



## Influenza Risk Assessment Tool (IRAT) - Virus Report

Prepared by the CDC Influenza Division

Highly pathogenic avian influenza A(H5N6) virus; clade 2.3.4.4b

Virus Strain: A/Sichuan/06681/2021

Date of Evaluation: October 2021

### 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 2014, 52 human infections with highly pathogenic avian influenza (HPAI) A(H5N6) clade 2.3.4.4b virus (H5N6 2.3.4.4b) have been reported to the World Health Organization, with 26 human infections reported in 2021 as of 19 November, all but one reported from China [4-5]. Most infected persons reported exposure to poultry or poultry environments prior to infection. The majority of infections have resulted in severe illness requiring hospitalization, with 9 deaths in 2021. In addition, surveillance reports indicate detection of A(H5N6) 2.3.4.4b in poultry, waterfowl, and environmental samples [6].

In 2013, an HPAI A(H5N6) virus was first detected in poultry in China [7-9]. From 2016-2019, A(H5N6) clade 2.3.4.4b virus was reported in wild birds and in domestic poultry from multiple countries throughout Asia, Europe, and Africa. However, during 2020-2021, A(H5N6) clade 2.3.4.4b virus was only reported in birds in four countries in Asia [6].

Genetic sequence data from the 2021 human infections suggest that the A(H5N6) 2.3.4.4b viruses remain adapted to poultry, with no evidence of mammalian adaptation or increased transmissibility [10-12]. Previously recommended H5 candidate vaccine viruses and antivirals are expected to be effective against A(H5N6) viruses currently circulating among poultry [6,13]. In addition, A(H5N6) virus analysis suggests that they remain susceptible to available influenza antiviral medications.

Using the IRAT, the Centers for Disease Control and Prevention (CDC) assessed the pandemic potential of HA clade 2.3.4.4b, AIV A(H5N6) and a representative virus, A/Sichuan/06681/2021.

### IRAT Evaluation

Influenza subject matter experts (SMEs) from CDC, the Food and Drug Administration, and Agricultural Research Service were asked to evaluate clade 2.3.4.4b A(H5N6) including representative virus, A/Sichuan/06681/2021, 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 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 was 5.3, in the middle range of the moderate risk category (Table 1). The average risk score for the virus to potentially impact public health was 6.3, also in the middle range of the moderate risk category (Table 2). The average SME confidence level in the available data of all 10 risk elements was 1.9 (range: 1.0-2.6) out of a possible confidence level of 0-4.

Slight variability was seen among SME point estimate scores in the risk elements of Global Distribution of Animal Influenza Viruses, and Infections in Animals, where the scores ranged from moderate to high risk, and in 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 each of the three risk elements resulted in adjusted ranges for the overall emergence risk and for the potential impact risk that continued to place this virus in the middle range of the moderate risk category, indicating that the categorization of 2.3.4.4b A(H5N6) including A/Sichuan/06681/2021 as moderate risk was unchanged by the range of scores within each of the three risk elements exhibiting variability.

Table 1: Estimated Weighted Risk of Potential Emergence

Risk Element	Weight (W)	Risk Score (RS)	W X RS
Human Infections	0.2929	5.80	1.70
Transmission in Animal Models	0.1929	3.60	0.69
Receptor Binding	0.1429	3.00	0.43
Population Immunity	0.1096	9.00	0.99
Infections in Animals	0.0846	6.40	0.54
Genomic Analysis	0.0646	5.25	0.34
Antigenic Relatedness	0.0479	4.25	0.20
Global Distribution in Animals	0.0336	6.20	0.21
Disease Severity and Pathogenesis	0.0211	8.25	0.17
Antiviral Treatment Options	0.0100	2.00	0.02
<b>TOTAL</b>	<b>1.0001</b>		<b>5.29</b>



Table 2: Estimated Weighted Risk of Potential Public Health Impact

Risk Element	Weight (W)	Risk Score (RS)	W X RS
Disease Severity and Pathogenesis	0.2929	8.25	2.42
Population Immunity	0.1929	9.00	1.74
Human Infections	0.1429	5.80	0.83
Antiviral Treatment Options	0.1096	2.00	0.22
Antigenic Relatedness	0.0846	4.25	0.36
Receptor Binding	0.0646	3.00	0.19
Genomic Analysis	0.0479	5.25	0.25
Transmission in Animal Models	0.0336	3.60	0.12
Global Distribution in Animals	0.0211	6.20	0.13
Infections in Animals	0.0100	6.40	0.06
<b>TOTAL</b>	<b>1.0001</b>		<b>6.32</b>

### Individual Risk Element Summaries

**Human Infections:** Sporadic human infections reported primarily from China have increased in frequency in 2021, and with epidemiological links to animal or animal environment sources. There are no reports of human-to-human transmission. Together, these data indicate moderate current risk to humans.

**Transmission in Animal Models:** No evidence of transmission in accepted mammalian models of human transmissibility for this virus. However, low replicative ability of 2.3.4.4b viruses in human airway *in vitro* models have been demonstrated, while other reports indicate limited or inconsistent transmission of 2.3.4.4 viruses between cohoused ferrets and no respiratory droplet transmission. Together, these data indicate low current risk to humans.

**Receptor Binding:** Sequence analysis of the hemagglutinin of the A/Sichuan/06681/2021 A(H5N6) virus compared to other H5 viruses indicates the hemagglutinin to possess an avian receptor binding site, that is, glycans with  $\alpha$ 2,3 galactose-linked sialic acid and lack of binding to  $\alpha$ 2,6 galactose-linked sialic acids. A/Sichuan/06681/2021 A(H5N6) virus also has 3 amino acid substitutions, S133A, T156A and T188I, which were associated with increased binding to human  $\alpha$ 2,6 receptors. Together, these data indicate low current risk to humans.

**Population Immunity:** There is little evidence of cross-reactive antibodies (<10%) for all age groups. With no widespread human-to-human transmission, no vaccine-induced immunity, available information of other H5 viruses, and little population immunity to N6, human population immunity against A(H5N6) viruses is expected to be minimal. Together, these data indicate high current risk to humans.

**Infections in Animals:** The virus shows sustained or endemic infections or disease in poultry or wild bird species, with sustained transmission in a multiple number of host species of wild and domestic birds. Also, there are multiple reports of sporadic human infections, and limited but no recent reports in other mammals. Together, these data indicate moderate current risk to humans.



**Genomic Analysis:** A(H5N6) viruses exhibit reassortment between different lineages and/or subtypes, especially with H5N8 and H5N1 viruses from wild birds. There is a lack of significant markers of mammalian adaptation. Together, these data indicate moderate current risk to humans.

**Antigenic Relatedness:** Antiserum generated after infection or vaccination with human (seasonal) influenza A virus antigens do not cross-react (have a lack of antigenic relatedness) with 2.3.4.4b A(H5N6) virus, and which contains 4 hemagglutinin amino acid changes from 2.3.4.4b H5N8 A/Astrakhan/3212/2020, for which a CVV is being prepared. Data from A(H5N6) 2.3.4.4b viruses A/duck/Vietnam/NCVD-20AD672/2020 and A/duck/Vietnam/NCVD029AD745/2020, which share 1 of the 4 amino acid changes, showed 4-8-fold reduction against current candidate vaccine virus A/Astrakhan/3212/2020-like. Together, these data indicate moderate current risk to humans.

**Global Distribution in Animals:** Distribution reports from 2017-2019 indicate both sporadic (Europe and Africa) and continued (Asia/Pacific) detections in multiple global regions without clearly defined geographic or territorial boundaries. From 2020-2021, reports indicate distribution in the Asia region only, although not geographically defined within the region, in both wild bird and domestic poultry populations, and likely endemic in a few countries. Together, these data indicate moderate current risk to humans.

**Disease Severity and Pathogenesis:** In 2021, reports of human infections with 2.3.4.4b A(H5N6) virus indicated increased frequency from previous years of severe disease and fatal illness documented with infection. The high case-fatality proportion among known cases suggest risk of severe outcomes is high even if milder infections have been missed. Information on severe or fatal disease in experimental animal models, such as ferrets or primates, is limited. Together, these data indicate high current risk to humans.

**Antivirals and Treatment Options:** There is no evidence of reduced susceptibility to any of the antiviral medications approved for human use. However, 2.3.4.4 A(H5N6) viruses, including from 16 A(H5N6) human cases, have reported M2-S31N, a marker of resistance to M2 blockers. Also, substitutions in PA (E199G, I38L/M/V, A37T), which may reduce baloxavir susceptibility were identified in a few avian 2.3.4.4 A(H5N6) viruses. Together these data indicate low current risk to humans.

### Comparison to other Viruses Scored with IRAT

The average score estimates for the potential emergence and public health impact risk elements for the 2.3.4.4b A(H5N6) virus were plotted along with a selection of 12 other influenza viruses scored using the IRAT (Figure). The estimates for the 2.3.4.4b A(H5N6) virus were in the moderate range for both risk of potential emergence and risk of potential public health impact. The average score estimates ranked this virus ninth for emergence risk and sixth for impact risk when compared to the other twenty-one viruses scored with the IRAT to date.

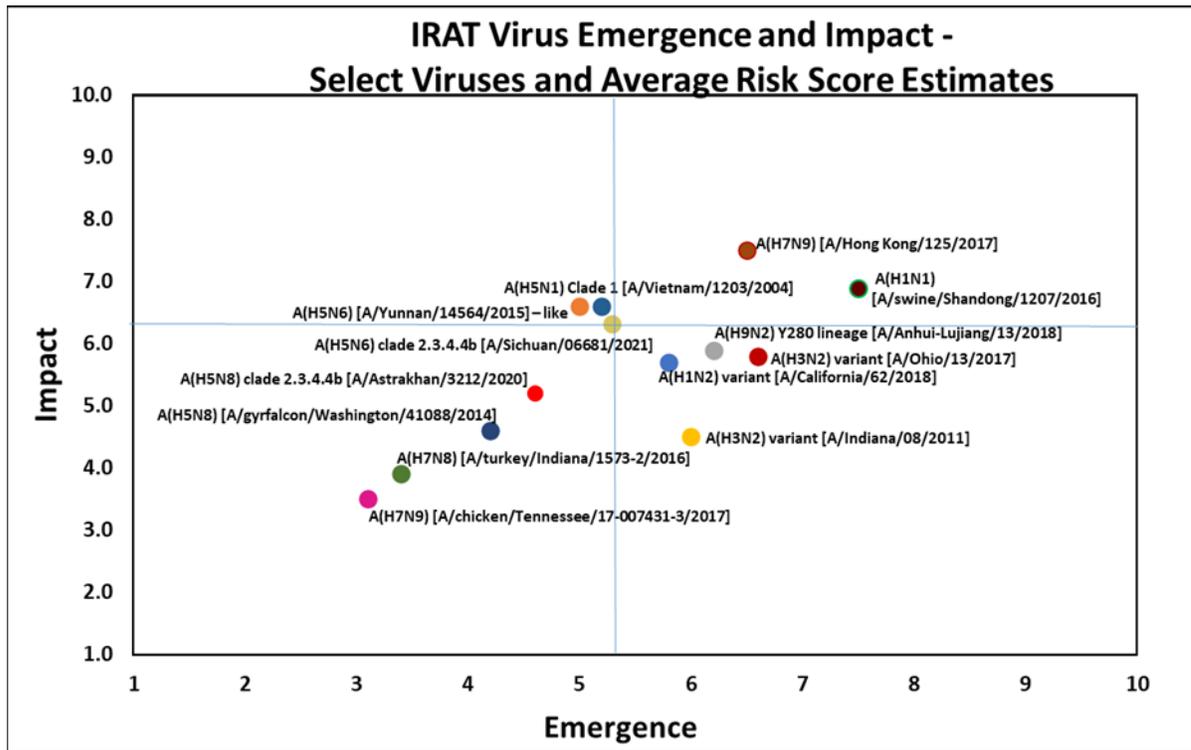


Figure: Potential pandemic risk for clade 2.3.4.4b A(H5N6) virus plotted by emergence and impact average weighted risk score estimates (highlighted with blue crossbars). Additional select viruses scored using IRAT are displayed for comparison.

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 estimates associated with the virus.

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