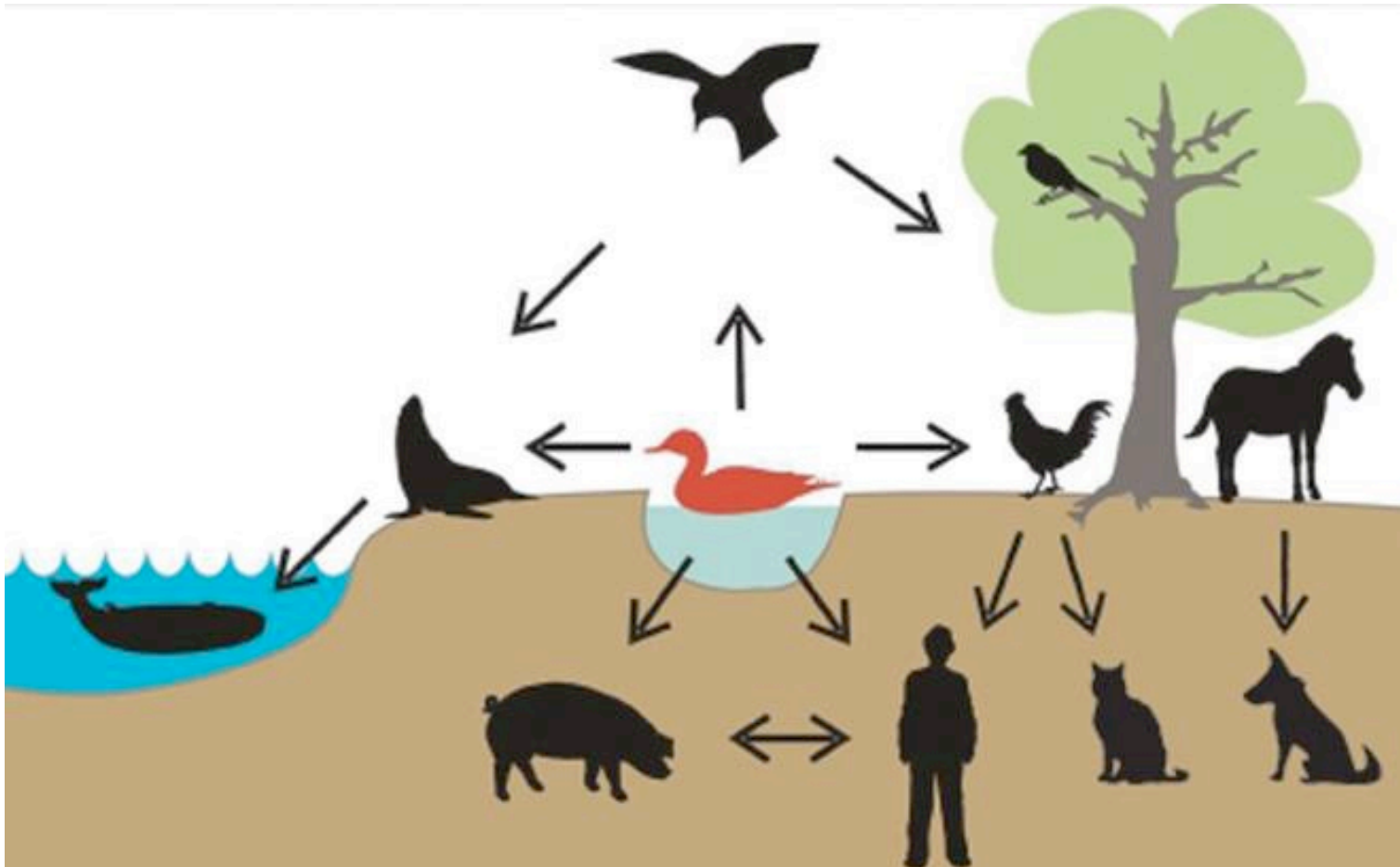# Influenza A virus Ecology
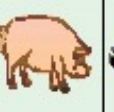

Influenza A virus reservoir. Wild aquatic birds are the main reservoir of influenza A viruses. Virus transmission has been reported from wild waterfowl to poultry, sea mammals, pigs, horses, and humans. Viruses are also transmitted between pigs and humans, and from poultry to humans. Equine influenza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

Ecology

Subtype distribution

Human subtypes:
H1N1, H2N2 and
H3N2.
Currently, subtypes
circulating in humans
are H3N2 and the
swine H1N1

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

Bat IAV
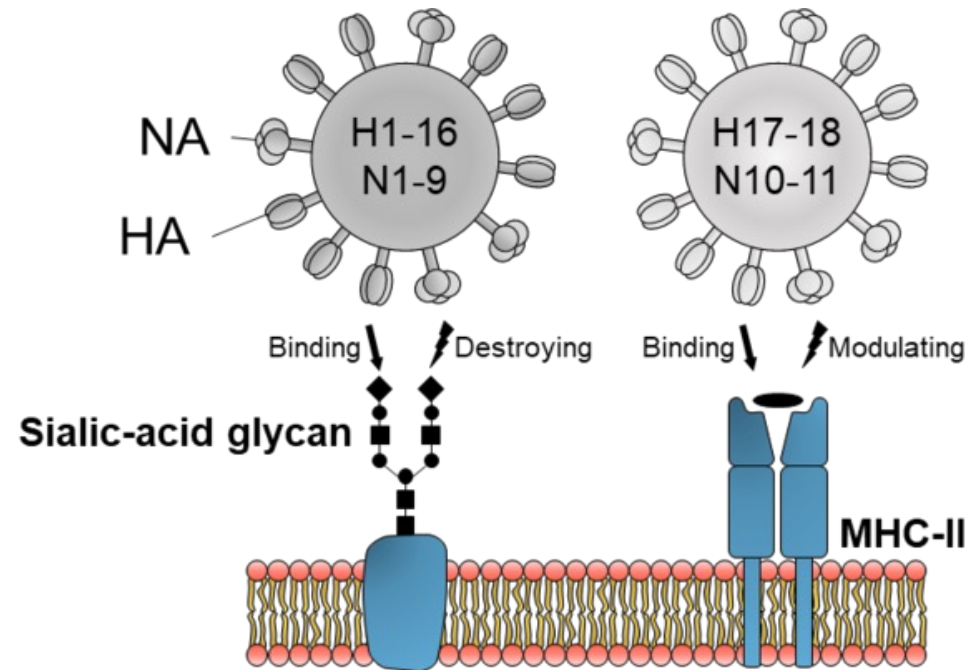
Model of the receptor binding and modulating activity of the known IAV surface glycoproteins. (A) Infection of a host cell is initiated by binding of HA subtypes H1–16 to sialic acid residues exposed on the host cell surface. These glycan structures are subsequently cleaved off by NA of the subtypes 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.

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 $\alpha2,6$ linkage (NeuAcα-2,6Gal)
Birds	sialic acid residue attached via an $\alpha2,3$ 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
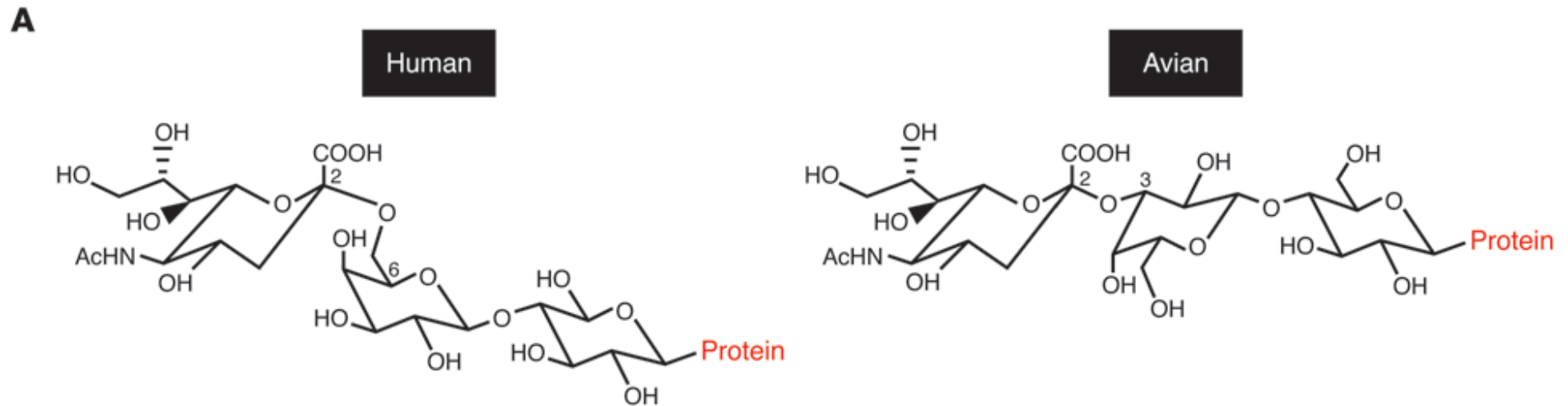
D, aspartic acid; E, glutamic acid; G, glycine; L, leucine; S, serine; Q, glutamine;

(**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.

Influenza A virus tropism.
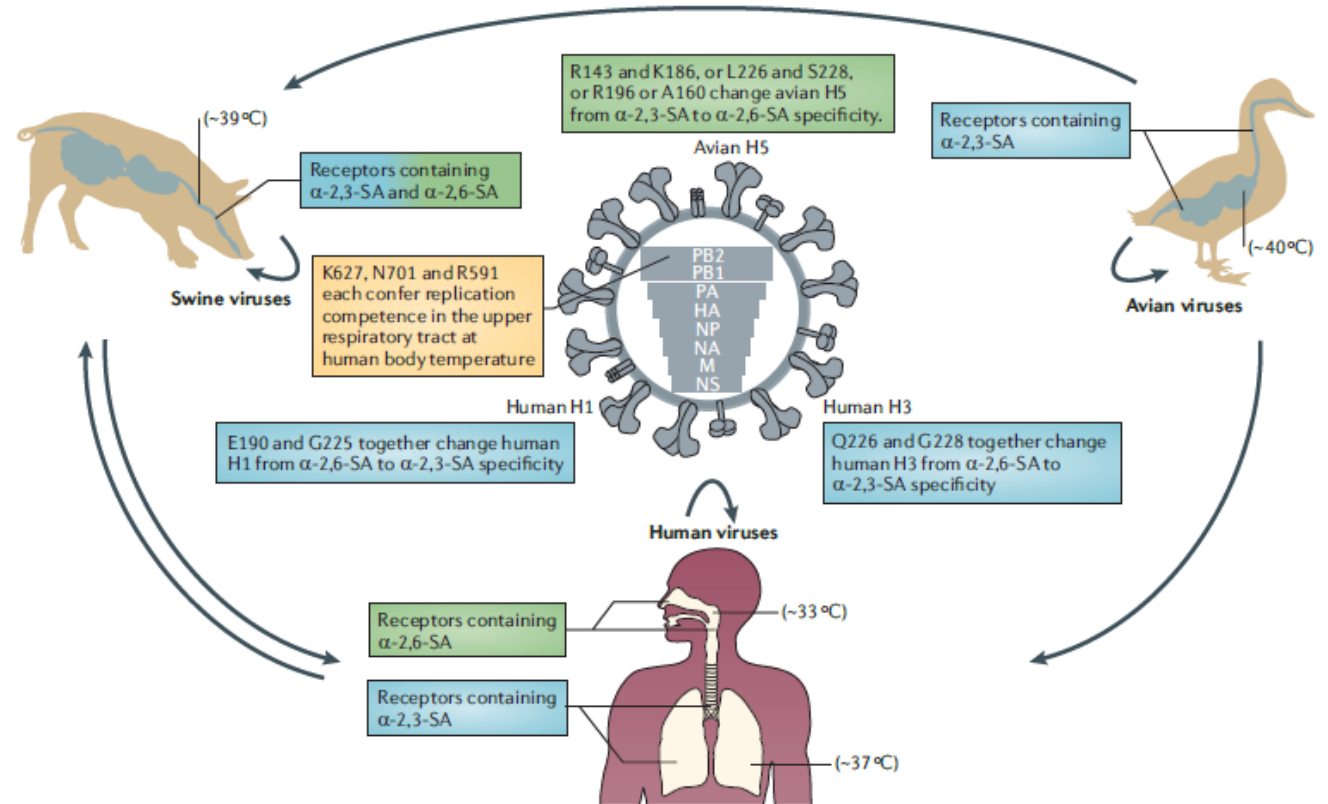
The anatomical expression patterns of the viral receptors in different hosts restricts infection and replication of influenza A viruses. The swine trachea contains receptors with α-2,3-linked and α-2,6-linked sialic acid (α-2,3-SA and α-2,6-SA) moieties that allow for binding of both avian and human 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.

Two mechanisms of influenza A virus evolution

Influenza A viruses undergo two types of evolutionary change that alter their major surface glycoproteins. These are antigenic shift, arising from reassortment of the genome segments following a dual infection of a single cell and mutation that is referred to in influenza as antigenic drift.
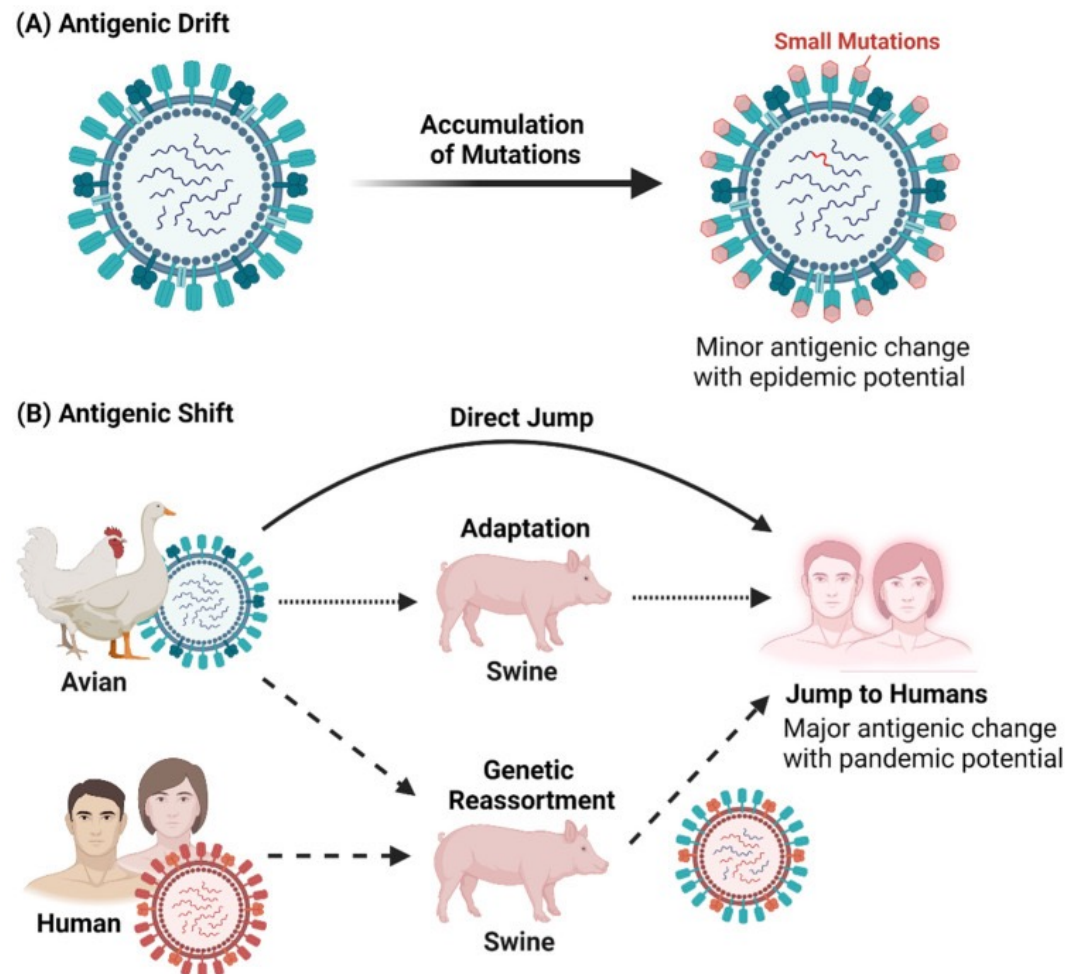
Antigenic drift

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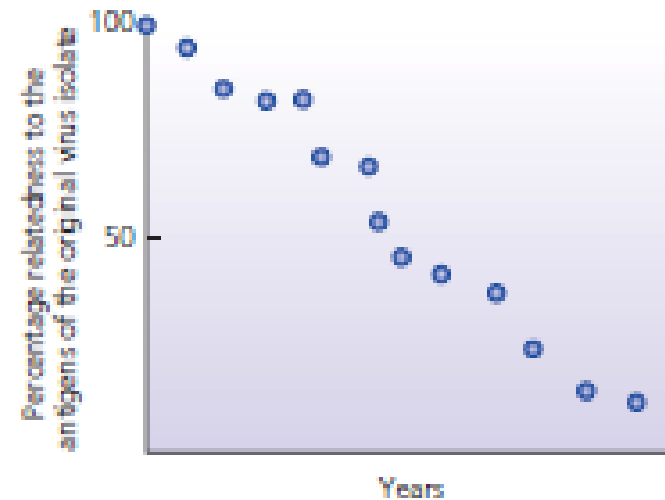
Diagram showing antigenic drift of type A influenza virus in humans. This could represent mutations within either the HA or NA genes. Each point is a virus strain isolated in a different year.

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.

1 Each year's flu vaccine contains three flu strains – two A strains and one B strain – that can change from year to year.

2 After vaccination, your body produces infection-fighting antibodies against the three flu strains in the vaccine.

Antibody

3 If you are exposed to any of the three flu strains during the flu season, the antibodies will latch onto the virus's HA antigens, preventing the flu virus from attaching to healthy cells and infecting them.

4 Influenza virus genes, made of RNA, are more prone to mutations than genes made of DNA.

Viral RNA

Antibody

HA antigen

Mutation

5 If the HA gene changes, so can the antigen that it encodes, causing it to change shape.

HA gene

HA antigen

Antibodies

6 If the HA antigen changes shape, antibodies that normally would match up to it no longer can, allowing the newly mutated virus to infect the body's cells.

This type of genetic mutation is called "ANTIGENIC DRIFT."

Link Studio for NIAID

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

The genetic change that enables a flu strain to jump from one animal species to another, including humans, is called "ANTIGENIC SHIFT." Antigenic shift can happen in three ways:

B **Without undergoing genetic change, a bird strain of influenza A can jump directly from a duck or other aquatic bird to humans.**

The new strain may further evolve to spread from person to person. If so, a flu pandemic could arise.

Bird influenza A strain

Bird host

HA antigen — NA antigen

Human influenza A strain

Human host

A-1 **A duck or other aquatic bird passes a bird strain of influenza A to an intermediate host such as a chicken or pig.**

C **Without undergoing genetic change, a bird strain of influenza A can jump directly from a duck or other aquatic bird to an intermediate animal host and then to humans.**

A-2 **A person passes a human strain of influenza A to the same chicken or pig. (Note that reassortment can occur in a person who is infected with two flu strains.)**

HA antigen — NA antigen

A-3 **When the viruses infect the same cell, the genes from the bird strain mix with genes from the human strain to yield a new strain.**

Viral entry intermediate host cell

New influenza strain

A-4 The new strain can spread from the intermediate host to humans.

Intermediate host cell

Genetic mixing

Link Studio for NIAID

Intermediate host (pig)

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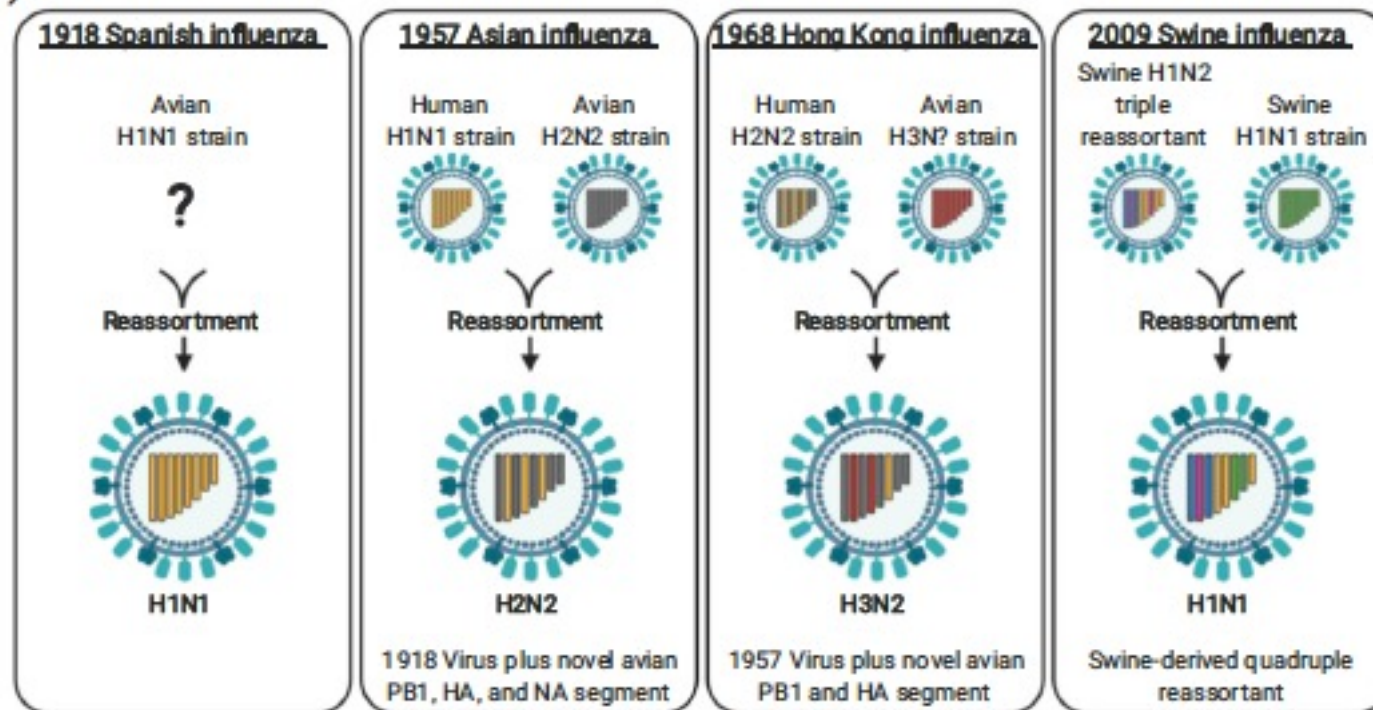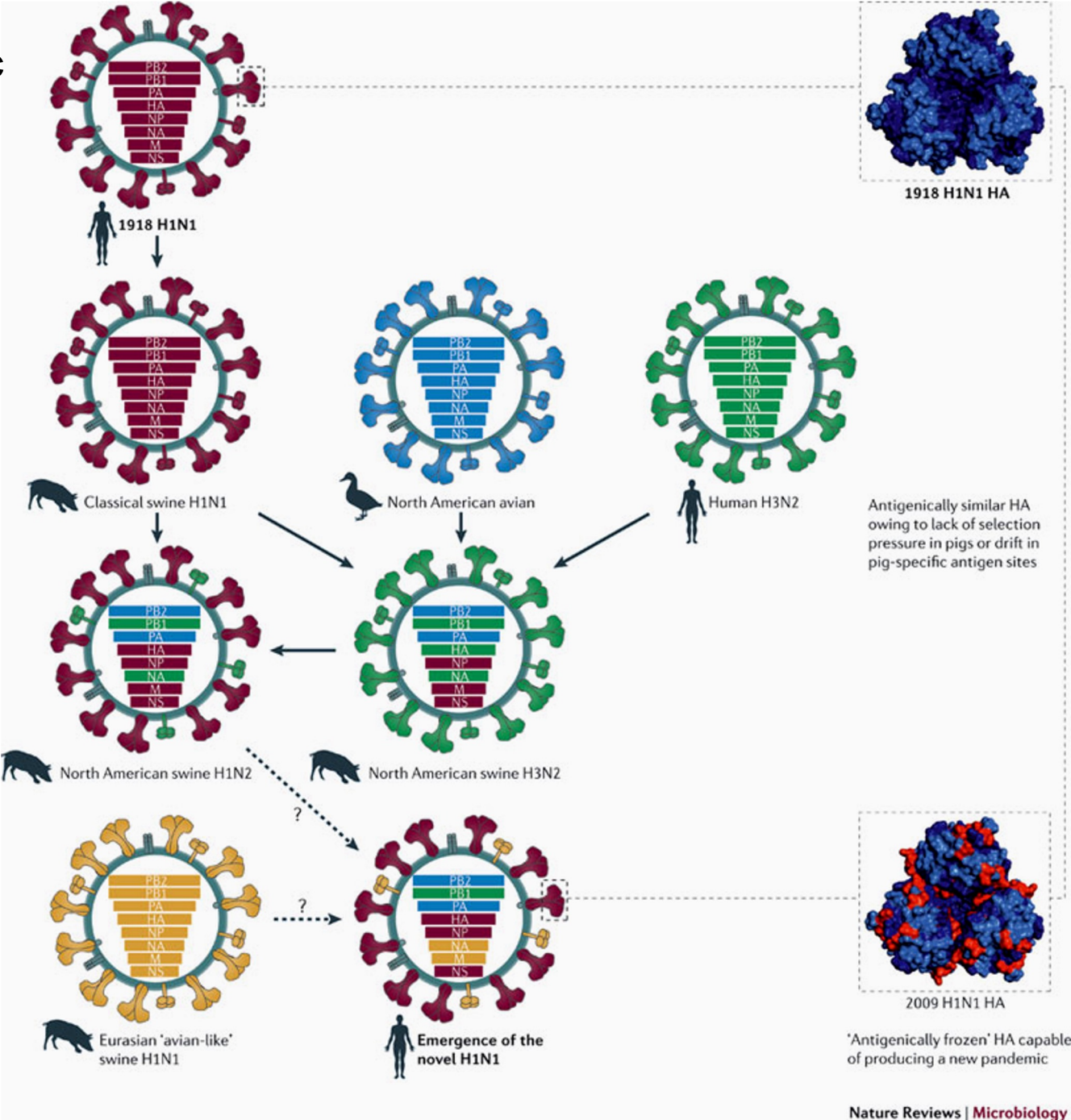
Reassortment Is the Key Driver in Infuenza A (IAV) Evolution

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.

2009 Pandemic H1N1 virus

1918 H1N1 HA

1918 H1N1

Classical swine H1N1

North American avian

Human H3N2

Antigenically similar HA owing to lack of selection pressure in pigs or drift in pig-specific antigen sites

North American swine H1N2

North American swine H3N2

Eurasian 'avian-like' swine H1N1

Emergence of the novel H1N1

2009 H1N1 HA

'Antigenically frozen' HA capable of producing a new pandemic

# 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.

# Mechanisms for the emergence of pandemic influenza virus strains.
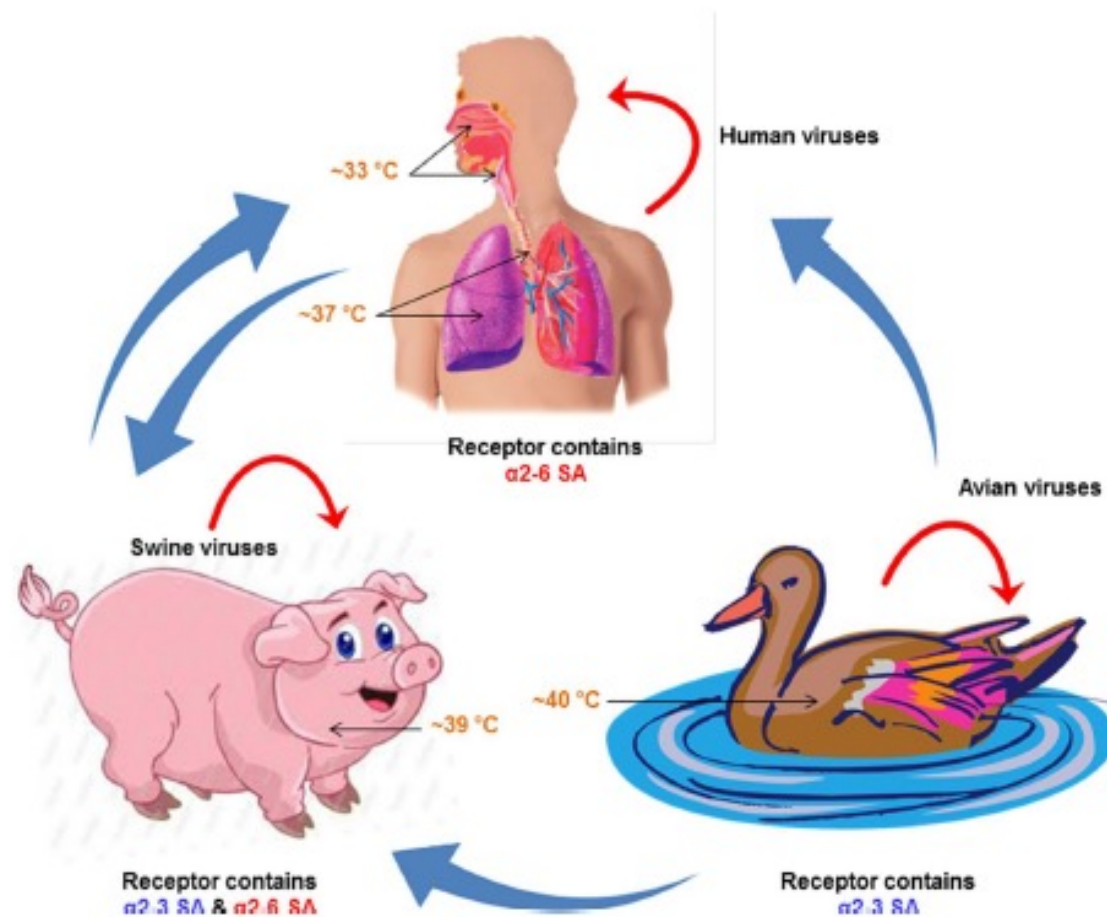
The virus keeps circulating among own species and sometimes jump the species barrier to generate a novel strain of pandemic potential

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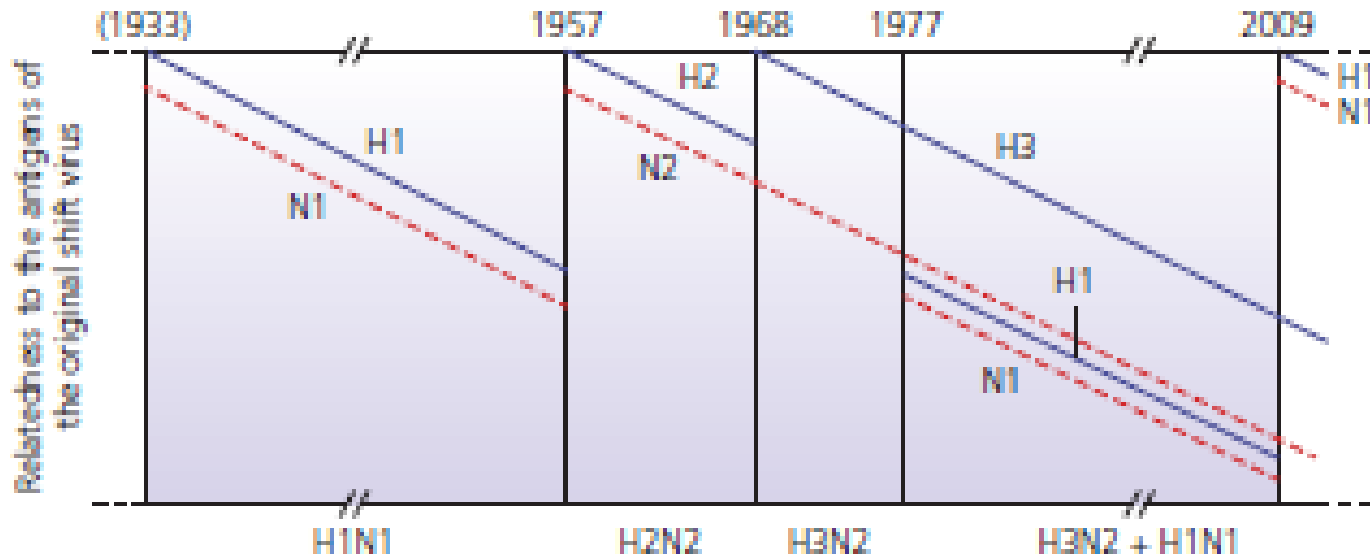
The first virus, isolated in 1933, was H1N1. This arose by antigenic drift from the 1918 virus. Other shift viruses appeared in 1957 (H2N2) and 1968 (H3N2). A 1950 H1N1 virus reappeared in 1977. A new H1N1 appeared in 2009. Drift is shown schematically. The 1957 N2 was acquired by the H3N2 shift virus,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

Atigenic drift vs antigenic shift
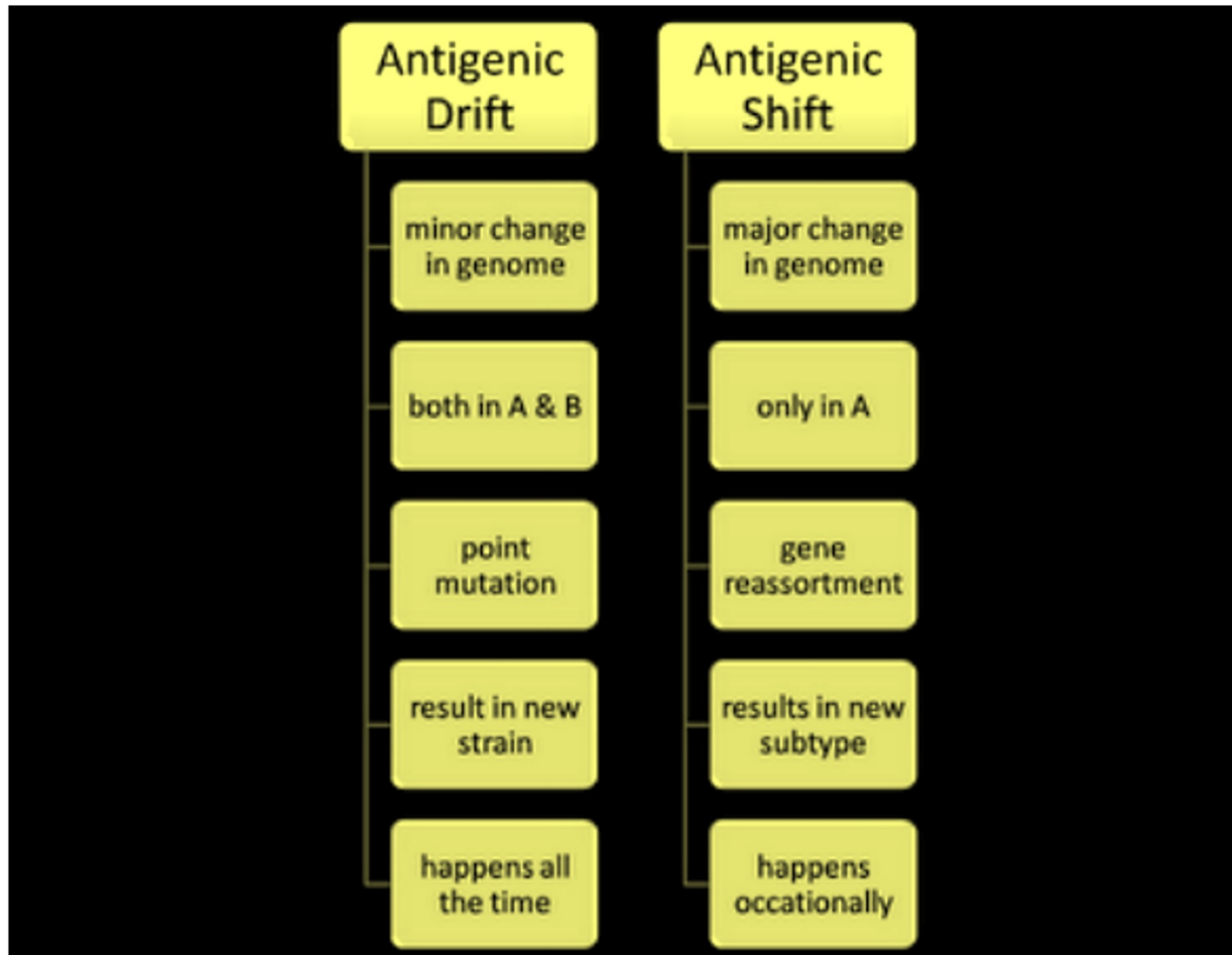
Flu Terms Defined

- 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. H5N1 is highly pathogenic, deadly to domestic fowl, and can be transmitted from birds to humans. There is no human immunity, and no vaccine is available.

Molecular determinants of pathogenicity

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
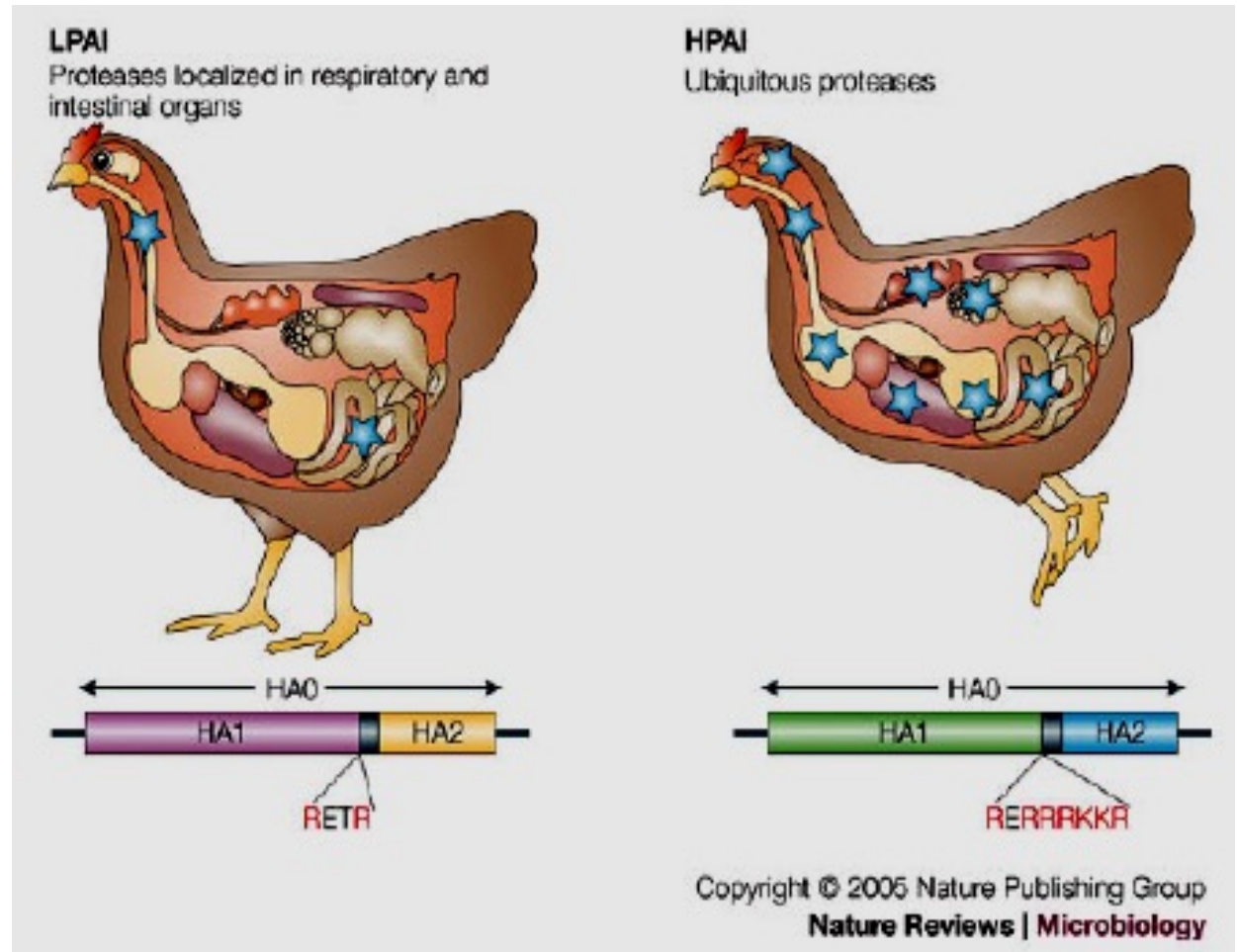
HA protein - attachment, fusion

S   S

membrane

inside of virion

host enzymes

S   S
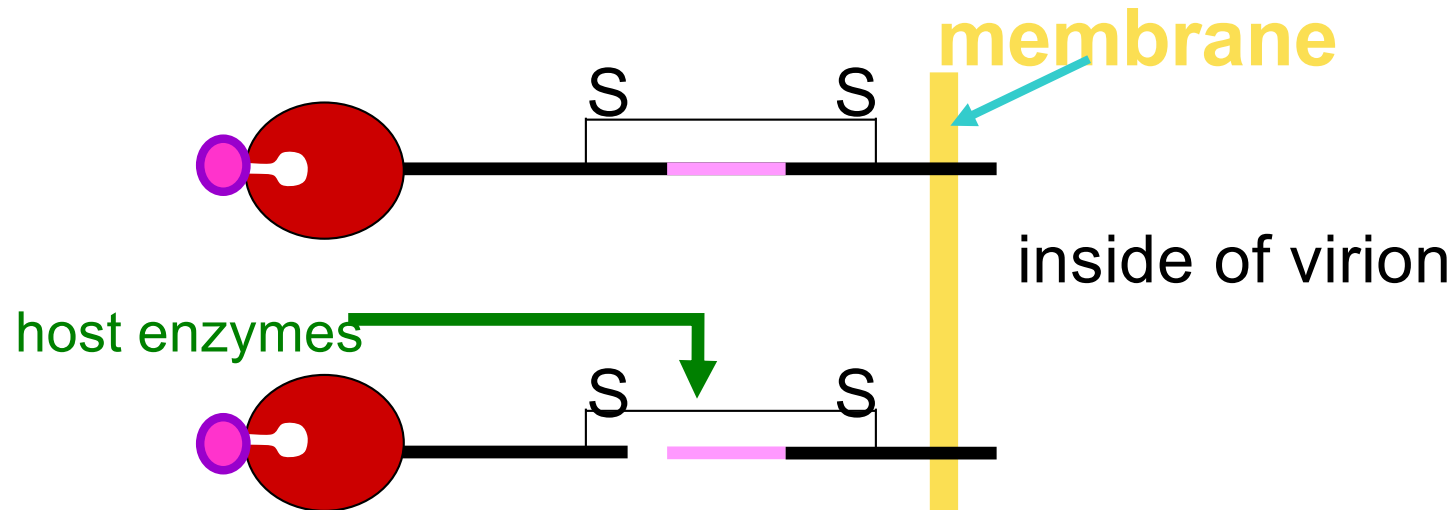
🟣 =antibody

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.

LPAI
Proteases localized in respiratory and intestinal organs

HPAI
Ubiquitous proteases

HA0

HA1   HA2

RETR

HA0

HA1   HA2

RERRRKKR

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Nature Reviews | Microbiology

Molecular determinants of pathogenicity

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

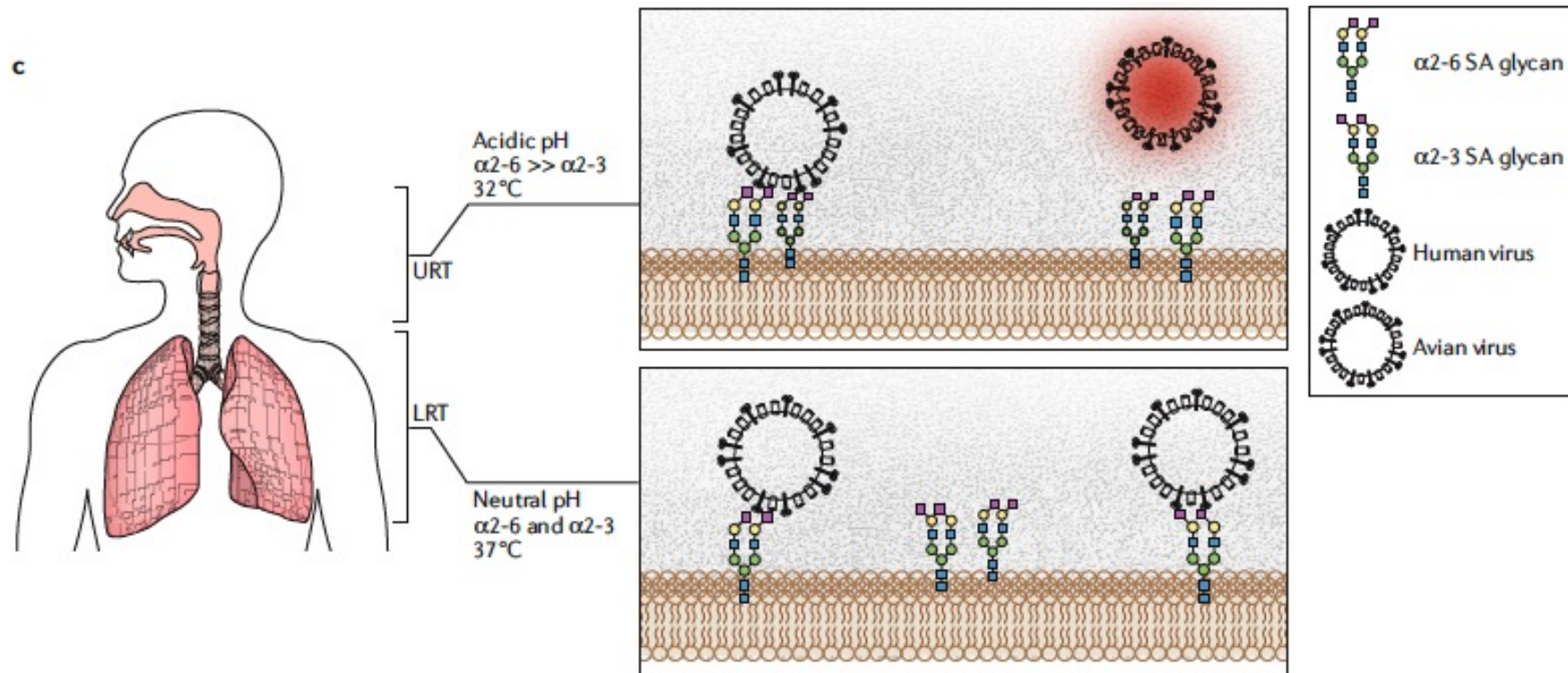**Human influenza A virus**
– H1, H2, H3: monobasic cleavage site

Avian isolates   Cleavage site

Avirulent strain (H5)	P Q - - - - [R] E T [R] ↓ G
Avirulent strain (H7)	P E X P - - - [K] X [R] G
Virulent strain (H5)	P Q - - [R K R K K R] G
Virulent strain (H7)	P E P S [K K R K K R] G

Human isolates: pandemic strains

1918 Spanish flu (H1N1)	P S - - - - I Q S [R] G
1957 Asian flu (H2N2)	P Q - - - - I E S [R] G
1968 Hong Kong flu (H3N2)	P E - - - - [K] Q T [R] G
1977 Russian flu (H1N1)	P S - - - - I Q S [R] G

Human isolates: avian strains from humans

1997 Hong Kong (H5N1)	P Q [R] E [R R R K K R] G
1999 Hong Kong (H9N2)	P Q - - - - [R] S S [R] G
2003 the Netherlands (H7N7)	P E I P - [K R R R] G
2004 Asian (H5N1)	P Q [R] E [(R) R R K K R] G

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 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.

# 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.

H1N1

Nose

Mouth

Lungs

Trachea
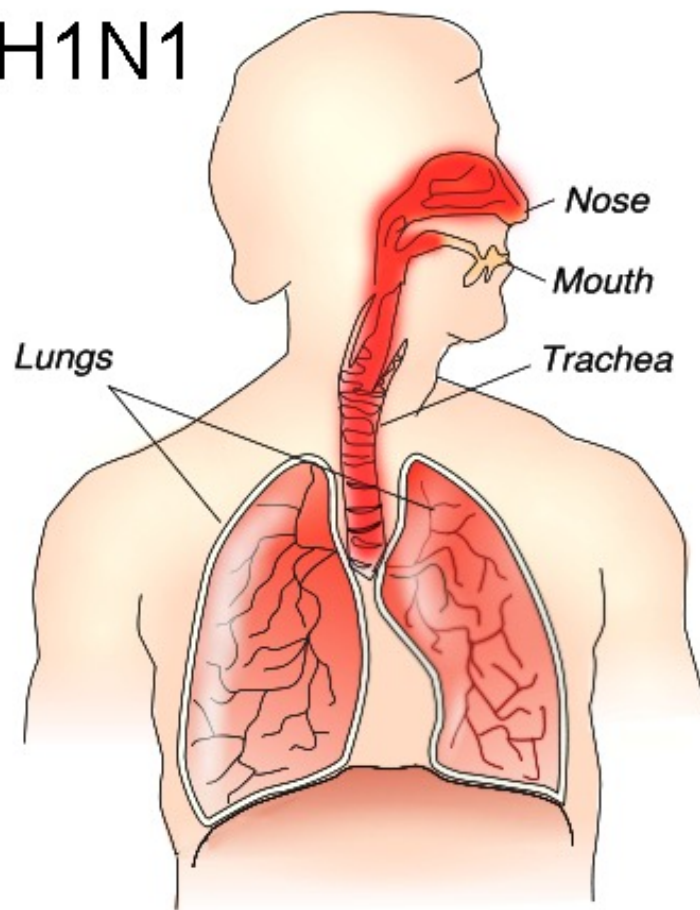
Easily spread
Rarely fatal

H5N1

Nose

Mouth

Lungs

Trachea
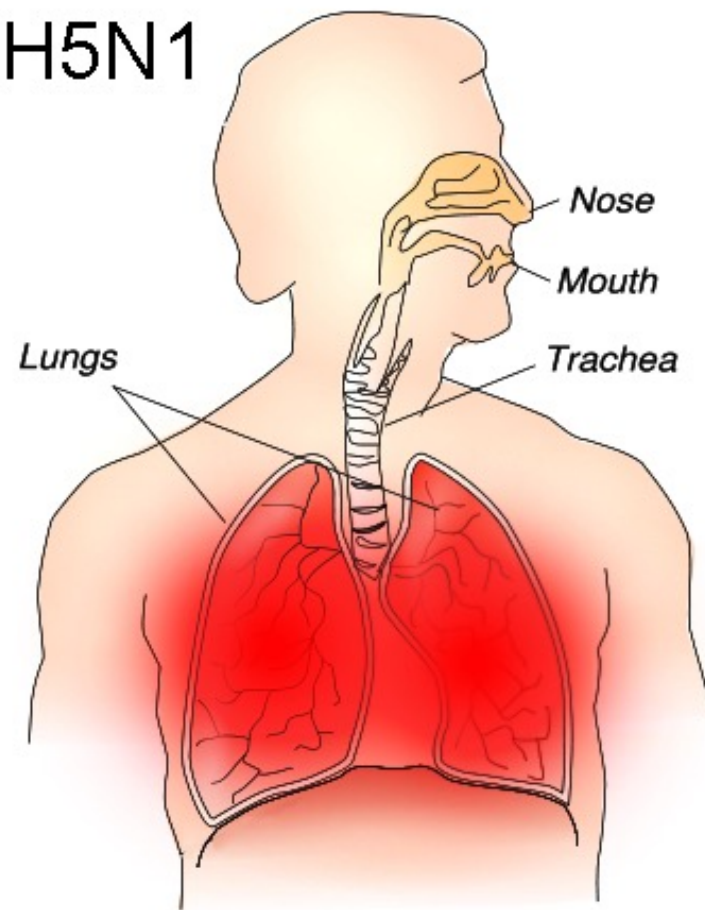
Spreads slowly
Often fatal

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.
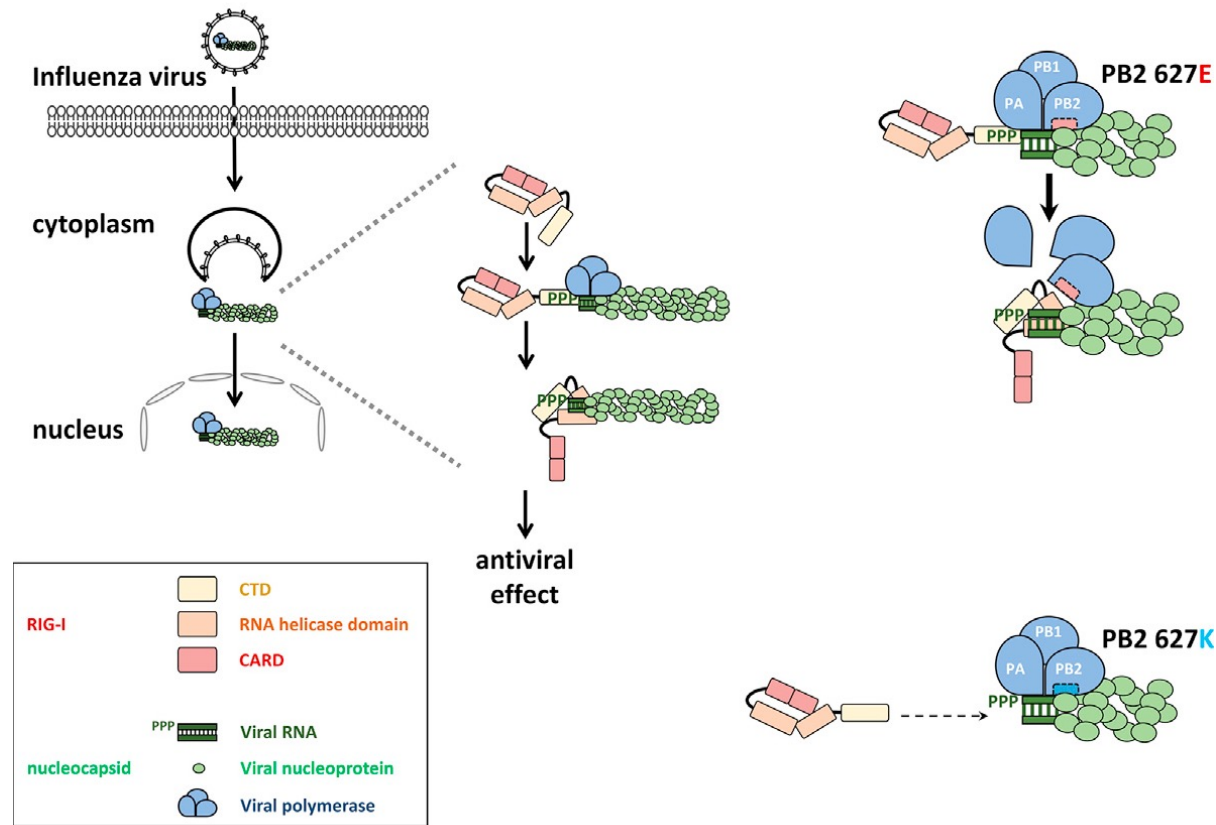
5′ppp dsRNA panhandle of incoming influenza virus nucleocapsids activates RIG-I
Human-adaptive mutation PB2-627K in the viral polymerase counteracts activation of RIG-I
RIG-I directly inhibits incoming nucleocapsids with the avian PB2-627E signature
Strength of polymerase binding to nucleocapsids determines RIG-I sensitivity

RIG-I Dually Functions as an Innate Immune Sensor Inducing IFN Expression and as a Direct Antiviral Restriction Factor
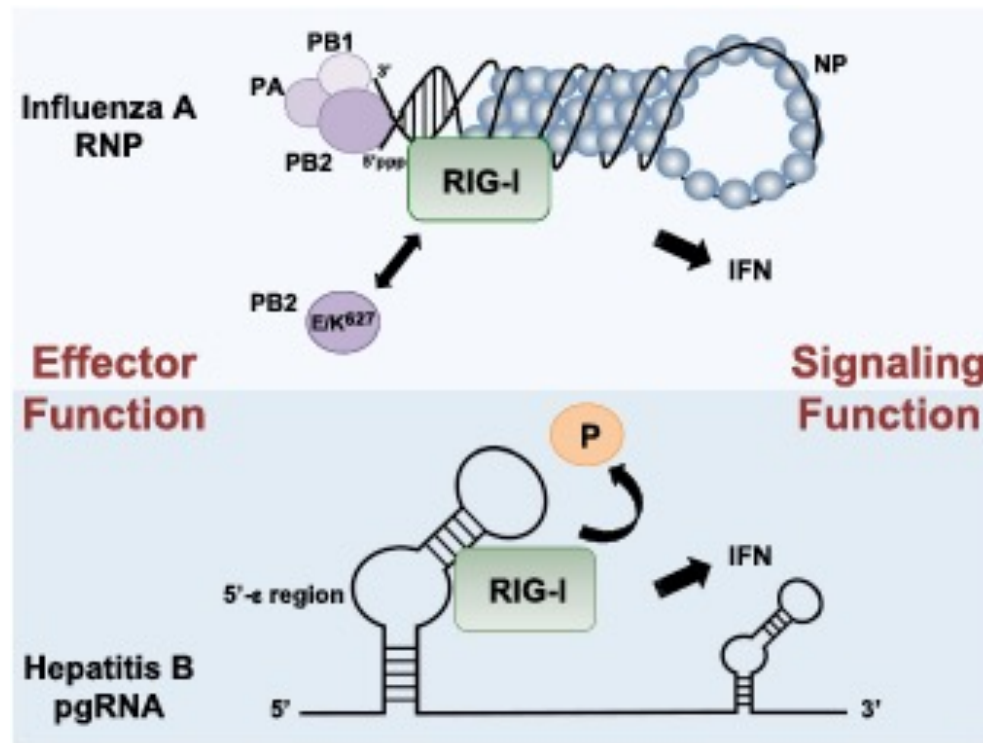
Upper: RIG-I binds to the 5′-triphosphorylated panhandle-RNA structure of RNPs during their short passage through the cytoplasm. Binding of RIG-I to the viral RNA is modulated by residue 627 in PB2. The RNPs of mammalian-adapted IAV strains, harboring PB2-627K, are poorly recognized by RIG-I. The RNPs of avian-adapted IAV strains, containing PB2-627E, are efficiently bound by RIG-I, which directly inhibits viral replication. Furthermore, sensing of IAV RNAs by RIG-I leads to downstream signaling and induction of IFNs. Lower: RIG-I binds to the 5′-ε stem-loop region of the HBV pregenomic RNA (pgRNA). Binding of RIG-I to pgRNA counteracts the interaction of the HBV polymerase (P) with the 5′-ε region, thereby directly inhibiting viral replication. Furthermore, recognition of pgRNA by RIG-I leads to signaling and induction of predominantly type III IFN.

Molecular determinants of human infection
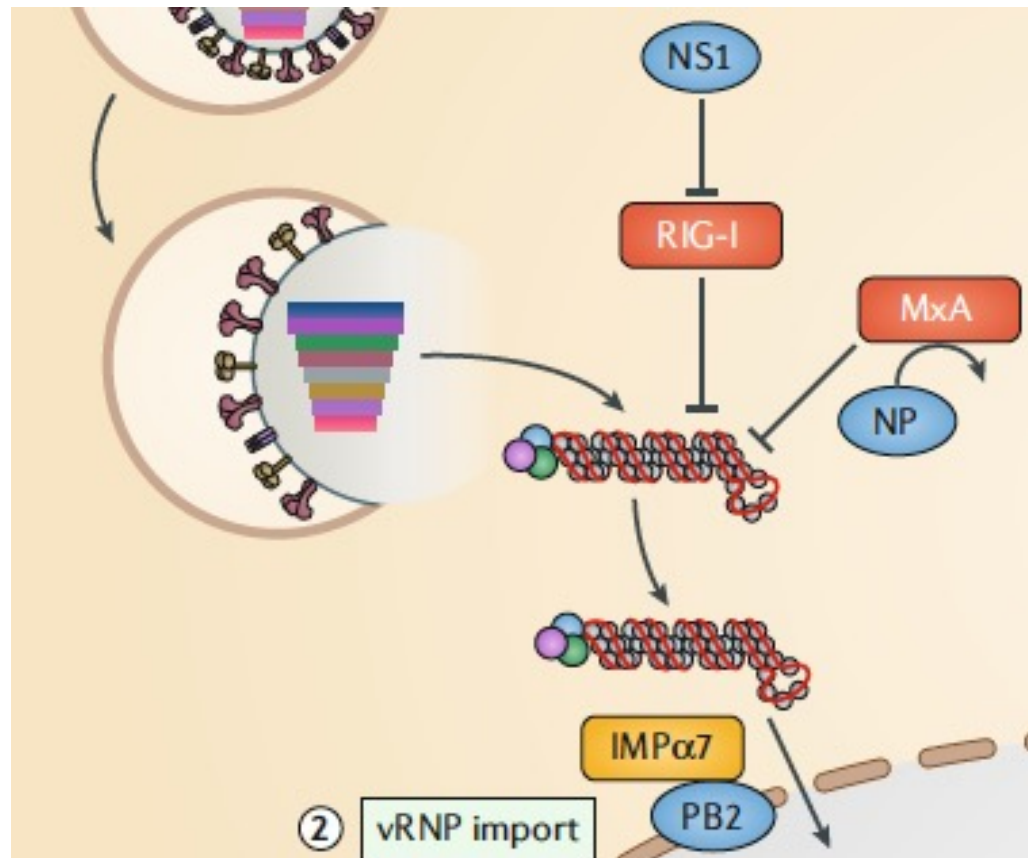
Retinoic acid-inducible gene I protein (RIG-I) and interferon-regulated resistance GTP-binding protein MxA restrict AIV vRNPs in the cytoplasm.

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.

Molecular determinants of human infection

The Mx (myxovirus resistance) proteins have a large N-terminal GTPase domain, a central interacting domain (CID) and a C-terminal leucine zipper (LZ) domain. Both the CID and the LZ domain are required to recognize target viral structures. The main viral target are viral nucleocapsid-like structures.
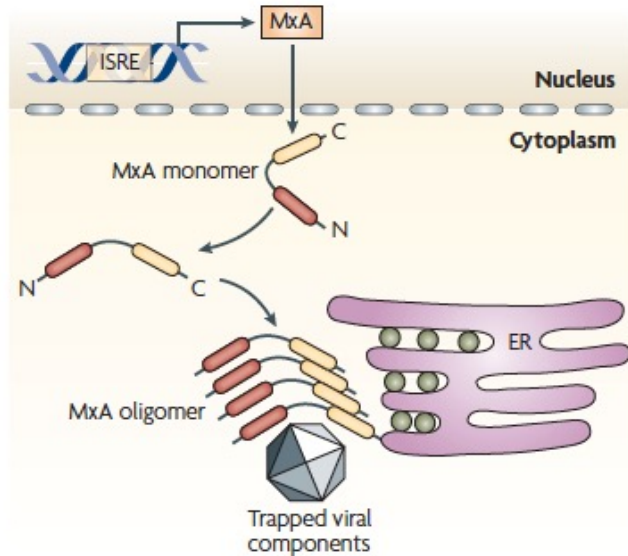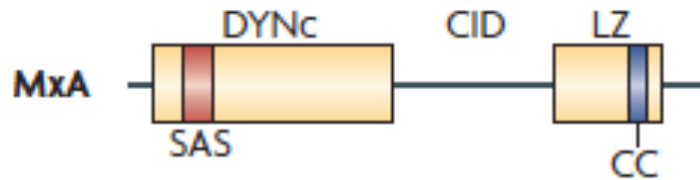

Mechanism of action of MxA. Following stimulation with type I interferons (IFNs), MxA (myxovirus-resistance A) gene expression is induced through an IFN-stimulated response element (ISRE) in the gene promoter. The MxA protein accumulates in the cytoplasm on intracellular membranes (such as the endoplasmic reticulum, ER) as oligomers formed by association between the leucine zipper (LZ) domain and central interactive domain of the protein. Following viral infection, MxA monomers are released and bind viral nucleocapsids or other viral components, to trap and then degrade them.

Molecular determinants of human infection
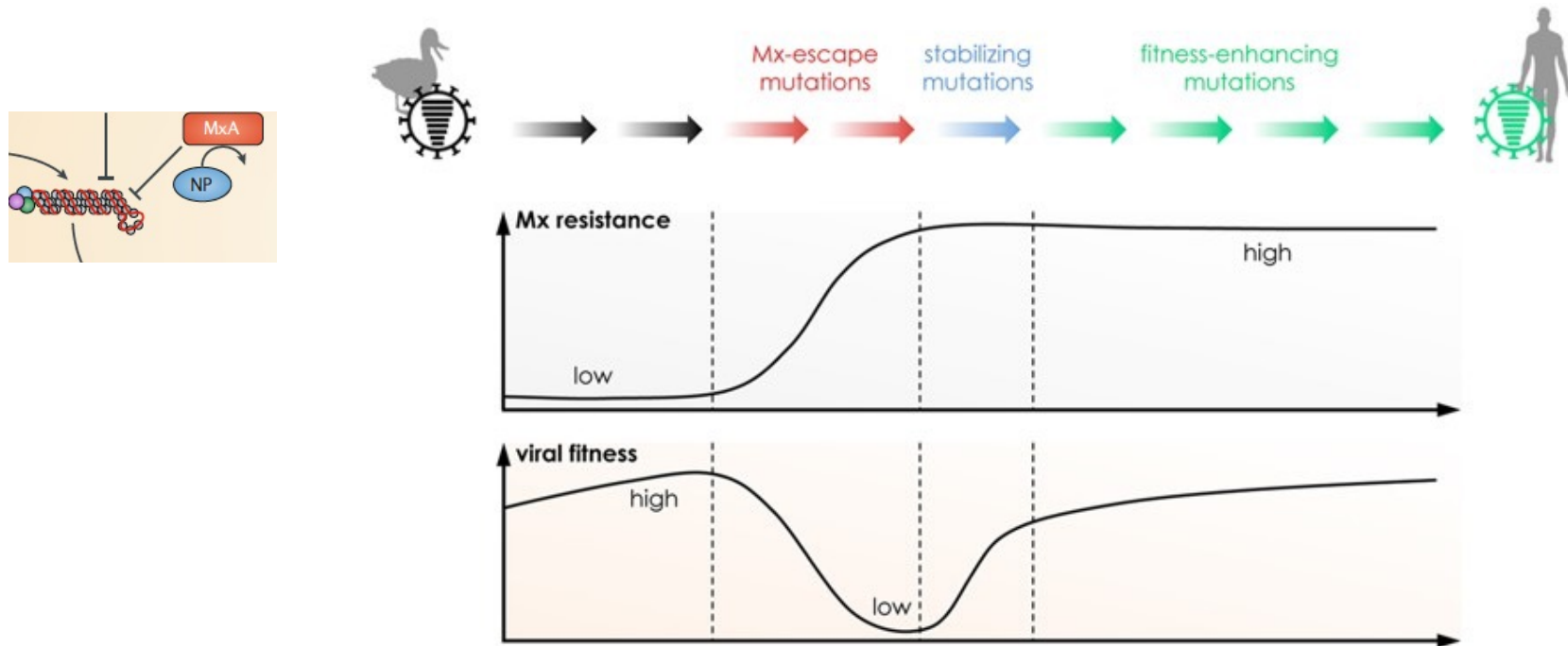
To establish a new lineage in the human population, avian influenza A viruses have to acquire several adaptive mutations in almost all viral proteins, including MxA escape mutations in NP. However, the acquisition of MxA escape amino acids in NP is associated with severely reduced viral fitness, due 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.

Virus and host-specific determinants of influenza virus replication
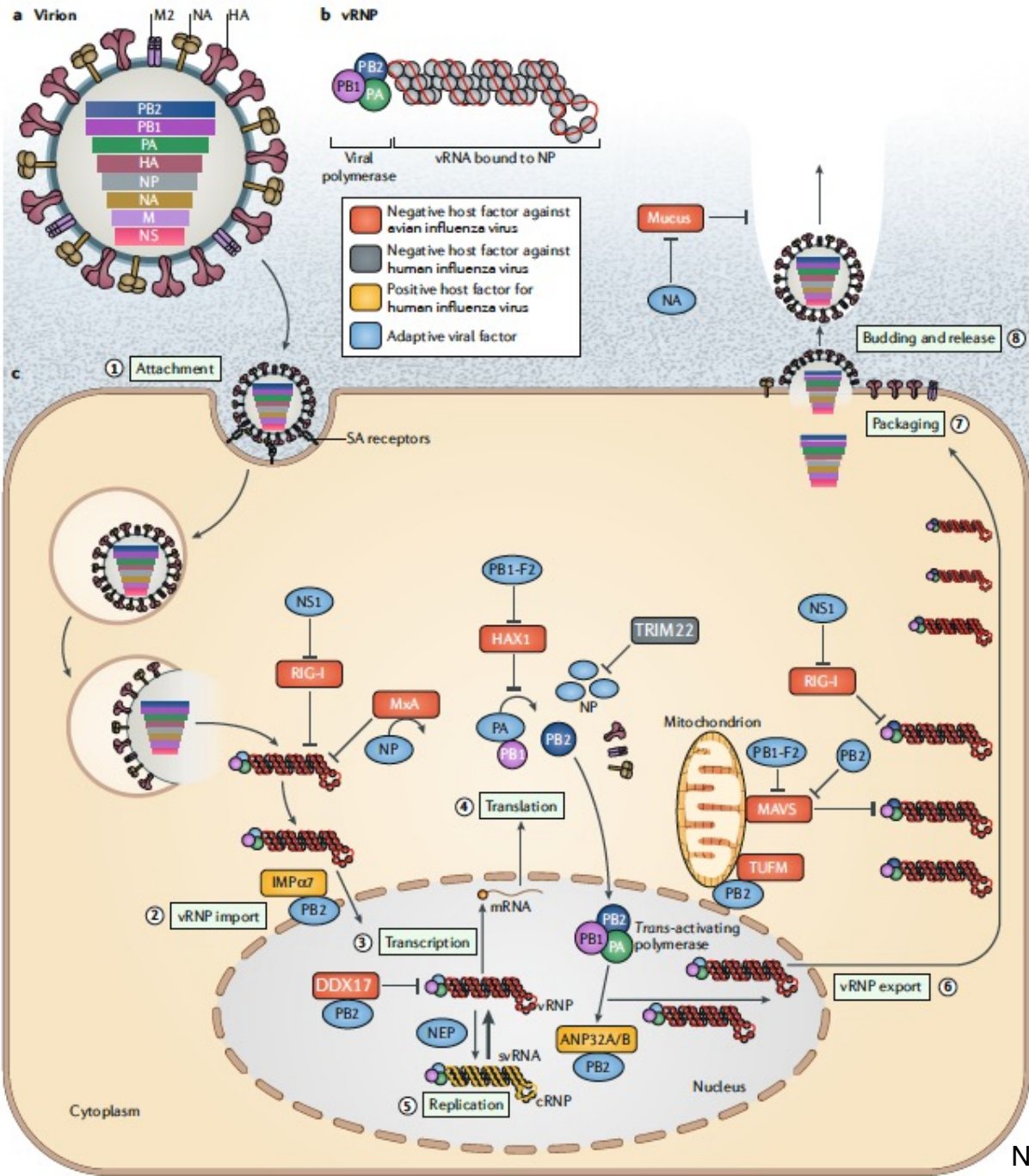
Virus and host-specific determinants of influenza virus replication

In human cells, avian influenza viruses (AIVs) may encounter negative host factors (red) that human-adapted viruses overcome by viral gene adaptation (blue). AIVs may be unable to co-opt positive human host factors (gold) and human-adapted viruses may develop susceptibility to restriction factors (dark grey). a | Influenza A viruses are enveloped viruses containing eight single-stranded negative-sense RNA gene segments that each encode one or more proteins. b | Each RNA segment (red line) surrounds an oligomeric nucleoprotein (NP) structure (light grey), and the viral promoters are bound by the heterotrimeric polymerase complex containing polymerase basic proteins 1 (PB1) and 2 (PB2) and polymerase acidic protein (PA); the entire structure is known as the viral ribonucleoprotein (vRNP) complex. The eight segments encode ten essential viral proteins: PB1, PB2, PA and NP for RNA replication; non-structural protein 1 (NS1) to evade the host innate response; matrix protein M1 as the main structural matrix of the virus particle; nuclear export protein (NEP) for nuclear export of vRNPs; and haemagglutinin (HA), matrix protein M2 and neuraminidase (NA), which are embedded in the virion envelope for virus attachment, uncoating and onward spread, respectively. In addition, several accessory proteins such as protein PB1-F2, PB1-N40, PA-X, PB2-S1, matrix protein M42 and NS3 may be encoded by some but not all virus strains.

Virus and host-specific determinants of influenza virus replication

c | Virus infection begins with cell attachment mediated by binding of HA to sialic acid (SA) receptors on the cell surface (step 1). Entry of the virion is by endocytosis, and the decrease in pH within the endosome triggers an irreversible conformational change in HA that exposes the hydrophobic fusion peptide and stimulates the fusion of the viral envelope with the endosomal membrane. At the same time, the passage of protons and potassium ions through the small ion channel M2 acidifies the virion interior and mediates dissociation of M1 from vRNPs, releasing the vRNPs into the cell cytoplasm. Interferon-regulated resistance GTP-binding protein MxA and retinoic acid-inducible gene I protein (RIG-I) restrict AIV vRNPs in the cytoplasm. Mutations in human-adapted NP evade MxA binding. Human-adapted vRNPs with PB2 627K are less vulnerable to RIG-I detection. vRNPs are imported into the nucleus (step 2). Humanizing mutations in PB2 enable importin-"7 (IMP"7; also known as KPNA6) use and enhance vRNP nuclear import. Primary transcription occurs in cis and in conjunction with the cellular RNA polymerase II (step 3). Viral mRNAs are exported to the cytoplasm for translation by the cellular machinery (step 4). Human-adapted NP is susceptible to degradation by tripartite motif-containing protein 22 (TRIM22). AIV PA is susceptible to inhibition by HS1-associating protein X1 (HAX1), but this can be counteracted by protein PB1-F2. The newly synthesized polymerase and NP proteins are imported into the nucleus to carry out replication and further (secondary) transcription (step 5).

Virus and host-specific determinants of influenza virus replication

Acidic leucine-rich nuclear phosphoprotein 32 family member A (ANP32A) or B (ANP32B) and small viral RNAs (svRNAs) promote viral RNA (vRNA) production from complementary RNA (cRNA) (yellow line). AIV polymerase cannot utilize human ANP32A or ANP32B and must gain human-adapting mutations such as PB2 627K. NEP can also overcome the AIV polymerase restriction. DEAD box protein 17 (DDX17) restricts AIV polymerase PB2 627E and promotes activity of human-adapted polymerase containing PB2 627K. Newly formed vRNPs are exported to the cytoplasm by M1 and the NEP (step 6). vRNPs and other viral products are detected by multiple cell sensors. Mitochondrial Tu elongation factor (TUFM) binds to AIV PB2 containing 627E, increasing autophagy and decreasing virus production. Human-adapted PB2 and protein PB1-F2 localize to mitochondria and prevent detection by mitochondrial antiviral signalling protein (MAVS). NS1 binds to RIG-I to prevent activation. vRNPs transported to the cell surface for packaging are assembled with the structural proteins (HA , NA , M1 and M2) (step 7). Progeny virions are formed by budding from host cell plasma membrane, and release is mediated by scission of the membrane by M2 (step 8). Onward spread is facilitated by the removal of SA from the cell surface, from viral particles and from mucus by NA. Short-stalk avian NAs are unable to escape human respiratory tract mucus; human-adapted viruses with long-stalk NAs can overcome this restriction.

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.

The 2016 inactivated vaccine contains three viruses (a trivalent vaccine), one H1N1 virus, one H3N2 virus and one influenza B viruse to represent the viruses posing a threat.

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.

Induction of Broadly Neutralizing H1N1 Influenza Antibodies by Vaccination
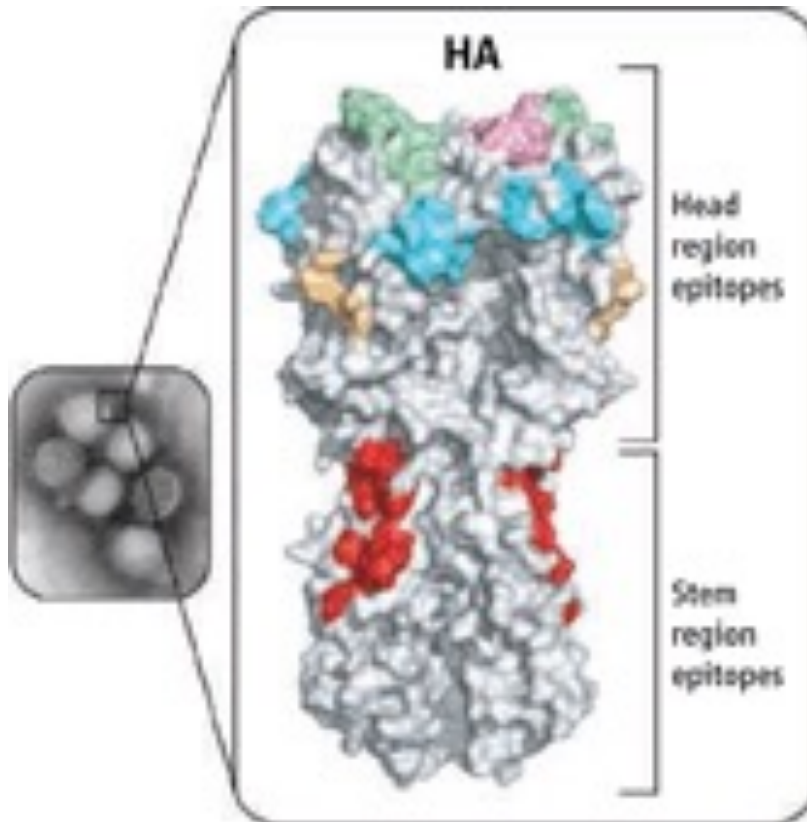
Most antibodies against influenza A virus (inset shows the 2009 H1N1 strain) bind to the highly variable part of the hemagglutinin (HA) glycoprotein at the surface of the virus particle (head region). In the H1 subtype, these antibodies recognize four major sites (Sa, Sb, Ca, and Cb are shown in green, pink, cyan, and yellow, respectively). The HA structure of the 2009 H1N1 virus is shown. Antibodies that neutralize multiple strains both within a virus subtype and from different subtypes bind to a highly conserved region (red) in the stem region of HA.

Towards a universal influenza vaccine
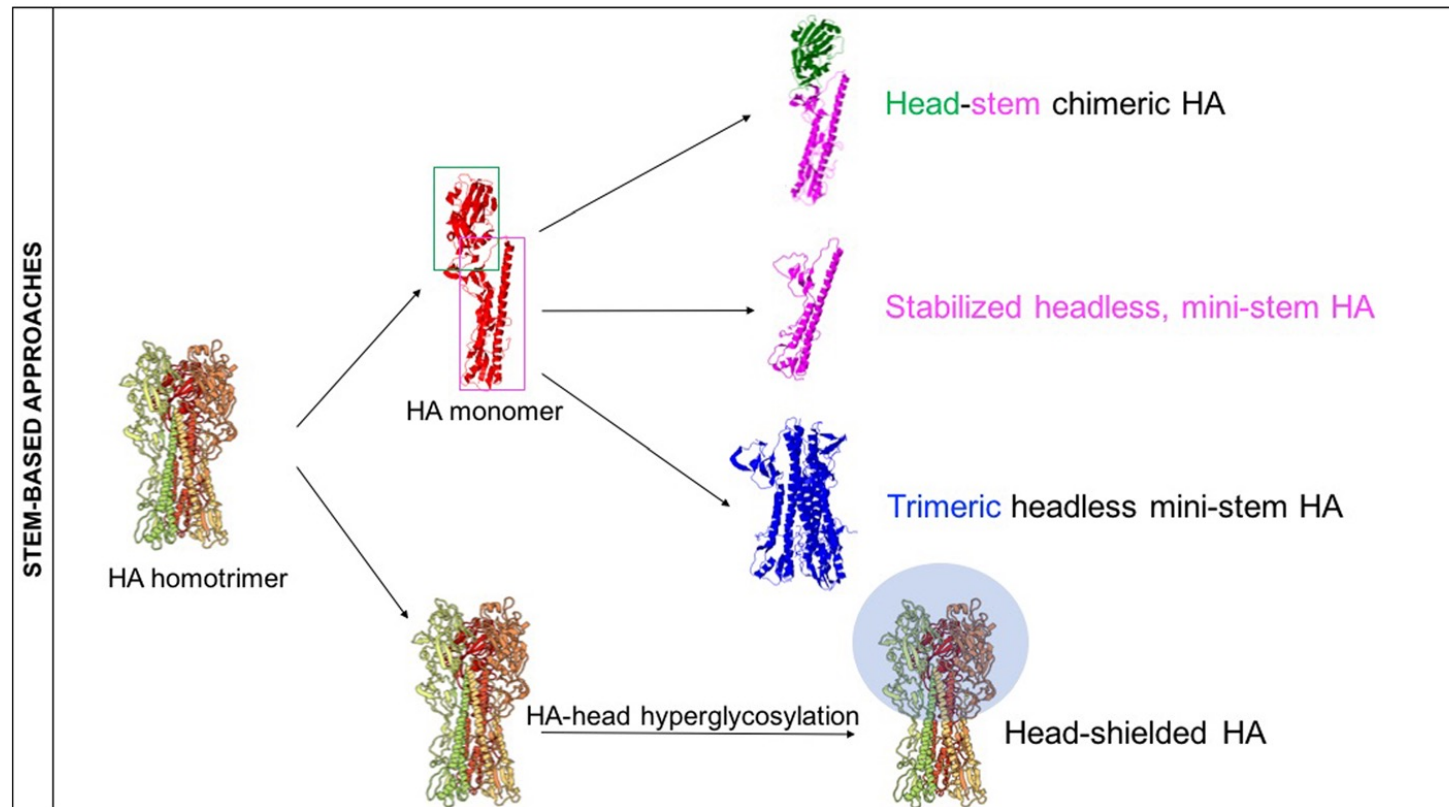
Schematic representation of approaches aimed at eliciting/boosting an antibody response against the HA stem region. These strategies rely on the chimerization of the HA molecule in order to direct the antibody response towards the stem region or on the masking of the head region (i.e. through the hyperglycosylation of the HA head).

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.

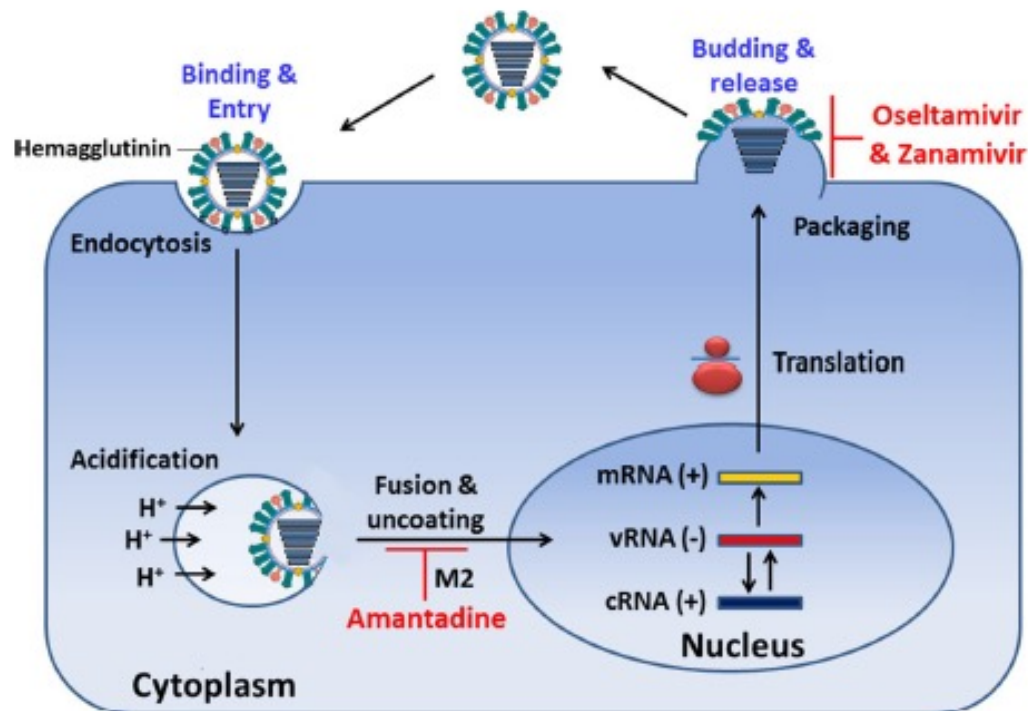**Table 20.3**

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)

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

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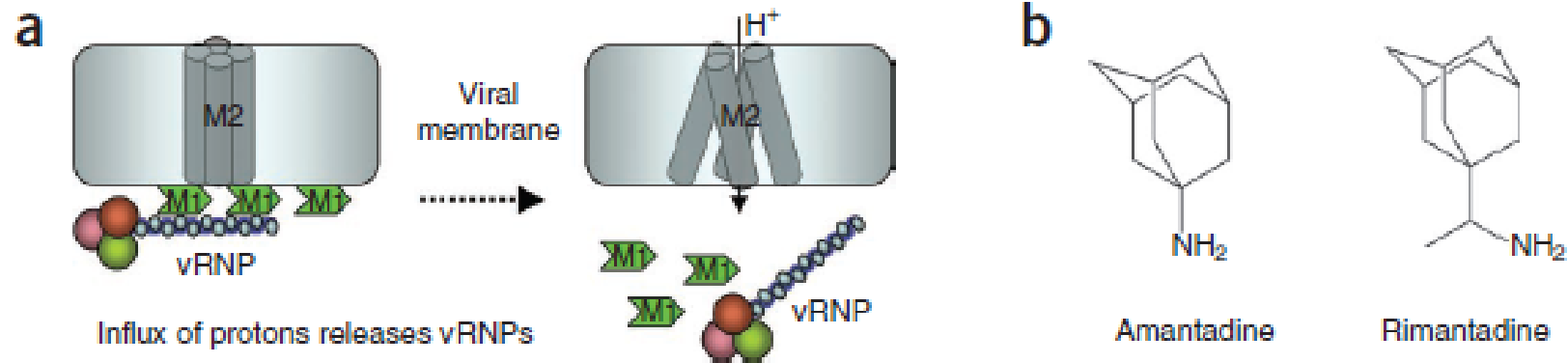
Amantadine and Rimantadine: Structure, function and inhibition of the proton channel M2 protein of influenza A. (**a**) The vRNPs are attached to the lipid bilayer membrane via M1 matrix proteins. Influx of the protons from endosome to virus through M2 channels releases vRNPs. (**b**) The adamantanes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

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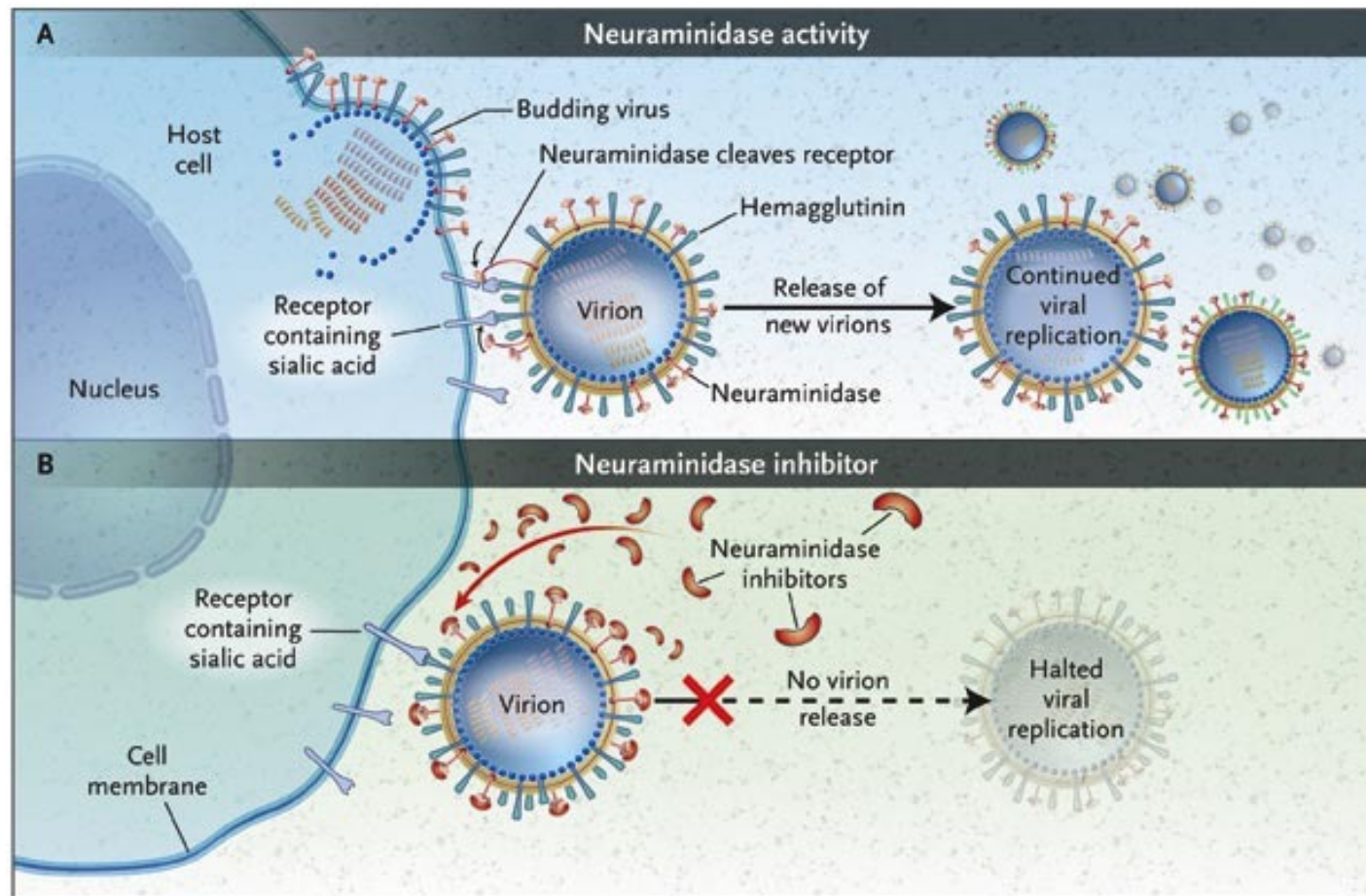
Zanamivir and Oseltamivir (Tamiflu): The neuraminidase inhibitors zanamivir and oseltamivir interfere with the release of progeny influenza virus from infected host cells, a process that prevents infection of new host cells and thereby halts the spread of infection in the respiratory tract

Host and viral determinants of influenza A virus species specificity

Jason S. Long[1], Bhakti Mistry[1], Stuart M. Haslam[2] and Wendy S. Barclay[1]*

Next-generation influenza vaccines: opportunities and challenges

Chih-Jen Wei[1], Michelle C. Crank[2], John Shiver[5], Barney S. Graham[2], John R. Mascola[2] and Gary J. Nabel[1]

Bat-Borne Influenza A Viruses: An Awakening

Kevin Ciminski[1,2] and Martin Schwemmle[1,2]

PLOS PATHOGENS

Bats reveal the true power of influenza A virus adaptability

Kevin Ciminski[1,2], Florian Pfaff[3], Martin Beer[3]*, Martin Schwemmle[1,2]*