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Zoonotic Risk Assessment of 2.3.4.4b H5Nx Avian Influenza-A Viruses Reveals Intermediate Host Systems as Key Determinants of Productive Replication in Primary Human Lung Tissues

Inhalt

Clade 2.3.4.4b H5Nx highly pathogenic avian influenza viruses (HPAIVs) have diversified extensively during global spread, yet the determinants of their zoonotic potential remain incompletely understood. We characterized eleven genetically distinct H5Nx isolates collected in Germany between 2016 and 2021 using comparative genomics and physiologically relevant human respiratory models. Despite representing multiple reassortant lineages with some substitutions linked to mammalian fitness, none encoded canonical mammalian-adaptive markers PB2-E627K, PB2-D701N, or PB2-Q591K. All isolates replicated efficiently in avian and mammalian cell lines regardless of propagation history. In contrast, primary human lung explants and differentiated nasal epithelial air-liquid interface cultures revealed a propagation-dependent phenotype: Egg-derived viruses exhibited no infectivity, while the same isolates propagated in MDCK cells established productive infection in both upper and lower respiratory tract models. Repropagation in eggs restored the restricted phenotype without adaptive mutations, implying reversible host-dependent factors, potentially including glycosylation-related changes. All viruses exhibited susceptibility to oseltamivir. These findings identify propagation host as a key determinant of 2.3.4.4b H5Nx infectivity in human respiratory tract, highlighting the value of primary human respiratory models for improving zoonotic risk assessment beyond genomic surveillance alone.

Keywords

H5Nx Viruses, Zoonotic Potential, Avian Influenza, Human Lung, ex vivo Infection

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No, I am not a junior scientist.

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