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The CEIRR Risk Assessment Pipeline Executive Report:

Assessment of the Pandemic Potential of 2.3.4.4b H5N1 Influenza Viruses

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

Executive Summary: Through movement of wild birds, highly pathogenic H5N1 influenza A viruses of the 2.3.4.4b lineage spread across the globe in 2020–2022. This expansion was marked by genetic diversification and frequent spillover into mammals, including US dairy cattle. Dozens of human cases have been documented. Replication in mammals has led to adaptation of concern for humans, but not the use of receptors prevalent in the human respiratory tract. 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, with nearly 1,000 human cases documented since 2003 and a fatality rate of 49%. Although longstanding, the threat of H5N1 is dynamic. A new lineage, 2.3.4.4b, emerged in Europe in 2016 and underwent a major geographic expansion in wild birds between 2020 and 2022, spreading across Europe and reaching Asia, Africa, North America and South America. As it expanded, the virus diversified genetically and spread from wild birds into dozens of mammalian species, including US dairy cattle. H5N1 infection of mammals is unusual and heightens potential for adaptation to humans. Dozens of human cases stemming from the US dairy outbreak have been documented. Because related viruses have not circulated widely in humans, population immunity against the virus is low.

Virus ecology and epidemiology | Geographic distribution in animals

- H5N1 2.3.4.4b virus was introduced into Texas dairy cattle from wild birds in late 2023 or early 2024. The movement of cattle, rather than further introductions from birds, enabled spread among US dairy herds.
- H5N1 2.3.4.4b viruses transmitted from cattle to humans, poultry, cats, and other species.
- Circulation in pigs has not been detected. Experimental inoculation of pigs showed them to be susceptible to infection with H5N1 2.3.4.4b viruses of both avian and mammalian origin. Only the viruses of mammalian origin transmitted to contact pigs. Mammalian adaptation may increase the risk for incursion into swine.

Properties of the Virus | Genetic diversity

- Genetic exchange between H5N1 2.3.4.4b viruses and low pathogenicity avian influenza viruses is common and has produced dozens of different viruses that carry the H5 2.3.4.4b HA gene. These viruses can show differing pathogenicity and transmissibility in animal models but the extent to which these changes have driven waves of infection in wild and domestic animals is unclear.
- Mutations in the PB2 gene that improve viral replication in mammals have been occurred repeatedly, following spillover into various mammalian hosts.

Properties of the Virus | Receptor Binding

- The HA protein of influenza A viruses binds to cellular receptors to initiate infection. The receptors used in avian hosts differ from those used in humans, making this viral trait an important determinant of pandemic potential.
- The receptor usage of multiple H5N1 2.3.4.4b viruses from wild birds and dairy cattle were tested and all used α2,3 receptors. This specificity is a feature of adaptation to birds and impairs viral propagation in humans.

Properties of the Virus | Transmission

- H5N1 2.3.4.4b viruses spread readily among ferrets when animals were placed in the same cage. Transmission that requires virus transfer through the air was observed in some cases but was not efficient. Ferrets are the primary animal model used to evaluate influenza virus transmission.
- Infectious influenza virus persists on milking equipment for hours but is inactivated under heating conditions that mimic pasteurization.

Attributes in the Human Population | Population Immunity

- Antibodies that bind to 2.3.4.4b H5 HA protein are prevalent in human sera, especially sera from those born prior to 1968, but antibodies that reduce infection were typically not detectable.
- Ferrets with immunity to seasonal human H1N1 influenza viruses were protected against infection and disease upon infection with H5N1 2.3.4.4b virus.