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HPAIV H5N1: Critical Research Needs on Animal Models

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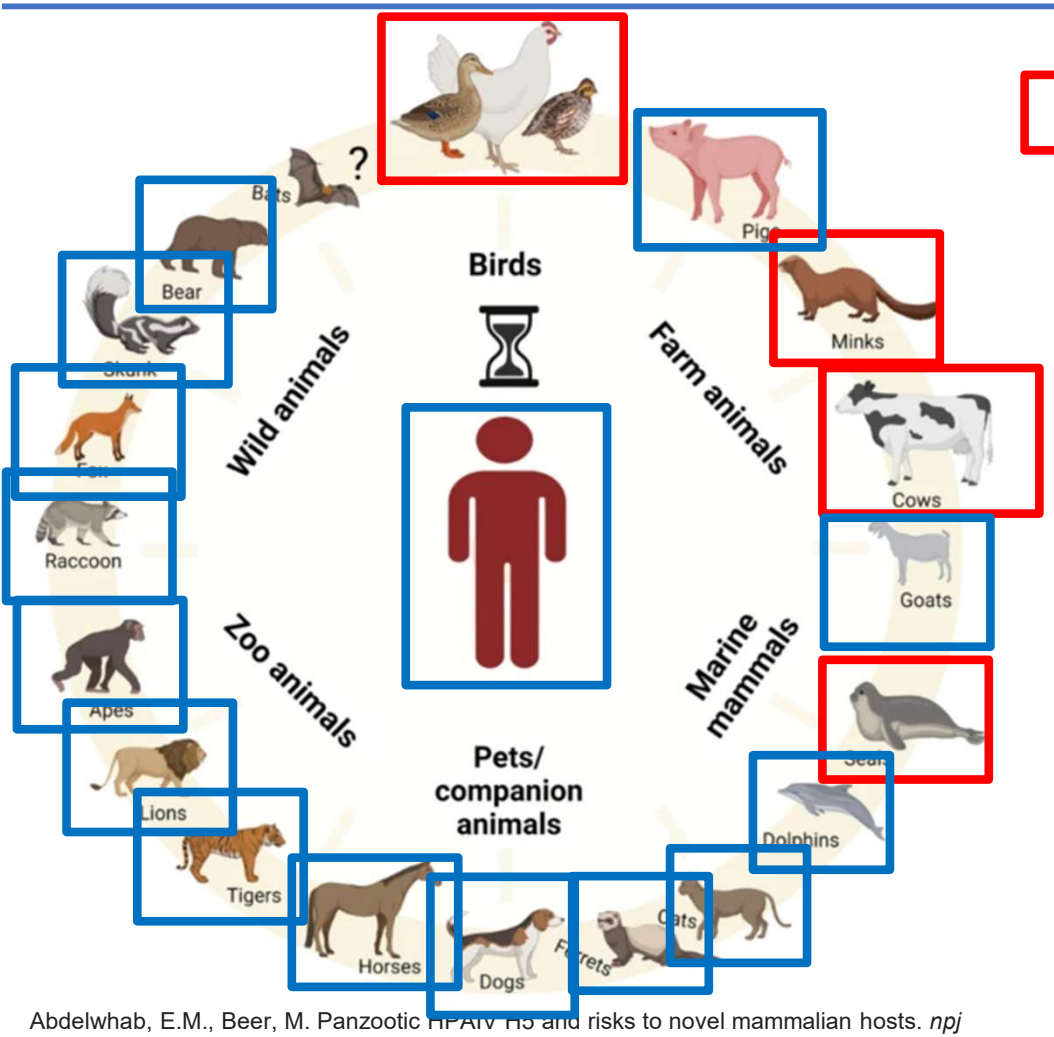
for
the „WHO animal group“

What research is important to prepare and respond to H5N1 influenza outbreaks?

19th March 2025

World Health Organization

HPAIV H5N1 2.3.4.4b - broad host range - spill-over - zoonotic risks



Abdelwhab, E.M., Beer, M. Panzootic HPAIV H5 and risks to novel mammalian hosts. *npj Viruses* **2**, 22 (2024). https://doi.org/10.1038/s44298-024-00039-z

Circulation

"dead-end"-host

Research questions:

Species-Specific Susceptibility and Pathogenesis

Immune Response (adaptive/innate) and Inflammation

Zoonotic Risks and Transmission Models

Testing of Vaccines and Antivirals

Viral Evolution and Host Adaptation

Comparative Models

Chronic and Long-Term Effects

Ethical and Practical Considerations

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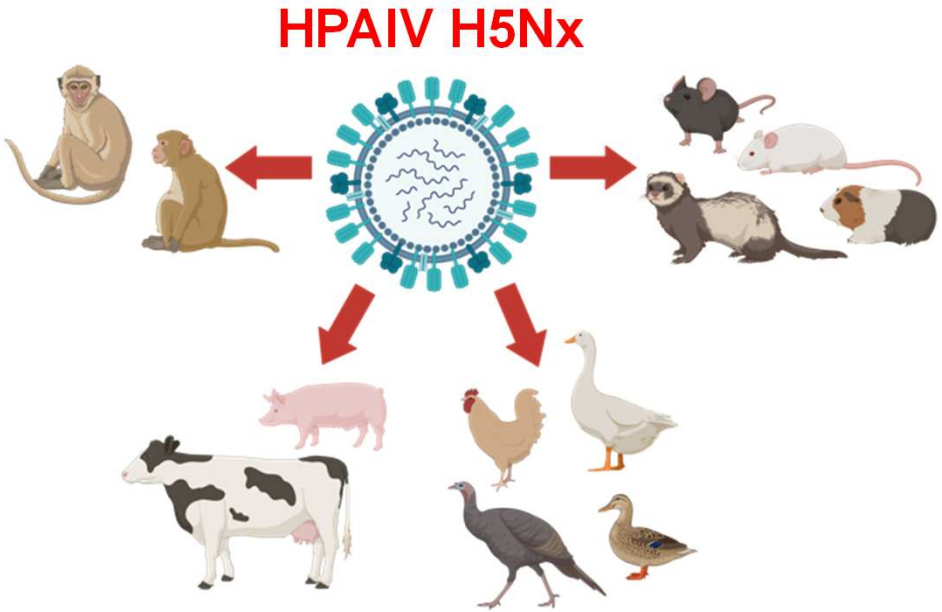
HPAIV H5N1 2.3.4.4b animal models – selection of key examples



Created with BioRender.com

Pathogenesis in target animals:

- Chicken/ducks (lethal infection)
- Ferrets (high susceptibility)
- Pigs (low susceptibility)
- Cows (replication in the mammary gland)

Zoonotic potential:

- MxA mouse model
- Ferrets (cave: encephalitis!)
- Non-human primates

Transmission models (direct/aerosol):

- Ferrets
- Guinea pigs
- (Pigs)

Vaccines/antivirals/cross immunity:

- Mouse models
- Ferrets
- Non-human primates
- (Pigs)

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H5N1 clade 2.3.4.4b: Key results - research needs/gaps (1)

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- General: **Genotype differences** in virulence and transmission
  (more than 200 genotypes/reassortants of clade 2.3.4.4b!)
- Ferrets: Moderate to fatal disease, **no or inefficient aerosol transmission**
  Protective cross immunity shown after H1N1pdm infection
- Human MxA mice: 2.3.4.4b viruses show **no escape from MxA response**
- Pigs: **Low susceptibility,** low level replication (dose/route dependent), **no transmission**
- Calves/cows: Intranasal infection inefficient, **no nasal spread**; highly efficient
  replication in the mammary gland, high level milk shedding
- Non-human primates: **Mild to severe disease** (**dose-dependent, route of infection**)
- Vaccine testing: **Successful** in mice, ferrets, non-human primates

H5N1 clade 2.3.4.4b: Key results - research needs/gaps (2)

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- **Harmonization** e.g. of inoculation titers, inoculation routes or group size
- **Pathogenesis data** in different in vivo models
- **Capacity to test the large number** of genotypes / reassortants
- Need for **alternative in vitro methods** (e.g. organoid cultures) to allow improved pre-selection (following 3R principles)

- Correlates to **determine zoonotic/pre-pandemic potential** (improved risk analysis/prediction; potential of possible ressortants, GoF)
- More data on **genotype-phenotype** association
- Analysis of **neurotropism** (birds, carnivores) and **exceptions** (humans, cows)
- **Susceptibility** of other ruminant species (goats, sheep, deer)

- Factors associated with **low susceptibility in pigs**
- **Barriers to efficient respiratory replication** and transmission (e.g. in cattle)

- **Availability of field data** and linking to trial data (e.g. missing field data from cows)

Thank you for your attention!