

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/mink/Spain/3691-8_22VIR10586-10**

Date of Evaluation: April 2023



**U.S. Department of
Health and Human Services**
Centers for Disease
Control and Prevention

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 have occurred, usually after exposure to infected animals or to a virus-contaminated environment. In order to prioritize and maximize pandemic preparedness investments, the Influenza Risk Assessment Tool (IRAT) was created [3]. The IRAT is used to examine multiple attributes of influenza A viruses that circulate among animals but have not gained the ability to transmit from human-to-human, and to evaluate the potential of these viruses to acquire this ability and the consequent potential public health impact. The IRAT is an evaluative tool, not a predictive tool, and is not intended to predict the next pandemic.

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 multiple 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]. This virus was first reported in migrating wild aquatic birds in North America in December 2021 and in South America in January 2023. In 2023, the virus has been detected in more than 50 countries in these five regions. The first detections in the United States were from migratory wild aquatic birds but the virus has also been detected in domestic poultry [6,7]. Sporadic incursions of the virus into aquatic and terrestrial carnivorous mammals have occurred in the United States and other regions, including an outbreak in a farmed mink unit in Spain [8,9].

Between 2022-2023, nine cases of human infection with A(H5N1) clade 2.3.4.4b viruses have been identified in Europe, Asia, and the Americas. Five of these cases resulted in severe/critical lower respiratory tract disease with one fatality [10-13].

Phylogenetic analysis of A(H5N1) clade 2.3.4.4b viruses shows high levels of genetic similarity to previously circulating A(H5Nx) clade 2.3.4.4b viruses, with little evidence of mammalian adaptation [10,14,15]. The hemagglutinin (HA) genes of currently circulating wild bird and poultry A(H5N1) clade 2.3.4.4b viruses show a high level of genetic similarity to previous clade 2.3.4.4 viruses, with some genetic variation noted among the N1 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 analysis suggests that a majority of viruses remain susceptible to available influenza antiviral medications [16,17].

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/mink/Spain/3691-8_22VIR10586-10 as the prototype strain.

IRAT Evaluation

Influenza subject matter experts (SMEs) from CDC and the United States Department of Agriculture: Agricultural Research Service were asked to evaluate these A(H5N1) clade 2.3.4.4b viruses including the prototype virus, A/mink/Spain/3691-8_22VIR10586-10, using the ten risk elements defined in the IRAT. Each SME scored 1 to 10 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 5.13, in the mid-low range of the moderate risk category (Table 1). The average risk score for the virus to potentially impact public health was 6.24, in the mid-range of the moderate risk category (Table 2). These scores reflect an increase of 0.69 in the emergence question and an increase of 1.17 in the impact question compared to the previous A(H5N1) evaluation last year, but both questions still fall into the moderate risk category. The average SME confidence level in the available data of all 10 risk elements was 2.32 (SME confidence range: 1.0-4.0).

Some variation was seen among SME point estimate scores in the risk elements Genomic Analysis and Transmission in Animal Models, where the scores ranged from moderate to high risk and low to moderate risk, respectively. This indicates some uncertainty in interpretation and confidence of the limited available data.

Sensitivity analyses using the lowest and highest scores for these two risk elements resulted in adjusted ranges for the overall emergence risk and the potential impact risk that continued to place this virus in the mid-range of the moderate risk category, indicating that the categorization of A(H5N1) clade 2.3.4.4b virus including A/mink/Spain/3691-8_22VIR10586-10, as moderate risk was unchanged by the range of scores within the Genomic Analysis and Transmission in Animal Models risk elements exhibiting variation.

Table 1: Estimated Weighted Risk of Potential Emergence¹ for Highly Pathogenic Avian Influenza A(H5N1) virus clade 2.3.4.4b; A/mink/Spain/3691-8_22VIR10586-10 evaluated in April 2023

Risk Element	Weight (W)	Risk Score (RS)	W X RS
Human Infections	0.2929	4.60	1.35
Transmission in Animal Models	0.1929	3.67	0.71
Receptor Binding	0.1429	3.00	0.43
Population Immunity	0.1096	9.20	1.01
Infections in Animals	0.0846	6.57	0.56
Genomic Analysis	0.0646	6.00	0.39
Antigenic Relatedness	0.0479	4.83	0.23
Global Distribution in Animals	0.0336	8.17	0.27
Disease Severity and Pathogenesis	0.0211	7.50	0.16
Antiviral Treatment Options	0.0100	3.25	0.03
Total	1.0001		5.13

¹ 1. Trock SC, Burke SA, Cox NJ. 2012. Development of an influenza virologic risk assessment tool. Avian Dis 56:1058-61.

2. Cox NJ, Trock SC, Burke SA. 2014. Pandemic preparedness and the Influenza Risk Assessment Tool (IRAT). Curr Top Microbiol Immunol 385:119-36.

3. Trock SC, Burke SA, Cox NJ. 2015. Development of Framework for Assessing Influenza Virus Pandemic Risk. Emerg Infect Dis 21:1372-1378.

Table 2: Estimated Weighted Risk of Potential Public Health Impact^{1,2} for Highly Pathogenic Avian Influenza A(H5N1) virus clade 2.3.4.4b; A/mink/Spain/3691-8_22VIR10586-10 evaluated in April 2023

Risk Element	Weight (W)	Risk Score (RS)	W X RS
Disease Severity and Pathogenesis	0.2929	7.50	2.20
Population Immunity	0.1929	9.20	1.77
Human Infections	0.1429	4.60	0.66
Antiviral Treatment Options	0.1096	3.25	0.36
Antigenic Relatedness	0.0846	4.83	0.41
Receptor Binding	0.0646	3.00	0.19
Genomic Analysis	0.0479	6.00	0.29
Transmission in Animal Models	0.0336	3.67	0.12
Global Distribution in Animals	0.0211	8.17	0.17
Infections in Animals	0.0100	6.57	0.07
Total	1.0001		6.24

¹ Trock SC, Burke SA, Cox NJ. 2012. Development of an influenza virologic risk assessment tool. *Avian Dis* 56:1058-61.

² Cox NJ, Trock SC, Burke SA. 2014. Pandemic preparedness and the Influenza Risk Assessment Tool (IRAT). *Curr Top Microbiol Immunol* 385:119-36.

³ Trock SC, Burke SA, Cox NJ. 2015. Development of Framework for Assessing Influenza Virus Pandemic Risk. *Emerg Infect Dis* 21:1372-1378.

Individual Risk Element Summaries

Human Infections: There have been 9 sporadic human cases of A(H5N1) clade 2.3.4.4b virus from multiple geographic regions. All cases reported avian or environmental exposure. There were no reports of human-to-human transmission.

Transmission in Animal Models: There is limited evidence of close contact transmission of A/mink/Spain/3691-8_22VIR10586-10/2022 between mink at a commercial mink farm reported recently. However, the HA protein of A/mink/Spain/3691-8_22VIR10586-10/2022 possesses no amino acid changes that indicate a propensity for human-to-human transmission. Multiple studies on A(H5Nx) clade 2.3.4.4 viruses related to A/mink/Spain/3691-8_22VIR10586-10/2022 (H5N1) have reported inconsistent evidence of direct contact transmission and no respiratory droplet transmission among ferret, mice, and guinea pig models.

Receptor Binding: Sequence analysis of the HA from recently isolated clade 2.3.4.4b viruses, including A/mink/Spain/3691-8_22VIR10586-10/2022, reveals no HA substitutions that could significantly increase binding to human-type, α 2,6-linked sialic acid receptors, or see a marked decrease in binding to avian-type α 2,3-linked sialic acid receptors. This indicates these A(H5N1) viruses currently maintain a typical avian-like pocket in the receptor binding site and predominantly bind to avian-type α 2,3-linked sialic acid receptors.

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 shared virus contaminated environments including water sources. This has caused sporadic infections

and sustained transmission in domestic poultry in Asia, Europe, Africa, and the Americas. Transmission among domestic poultry is controlled through depopulation and other mitigation efforts in countries with resources. There have been sporadic infections and non-sustained transmission in multiple aquatic and carnivorous terrestrial mammals, potentially exposed through eating infected birds or in heavily contaminated environments. Also, detections in limited farmed animal species suggest likely prolonged exposure to infected birds and contaminated environments, although limited non-sustained mammal-to-mammal transmission cannot be ruled out.

Genomic Analysis: The A/mink/Spain/3691-8_22VIR10586-10/2022 virus has undergone reassortment between different Eurasian lineage avian influenza subtypes. The segments are moderately to significantly divergent from known host-adapted viruses of low risk. Molecular signatures of importance for mammalian/human infection and disease have been routinely reported in wild mammals and were also reported in the mink virus but not in birds.

Antigenic Relatedness: Recently circulating 2.3.4.4b A(H5N1) viruses show an 8-fold difference or less to stockpiled or non-stockpiled pre-pandemic vaccine candidate viruses in 1-way HI assay. This included the A/mink/Spain/3691-8_22VIR10586-10/2022 A(H5N1) virus which also had a less than 8-fold difference. Because the Spanish mink virus is antigenically distinct from seasonal influenza A(H1N1)pdm09 and A(H3N2) vaccine viruses, seasonal influenza vaccines are not expected to provide any protection against infection with this or any other A(H5N1) clade 2.3.4.4b viruses.

Global Distribution in Animals: Viruses closely related to the A/mink/Spain/3691-8_22VIR10586-10/2022 virus have been identified in multiple countries in Europe. Viruses from the A(H5N1) 2.3.4.4b clade have wide geographic distribution in multiple countries within Asia, Europe, Africa, and the Americas, spread primarily by multiple species of migratory aquatic birds and some predatory birds. Virus transmission from wild waterfowl to domestic poultry may be through direct or indirect sources. Outbreaks in commercial and backyard poultry in all global regions are common and, in some countries, widespread. Sporadic infections in multiple species of aquatic and wild carnivorous mammals have been reported.

Disease Severity and Pathogenesis: There have been 9 reported human cases of A(H5N1) clade 2.3.4.4b virus infection reported in 2022-2023. Five of the cases had severe disease with one reported fatality. Four cases were asymptomatic or mildly symptomatic and may represent transient environmental contamination rather than actual infection.

Antivirals and Treatment Options: Nearly all analyzed A(H5N1) clade 2.3.4.4b viruses circulating in wild birds and identified in poultry, mammals, and humans, did not have known markers of resistance or reduced susceptibility to FDA-approved antivirals for treatment of influenza. A few A(H5N1) clade 2.3.4.4b viruses collected from domestic and wild birds in North America had known markers of resistance to the M2 inhibitors amantadine and rimantadine, the NA inhibitors oseltamivir and peramivir, or the CEN inhibitor baloxavir.

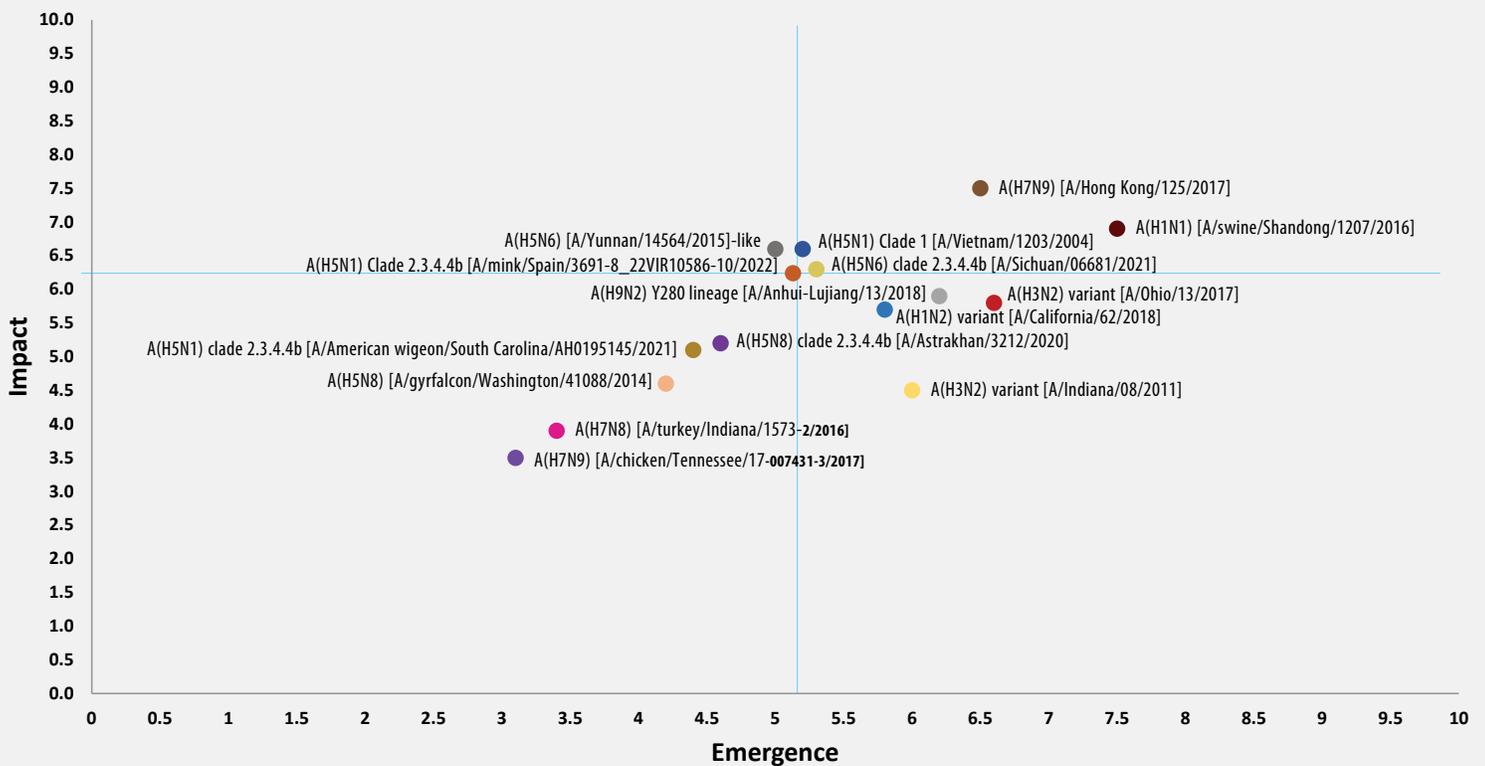
Comparison to other Viruses Scored with IRAT

The average score estimates for the potential emergence and public health impact risk elements for this A(H5N1) clade 2.3.4.4b virus were plotted along with a selection of 14 other previous influenza viruses scored using the IRAT (figure below). The estimates for this A(H5N1) clade 2.3.4.4b virus were in the mid-moderate range for both risk of potential emergence and risk of potential public health impact. The average score estimates ranked this virus eleventh for emergence risks and seventh for impact risks when compared to the other 23 viruses scored with the IRAT to date.

Figure—IRAT Virus Emergence and Impact—Average Risk Scores: Updated 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 selected 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.

For accessible explanation of the graph go to [Appendix for Accessibility on page 8](#).



References

1. Centers for Disease Control and Prevention. Influenza in Animals; <https://www.cdc.gov/flu/other/index.html>; accessed 24 May 2023.
2. World Health Organization. Influenza at the Human-Animal Interface; [Global Influenza Programme \(who.int\)](#); accessed 24 May 2023.
3. Centers for Disease Control and Prevention. Influenza Risk Assessment Tool; <https://www.cdc.gov/flu/pandemic-resources/national-strategy/risk-assessment.htm>; accessed 24 May 2023.
4. Animal and Plant Health Inspection Service. [USDA APHIS | 2022 Detections of Highly Pathogenic Avian Influenza](#); accessed 24 May 2023.
5. Centers for Disease Control and Prevention. Evolution of Influenza A(H5) Clade 2.3.4.4b. *Information for the WHO Consultation on the Composition of Influenza Vaccines (Northern Hemisphere) Zoonotic Virus Report*; February 21-24, 2022.
6. Food and Agriculture Organization. [Global Avian Influenza Viruses with Zoonotic Potential situation update](#); accessed 24 May 2023.
7. Bevins SN, Shriner SA, Cumbee JC, Dillone KE, Douglass KE, Ellis JW, et al. Intercontinental movement of highly pathogenic avian influenza A(H5N1) clade 2.3.4.4 virus to the United States, 2021. *Emerg Infect Dis.* 2022 May [18 Apr 2022]. <https://doi.org/10.3201/eid2805.220318>.
8. Montserrat A, Isabella M, Azucena S, Bianca Z, Alice F, et al. Highly pathogenic avian influenza A(H5N1) virus infection in farmed minks, Spain, October 2022. *Euro Surveill.* 2023. <https://doi.org/10.2807/1560-7917.ES.2023.28.3.2300001>
9. World Organisation for Animal Health. Statement on avian influenza and mammals; <https://www.woah.org/en/statement-on-avian-influenza-and-mammals>; accessed 24 May 2023
10. Centers for Disease Control and Prevention. [Technical Report: Highly Pathogenic Avian Influenza A\(H5N1\) Viruses](#); accessed 24 May 2023.
11. World Health Organization. [Human Infection caused by Avian Influenza A \(H5N1\)—Chile](#); accessed 24 May 2023.
12. World Health Organization. [Assessment of risk associated with recent influenza A\(H5N1\) clade 2.3.4.4b viruses](#); accessed 24 May 2023.
13. Centers for Disease Control and Prevention. [Current U.S. Bird Flu Situation in Humans | Avian Influenza \(Flu\) \(cdc.gov\)](#); accessed 24 May 2023.
14. Pulit-Penalosa et al. [Characterization of highly pathogenic avian influenza H5Nx viruses in the ferret model | Scientific Reports \(nature.com\)](#); *Sci Rep* 10, 12700 (2020).
15. Puryear W, Sawatzki K, Hill N, Foss A, Stone JJ, Doughty L, et al. Highly Pathogenic Avian Influenza A(H5N1) Virus Outbreak in New England Seals, United States. *Emerg Infect Dis.* 2023 Apr;29(4):786-791. doi: [10.3201/eid2904.221538](https://doi.org/10.3201/eid2904.221538).
16. Centers for Disease Control and Prevention. [Interim Guidance on Influenza Antiviral Chemoprophylaxis of Persons Exposed to Birds with Avian Influenza A Viruses Associated with Severe Human Disease or with the Potential to Cause Severe Human Disease | Avian Influenza \(Flu\) \(cdc.gov\)](#); accessed 24 May 2023.
17. Centers for Disease Control and Prevention. [Prevention and Antiviral Treatment of Bird Flu Viruses in People | Avian Influenza \(Flu\) \(cdc.gov\)](#); accessed 24 May 2023.

Appendix for accessibility

Figure—IRAT Virus Emergence and Impact—Average Risk Scores

This dot graph plots the average weighted risk scores for “public health impact” and “emergence” for viruses subjectively assessed by the IRAT’s panel of expert reviewers. This graph includes the April 2023 assessment for the A(H5N1) Clade 2.3.4.4b [A/mink/Spain/3691-8_22VIR10586-10/2022] virus. This mink virus scores slightly higher for risk of “public health impact” and “emergence” compared with the previously assessed H5N1 clade 2.3.4.4b virus: A/American wigeon/South Carolina/AH0195145/2021, which was assessed in March 2022. The average risk score for the estimated potential “emergence” of the mink virus was 5.13, which falls within the range of the moderate risk category. In comparison, the American wigeon virus scored a 4.4, which falls within the lower range of the moderate risk category. The average risk score for the mink virus to potentially “impact public health” was 6.24, which also falls within the range of the moderate risk category. In comparison, the American wigeon virus scored a 5.1, which falls within the lower range of the moderate risk category. In addition to these viruses, a selection of 14 other influenza viruses previously assessed by the IRAT have been plotted for comparison. Among all of the viruses plotted, the virus that scores highest in terms of risk of “emergence” is A/H1N1[A/swine/Shandong/1207/2016], which has a weighted average risk of “emergence” score of 7.5 and a weighted average risk of “public health impact” score of 6.9. The virus that scores highest in terms of risk of “public health impact” is A(H7N9) [A/Hong Kong/125/2017], which has a weighted average risk of “public health impact” score of 7.5 and a weighted average risk of “emergence” score of 6.5. [\[Return to page 6\]](#)