

# 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 Viruses:

A/California/147/2024 and A/Washington/239/2024

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## Introduction

Human infections with avian influenza A viruses (AIVs) that commonly circulate among animals are rare and the likelihood of sustained human-to-human transmission of these viruses has remains low [1,2]. While sporadic human infections with animal influenza A viruses have occurred, usually after exposure to infected animals or to a virus-contaminated environment, no cases of human-to-human transmission of AIVs have been reported since 2007. The Influenza Risk Assessment Tool (IRAT) was created to prioritize and maximize pandemic preparedness investments [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 efficiently 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 influenza A virus or impact.

## Situation

Since December 2021, highly pathogenic avian influenza (HPAI) A(H5N1) viruses, clade 2.3.4.4b, have 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 all states [4].

HPAI A(H5N1) clade 2.3.4.4b viruses emerged in 2020, spreading across Europe, Asia, and Africa, in both wild aquatic birds and domestic poultry, and by 2021, replaced the previously circulating HPAI A(H5N8) clade 2.3.4.4b viruses [5]. HPAI A(H5N1) clade 2.3.4.4b viruses were first reported in migrating wild aquatic birds in North America in December 2021, domestic poultry in the United States in February 2022, and in South America in January 2023 [6,7]. By 2023, the virus had been detected in approximately 70 countries. 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 and elephant seals in Argentina [8-10]. In March 2024, HPAI A(H5N1) was first detected in dairy cattle in the United States, and by April 1, 2024, A(H5N1) was detected in a dairy worker who had direct exposure to dairy cattle presumed to be infected with A(H5N1).

From January 2022 through March 14, 2025, 104 cases of influenza A(H5N1) virus infection in humans have been reported globally. Of those with available sequence data, 61 of these cases were identified with HPAI A(H5N1) clade 2.3.4.4b viruses, including 56 cases in the U.S. that were confirmed as clade 2.3.4.4b by sequence analysis out of the 71 total cases detected. Eight of these cases resulted in severe/critical lower respiratory tract disease with two fatalities [11-17].

In the United States, the first case of A(H5) was reported in April 2022 in a farm worker who experienced fatigue without any other symptoms while depopulating poultry at a poultry farm with confirmed HPAI A(H5N1) [16]. However, it is possible that this case did not represent a true infection, but rather detection of a low level of A(H5N1) viral RNA in a respiratory specimen due to environmental contamination. Additionally,

full sequence data is not available for this A(H5N1) case. Environmental contamination was previously attributed to two asymptomatic cases in poultry workers reported in Spain [18].

In the United States, since April 2024, 70 cases of A(H5) have been reported in twelve states; 68 cases were in adults aged  $\geq 18$  years. Codon-complete influenza genomic sequence data, including the neuraminidase gene segment, has not been recoverable for all of these human cases identified. Forty-one A(H5) cases have been associated with the ongoing multi-state outbreak of A(H5N1) in dairy cattle, with 36 cases in California, two cases in Michigan, and one case each in Colorado, Nevada, and Texas. All infections occurred in dairy workers who had direct exposure to cattle infected, or presumed to be infected, with A(H5N1) virus. Infections associated with U.S. dairy cattle to date have involved mild respiratory symptoms or conjunctivitis. No patients have been hospitalized [15,16,19-21].

Twenty-four U.S. A(H5) cases have been detected in farm workers who were involved in the depopulation of poultry at poultry facilities experiencing an outbreak of HPAI A(H5N1) virus. Eleven of these cases were in Washington state, nine in Colorado, and one each in Iowa, Ohio, Oregon, and Wyoming [21,22]. These workers reported symptoms after being exposed to A(H5N1) virus-infected poultry. Most of these workers who tested positive reported mild illness, such as redness/watery eyes and respiratory symptoms. However, one case in Ohio was severe and required hospitalization; the patient subsequently recovered [15,23].

The exposure source was unknown for three cases, comprised of two pediatric cases in children in California and one adult case in Missouri. The Missouri case was the first reported hospitalization of a patient in the United States with A(H5N1) [15]. This person had multiple underlying conditions and presented to the emergency department with acute chest pain, nausea, vomiting, diarrhea, and weakness, without respiratory symptoms [15].

Additionally, two cases reported exposures to backyard poultry flocks and/or wild birds. The first of these was a person in Louisiana, who also had underlying health conditions and was the first and only A(H5N1) virus-associated death in the United States, and the second was a person in Wyoming with underlying health conditions who was hospitalized and subsequently recovered [24,25].

Phylogenetic analysis of HPAI A(H5N1) clade 2.3.4.4b viruses showed high levels of genetic similarity to previously circulating HPAI A(H5Nx) clade 2.3.4.4b viruses, with little evidence of mammalian adaptation [11, 26,27]. Specifically, while the N1 neuraminidase (NA) gene, which is wild bird adapted, shows some genetic variation as a result of reassortment, the hemagglutinin (HA) genes of currently circulating wild bird, dairy cattle and poultry HPAI A(H5N1) clade 2.3.4.4b viruses share high levels of genomic similarity to each other and earlier clade 2.3.4.4b viruses [5,7].

The influenza A(H5N1) virus hemagglutinin proteins from human cases and animals detected during the current 2024-2025 outbreak are antigenically related to three available candidate vaccine viruses (CVVs). In addition, A(H5N1) virus genetic and phenotypic analysis suggest that these viruses remain susceptible to available FDA-approved influenza antiviral medications [28,29].

Using the IRAT, the Centers for Disease Control and Prevention (CDC) assessed the pandemic potential of HPAI clade 2.3.4.4b, A(H5N1) viruses using two viruses: A/California/147/2024 and A/Washington/239/2024. A/California/147/2024 is representative of clade 2.3.4.4b HPAI A(H5N1) B3.13 genotype viruses detected in the majority of dairy cattle in the U.S. While A/Washington/239/2024 is

representative of clade 2.3.4.4b HPAI A(H5N1) D1.1 genotype viruses currently circulating in wild birds and detected in most poultry in the United States. Previously, CDC assessed three other AIV A(H5N1) clade 2.3.4.4b viruses, the A/American wigeon/South Carolina/AH0195145/2021, the A/mink/Spain/3691-8\_22VIR10586-10/2022, and A/Texas/37/2024. These three viruses had overall estimated IRAT scores in the moderate risk category range of 4.0 to 7.9.

## IRAT Evaluation

Influenza subject matter experts (SMEs) from the Department of Agriculture, Department of Defense, Department of Health and Human Services, and Department of Interior were asked to evaluate the HPAI A(H5N1) virus clade 2.3.4.4b viruses, A/California/147/2024 and A/Washington/239/2024, using the ten risk elements defined in the IRAT. Each SME scored 1 to 5 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 these viruses in the moderate risk category, which ranges from 4.0 to 7.9. The average risk scores for the estimated potential emergence were 5.59 and 5.21 for the A/California/147/2024 and A/Washington/239/2024 viruses, respectively. Placing them in the mid-low range of the moderate risk category (Table 1). The average risk score for the A/California/147/2024 and A/Washington/239/2024 viruses to potentially impact public health were 5.91 and 6.00, respectively, in the mid-range of the moderate risk category (Table 2). These scores reflect a decrease of at least 0.20 in the emergence question and a decrease of at least 0.09 in the impact question compared to the previous A(H5N1) virus evaluation last year, A/Texas/37/2024; however, both scores still fall into the moderate risk category, and overlap with the scores from the A/Texas/37/2024 virus. The SMEs are asked to rate the confidence in their score, with zero being low confidence and four being exact measure, the average SME confidence level in the available data of all 10 risk elements for the A/California/147/2024 and A/Washington/239/2024 viruses was 2.46 and 2.32, respectively. (SME confidence range: 0.00-4.00).

Some variation was seen among SME point estimate scores for the A/California/147/2024 virus risk elements, Disease Severity and Pathogenesis, Human Infections, and Infections in Animals, where the scores ranged from moderate to high risk. Additionally, for the A/Washington/239/2024 virus the point estimate scores for Disease Severity and Pathogenesis, Global Distribution of Animal Influenza Viruses, and Human Infections risk elements ranged from moderate to high risk. This indicates some uncertainty in interpretation and confidence of the available data.

Sensitivity analyses using the lowest and highest scores for these four 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 HPAI A(H5N1) virus, clade 2.3.4.4b, including A/California/147/2024 and A/Washington/239/2024, as moderate risk was unchanged by the range of scores within the risk elements exhibiting variation.

Table 1: Estimated Weighted Risk of Potential Emergence<sup>1</sup> for Clade 2.3.4.4b Highly Pathogenic Avian Influenza A(H5N1) viruses, A/California/147/2024 and A/Washington/239/2024, evaluated in March 2025

Risk Element	Weight (W)	A/California/147/2024		A/Washington/239/2024	
		Risk Score (RS)	W X RS	Risk Score (RS)	W X RS
Human Infections	0.2929	5.70	1.67	5.40	1.58
Transmission in Animal Models	0.1929	5.17	1.00	4.50	0.87
Receptor Binding	0.1429	2.67	0.38	2.50	0.36
Population Immunity	0.1096	8.50	0.93	8.67	0.95
Infections in Animals	0.0846	7.17	0.61	5.33	0.45
Genomic Analysis	0.0646	6.40	0.41	6.00	0.39
Antigenic Relatedness	0.0479	4.00	0.19	4.13	0.20
Global Distribution in Animals	0.0336	6.83	0.23	7.00	0.24
Disease Severity and Pathogenesis	0.0211	6.43	0.14	6.86	0.14
Antiviral Treatment Options	0.0100	3.33	0.03	3.67	0.04
<b>TOTAL</b>	<b>1.0001</b>		<b>5.59</b>		<b>5.21</b>

Table 2: Estimated Weighted Risk of Potential Public Health Impact<sup>1</sup> for Clade 2.3.4.4b Highly Pathogenic Avian Influenza A(H5N1) viruses, A/California/147/2024 and A/Washington/239/2024, evaluated in March 2025

Risk Element	Weight (W)	A/California/147/2024		A/Washington/239/2024	
		Risk Score (RS)	W X RS	Risk Score (RS)	W X RS
Disease Severity and Pathogenesis	0.2929	6.43	1.88	6.86	2.01
Population Immunity	0.1929	8.50	1.64	8.67	1.67
Human Infections	0.1429	5.70	0.81	5.40	0.77
Antiviral Treatment Options	0.1096	3.33	0.37	3.67	0.40
Antigenic Relatedness	0.0846	4.00	0.34	4.13	0.35
Receptor Binding	0.0646	2.67	0.17	2.50	0.16
Genomic Analysis	0.0479	6.40	0.31	6.00	0.29
Transmission in Animal Models	0.0336	5.17	0.17	4.50	0.15
Global Distribution in Animals	0.0211	6.83	0.14	7.00	0.15
Infections in Animals	0.0100	7.17	0.07	5.33	0.05
<b>TOTAL</b>	<b>1.0001</b>		<b>5.91</b>		<b>6.00</b>

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## Individual Risk Element Summaries

**Human Infections:** Since April 2024, there have been 70 confirmed human infections with influenza A(H5) virus reported in the United States. All cases have been sporadic and all but three have had known exposures to infected animals or animals presumed to be infected with HPAI A(H5N1) viruses. Additionally, human-to-human transmission of influenza A(H5) virus has not been identified to date. Documented cases generally reported were wearing only partial or no PPE for protection when exposed to animals. Cases have now been documented in twelve states, which is more widespread than earlier in the outbreak. However, this reflects the more geographically widespread prevalence of HPAI A(H5N1) viruses, clade 2.3.4.4b, in animals, namely dairy cattle and birds.

**Transmission in Animal Models:** Animal studies have been previously conducted to assess the transmissibility of the clade 2.3.4.4 (H5) viruses [25]. Efficient airborne or respiratory droplet transmission (RDT) of clade 2.3.4.4 A(H5N1), A(H5N2), A(H5N6), and A(H5N8) viruses has not been demonstrated in any animal model examined [30,31]. These results are consistent with low risk to humans and are similar to other avian influenza A(H5) viruses that have not been fully adapted to humans and preferentially bind to  $\alpha$ 2,3-linked sialic acid (SA) receptors. Unpublished CDC data on the clade 2.3.4.4b A/Washington/239/2024 virus in ferrets shows that it did not transmit by RDT transmission, and the A/California/147/2024 is genetically related to the clade 2.3.4.4b A/Washington/239/2024 (H5N1) virus. In addition, there was inefficient transmission in the direct contact model yielding 2 of 3 transmission events further suggesting a low-to-moderate risk for this current H5N1 virus.

**Receptor Binding:** Sequence analysis of the A/California/147/2024 virus (genotype B3.13) and A/Washington/239/2024 virus (genotype D1.1) did not show any characteristic HA substitutions at residues 190, 225, 226, and 228 (H3 numbering) that were previously shown to switch binding preference from avian-like ( $\alpha$ 2,3-linked sialic acid) to human-like ( $\alpha$ 2,6-linked sialic acid) receptors. Compared to A/Texas/37/2024, the first human B3.13 virus, A/California/147/2024 has three HA substitutions (D95G, V135M and S323N); only position 135 resides in the receptor-binding site. While the HA of A/Washington/239/2024 belongs to a distinct Eurasian lineage of clade 2.3.4.4b (EA3) compared to A/Texas/37/2024 (EA1) and has eight substitutions, none are in the receptor-binding site.

**Population Immunity:** Several recent studies have suggested that pre-existing antibodies could confer some protection against A(H5N1) virus infection and lessen severe disease. In two different studies conducted in ferrets, ferrets that were previously infected with or who had antibodies to seasonal influenza A(H1N1)pdm09 virus had developed cross-reactive antibodies to some components of an HPAI A(H5N1) virus and had less severe disease [32,33]. Additionally, CDC conducted a comprehensive assessment of the population immunity in the United States to HPAI clade 2.3.4.4b A(H5N1) viruses using 1794 sera collected from 723 people during 2021-February 2024 [34]. No neutralizing antibody titers to 2.3.4.4b A(H5N1) virus and low HA head binding antibodies to these viruses were detected. However, there were substantial levels of pre-existing neuraminidase antibodies (both NA binding antibodies and functional NA inhibitor (NAI) antibodies), and various levels of HA stalk antibodies in the population. NAI and HA stalk antibodies are associated as correlates of protection against influenza. Notably, NAI antibodies can reduce viral replication and are associated with lessening of disease severity. These data demonstrate that although the pre-existing neutralizing antibodies to clade 2.3.4.4b A(H5N1) viruses in the population were low to none, the US population is not totally immunologically naive to the 2.3.4.4b A(H5N1) viruses.

**Infections in Animals:** Since the emergence of B3.13 genotype viruses in March 2024, such as the A/California/147/2024 virus, there has been sustained transmission among dairy cattle and repeated sporadic infections in multiple other species (e.g., wild birds, cats, mice, domestic poultry) and humans. Additionally, the D1.1 genotype viruses, such as the A/Washington/239/2024 virus, are among the most common viruses currently circulating in wild birds and detected in poultry in North America, and the two documented transmissions of D1.1 genotype viruses to dairy cattle may suggest a low barrier of transmission to dairy cows. These events meet the criteria of moderate risk.

**Genomic Analysis:** Both the A/California/147/2024 virus (genotype B3.13) and A/Washington/239/2024 virus (genotype D1.1) arose through reassortment between Eurasian highly pathogenic avian influenza (HPAI) viruses and North America low pathogenic avian influenza A viruses. However, in the year since the first B3.13 isolate was found, these viruses have not undergone further reassortment in dairy cattle and have not acquired many new mutations relevant to mammalian adaptation. A/California/147/2024, like the majority of B3.13 isolates, does contain the PB2 M631L mutation, which is a marker of mammalian adaptation. Additionally, the PB2 E627K mutation found in the early A/Texas/37/2024 virus has not been commonly found in other B3.13 viruses. The PB2 M631L mutation has not been found in the D1.1 genotype viruses, and the PB2 E627K mutation is very rare. Both genotypes, however, contain the polybasic cleavage site in the HA which is a marker of virulence in mammals and birds.

**Antigenic Relatedness:** Antigenic testing showed that clade 2.3.4.4b A(H5) CVVs had good cross-reactivity with A/California/147/2024 and related viruses. Cross-reactivity of a majority of these viruses was equivalent or within 4-fold to homologous virus titers to IDCDC-RG78A (A/American Wigeon/South Carolina/22-000345-001/2021-like CVV), IDCDC-RG71A (A/Astrakhan/3212/2020-like CVV) and IDCDC-RG80A (A/chicken/Ghana/AVL-763\_21VIR7050-39/2021-like CVV). Antigenic analysis of A/Washington/239/2024 (D1.1 genotype) from CDC showed the virus reacted well to post-infection ferret antisera raised against current CVVs, such as the A/Astrakhan/3212/2020, A/American Wigeon/South Carolina/22-000345-001/2021 and A/chicken/Ghana/AVL-763\_21VIR7050-39/2021 CVVs.

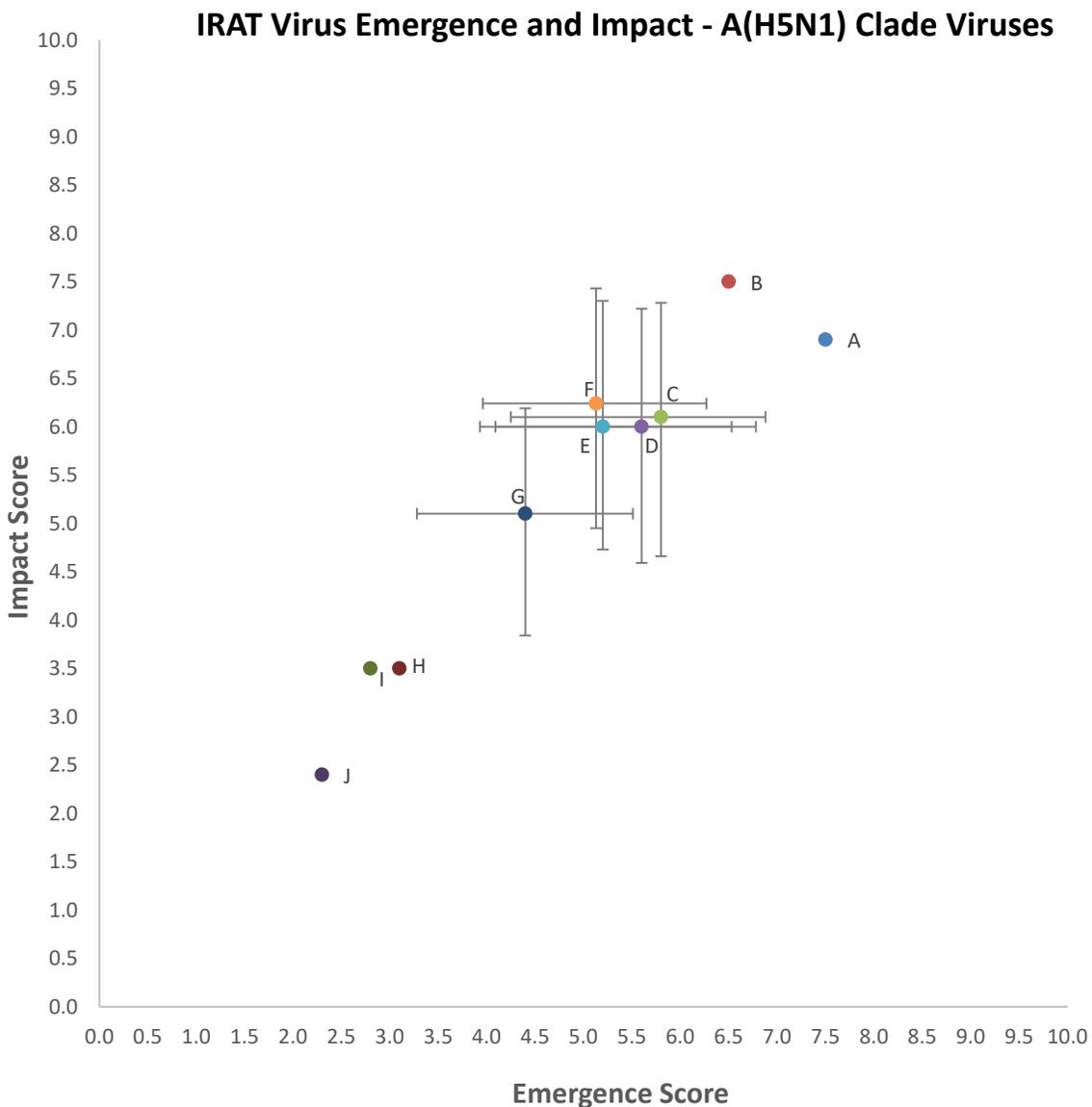
**Global Distribution in Animals:** Considering the B3.13 viruses as a group: These viruses are widespread within the United States, having been identified in dairy cattle in at least 17 states. Spread within and between states may be related to dairy cattle movement, but this has not been demonstrated in every situation, and it remains possible that these viruses are also spreading via wild birds, fomites, or feeding practices. Spread has been rapid; within a year of the first identified case, more than 1000 infected dairy herds in 17 states have been found, as well as infections in many other species, and this is probably a significant underestimate in the absence of routine testing. Considering the D1.1 viruses as a group: These viruses have rapidly spread from the West Coast to multiple regions within the United States (Midwest, Southwest, Southern states), generally consistent with wild bird migration patterns. The viruses are endemic within wild birds but also have repeatedly caused infections in other species (domestic poultry, cats, cattle) and humans. Sustained transmission may have occurred within dairy herds and poultry flocks, although the details are unclear. The virus has not yet become endemic in species other than wild birds, although information is lacking for cattle, in particular. Further studies of cattle, wild birds, and other species (domestic poultry, cats) in the United States and in other countries would help with understanding the extent of spread.

**Disease Severity and Pathogenesis:** From March 2024 to present, 52 human infections with A(H5) clade 2.3.4.4b B3.13 genotype viruses, such as A/California/147/2024, have been identified. Except for one hospitalized case in MO with an unknown exposure source, all cases of human infection with this virus have been mild. No cases with direct exposure to infected dairy cows have been hospitalized and none have died. The most common clinical manifestation has been conjunctivitis. All cases have had complete resolution of symptoms and most received early antiviral treatment. Because there have been human cases of infection with this virus, it falls in the moderate risk category. In contrast, both mild and severe illness has been reported with infection by A(H5) clade 2.3.4.4b D1.1 genotype viruses such as A/Washington/239/2024, including four human cases (including the patient in Canada) with severe lower respiratory disease, including one fatality [35]. While there have been other mild illnesses among workers being monitored after occupational exposure to infected poultry and dairy cattle, the proportion of known human cases of A(H5) clade 2.3.4.4b D1.1 genotype viruses in North America with severe disease (4 of 17) is concerning. The four cases hospitalized in the United States had delayed care and/or underlying conditions that may increase the risk of severe outcomes. Ferret models indicate high lethality with this virus. Findings from the ferret study report for this A(H5) clade 2.3.4.4b D1.1 genotype virus indicate: "virus possessed a high capacity to cause fatal disease, characterized by high morbidity, viremia, and extrapulmonary spread to multiple organs" [36]. While there is some limited evidence in animal models of disease attenuation in ferrets from challenge with other 2.3.4.4b virus when ferrets had previous exposure to influenza A(H1N1)pdm09 virus, similar studies have not yet been reported for this virus.

**Antivirals and Treatment Options:** Neither A/California/147/2024 nor A/Washington/239/2024 virus has known or suspected mutations associated with reduced susceptibility to FDA-approved antivirals (NA, PA-CEN, and M2 inhibitors). The NA inhibitor oseltamivir was 12-fold less effective at inhibiting the NA enzyme activity of A/California/147/2024 and 11-fold less effective at inhibiting the NA enzyme activity of A/Washington/239/2024 compared to seasonal influenza A viruses in a biochemical assay [36-39]: this inhibition effect has been previously observed [40]. NA-H275Y has not yet been detected in genotype B3.13 viruses, including A/California/147/2024. However, these viruses share a combination of NA-R257K and NA-T289M mutations, which are considered "permissive" mutations as they can counteract the functional defect caused by NA-H275Y [41]. Additionally, genotype D1.1 viruses share the NA-T289M mutation [42]. Phenotypic data by CDC [33-35] and St. Jude [43-45] showed that clade 2.3.4.4b viruses (lacking any PA mutations of concern), including A/California/147/2024 and A/Washington/239/2024, were susceptible to baloxavir. Finally, in addition to detections in the United States, A(H5N1) clade 2.3.4.4b D1.1 genotype viruses were observed in poultry in British Columbia, Canada. Analysis of these viruses revealed a mutation in NA-H275Y and showed resistance to oseltamivir [46].

### Comparison to other Viruses Scored with IRAT

The average score estimates for the potential emergence and public health impact risk scores for the HPAI A(H5N1) clade 2.3.4.4b A/California/147/2024 and A/Washington/239/2024 viruses were plotted along with the scores of the virus that has had the highest emergence score, A(H1N1) [A/swine/Shandong/1207/2016], the virus with the highest impact score, (A(H7N9) [A/Hong Kong/125/2017]), the three lowest scoring viruses, and the previous A(H5N1) clade 2.3.4.4b viruses scored using the IRAT (Figure). The estimates for the current A(H5N1) clade 2.3.4.4b viruses were in the mid-moderate range for both risk of potential emergence and risk of potential public health impact. Additionally, the range of the mean low acceptable and the mean high acceptable scores of A/California/147/2024 and A/Washington/239/2024 viruses overlap with the previously scored A(H5N1) clade 2.3.4.4b viruses (Figure).



Label	Influenza Virus	Emergence Score	Impact Score
<b>A</b>	A(H1N1) [A/swine/Shandong/1207/2016]	7.50	6.90
<b>B</b>	A(H7N9) [A/Hong Kong/125/2017]	6.50	7.50
<b>C</b>	A(H5N1) [A/Texas/37/2024]	5.79	6.12
<b>D</b>	A(H5N1) [A/California/147/2024]	5.59	5.91
<b>E</b>	A(H5N1) [A/Washington/239/2024]	5.21	6.00
<b>F</b>	A(H5N1) [A/mink/Spain/3691-8_22VIR10586-10/2022]	5.13	6.24
<b>G</b>	A(H5N1) [A/American wigeon/South Carolina/AH0195145/2021]	4.44	5.10
<b>H</b>	A(H7N9) [A/chicken/Tennessee/17-007431-3/2017]	3.10	3.50
<b>I</b>	A(H7N9) [A/chicken/Tennessee/17-007147-2/2017]	2.80	3.50
<b>J</b>	A(H1N1) [A/duck/New York/1996]	2.30	2.40

Figure: Updated potential pandemic risk for HPAI A(H5N1) clade 2.3.4.4b viruses plotted by emergence and impact average weighted risk score estimates. The most recent 2.3.4.4b viruses scored are labeled “B” (A/California/147/2024) and “C” (A/Washington/239/2024). 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.

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