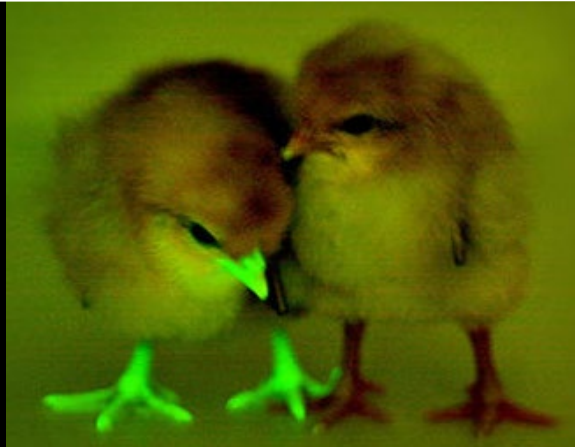
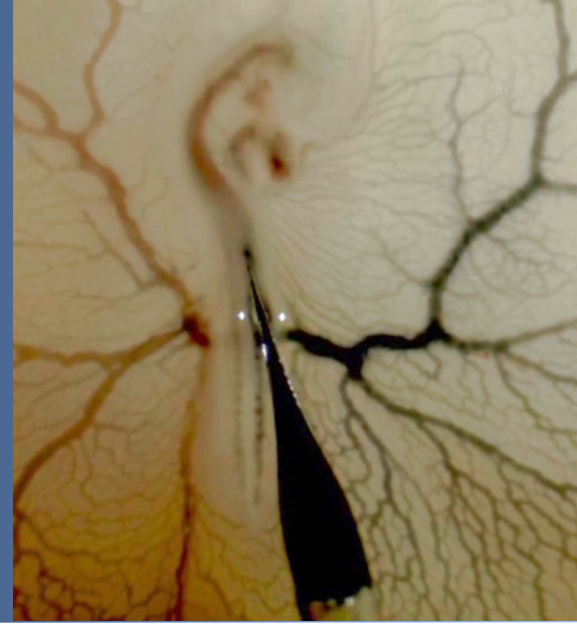




A Brief Overview of Avian Influenza Virus

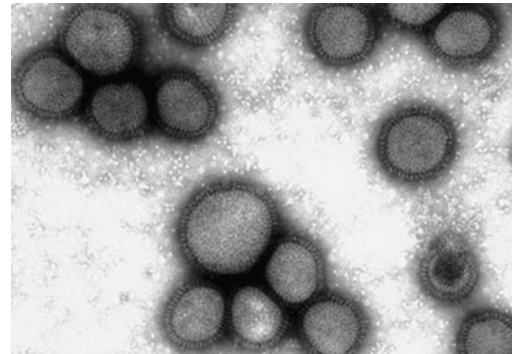
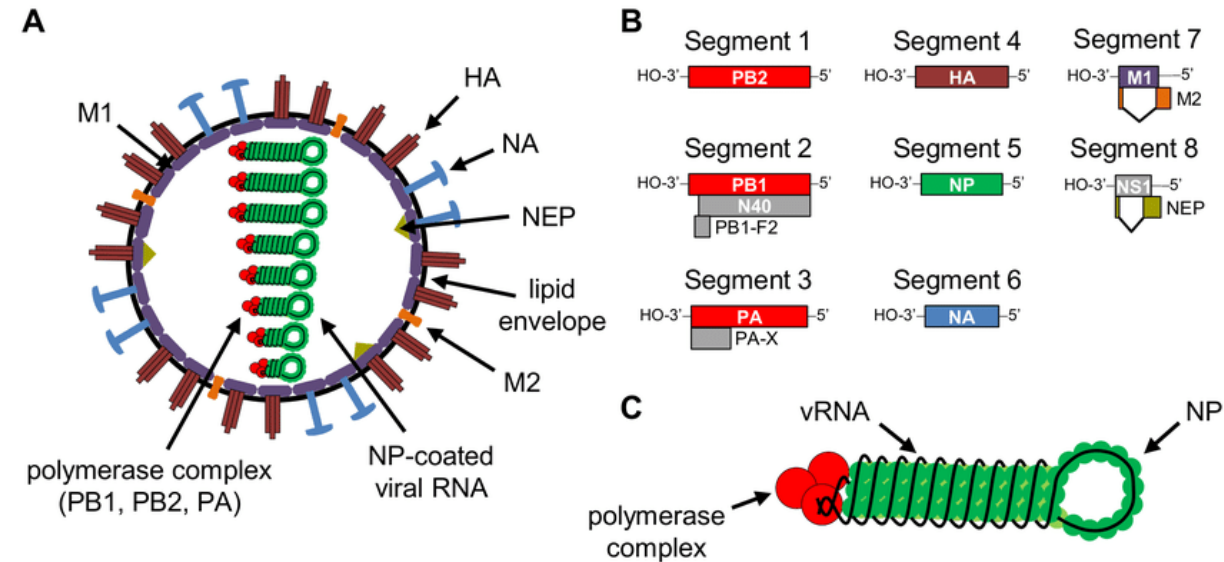


Darrell R. Kapczynski

U.S. National Poultry Research Center, ARS, USDA, Athens, Georgia, U.S.A
NASEM Heritable Genetic Modification of Food Animals- Feb 28th, 2024

Avian influenza virus

- ❑ AIV is classified in the family Orthomyxoviridae, genus Influenza A (Type A).
- ❑ Contains a segmented, negative-sense RNA genome wrapped in enveloped, pleomorphic particles.
- ❑ 8 RNA Segments coding for 10+ proteins
- ❑ Virus subtype defined by surface proteins
 - Hemagglutinin (HA) H1-H16- **attachment**
 - Neuraminidase (NA) N1-N9- **release**
- ❑ Receptor binding to host cells:
 - ❑ Avian influenza HA binds alpha 2,3 linked sialic acid gal
 - ❑ Human influenza HA binds alpha 2,6 linked sialic acid gal



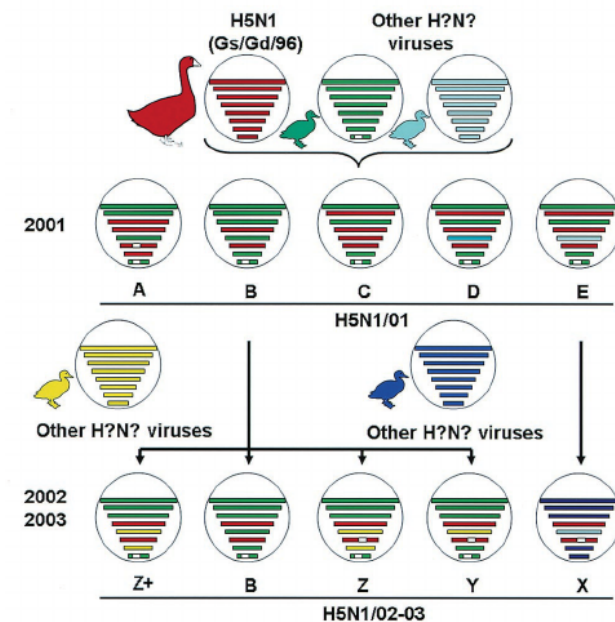
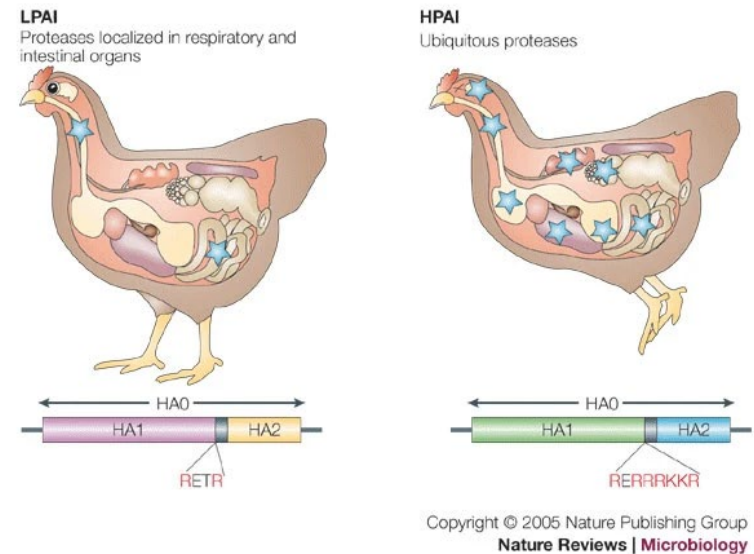
Poultry origin



Wild bird origin

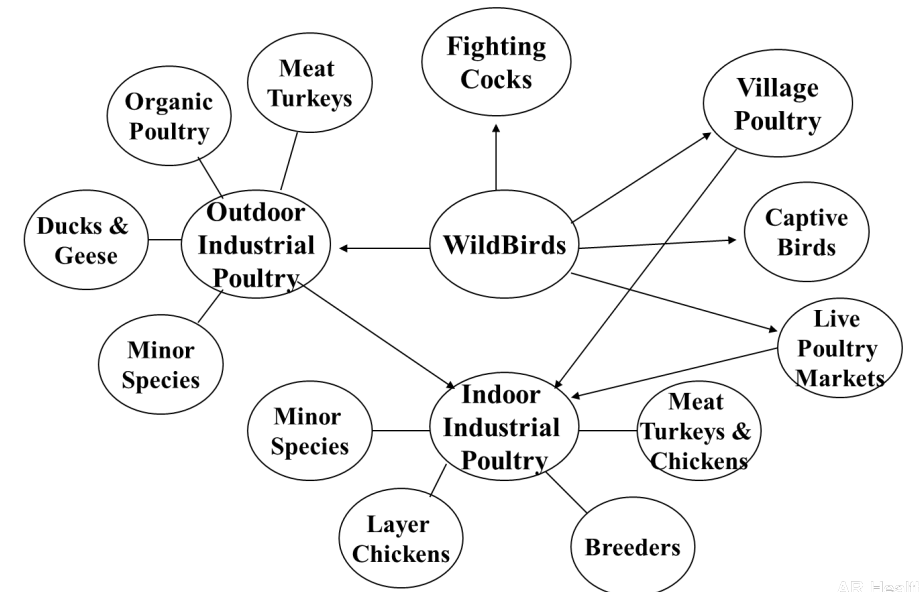
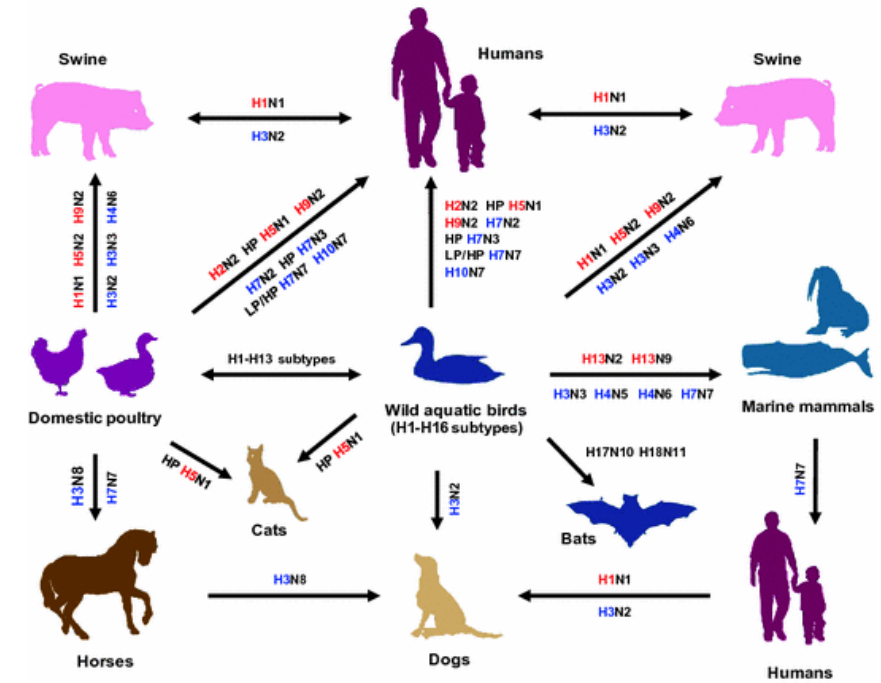
Avian influenza virus

- The viruses are divided into low-pathogenic AI (LPAI) and highly pathogenic AI (HPAI) strains. HPAI strains result in high mortality, while LPAI causes milder symptoms, but have demonstrated the ability to mutate and evolve into HPAI.
- In molecular terms, HPAI viruses are defined as possessing an **H5 or H7** subtype HA with a polybasic sequence at the cleavage site that confers HA cleavage in deep tissue with furin-like enzymes.
- LPAIV-→HPAIV Increase in basic amino acids at HA cleavage site. Genetic insertion of chicken 16S RNA (H7N3 Mexico, 2013).
- Genetic drift-Substitution rate $\sim 5 \times 10^{-3}$ per site per year (10-70 nucleotides per year across genome).
- Genetic shift-Reassortments between all segments. Segment swapping-infection by two or more viruses in a host.
 - Generates reassortants within wild birds.

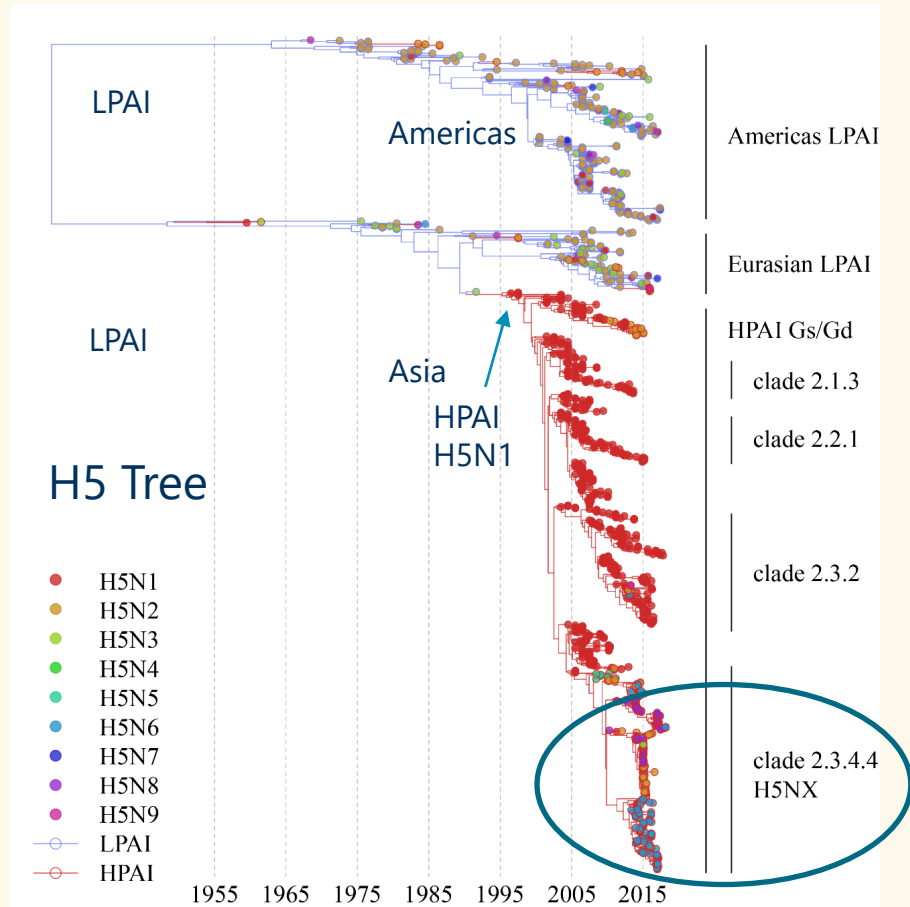


Ecology of Avian Influenza Virus

- Avian influenza virus (AIV) is endemic in wild birds
- Transmission of AIV from wild birds to poultry species (ducks, chickens, turkeys) occurs commonly
- AIV on rare occasions may become adapted to and become endemic in poultry species (chickens and turkeys)
- AIV once adapted to chickens and turkeys can be difficult to eradicate



A Brief History of High Path Bird Flu (H5)



- HPAI H5N1 circulating in Asia since 1996 (Goose/Guangdong/1996)
- Major outbreak in wild birds (Qinghai lake) 2005
- Ongoing epidemics in Asia and Europe
- Spread between domestic birds, but also to/from wild birds
- Unusual HPAI H5 clade – multiple NA subtypes



Influenza A Viruses Separate Into Genetic Lineages



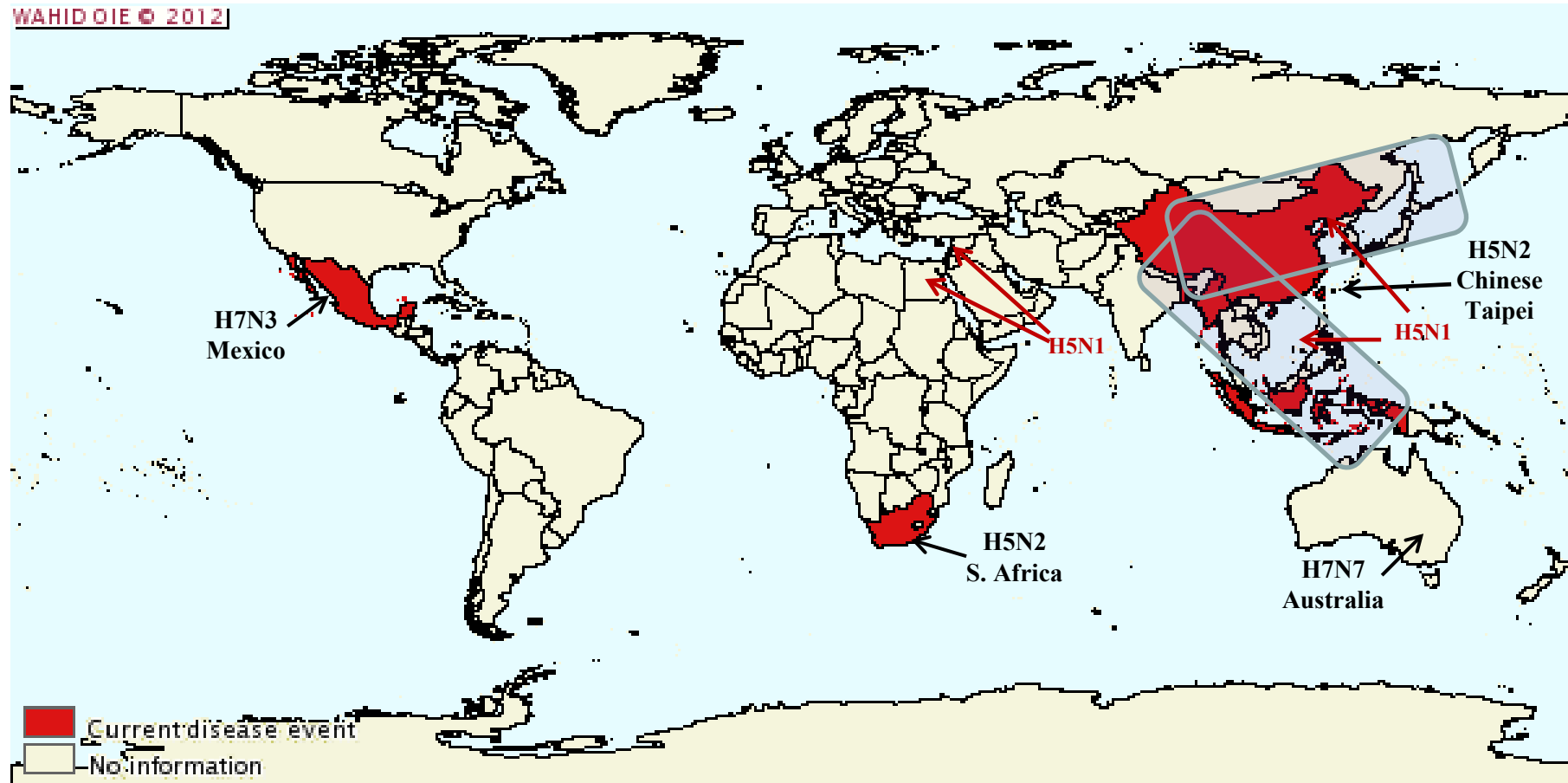
North American

H1
H2
H3
H4
H5
H6
H7
H8
H9
H10
H11
H12
H13
H14
H15



Eurasian

HPAI (2011-2013): 20 countries



H5N1 HPAI

16 countries – poultry,
wild birds, humans

H5N2 HPAI

S. Africa – ostriches
Chinese Taipei - poultry

H7N3 HPAI

Mexico - layers

H7N7 HPAI

Australia - layers

First long range transmission by wild birds 2014-2015



Species adaption of
virus to host:

Sick birds do fly

- if they are wild
anseriformes
- if H5N8/X

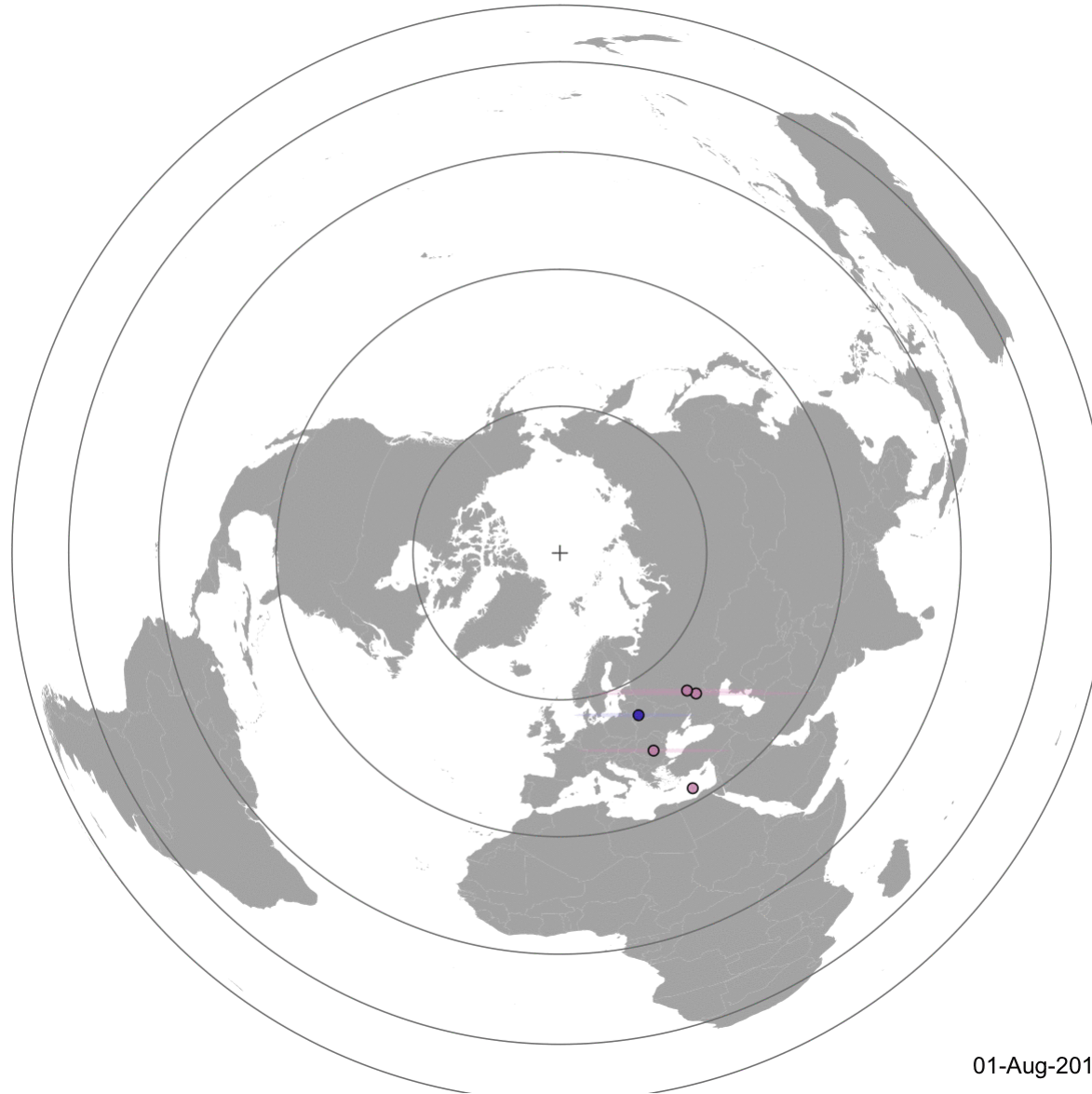
First detection of Asian lineage
H5 HPAIV in U.S.

North Pole Projection



H5NX 2020-2023 Reassortants From North Pole

- H5N1/2020/R2_Europe
- H5N1/2021/R2_Europe
- H5N1/2021/R4_Asia
- H5N1/2021/R5_Europe
- H5N1/2021/R7_Europe
- H5N1/2022/R1_NAmerica
- H5N1/2022/R10_NAmerica
- H5N1/2022/R12_Europe
- H5N1/2022/R13_NAmerica
- H5N1/2022/R2_NAmerica
- H5N1/2022/R3_NAmerica
- H5N1/2022/R4_NAmerica
- H5N1/2022/R8_NAmerica
- H5N5/2020/R1_Europe
- H5N8/2020/R1_Europe
- H5N8/2020/R2_Asia
- Other



01-Aug-2019

Record avian flu outbreak sees 48m birds culled in UK and EU

By Malcolm Prior
BBC News Rural Affairs Producer

42 minutes ago



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Avian flu infects 3 turkey flocks in same Missouri county

APHIS reported that 71,800 commercial meat turkeys in Dallas County have been claimed as a result of avian influenza.

Roy Graber
February 23, 2024



Source: pink.candy | BigStockPhoto.com

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Dr. Samantha Lycett at Univ. of Edinburgh.

Increased detections of H5N1 clade 2.3.4.4 HPAIV in mammals

Species jump into terrestrial and marine mammals.
No interspecies transmission reported to date.

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Animal DiseasesAvian InfluenzaShare your anniversary wish

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WAHIS

- Prevention and control
- International collaboration
- Resources
- FAQ

Information provided to WOA for detections of infection with high pathogenicity avian influenza virus in mammals according to Terrestrial Code Articles 1.1.3 or 1.1.5.

WOAH strongly encourages Delegates to report in a timely manner all cases of infection with high pathogenicity avian influenza viruses (HPAIV) detected in birds and in other species.

Summary of reports made according to Article 1.1.3.

Serotype, country, and species	Earliest outbreak report date	Latest outbreak report date	Number of outbreaks reported	More information
H5				
Argentina	25/08/2023	27/10/2023	18	
Chile	24/02/2023	28/07/2023	34	
Peru	17/08/2023	17/08/2023	3	
Uruguay	10/05/2023	15/11/2023	12	
H5N1				
Brazil	05/10/2023	15/12/2023	5	
Canada	06/05/2022	01/02/2024	40	
China (People's Rep. of)	25/02/2015	25/02/2015	1	
Estonia	17/12/2021	17/12/2021	1	
Finland	13/07/2023	15/02/2024	76	
France	28/12/2022	06/03/2023	2	
Germany	02/05/2023	06/02/2024	14	
Ireland	14/02/2022	20/12/2022	2	
Italy	05/05/2023	13/07/2023	3	
Japan	11/04/2022	03/07/2023	4	
Korea (Rep. of)	26/07/2023	04/08/2023	2	
Latvia	14/07/2023	14/07/2023	2	
Norway	26/07/2023	26/07/2023	1	
Russia	28/08/2023	28/08/2023	1	
United States of America	10/05/2022	16/02/2024	168	
H5N5				
Canada	24/05/2023	11/08/2023	2	
H5N8				
Denmark	10/04/2023	10/04/2023	1	

Summary of reports made according to Article 1.1.5.

Serotype, country, and species	First report date	Latest report date	Number of reports	M
H5N1				
Chile	03/05/2023	03/05/2023	1	
Denmark	25/09/2023	25/09/2023	1	
Peru	07/02/2023	07/02/2023	1	
Poland	12/07/2023	12/07/2023	1	
South Georgia and the South Sandwich Islands	13/01/2024	13/01/2024	1	
Spain	21/10/2022	21/10/2022	1	
Sweden	09/08/2023	15/01/2024	2	
United Kingdom	20/12/2022	26/10/2023	8	
H5N2				
United Kingdom	23/03/2023	23/03/2023	1	

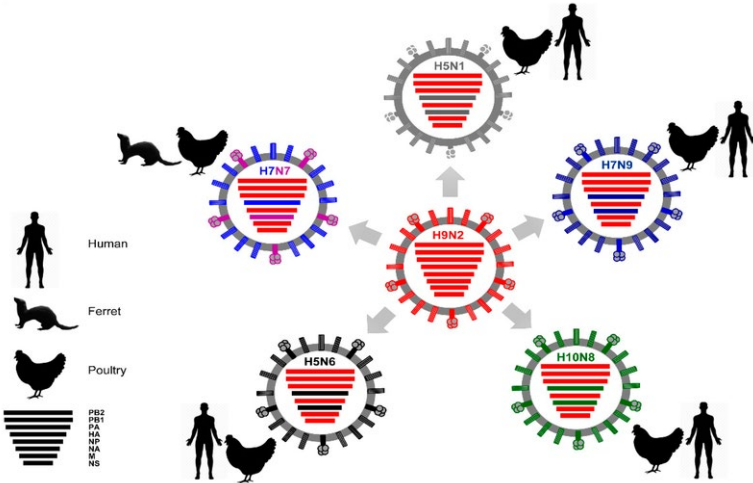
Mass sea lion deaths in Peru raise further fears bird flu is jumping between mammals

Scientists are monitoring the outbreak to see if the H5N1 virus was transmitted between the sea mammals or caught it directly from birds in the South American country



Scientists at the Paracas National Reserve inspecting a dead sea lion (Photo: Semang/Getty)

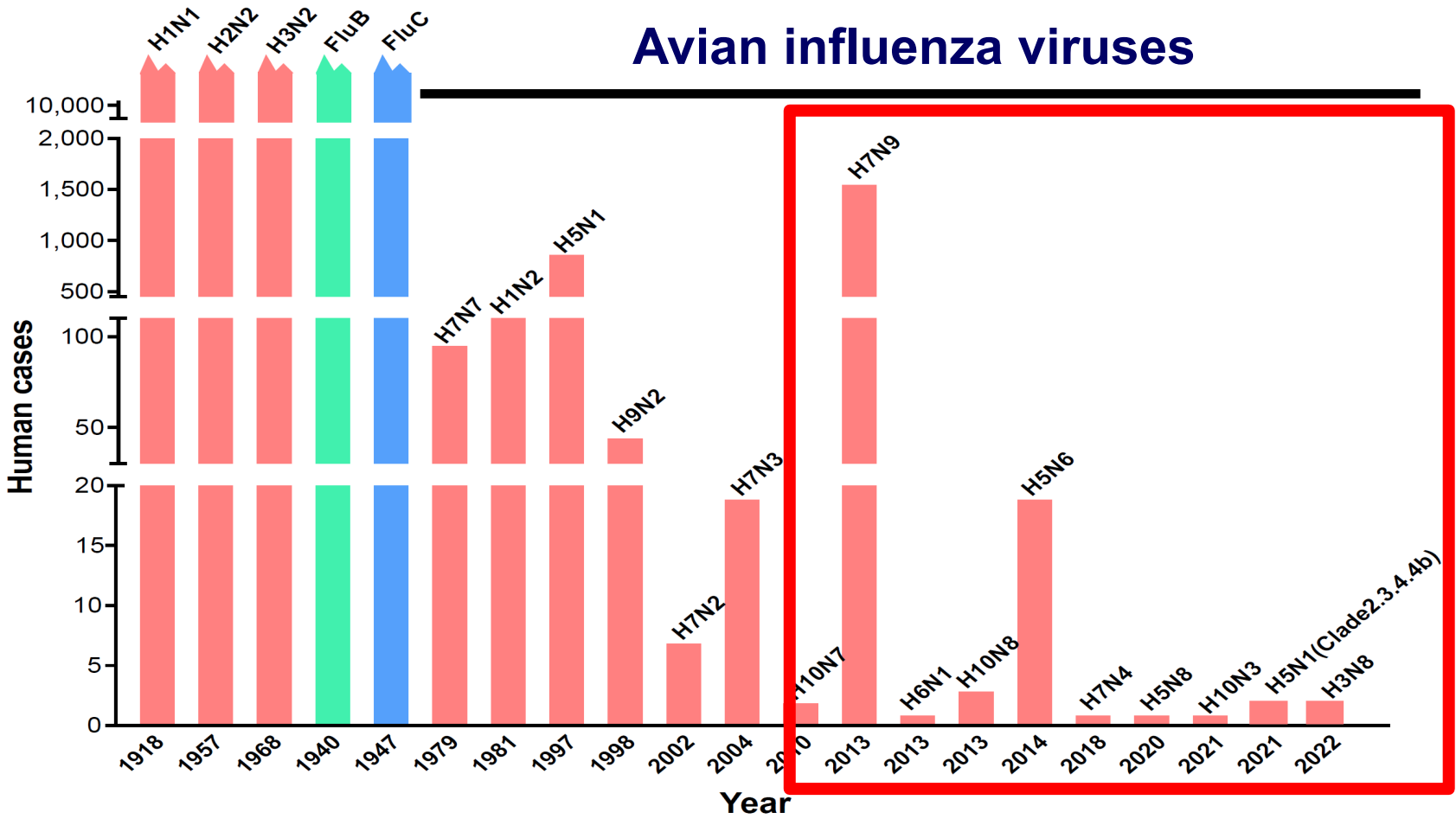
iNews 10/02/23



Avian influenza virus and human infections



At least **15 subtypes** of AIV have been identified that could directly infect human.



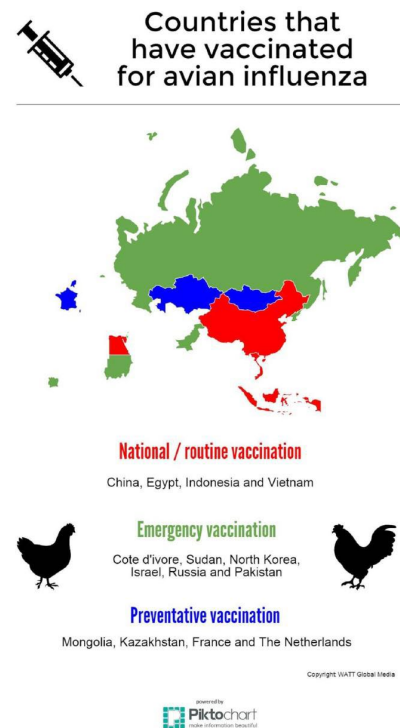
Strategies for control of HPAI

Traditional

Biosecurity



Vaccination



<https://www.wattagnet.com/articles/26165-infographic-nations-that-have-vaccinated-for-avian-flu>

Depopulation policy

“stamping out”

Genetic engineering

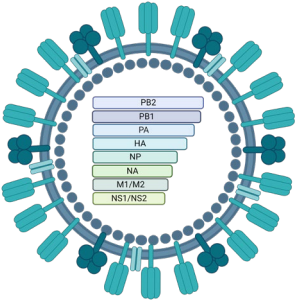
Disease resistance



Targets to research

- ❖ Inhibit virus attachment
 - ❖ Viral receptor
 - ❖ HA binding
- ❖ Inhibit virus replication
 - ❖ Polymerase complex
 - ❖ ANP32 family
- ❖ Enhance innate immunity
 - ❖ Adaptive immunity too slow to control mortality
 - ❖ MX, TLR7, RIG-I
 - ❖ CRISPR/Cas 13 family

Targeting AIV genome with CRISPR-Cas13A *in vitro*



PB2

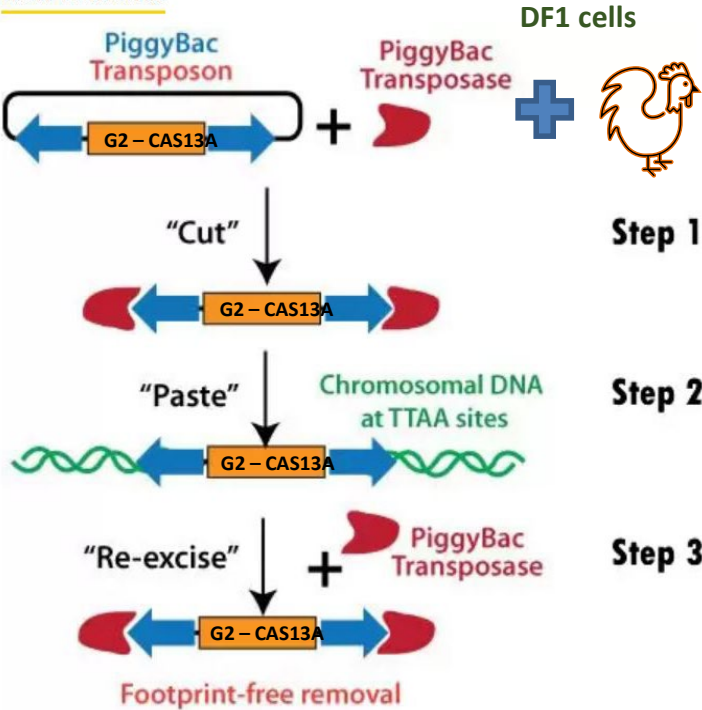
G2 = is the genome sequence (binds to mRNA)
M4 = is complimentary sequence (binds to vgRNA)

g2

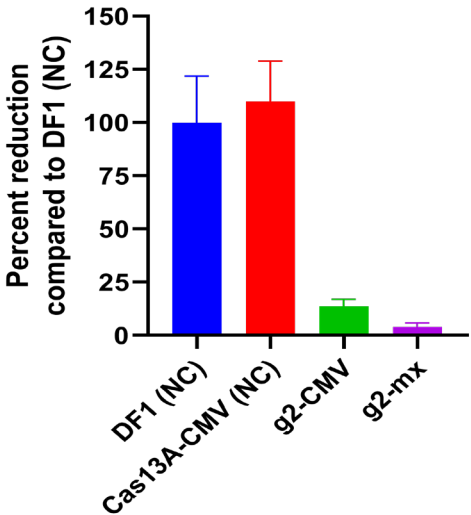
m4

HPAIV

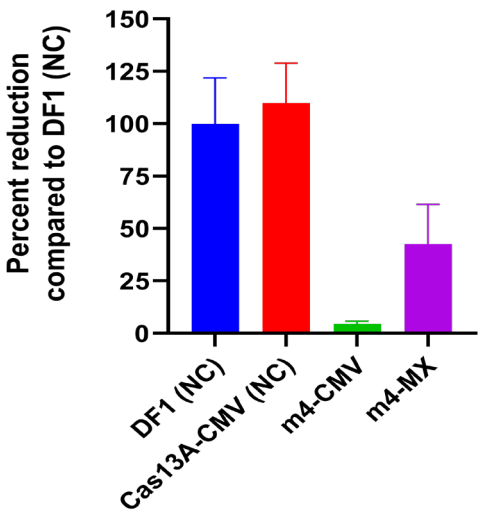
How it works



A/Tk/Minnesota/2015 H5N1

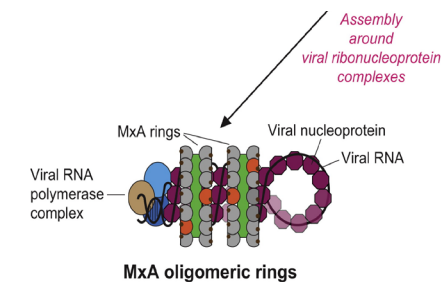


A/Tk/Minnesota/2015 H5N1

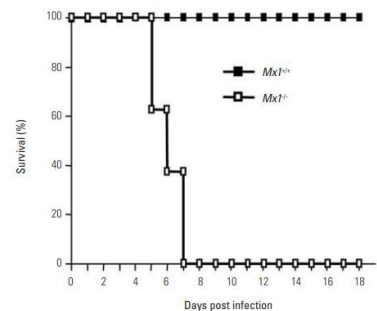


Host-derived targets using Mouse Mx *in vitro*

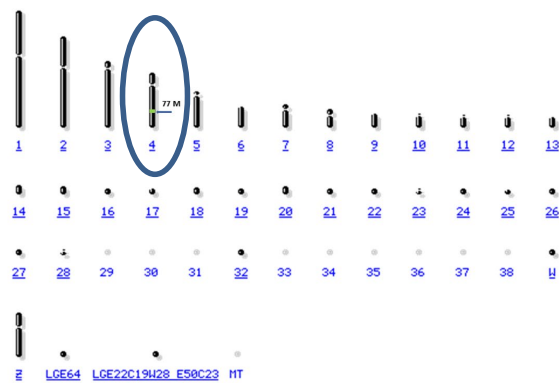
- ❖ Mx proteins are interferon-induced GTPases that directly interact with viral proteins to inhibit viral replication
- ❖ Mouse Mx1 is a critical determinant of influenza resistance
- ❖ Chicken Mx has conflicting reports on its effectiveness against AIV
- ❖ Inserted mouse Mx1 under control of the chicken Mx promoter



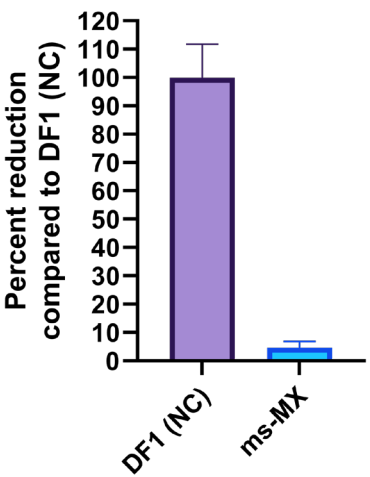
<https://doi.org/10.1016/j.immuni.2011.07.012>



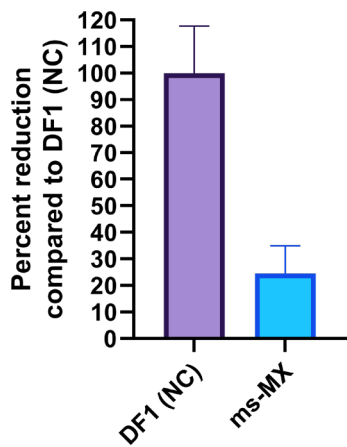
Chicken genome – insert at chromosome 4



A/Tk/Wisc/68 H5N9



A/AmWidgeon/South Carolina/21 H5N1



Virus name	strain	Pathogenicity	Percent Reduction compared to DF1 control
A/Tk/Wisc./68	H5N9	LPAI	90%
A/Ck/CA/03	H6N2	LPAI	80%
A/Ck/NJ/97	H9N2	LPAI	90%
A/AmWidgeon/SC/2021	H5N1	HPAI	75%
A/Ck/Jalisco/2012	H7N3	HPAI	90%
A/Tk/Minn./2015	H5N1	HPAI	95%
A/Tk/poland/2021 HPAI	H5N8	HPAI	70%

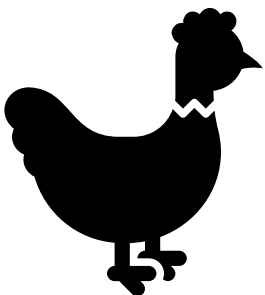
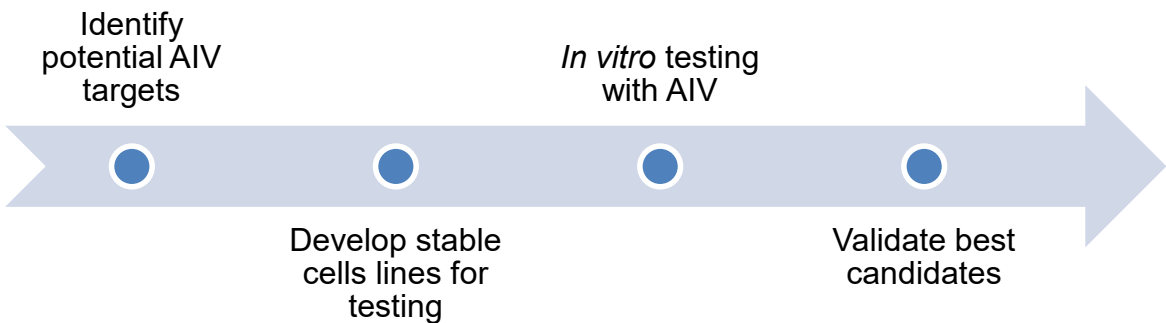
Conclusions & future directions

The current global transmission and infection landscape of AIV in birds and mammals supports evidence that these viruses are entrenched in migratory waterfowl.

Gene-editing approaches to genetically modify poultry offer a means to control highly pathogenic avian influenza virus and limit or restrict infections in birds, and limit transmission to other birds and mammals.

In the absence of vaccine usage, gene-editing offers an alternative avenue to breeding animals for disease resistance and farm biosecurity.

Do gene-edited animals with disease resistance create a novel pool with unique characteristics ?



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