

Emerging H5N5 clade 2.3.4.4b viruses with enhanced fitness in birds and mammals

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H5N5 HPAIV clade 2.3.4.4b have increased in prevalence across Eurasia and North America and were associated with human infection in the US. Their evolution and zoonotic potential remain insufficiently characterised.

We analysed global H5N5 prevalence (2000–2026) and assessed 4 representative viruses in chickens and ducks. Zoonotic potential was evaluated in airway epithelial (ALI) cultures and ferrets. NA activity, replication, antigenicity, and antiviral susceptibility were compared.

H5N5 viruses show intercontinental spread with distinct Eurasian and North American lineages and multiple introductions into Canada and Japan. Recent strains after 2023 form a cluster with NA stalk deletions and mammalian markers. These viruses exhibit significantly increased NA activity since 2020, while remaining susceptible to NA inhibitors.

Recent isolates were more virulent and transmissible, with higher replication efficiency in chickens and ducks than earlier H5N5 viruses. In ferrets, they caused severe systemic disease with neurological signs and weight loss. Replication was observed in ALI cultures.

Our findings demonstrate H5N5 clade 2.3.4.4B HPAIV acquired enhanced NA activity, expanded host range, and capacity for severe disease in mammals. Increasing prevalence in wild birds, poultry, and mammals, combined with intercontinental spread and preserved antiviral susceptibility, supports inclusion in pandemic preparedness. Recent H5N5 mammalian potential warrants urgent risk assessment.

Keywords

H5N5, clade 2.3.4.4B, highly pathogenic avian influenza, ferret model, zoonotic risk, neuraminidase activity, intercontinental spread

Professional status of the speaker

Postdoc

Junior scientist status

Yes, I am a junior scientist.

Registration ID

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