culture-based assays confirmed this virus to be susceptible to the M2 blocker amantadine and the PA inhibitor baloxavir.

Comparison to other Viruses Scored with IRAT

The average score estimates for the potential emergence and public health impact risk elements for the A(H5N1) clade 2.3.4.4b virus were plotted along with a selection of 13 other influenza viruses scored using the IRAT (Figure). The estimates for the A(H5N1) clade 2.3.4.4b virus were in the lower moderate range for both risk of potential emergence and risk of potential public health impact. The average score estimates ranked this virus fourteenth for both emergence and impact risks when compared to the other 22 viruses scored with the IRAT to date.

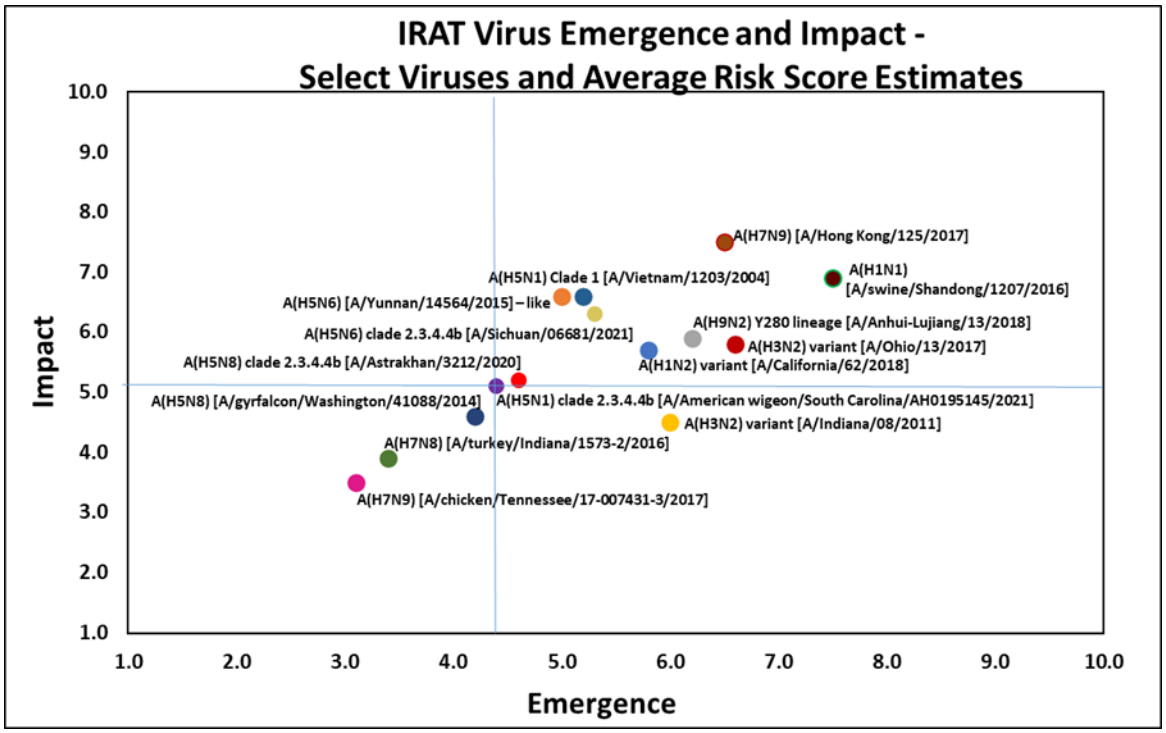

Figure: Potential pandemic risk for A(H5N1) clade 2.3.4.4b virus plotted by emergence and impact average weighted risk score estimates (highlighted with blue crossbars). Additional select viruses scored using the IRAT are displayed for comparison.

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

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