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The CEIRR Risk Assessment Pipeline Executive Report:

Assessment of the Pandemic Potential of 2.3.4.4b H5N1 Influenza Viruses of the D1.1 genotype

Prepared by the CEIRR Risk Assessment Pipeline
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Priority for Risk Assessment and Risk Mitigation: High

Executive Summary: Highly pathogenic H5N1 avian influenza viruses of the 2.3.4.4b lineage continue to circulate widely in animals in North America. The D1.1 genotype dominated this circulation in 2025 and infected several humans. While population immunity specific for this virus is low, prior infection with seasonal influenza is expected to offer some protection. Continued monitoring of prevalence and research on the evolution and transmission of these viruses will help clarify pandemic risk.

Background: Wild birds are the ultimate source of all influenza pandemics, of which there have been four since 1918. H5N1 influenza viruses circulating in wild birds and poultry have been a concern for decades. Since 2003, WHO has documented approximately 1,000 human cases with a fatality rate of 49%. Although longstanding, the threat of H5N1 is dynamic. Since 2022, highly pathogenic H5N1 avian influenza of the 2.3.4.4b lineage has become established in the wild birds of North America. These viruses have diversified through genetic exchange with low pathogenicity strains, giving rise to dozens of distinct 2.3.4.4b genotypes. In 2025, the D1.1 genotype spread widely within North American wild birds and spilled over repeatedly into poultry and several mammalian species including humans. H5N1 infection of mammals is unusual and heightens potential for adaptation to humans. Because related viruses have not circulated widely in humans, population immunity against the virus is low. The following data summary focuses on features of the D1.1 genotype that differ from previously dominant forms of H5N1 2.3.4.4b viruses.

Properties of the Virus | Genetic diversity

- Genetic exchange between H5N1 2.3.4.4b viruses and low pathogenicity avian influenza viruses is common. The D1.1 genotype formed through such reassortment following an introduction of 2.3.4.4b virus to the West Coast of North America.
- The NA gene of the D1.1 genotype differs from those of previous genotypes that spread widely in North America. This gene encodes a major antigenic determinant of the virus, such that D1.1 may be recognized differently by the human immune system.
- Mutations in the PB2 gene that improve viral replication in mammals have been detected following spillover into mammalian hosts, including humans.

Virus ecology and epidemiology | Geographic distribution in animals

- In 2025, viruses of the D1.1 genotype spread in wild birds across the United States and Canada. They have not been reported outside of North America.
- The virus spread from wild birds into poultry, cats, cattle and other species. Human cases were associated with poultry outbreaks, cattle outbreaks or had no known exposures.

Attributes in the Human Population | Population Immunity

- Human sera contain antibodies that bind to and prevent the activity of the NA protein of D1.1 viruses. Levels are slightly higher than those detected with the NA of other clade 2.3.4.4b H5N1 viruses. These antibodies could provide some protection against infection or disease.
- Ferrets with immunity to seasonal human H1N1 influenza viruses were protected against infection and disease upon infection with D1.1 genotype H5N1 virus.