

Emergence virale et risque pandémique: exemple des souches aviaires de virus grippal

M1 Microbiologie-Pathologies

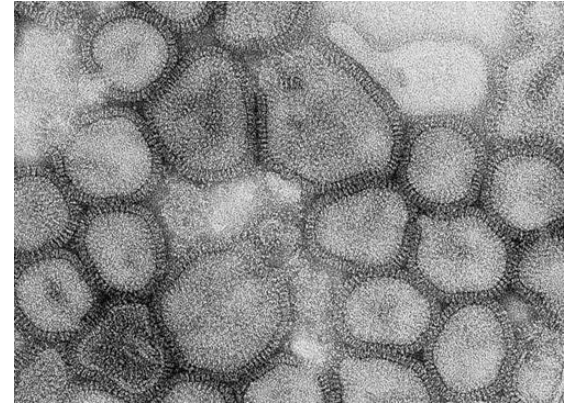
BM Imbert-Marcille

Année 2024-2025

Les virus respiratoires émergents

- Plus de 1400 pathogènes humains identifiés à ce jour:
 - 65% d'entre eux sont d'origine animale
 - 5% sont des virus...mais 1/3 des agents identifiés dans les infections émergentes au XXème siècle sont des virus
 - L'adaptation des virus à l'homme est le plus souvent rendue possible par des mutations du virus animal
- Nombreux nouveaux virus « respiratoires » identifiés depuis 2000
 - Certains au pouvoir pathogène encore « incertain »
 - D'autres identifiés comme de réels pathogènes: Metapneumovirus, Coronavirus du SARS, virus grippaux aviaires
- Pandémie de SARS-CoV2
- Intérêt du modèle Influenzaevirus (virus grippal), pour étudier
 - le passage de virus animaux à l'homme
 - les mécanismes de la diffusion pandémique des maladies infectieuses et la mise en place de mesures de prévention
 - la physiopathologie des atteintes pulmonaires virales

Structure des virus grippaux



-PB1,PB2, PA:
transcriptase

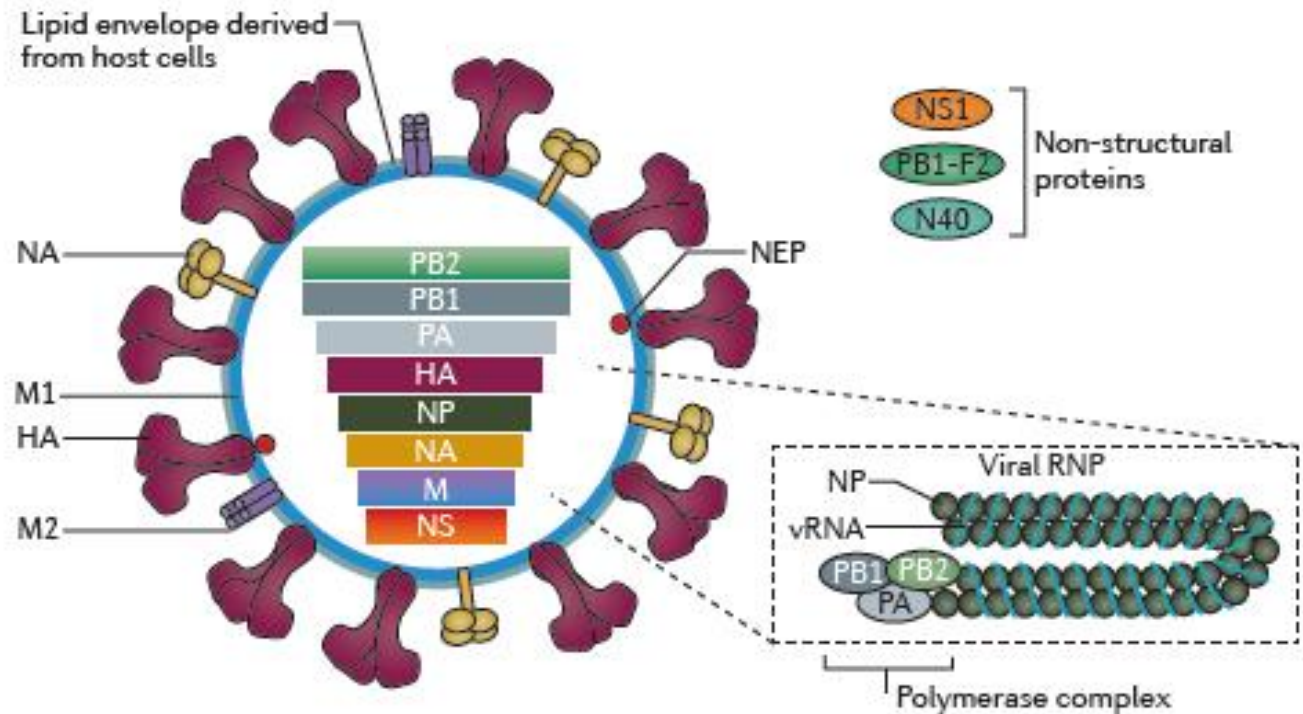
-HA:
hémagglutinine

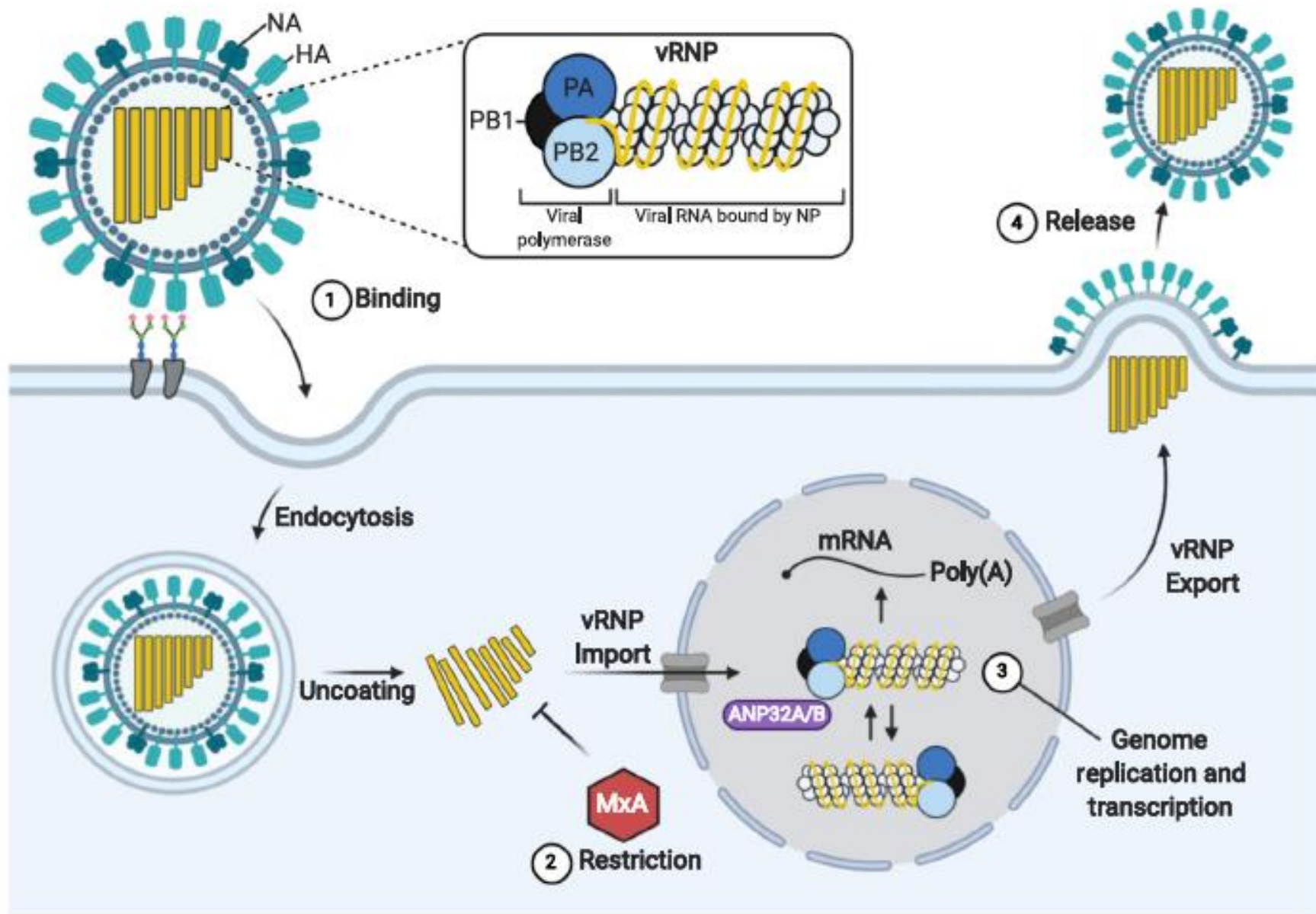
-NP:
nucléocapside

-NA:
neuraminidase

-M: prot matrice
M1 et canal
ionique M2

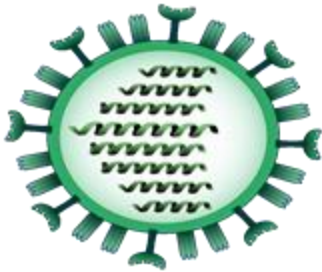
-NS: prot non
structurales



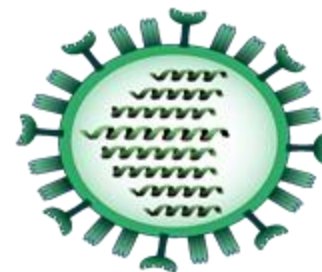


Trois types et de nombreux sous-types

Type B



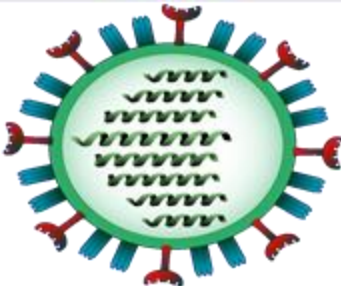
Type C (7 seg)



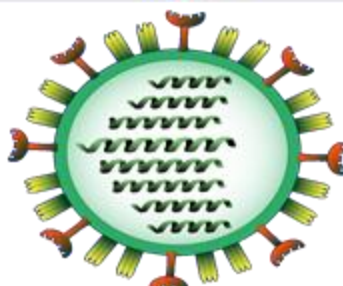
Type A (144 sous-types possibles)



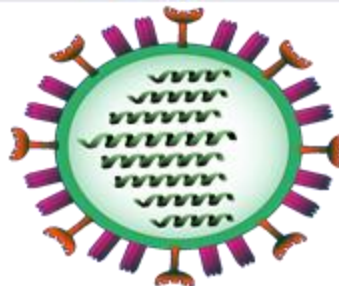
H1N1



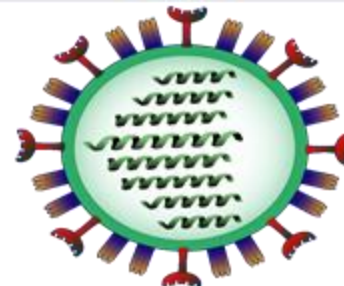
H2N2



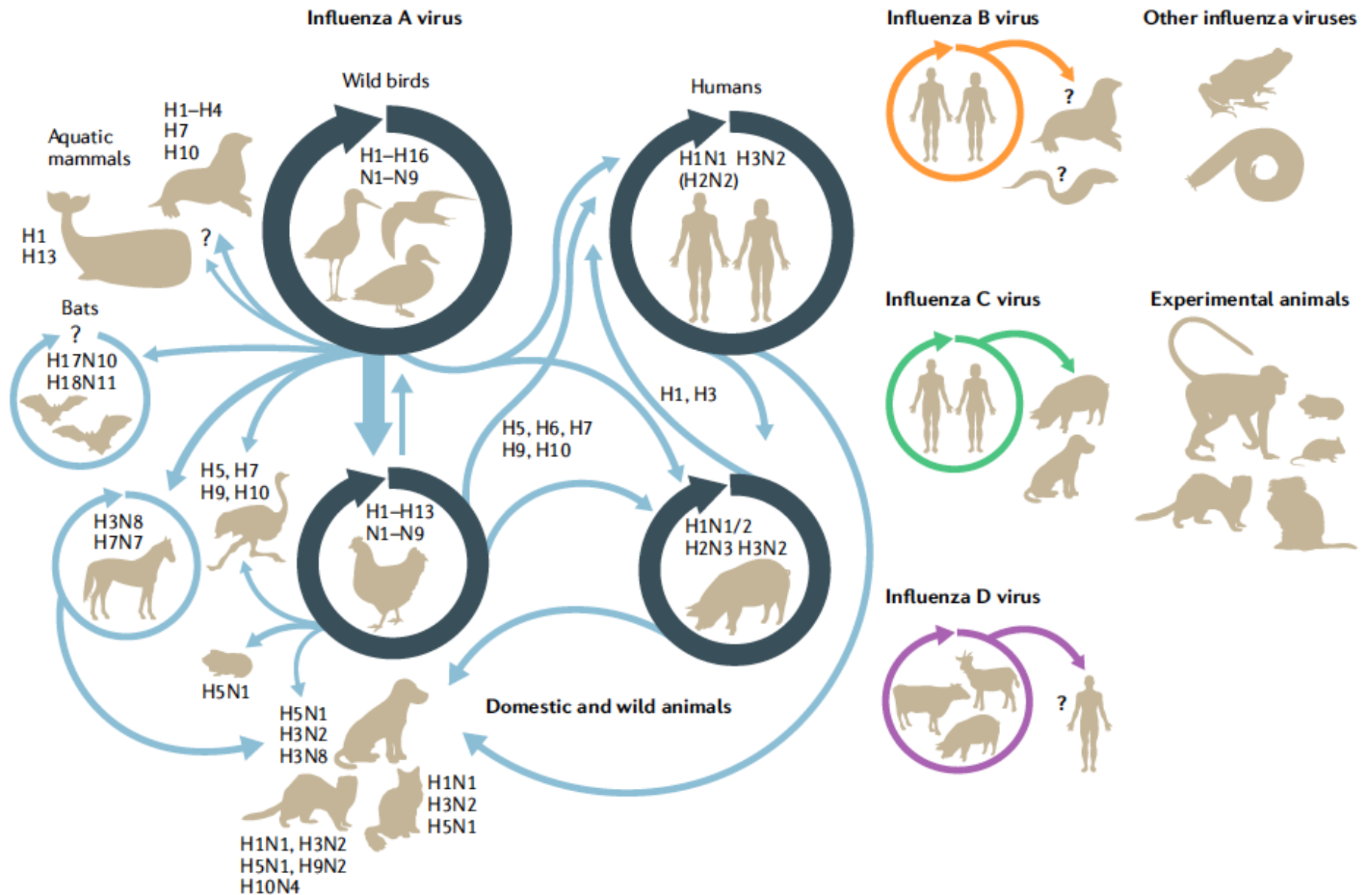
H3N2



H5N1

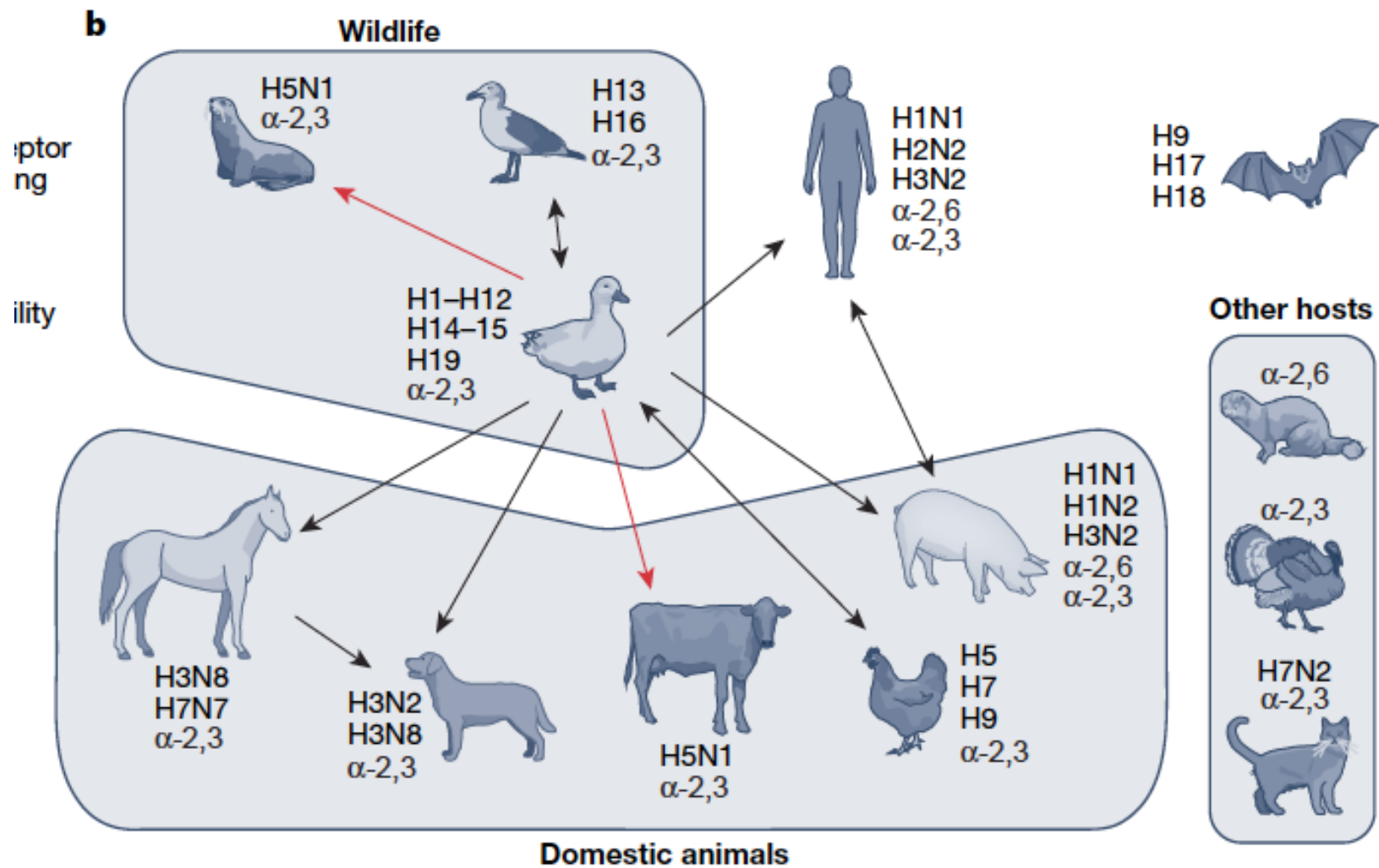


Diversité et tropisme animaux des virus grippaux

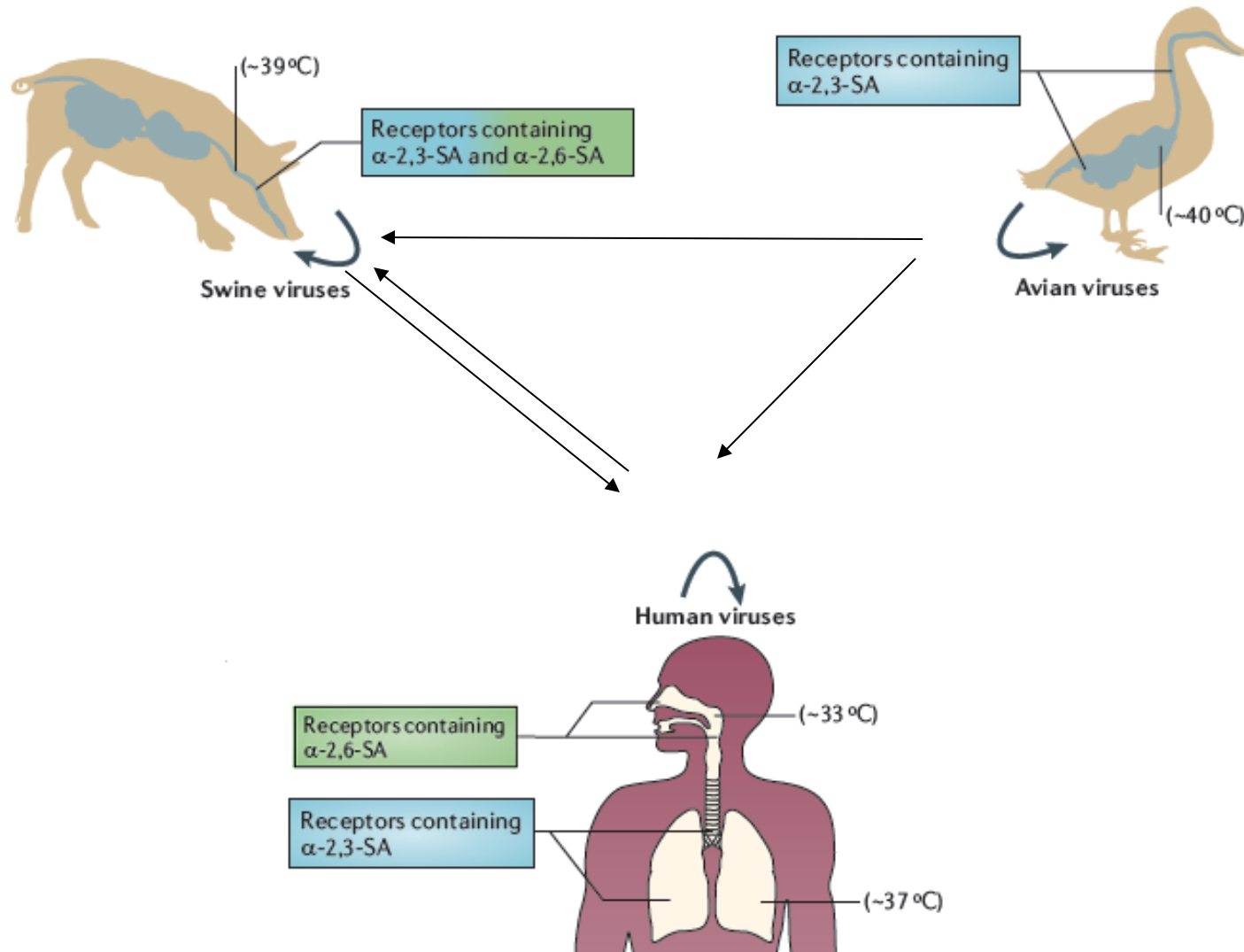


Les caractéristiques de HA et de NA (gp d'enveloppe)

- **Hémagglutinine: détermine en premier la spécificité d'hôte**
 - Clivage de HAo en HA1 et HA2 par protéases de l'hôte
 - Attachement du virus à la cellule: R aux acides sialiques liés au galactose par des liaisons glycosidiques:
 - de type NeuAc α 2,3Gal (Virus aviaires et autres non humains dont porc)
 - de type NeuAc α 2,6Gal (Virus humains, virus porcins)
 - Activité fusogène de HA2 (dans vésicule d'endocytose)
 - Cible majeure de la réponse anticorps
- **Neuraminidase:**
 - Activité sialidase, permettant libération des virions néoformés par coupure entre l'acide sialique et l'hémagglutinine
 - Cible des anticorps et de l'oseltamivir (et zanamivir)



Les souches aviaires s'accrochent aux acides sialiques ayant des liaisons NeuAc $\alpha 2,3$ Gal
Les souches humaines s'accrochent aux acides sialiques ayant des liaisons NeuAc $\alpha 2,6$ Gal



La variabilité génétique...et ses conséquences

- **Variabilité liée aux erreurs de l'ARN polymérase (tous types)**
 - Modifications progressives de HA et/ou de NA = glissements antigéniques ou dérive antigénique
 - **Responsable des épidémies saisonnières**
 - Explique reformulation annuelle du vaccin (en fonction de circulation dans hémisphère sud)
- **Variabilité liée à des « sauts/cassures antigéniques » (uniquement type A)**
 - Par réassortiment génique entre deux types de virus ou par « infection directe »...
 - **Responsable des pandémies**
 - Pas de vaccin tant que la nouvelle souche infectant l'homme n'a pas été identifiée...

Pandémies grippales

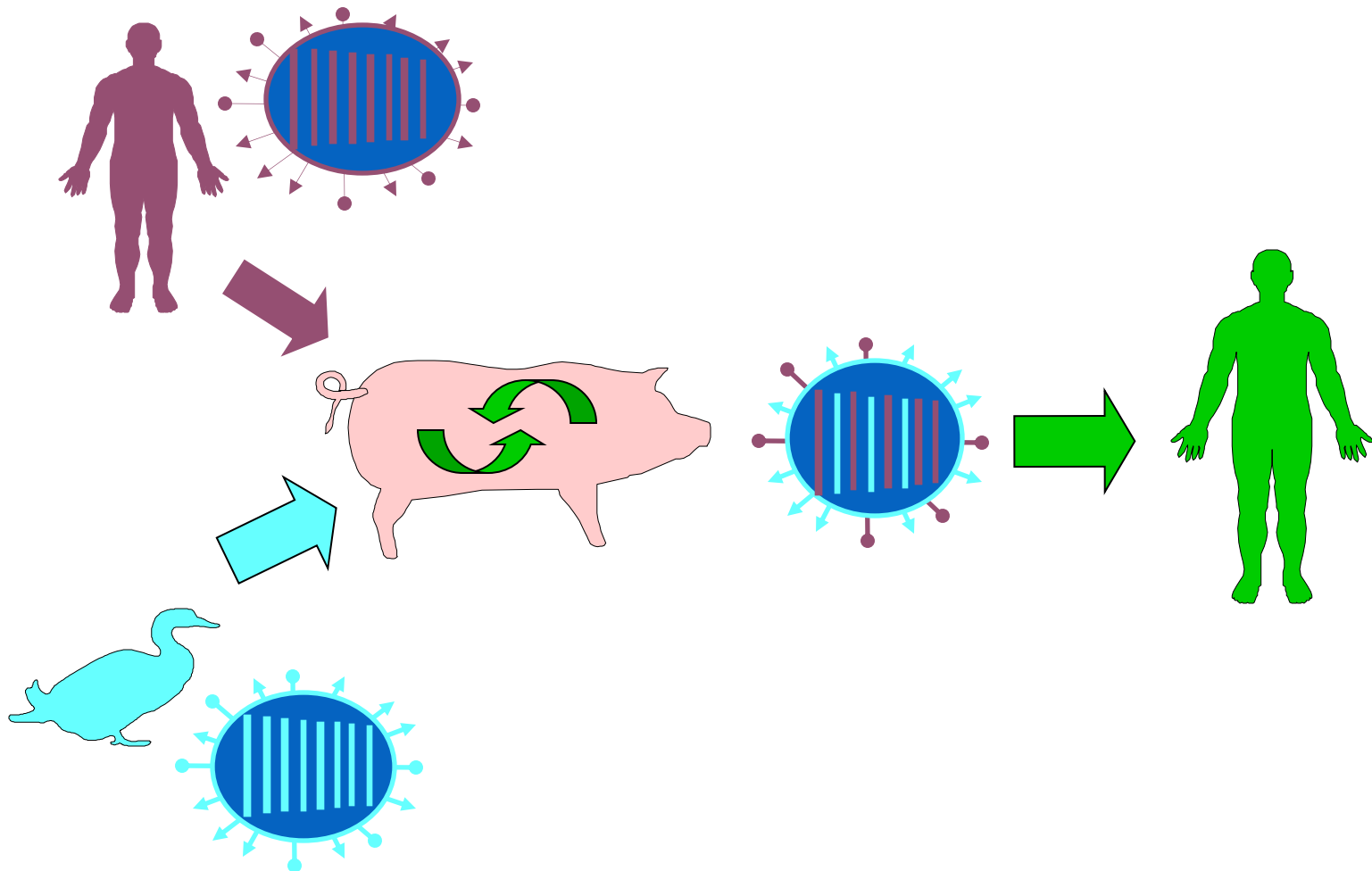
Mortalité au cours des pandémies du XX^e siècle

1918-19	« Grippe espagnole » A(H1N1)	≈ 40 millions de décès dans le monde
1957-58	« Grippe asiatique » A(H2N2)	1 million de décès dans le monde
1968-69	« Grippe de Hong-Kong » A(H3N2)	0,8 millions de décès dans le monde
1977	« Grippe russe » A(H1N1)	

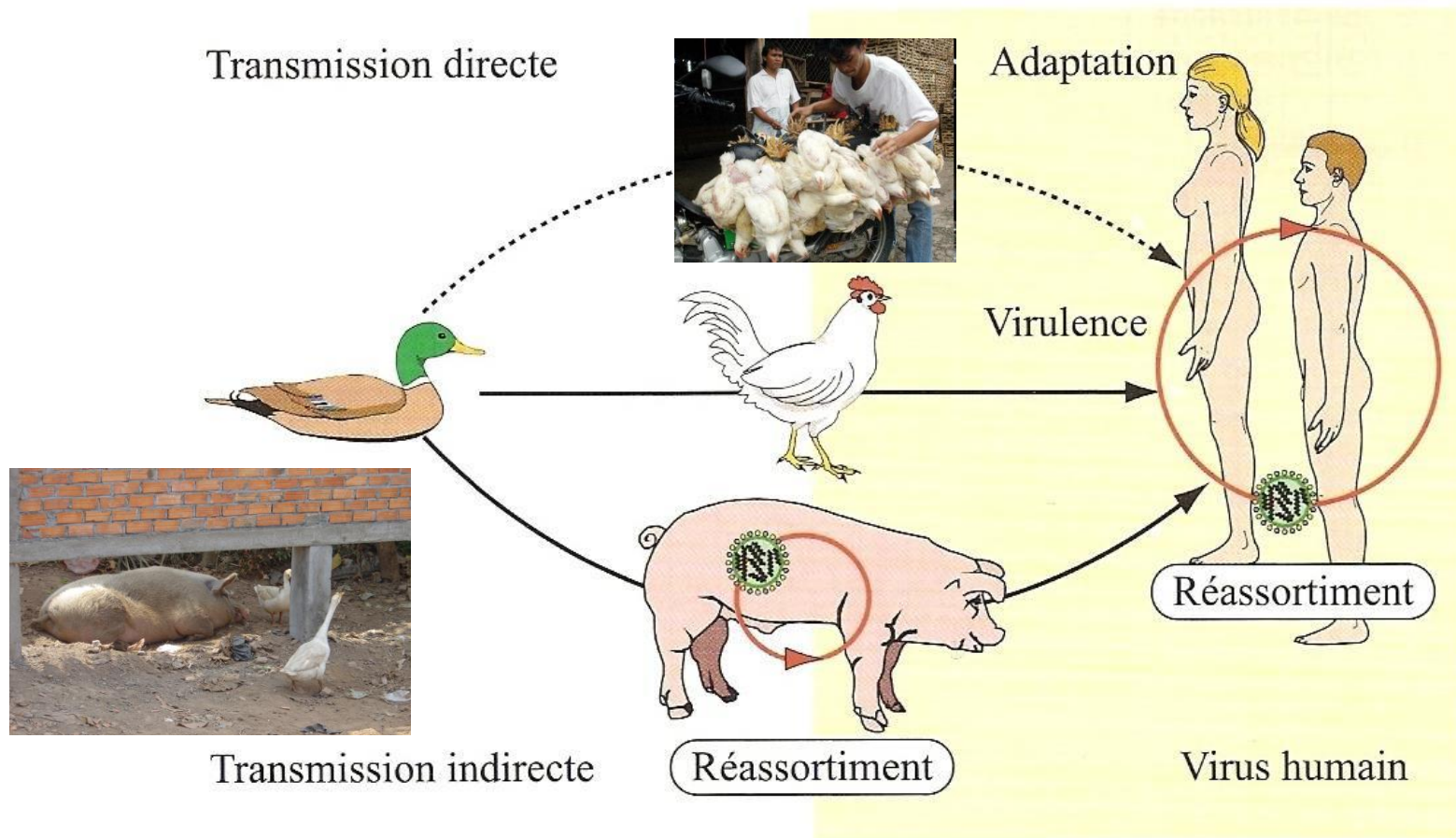


- Les pandémies ont lieu tous les 10 à 40 ans
- Jusqu'à 50 % de la population mondiale peut être affectée
- Virus nouveau pour la population humaine
- Taux de létalité généralement élevé
- 1997 "grippe du poulet" (H5N1) à Hong Kong – rappel de la menace pandémique
- 2009

Réassortiment entre virus grippaux



Origines possibles des virus pandémiques



1918 "Spanish influenza"

1957 "Asian influenza"

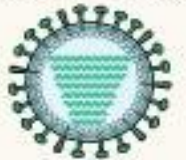
1968 "Hong Kong influenza"

Next pandemic influenza

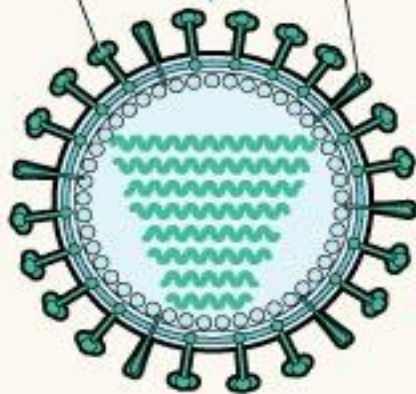
H1N1 influenza virus



Bird-to-human
transmission of H1N1 virus

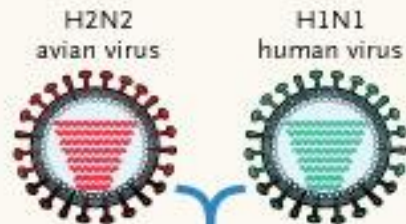


Hemagglutinin Neuraminidase

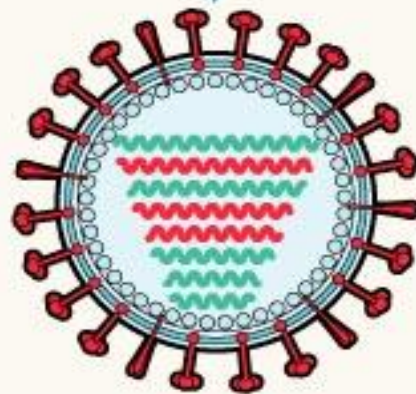


All 8 genetic segments
thought to have originated
from avian influenza virus

H2N2 influenza virus

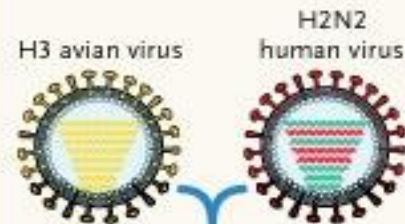


Reassortment

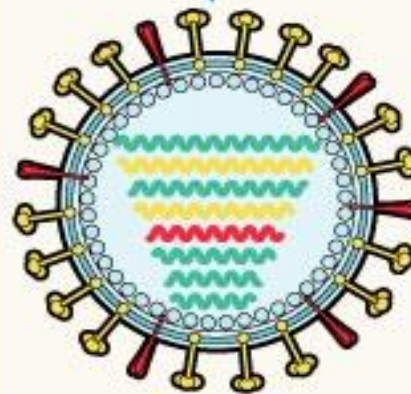


3 new genetic segments from
avian influenza virus introduced
(HA, NA, PB1);
contained 5 RNA segments
from 1918

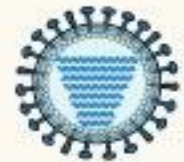
H3N2 influenza virus



Reassortment



2 new genetic segments from
avian influenza virus introduced
(HA, PB1);
contained 5 RNA segments
from 1918



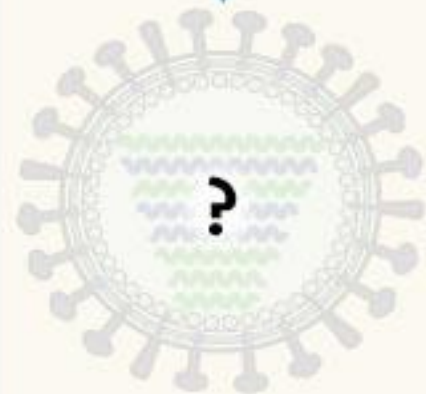
Avian virus

or

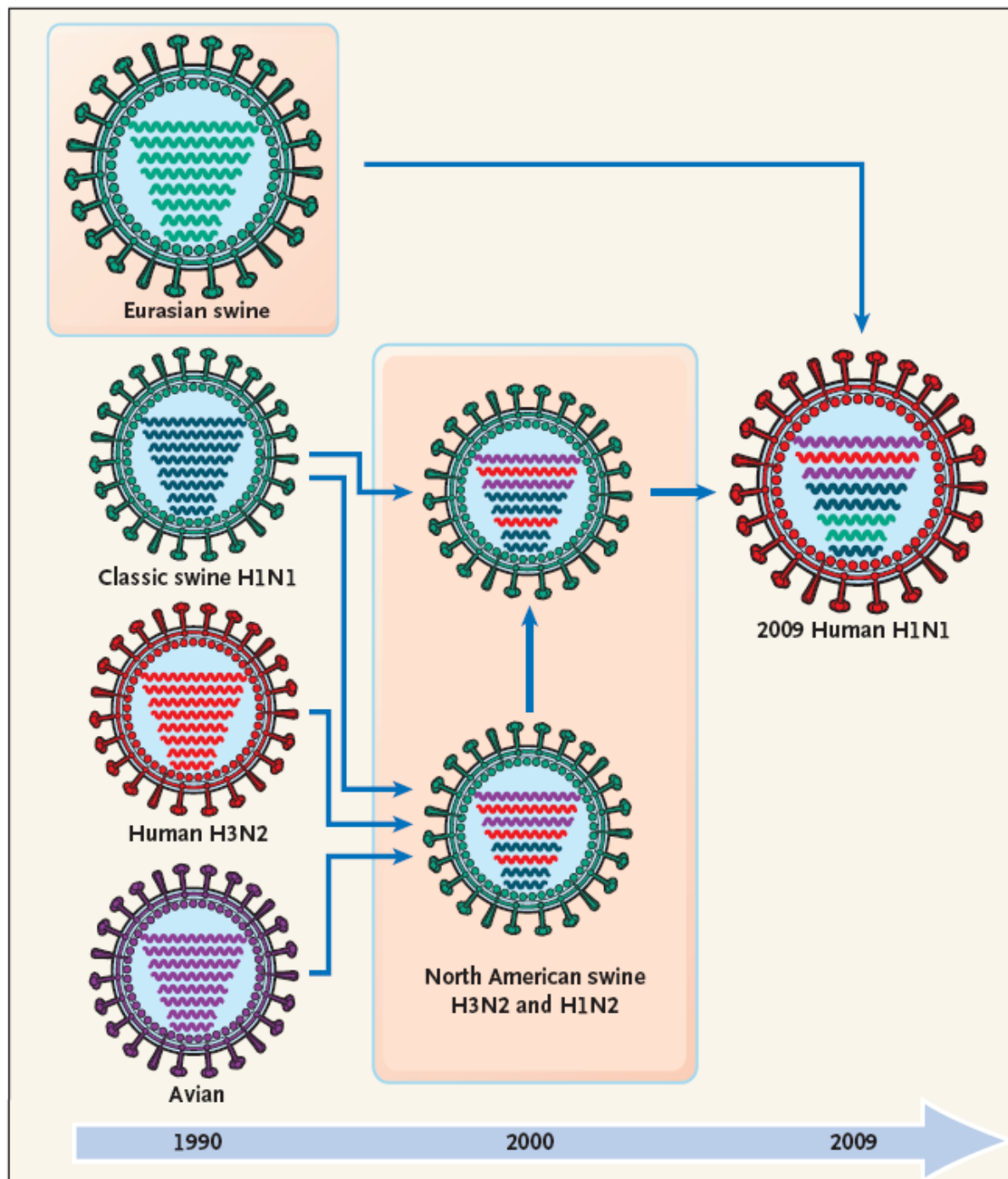


Avian virus

H3N2
human virus



All 8 genes new or further
derivative of 1918 virus



Les virus aviaires (IAV)

- Représentent la très grande majorité des virus de type A car les oiseaux (notamment aquatiques migrateurs) sont le réservoir naturel
- Chez les oiseaux (sauvages ou domestiques) :
 - multiplication du virus dans les intestins
 - présence en grande quantité dans les excréments
 - Pas de signes cliniques pour la plupart des souches (souches Low Pathogenic Avian Influenza LPAI)
 - Certaines souches sont hautement pathogènes (souches HPAI)
 - Responsables de l'Influenza aviaire
 - mortalité +++
 - possibilité de transmission à d'autres animaux (notamment les volailles) et à l'homme
 - Elles sont de type H5 ou H7 (voire H9) et portent un site de clivage particulier au niveau du précurseur de l'hémagglutinine

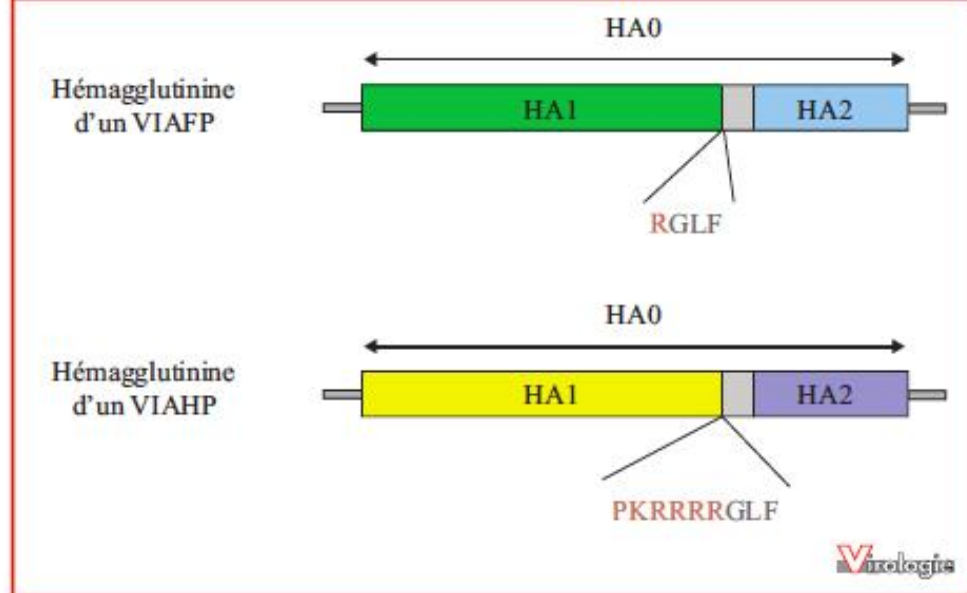


Figure 2. Hémagglutinines des virus influenza aviaires faiblement et hautement pathogènes. Le clivage protéolytique de la molécule précurseur HA0 en deux sous-unités HA1 et HA2 se fait au niveau d'un site de clivage qui est monobasique pour les VIAFP et polybasique pour les VIAHP.

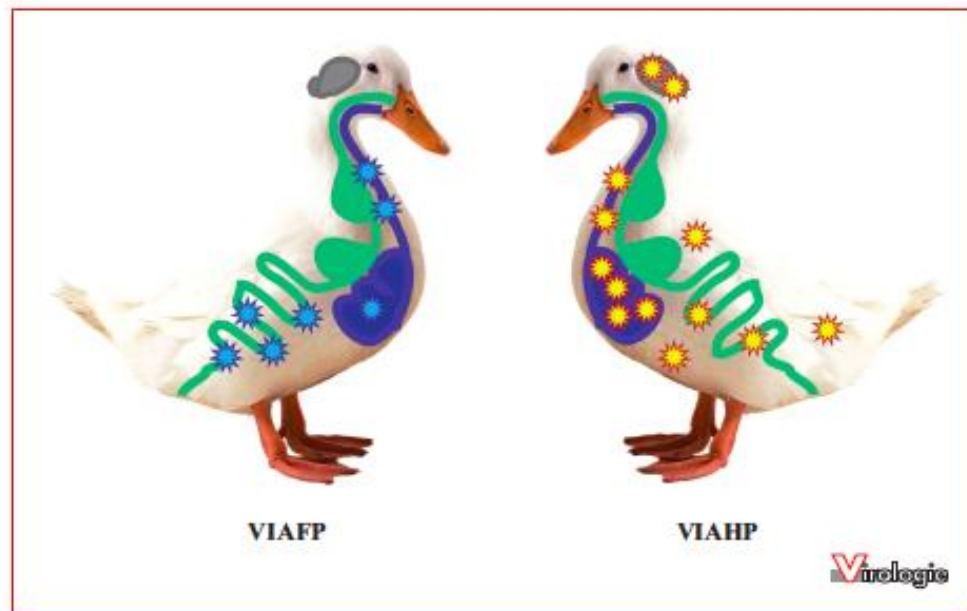
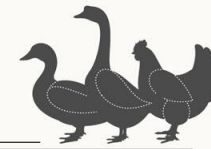


Figure 3. Réplication des virus influenza aviaires faiblement et hautement pathogènes chez les oiseaux. Les étoiles indiquent les sites de réplication virale. La réplication des VIAFP est généralement limitée aux appareils respiratoires et digestifs, tandis que les VIAHP peuvent se répliquer de manière systémique.

Emergence and Evolution of H5N1 BIRD FLU



H5N1

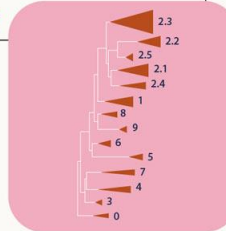


1996-1997 H5N1 bird flu virus first detected

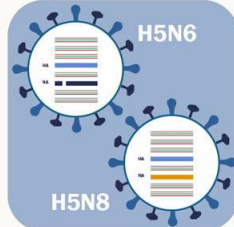
In 1996, highly pathogenic avian influenza H5N1 virus is first identified in domestic waterfowl in Southern China. The virus is named A/goose/Guangdong/1/1996. In 1997, H5N1 poultry outbreaks happen in China and Hong Kong with 18 associated human cases (6 deaths) in Hong Kong. This virus would go on to cause more than 860 human infections with a greater than 50% death rate.

H5N1 spreads 2003-2005

For several years, H5N1 viruses were not widely detected; however, in 2003, H5N1 re-emerges in China and several other countries to cause widespread poultry outbreaks across Asia. In 2005, wild birds spread H5N1 to poultry in Africa, the Middle East and Europe. The hemagglutinin (HA) gene of the virus diversifies into many genetic groups (clades). Multiple genetic lineages (genotypes) are detected.



H5N6



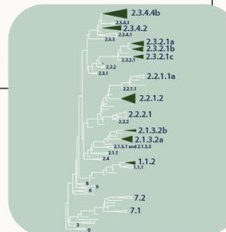
H5N8

2014-2016 H5N6 and H5N8 viruses emerge

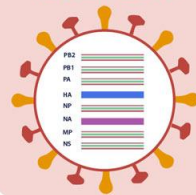
Gene-swapping of H5 viruses from poultry and wild birds leads to emergence/detection of H5N6 and H5N8 virus subtypes. HA diversifies further into clade 2.3.4.4 in Asia, Africa, Europe, the Middle East and North America. H5 viruses with various neuraminidase (NA) genes continue to be detected, including in U.S. wild birds and poultry.

2.3.4.4b viruses spread widely 2018-2020

H5N6 and H5N8 viruses become predominant globally, replacing the original H5N1 viruses. As of 2022, there have been more than 70 reported H5N6 human infections and 7 H5N8 human infections. The H5 HA diversifies further into clade 2.3.4.4b which becomes predominant in Asia, Africa, Europe, and the Middle East.



H5N1 clade 2.3.4.4b



2021-2022 H5N1 found in Canada, US

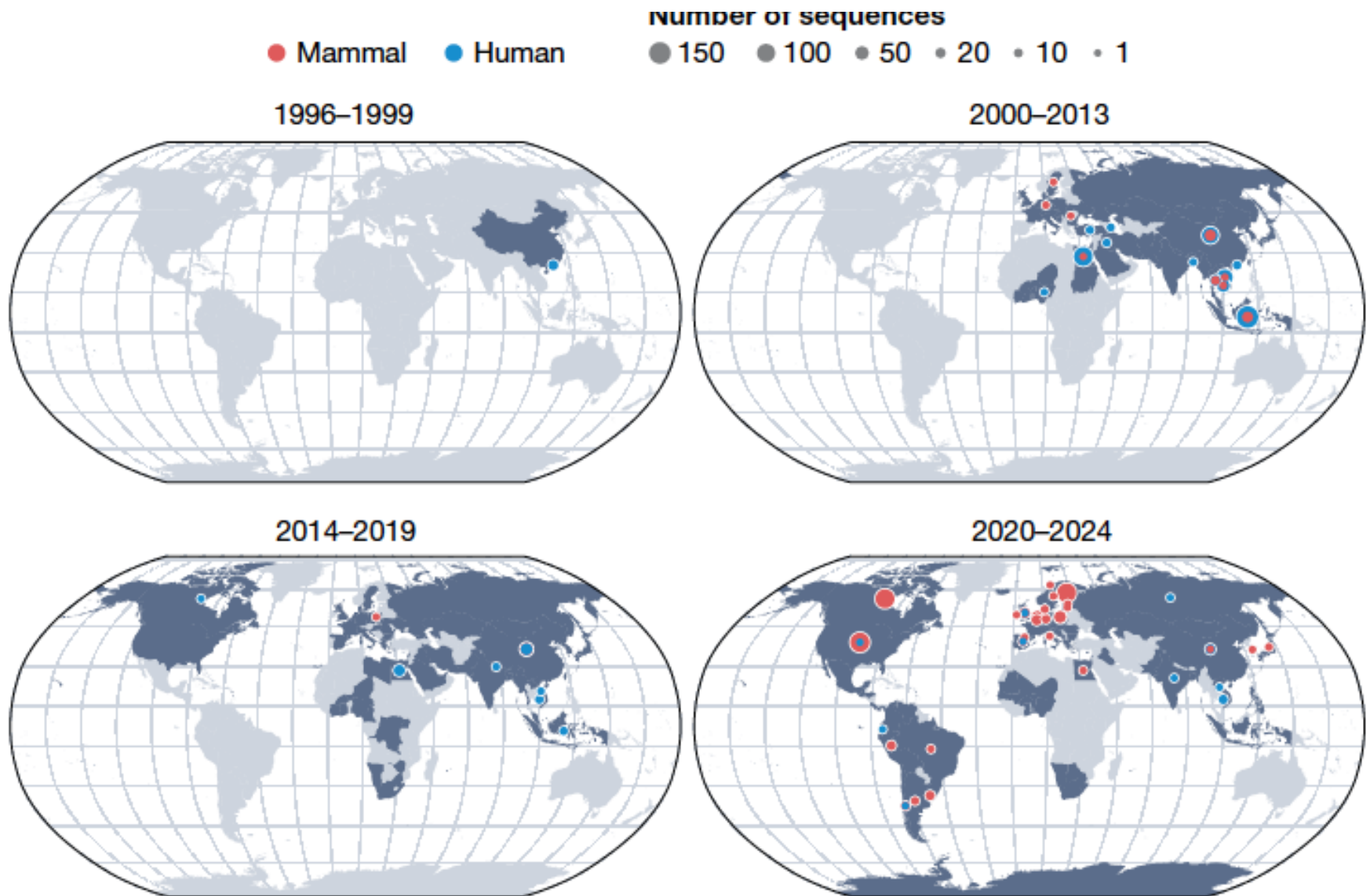
A new H5N1 virus belonging to clade 2.3.4.4b with a wild bird adapted N1 NA gene emerges. Clade 2.3.4.4b H5N1 viruses become predominant in Asia, Africa, Europe, and the Middle East by the end of 2021. The virus is detected in Canada and U.S. wild birds in late 2021. In February 2022, the virus begins causing outbreaks in U.S. commercial and backyard poultry. At this time, two human cases with current H5N1 bird flu viruses have been reported. One occurred in the United Kingdom in 2021 and one in the United States in 2022.

More information is available:

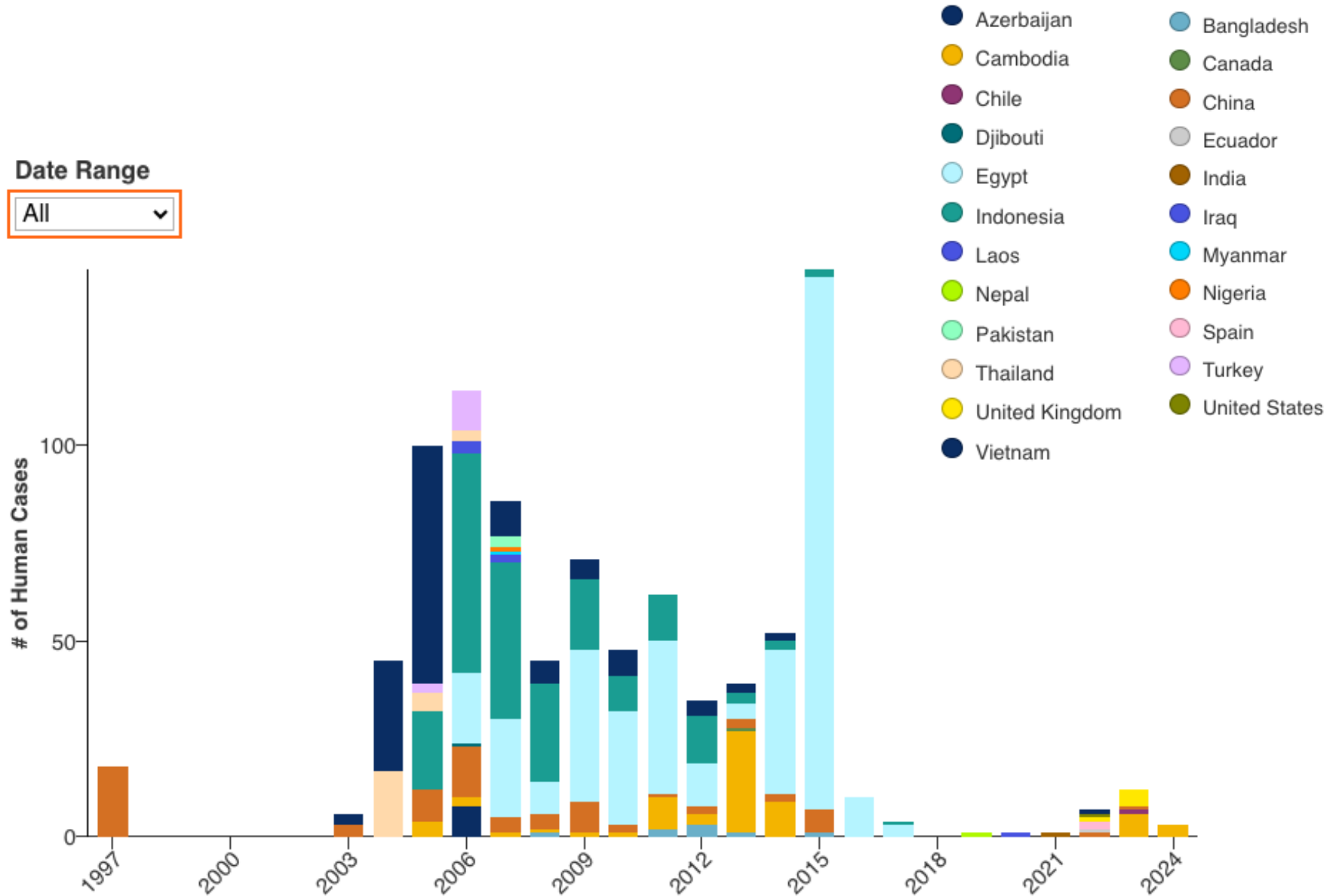
<https://www.cdc.gov/flu/avianflu/inhumans.htm>.



Extension géographique du H5N1



Cas humains de grippe aviaire H5N1 depuis 1997 (sources OMS/CDC)



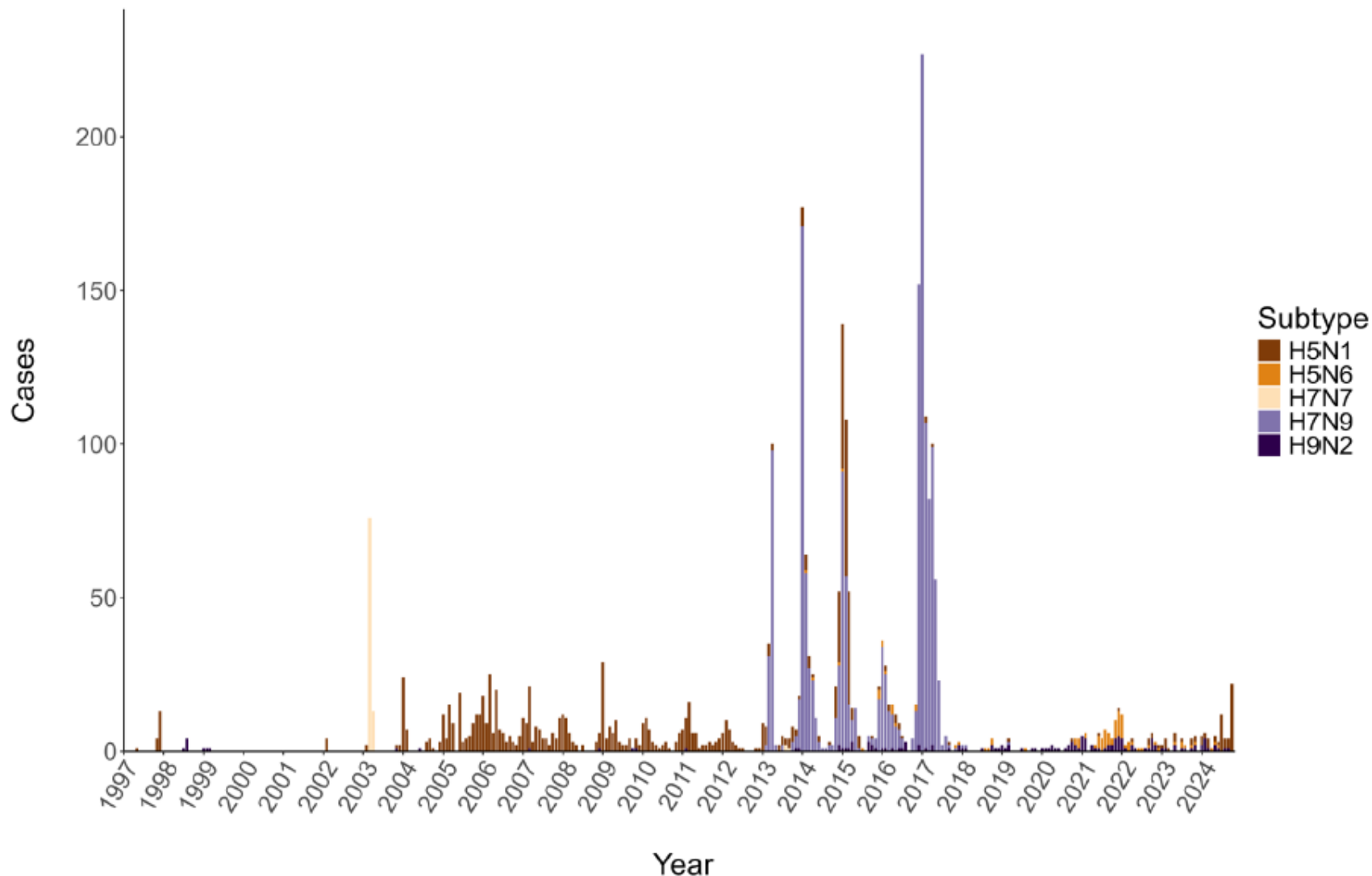


FIGURE 4 Distribution of reported cases of avian influenza virus in humans by the time of onset or detection from 1997 to 31 October 2024, including subtypes in which more than a total of 10 cases have been reported in humans. The figure includes detections of A(H5N1) due to suspected environmental contamination reported in 2022 (three detections) and 2023 (three detections, one inconclusive). Human cases of A(H5) cases epidemiologically linked to A(H5N1) outbreaks at poultry and dairy cattle farms in the USA in 2024 are included in the number of cases of A(H5N1).

TABLE 2 Reported cases or detections of avian influenza virus in humans for subtypes of zoonotic avian influenza for which human cases have been reported since 1 November 2021.

Subtype	Cases reported since first report						Cases reported 2021-11-01–2024-10-31		
	First report	Last reported	Cases reported <i>n</i>	Deaths		Reporting countries	Cases reported <i>n</i>	Deaths	
				<i>n</i>	%			<i>n</i>	%
A(H3N8)	2022	2023	3	1	33	1	3	1	33
A(H5N1)	1997	2024	954	464*	50*	24	71	8	11
A(H5N2)	2024	2024	1	1	100	1	1	1	100
A(H5N6)	2014	2024	93	36	39	2	42	15	36
A(H5N8)	2021	2021	7	0	0	1	0	0	0
A(H9N2)	1998	2024	142	2	1	10	48	1	2
A(H10N3)	2021	2024	3	0	0	1	2	0	0
A(H10N5)	2024	2024	1	1	100	1	1	1	100

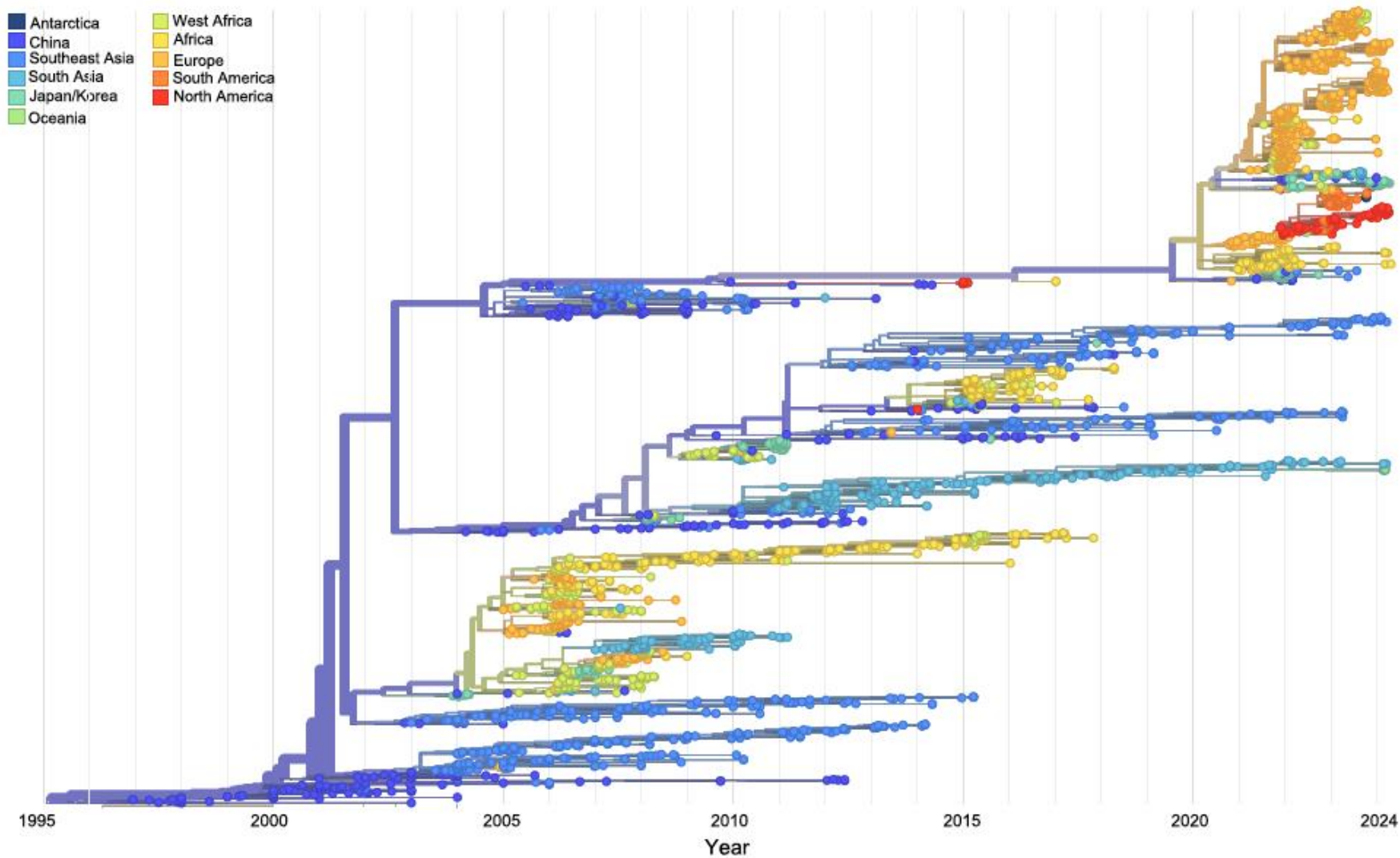


Figure 1. Phylogenetic tree of hemagglutinin sequences of H5N1 viruses. Tips are colored by the region in which the specimens were collected. Clade 2.3.3.4b viruses are shown in the upper right portion of the tree. Figure produced from Nextstrain [8, 9] with permission from Louise Moncla.

Génèse du premier réassortant H5N1 lignage 2.3.4.4b

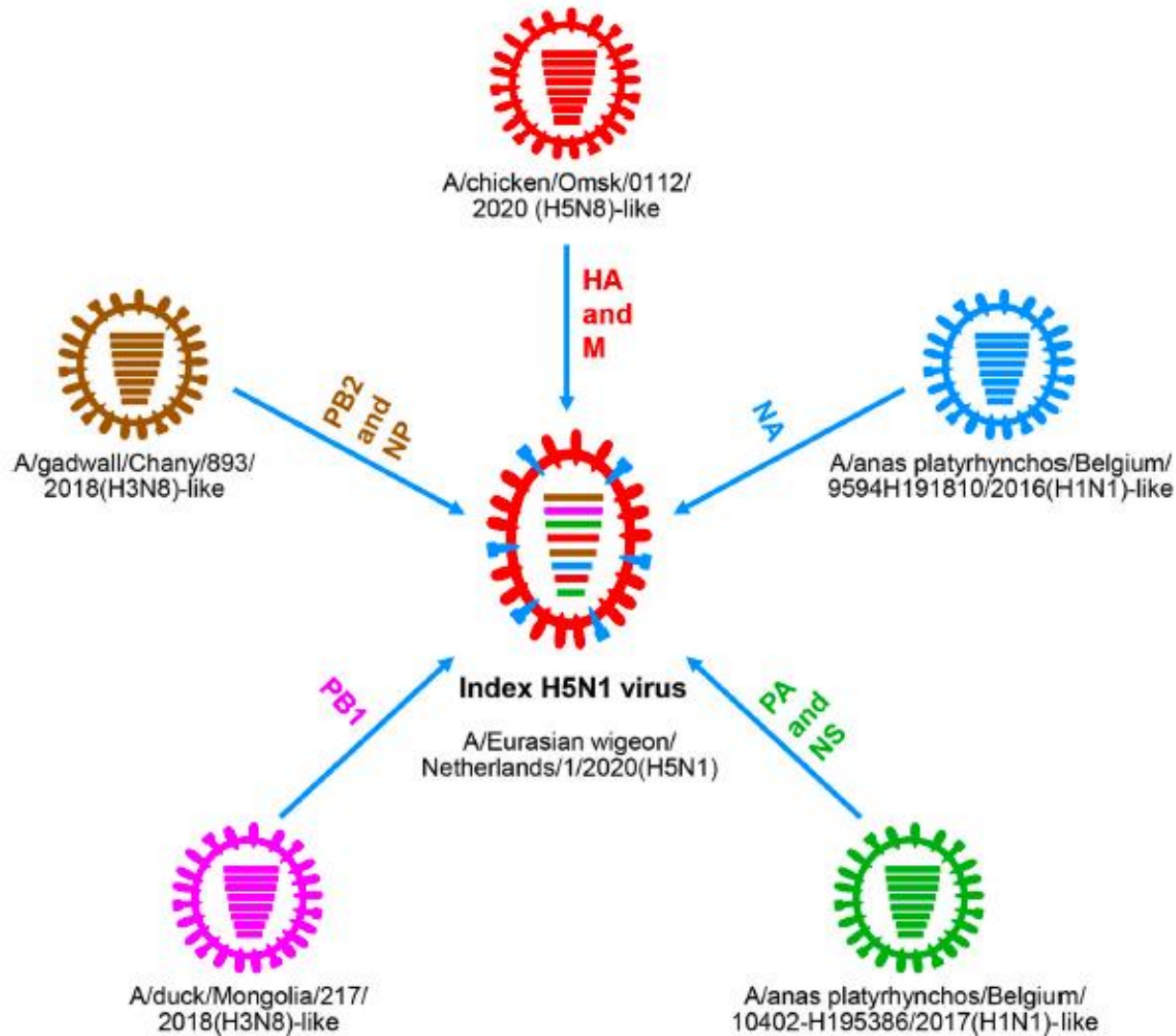
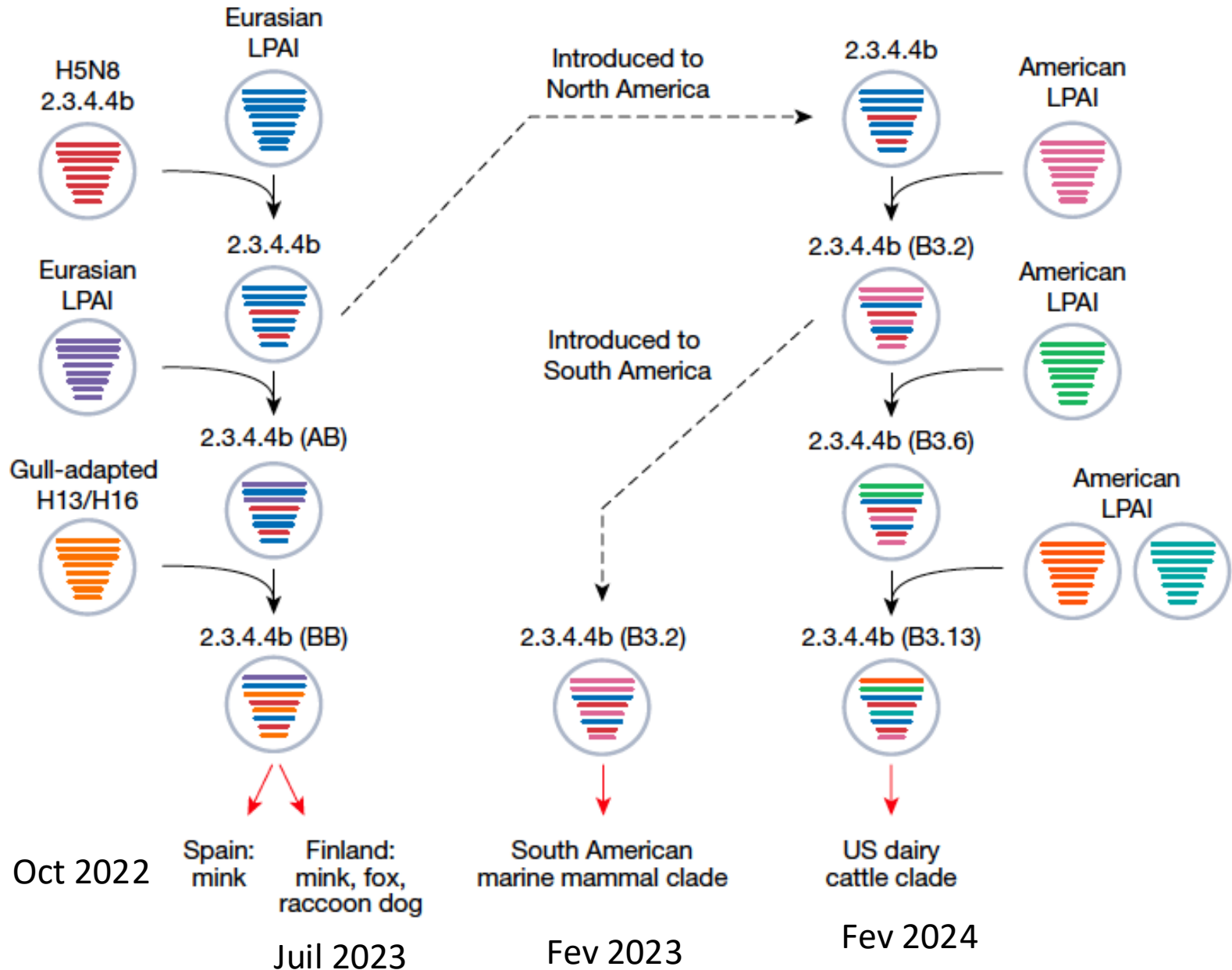


Figure 2. Formation of the index H5N1 virus bearing the 2.3.4.4b HA gene in 2020. The eight bars represent the eight gene segments (from top to bottom: PB2, PB1, PA, HA, NP, NA, M, and NS), and the colour of the bar indicates the closest donor strain of the gene segment.

4 passages significatifs vers les mammifères depuis 2020



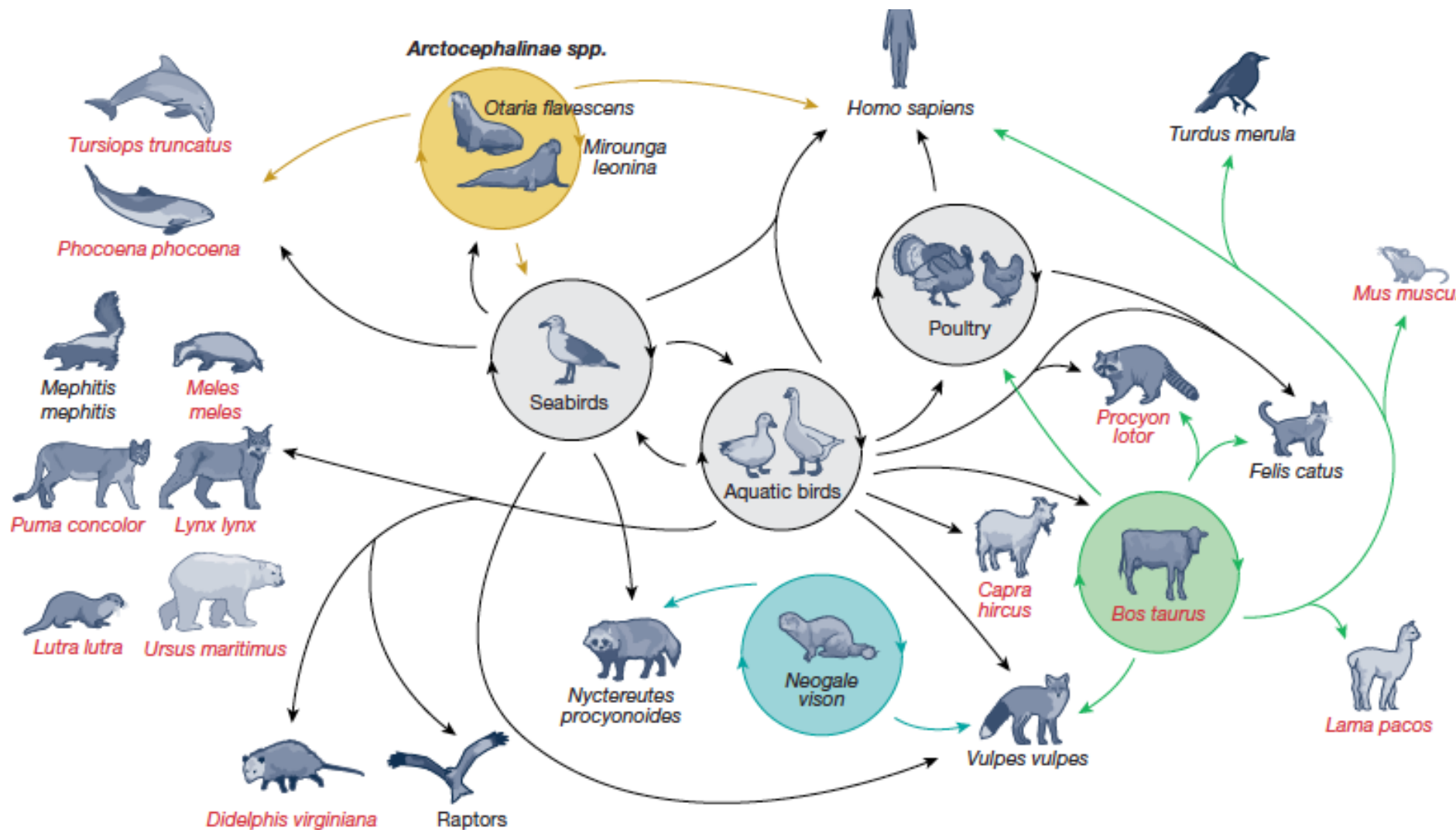
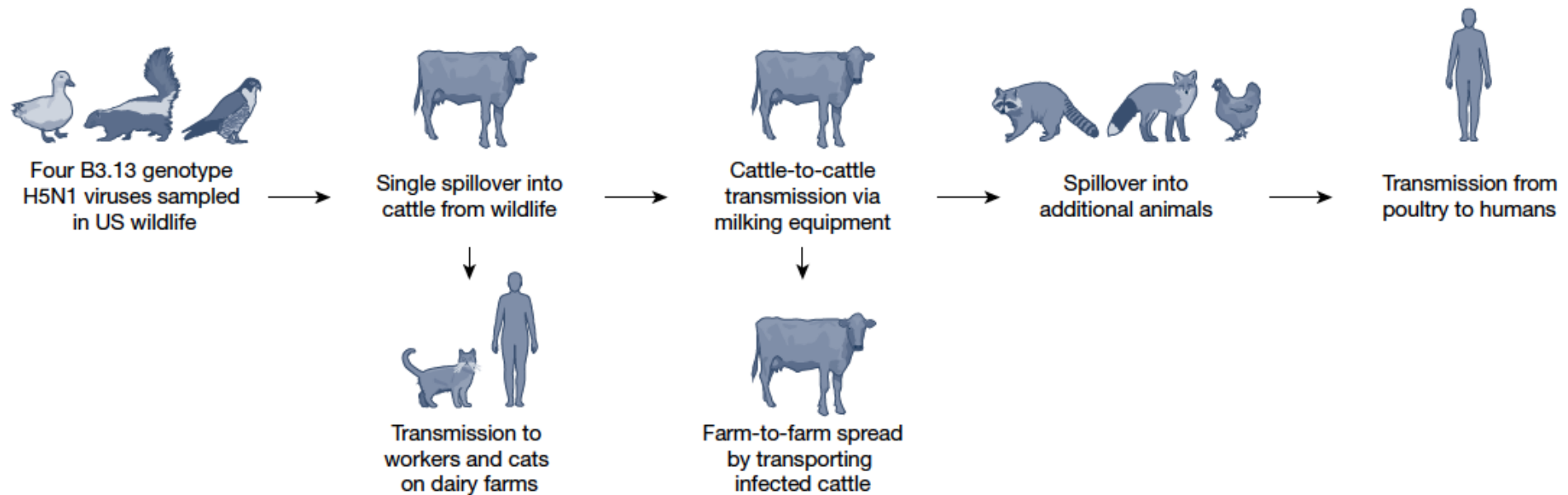


Fig. 2 | Multi-host ecology of H5N1 clade 2.3.4.4b since 2020. Wild aquatic

mammals), green (US dairy cattle) and blue (European mink), with arrows in

Transmissions lors de l'épizootie aux USA





H5 Bird Flu: Current Situation

National situation summary

Person-to-person spread

NONE

There is no known person-to-person spread at this time.

Current public health risk

LOW

The current public health risk is Low.

Cases in the U.S.

70 cases

Deaths in U.S.

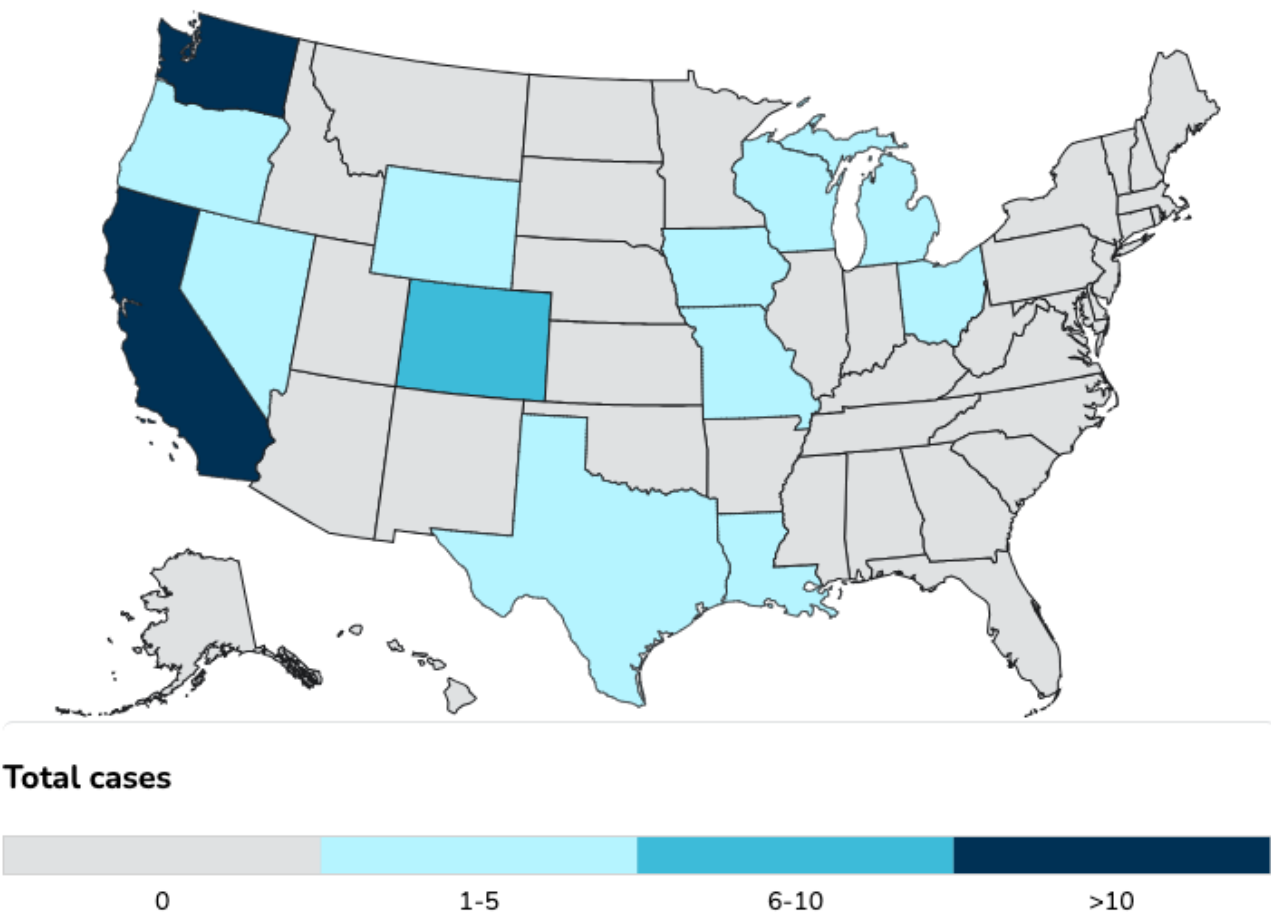
1 cases

National Total Cases: 70

Cases	Exposure Source
41	Dairy Herds (Cattle)*
24	Poultry Farms and Culling Operations*
2	Other Animal Exposure†
3	Exposure Source Unknown‡

NOTE: One additional case was previously detected in a poultry worker in Colorado in 2022. Louisiana reported the first H5 bird flu death in the U.S.

*Exposure Associated with Commercial Agriculture and Related Operations
†Exposure was related to other animals such as backyard flocks, wild birds, or other mammals
‡Exposure source was not able to be identified



La grippe zoonotique chez l'homme

- Contamination accidentelle d'un homme par un virus zoonotique, le plus souvent aviaire (= grippe aviaire)
- Dans la majorité des cas: transmission respiratoire
 - par contacts répétés et proches avec les déjections et sécrétions respiratoires des volailles infectées (pas de cas de contamination directe avec oiseaux sauvages)
 - Touche les sujets jeunes (médiane d'âge 14 ans)
 - Mortalité: 60% (délai infection-décès: 4-30 jours, médiane 12)
 - Dans plus de 50% des cas: insuffisance resp consécutive à une pneumopathie, diarrhées, lymphopénies, augmentation des transaminases
- Transmission au niveau de la conjonctive
 - Cas actuel pour H5N1 aux USA et antérieurement pour l'épizootie H7N7 en 2004 aux Pays-bas
 - Conjonctivite, pas de signes respiratoires => pas de caractère de gravité

Principales mutations permettant l'adaptation des virus aviaires à l'homme

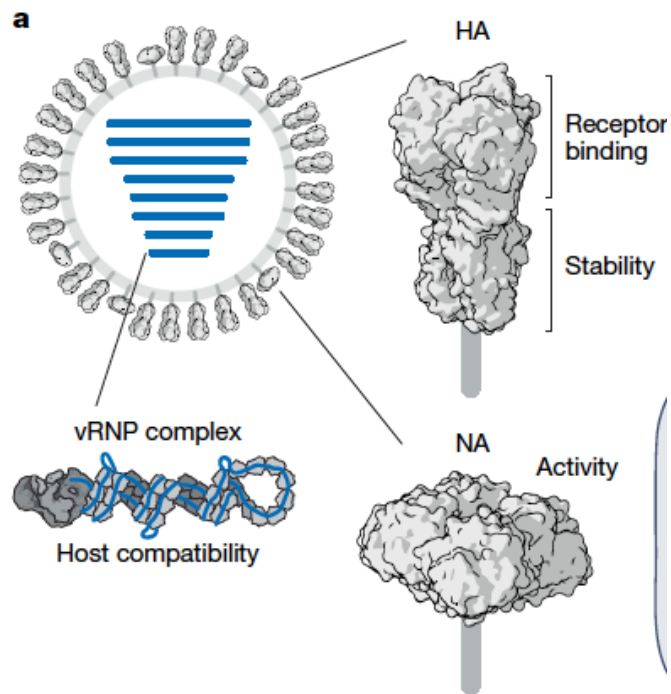
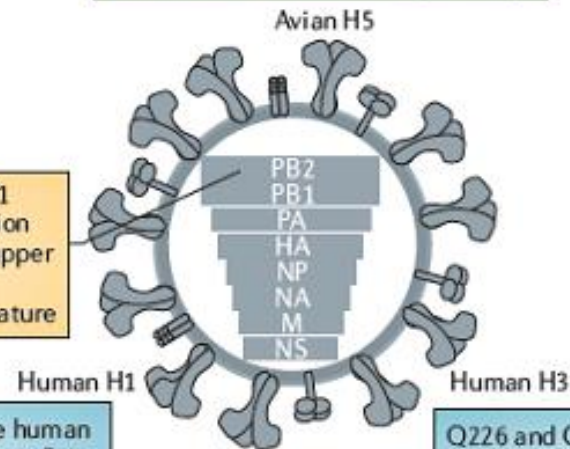


Fig. 5 | How IAVs adapt to new host species. a, Molecular fea

R143 and K186, or L226 and S228, or R196 or A160 change avian H5 from α -2,3-SA to α -2,6-SA specificity.

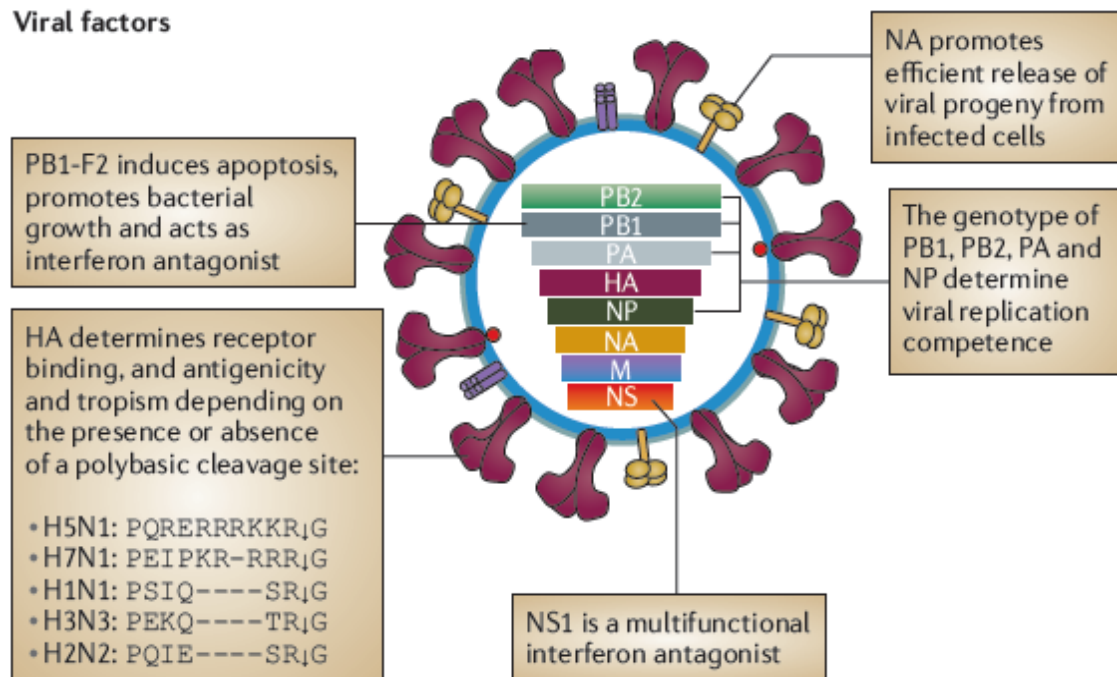
K627, N701 and R591 each confer replication competence in the upper respiratory tract at human body temperature

E190 and G225 together change human H1 from α -2,6-SA to α -2,3-SA specificity

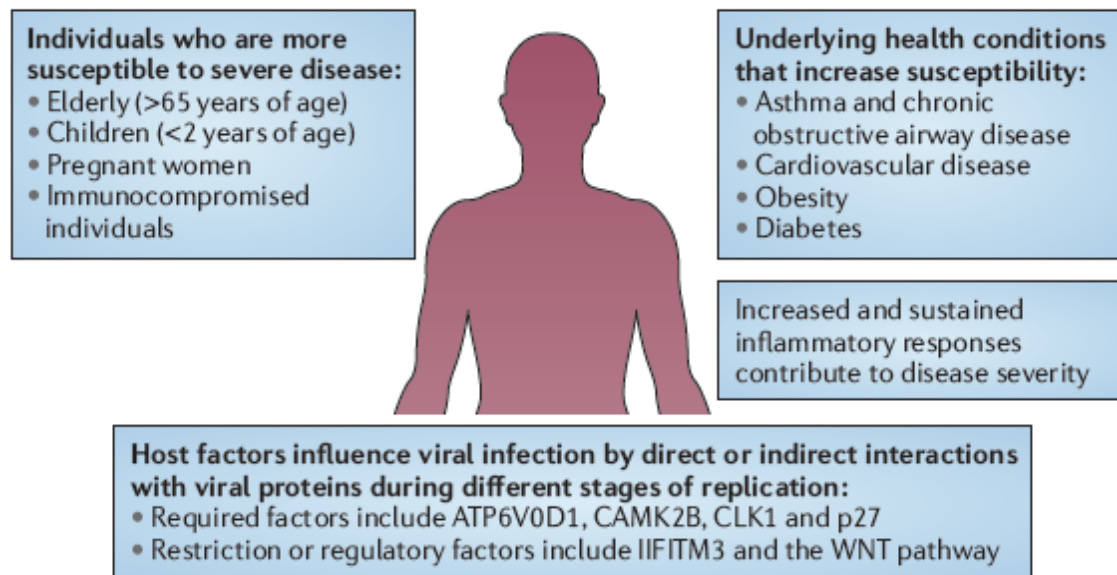


Q226 and G228 together change human H3 from α -2,6-SA to α -2,3-SA specificity

Viral factors



Host factors



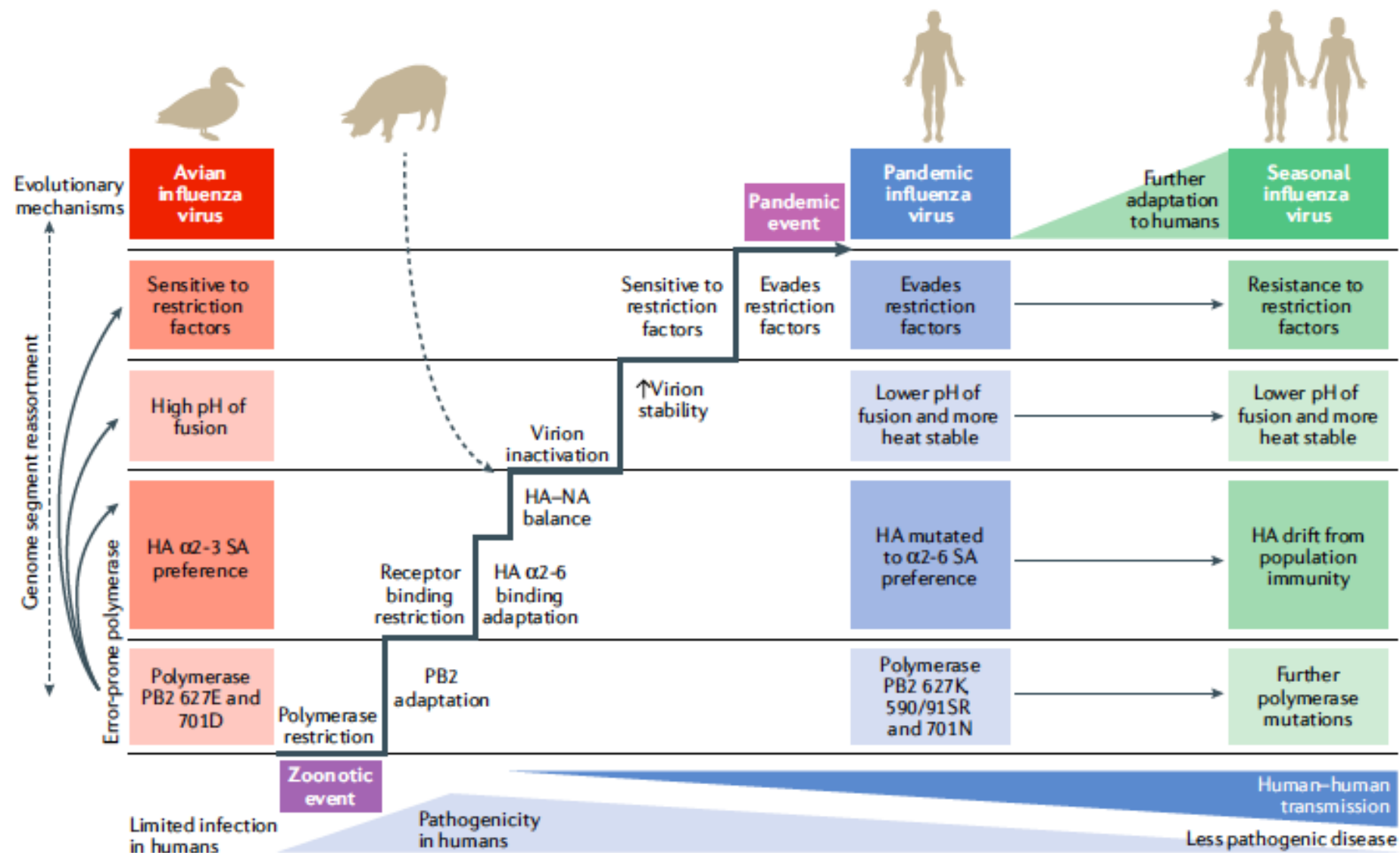


Fig. 4 | Cumulative influenza virus adaptations required to overcome species restriction and initiate a new pandemic. Influenza viruses circulating in the avian reservoir (red) face multiple host range barriers that must be overcome

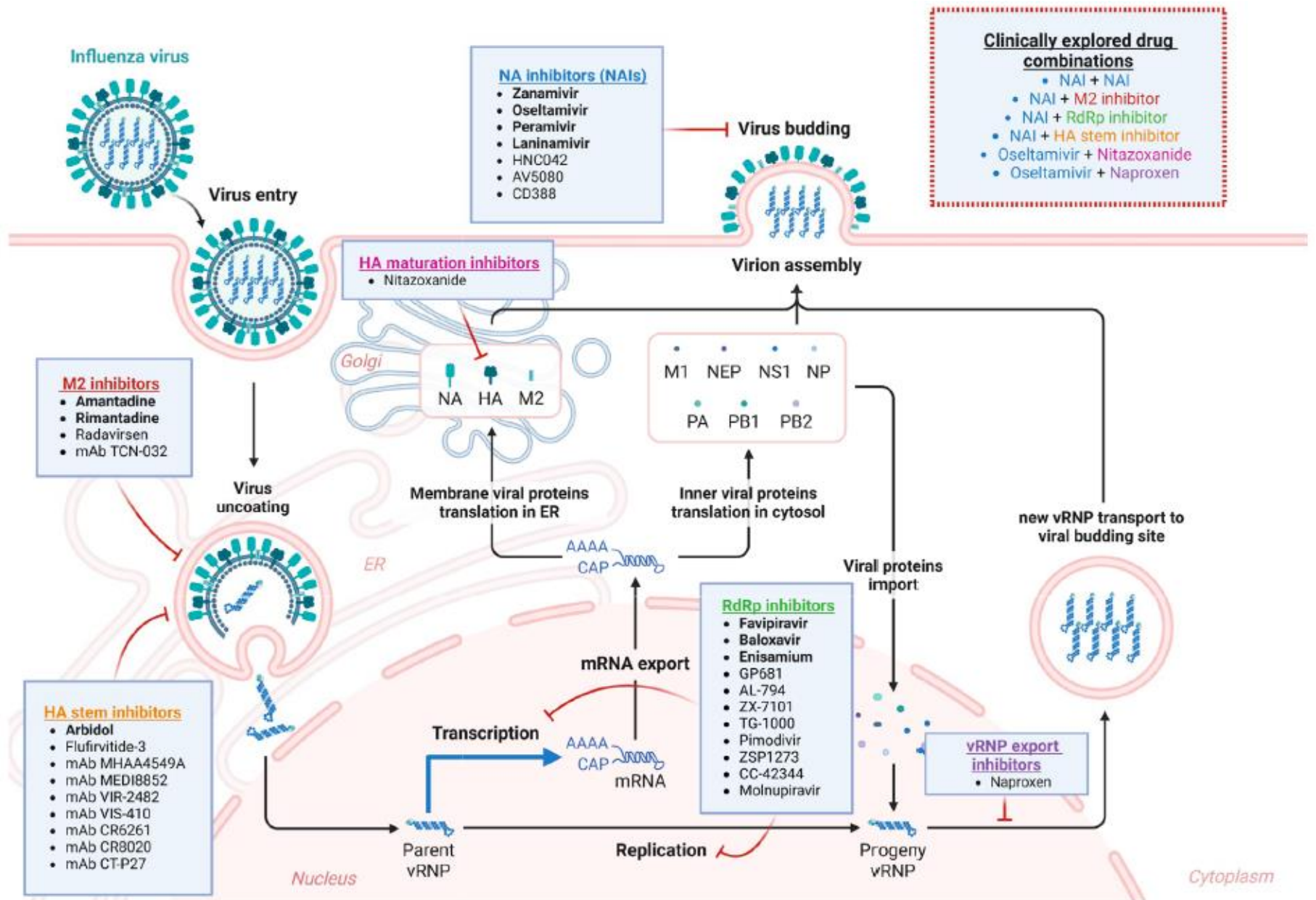


Fig. 1 Replication cycle of influenza virus and crucial steps targeted by virus-directed antiviral compounds. Drugs approved for the treatment of influenza virus infection are indicated in bold. In the inset, clinically evaluated drug combinations are reported (Figure created with BioRender)

Oral

Rimantadine, oseltamivir, baloxavir, favipiravir, arbidol, pimodivir, etc.

Intranasal

Flufirvitide-3

Inhalation

Zanamivir, laninamivir, aprotinin

Pulmonary delivery

Nanoparticle-based delivery systems

Intravenous

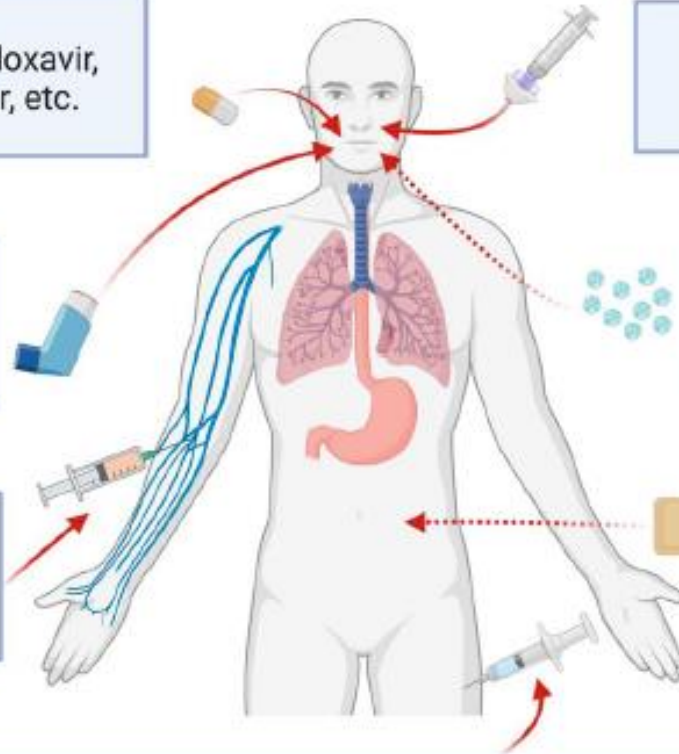
Zanamivir, peramivir, HNC042, mAb CR8020

Transdermal

Microneedle patches and hydrogel-based systems

Intramuscular, subcutaneous

mAb VIR-2482 and mAb CD388



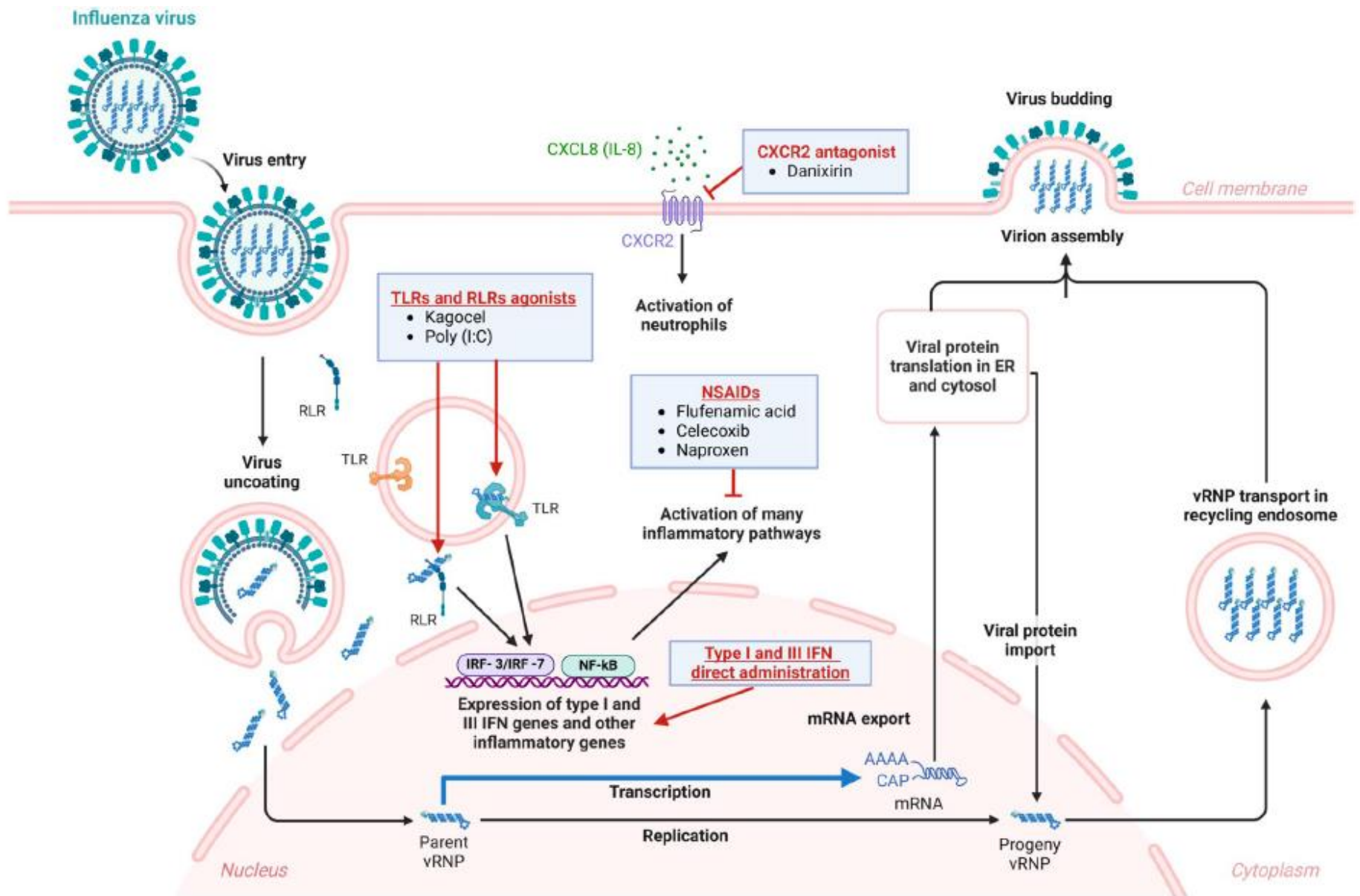
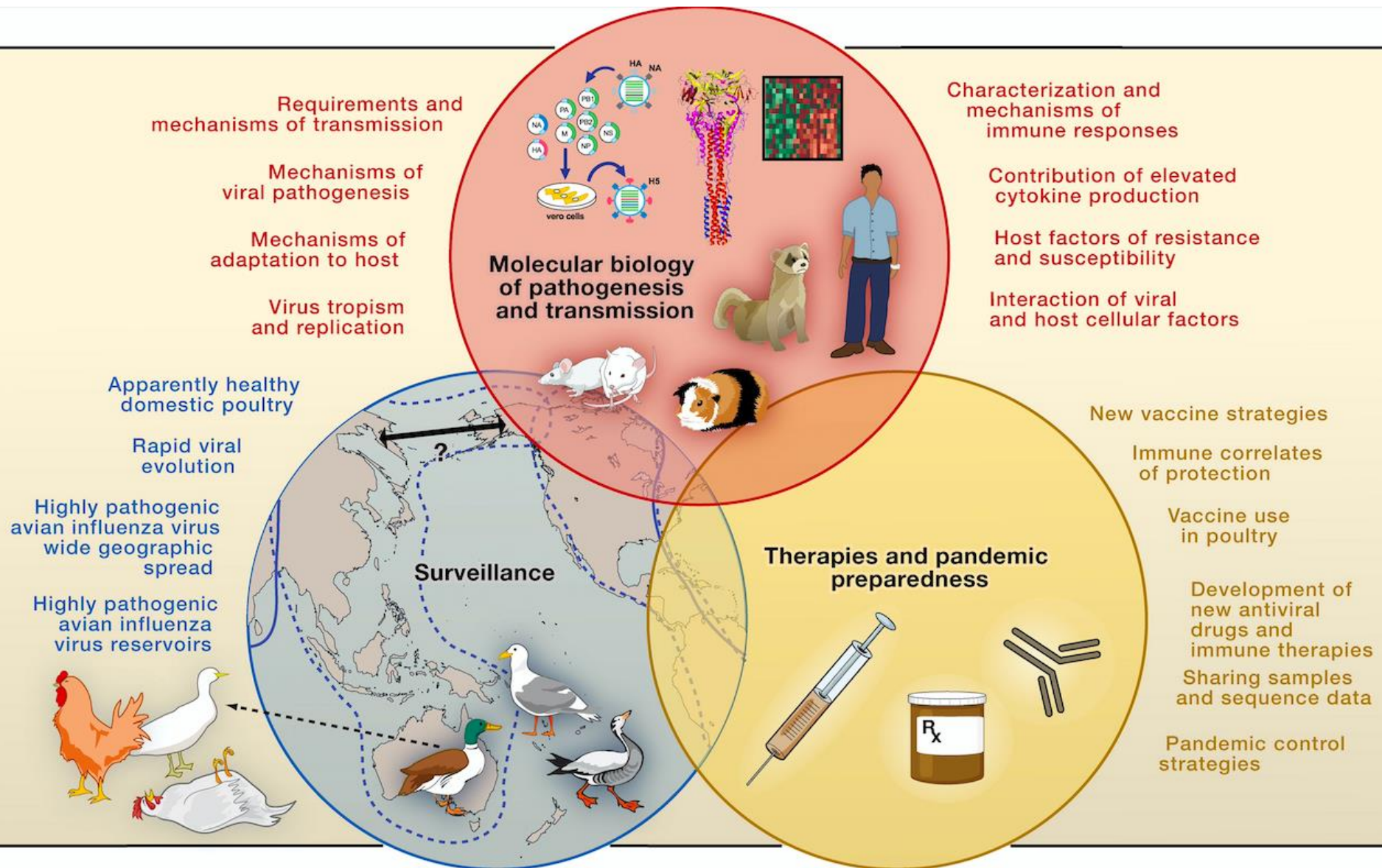
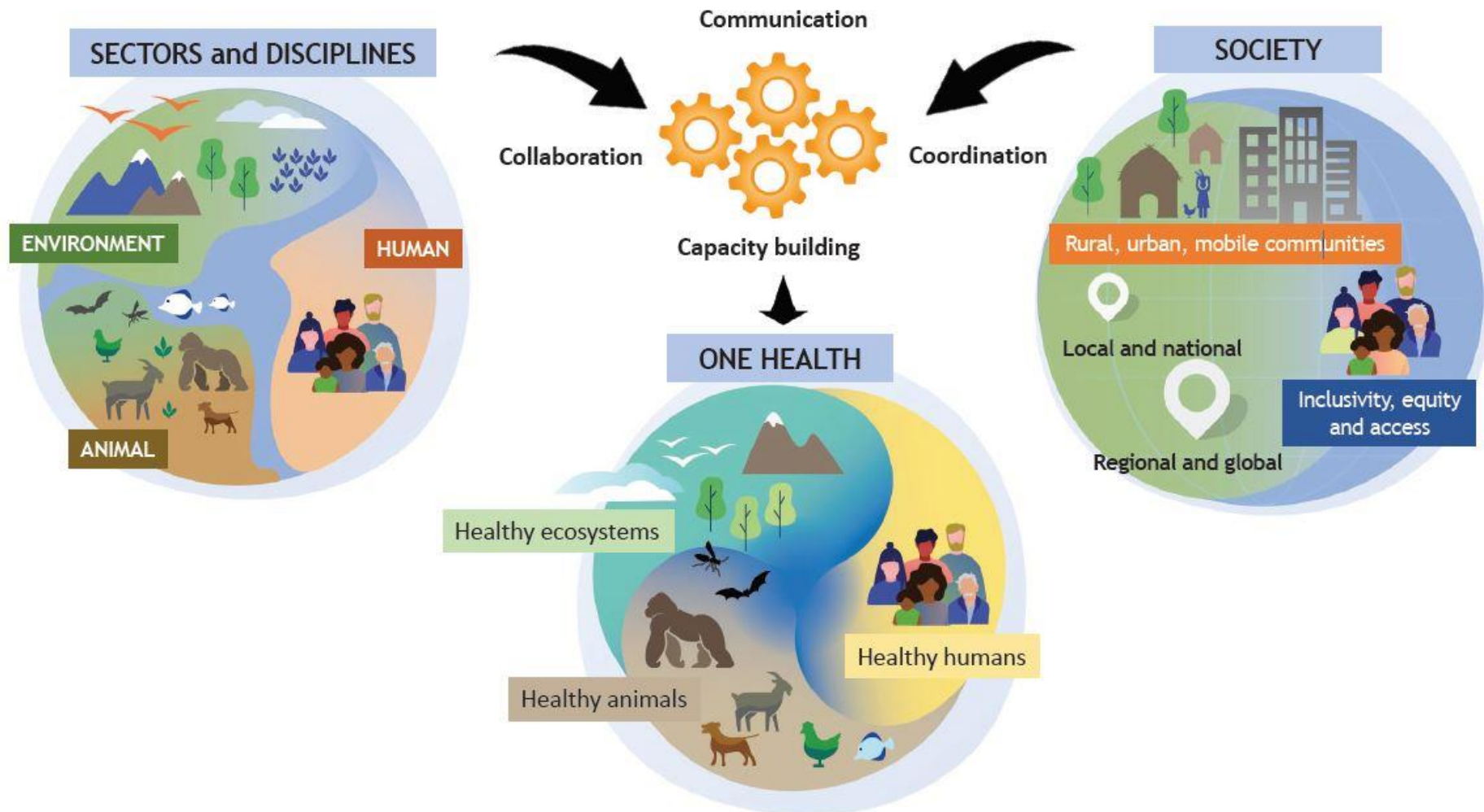


Fig. 3 Immunomodulatory and anti-inflammatory agents for the treatment of influenza virus infection. The four main classes of host-targeted immunomodulatory and anti-inflammatory agents repurposed for flu therapy are shown, along with the molecular targets and cell-

ular pathways that they modulate in the context of host cell immune response. *IFN* interferon, *NSAIDs* nonsteroidal anti-inflammatory drugs, *RLRs* RIG-I-like receptors, *TLRs* Toll-like receptors. (Figure created with BioRender)



Le concept « ONE HEALTH »



Quelques références!

The global H5N1 influenza panzootic in mammals

304 | Nature | Vol 637 | 9 January 2025

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The Journal of Infectious Diseases

ID TRANSLATIONAL SCIENCE UPDATE

JID 2024:230 (15 September) • 533

An Update on Highly Pathogenic Avian Influenza A(H5N1) Virus, Clade 2.3.4.4b

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SCIENTIFIC OPINION



Preparedness, prevention and control related to zoonotic avian influenza

EFSA Panel on Animal Health and Animal Welfare (AHAW)* | ECDC* | Julio Alvarez¹ |

Cellular and Molecular Life Sciences (2025) 82-75
<https://doi.org/10.1007/s00018-025-05611-1>

Cellular and Molecular Life Sciences

REVIEW



Antiviral strategies against influenza virus: an update on approved and innovative therapeutic approaches

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