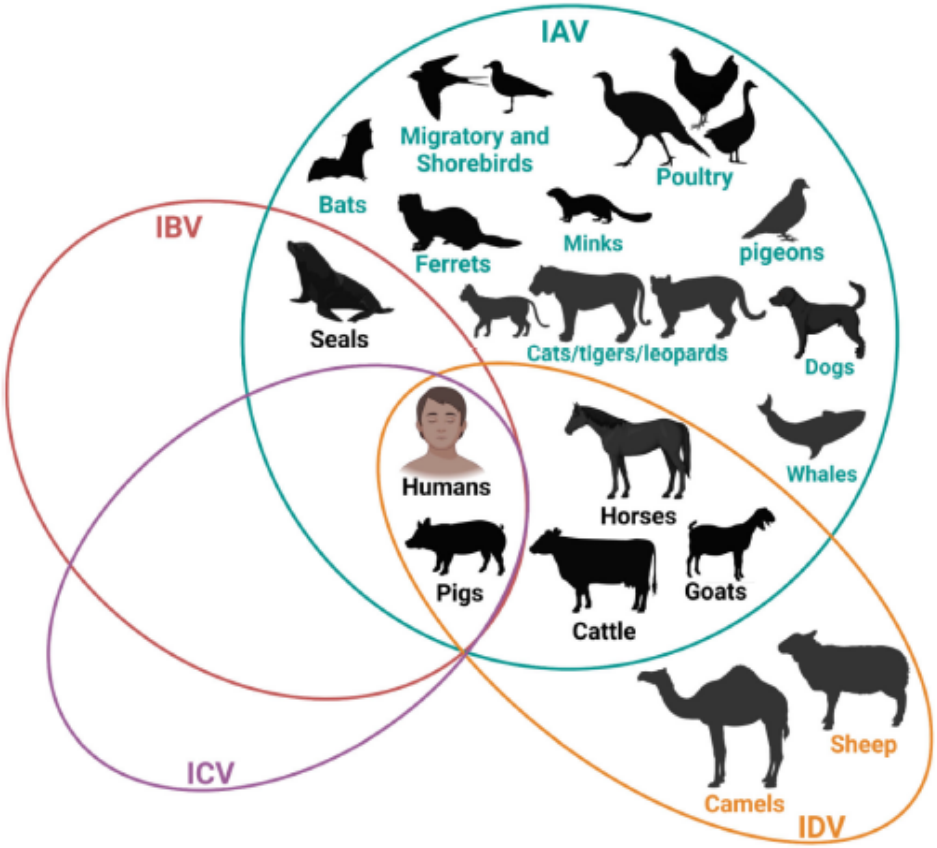
•I **virus di tipo A** circolano sia nell'uomo che in altre specie animali e sono ulteriormente suddivisi in sottotipi, distinti in base alle differenze tra le proteine di superficie: emagglutinina (HA) e neuramminidasi (NA), verso le quali si indirizza la risposta immunitaria dei soggetti infettati o vaccinati.

•I **virus di tipo B** sono presenti solo nei mammiferi e non esistono sottotipi distinti nell'ambito delle loro proteine di superficie HA e NA.

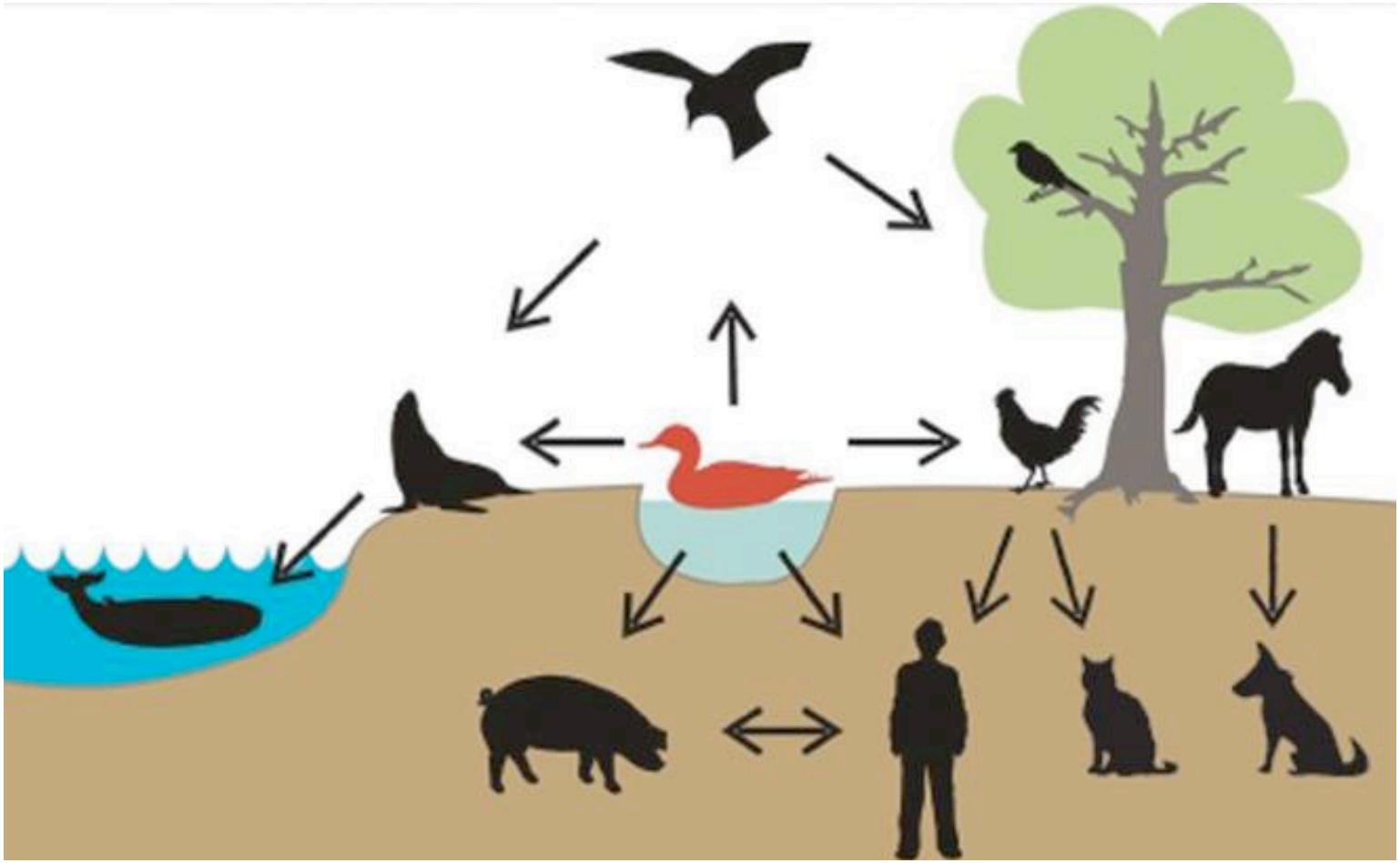
•I **virus di tipo C**, mammiferi, danno una infezione generalmente asintomatica o simile al raffreddore comune.

•I **virus di tipo D**, sono stati identificati più recentemente e isolati nei suini e nei bovini.



(a) documented hosts for influenza viruses show the broad-spectrum animal host species of IAV compared to IBV, ICV, and IDV https://doi.org/10.1128/mbio.02542-24

Influenza A virus Ecology



Influenza A virus reservoir. Wild aquatic birds are the main reservoir of influenza A viruses. Virus transmission has been reported from wild waterfowl to poultry, sea mammals, pigs, horses, and humans. Viruses are also transmitted between pigs and humans, and from poultry to humans. Equine influenza viruses have been transmitted to dogs.

Ecology Subtype distribution

Alla base della epidemiologia dell'influenza vi è la marcata tendenza di tutti i virus influenzali a variare, cioè ad acquisire cambiamenti nelle proteine di superficie che permettono loro di aggirare la barriera costituita dalla immunità presente nella popolazione che in passato ha subito l'infezione influenzale.

Ad oggi sono stati identificati 16 sottotipi di emagglutinina e 9 di neuramminidasi di Influenza A.

Nell'uomo H1N1, H3N2 come responsabili di influenza nel corso degli ultimi decenni.

I **virus dell'influenza A** si classificano in sottotipi a seconda di due proteine di superficie: emoagglutinina (HA) e neuraminidasi (NA).

Two additional HA and NA subtypes have been found in bats (2012-2013)

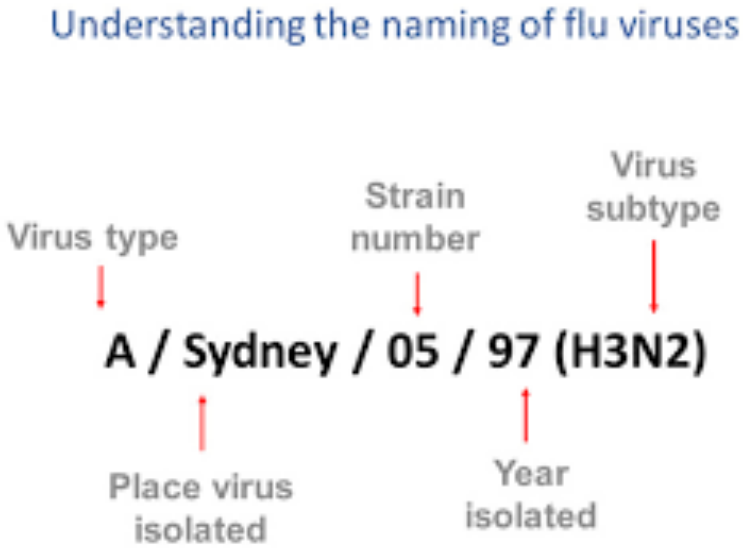
https://www.epicentro.iss.it/influenza/tec

The World Health Organization (WHO) created an internationally accepted naming system for influenza strains. The name includes the following information:

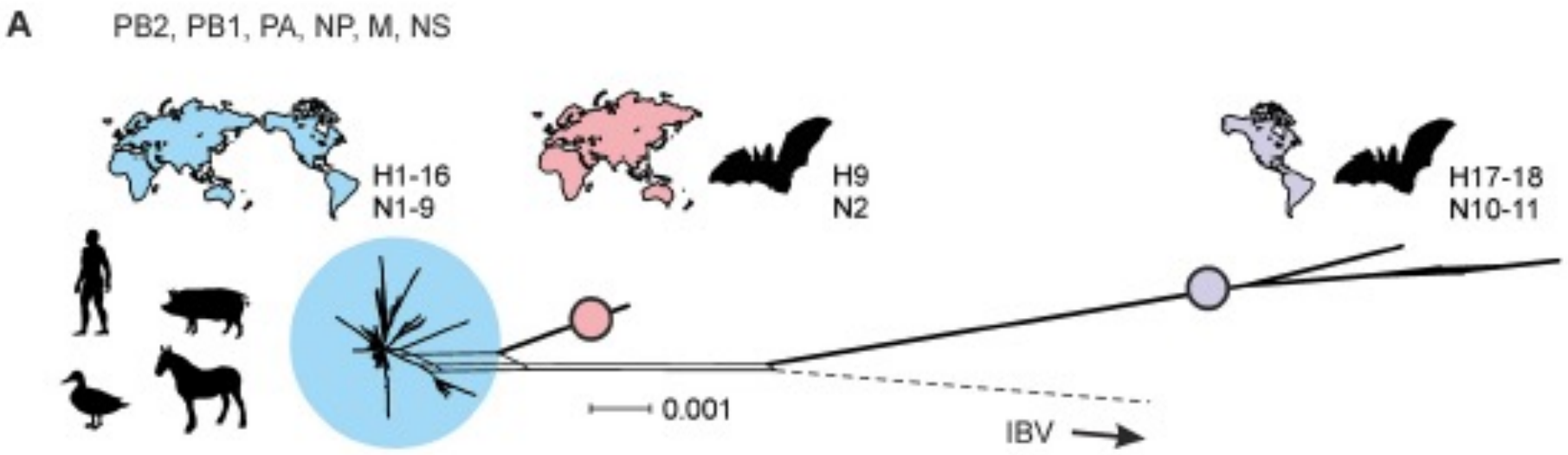
- **Type**: The influenza virus type, such as A, B, or C
- **Host**: The host of origin, such as swine, equine, or chicken
- **Location**: The geographical origin, such as Denver or Taiwan
- **Strain**: The strain number, which is often a sample identifier
- **Year**: The year the sample was collected
- **Subtype**: The hemagglutinin and neuraminidase subtype for influenza A viruses

- (Duck example): avian influenza A, A/duck/Alberta/35/76 (H1N1)

- (Human example): seasonal influenza A, A/Perth/16/2019 (H3N2)



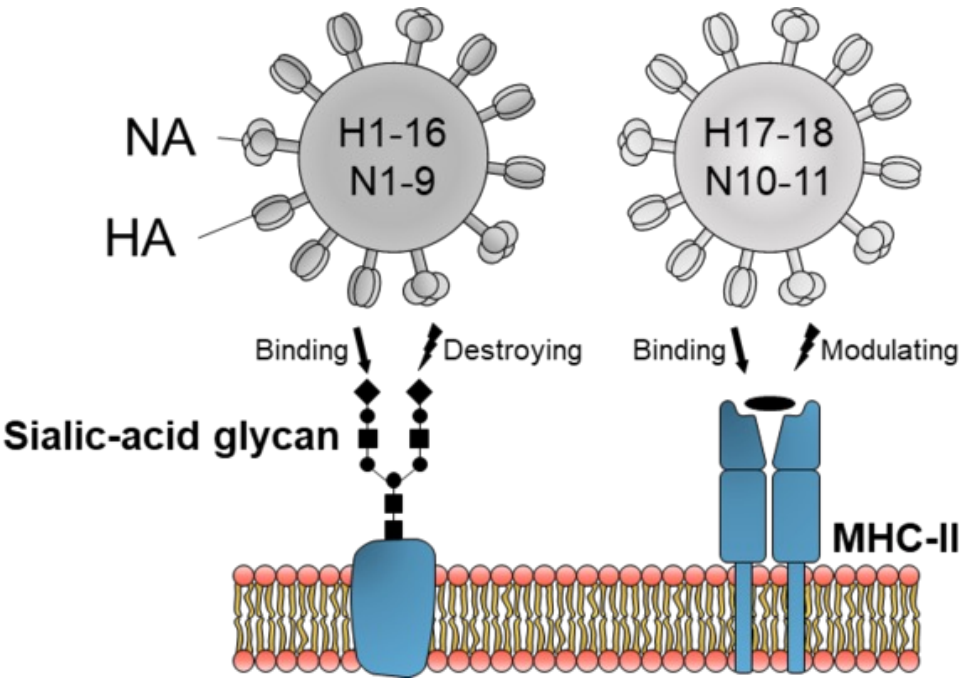
Bat IAV



New and Old World bat IAVs did most likely split into two genetic branches as a result of either geographic separation or multiple early spillover events of ancient viruses.

Phylogenetic backdating of the internal gene segments suggests that the precursor of the New World bat IAVs separated from all other lineages morethan 650 years ago, although some uncertainties commonly associated with molecular clock analyses exist

Bat IAV



H17 and H18 of the New World bat influenza strains cannot use sialic acid receptors for infection Instead, both New World bat–derived HA subtypes utilize major histocompatibility complex class II (MHC-II) molecules for cell entry. Importantly, MHC-II proteins of multiple species, including chicken, pigs, mice, and humans, could serve as receptors, indicating that receptor usage by bat IAVs does could not provide a tight species barrier but is compatible with a broad host range… A potential yet to be confirmed

Model of the receptor binding and modulating activity of the known IAV surface glycoproteins. (A) Infection of a host cell is initiated by binding of HA subtypes H1–16 to sialic acid residues exposed on the host cell surface. These glycan structures are subsequently cleaved off by NA of the subtypes N1–9 in order to facilitate the release of viral particles. (B) The H17 and H18 HA proteins of New World bat iAVs utilize MHC-II molecules for cell entry. Preliminary data suggest that the New World bat IAV N11 NA protein decreases MHC-II surface expression by a yet unknown mechanism, allowing unhindered release of budding particles.

PLOS Pathogens I https://doi.org/10.1371/journal.ppat.1008384 April 16, 2020

PNAS PNAS PNAS

The neuraminidase of bat influenza viruses is not a neuraminidase

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Department of Microbiology, Department of Medicine, Division of Infectious Diseases, and Global Health and Emerging Pathogens Institute, Mount Sinai School of Medicine, New York, NY 10029

Influenza A viruses are classified into subtypes according to their two viral glycoproteins, hemagglutinin (HA) and neuraminidase (NA). These viruses are known to infect multiple animal species, including humans, pigs, horses, dogs, sea mammals, chickens, ducks, and other birds. Although humans are sporadically infected with avian influenza virus strains belonging to multiple subtypes, only H1, H2, and H3 HA subtypes and N1 and N2 NA subtypes have been documented to cause pandemics and annual epidemics of influenza in humans. By contrast, all H16 and N9 subtypes of influenza A viruses are found circulating in birds. The recent discovery of influenza A viruses clearly distinct from any known avian influenza A virus subtype in little yellow-shouldered bats from Guatemala has been the first example of an influenza A virus subtype not found in avian species (1). Bat influenza viruses have glycoproteins related to the HA and NA of influenza A virus, which prompted to the

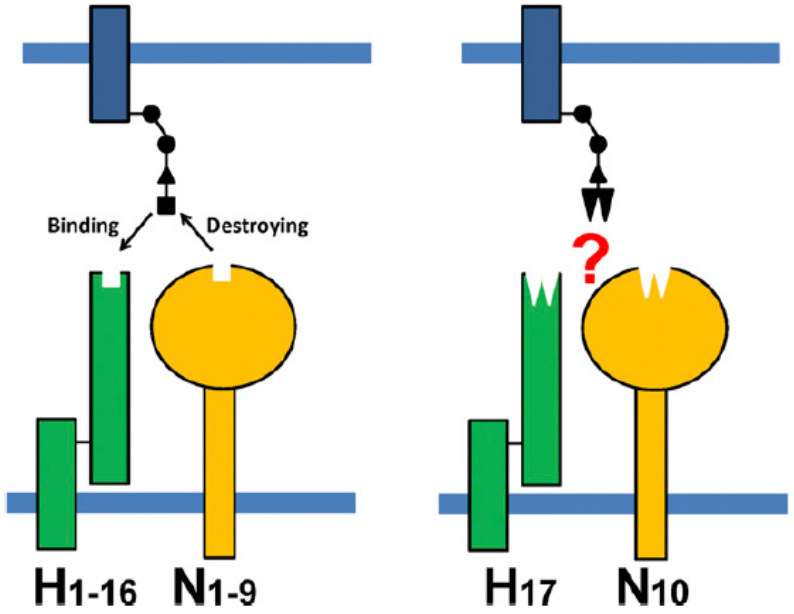


Fig. 1. H1 to H16 HA subtypes bind to sialic acid-containing receptors and mediate influenza A virus entry. N1 to N9 NA subtypes cleave sialic acids and destroy the receptor, mediating virus spread. The structure of the N10 subtype from the recently discovered bat influenza viruses (2, 3) shows profound changes in the active site of this NA-like molecule that prevent sialidase activity. It remains to be determined (*i*) whether the H17 HA from bat influenza viruses binds sialic acids, (*ii*) what the receptor of bat influenza viruses is, and (*iii*) whether the N10 NA-like protein from bat influenza virus has receptor-destroying activity.

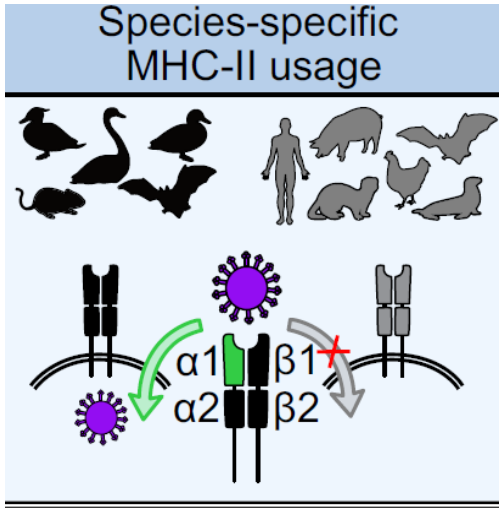
76.131.

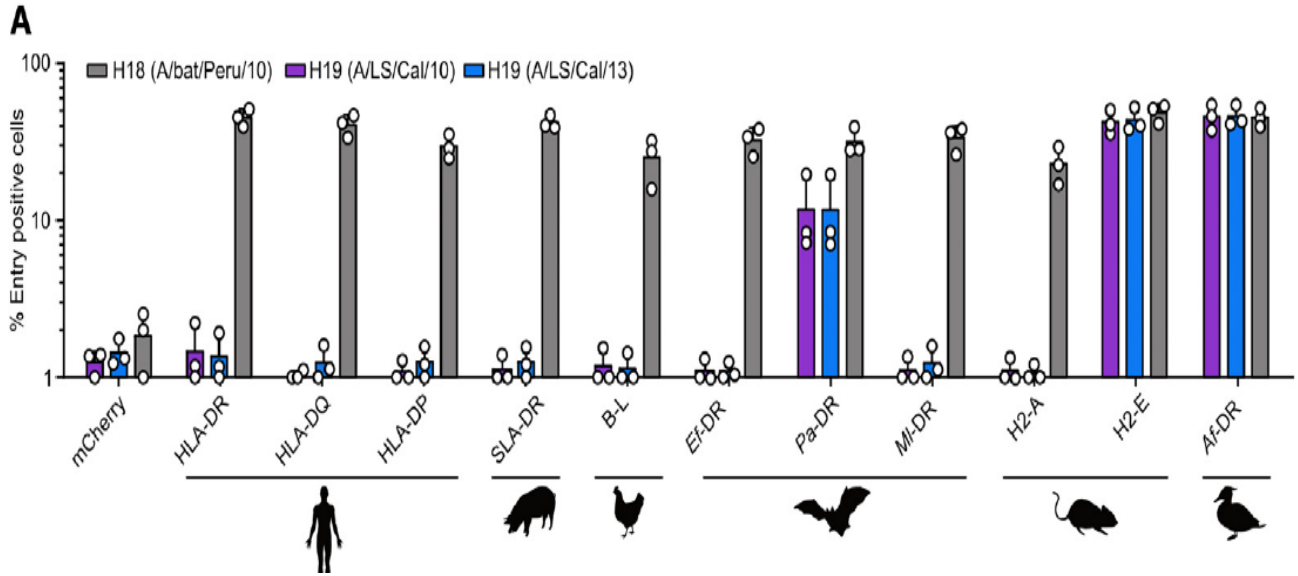
Cell Host & Microbe

H19 influenza A virus exhibits species-specific MHC class II receptor usage

https://doi.org/10.1016/j.chom.2024.05.018

Avian influenza A virus (IAV) surveillance in Northern California, USA, revealed unique IAV hemagglutinin (HA) genome sequences in cloacal swabs from lesser scaups. We found two closely related HA sequences in the same duck species in 2010 and 2013. Phylogenetic analyses suggest that both sequences belong to the recently discovered H19 subtype, which thus far has remained uncharacterized. We demonstrate that H19 does not bind the canonical IAV receptor sialic acid (Sia). Instead, H19 binds to the major histocompatibility complex class II (MHC class II), which facilitates viral entry. Unlike the broad MHC class II specificity of H17 and H18 from bat IAV, H19 exhibits a species-specific MHC class II usage that suggests a limited host range and zoonotic potential. Using cell lines overexpressing MHC class II, we rescued recombinant H19 IAV. We solved the H19 crystal structure and identified residues within the putative Sia receptor binding site (RBS) that impede Sia-dependent entry.





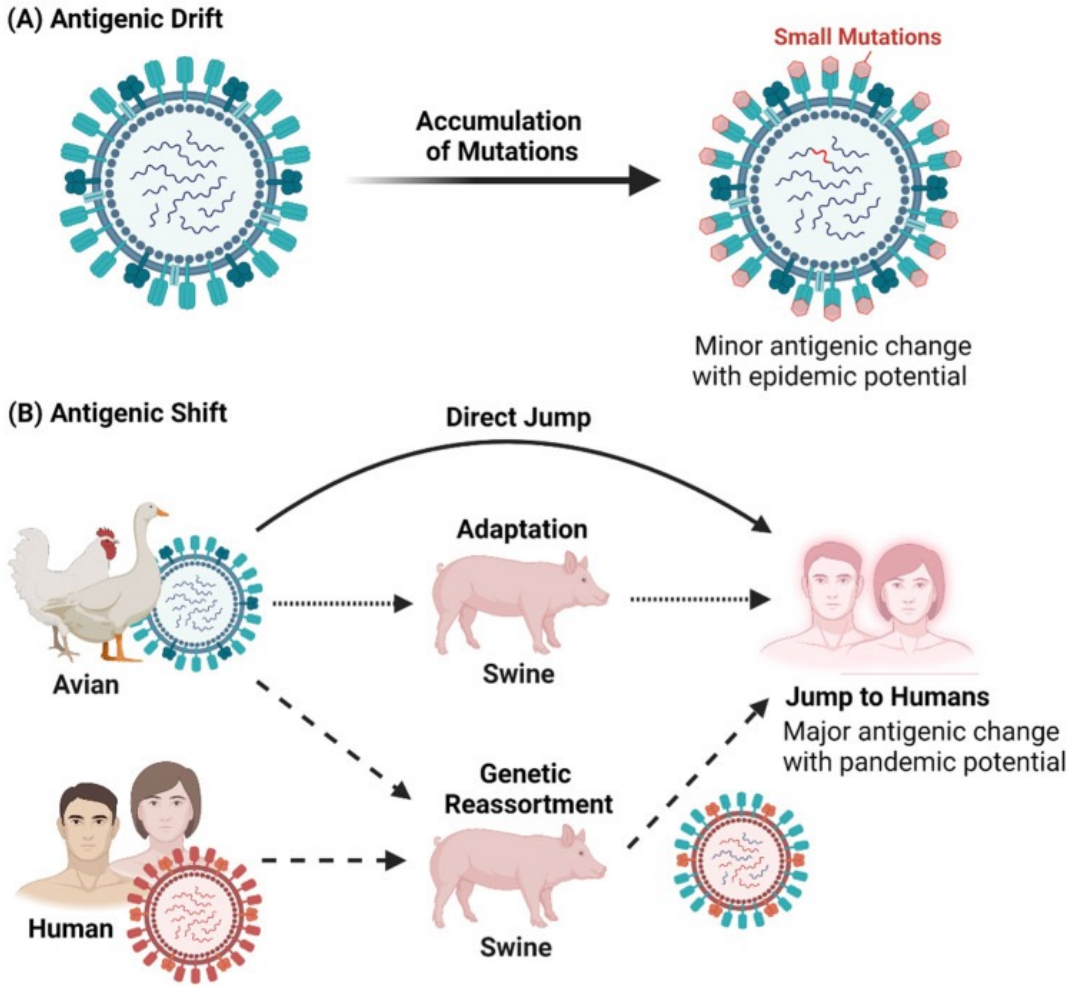
Human Leukocyte Antigen HLA= MHC

HLA-DR orthologs from duck, swan, bat, and mouse function as entry receptors for H19

Lesser scaup=moretta americana o anatra tuffatrice

Two mechanisms of influenza A virus evolution

Influenza A viruses undergo two types of evolutionary change that alter their major surface glycoproteins. These are: i) antigenic drift, resulting from mutations ii) antigenic shift, arising from reassortment of the genome segments following a dual infection of a single cell



Viruses. 2021 Nov; 13(11): 2276.

Antigenic drift

The name ’antigenic drift’ is very apt as the process is a gradual one of accumulating mutations. It has been determined that a virus must acquire on average 4 amino acid substitutions in 2 antigenic sites to be able to infect a person who was previously infected with the ‘parental’ virus from which the drift variant arose. In practice, a drift variant that can cause significant disease, infecting a large proportion of the population anew, becomes predominant approximately every four years.

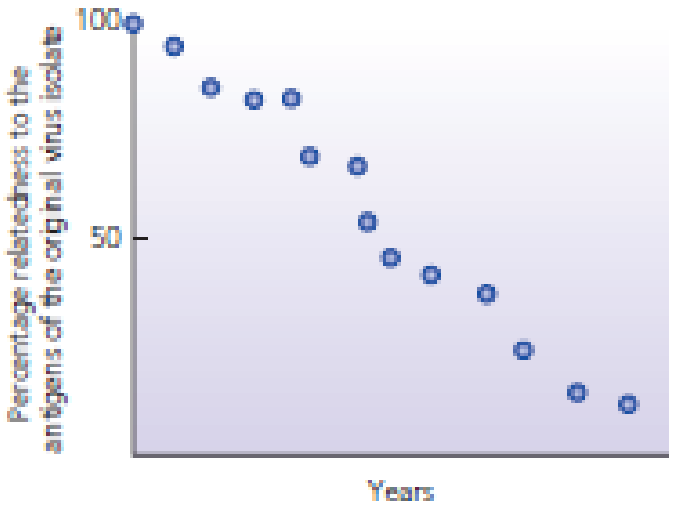


Diagram showing antigenic drift of type A influenza virus in humans. This could represent mutations within either the HA or NA genes. Each point is a virus strain isolated in a different year.

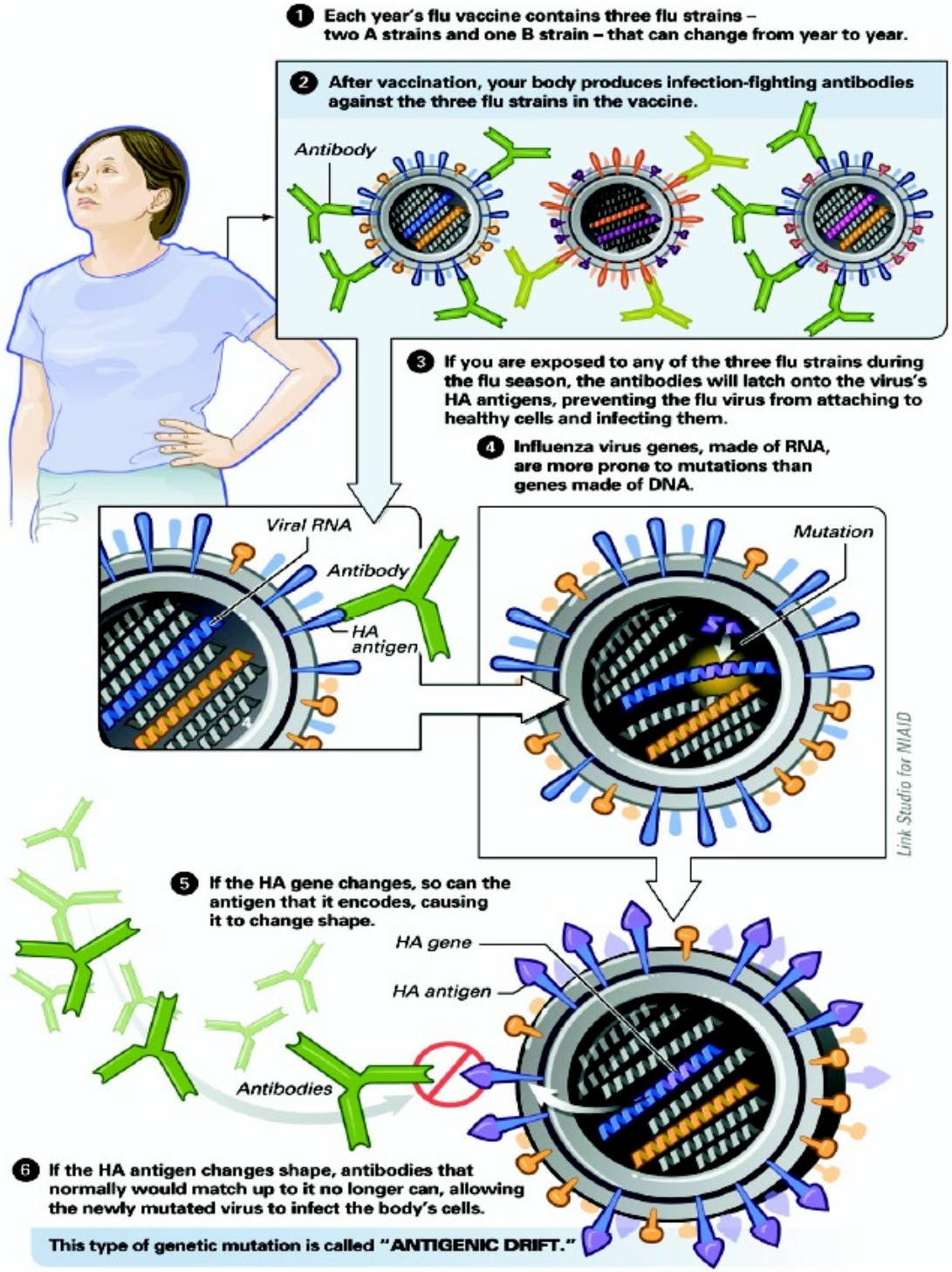
Introduction to modern virology, Dimmock et al. Ed., 7th edition, 2016

Antigenic drift

Influenza viruses can change through antigenic drift, which is a process in which mutations to the virus genome produce changes in the viral HA or NA.

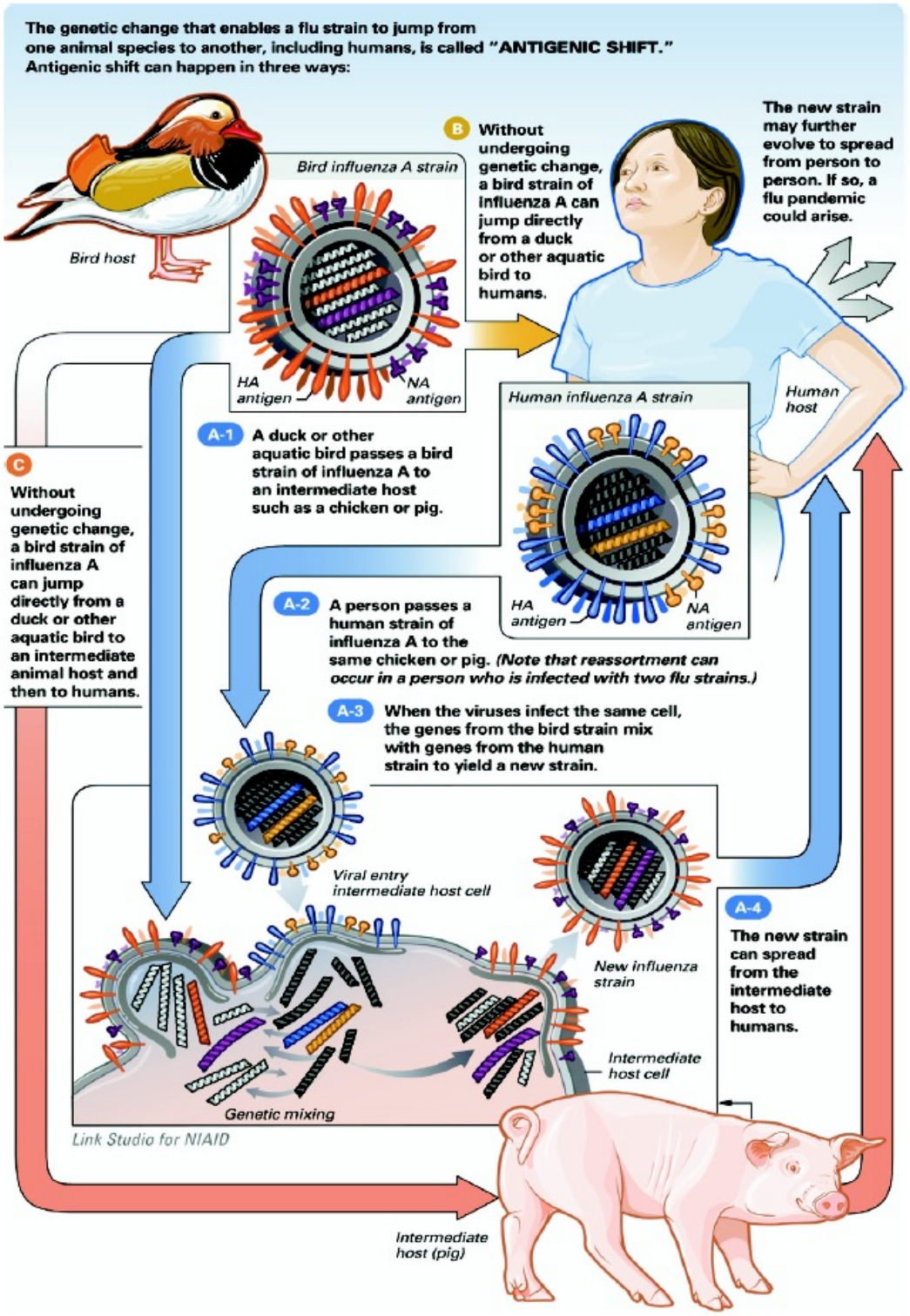
Drift is a continuous ongoing process that results in the emergence of new strain variants. The amount of change can be subtle or dramatic, but eventually one of the new variant strains becomes dominant, usually for a few years, until a new variant emerges and replaces it. In essence, drift affects the influenza viruses that are already in worldwide circulation.

This process allows influenza viruses to change and re-infect people repeatedly through their lifetime and is the reason the influenza virus strains in vaccine must be updated each year.

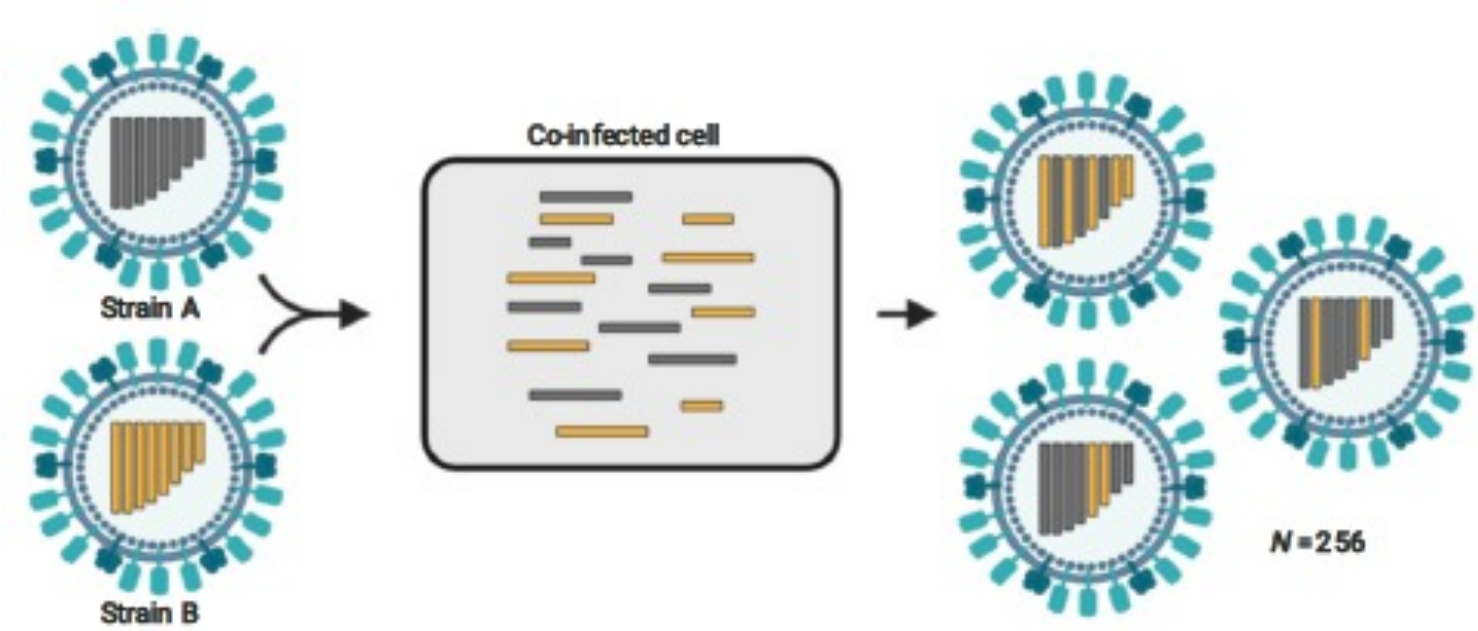


Antigenic shift

The genetic change that enables a flu strain to jump from one animal species to another, including humans, is called antigenic shift.
Shift Influenza viruses, able of spreading person to person, are responsible of pandemic.
Antigenic shift can happen in three ways



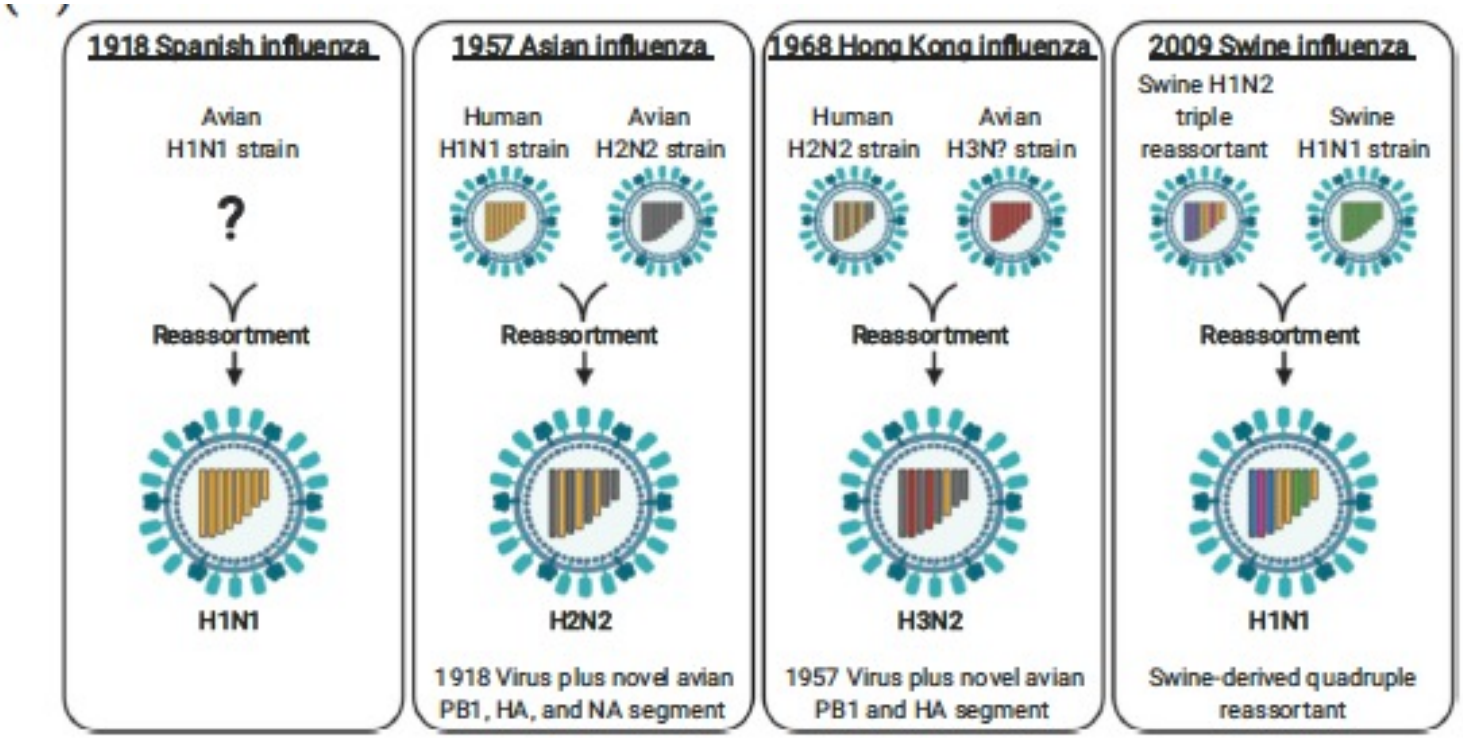
Reassortment



Co-infection of a cell with two distinct parental viruses allows the exchange of genome segments (i.e., reassortment) and the generation of progeny virions with a novel genomic composition. In theory, co-infection with two distinct strains can give rise to 256 different genotypes.

Trends in Molecular Medicine, February 2021, Vol. 27, No. 2

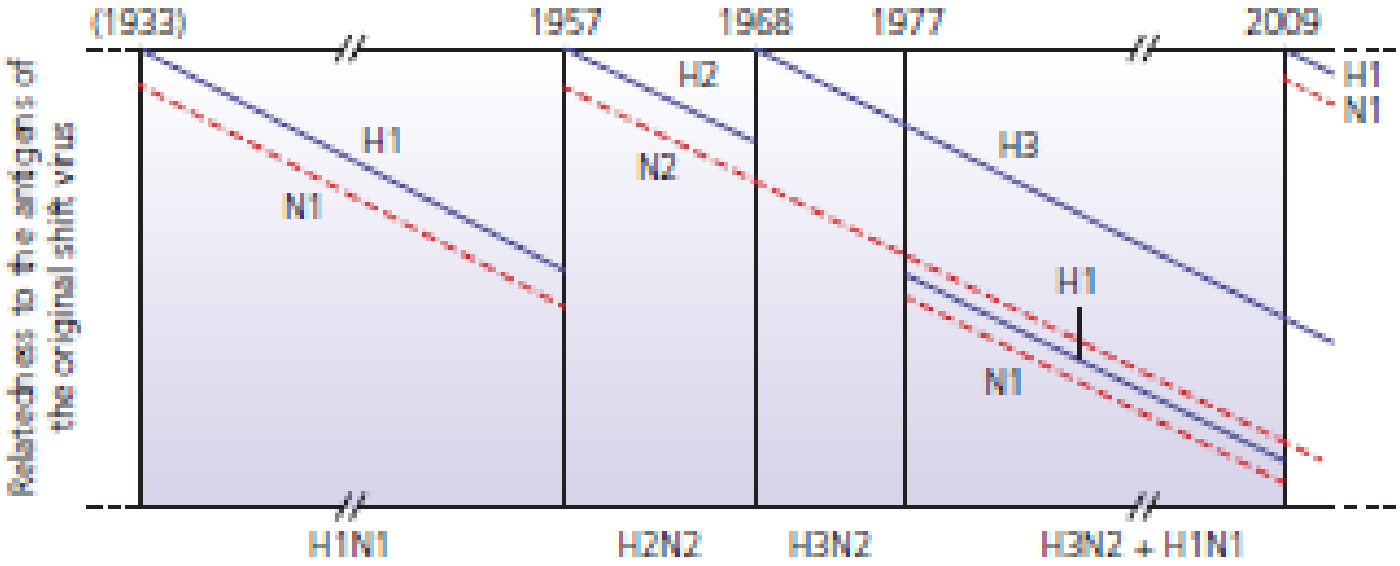
Reassortment Is the Key Driver in Infuenza A (IAV) Evolution



Reassortment was responsible for at least three of four pandemic IAVs in the past. It is currently unclear whether all eight genome segments of the 1918 pandemic virus were of avian origin or whether reassortment in humans or swine preceded the pandemic outbreak. Descendants of the 1918 pandemic virus remained in the human population as seasonal infuenza epidemics and were subject to antigenic drift. Reassortment between the drifted 1918 strain and an avian H2N2 strain resulted in the Asian infuenza pandemic in 1957. Similarly, reassortment between the drifted 1957 pandemic virus and an avian H3N? virus gave rise to the 1968 Hong Kong infuenza pandemic. Until 2009, the H1N1 and the H3N2 strains co-circulated as seasonal infuenza epidemics in the human population. In 2009, the H1N1pdm09 swine infuenza virus emerged as a quadruple reassortant between a triple reassortant virus of the North American swine lineage and an H1N1 Eurasian avian-like swine virus. The H1N1pdm09 virus replaced the descendants of the 1918 virus, but not the H3N2 virus in the human population.

Trends in Molecular Medicine, February 2021, Vol. 27, No. 2

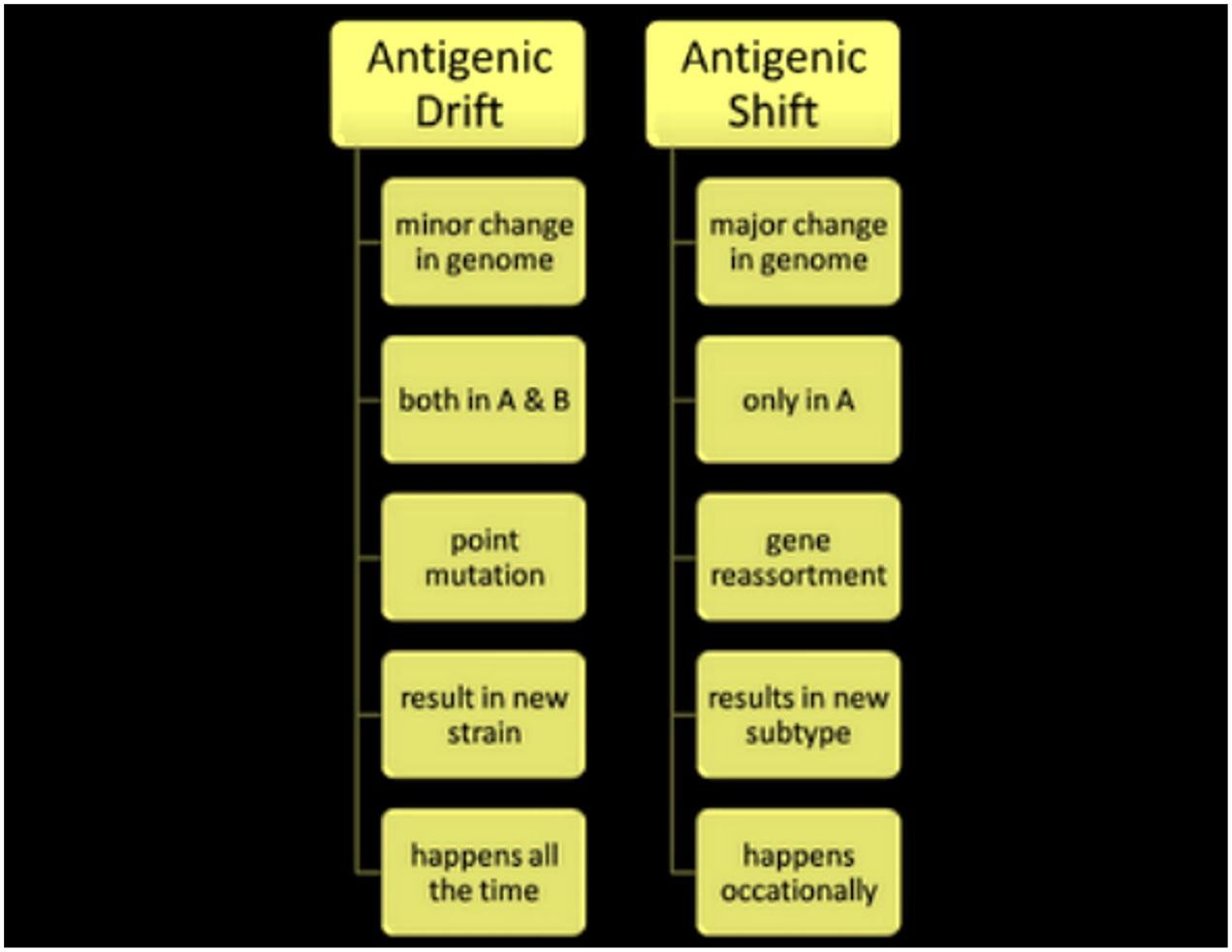
Course of antigenic shift and drift of influenza A viruses in humans



The first virus, isolated in 1933, was H1N1. This arose by antigenic drift from the 1918 virus. Other shift viruses appeared in 1957 (H2N2) and 1968 (H3N2). A 1950 H1N1 virus reappeared in 1977. A new H1N1 appeared in 2009. Drift is shown schematically. The 1957 N2 was acquired by the H3N2 shift virus, and has drifted from 1957 to the present day.

Introduction to modern virology, Dimmock et al. Ed., 7th edition, 2016

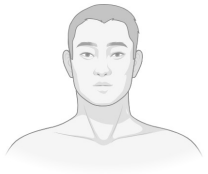
Atigenic drift vs antigenic shift



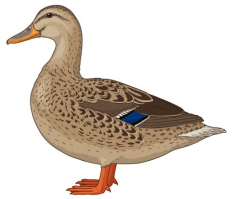
Species Barrier

The influenza A virus HA protein binds to a sialic acid, N-acetylneuraminic acid (NANA), that is terminally linked to a carbohydrate moiety of a glycoprotein or glycolipid.

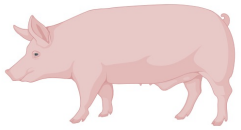
Receptor diversity

Human 

Sialic acid residue attached via an α2,6 linkage (NeuAcα-2,6Gal)

Birds 

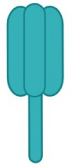
sialic acid residue attached via an α2,3 linkage (NeuAcα-2,3Gal)

Swine 

has both receptors

Species Barrier

In particular, this property depends primarily (but not exclusively) on the aminoacid at position 226 in the hemagglutinin protein.

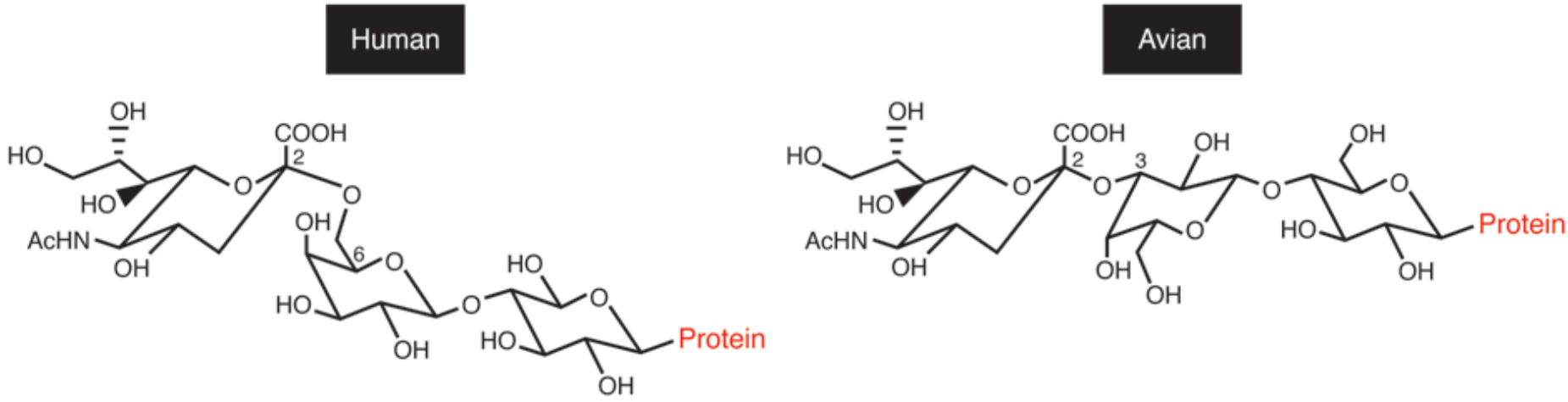


Human viruses
$HA226_{leu\ (leucine)}$

Avian viruses
$HA226_{gln\ (glutamine)}$

Avian versus human influenza virus preference for sialic acid receptor linkages

A



B

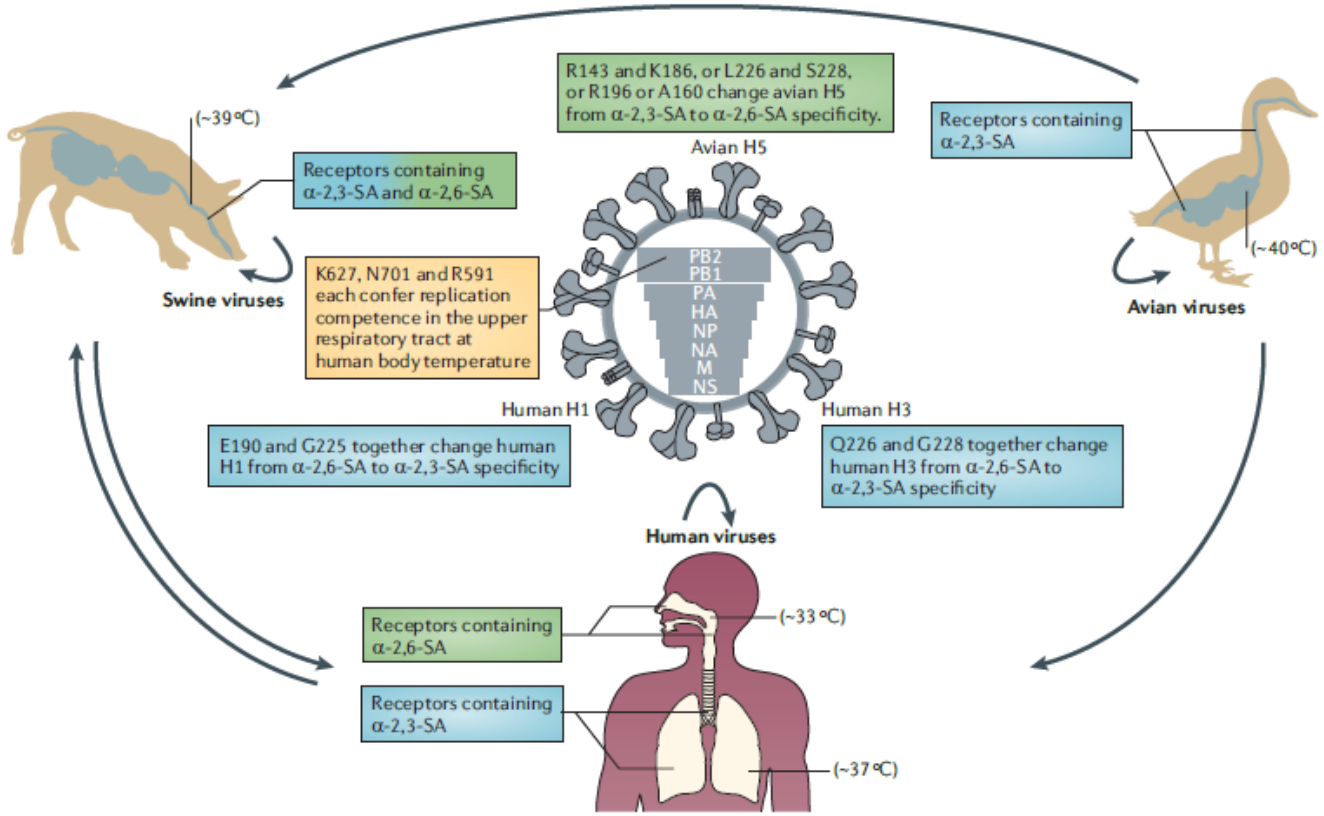
Subtype	Human preference	Avian preference
H1	D190, D225	E190, G225
H2/H3	L226, S228	Q226, G228

D, aspartic acid; E, glutamic acid; G, glycine; L, leucine; S, serine; Q, glutamine;

(**A**) Sialic acid α2,6 and α2,3 linkage to a cell surface glycoprotein is bound preferentially by HA of human and avian influenza viruses, respectively. (**B**) Crucial residues in HA that dictate receptor preference for human or avian influenza viruses.

The Journal of Clinical Investigation Volume 121 Number 1 January 2011

Influenza A virus tropism



The anatomical expression patterns of the viral receptors in different hosts restricts infection and replication of influenza A viruses. The swine trachea contains receptors with α-2,3-linked and α-2,6-linked sialic acid (α-2,3-SA and α-2,6-SA) moieties that allow for binding of both avian and human viruses, leading to the idea that pigs can serve as the 'mixing vessel' in which reassortment of human and avian viruses can occur. Avian viruses bind preferentially to α-2,3-SA, which is found on receptors in the gut and respiratory tract of birds. By contrast, human-adapted viruses (for example, seasonal H1N1, H3N2 and 2009 pandemic H1N1 viruses) have a higher affinity for α-2,6-SAs, which are expressed in the upper respiratory tract of humans. Human infection with a non-human-adapted virus is rare and is usually a result of a direct spillover transmission event. Viral proteins and their specific residues that affect receptor binding and have been established as adaptations to the human host are listed; H1, H3 and H5 are variations of the haemagglutinin (HA) protein, and PB2 is an RNA-dependent RNA polymerase component.

Influenza A virus tropism and Sialic acid receptors in humans

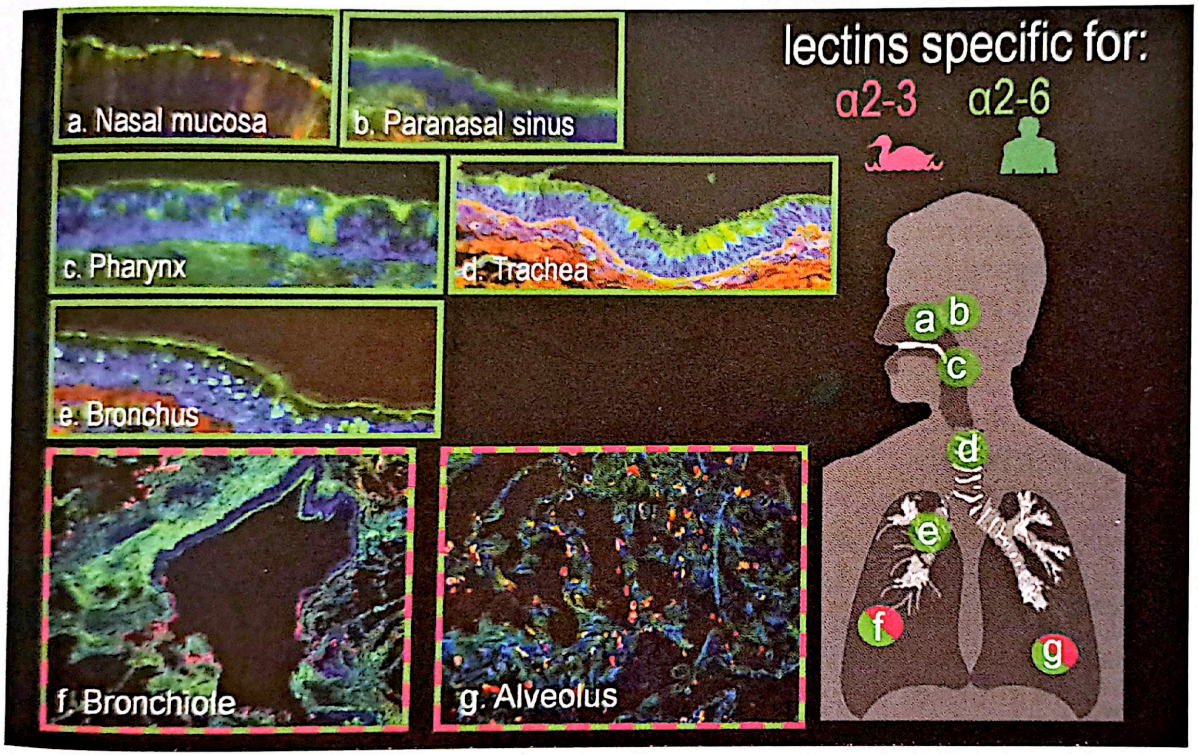


FIGURE 41.10. Expression of human virus (Siaα2,6Gal) and avian virus (Siaα2,3Gal) receptors in human respiratory tissue. The indicated tissues were tested with *Sambucus nigra* lectin (*green*), indicating the presence of sialic acid linked to galactose by an α2,6-linkage (Siaα2,6Gal), or with *Maackia amurensis* lectin (*red*), indicating the presence of Siaα2,3Gal. Cells were counterstained with DAPI (4,6-diamidino-2-phenylindole; *blue*). In the nasal mucosa, paranasal sinuses, pharynx, trachea, and bronchus, Siaα2,6Gal dominated. In the bronchiole and alveolus, both Siaα2,6Gal and Siaα2,3Gal were detected. (From Shinya K, Ebina M, Yamada S, et al. Avian flu: influenza virus receptors in the human airway. *Nature* 2006;440:435–436, with permission.)

One study found higher amount of Siaα-2,3Gal in the respiratory tract of children vs adults

Another study described Siaα-2,3Gal expression in epithelial cells of human eye (conjunctivitis associated)

Flu Terms Defined

- Seasonal (or common flu)- is a respiratory illness that can be transmitted person to person. Most people have some immunity, and a vaccine is available

- Pandemic flu- is virulent human flu that causes a global outbreak or pandemic, of serious illness. Because there is little natural immunity, the disease can spread easily from person to person

- Avian (or bird) flu (AI)- is caused by influenza viruses that occur naturally among wild birds. Low pathogenic is common in birds and causes few problems.

Flu in Humans

Parameter	Influenza virus
Receptor usage	Sialic acid
Viral surface protein processing	Haemagglutinin processing by trypsin-like proteases
Cellular tropism	Respiratory epithelial cells: types I and II alveolar epithelial cells; ciliated cells
Tissues affected and pathology	Upper respiratory tract; lower respiratory tract (severe cases)
Viral recognition in airway epithelial cells	TLR3; RIG-I; ZBP1
Site of viral replication	Nuclear
Viral evasion of initial host response	NS1; PB2; PB1-F2
Extrapulmonary complications	Limited; cardiac: myocarditis (rare); neurological: encephalitis (rare)
Viral evolution and antigenicity	Antigenic shift; antigenic drift
Prior immunity	Previous infection; vaccination; subtype specificity

Infection in humans

Influenza virus and disease. Human infection with influenza viruses produces a broad spectrum of clinical disease severity, which ranges from asymptomatic infection to death. Adaptive immune memory from prior exposure by either natural infection or immunization can prevent infection or limit the development of symptoms or severe complications (TABLE 1). Young children without prior exposure who are immunologically naive to influenza virus are at risk of severe disease[20].

Most commonly, upper respiratory tract (URT) signs of tracheobronchitis and pharyngitis coupled with constitutional symptoms, including fever, malaise and myalgia, are reported by symptomatic individuals. However, severe disease phenotypes, including hospitalization, pneumonia, acute respiratory distress syndrome (ARDS) and death are witnessed more frequently in high-risk patient populations.

Flu in Humans

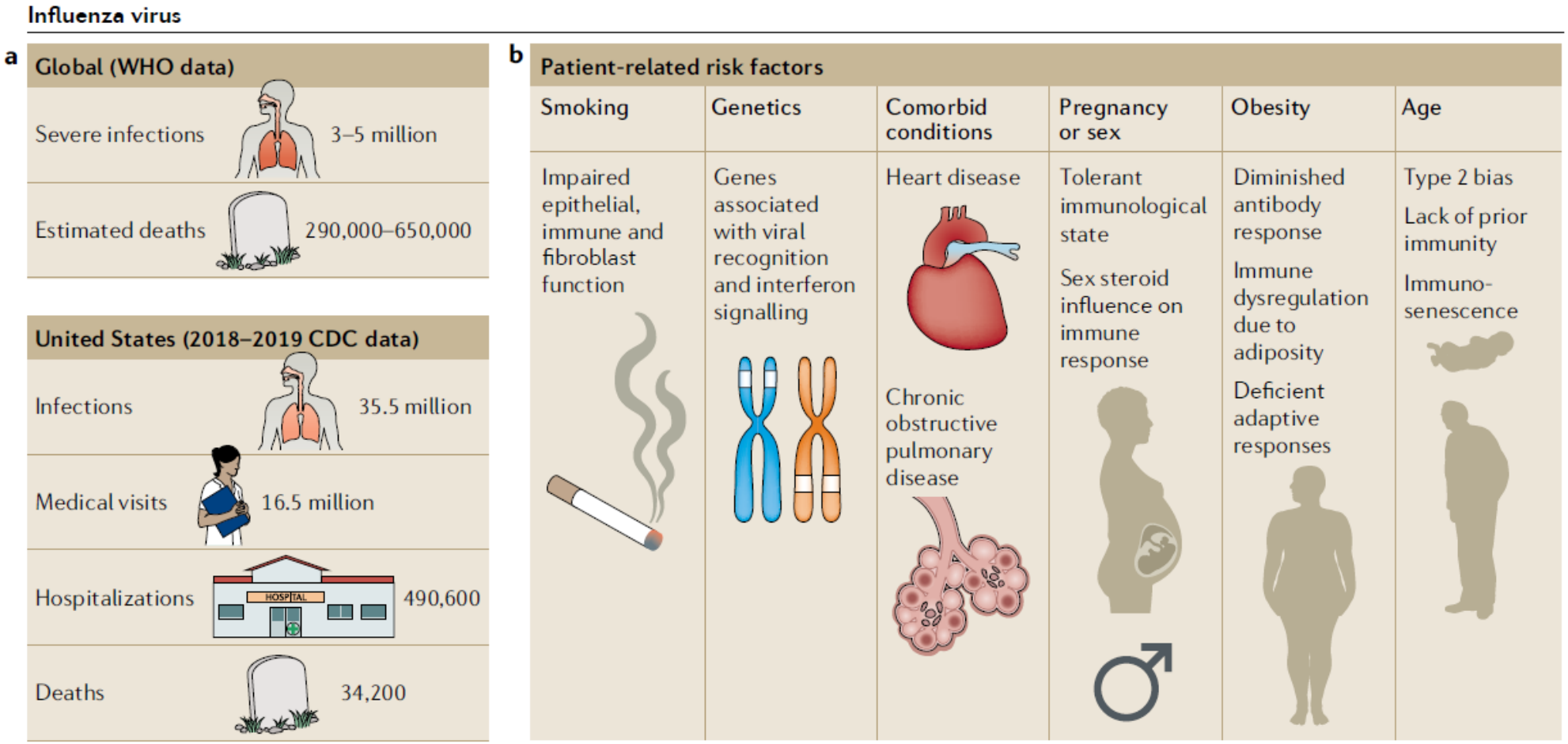
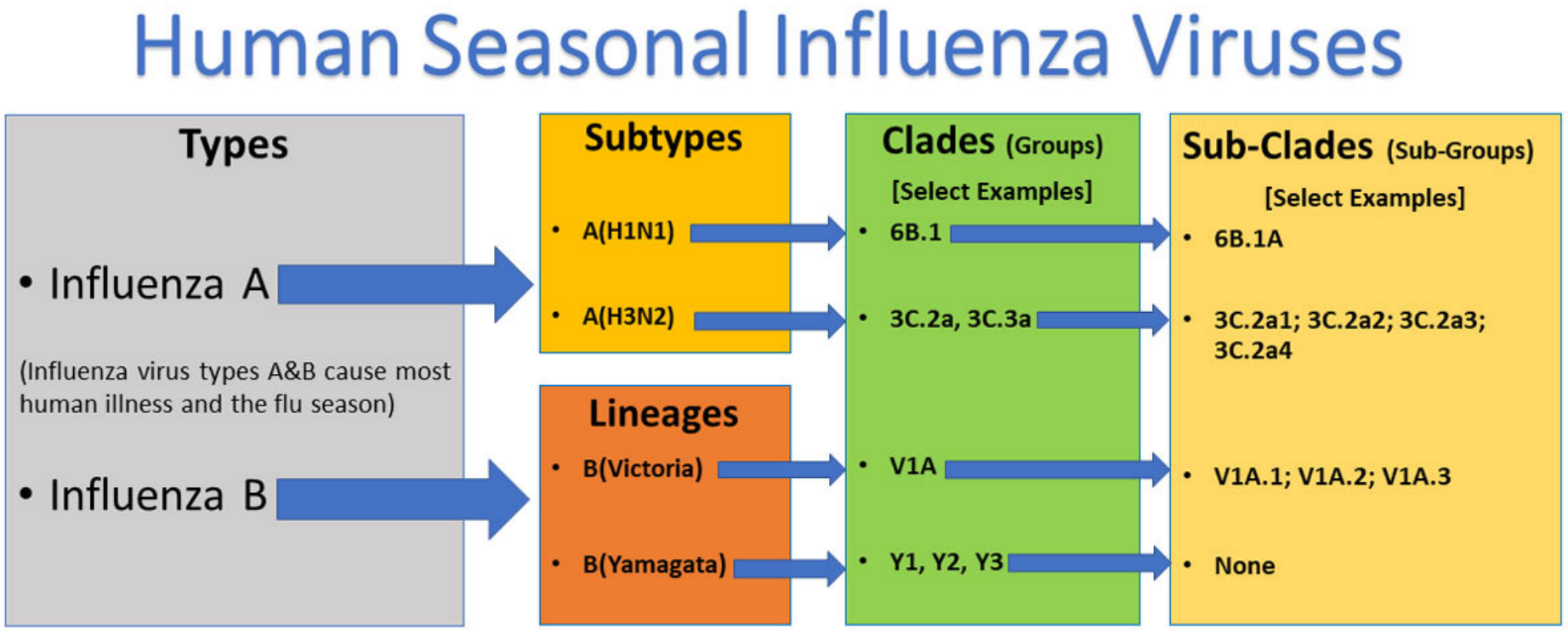


Fig. 1 | **Patient-related risk factors for severe influenza virus a** | Estimates of yearly influenza virus infections worldwide and in the United States (2018–2019 season) **b** | Risk factors associated with severe influenza virus infection in epidemiological and genetic studies

The reason for the Season

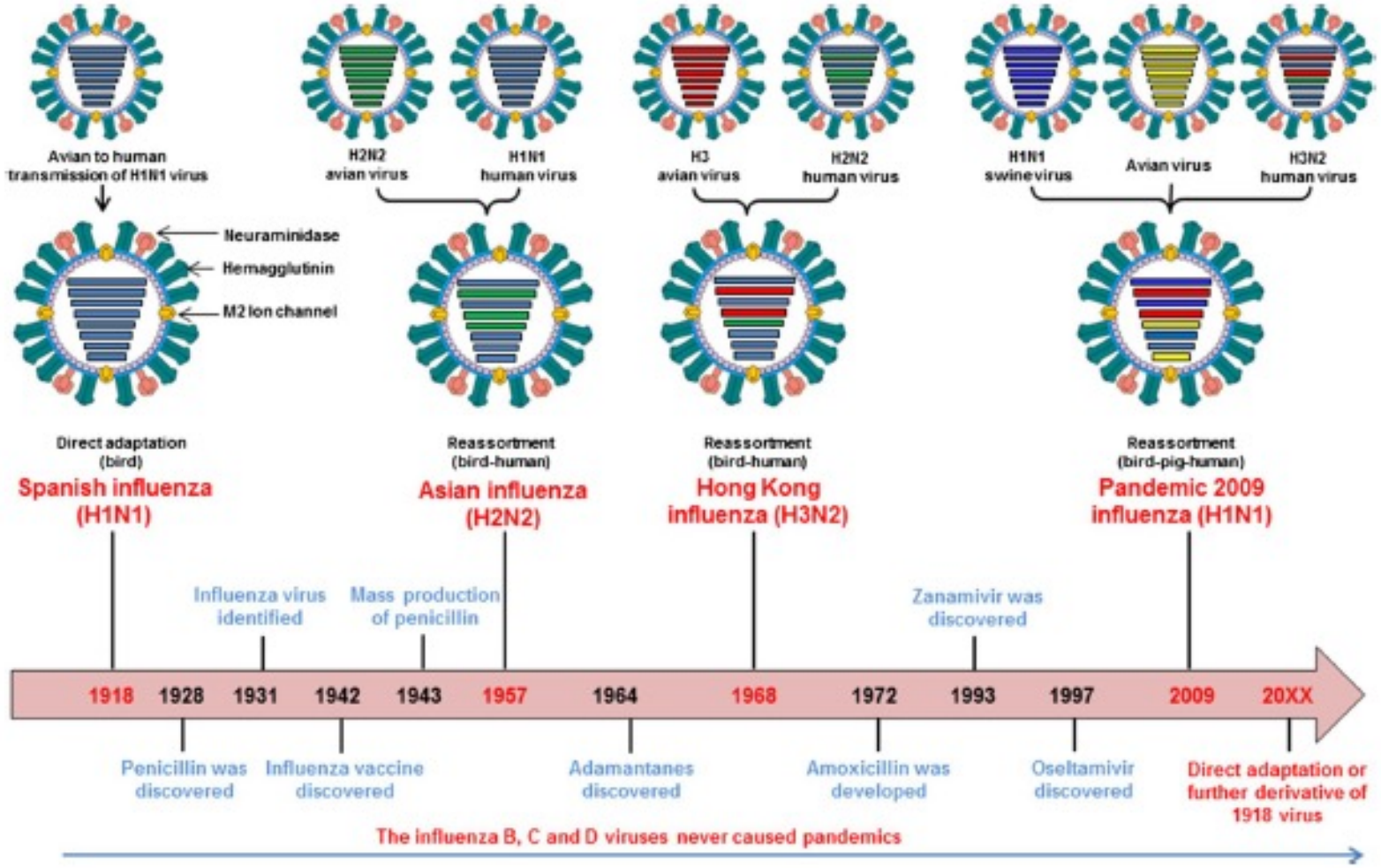
In temperate climates, seasonal epidemics occur mainly during winter, while in tropical regions, influenza may occur throughout the year, causing outbreaks more irregularly.

During the winter, people spend more time indoors with the windows sealed, so they are more likely to breathe the same air as someone who has the flu and thus contract the virus. The influenza virus may survive better in colder, drier climates, and therefore be able to infect more people



https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)

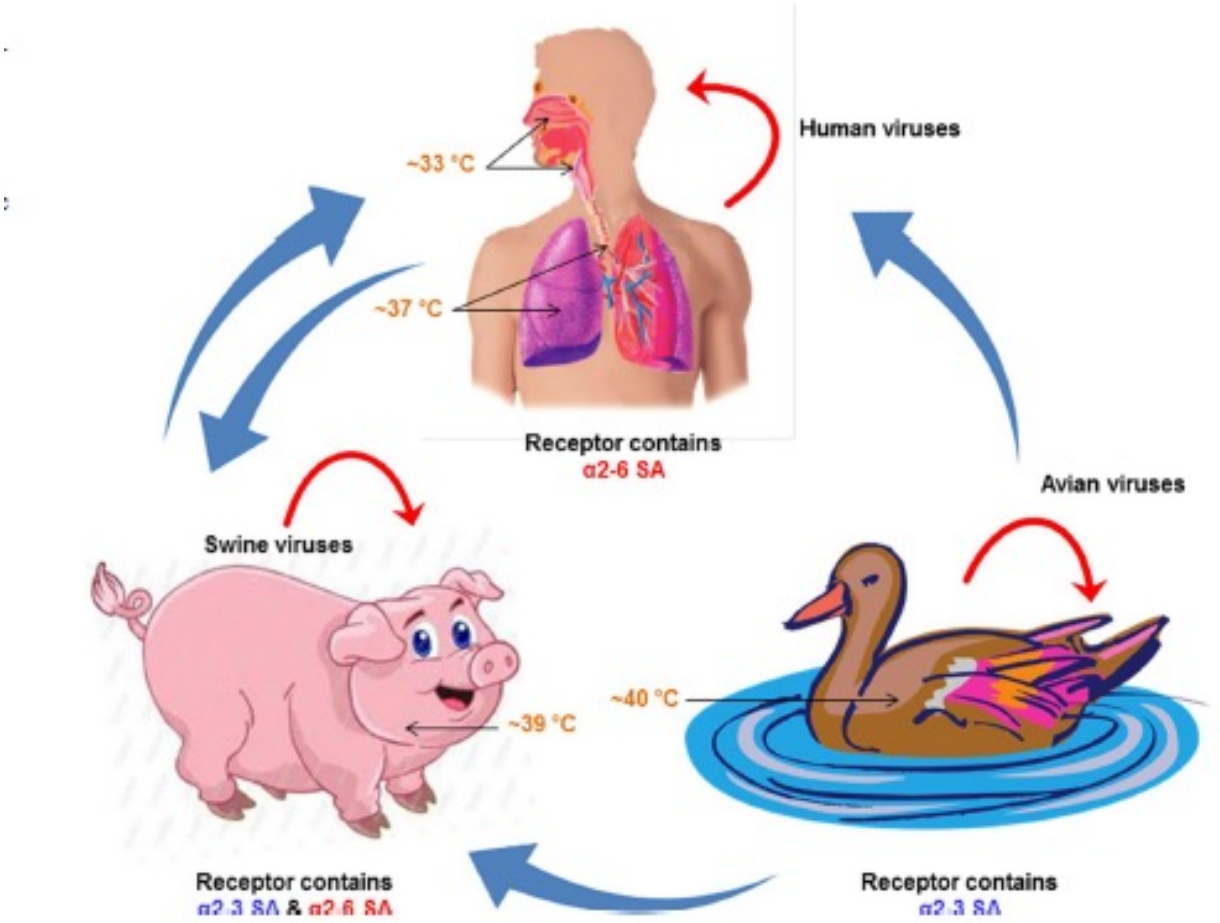
A time line of major influenza pandemics and the responsible influenza strains



In 1918, an H1N1 virus closely related to avian viruses adapted to replicate efficiently in humans. In 1957 and in 1968, reassortment events led to new viruses that resulted in pandemic influenza. The 1957 influenza virus (Asian influenza, an H2N2 virus) acquired three genetic segments from an avian species (hemagglutinin, neuraminidase, and polymerase gene, PB1), the 1968 influenza virus (Hong Kong influenza, an H3N2 virus) acquired two genetic segments from an avian species (hemagglutinin and PB1), and the 2009 swine H1N1 pandemics.

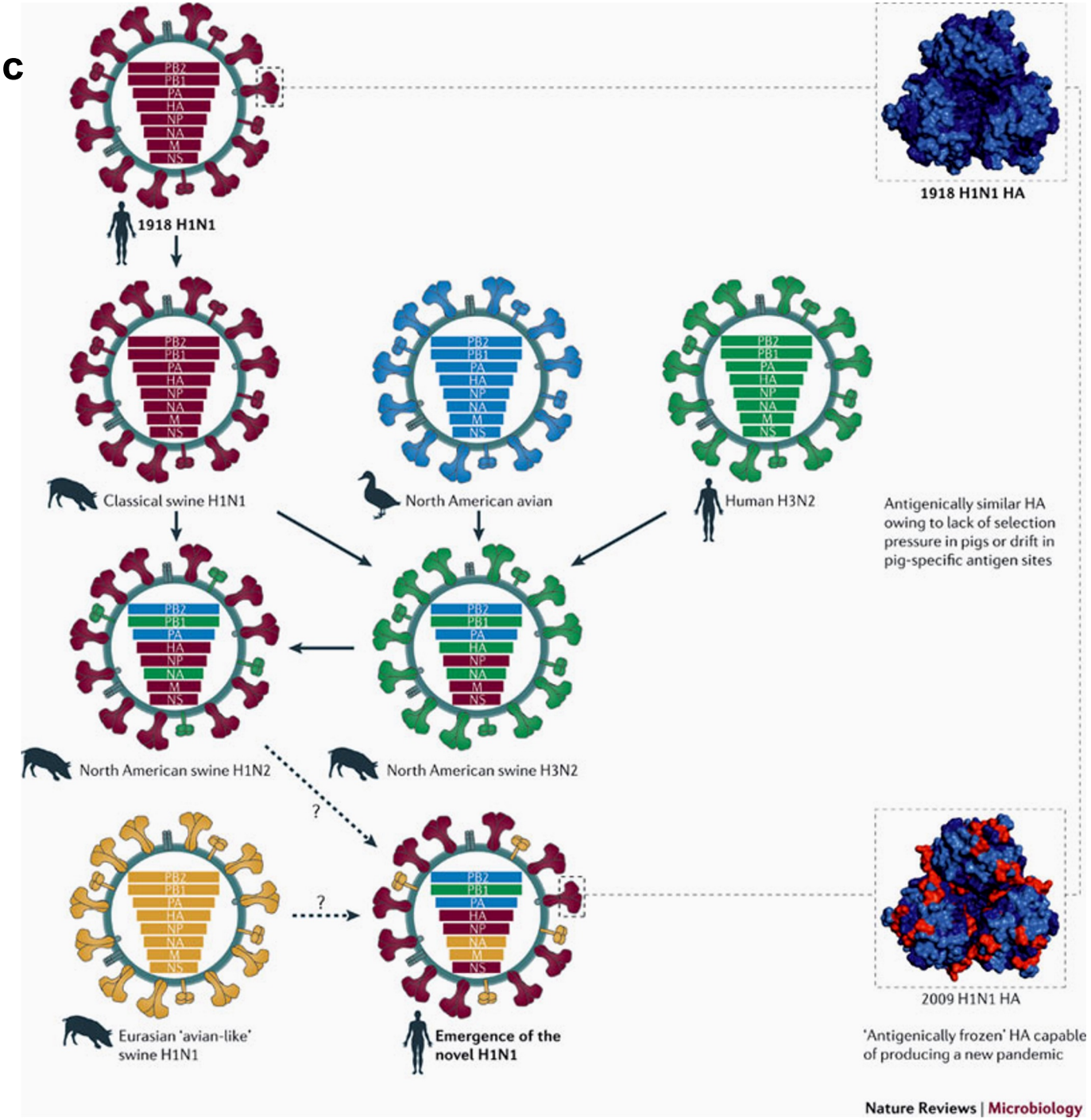
Archives of Virology (2018) 163:831–844 https://doi.org/10.1007/s00705-018-3708-y

Mechanisms for the emergence of pandemic influenza virus strains.



The virus keeps circulating among own species and sometimes jump the species barrier to generate a novel strain of pandemic potential

2009 Pandemic H1N1 virus



Nature Reviews | Microbiology
AUGUST 2011 | VOLUME 9

Emergence of an ‘antigenically frozen’ 2009 pandemic H1N1 virus

Influenza viruses similar to the 1918 pandemic H1N1 virus became established in domestic pigs between 1918 and 1920; this lineage is referred to as the classical swine lineage.

In 1979, a distinct Eurasian ‘avian-like’ H1N1 virus emerged in European pigs and has since co-circulated with the classical swine H1N1 viruses.
Triple-reassortant swine origin influenza virus (SOIV) H1 viruses of different strains and subtypes (for example, H3N2 and H1N2) emerged and became predominant among North American pig herds in the 1990s.
All of these viruses provided the genetic pool for the genesis of the 2009 pandemic H1N1 SOIV, possibly owing to further reassortment in pigs.

Thus, the 2009 pandemic H1N1 virus is composed of PB2 and PA segments from North American avian viruses, the PB1 segment of the human H3N2 viruses, haemagglutinin (HA; of the H1 subtype), nucleoprotein (NP) and NS segments derived from classical swine H1N1 viruses, and the neuraminidase (NA; of the N1 subtype) and M segments of Eurasian ‘avian-like’ swine viruses.

Sequence and antigenic analyses of the 2009 pandemic H1N1 virus show that there are similarities between the HA of this virus and that of the 1918 and human H1N1 viruses that circulated sometime between 1918 and the 1950s. The antigenic similarities between the 1918 and 2009 pandemic H1N1 viruses are represented in the crystal structure models of the trimeric configuration of the HA protein globular head, as seen from a top view. The antigenic sites of the HA proteins are shown in light blue, non-antigenic sites are shown in dark blue. The sites that differ between the 1918 and 2009 HA proteins are depicted in red.

Avian Influenza

Features of LPAI and HPAI viruses

- Virus a bassa patogenicità (LP)

  Sottotipi: H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12 , H13, H14, H15, H16

  - Non danno malattie fra gli uccelli selvatici
  - Sono associati a leggere patologie tra il pollame domestico
  - Sono diffusi a livello mondiale

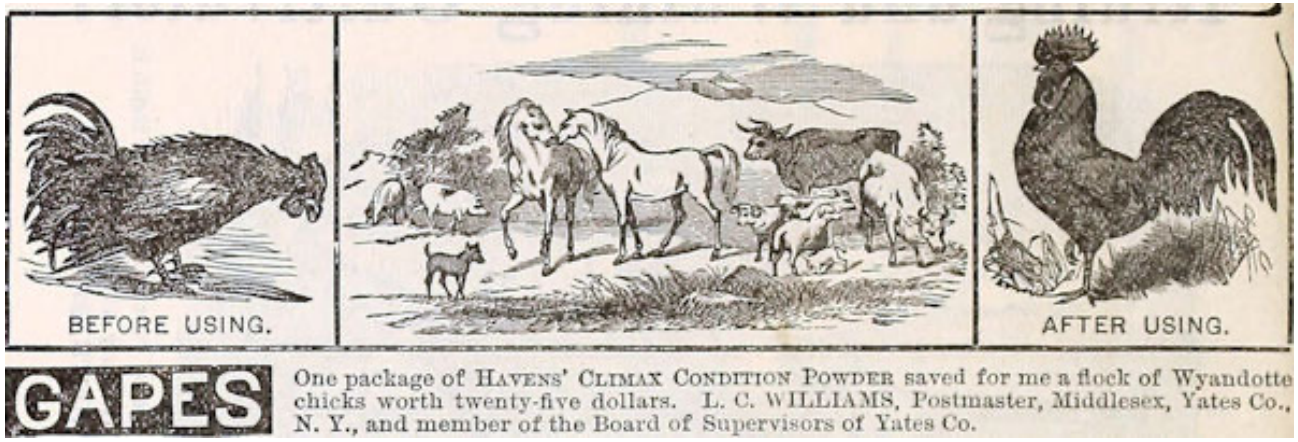
- Virus ad alta patogenicità (HP)

  Sottotipi : H5 H7 in alcune situazioni:

  - Possono evolvere in virus ad HP causando malattia grave fra gli uccelli domestici (e selvatici)
  - Alto tasso di mortalità tra il pollame domestico (90-100%)
  - Non è ancora chiaro se la distinzione tra "alta patogenicità" e "bassa patogenicità" è correlato al rischio di malattia tra gli umani

Avian Influenza

L'influenza aviaria ad alta patogenicità, un tempo definita peste aviaria, é stata diagnosticata e descritta per la prima volta come una malattia devastante nel 1878 da uno studioso italiano, Edoardo Perroncito, che osservò una gravissima malattia del pollame nelle fattorie delle colline piemontesi. Nel 1901 si definì che l'agente eziologico di questa malattia era un virus. Nel 1955 venne dimostrato che il responsabile era il virus influenzale di tipo A.



At the time, "fowl cholera," a deadly respiratory disease, caused by the bacterium *Pasteurella multocida*, was common and believed to be the culprit of the disease. Advertisement offering treatment for birds with Fowl Cholera, 1890.

La definizione di ≪influenza aviaria ad alta patogenicita≫ (HPAI) venne adottata nel 1981 durante il primo Simposio internazionale sull'influenza aviaria di Beltsville (USA).

Nel 1992, la direttiva comunitaria europea 92/40/CEE ha stabilito che il termine influenza aviaria si applica solo alle infezioni sostenute da ceppi H5 e H7

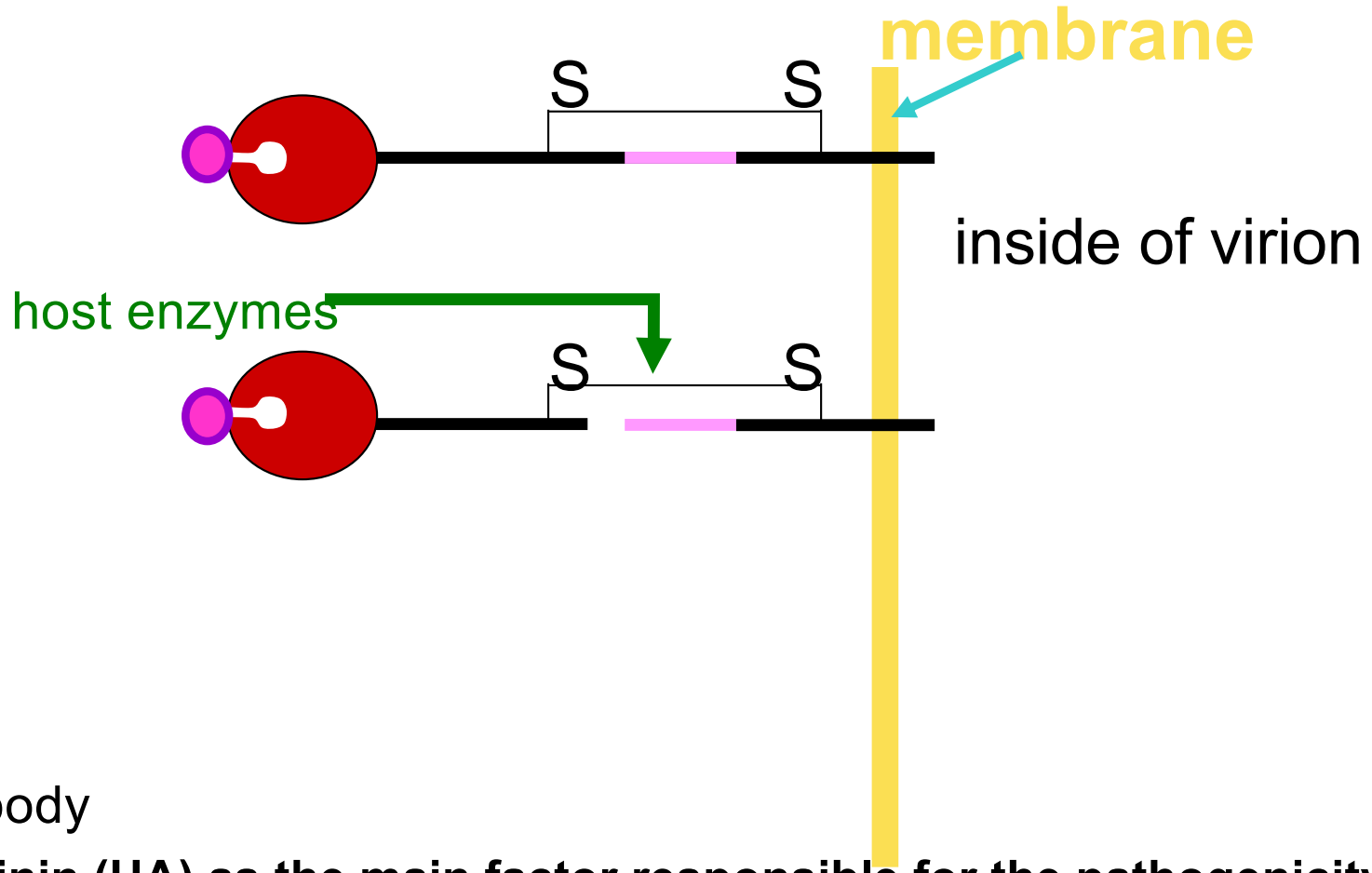
H1						N1					
H2						N2					
H3						N3					
H4						N4					
H5						N5					
H6						N6					
H7						N7					
H8						N8					
H9						N9					
H10											
H11											
H12											
H13											
H14											
H15											
H16											

La più grande varietà di virus dell'influenza aviaria e stata isolata dagli uccelli selvatici e in particolare da volatili acquatici.
La particolare etologia di queste specie, caratterizzata dalla tendenza a vivere in gruppi numerosi, la possibilità di compiere lunghe migrazioni e l'affinità per l'ambiente acquatico (via di diffusione del virus) li rendono degli ospiti ideali.

Le specie che fungono da serbatoio epidemiologico, avendo la capacita di infettarsi con diversi sottotipi contemporaneamente, assicurano le condizioni necessarie per il riassortimento genetico e consentono quindi la persistenza dei virus dell'influenza aviaria in natura e la comparsa di nuove varianti. I virus influenzali hanno avuto nel corso del tempo la capacità di adattarsi alle specie serbatoio andando verso una attenuazione della patogenicità. Questi uccelli consentono quindi la permanenza in natura dei virus a bassa patogenicità.

I focolai sostenuti da virus ad alta patogenicità negli uccelli selvatici sono rari in natura, in quanto non rappresentano una strategia ecologica vincente

HA protein - attachment, fusion

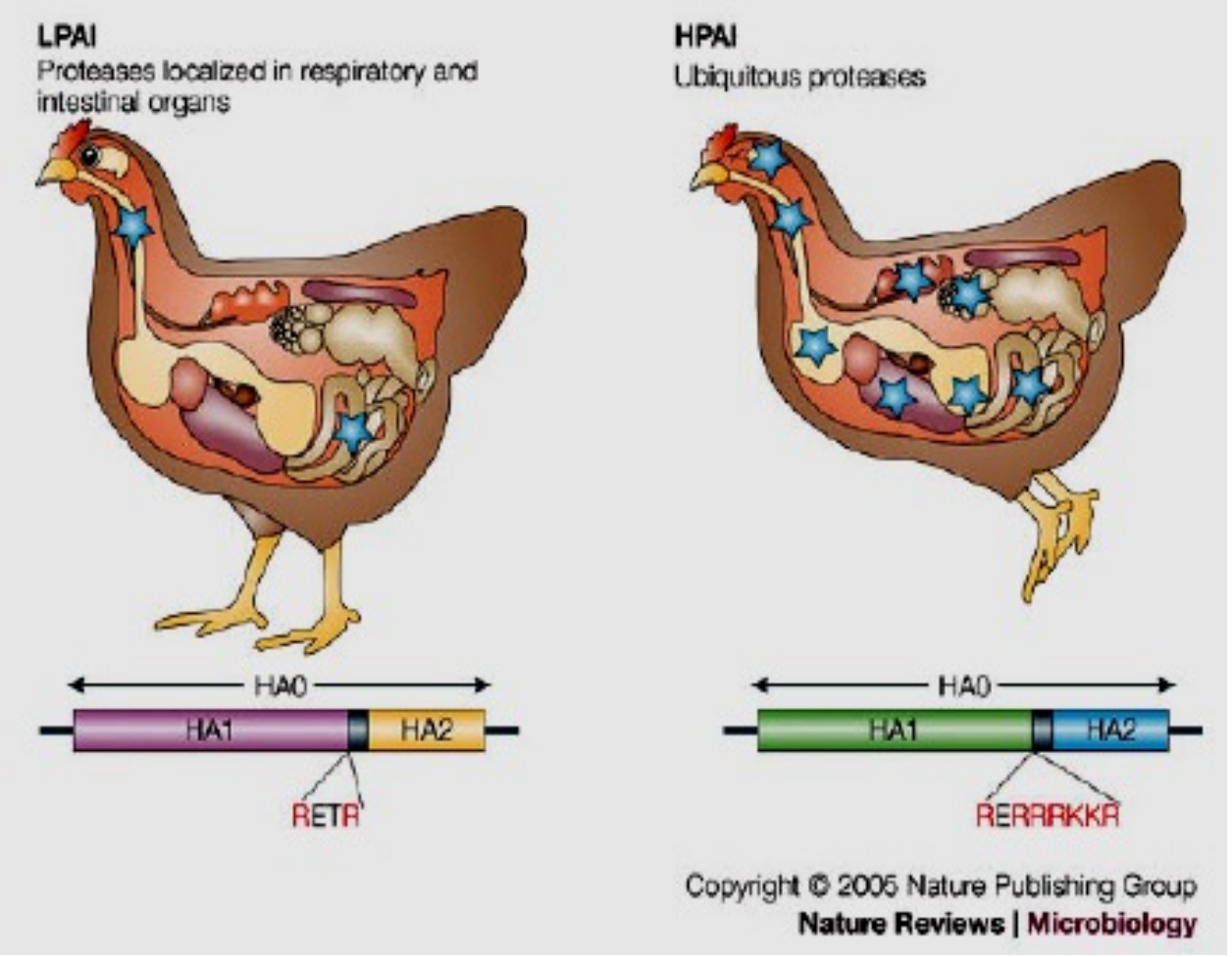


Hemagglutinin (HA) as the main factor responsible for the pathogenicity of avian viruses in domestic birds. The post-translational cleavage of HA0, in the two HA1 and HA2 subunits by the host proteases, generates a fusogenic domain at the amino-terminal end of HA2 which mediates the fusion between the viral envelope and the endosome membrane .

Molecular determinants of pathogenicity

Haemagglutinin (HA) as a major determinant of the pathogenicity of avian influenza viruses in poultry.

Post-translational proteolytic cleavage of the HA precursor molecule (HA0) into HA1 and HA2 subunits by host proteases generates a fusogenic domain at the amino terminus of HA2 (shown in grey), which mediates fusion between the viral envelope and the endosomal membrane. Therefore, proteolytic activation of the HA molecule is essential for viral infectivity. The HAs of low-pathogenicity avian influenza (LPAI) viruses do not contain a series of basic amino acid (RETR) at the protease cleavage site and are cleaved by proteases that are localized in respiratory and intestinal organs, resulting in mild localized infections. By contrast, the HAs of high-pathogenicity avian influenza (HPAI) viruses possess multiple basic amino acids at the cleavage site (RERRRKKR), which are cleaved by ubiquitous proteases in a wide range of organs, resulting in lethal systemic infection.



Molecular determinants of pathogenicity

Avian influenza A virus
– Virulent (H5, H7): multibasic cleavage site
– Avirulent (H1-H16): monobasic cleavage site
Human influenza A virus
– H1, H2, H3: monobasic cleavage site

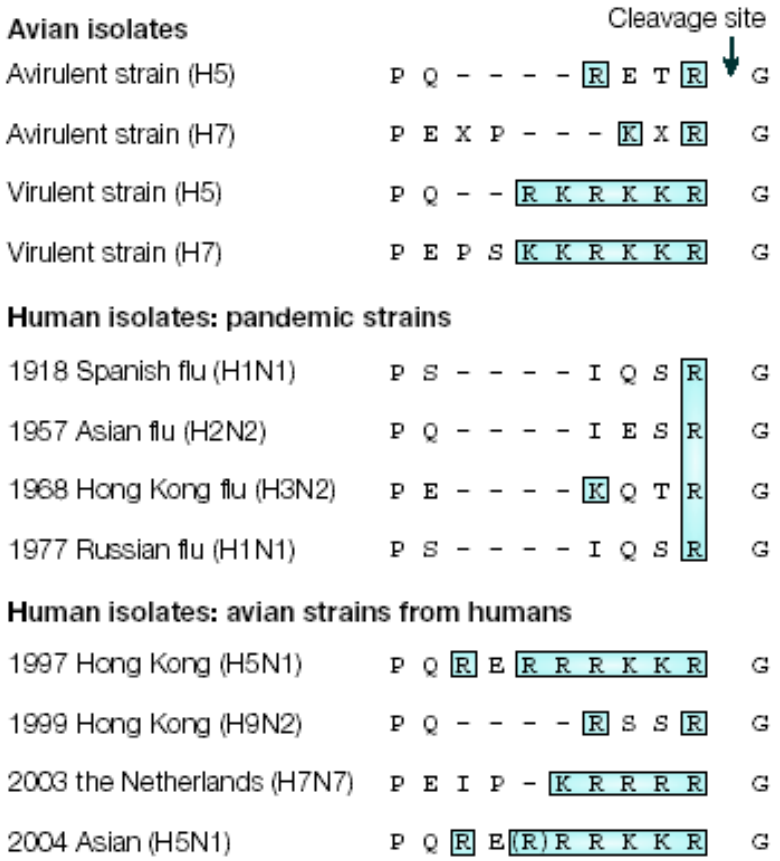


Figure 3 | **HA cleavage site sequence of influenza A viruses.** Basic amino acids are shown in blue boxes. Dashes are for the purpose of alignment only.

Avian Influenza (Bird Flu)

EXPLORE TOPICS

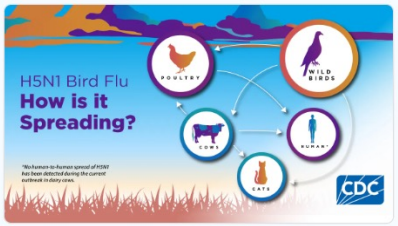
SEARCH

NOVEMBER 15, 2024 ESPAÑOL

H5 Bird Flu: Current Situation

WHAT TO KNOW

- H5 bird flu is widespread in wild birds worldwide and is causing outbreaks in poultry and U.S. dairy cows with several recent human cases in U.S. dairy and poultry workers.
- While the current public health risk is low, CDC is watching the situation carefully and working with states to monitor people with animal exposures.
- CDC is using its flu surveillance systems to monitor for H5 bird flu activity in people.



https://www.cdc.gov/bird-flu/situation-summary/index.html

Influenza aviaria

L'influenza aviaria è una malattia virale che colpisce prevalentemente gli **uccelli selvatici,** che fungono da serbatoio e possono eliminare il virus attraverso le feci. Solitamente tali uccelli non si ammalano, ma possono essere molto contagiosi per gli **uccelli domestici** come polli, anatre, tacchini e altri animali da cortile.

L'influenza nel pollame si presenta regolarmente nel territorio nazionale, sia nella forma causata da virus a **bassa patogenicità (LPAI)** sia da virus ad **alta patogenicità (HPAI)**. Questa malattia, soprattutto quando sostenuta da ceppi altamente patogeni, ha **conseguenze devastanti**: non solo per l'elevato tasso di mortalità che può essere raggiunto, ma anche per il forte impatto economico che ne consegue, dovuto all'adozione di politiche di eradicazione e alle restrizioni al commercio imposte nelle zone in cui sorgono i focolai.

L'importanza del controllo sanitario per questa malattia non è legato solo a un problema di sanità animale ma anche di salute pubblica. Infatti **i virus influenzali appartenenti al tipo A possono infettare anche altri animali (maiali, cavalli, cani, balene) nonché l'uomo**. Data l'elevata frequenza con cui questi virus vanno incontro a fenomeni di mutazione, c'è la possibilità che da un serbatoio animale possa originare un nuovo virus per il quale la popolazione umana risulta suscettibile, dando modo alla malattia di estendersi a livello globale e provocando quindi una pandemia.

https://www.izsvenezie.it/temi/malattie-patogeni/influenza-aviaria/

Highly pathogenic avian influenza virus detection in Europe

Settings

Main bird categories:

(●) All birds ( ) Poultry ( ) Wild birds

Subtypes:

- [x] A(Not typed)
- [x] A(H5Nx)
- [x] A(H5N1)
- [x] A(H7N5)
- [x] A(H5N2)
- [x] A(H5N3)
- [x] A(H5N4)
- [x] A(H5N5)
- [x] A(H5N6)
- [x] A(H5N8)

Bird Sub-categories:

- [x] Captive birds
- [x] Poultry
- [x] Wild birds

Choose mininum date:

2016-10-01 — 2024-10-01

2016-10-01 2018-06-09 2020-02-15 2021-10-23 2023-07-01 2025-03-07

Choose maximum date:

2024-10-01 — 2025-03-07

2024-10-01 2024-11-12 2024-12-24 2025-02-04 2025-03-07

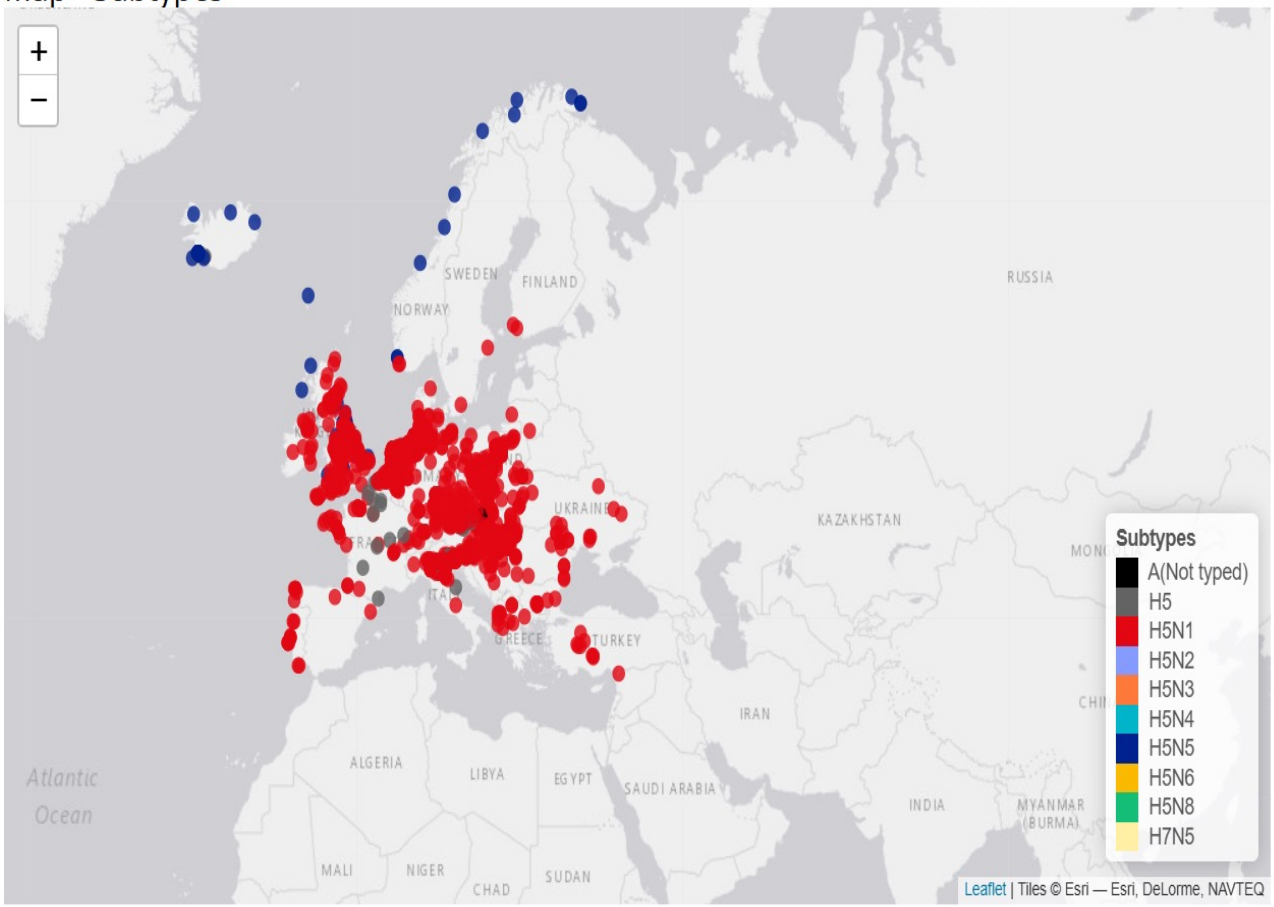
Press play above to animate the graphics (adding 7 days to the maximum date)

Summary per country

Show 4 entries

Search:

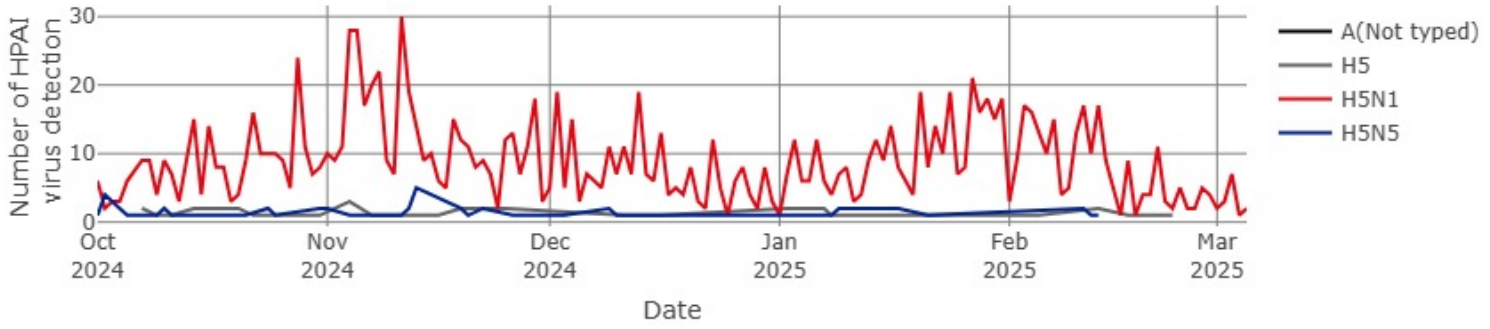
Map - Subtypes



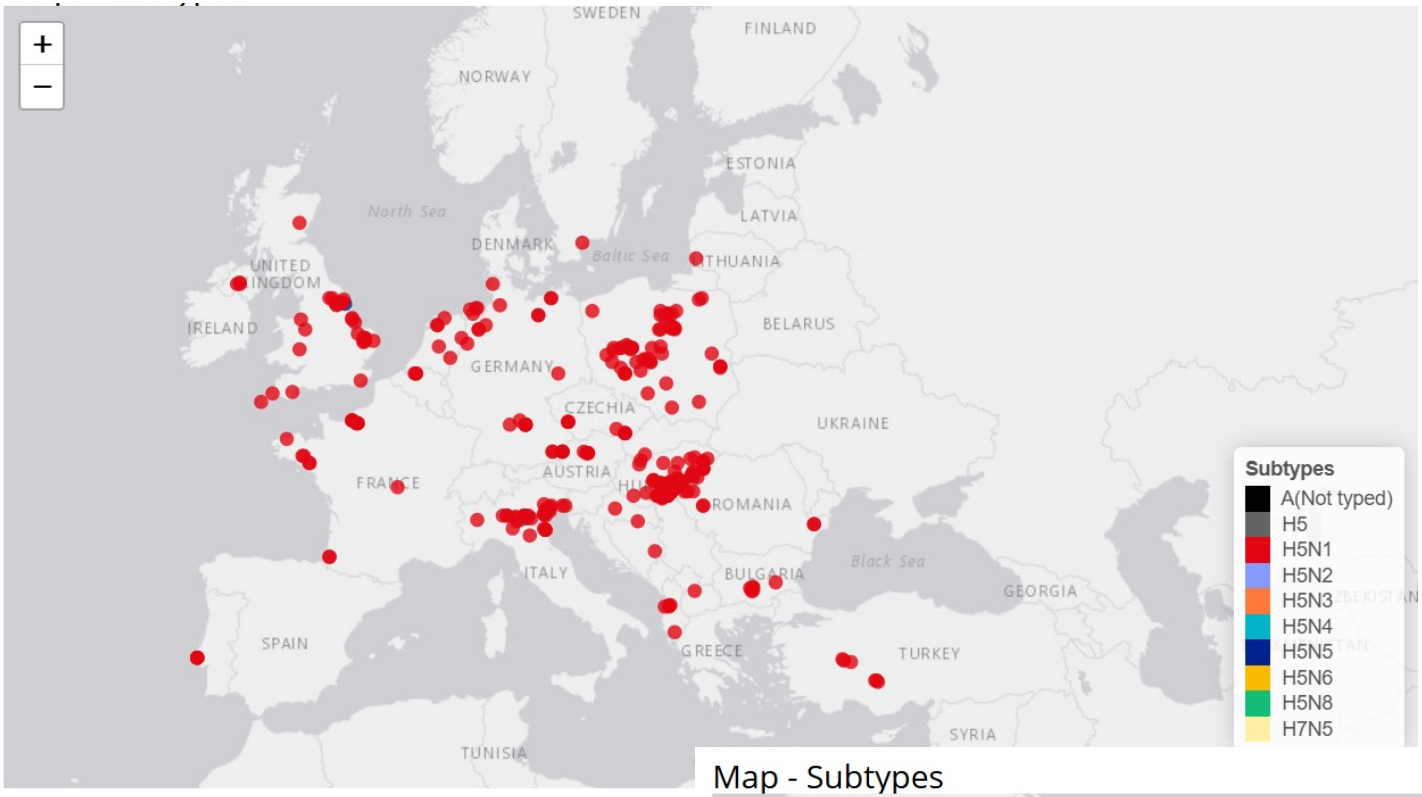
SOURCE: ADIS updated on 07/03/2025 and WAHIS updated on 10/03/2025

**United Kingdom (except Northern Ireland) data are sourced from ADNS up to 31/12/2020 and then from WOAH. United Kingdom (Northern Ireland) data are from ADIS.*

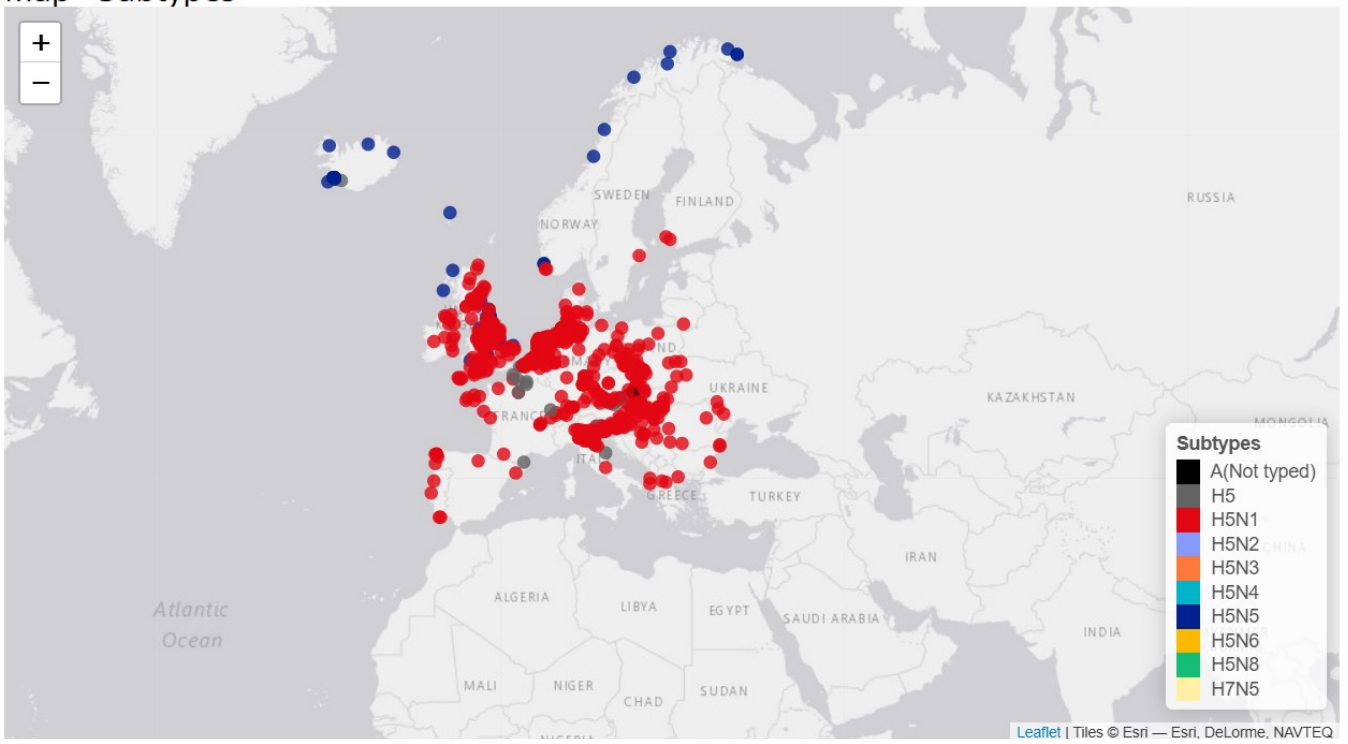
Time series



Poultry



Wild birds



Avian Influenza (Bird Flu)

EXPLORE TOPICS

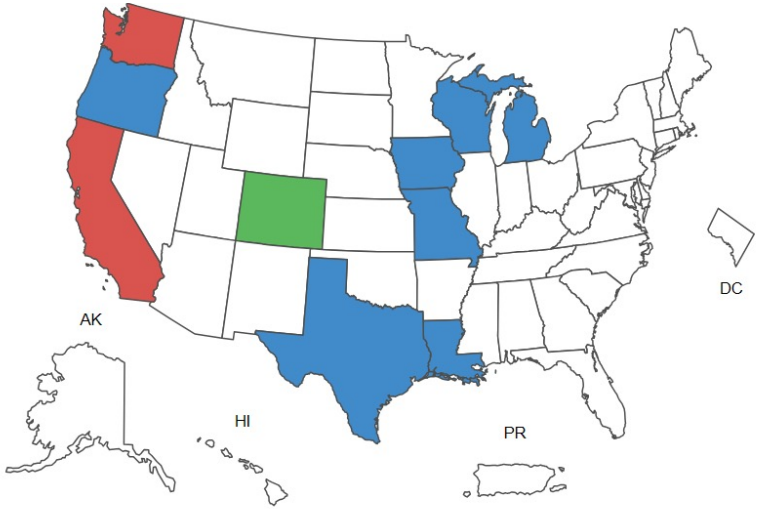
SEARCH

APRIL 3, 2025 ESPAÑOL

Current Situation: Bird Flu in Dairy Cows

WHAT TO KNOW

A multistate outbreak of HPAI A(H5N1) bird flu in dairy cows was first reported on March 25, 2024. This is the first time that these bird flu viruses had been found in cows. In the United States, since 2022, USDA APHIS has reported HPAI A(H5N1) virus detections in more than 200 mammals.



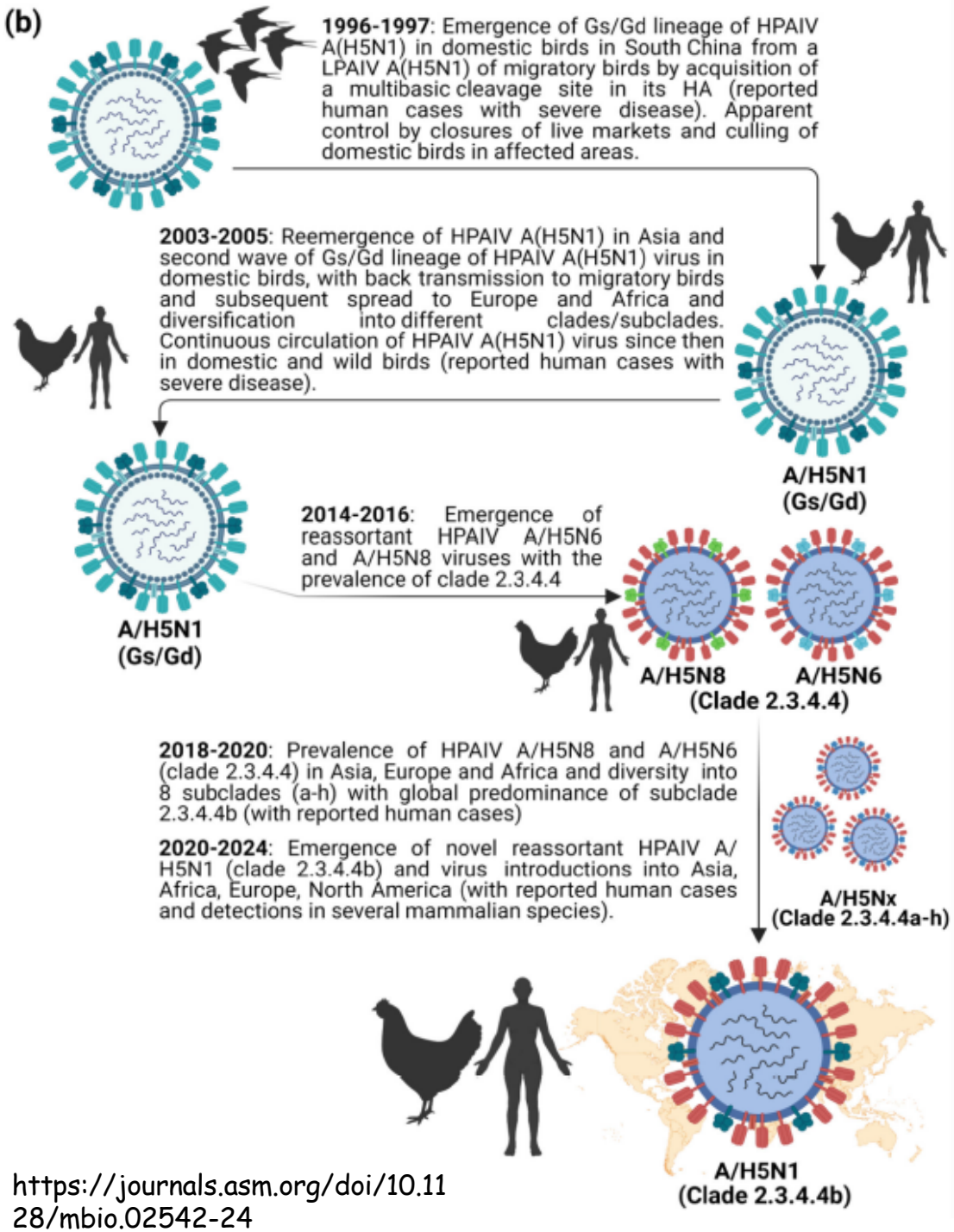
U.S. states that have reported human case(s) of influenza A(H5) virus infection.

Vaccination

Getting a seasonal flu vaccine will not protect against H5N1 bird flu

While getting a seasonal flu vaccine only prevents seasonal flu and will not protect against H5N1 bird flu, it is important that people who may have frequent exposure to infected or potentially infected birds or other animals get a seasonal flu vaccine, ideally 2 weeks before their potential exposure. This is because it can reduce the prevalence and severity of seasonal flu and might reduce the very rare risk of coinfection with a human seasonal virus and an avian virus at the same time, and the theoretical risk that reassortment between the two could result in a new virus. Such dual infections, while very rare, could theoretically result in genetic reassortment of the two different influenza A viruses and lead to a new influenza A virus that has a different combination of genes, and which could pose a significant public health concern.

https://www.cdc.gov/bird-flu/situation-summary/mammals.html



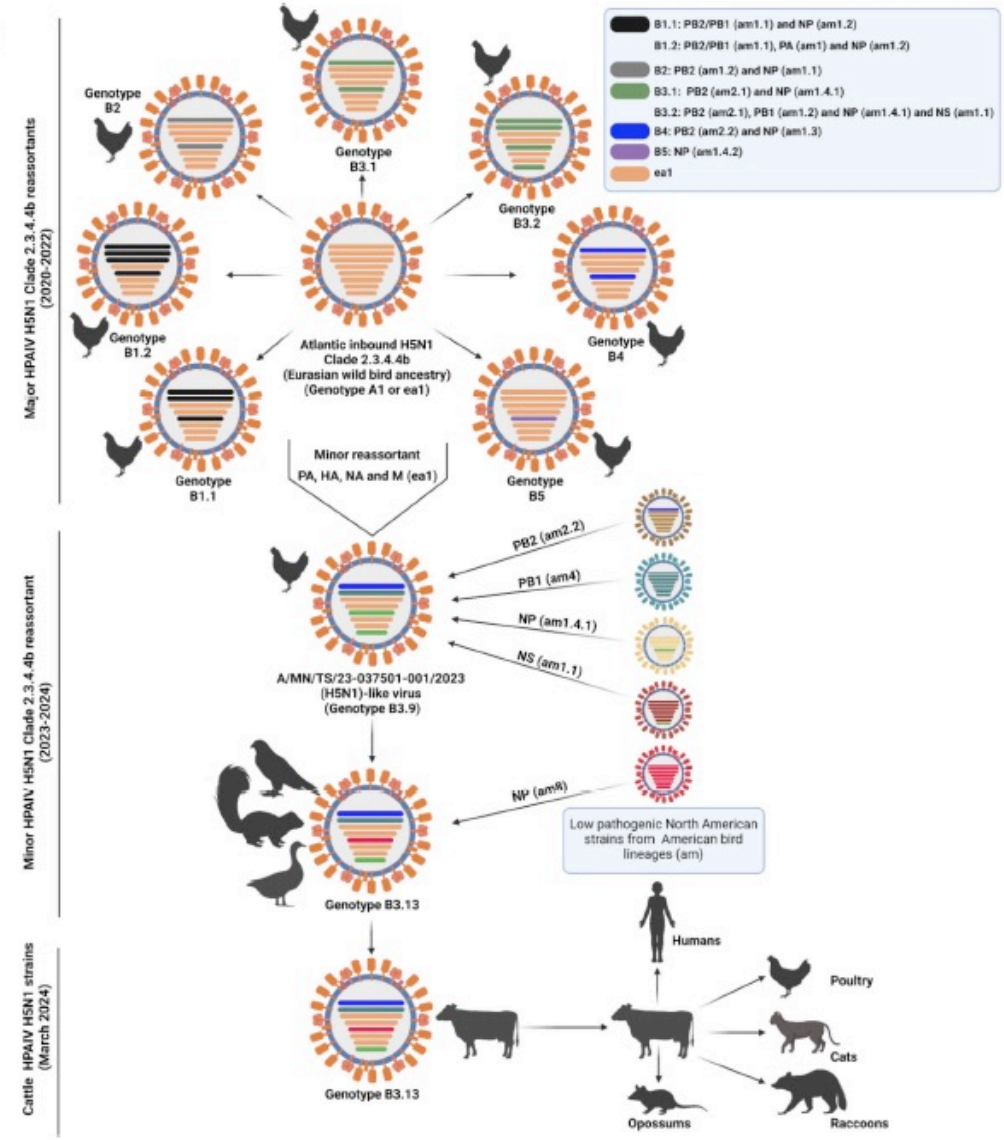
https://journals.asm.org/doi/10.1128/mbio.02542-24

(b) Documented history of highly pathogenic avian influenza virus (HPAIV) H5N1 emergence in migratory birds in 1996 and key evolutionary occurrences until 2024

Avian influenza A (H5N1) virus in dairy cattle: origin, evolution, and cross-species transmission

Ahmed Mostafa,[1,2] Mahmoud M. Naguib,[3,4] Aitor Nogales,[5] Ramya S. Barre,[1] James P. Stewart,[3] Adolfo García-Sastre,[6,7,8,9,10,11] Luis Martinez-Sobrido[1]

Although replication of the virus in cows appears to be mainly confined to the mammary tissue, with high levels of viral loads detected in milk, infected cats and poultry showed severe respiratory disease, neurologic signs, and eventually died. Furthermore, several human infections with HPAIV H5N1 have also been reported in dairy farm workers and were attributed to exposures to infected dairy cattle. This is believed to represent the first mammalian-to-human transmission report of the HPAIV H5N1. Fortunately, infection in humans and cows, as opposed to other animals, appears to be mild in most cases.



https://journals.asm.org/doi/10.1128/mbio.02542-24

TABLE 1 Amino acid variations, associated with increased mammalian host adaptation and pathogenicity, reported in HPAIV H5N1 isolated from cattle with frequency ≥90%

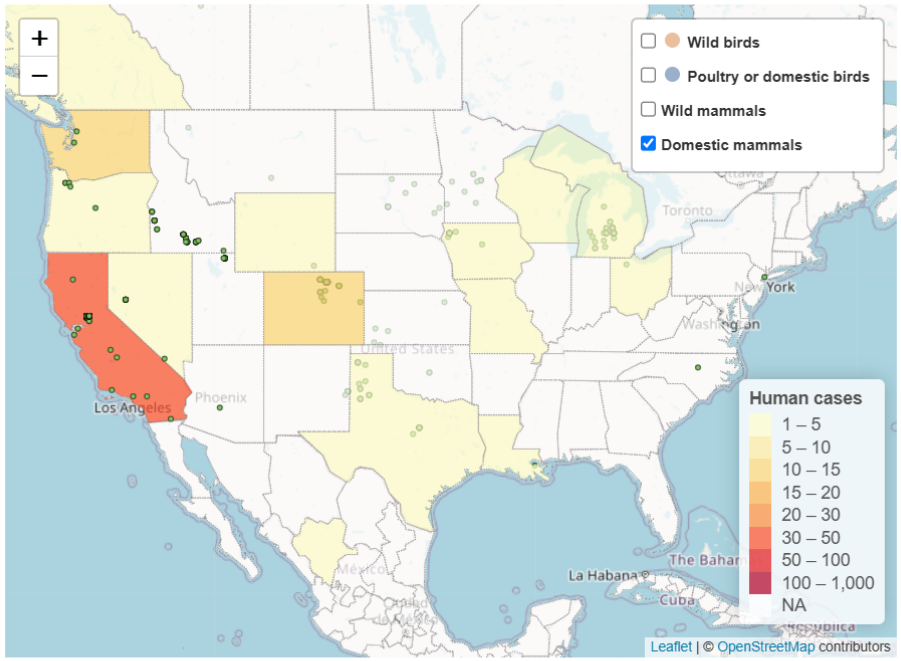
Gene	Amino acid mutation	Function	References
PB2	M631L	Human adaptive mutation that enhances polymerase activity and replication of mouse-adapted human and avian IAVs via adapting viral polymerases to use mammalian ANP32 proteins	(31, 35–37)
HA	172A	Enhances binding to α2–6 SA receptor without affecting the binding to α2–3 SA receptor	(31, 38)
	T199I	Contributes to decreased virion thermostability and increased HA activation pH and increases receptor binding breadth to mammalian- and avian-type sialic acid (SA) receptors via increasing receptor binding site flexibility	(31, 36, 39)
NP	V105M	Contribute to increased virulence, enhanced viral replication, severe pulmonary edema, and excessive inflammatory cellular infiltration in mammals	(31, 40, 41)
NA	N70S/D	Associated with decreased susceptibility of influenza infection to zanamivir	(42)
NA	N71S	Reported in immunocompromised patients with seasonal influenza infection that resist oseltamivir (E119V [100%]) after long-term treatment (139 days) with cumulative zanamivir therapy (E119V [100%] and N71S [100%])	(31, 43)
NS	V205I/G	Enhances the viral polymerase function and increases viral replication and lethality in mice	(44, 45)

Sebbene siano stati identificati cambiamenti minori nella sequenza del virus identificato nell'uomo rispetto a quelle riscontrate nei bovini, entrambe le sequenze mantengono le caratteristiche genetiche tipiche dei virus aviari e per la maggior parte mancano di mutazioni che li renderebbero più adatti ad infettare i mammiferi. Date le caratteristiche genetiche di questo ceppo, l'attuale rischio per la popolazione umana rimane basso.

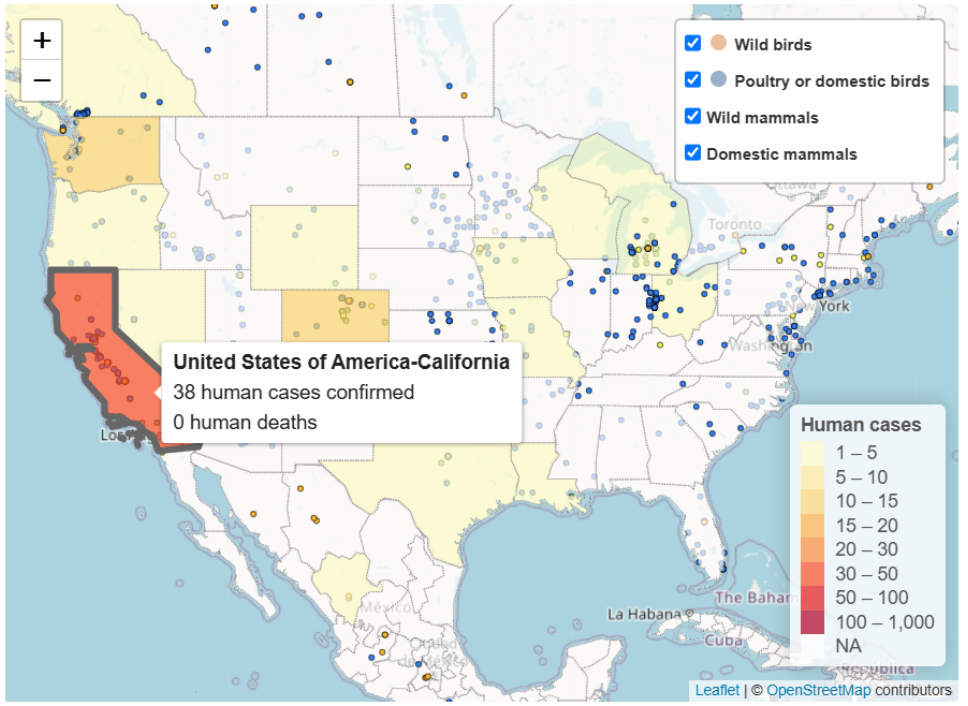
72	1	825	1,075
Human confirmed cases	Human deaths	Number of outbreaks (Birds)	Number of outbreaks (Mammals)

Epicurve | Table | Clinical characteristics | Map

Geographic distribution of human cases of Influenza A(H5N1) by country and subnational level in the region of the Americas. 27 March 2024 - 07 March 2025

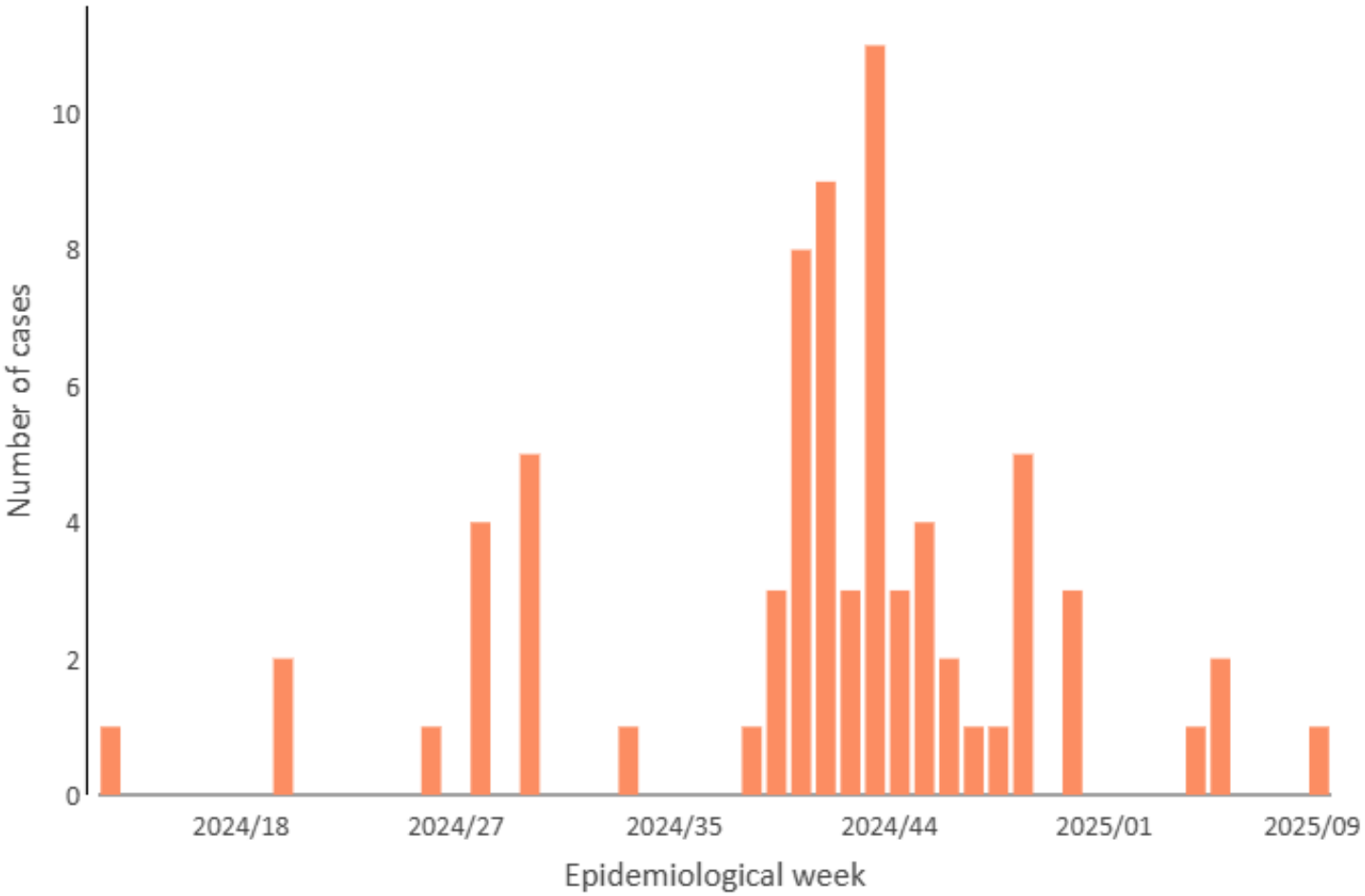


Geographic distribution of human cases of Influenza A(H5N1) by country and subnational level in the region of the Americas. 27 March 2024 - 07 March 2025

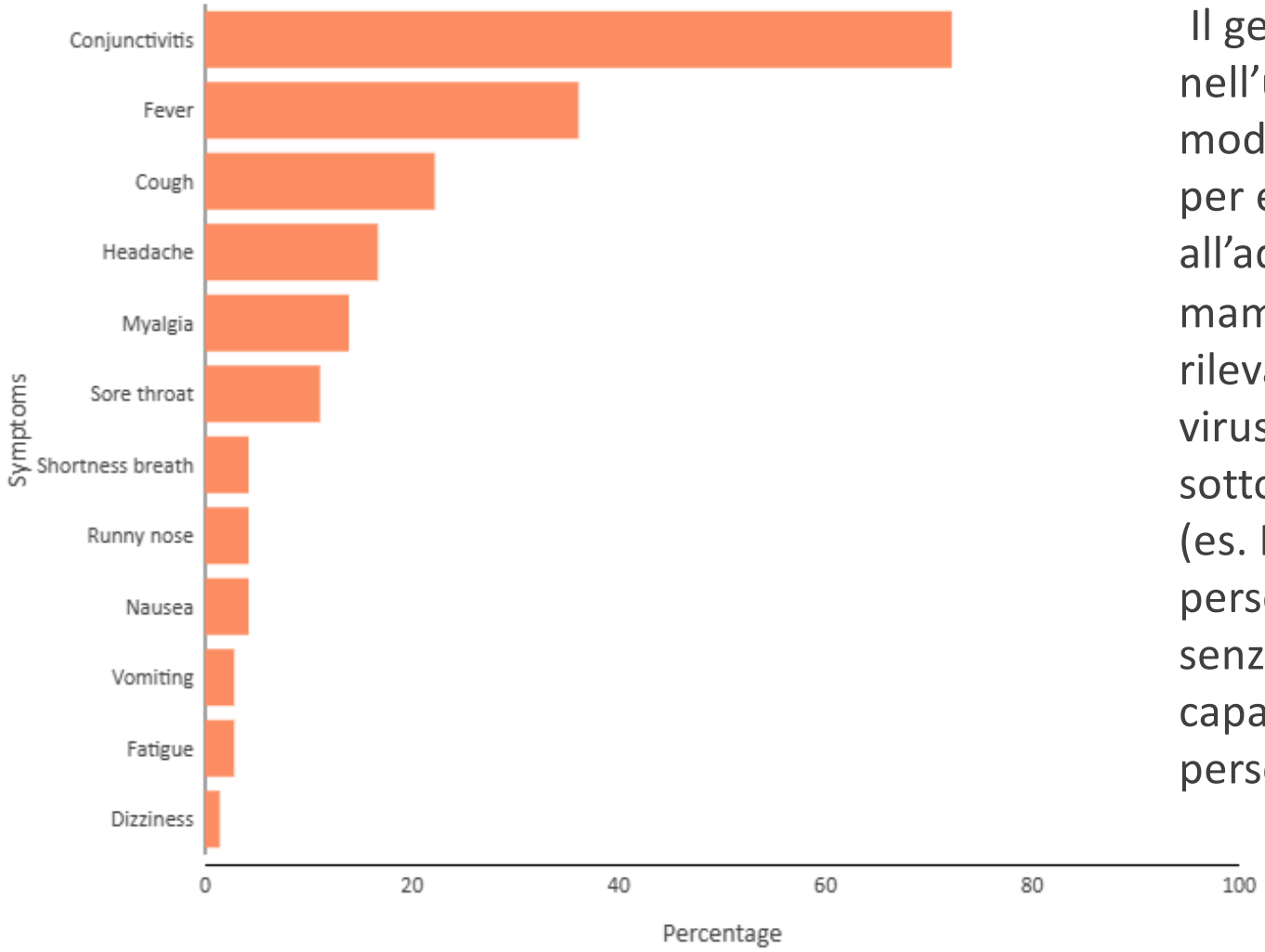


https://shiny.paho-phe.org/h5n1/

Trends of human cases of influenza A(H5N1) in the region of the Americas by epidemiological week*. 27 March 2024 - 07 March 2025



Frequency of clinical symptoms among human cases of influenza A(H5N1) in the region of the Americas (n=72). 27 March 2024 - 07 March 2025



Il genoma del virus trovato nell'uomo presentava una modifica (PB2 E627K) nota per essere associata all'adattamento virale ai mammiferi, che era già stata rilevata in precedenza in virus HPAI H5N1 e altri sottotipi di influenza aviaria (es. H7N9) identificati in persone e animali infetti ma senza aver mai acquisito la capacità di diffondersi tra le persone.

E glutamic acid; K lysine

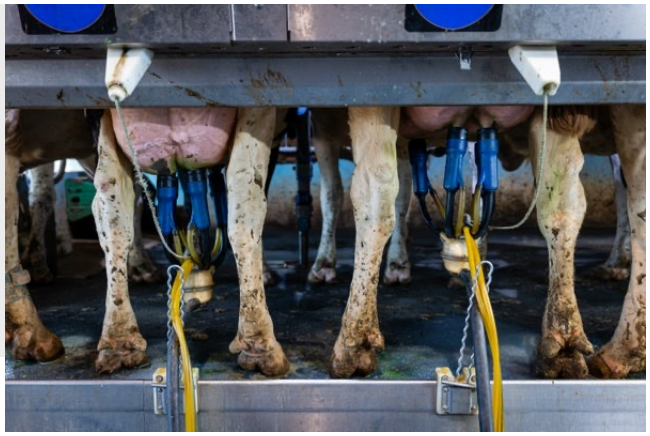
https://www.scientificamerican.com/article/why-bird-flu-is-causing-eye-infections-in-dairy-workers/

JUNE 3, 2024 | 5 MIN READ

Why Bird Flu Is Infecting People's Eyes

Three U.S. dairy workers have been infected with H5N1 after contact with sick cows, and all of them developed eye symptoms

BY TANYA LEWIS EDITED BY DEAN VISSER



Infected cows have very high levels of virus in their milk, and early reports indicate that it is being spread by contaminated milking equipment, although other methods of transmission are also possible. Several cats that drank raw milk from infected cows developed neurological symptoms and died. Pasteurizing milk appears to effectively neutralize the H5N1 virus.

The workers were most likely exposed to the virus in contaminated milk—by getting it on their hands and then touching their eyes, for example, or via milk droplets (or even microscopic particles called aerosols) from a cow's udder or milking equipment.

In recent weeks, three human infections with the virus have been confirmed—all in dairy workers who had contact with sick cows. All three developed symptoms of eye infections known as conjunctivitis. The latest case, reported in Michigan this week, also involved respiratory symptoms more typical of a flu infection. (early report 2024)

Effectiveness of pasteurization for the inactivation of H5N1 influenza virus in raw whole milk

Tamiru N. Alkie [a], Neda Nasheri [b,c,*], Pablo Romero-Barrios [b], Angela Catford [b], Jay Krishnan [d], Lemarie Pama [a], Kathleen Hooper-McGrevy [a], Charles Nfon [a,g], Todd Cutts [d], Yohannes Berhane [a,e,f,g,**]

La pastorizzazione si definisce:

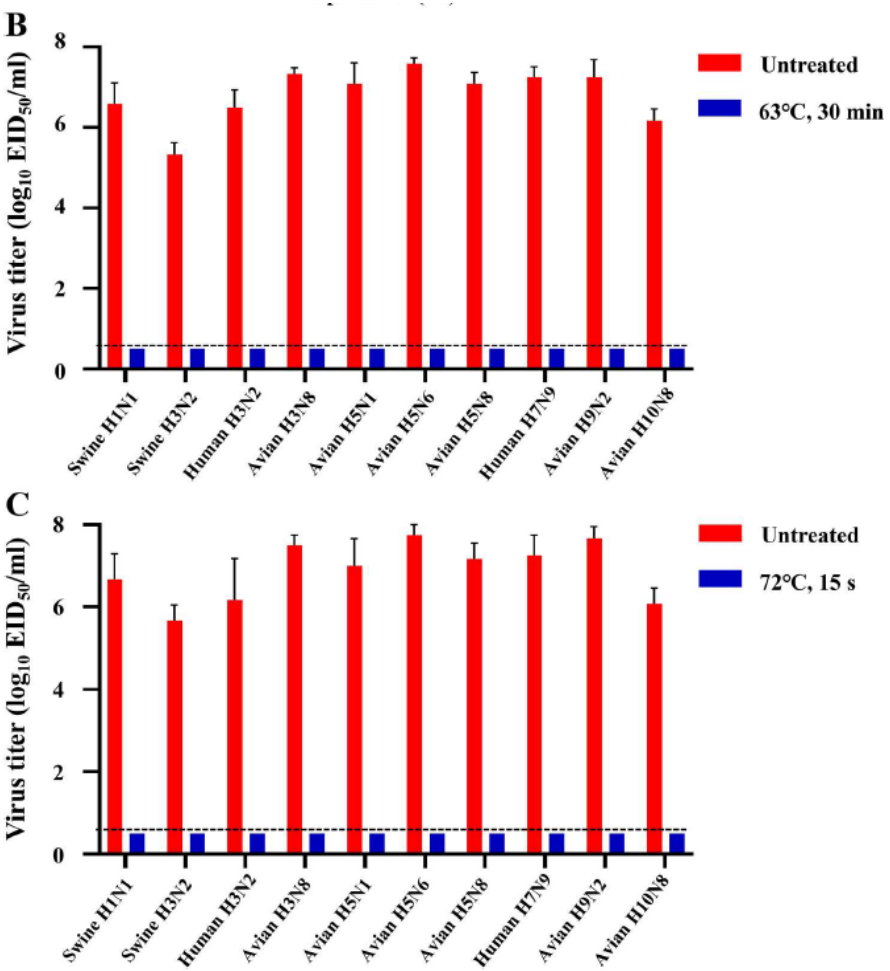
•Bassa → 60-65 ° C per 30 minuti (Impiegata nel trattamento di alimenti delicati quali vino e birra)
•Alta → 75-85 ° C per 2-3 minuti
•Rapida o HTST (High Temperature Short Time) → 75-85 ° C per 15-20 secondi

Tali temperature comportano l'inattivazione degli enzimi e dei microrganismi patogeni; spore e microrganismi termofili rimangono intatti in quanto le temperature non sono sufficientemente elevate come avviene invece nella sterilizzazione.
Si hanno inoltre ridotte perdite dal punto di vista nutrizionale e organolettico.

Emerging Microbes & Infections
2024, VOL. 13, 2364732 (4 pages)
https://doi.org/10.1080/22221751.2024.2364732

Does pasteurization inactivate bird flu virus in milk?

Pengfei Cui[a], Yichao Zhuang[a], Yaping Zhang[a], Lei Chen[a], Puze Chen[a], Jiaqi Li[a], Lulu Feng[a], Qin Chen[a], Fei Meng[a], Huanliang Yang[a], Yongping Jiang[a], Guohua Deng[a], Jianzhong Shi[a,b], Hualan Chen[a] and Huihui Kong[a]



CARATTERISTICHE DI RESISTENZA DEL VIRUS DELLA INFLUENZA AVIARIA

pH	Inattivato a PH ≤ 2
Agenti chimici	*Inattivato da solventi organici e detergenti* Sodio desossicolato: sensibile Sodio desossisolfato: sensibile *In presenza di materiale organico* Formaldeide: sensibile Gluteraldeide: sensibile ß-propiolattone: sensibile Etilenamina: sensibile *Dopo la rimozione di materiale organico* Fenoli: sensibile Sali quaternari d'ammonio: sensibile Ipoclorito di sodio: sensibile Perossimonosolfato di potassio: sensibile Acidi diluiti: sensibile Idrossilamina: sensibile Soventi lipidici: sensibile *Su superfici pulite, dopo la rimozione di materiale organico* Ipoclorito di sodio (5.25%): sensibile Idrossido di sodio (2%): sensibile Fenoli: sensibile Ionofori acidificati: sensibile Biossido di cloro: sensibile Agenti ossidanti forti: sensibile Carbonato di sodio (4%): sensibile Silicato di sodio (0.1%): sensibile
Agenti fisici	La pastorizzazione e la cottura sono efficaci mezzi di inattivazione. Temperatura: 60°C x 188 secondi: inattivato in uova intere 60°C x 507 secondi: inattivato in carne di pollame Inattivato da una temperatura a 'cuore' minima di 70°C dei prodotti carnei per almeno 3.5 secondi. Resiste quando congelato.
Resistenza in condizioni naturali	La permanenza nell'ambiente è spesso sottostimata. Condizioni di freddo e di umidità e la presenza di materiale organico favoriscono un alunga resistenza.

	Questo avviene su molte superfici d'acqua. Vitale in feci liquide: 4°C x 30-35 giorni 20°C x 7 giorni Permanenza in: - feci di pollame tenute a 25–32°C all'ombra LPAI H7N2: fino a due settimane in feci e gabbie: resistente in acqua: 28°C x 26-30 giorni 17°C x 94-158 giorni Il compostaggio uccide il virus nelle carcasse di pollame in < 10 giorni.

Il segretario alla Salute degli Stati Uniti Robert Kennedy Jr. ha avuto un'idea quantomeno controversa per risolvere l'influenza aviaria che sta decimando gli allevamenti del paese e alimentando la grave crisi delle uova: lasciare che il virus si diffonda, in modo da poter identificare gli animali immuni e preservarli.

Quando viene rilevato anche solo un caso tutti gli animali dell'allevamento vengono uccisi, e gli allevatori rimborsati in parte. Secondo il dipartimento dell'Agricoltura nel dicembre del 2024 sono stati abbattuti 18 milioni di tacchini, polli e galline da uova. Nel gennaio del 2025 il numero è arrivato a 23 milioni. In totale gli uccelli colpiti dall'aviaria sono stati 167 milioni.

Il problema sarebbe innanzitutto etico: gli uccelli infetti possono sviluppare gravi sintomi respiratori, diarrea, tremori e torsioni del collo. «La malattia causerebbe morti molto dolorose in quasi il 100 per cento dei casi dei polli e dei tacchini»

C'è poi la questione sanitaria. Ogni contagio è un'altra opportunità per il virus di evolversi in una forma più forte sviluppando la capacità di diffondersi tra le persone

Infine c'è il danno economico: lasciare che il virus si diffonda espone gli allevatori a perdite ancora più elevate di quelle che ci sono state finora.

Avian influenza infection in humans

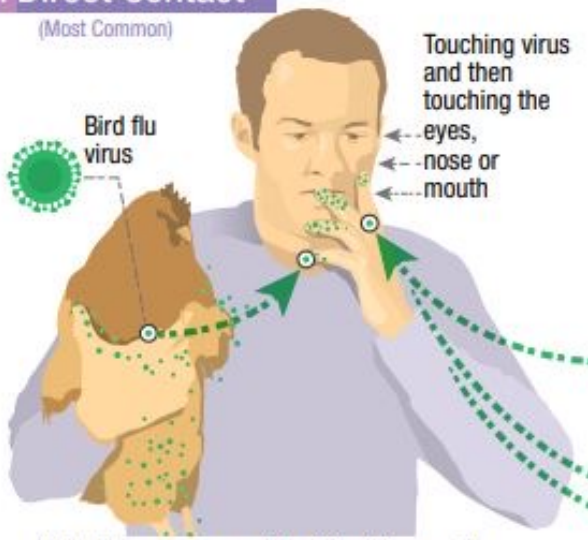
Direct transmission from poultry to humans does appear responsible for sporadic H5N1 and H7N9 **spillover infections**, which have caused 455 deaths among 861 cases documented from 2003 to 2020 (H5N1) and 616 deaths among 1568 cases reported between 2013 and 2020 (H7N9). However, despite a high case fatality rate (~52% for H5N1 and ~39% for H7N9), productive infections by avian IAV appear rare, and human-to-human transmission even more rare.

How Infected Backyard Poultry Could Spread Bird Flu to People

Human Infections with Bird Flu Viruses Rare But Possible

1 Direct Contact

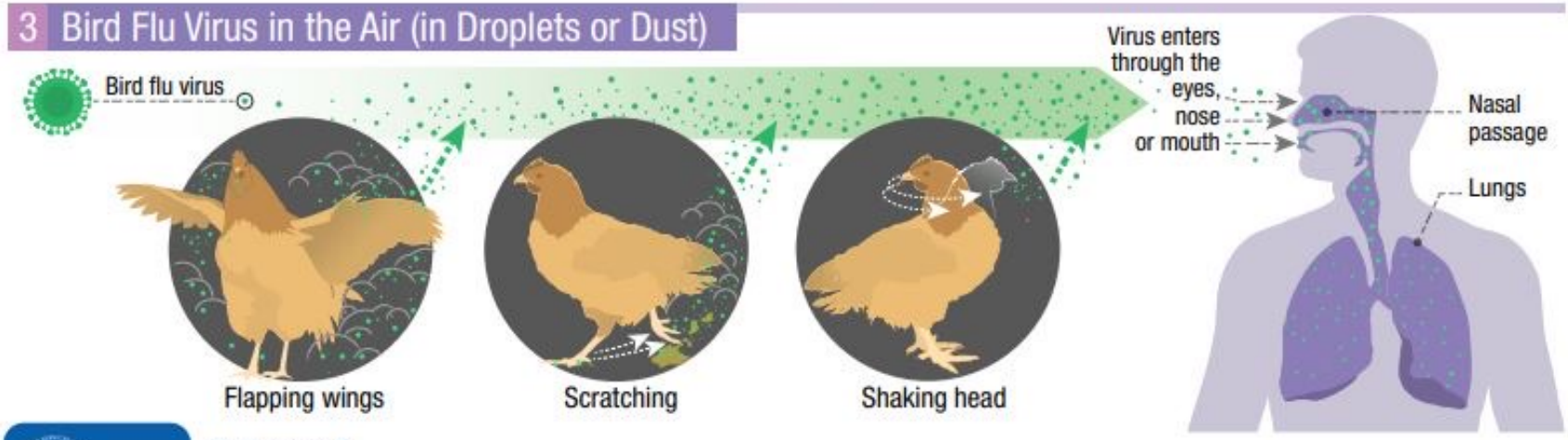
(Most Common)



Infection can occur without touching poultry.

2 Contaminated Surfaces

3 Bird Flu Virus in the Air (in Droplets or Dust)

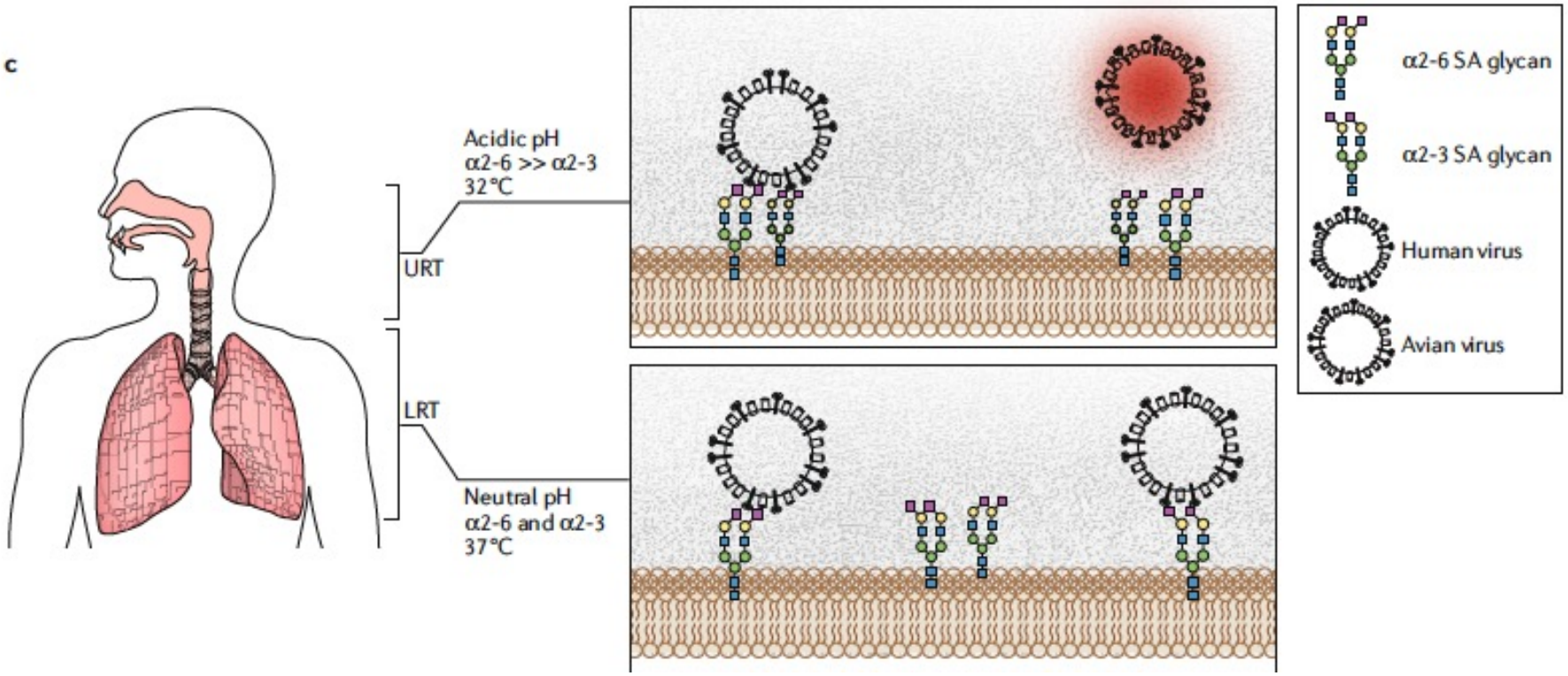


U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

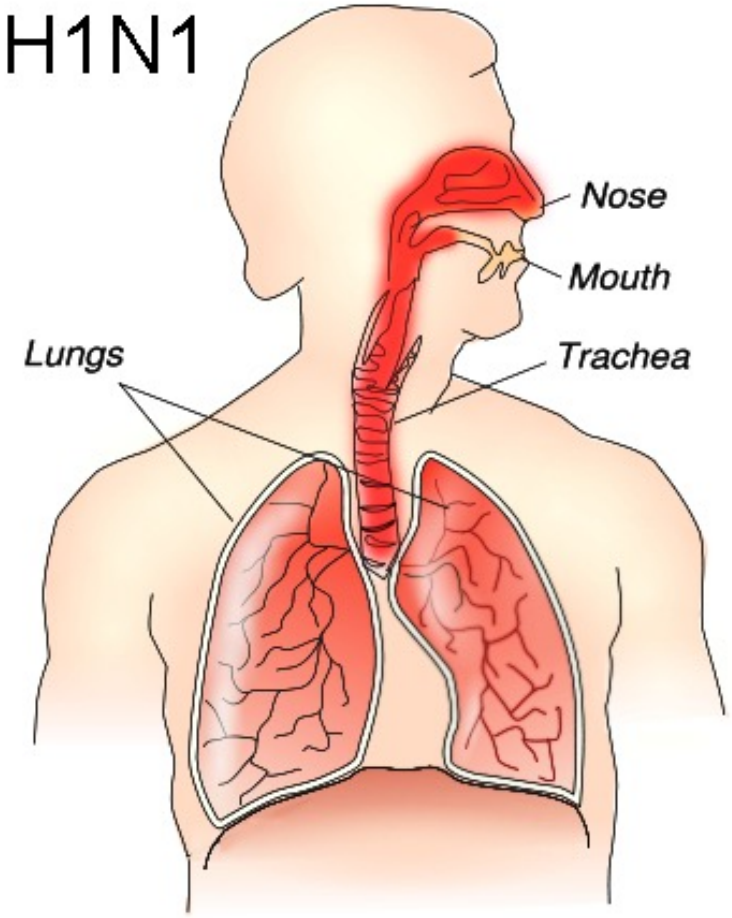
www.cdc.gov/flu/avianflu/avian-in-humans.htm

CS261152

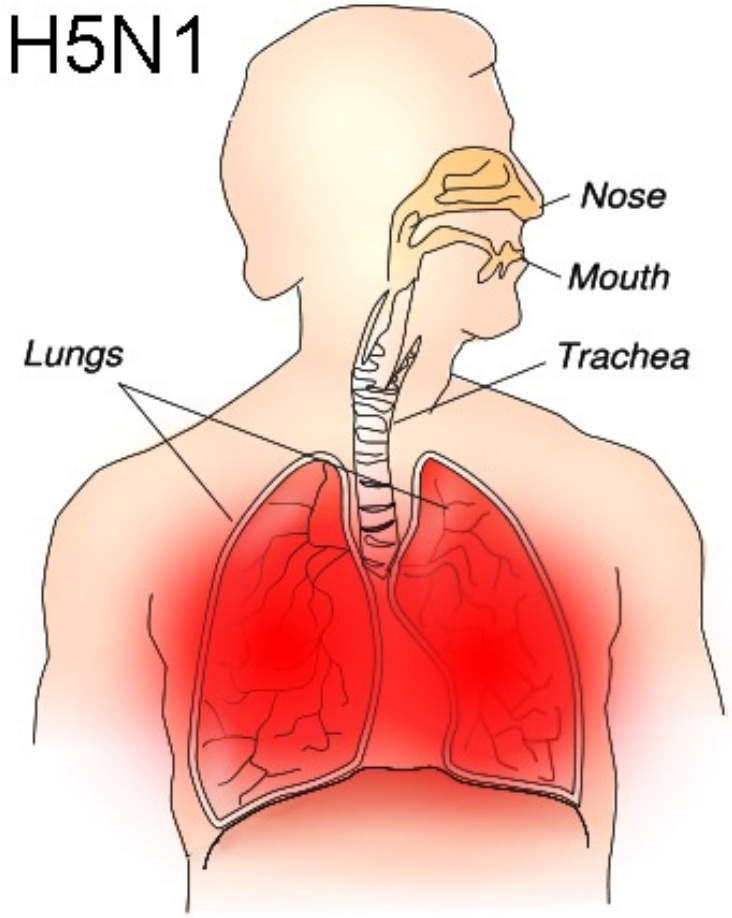
SA differences and pH gradients exist along the human respiratory tract



α2-6 SA receptors predominate in the upper respiratory tract (URT), to which human influenza A virus (blue) but not avian influenza virus (AIV) (red) can bind. Both α2-3 and α2-6 SA receptors are present in the lower respiratory tract (LRT). The pH in the URT is mildly acidic and gradually increases from the URT to the LRT. The haemagglutinins (HAs) of human influenza A viruses are more pH stable (pH 5.0–5.4) whereas the HAs of some AIVs are less pH stable (up to pH 6.1) and may be inactivated in the human URT. The temperature is lower in the URT than in the LRT. Human influenza A virus polymerases are more active than AIV polymerases at lower temperatures.



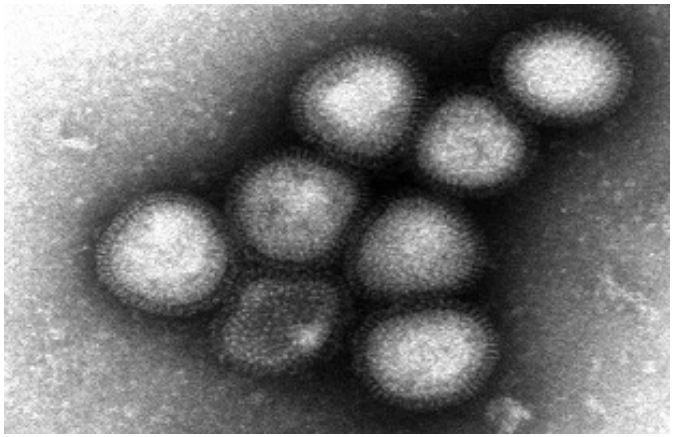
Easily spread
Rarely fatal



Spreads slowly
Often fatal

Avian influenza A(H7N9) virus

Avian influenza A(H7N9) is a subtype of influenza viruses that have been detected in birds in the past. This particular A(H7N9) virus had not previously been seen in either animals or people until it was found in March 2013 in China. However, since then, infections in both humans and birds have been observed. The disease is of concern because most patients have become severely ill. Most of the cases of human infection with this avian H7N9 virus have reported recent exposure to live poultry or potentially contaminated environments, especially markets where live birds have been sold. This virus does not appear to transmit easily from person to person, and sustained human-to-human transmission has not been reported.

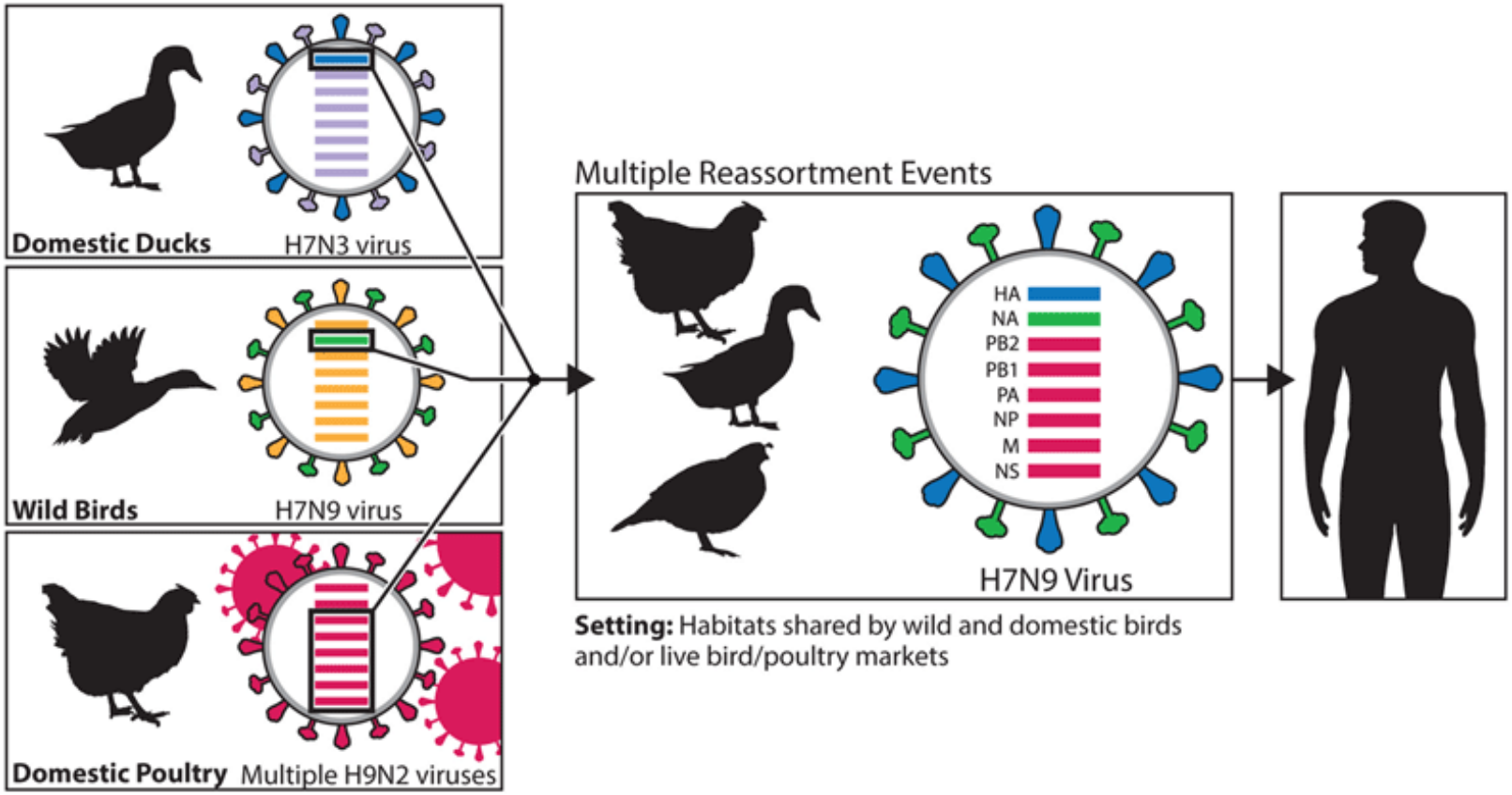


Courtesy of WHO Collaborating Centre for Reference and Research on Influenza, National Institute of Infectious Diseases, Japan

HA

NA

Genetic Evolution of H7N9 Virus in China, 2013

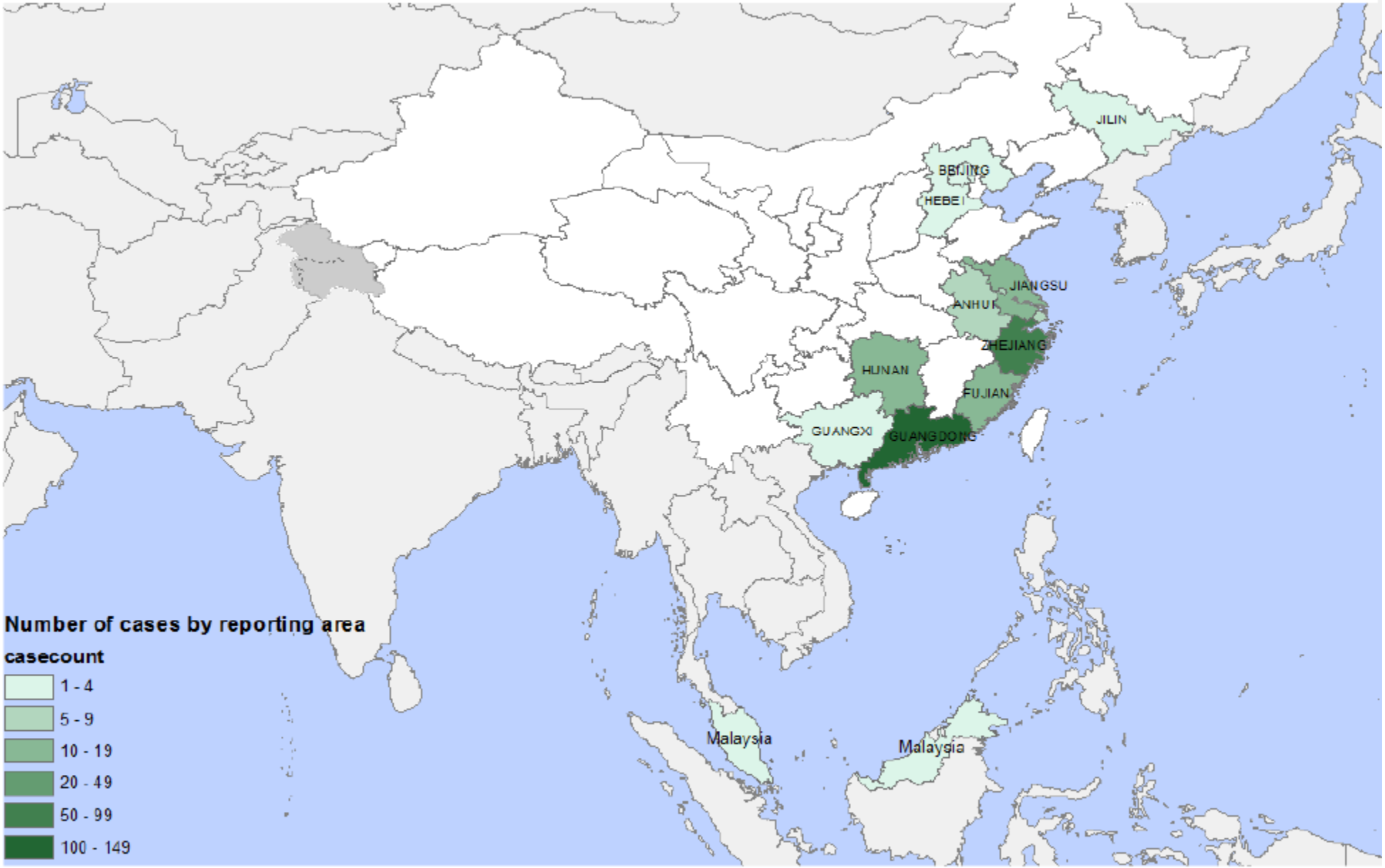


Setting: Habitats shared by wild and domestic birds and/or live bird/poultry markets

The eight genes of the H7N9 virus are closely related to avian influenza viruses found in domestic ducks, wild birds and domestic poultry in Asia. The virus likely emerged from "reassortment," a process in which two or more influenza viruses co-infect a single host and exchange genes. This can result in the creation of a new influenza virus. Experts think multiple reassortment events led to the creation of the H7N9 virus. These events may have occurred in habitats shared by wild and domestic birds and/or in live bird/poultry markets, where different species of birds are bought and sold for food. As the above diagram shows, the H7N9 virus likely obtained its HA (hemagglutinin) gene from domestic ducks, its NA (neuraminidase) gene from wild birds, and its six remaining genes from multiple related H9N2 influenza viruses in domestic poultry.

Centers for Disease Control and Prevention
National Center for Immunization and Respiratory Diseases

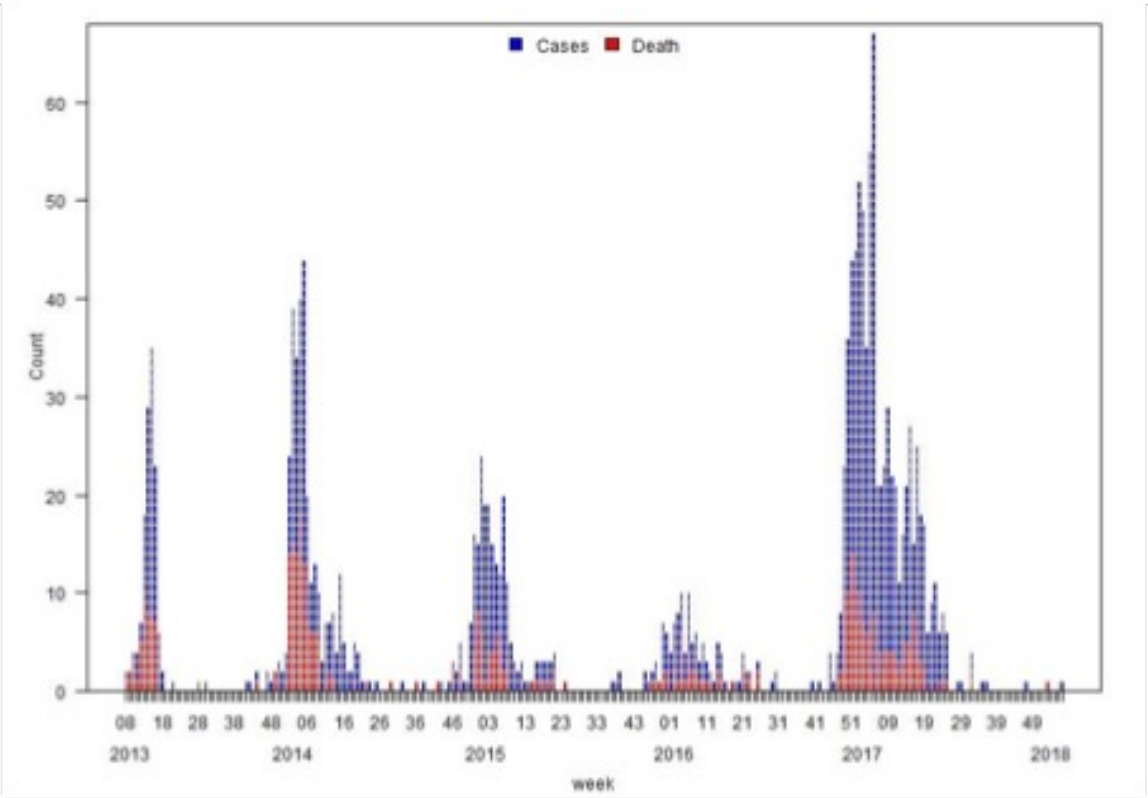
Areas reporting confirmed human cases for influenza A(H7N9) to WHO from 2013-06-01 *



*All dates refer to onset of illness
Data as of 09/04/2014
Source: WHO

World Health Organization

Epidemiological curve of avian influenza A(H7N9) cases in humans by week of onset, 2013-2018.



5 ondate tra il 2013 ed il 2018

1568 laboratory-confirmed cases of H7N9 virus infection in humans (616 deaths)

The outbreak shows a seasonal pattern:

- The first wave in spring 2013 resulted in **135 cases**
- The second wave led to **320 cases**
- The third wave caused **223 cases**
- The fourth wave caused **120 cases**
- The fifth wave resulted in **766 cases**
- In 2018 **4 cases**

To control H7N9 influenza virus, an H5/H7 bivalent inactivated vaccine was initiated in China in September 2017 (for veterinary use). The vaccine was updated and an H5/H7 trivalent inactivated vaccine had been used since December 2018. It reduced dramatically the infections in poultry and transmission to humans.

In 2016 a virus strain emerged which was highly pathogenic to chickens. In order to contain the HPAI outbreak, the Chinese authorities in 2017 initiated a large-scale vaccination campaign against avian influenza in poultry. Since then, the number of outbreaks in poultry, as well as the number of human cases, dropped significantly. In humans, symptoms and mortality for both LPAI and HPAI strains have been similar

RESEARCH ARTICLE

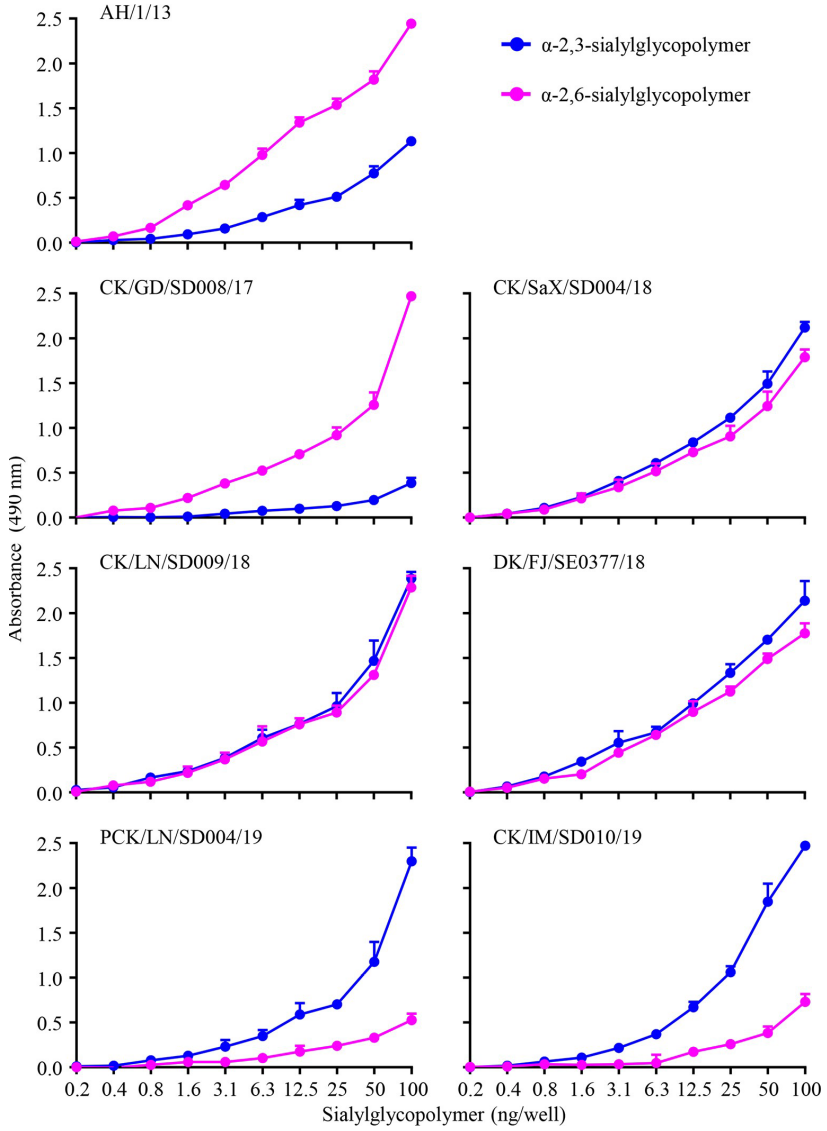
Genetic and biological properties of H7N9 avian influenza viruses detected after application of the H7N9 poultry vaccine in China

Author summary

Human infection with H7N9 virus has been successfully prevented since the application of an H7N9 vaccine in poultry in September 2017 in China; however, the H7N9 virus has not been eradicated from poultry. In this study, we evaluated the genetic and biologic properties of H7N9 viruses detected in poultry in China from February 2018 to December 2019. We found that the H7N9 viruses gradually lost their binding to human-type receptors and were antigenically different from the H7N9 vaccine strain that was used in China for H7N9 influenza control in poultry. We further uncovered the genetic changes that facilitate the escape of the H7N9 viruses from vaccine-induced immunity. Our study provides important insights into H7N9 virus evolution and control.

Although no human H7N9 infections have been reported since February 2019, the virus is still circulating in poultry, particularly in laying hens, and remains a potential threat to poultry industry and public health. Furthermore, since 2017, the H7N9 virus has undergone multiple instances of antigenic drift to evade immune pressure from vaccines.

Diminuisce l'affinità con α2-6



Diminuisce l'immunogenicità del vaccino

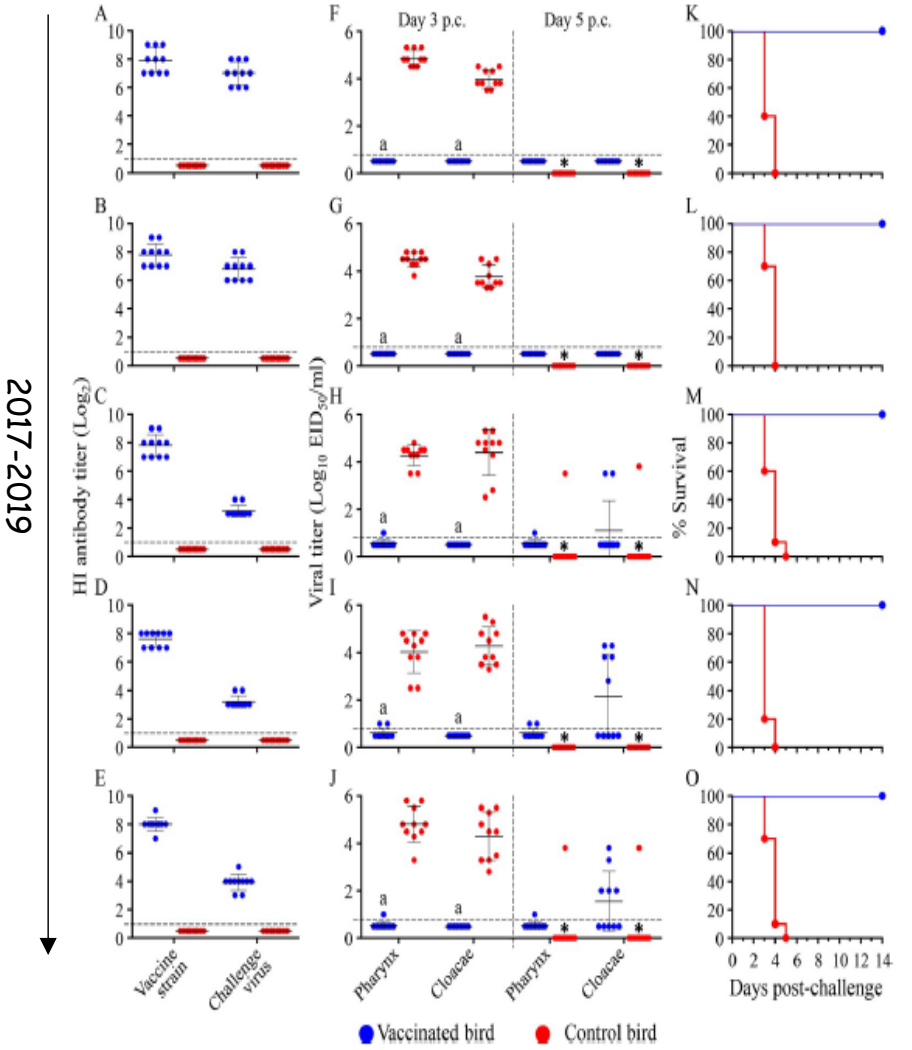


Fig 5. Protective efficacy of H5/H7-Re2 trivalent inactivated vaccine against challenge with different H7N9 viruses in chickens. HI antibody titers (**A-E**), virus shedding titers (**F-J**), and survival patterns (**K-O**) of chickens challenged with the H7N9 highly pathogenic viruses CK/GX/SD098/17 (**A, F, and K**), CK/SX/SD006/18 (**B, G, and L**), PCK/LN/SD004/19 (**C, H, and M**), CK/IM/SD010/19 (**D, I, and N**), and CK/LN/SD25/19 (**E, J, and O**). The dashed lines shown in **A-E** show the cutoff value for seroconversion and those in **F-J** show the lower limit of virus detection. Virus titers shown in **F-J** are the means from the birds that survived. A value of 0.5 was assigned to virus shedding-negative birds for statistical purposes. The asterisks indicate that the bird(s) died before that day, and therefore virus shedding data were not available for statistical analysis. All of the chickens in these control groups died within 5 days of challenge. The letter "a" indicates $p < 0.001$ compared with the corresponding titers of the control birds.

Diminuzione dei titoli anticorpali verso ceppi più recenti, alcuni vaccinati rilasciano il virus se infettati con ceppi recenti, tutti i vaccinati sopravvivono.

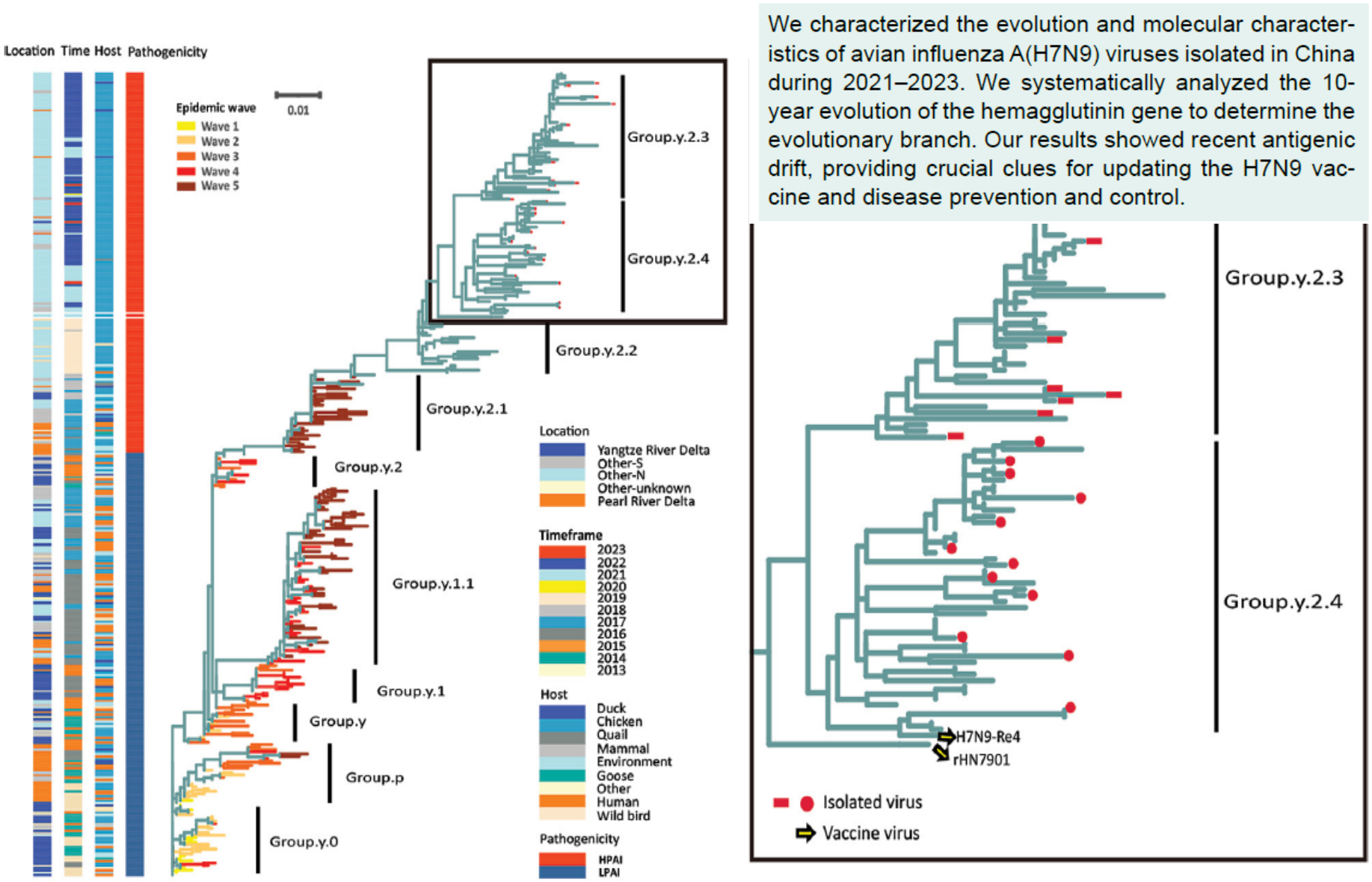


Figure 1. Phylogenetic analysis of evolution and antigenic differentiation of avian influenza A(H7N9) virus, China. Colors in columns at left show locations, timeframes, hosts, and pathogenicity of virus strains. The maximum-likelihood phylogenetic tree of the hemagglutinin gene depicts viruses corresponding to epidemic waves 1–5. Tree on right shows detail of Group.y.2.3 (red rectangles) and Group.y.2.4.4 (red circles) in comparison with vaccine strains. Scale bar indicates nucleotide substitutions per site. LPAI, low-pathogenicity avian influenza; HPAI, highly pathogenic avian influenza; Other-N, sites in the northern region; Other-S, sites in the southern region.

USDA launches biosecurity steps for poultry producers, adds details on H7N9 avian flu detection

Lisa Schnirring, *March 19, 2025*

Topics: Avian Influenza (Bird Flu)

H7N9 in Mississippi poultry likely reflects recent jump from wild birds

Following the recent detection **highly pathogenic H7N9** avian flu at a Mississippi broiler farm, APHIS yesterday provided **more details**. It said some North American low pathogenic H7 viruses that it has detected as part of its wild bird surveillance are closely related to the highly pathogenic H7N9 virus, indicating a recent spillover from a low-pathogenic wild bird virus.

The group said it closely monitors the low pathogenic H5 and H7 subtypes, because they can mutate into highly pathogenic versions in poultry species such as chickens and turkeys.

The outbreak recently detected in Mississippi was the first involving H7N9 in US poultry since 2017.

Veterinary medicines

As of May 2024, two veterinary vaccines are authorised in the EU for the prevention of avian influenza A, subtype H5, in **chickens**:

- Nobilis Influenza H5N2 - a conventional, inactivated vaccine, which could potentially help address the risk of highly pathogenic avian influenza, but it is currently produced in limited quantities.

- Innovax ND-H5 - a vector vaccine where the vector, a turkey herpesvirus, expresses the fusion protein gene of the Newcastle disease virus and the haemagglutinin gene of the avian influenza virus subtype H5.

Other **vaccine candidates** are at different stages of development.

Farmed poultry are not routinely vaccinated against avian influenza in the EU.

Following a request from the European Commission, EFSA has provided a scientific opinion on possible **vaccination and monitoring strategies** in Europe. For more information see:

- EFSA: Vaccination of poultry against highly pathogenic avian influenza. Part 1: Available vaccines and vaccination strategies
- EFSA: Vaccination of poultry against highly pathogenic avian influenza. Part 2: Surveillance and mitigation measures

Vaccination against highly pathogenic avian influenza is common in some regions outside the EU. Several vaccines are thus available, although not currently authorised in the EU. EMA ran a survey in February 2023 to gather relevant information on these vaccines and offered to discuss EU authorisation with their manufacturers.

https://www.ema.europa.eu/en/human-regulatory-overview/public-health-threats/avian-influenza-bird-flu#veterinary-medicines-14444

Table 1 | Importance of the key genetic mutations in viral proteins of influenza A H7N9 viruses in the year 2013.

Gene	Mutation	Importance of the mutation	Reference
Hemagglutinin (H3 numbering)	Gln226Leu	Increased binding affinity to α-2,6-linked sialic acid receptor	Connor et al. (1994), Ha et al. (2001), Chutinimitkul et al. (2010), Herfst et al. (2012)
	Gly186Val	Increased binding affinity to α-2,6-linked sialic acid receptor	Gambaryan et al. (2012), Xiong et al. (2013b)
	Thr160Ala	Increased binding affinity to α-2,6-linked sialic acid receptor	Wang et al. (2010)
	Multibasic amino acid at HA0 cleavage site	Cleavage by ubiquitous proteases	Senne et al. (1996), Subbarao et al. (2003)
Neuraminidase (viral release from host cell surface)	Arg292Lys	Neuraminidase resistance	Gubareva et al. (1997), McKimm-Breschkin et al. (1998)
	Deletions in stalk region	Increased virulence	Matrosovich et al. (1999)
PB2 (viral replication)	Asp701Asn	Mammalian adaptation	Li et al. (2005), Gao et al. (2009)
	Leu89Val	Enhanced polymerase activity	Hatta et al. (2001), Labadie et al. (2007)
	E627K	Enhanced viral replication and virulence in mice model	Hatta et al. (2001), Labadie et al. (2007)
PB1 (viral replication)	Ile368Val	Enables droplet transmission in ferrets	Herfst et al. (2012)
PB1-F2 (induce cellular apoptosis and inhibit function of type I interferon)	Full-length	Full-length PB1-F2 needed for virulence in mice	Zamarin et al. (2006)
Matrix protein M1 (viral assembly and budding)	Asn30Asp	Increased virulence in a mice model	Fan et al. (2009)
	Thr215Ala	Increased virulence in a mice model	Fan et al. (2009)
Matrix protein M2	Ser31Asn	Amantadine resistance	Hay et al. (1985), Pinto et al. (1992)
NS1 (counteracts host antiviral response)	Pro42Ser	Increased virulence in mice Signaling of host proteins	Jiao et al. (2008)
	Deletion of PDZ-binding motif		Jackson et al. (2008)

Molecular determinants of human infection

• ***PB2.*** Lys627 in PB2 is considered to be as an important determinant for pathogenicity in humans.

– The 1997 H5N1 isolates from humans in Hong Kong formed two groups based on their pathogenicity in mice.

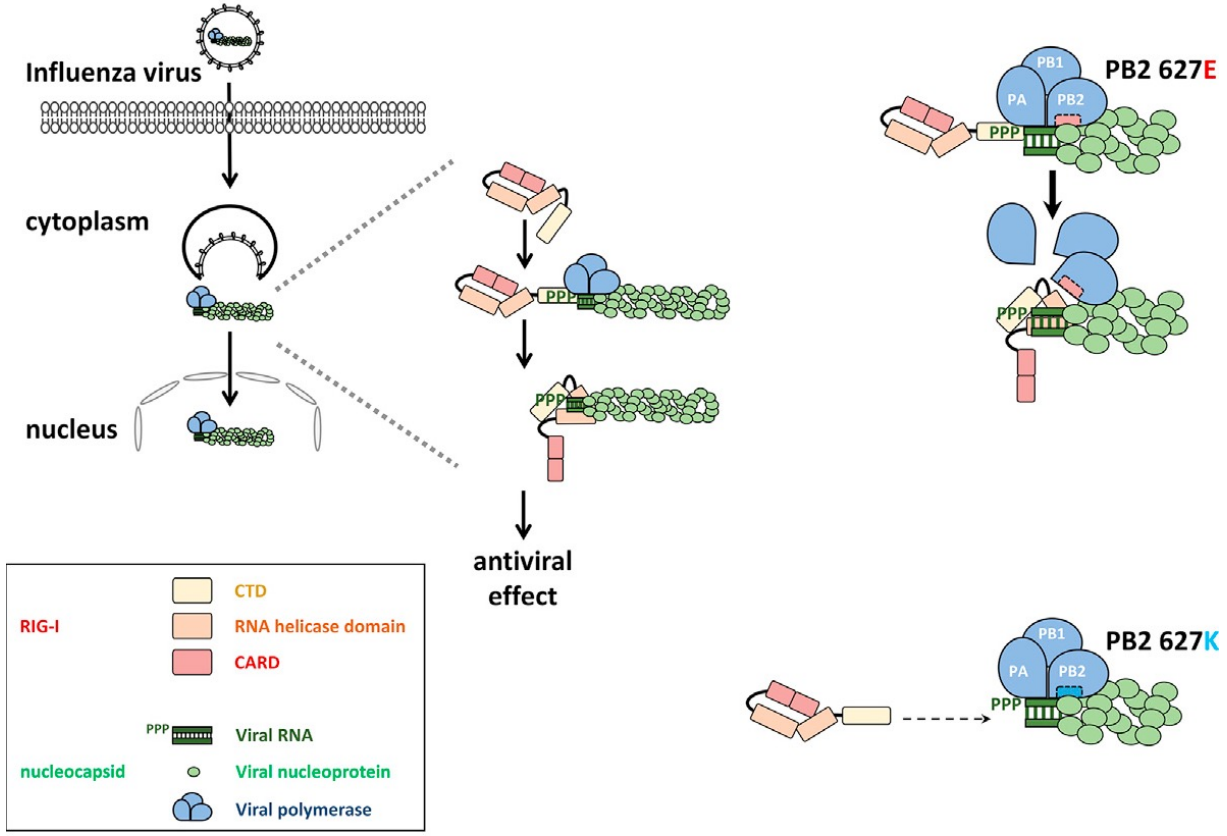
• The amino acid at position 627 of PB2 determines the efficiency of virus replication in mice: Lys627, instead of the Glu627 that is found in avian viruses, is crucial for high virulence. This amino acid enhances viral growth in mice and probably in humans.

– The 2003 H7N7 virus isolated from the fatal human case of pneumonia in the Netherlands also possessed Lys627 in PB2, in contrast to avian viruses isolated during the outbreak and other human isolates from non-fatal cases of conjunctivitis.

– Many, but not all, of the 2004 H5N1 viruses isolated from humans in Vietnam harbored Lys627 in PB2.

Molecular determinants of human infection

Lys627 in PB2, instead of glutamic acid, is considered to be an important determinant for pathogenicity in humans.



5′ppp dsRNA panhandle of incoming influenza virus nucleocapsids activates RIG-I

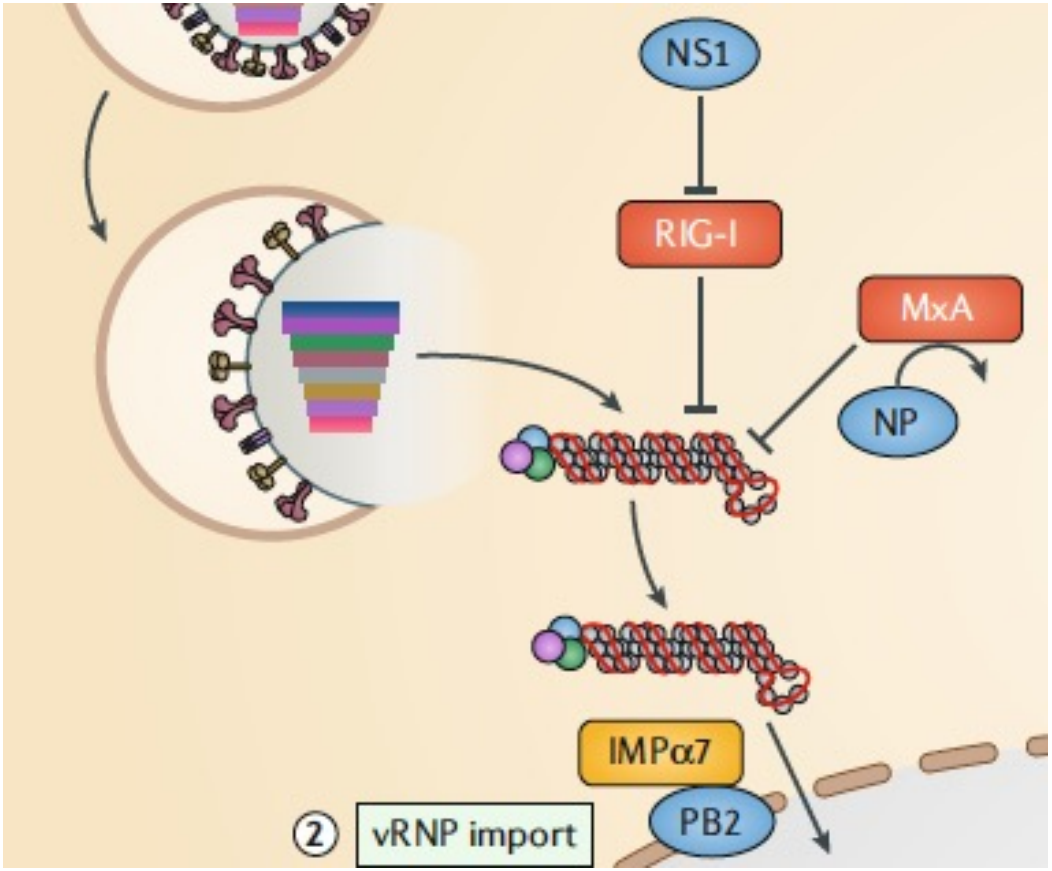
Human-adaptive mutation PB2-627K in the viral polymerase counteracts activation of RIG-I

RIG-I directly inhibits incoming nucleocapsids with the avian PB2-627E signature

Strength of polymerase binding to nucleocapsids determines RIG-I sensitivity

Cell Host & Microbe, Volume 17, Issue 3, 11 March 2015

Molecular determinants of human infection



Retinoic acid-inducible gene I protein (RIG-I) and interferon-regulated resistance GTP-binding protein MxA restrict AIV vRNPs in the cytoplasm.
Human-adapted vRNPs with PB2 627K are less vulnerable to RIG-I detection. vRNPs are imported into the nucleus. Humanizing mutations in PB2 enable importin-α7 use and enhance vRNP nuclear import.
Mutations in human-adapted NP evade MxA binding.

NATURE REVIEWS | MICROBIOLOGY REVIEWS
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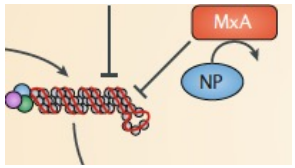
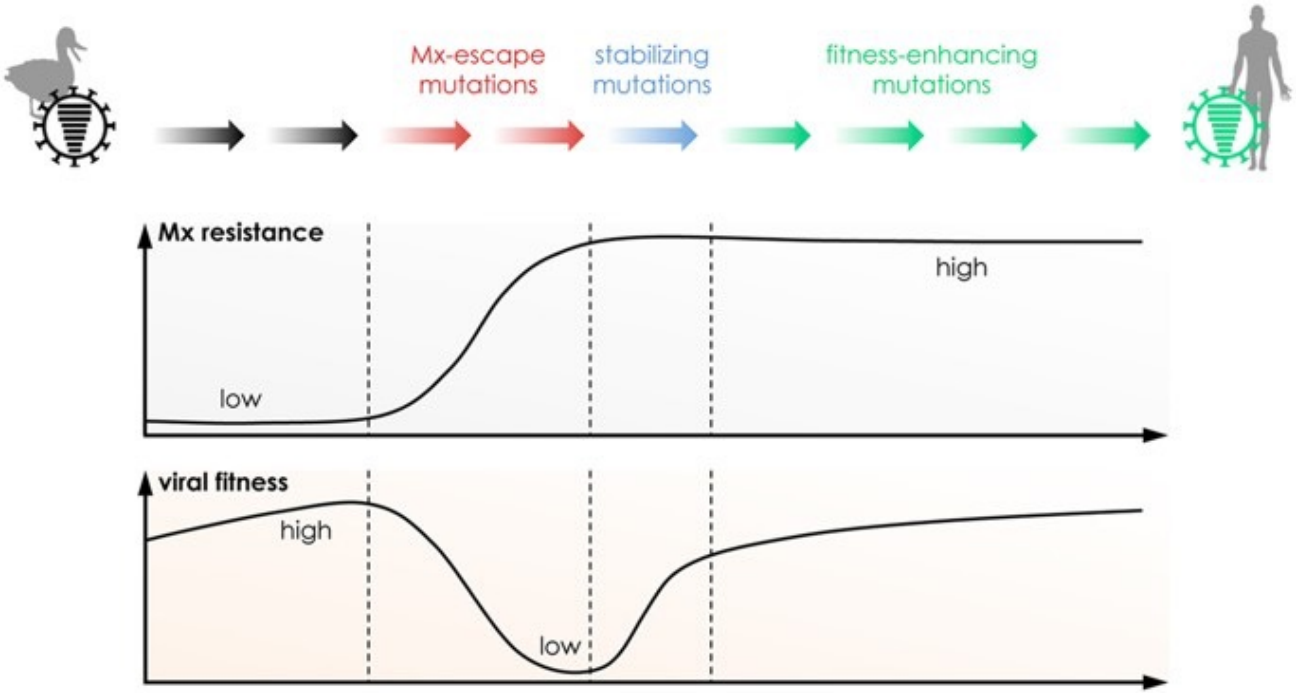
Molecular determinants of human infection

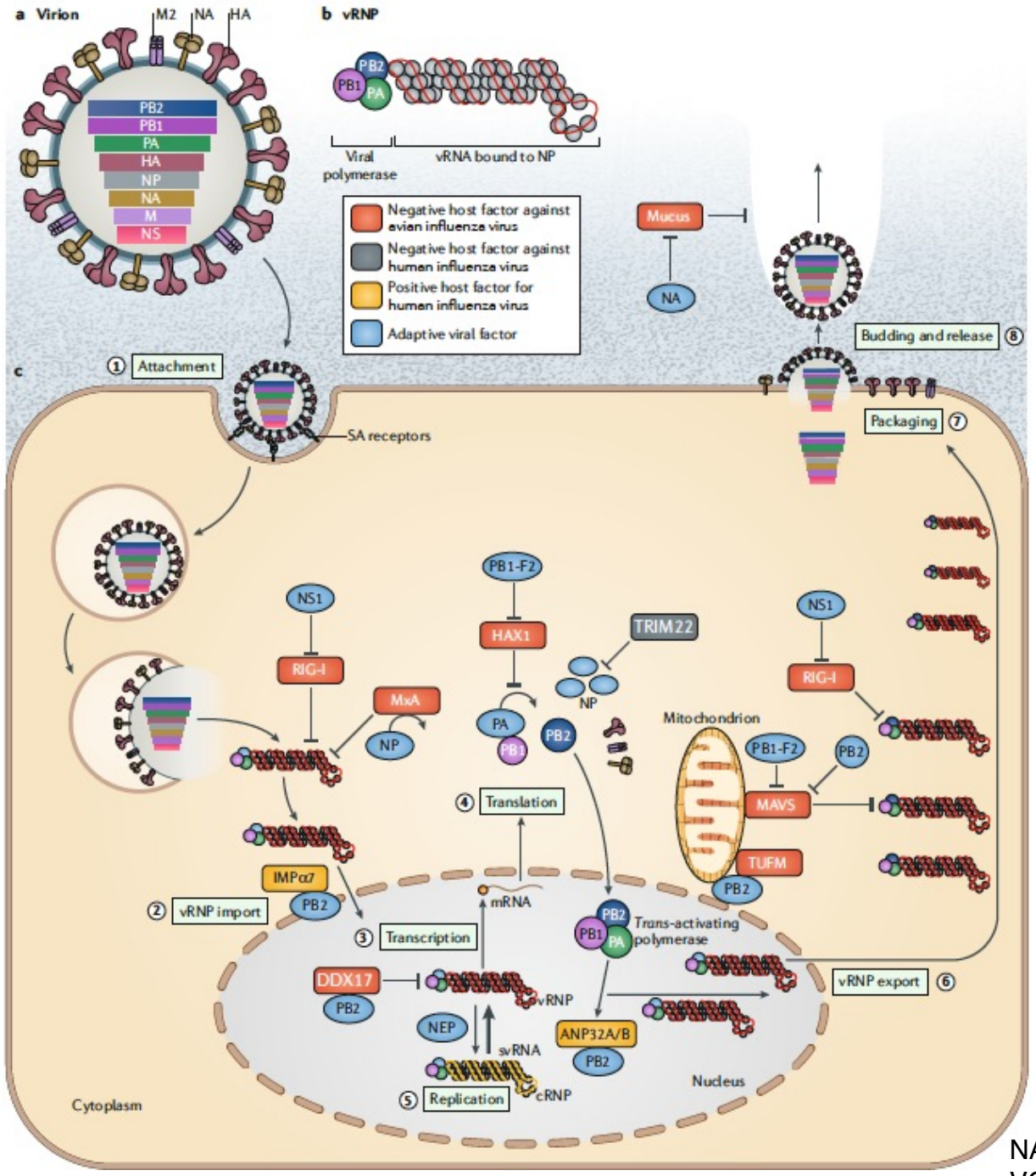




To establish a new lineage in the human population, avian influenza A viruses have to acquire several adaptive mutations in almost all viral proteins, including MxA escape mutations in NP. However, the acquisition of MxA escape amino acids in NP is associated with severely reduced viral fitness, due to impaired nuclear import of vRNPs. Stabilizing mutations in NP (e.g. 16D) are required to overcome this fitness restriction, but are not sufficient to restore viral growth properties. As a consequence further additional mutations in NP and probably other viral gene products are required.

Scientific **RepoRts** | 6:23138 | DOI: 10.1038/srep23138

Virus and host-specific determinants of influenza virus replication



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Anti-influenza treatments

- **Vaccine**

  Vaccines are available to prevent influenza virus infection.

  These take two forms: inactivated and live vaccines. The vaccines have to be reformulated each year to provide protection against the currently circulating virus strains.

  Typically, the inactivated vaccine is reformulated twice a year, once for the northern hemisphere and once for the southern hemisphere because they experience their influenza virus seasons out of phase with each other and significant virus evolution can occur in the interim.

Vaccino per l'influenza stagionale

Stagione influenzale 2025-2026

Il 28 febbraio 2025 l'Organizzazione Mondiale della Sanità (OMS) ha pubblicato le raccomandazioni per la composizione dei vaccini per la stagione influenzale 2025-2026 nell'emisfero settentrionale. L'aggiornamento periodico dei virus contenuti nei vaccini antinfluenzali è necessario affinché i vaccini siano efficaci, data la natura in continua evoluzione di questi virus, compresi quelli che circolano e infettano gli esseri umani. L'OMS raccomanda che i vaccini trivalenti da utilizzare nella prossima stagione influenzale contengano quanto segue:

Vaccini ottenuti in uova embrionate di pollo

- un A/Victoria/4897/2022 (H1N1)pdm09-like virus
- un A/Croatia/10136RV/2023 (H3N2)-like virus
- un B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

Vaccini ottenuti su colture cellulari o vaccini ricombinanti

- un A/Wisconsin/67/2022 (H1N1)pdm09-like virus
- un A/District of Columbia/27/2023 (H3N2)-like virus
- un B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

La raccomandazione per la componente B/Yamagata lineage dei vaccini quadrivalenti rimane invariata rispetto alle raccomandazioni della scorsa stagione: un B/Phuket/3073/2013 (B/Yamagata lineage)-like virus. Per approfondire consulta il documento completo "Recommended composition of influenza virus vaccines for use in the 2025-2026 northern hemisphere influenza season".

https://www.epicentro.iss.it/influenza/raccomandazioni-ministero

Will seasonal influenza virus vaccines provide protection against avian influenza A(H5N1) virus infection?

Current seasonal influenza vaccines are unlikely to protect people against infection with avian influenza A(H5N1) viruses based on currently available data.

However, it is important that people, who may have frequent exposure to infected or potentially infected birds or other animals, get a seasonal influenza vaccine, as it can reduce the prevalence and severity of seasonal influenza and may reduce the rare risk of coinfection with a seasonal influenza virus and avian influenza A(H5N1) virus.

Further research on the ability of seasonal influenza vaccines to protect against infections and disease severity with avian influenza A(H5N1) viruses is needed.

Anti-influenza treatments

Antiviral drugs

Small molecule chemical inhibitors that act against influenza virus can be used to treat disease. These are Amantadine and Rimantadine and Zanamivir and Oseltamivir (Tamiflu)

However, the virus mutates readily to generate resistant strains.

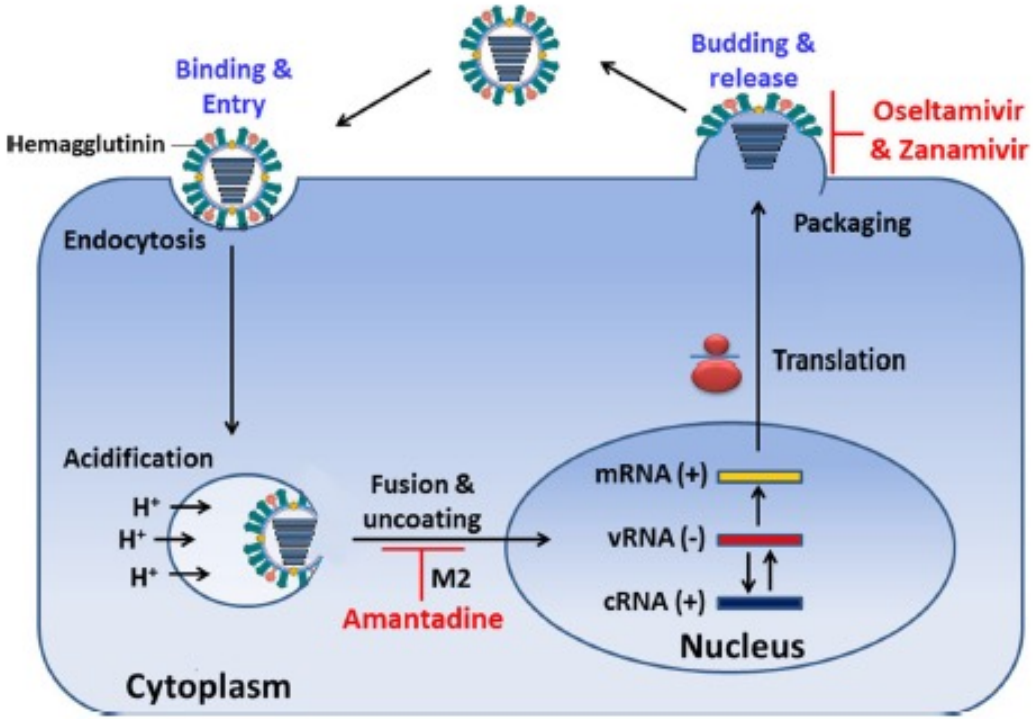


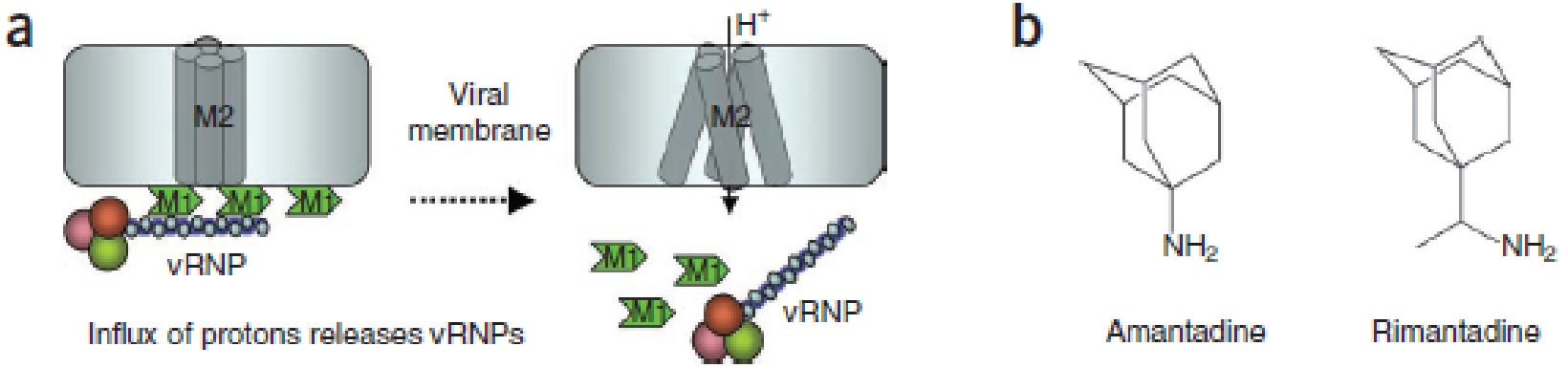
Table 20.3
Small molecule anti-influenza virus inhibitors. The target proteins for the molecules are indicated.

Inhibitor	Target protein
Amantadine	M2 protein (flu A only)
Rimantadine	M2 protein (flu A only)
Oseltamivir	NA protein (flu A and flu B)
Zanamivir	NA protein (flu A and flu B)

Archives of Virology (2018) 163:831–844 https://doi.org/10.1007/s00705-018-3708-y

Introduction to modern virology, Dimmock et al. Ed., 7th edition, 2016

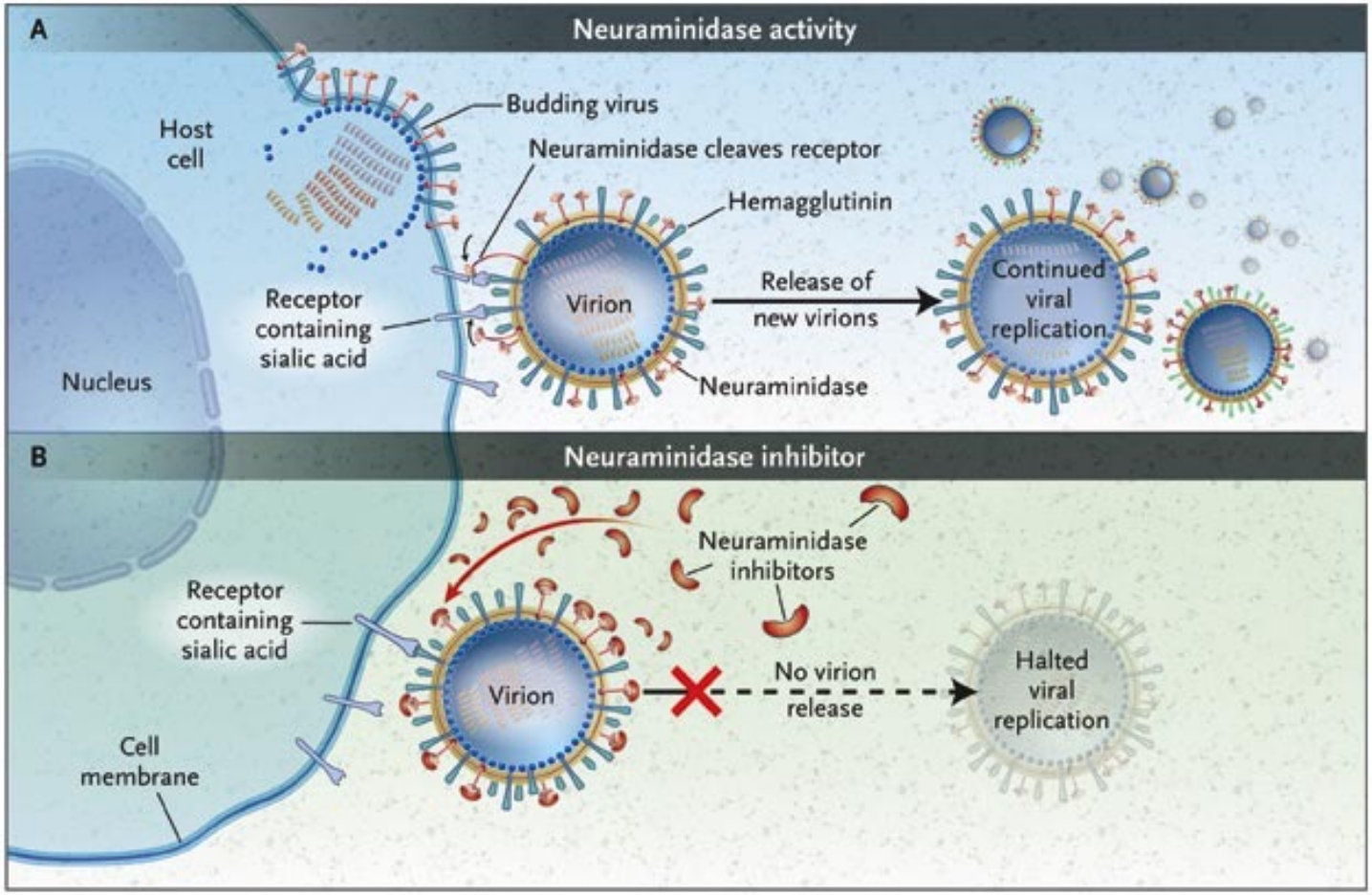
Anti-influenza treatments



Amantadine and Rimantadine: Structure, function and inhibition of the proton channel M2 protein of influenza A. (**a**) The vRNPs are attached to the lipid bilayer membrane via M1 matrix proteins. Influx of the protons from endosome to virus through M2 channels releases vRNPs. (**b**) The adamantanes (amantadine and rimantadine) inhibit the proton flow through the tetrameric M2 channel. .

Das K et al ***NATURE STRUCTURAL & MOLECULAR BIOLOGY*** 2010

Anti-influenza treatments



Zanamivir and Oseltamivir (Tamiflu): The neuraminidase inhibitors zanamivir and oseltamivir interfere with the release of progeny influenza virus from infected host cells, a process that prevents infection of new host cells and thereby halts the spread of infection in the respiratory tract

N Engl J Med 2005