奈良県臨床検査技師会 遺伝子染色体検査部門定期講習会

「え，鳥インフルエンザ？でもちょっと気になるかも…」

2023年7月20日~8月20日

使用上の注意点

- 本資料は個人利用のみ可能です。

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https://vbms.unl.edu/VDC/documents/HPAI_Cats.pdf

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INSTITUTE OF AGRICULTURE AND NATURAL RESOURCES
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VETERINARY DIAGNOSTIC CENTER

Highly Pathogenic Avian Influenza in Mammals: A Case Report of Two Domestic Cats

In January, an outdoor, adult, domestic longhaired cat presented to the University of Nebraska Veterinary Diagnostic Center for postmortem examination after a history of rapid decline with clinical signs of anorexia, recumbency, anisocoria, pyrexia, seizures, tremors, nystagmus, loss of proprioception, and hyperesthesia. Gross necropsy revealed only a few visible changes to the organs including pulmonary congestion and edema, mild pericardial transudative effusion, and a subtle darkening of areas of the cerebrocortical grey matter. Complete histopathology examination revealed necrotizing lesions in the kidney, liver, adrenal gland, and pancreas; encephalitis with patches of extensive neuronal degeneration and necrosis, particularly in the cerebral cortex; and edema, vessel congestion, and mild inflammation in the lung and epicardium. The lesions were recognized as suspicious for highly pathogenic avian influenza virus infection, which was confirmed with molecular diagnostics. The PCR Ct value for avian influenza in the brain of this cat was remarkably low (12), indicating a very large amount of virus in the brain, as consistent with an acute infection. Highly pathogenic avian influenza Eurasian strain H5N1 was verified by molecular assay at National Veterinary Services Laboratories (NVSL).

Three other outdoor domestic cats of this household were noted at risk, and one of them developed clinical signs shortly after the first affected cat. This cat was described as somnolent and had episodes of walking in circles (circling). The cat was responsive to stimuli and seemed to eat and drink normally. It lived 10 days with neurologic impairment, when the cat suddenly became laterally recumbent with continual tremors, necessitating

https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON476

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Influenza A(H5N1) in cats – Poland

Русский

16 July 2023

Situation at a glance

On 27 June 2023, the IHR National Focal Point of Poland notified WHO of unusual deaths in cats across the country. As of 11 July, 47 samples have been tested from 46 cats and one captive caracal, of which 29 were found to be positive for influenza A (H5N1). Fourteen cats are reported to have been euthanized, and a further 11 died, with the last death reported on 30 June. The source of the exposure of cats to the virus is currently unknown and epizootic investigations are ongoing.

Sporadic infection of cats with A(H5N1) has previously been reported, but this is the first report of a high numbers of infected cats over a wide geographical area within a country.

As of 12 July, no human contacts of A(H5N1) positive cats have reported symptoms, and the surveillance period for all contacts is now complete.

The risk of human infections following exposure to infected cats at the national level is assessed as **low for the general population**, and **low to moderate for cat owners and those occupationally exposed** to H5N1-infected cats (such as veterinarians) without the use of appropriate personal protective equipment.

WHO continues to monitor the situation and work in close collaboration with the animal and public health sectors, regional agencies, the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (WOAH), and other partner agencies in Poland.

Description of situation

See all DONs related to this event >

https://www.who.int/news/item/12-07-2023-ongoing-avian-influenza-outbreaks-in-animals-pose-risk-to-humans

Ongoing avian influenza outbreaks in animals pose risk to humans

Situation analysis and advice to countries from FAO, WHO, WOAH

12 July 2023 | Statement | Geneva/Paris/Rome | Reading time: 6 min (1743 words)

The current outbreaks of avian influenza (also called "bird flu") have caused devastation in animal populations, including poultry, wild birds, and some mammals, and harmed farmers' livelihoods and the food trade. Although largely affecting animals, these outbreaks pose ongoing risks to humans.

The Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO), and the World Organisation for Animal Health (WOAH) are urging countries to work together across sectors to save as many animals as possible and to protect people.

Avian influenza viruses normally spread among birds, but the increasing number of H5N1 avian influenza detections among mammals—which are biologically closer to humans than birds are—raises concern that the virus might adapt to infect humans more easily. In addition, some mammals may act as mixing vessels for influenza viruses, leading to the emergence of new viruses that could be more harmful to animals and humans.

The goose/Guangdong-lineage of H5N1 avian influenza viruses first emerged in 1996 and have been causing outbreaks in birds since then. Since 2020, a variant of these viruses belonging to the H5 clade 2.3.4.4b has led to an

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https://www.who.int/news/item/12-07-2023-ongoing-avian-influenza-outbreaks-in-animals-pose-risk-to-humans

- 鳥インフルエンザウイルスは通常、鳥類間で広がるが、哺乳類の間でのH5N1鳥インフルエンザの検出件数が増加しており、ウイルスが人間に容易に感染するように適応する可能性が懸念されている。
- さらに、一部の哺乳類はインフルエンザウイルスの混合容器となる可能性があり、動物や人間により有害な新しいウイルスの発生を引き起こす可能性がある。

https://www.who.int/news/item/12-07-2023-ongoing-avian-influenza-outbreaks-in-animals-pose-risk-to-humans

- H5N1鳥インフルエンザウイルスのGoose/Guangdong系統は1996年に初めて現れ、それ以来鳥類の発生を引き起こしてきた。
- 2020年以降、このウイルスのH5クレード2.3.4.4bに属する変異株がアフリカ、アジア、ヨーロッパの多くの国で野鳥や家禽の前例のない数の死亡を引き起こしており、2021年には北アメリカに、2022年には中南米にも広がった。

https://www.who.int/news/item/12-07-2023-ongoing-avian-influenza-outbreaks-in-animals-pose-risk-to-humans

- 2022年には、5大陸の67か国がWOAHに家禽や野鳥でのH5N1高病原性鳥インフルエンザの発生を報告し、被害を受けた農場や村での死亡または殺処分により1億3100万羽以上の家禽が失われた。
- 2023年には、主にアメリカ大陸で病気が広がり、別の14か国が発生を報告した。
- インフルエンザA(H5N1)クレード2.3.4.4bウイルスによる野鳥の大量死の事例も報告されている。

https://www.who.int/news/item/12-07-2023-ongoing-avian-influenza-outbreaks-in-animals-pose-risk-to-humans

哺乳類における鳥インフルエンザの最近の発生拡大の監視

- 哺乳類の致命的な発生が増加しているとの報告がある。
- スペインの養殖ミンク、アメリカ合衆国のアシカ、ペルーとチリのアシカなど、陸上および海洋の哺乳類が影響を受けており、2022年以降、少なくとも10か国で26種が影響を受けたことが確認されている。
- 鳥インフルエンザが新たな地理的地域に広がり、野鳥の異常な大量死や哺乳類の発生が懸念される急激な増加が見られている。

https://www.who.int/news/item/12-07-2023-ongoing-avian-influenza-outbreaks-in-animals-pose-risk-to-humans

人間へのリスクの評価

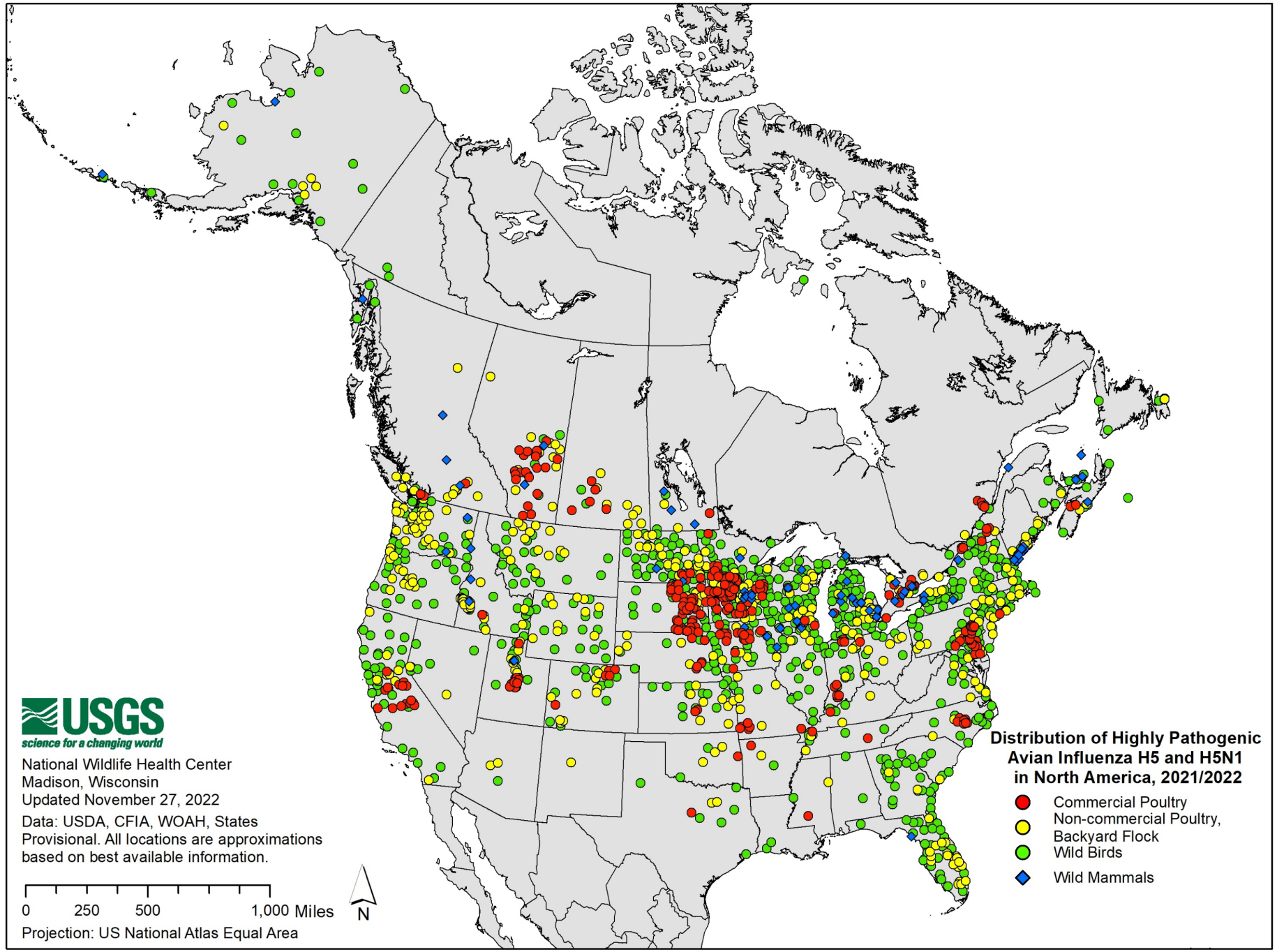
- 人間へのインフルエンザA(H5N1)クレード2.3.4.4bウイルスの散発的な検出も報告されていますが、非常にまれであり、2021年12月以降の報告は8例のみ。
- 人間への感染は高い致死率を伴う重篤な疾患を引き起こすことがある。
- 現時点で検出された人間の症例は、主に感染鳥との密接な接触や汚染された環境と関連している。
- 現時点で利用可能な情報によれば、このウイルスは容易に人から人への感染は起こらないが、そのような変化をもたらす可能性のあるウイルスの進化を識別するために警戒が必要。

https://www.who.int/news/item/12-07-2023-ongoing-avian-influenza-outbreaks-in-animals-pose-risk-to-humans

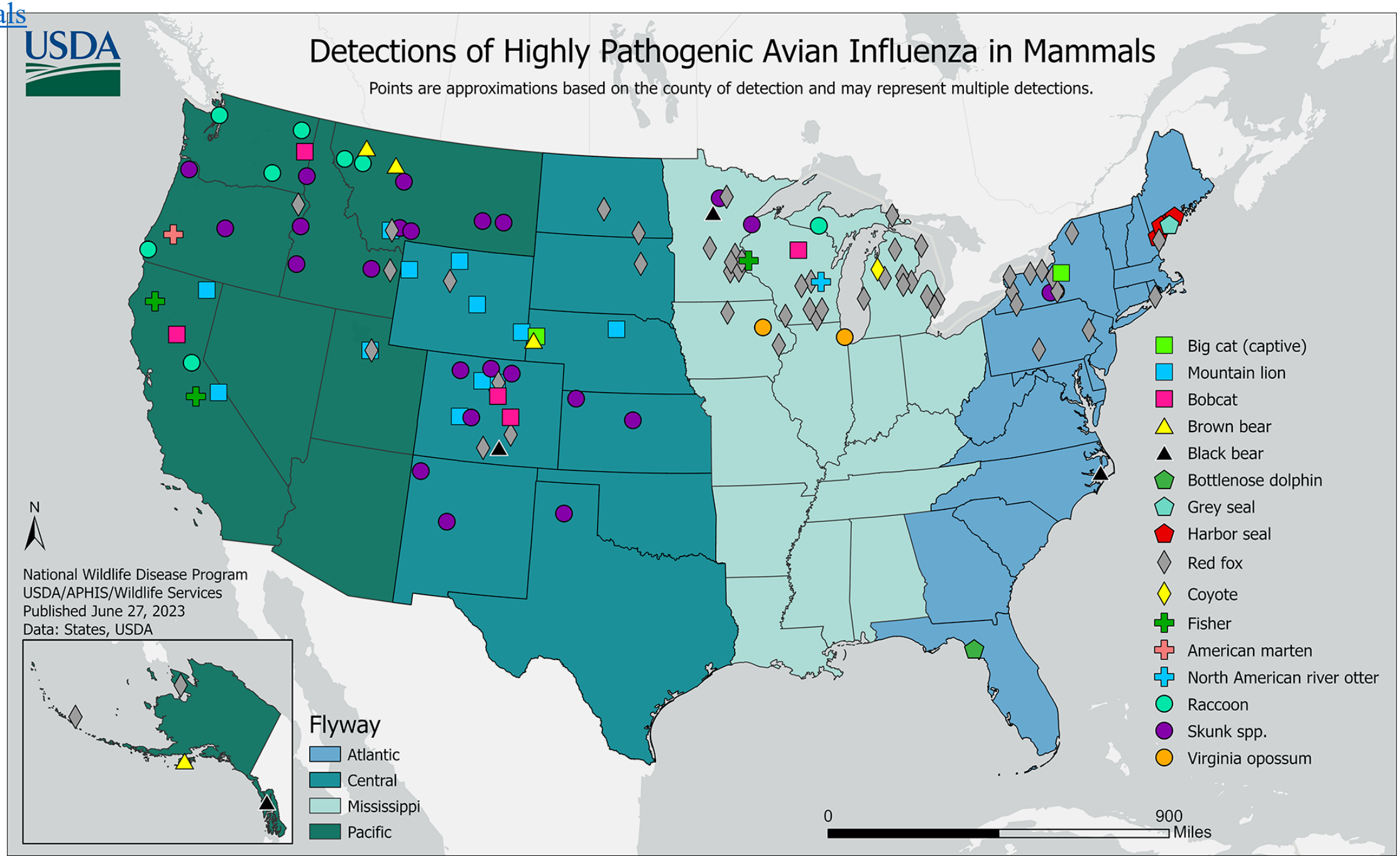
人間へのリスクの評価

- 現在、哺乳類を含む、より容易にウイルスが拡散するのを助ける可能性のあるウイルスの変異を特定するための研究が進行している。
- FAOでは、危険評価と疾病制御のための分子疫学のモニタリングおよび遺伝子配列の迅速な共有の必要性に注意を喚起してる。

https://www.usgs.gov/media/images/distribution-highly-pathogenic-avian-influenza-h5-and-h5n1-north-america-20212022



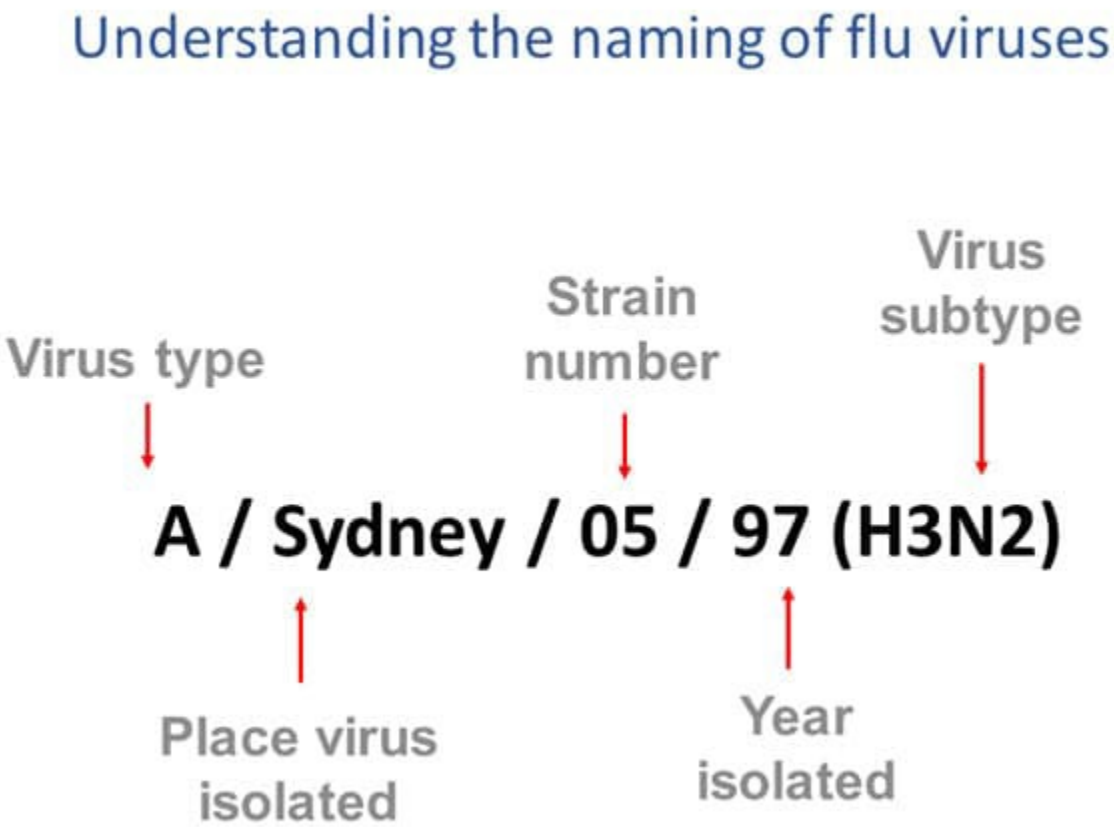
https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-disease-information/avian/avian-influenza/hpai-2022/2022-hpai-mammals



The negative-stranded ssRNA viruses

Mononegavirales				
	Bornaviridae		*Bornavirus*	*Borna disease virus*
	Rhabdoviridae		*Vesiculovirus*	*Vesicular stomatitis Indiana virus*
			Lyssavirus	*Rabies virus*
			Ephemerovirus	*Bovine ephemeral fever virus*
			Novirhabdovirus	*Infectious hematopoietic necrosis virus*
			Cytorhabdovirus	*Lettuce necrotic yellows virus*
			Nucleorhabdovirus	*Potato yellow dwarf virus*
	Filoviridae		*Marburgvirus*	*Lake Victoria marburgvirus*
			Ebolavirus	*Zaire ebolavirus*
	Paramyxoviridae	*Paramyxovirinae*		
			Rubulavirus	*Mumps virus*
			Avulavirus	*Newcastle disease virus*
			Respirovirus	*Sendai virus*
			Henipavirus	*Hendra virus*
			Morbillivirus	*Measles virus*
		Pneumovirinae		
			Pneumovirus	*Human respiratory syncytial virus*
			Metapneumovirus	*Avian metapneumovirus*
	Unassigned		*Varicosavirus*	*Lettuce big-vein associated virus*
			Ophiovirus	*Citrus psorosis virus*
	Orthomyxoviridae		*Influenzavirus A*	*Influenza A virus*
			Influenzavirus B	*Influenza B virus*
			Influenzavirus C	*Influenza C virus*
			Thogotovirus	*Thogoto virus*
			Isavirus	*Infectious salmon anemia virus*
	Bunyaviridae		*Orthobunyavirus*	*Bunyamwera virus*
			Hantavirus	*Hantaan virus*
			Nairovirus	*Dugbe virus*
			Phlebovirus	*Rift Valley fever virus*
			Tospovirus	*Tomato spotted wilt virus*
	Unassigned		*Tenuivirus*	*Rice stripe virus*
	Arenaviridae		*Arenavirus*	*Lymphocytic choriomeningitis virus*

https://www.cdc.gov/flu/avianflu/timeline/avian-timeline-background.htm

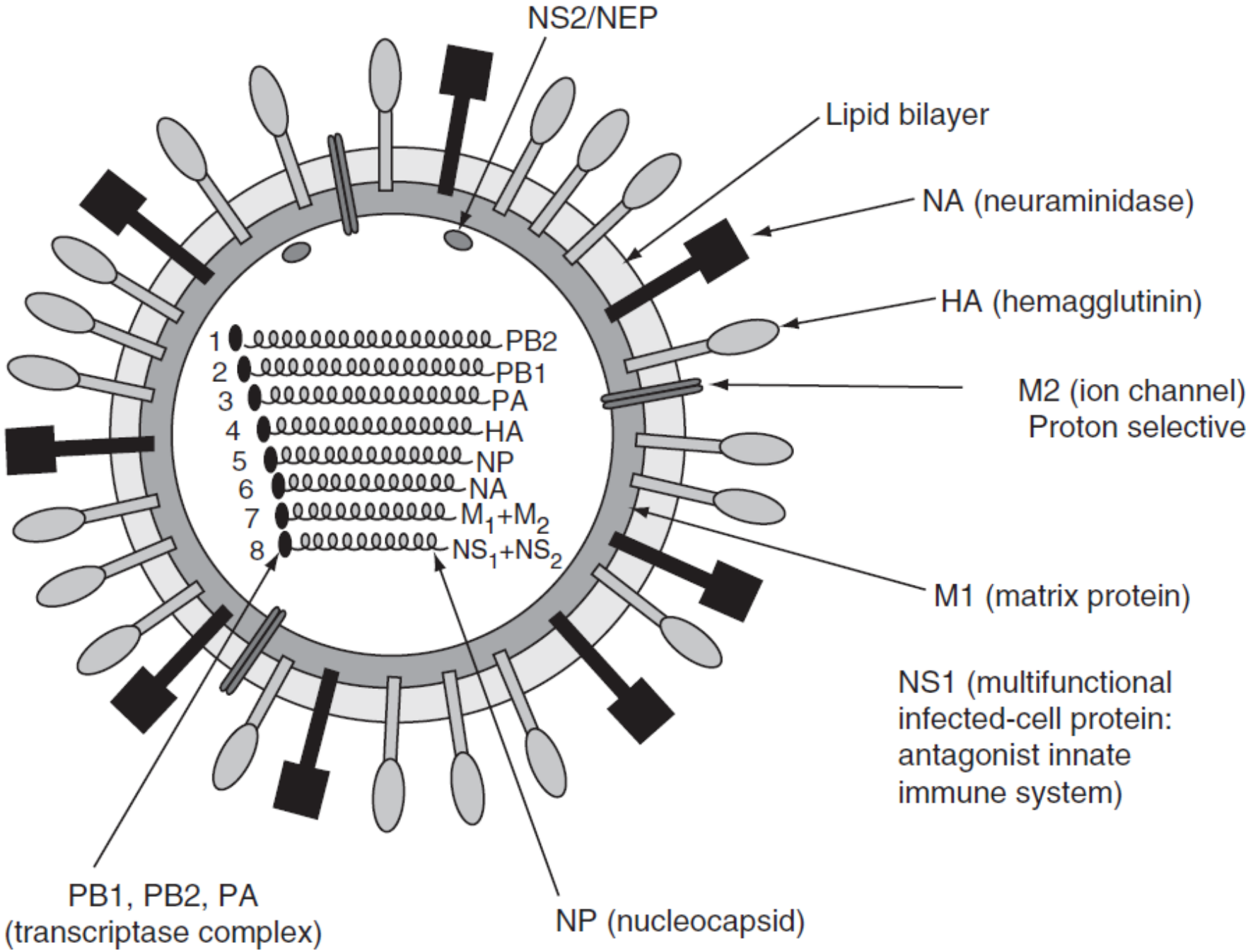


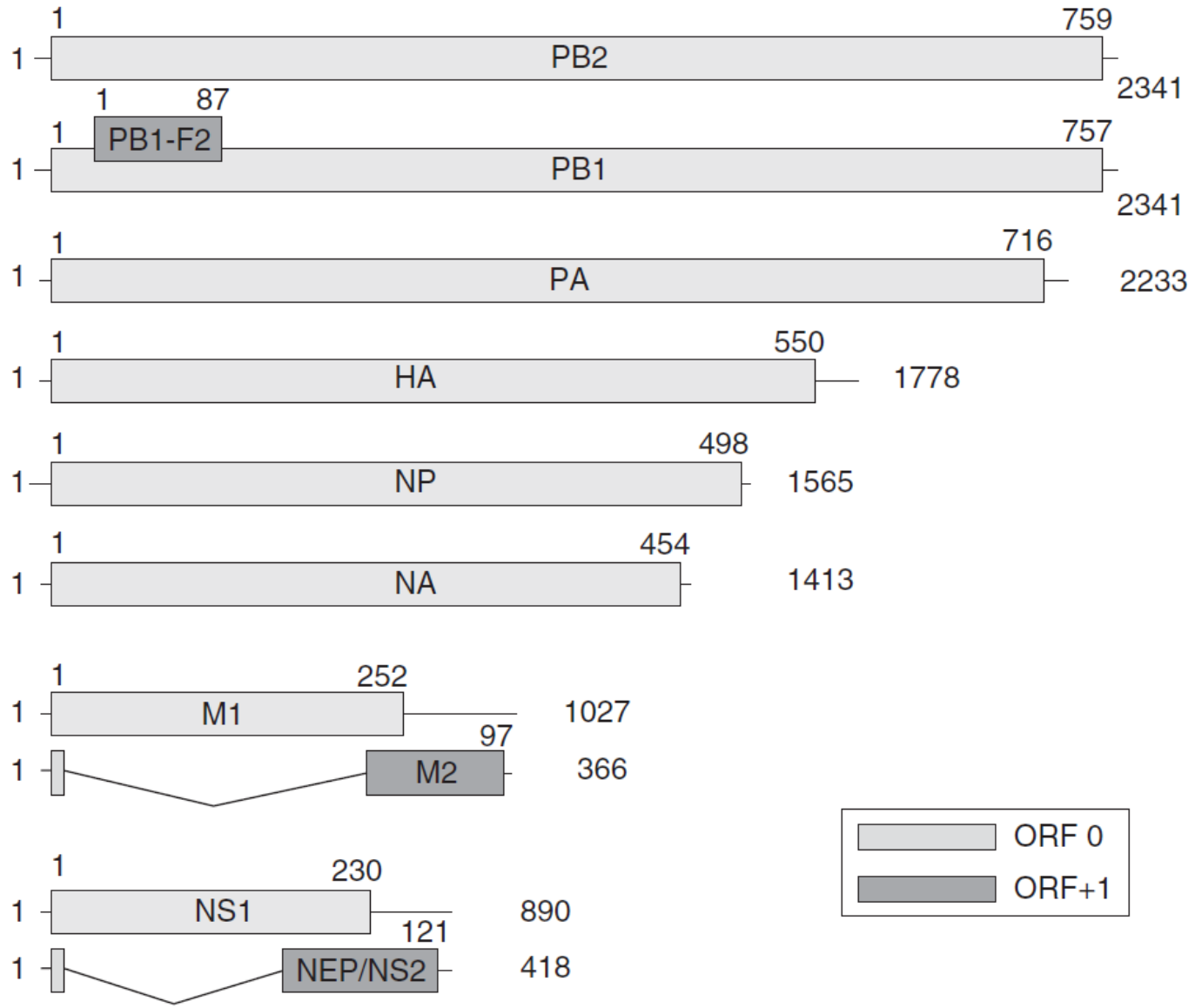
Bulletin of the World Health Organization, 58 (4): 585-591 (1980)

A revision of the system of nomenclature for influenza viruses: a WHO Memorandum*

In February 1980, the World Health Organization convened a meeting to consider information relevant to the nomenclature of influenza viruses and to make definitive proposals for the revision of the system which has been in use since 1971. The WHO recommendations are based on data derived from double immunodiffusion reactions involving haemagglutinin and neuraminidase antigens. The revised system of nomenclature is similar to the 1971 system in that it consists of two parts: (a) a type and strain designation, and (b) for influenza A viruses, a description of the antigenic specificity (subtype) of the surface antigens (H and N). The strain designation for influenza virus types A, B, and C contains information on the antigenic type of the virus (based on the antigenic specificity of the nucleoprotein), the host of origin (for strains isolated from non-human sources), geographical origin, strain number, and year of isolation. For influenza A viruses, the antigenic description, in parentheses, follows the strain designation and comprises two indices describing the antigenic subtype of the haemagglutinin and of the neuraminidase antigens. For the influenza A viruses from all species, the H antigens are grouped into 12 subtypes, H1–H12, while the N antigens are divided into 9 subtypes, N1–N9. Reference strains of influenza viruses are maintained by the WHO Collaborating Centres for Reference and Research on Influenza and the WHO Centres for the Study of Influenza Ecology in Animals,

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2395936/


NS2/NEP
Lipid bilayer
NA (neuraminidase)
HA (hemagglutinin)
M2 (ion channel)
Proton selective
1 PB2
2 PB1
3 PA
4 HA
5 NP
6 NA
7 M1+M2
8 NS1+NS2
M1 (matrix protein)
NS1 (multifunctional
infected-cell protein:
antagonist innate
immune system)
PB1, PB2, PA
(transcriptase complex)
NP (nucleocapsid)



PB2: Component of RNA polymerase, cap recognition

PB1-F2: Pro-apoptotic activity

PB1: Component of RNA polymerase, endonuclease activity, elongation

PA: Component of RNA polymerase, protease

HA: Surface glycoprotein, receptor binding, fusion activity, major antigen

NP: RNA binding, RNA synthesis, RNA nuclear import

NA: Surface glycoprotein, neuraminidase activity, major antigen

M1: Matrix protein, interaction with vRNPs and surface glycoproteins, nuclear export, budding

M2: Membrane protein, ion channel activity, assembly

NS1: Multifunctional protein, viral IFN antagonist

NEP/NS2: Nuclear export of vRNPs

Figure 3 Genome structure of influenza A/Puerto Rico/8/34 virus. RNA segments (in nucleotides) shown in positive sense and their encoded proteins (in amino acids). The lines at the 5′ and 3′ termini represent the noncoding regions. The PB1 segment contains a second ORF in the +1 frame resulting in the PB1-F2 protein. The M2 and NEP/NS2 proteins are encoded by spliced mRNAs (the introns are indicated by the V-shaped lines). Adapted from Palese P and Shaw ML (2006) *Orthomyxoviridae*: The viruses and their replication. In: Knipe DM and Howley PM (eds.) *Fields Virology*, 5th edn., pp. 1647–1689. Philadelphia, PA: Lippincott Williams and Wilkins.

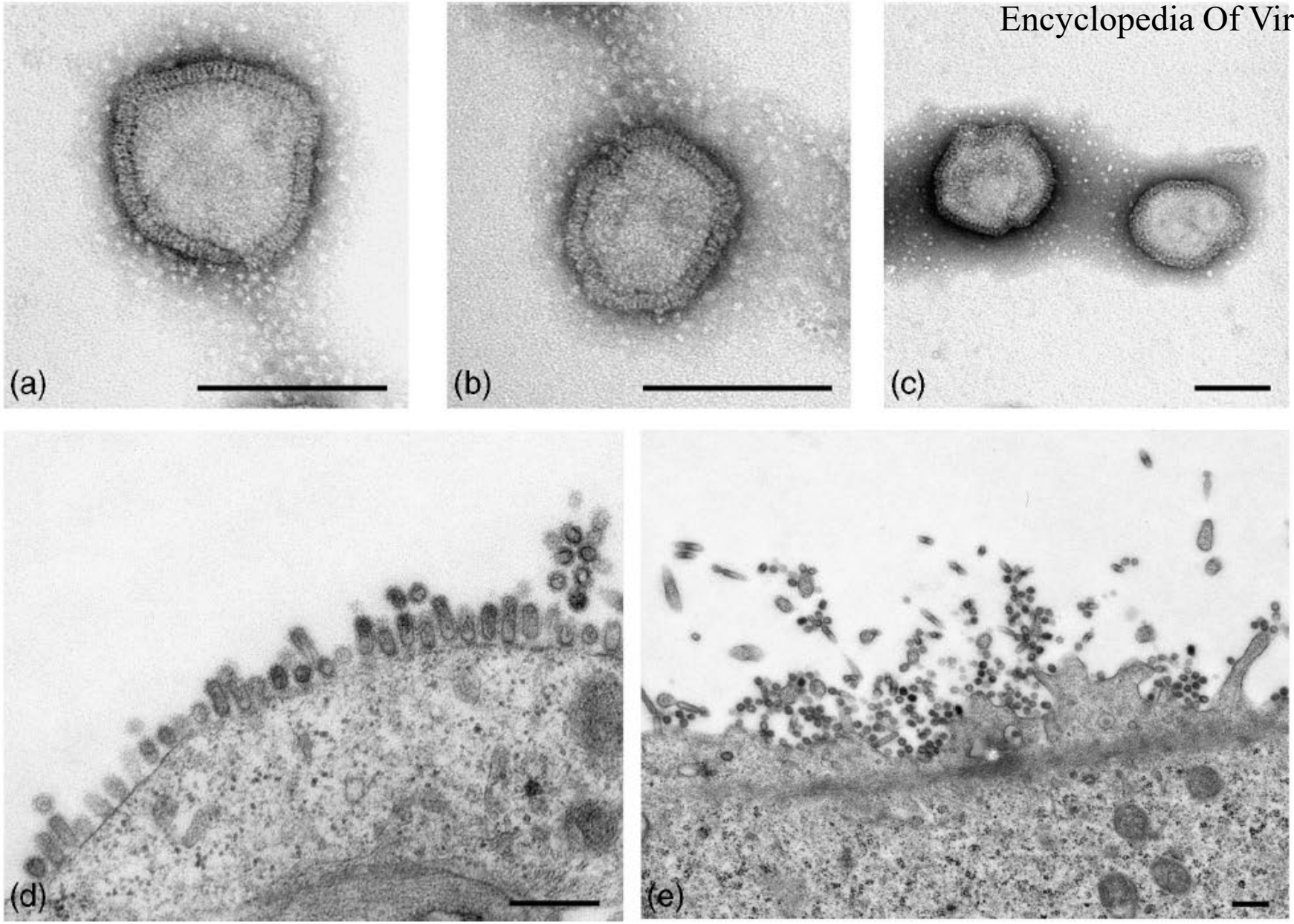
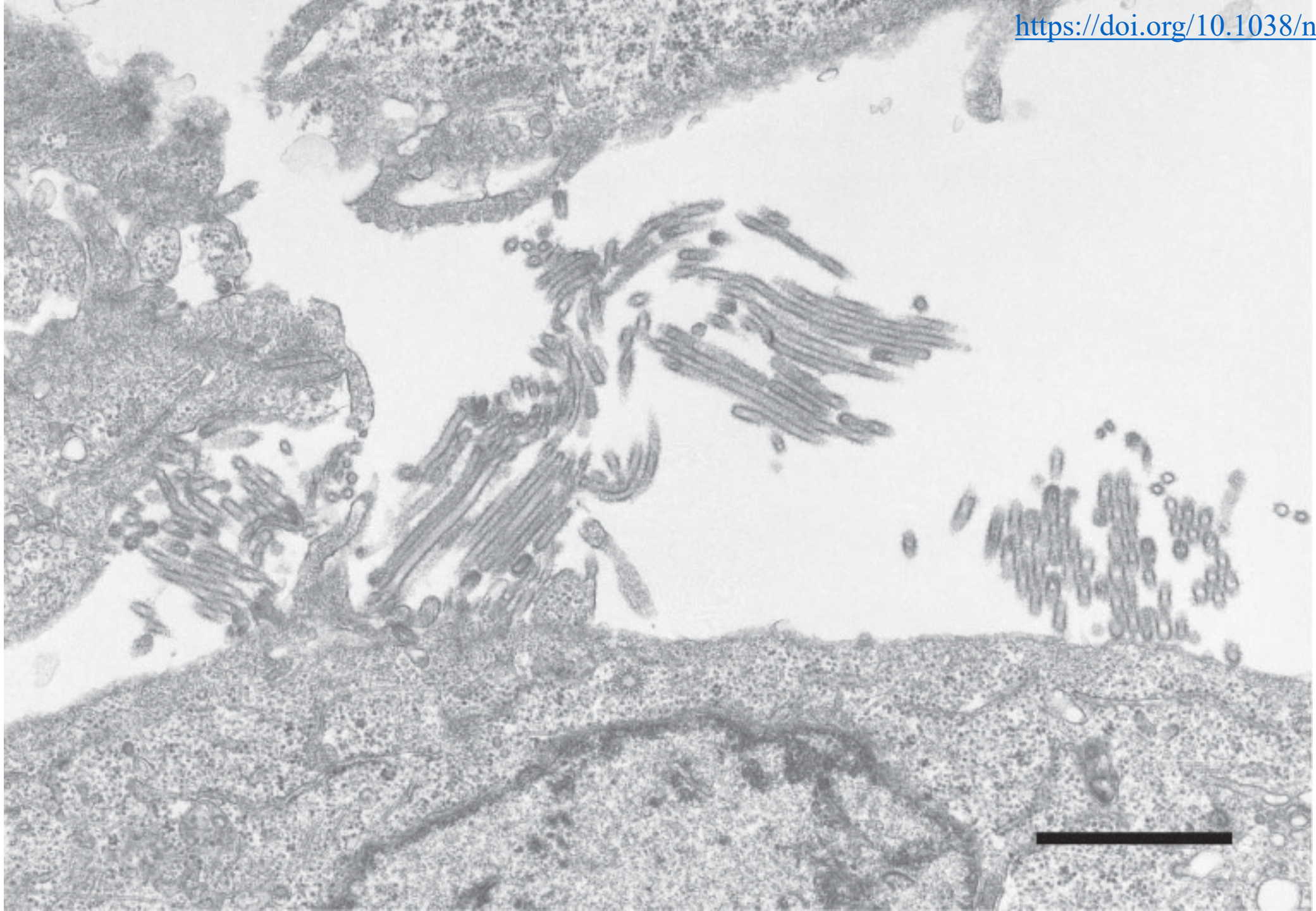
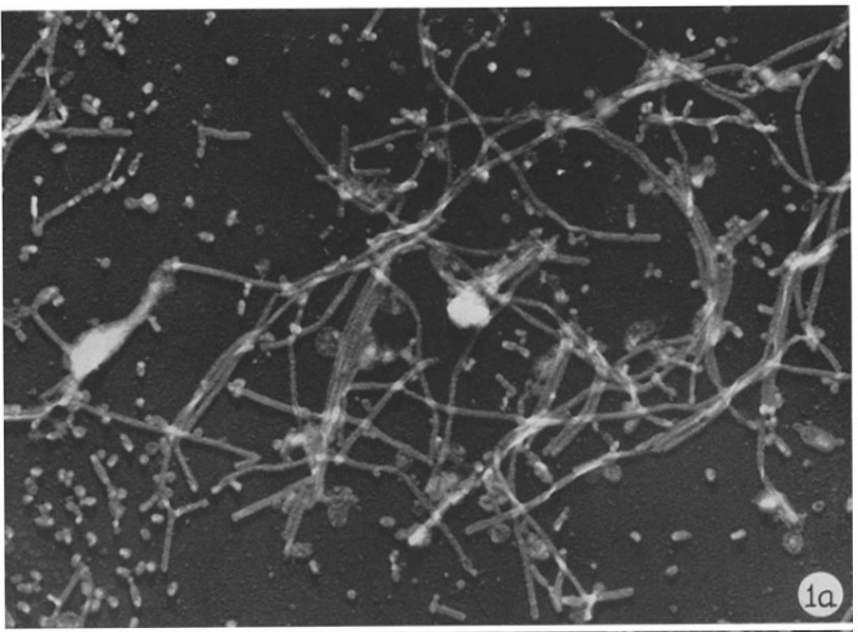


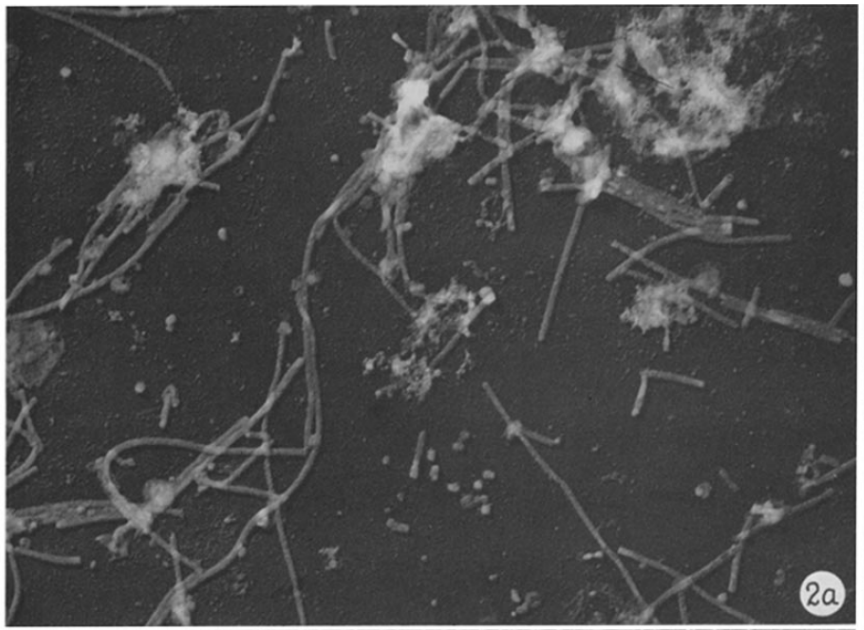
Figure 1 Electron micrographs of purified influenza virus virions (A/Udorn/72) (a–c) and A/WSN/33 virions budding from the surface of infected MDCK cells (d, e). Scale = 100 nm (a–c), 500 nm (d, e). Data provided by Dr. George Leser, Northwestern University, Evanston, IL, USA.

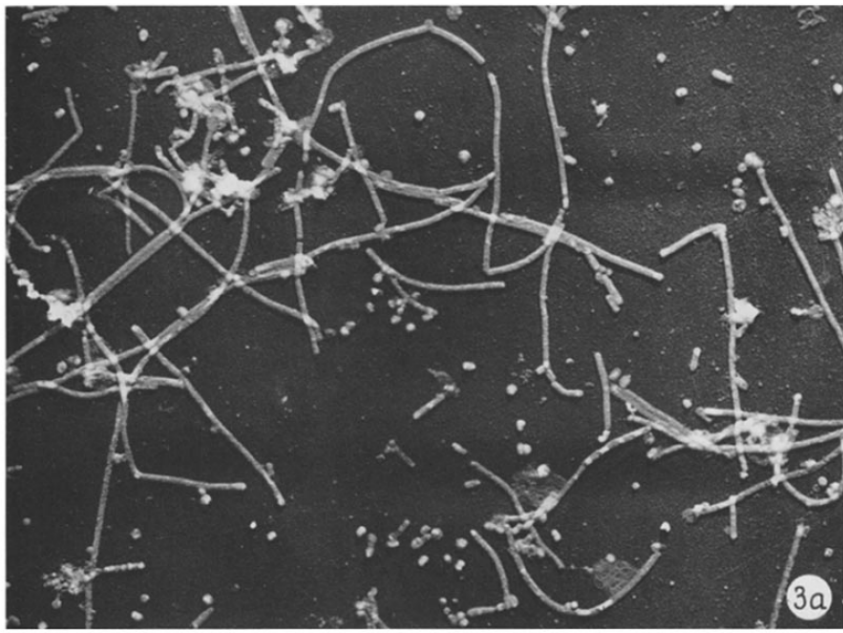
https://doi.org/10.1038/nature08157

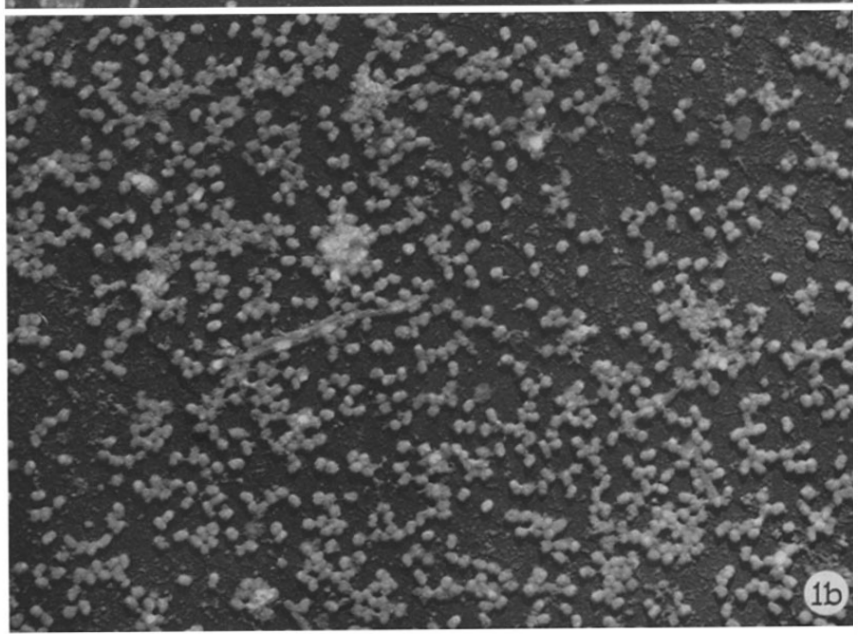


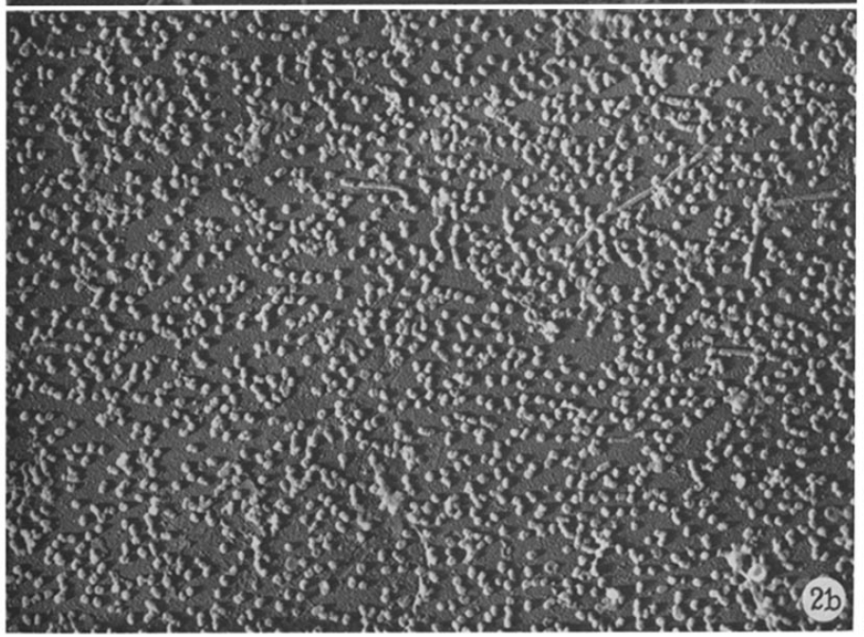
https://doi.org/10.1084%2Fjem.112.5.945

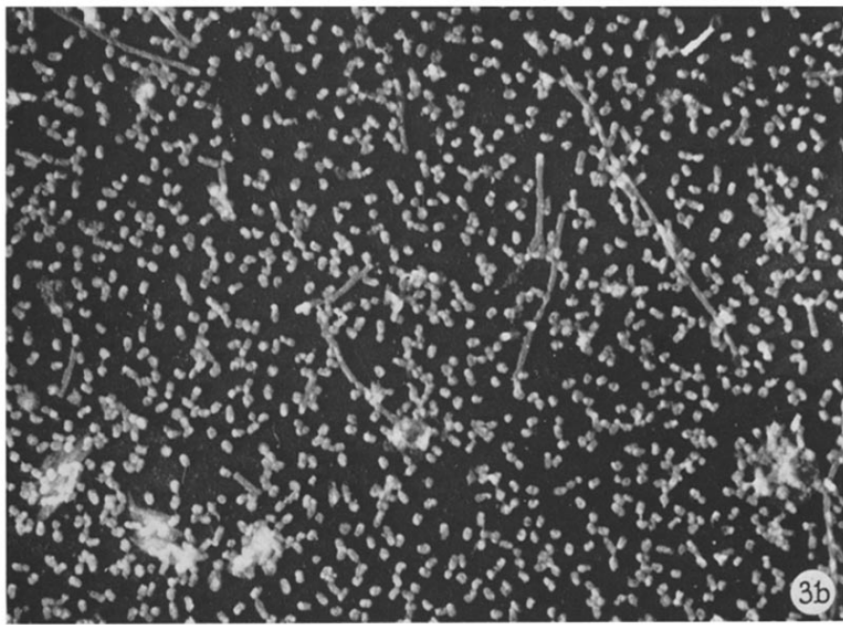












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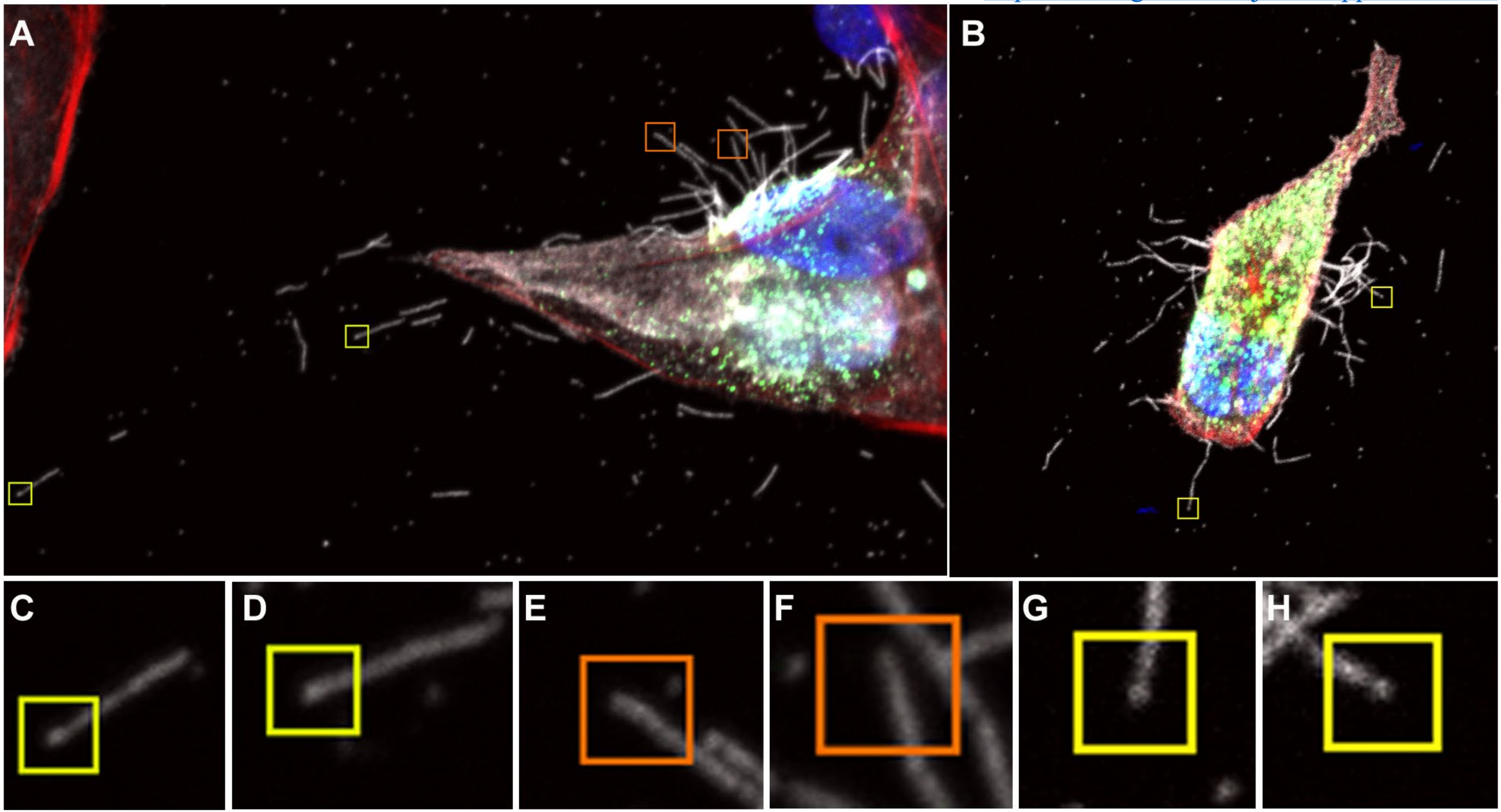

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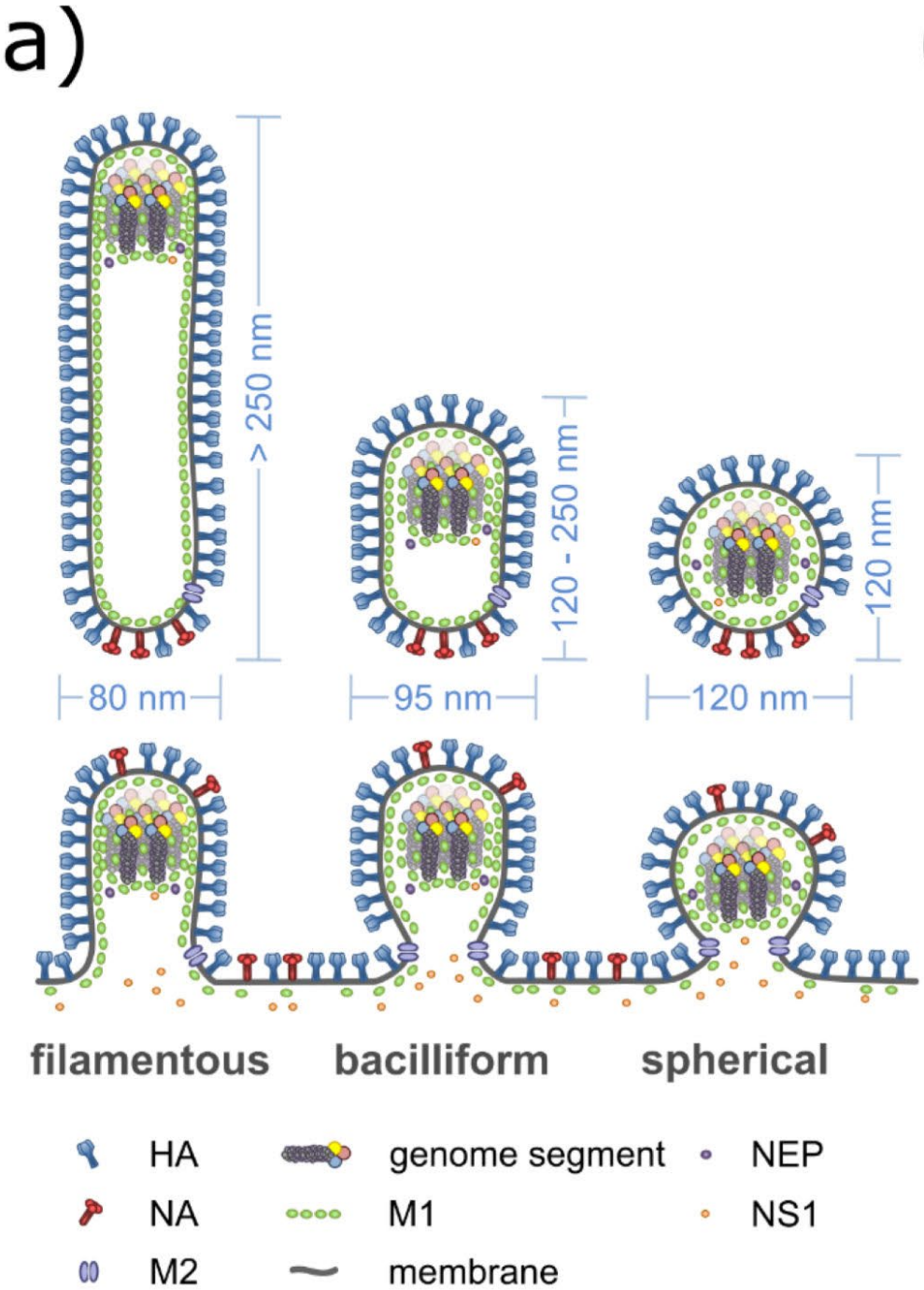
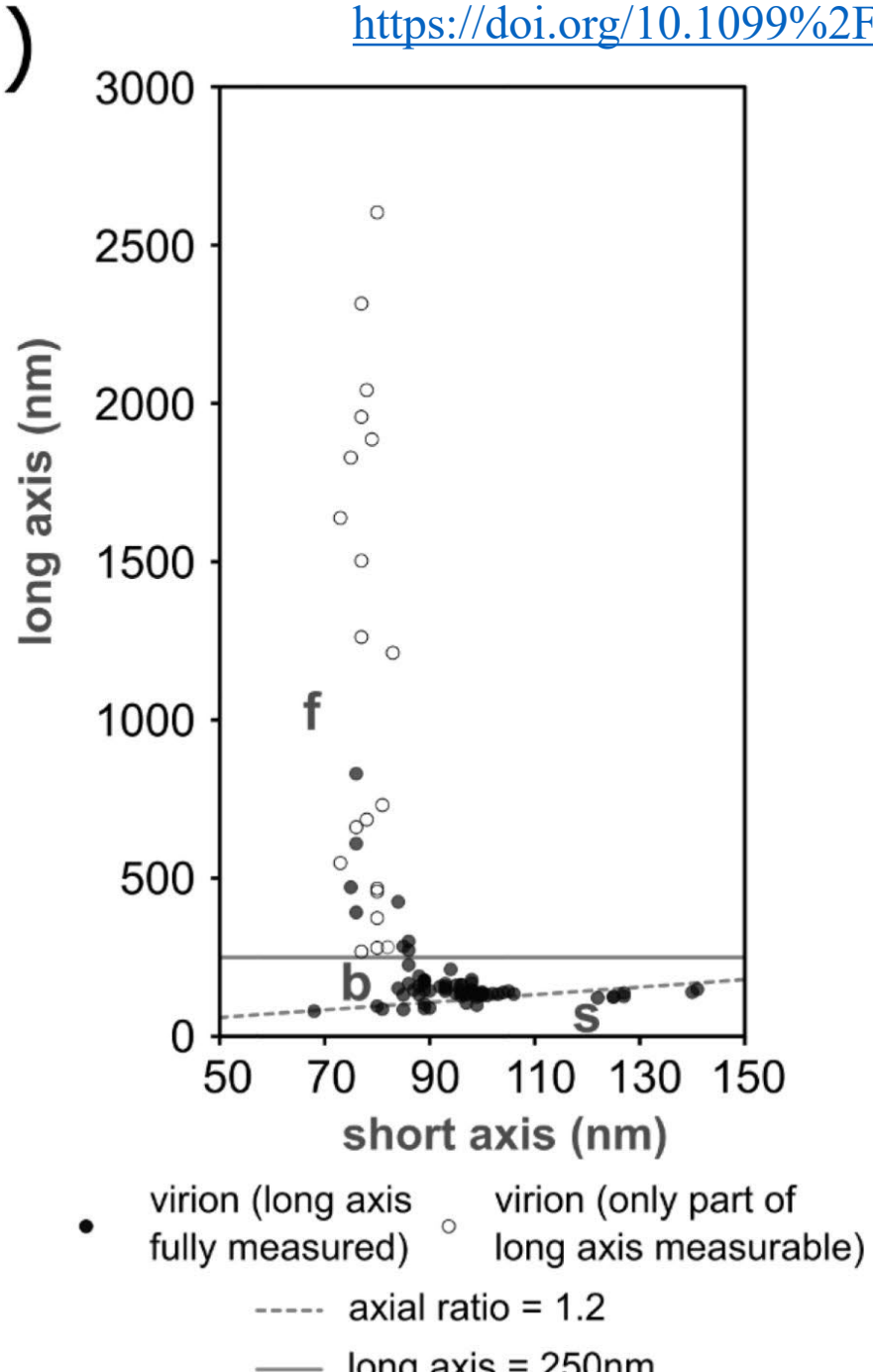




https://www.seirogan.co.jp/fun/infection-control/influenza/influenza.html

A型インフルエンザウイルスの144種類の亜型（※表をクリックすると拡大します）

NA＼HA	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	H1N1 1918年 スペインかぜ 2009年 新型インフルエンザ	H2N1	H3N1	H4N1	H5N1 鳥インフルエンザが人に感染	H6N1	H7N1	H8N1	H9N1	H10N1	H11N1	H12N1	H13N1	H14N1	H15N1	H16N1
2	H1N2	H2N2 1957年 アジアかぜ	H3N2 1968年 香港かぜ	H4N2	H5N2 鳥インフルエンザが人に感染	H6N2	H7N2	H8N2	H9N2 鳥インフルエンザが人に感染	H10N2	H11N2	H12N2	H13N2	H14N2	H15N2	H16N2
3	H1N3	H2N3	H3N3	H4N3	H5N3	H6N3	H7N3 鳥インフルエンザが人に感染			H10N3	H11N3	H12N3	H13N3	H14N3	H15N3	H16N3
4	H1N4	H2N4	H3N4	H4N4	H5N4	H6N4	H7N4			H10N4	H11N4	H12N4	H13N4	H14N4	H15N4	H16N4
5	H1N5	H2N5	H3N5	H4N5	H5N5	H6N5	H7N5	H8N5	H9N5	H10N5	H11N5	H12N5	H13N5	H14N5	H15N5	H16N5
6	H1N6	H2N6	H3N6	H4N6	H5N6	H6N6	H7N6	H8N6	H9N6	H10N6	H11N6	H12N6	H13N6	H14N6	H15N6	H16N6
7	H1N7	H2N7	H3N7	H4N7	H5N7	H6N7	H7N7 鳥インフルエンザが人に感染	H8N7	H9N7	H10N7	H11N7	H12N7	H13N7	H14N7	H15N7	H16N7
8	H1N8	H2N8	H3N8	H4N8	H5N8	H6N8	H7N8	H8N8	H9N8	H10N8	H11N8	H12N8	H13N8	H14N8	H15N8	H16N8
9	H1N9	H2N9	H3N9	H4N9	H5N9	H6N9	H7N9 2013年 鳥インフルエンザが人に感染	H8N9	H9N9	H10N9	H11N9	H12N9	H13N9	H14N9	H15N9	H16N9

人で新型インフルエンザまたは鳥インフルエンザ発症がみられた亜型

全体

	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	H15	H16	H17	H18
N1	36142	58	134	20	6986	553	326	1	25	62	39	8	2					
N2	3965	247	35317	198	1171	921	527	4	5124	39	131	8	106	2	1			
N3	80	287	40	33	185	15	820	3	12	139	56	6	9	12		269		
N4	10	4	8	24	12	41	58	191	6	80	6	13	1	2	1			
N5	15	32	26	26	45	109	7	1	17	158	10	175		4	6			
N6	41	8	369	1641	386	355	60	1	6	71	27	6	268	6	3			
N7	11	25	15	12	14	6	563	1	10	632	10	5		2	1			
N8	26	17	2714	294	282	292	40	2	9	105	24	7	110	2	1	1		
N9	60	76	15	32	42	18	1223		26	35	498	6	22		8	1		
N10																	3	
N11																		2

その他

	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	H15	H16	H17	H18
N1	6581	56	129	19	6373	549	315	1	25	61	39	8	2					
N2	3834	104	3771	198	1159	909	523	4	5049	38	131	8	106	2	1			
N3	80	284	40	33	179	15	807	3	10	139	56	6	9	12		269		
N4	10	4	8	23	12	41	57	189	6	77	6	13	1	2	1			
N5	15	32	26	24	45	108	7	1	17	157	10	175		4	6			
N6	40	8	368	1636	361	355	60	1	6	71	27	6	268	6	3			
N7	11	25	15	12	14	6	526	1	9	628	10	5		2	1			
N8	25	11	2656	290	281	288	40	2	9	99	24	7	110	2	1	1		
N9	57	75	15	32	41	18	819		26	35	497	6	22		8	1		
N10																	3	
N11																		2

人間

	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	H15	H16	H17	H18
N1	29483	1	4	1	511		7			1								
N2	118	131	31380		6	2	4		62	1								
N3		3			5		11											
N4				1			1			2								
N5				2		1				1								
N6				1	4	5												
N7							28		1	4								
N8	1	6	54	4	1	4				5								
N9		1			1		401				1							
N10																		
N11																		

TABLE 21.1 Distribution of Hemagglutinin (HA) Subtypes Between Different Birds (Class *Aves*) and Mammals (Class *Mammalia*)

HA Subtype	Host of Origin					
	Mammalia			Aves		
	Humans	Swine	Equines	Anserifonnes (e.g., Dabbling Ducks)	Charadriiformes and Procellariiformes (e.g., Shorebirds, Gulls, Seabirds)	Gallifonnes (Domestic Poultry)
H1	+	++		+	+	++[c]
H2	(++)[a]			+	+	+
H3	++	++	++	++	++	++[c]
H4		±		++	+	+
H5	±	±		+	+	++[b]
H6				++	+	+
H7	±	±	(++)[a]	+	+	++[b]
H8				±		±
H9	±	±		+	++	++
H10				+	+	+
H11				+	++	+
H12				+	+	±
H13				+	++	+
H14[c]				±		
H15[c]				±	±	
H16[c]					+	

±, sporadic; +, several reports; ++, most common.
[a]Previously common but now not reported.
[b]Both low-pathogenicity and high-pathogenicity viruses.
[c]Primarily swine influenza virus infections of domestic turkeys.
[From Avian Influenza *(D. E. Swayne, ed.), p. 63. Copyright © John Wiley & Sons (2008), with permission.]*

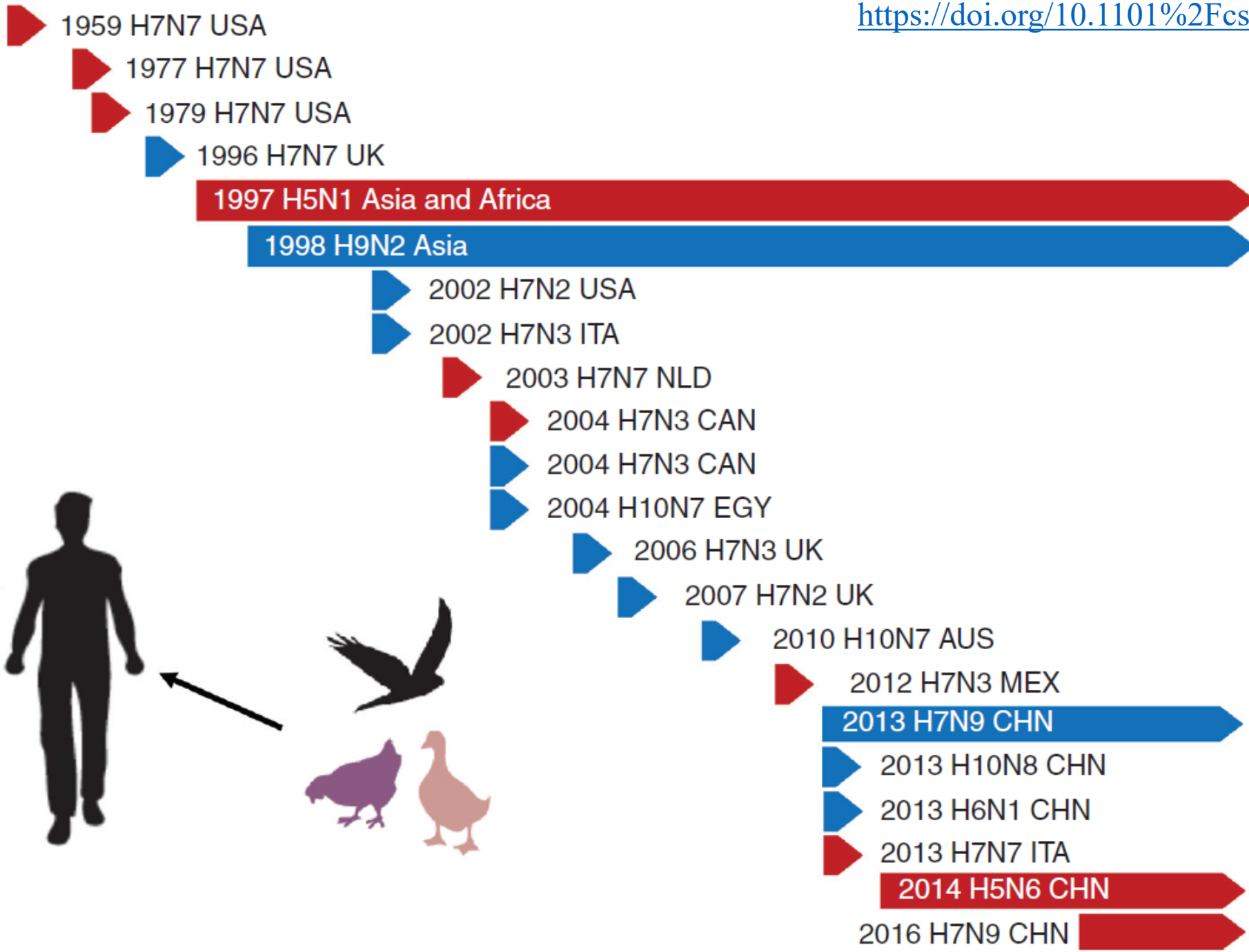
https://www.cdc.gov/flu/other/animal-flu.html

Subtype	People	Poultry	swine	Bats / Other
H1				
H2				
H3				Other Animals
H4				Other Animals
H5				
H6				
H7				Other Animals
H8				
H9				
H10				
H11				
H12				
H13				
H14				
H15				
H16				
H17				
H18				

https://www.cdc.gov/flu/other/animal-flu.html

Subtype	People	Poultry	Pigs	Bats / Other
N1				
N2				
N3				
N4				
N5				
N6				
N7				Other Animals
N8				Other Animals
N9				
N10				
N11				

https://doi.org/10.1101%2Fcshperspect.a038620



EPIZOOZIA TIFOIDE

NEI GALLINACEI

PER

EDOARDO PERRONCITO

TORINO
TIP. E LIT. CAMILLA E BERTOLERO
Via Ospedale, 18
—
1878.

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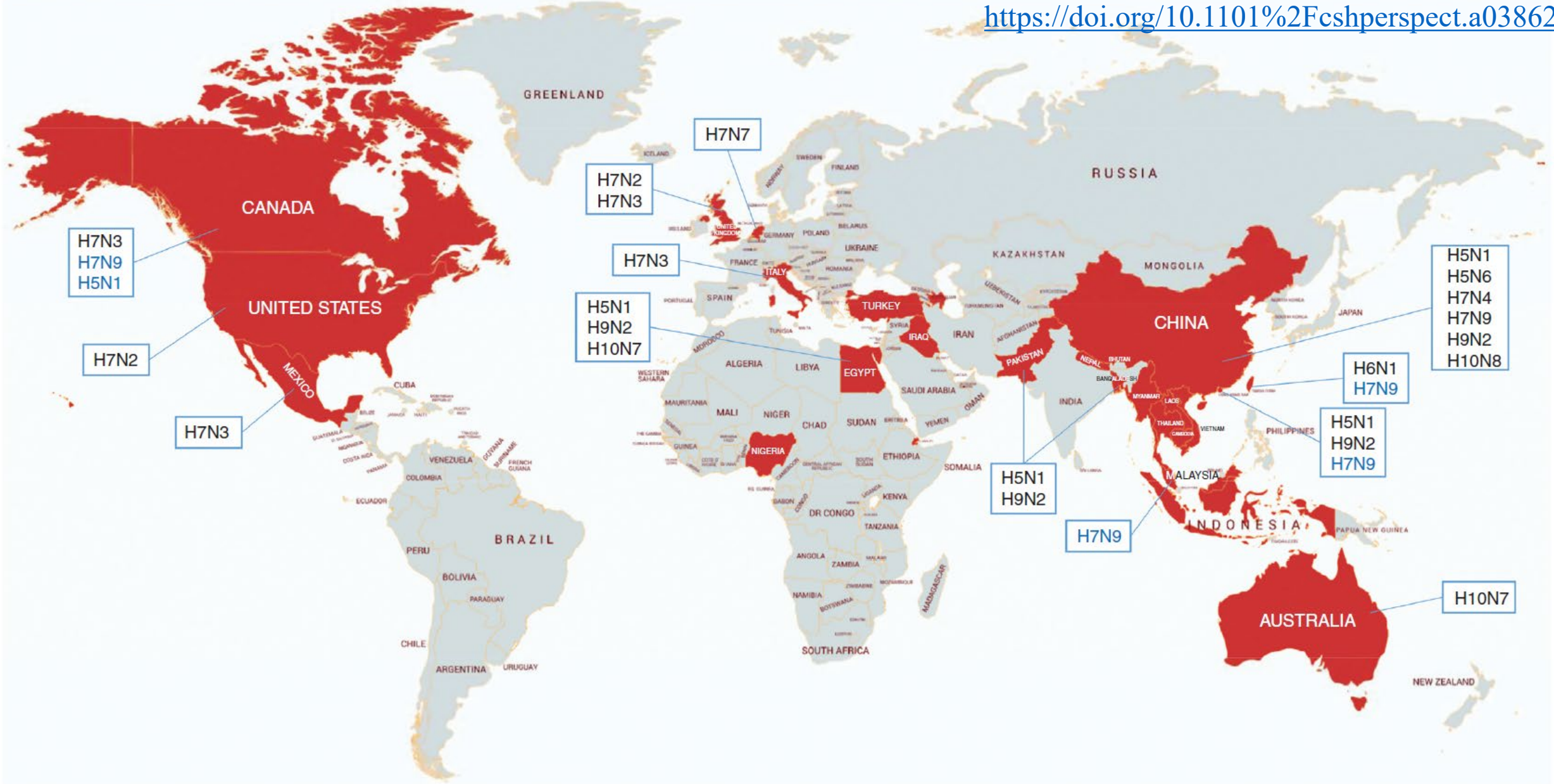


Figure 2. Areas with confirmed human cases of avian influenza virus (AIV) infection since 2000. The affected countries are colored in red. Labels indicate cases other than H5N1; imported cases are shown in blue. The map was created with mapchart.net.

https://www.cdc.gov/flu/avianflu/h5n1-human-infections.htm

Person-to-Person Spread of HPAI

1997
Hong Kong
H5N1

血清学的研究により証明、限定的で非持続的

2003
Netherlands
H7N7

2人の家禽労働者から3人の家族に限定的かつ非持続的に伝播した

2004
Thailand
H5N1

感染した病児と、その病児が入院している間の母親と叔母との間でで限定的かつ非持続的に人から人へ伝播した証拠があった

2005
Indonesia
H5N1

有症者と無防備な状態で長期間接触した症例で家庭内における限定的かつ非持続的な個人間伝播が否定できなかった

2006
Indonesia
H5N1

確認された8人の家族内クラスター間で発生した可能性がある

2007
China
H5N1

病気の息子とその父親の間で長期にわたる非常に接近した無防備な暴露によって起こったと考えられている

2007
Pakistan
H5N1

兄弟間

2013
China
H7N9

ほとんどは家族間・家庭内だが、無関係な人の間で限定的かつ非持続的な拡散が病院内での少数の症例で報告されている

https://www.woah.org/fileadmin/Home/eng/Health_standards/tahm/3.03.04_AI.pdf

CHAPTER 3.3.4.

AVIAN INFLUENZA (INCLUDING INFECTION WITH HIGH PATHOGENICITY AVIAN INFLUENZA VIRUSES)

SUMMARY

Influenza A is caused by specified viruses that are members of the family Orthomyxoviridae *and placed in the genus* Alphainfluenzavirus (Influenzavirus *A or influenza A virus*). *There are seven influenza genera but only influenza A viruses are known to infect birds. Diagnosis is by isolation of the virus or by detection and characterisation of fragments of its genome. This is because infections in birds can give rise to a wide variety of clinical signs that may vary according to the host, strain of virus, the host's immune status, presence of any secondary exacerbating organisms and environmental conditions.*

Detection of the agent: *Suspensions in antibiotic solution of oropharyngeal and cloacal swabs (or faeces) taken from live birds, or of faeces and pooled samples of organs from dead birds, are*

https://www.woah.org/fileadmin/Home/eng/Health_standards/tahm/3.03.04_AI.pdf

- 病原性の高いA型インフルエンザウイルスとは，致死性であるあらゆるインフルエンザAウイルス．
  - ✓ 1/10希釈液0.2mlを静脈内接種した後，10日以内に4～8週齢の感受性鶏8羽中6～7羽が致死する．
  - ✓ 静脈内病原性指数（intravenous pathogenicity index; IVPI）が1.2より大きい．
  - ✓ IVPIとは，10日間の期間にわたる一つの観察あたりの鳥ごとの平均スコアを指す．IVPIが3.00の場合はすべての鳥が24時間以内に死亡したことを意味し、0.00の場合は10日間の観察期間中に鳥がいかなる臨床的な兆候も示さなかったことを意味する．

https://www.woah.org/fileadmin/Home/eng/Health_standards/tahm/3.03.04_AI.pdf

- 鶏の病原性が低い全てのH5及びH7ウイルスについては，ヘマグルチニン分子（HA0）の連結ペプチド（すなわち切断部位）のアミノ酸配列を決定する必要がある．

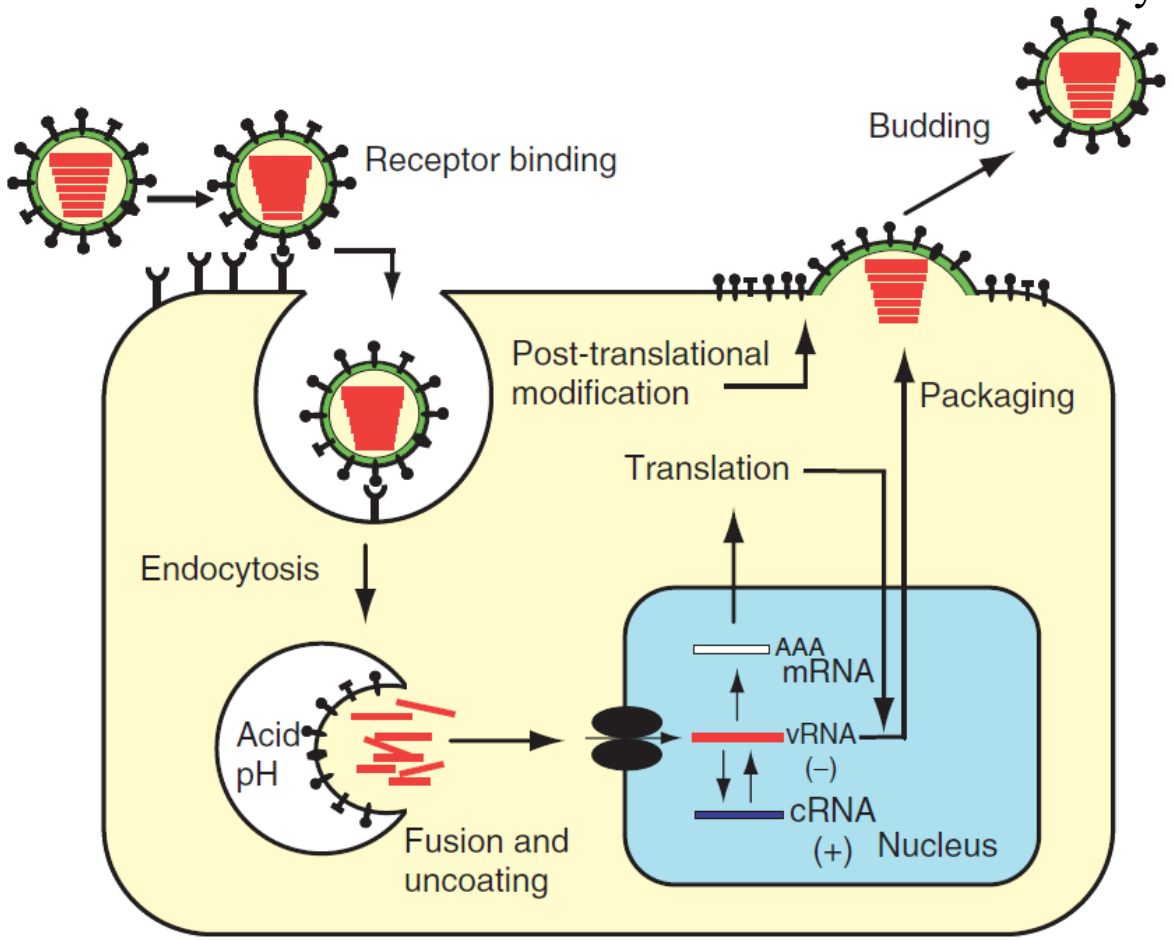
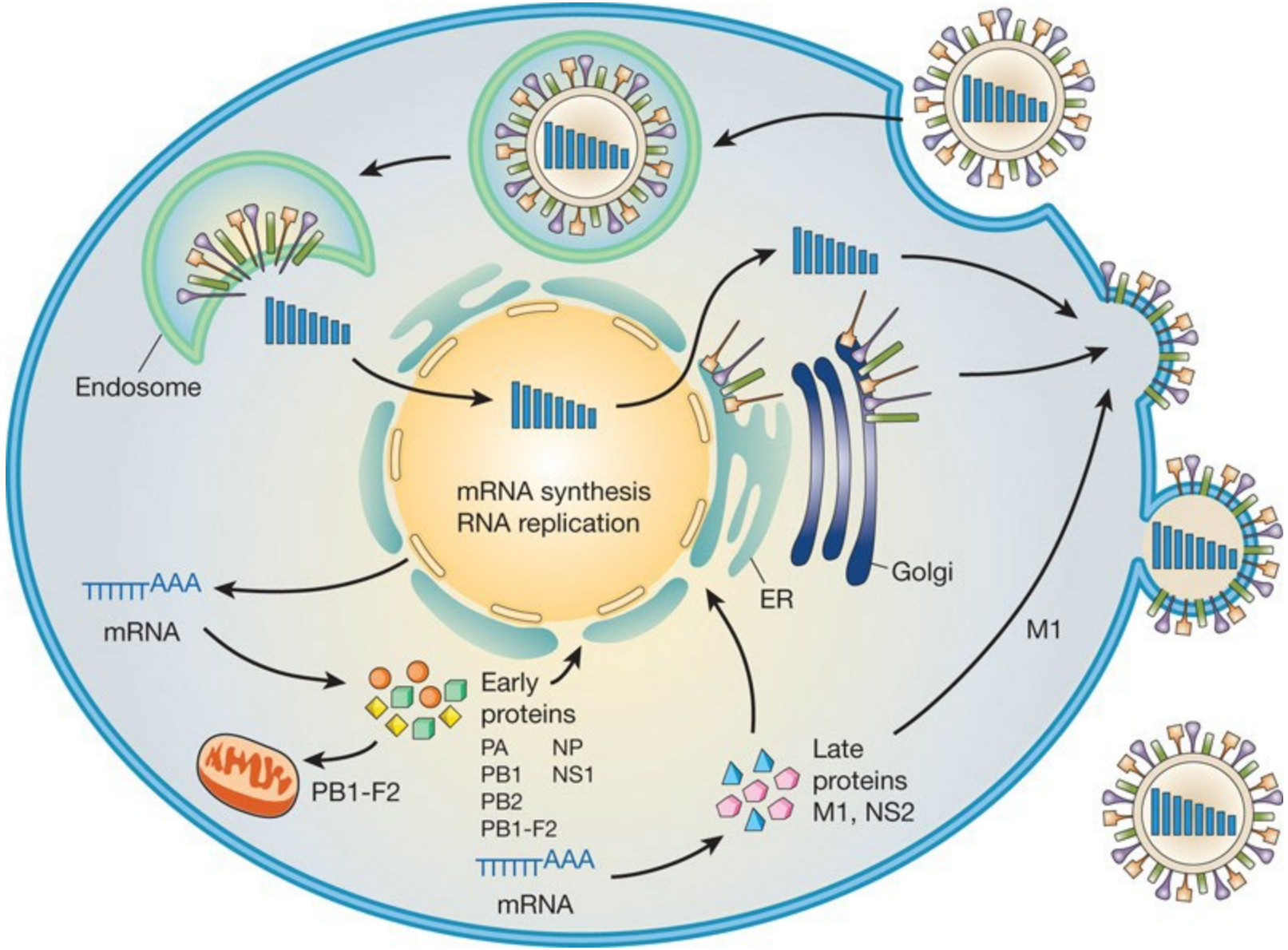


Figure 2 Virus attachment to the host cell is mediated by interaction of the HA protein with sialic acid-containing receptors. During endocytosis the interior of the endocytic vesicle becomes acidified. This induces conformational changes in HA which triggers its fusion activity and leads to fusion between the viral and endosomal membranes. The interior of the virus also becomes acidified due the ion channel activity of the M2 protein. The low pH dissociates the M1 protein from the RNP complexes, which are then transported into the nucleus. Viral RNAs are transcribed into mRNA and are replicated through a cRNA intermediate. Following export into the cytoplasm, the mRNAs are translated into viral proteins. The HA, NA, and M2 proteins are transported to the surface via the endoplasmic reticulum and Golgi (where they undergo post-translational modification). The remaining viral proteins are transported into the nucleus where they are required for either replication or nuclear export of newly synthesized vRNA. Virus assembly takes place at the apical plasma membrane which involves packaging of the eight RNPs into budding virus particles. Efficient release of budding particles requires the activity of the viral neuraminidase.

https://doi.org/10.1038/nature08157



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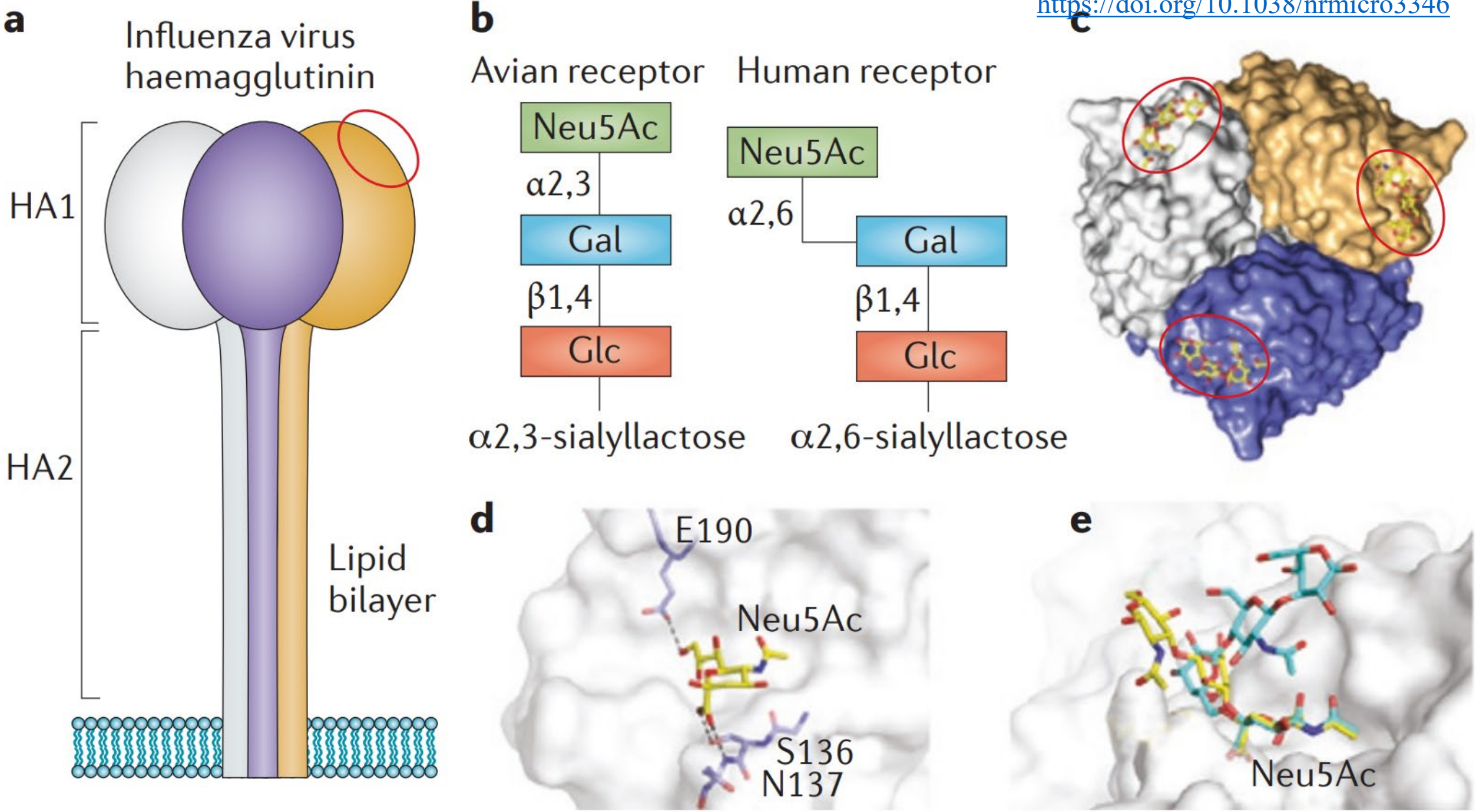

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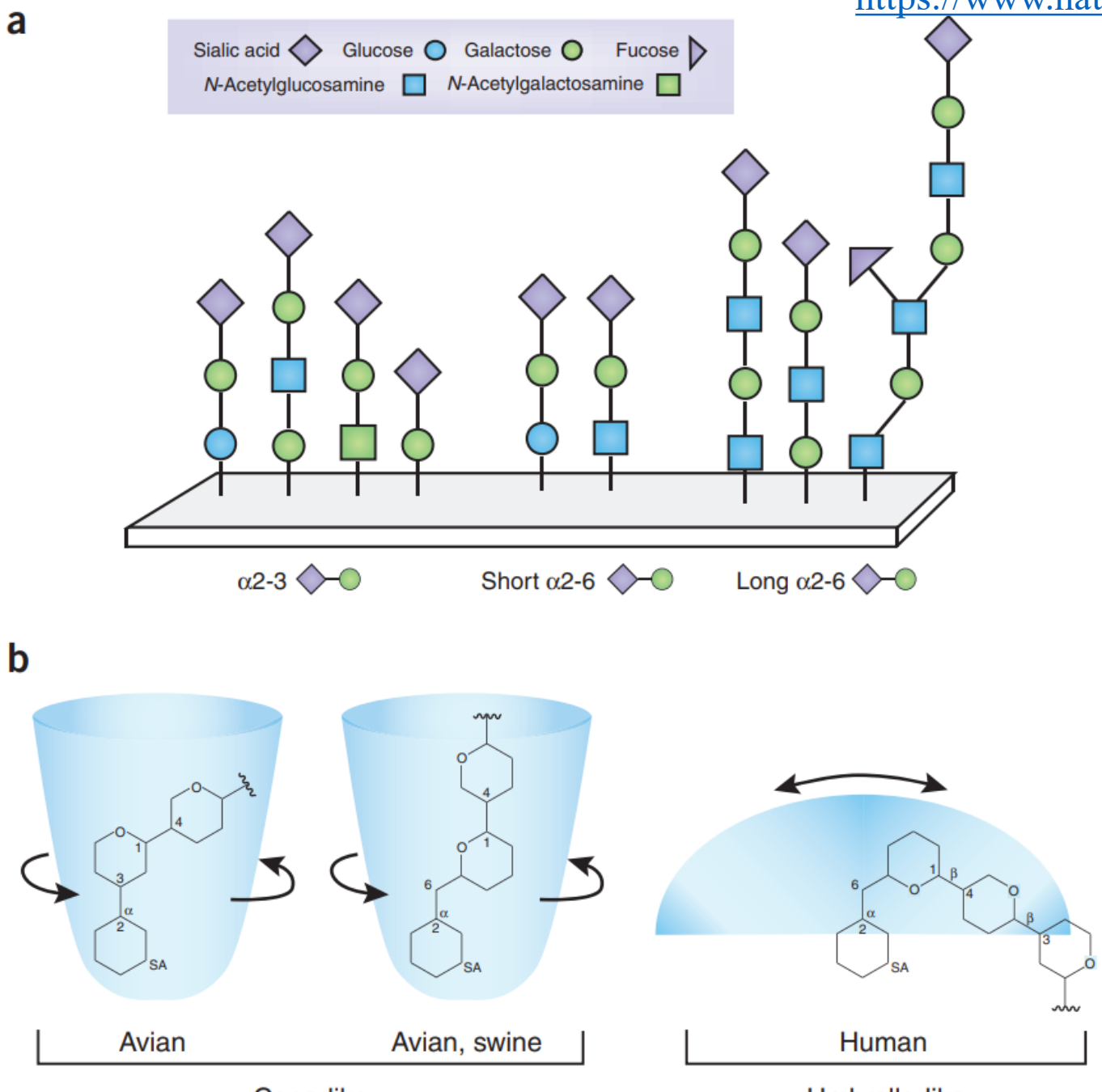

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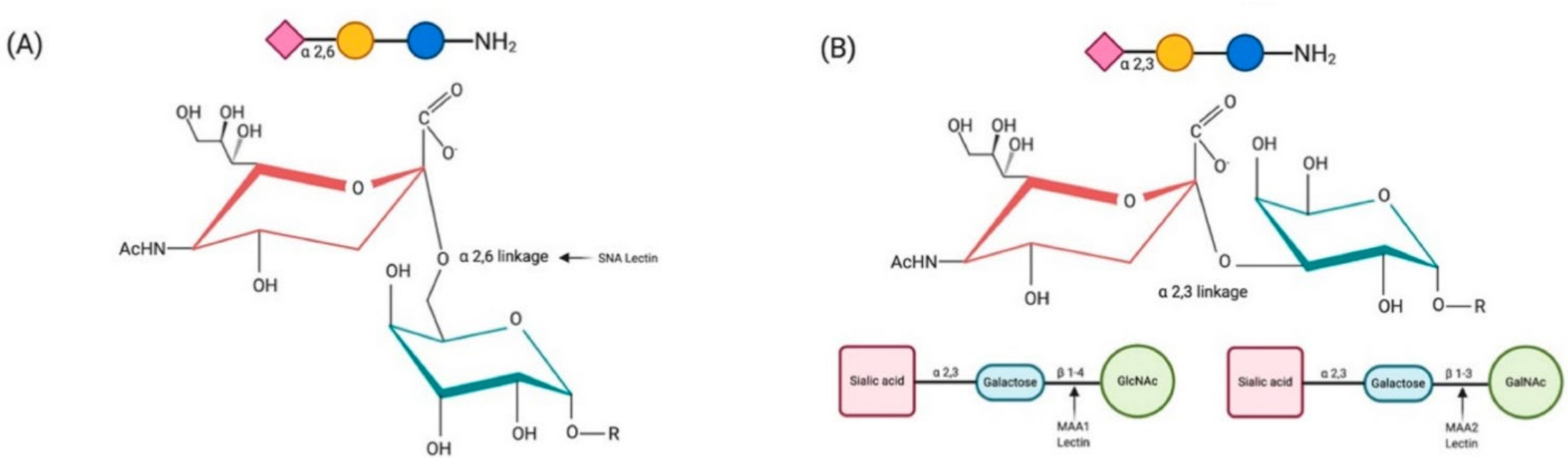
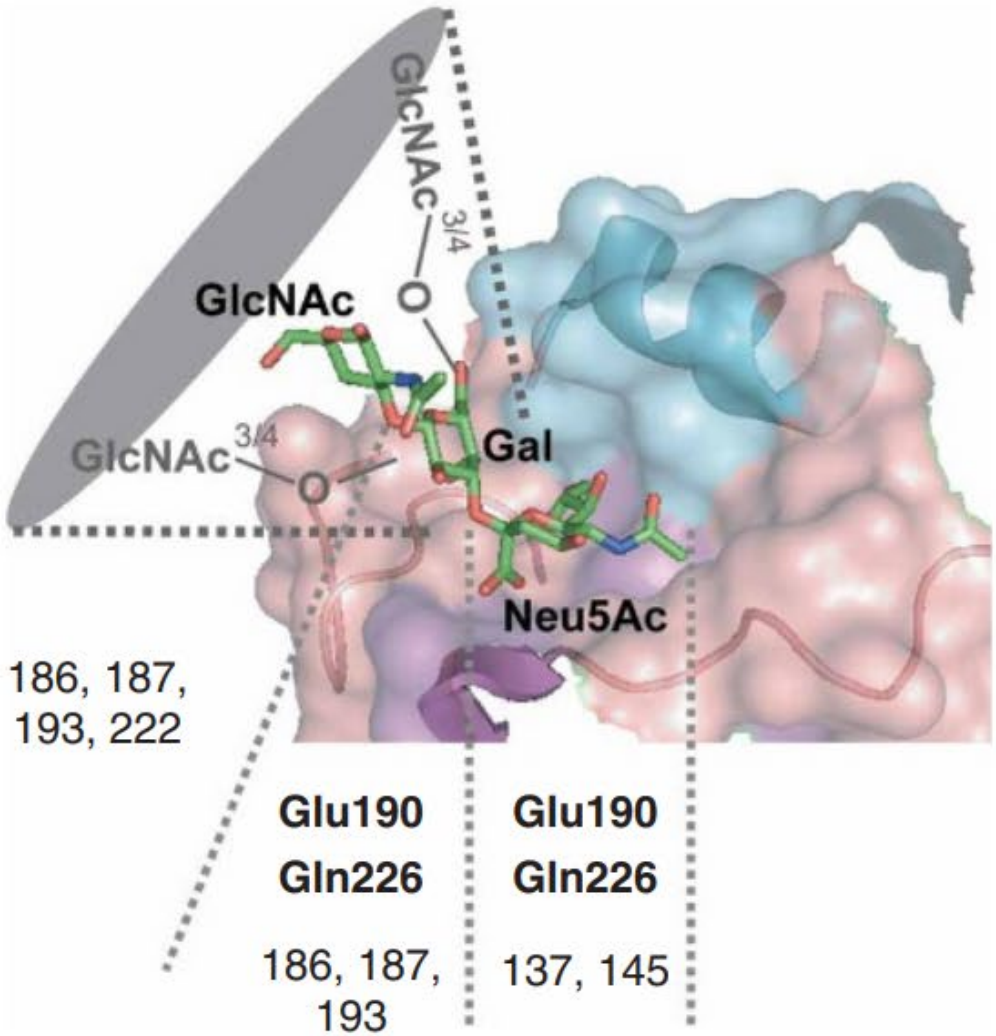
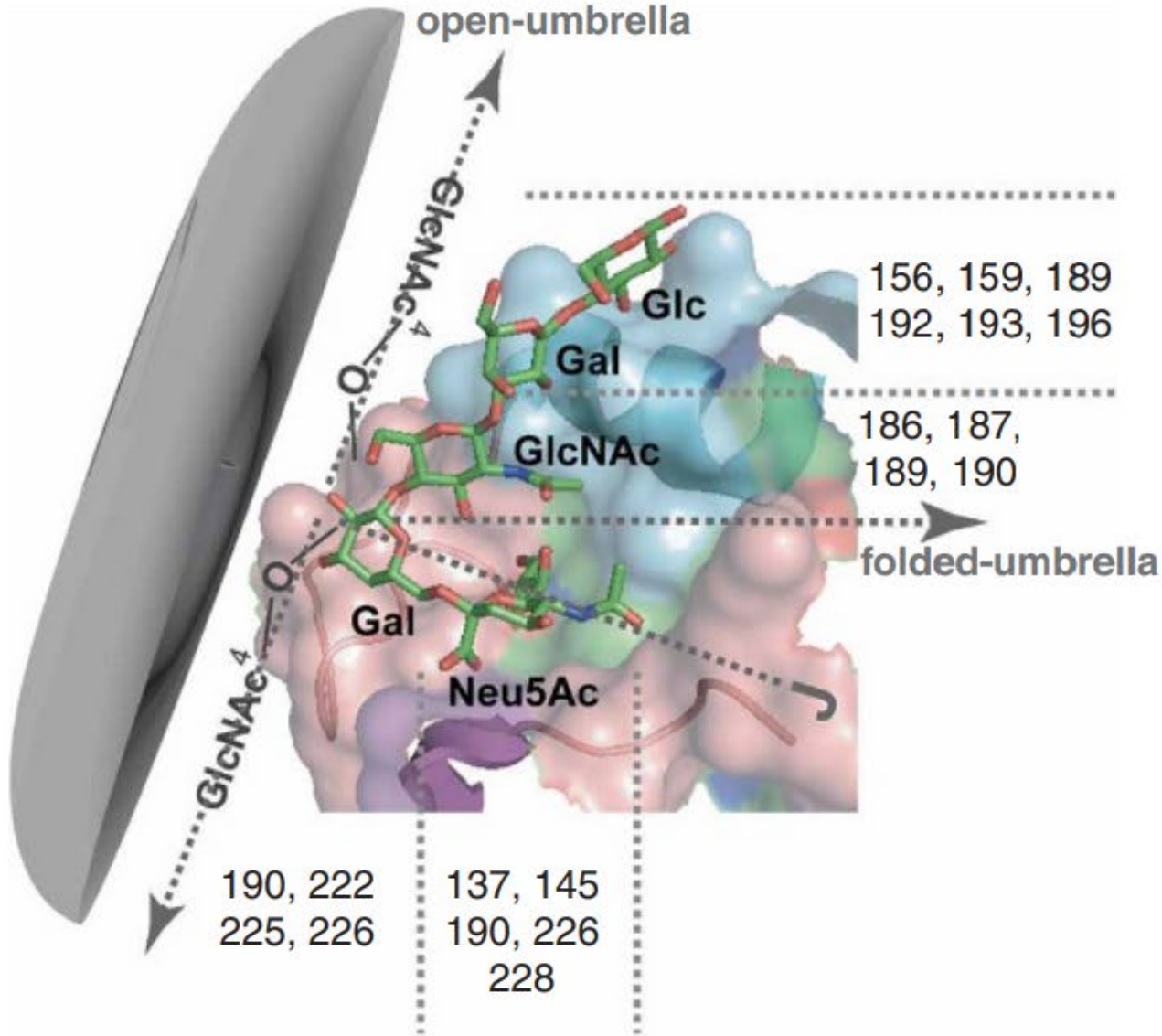


Figure 1. Schematic illustration of SAα2,6-Gal (**A**) and SAα2,3-Gal (**B**) receptors highlighting the binding pattern of linkage-specific lectins.

https://doi.org/10.1038/nbt1375





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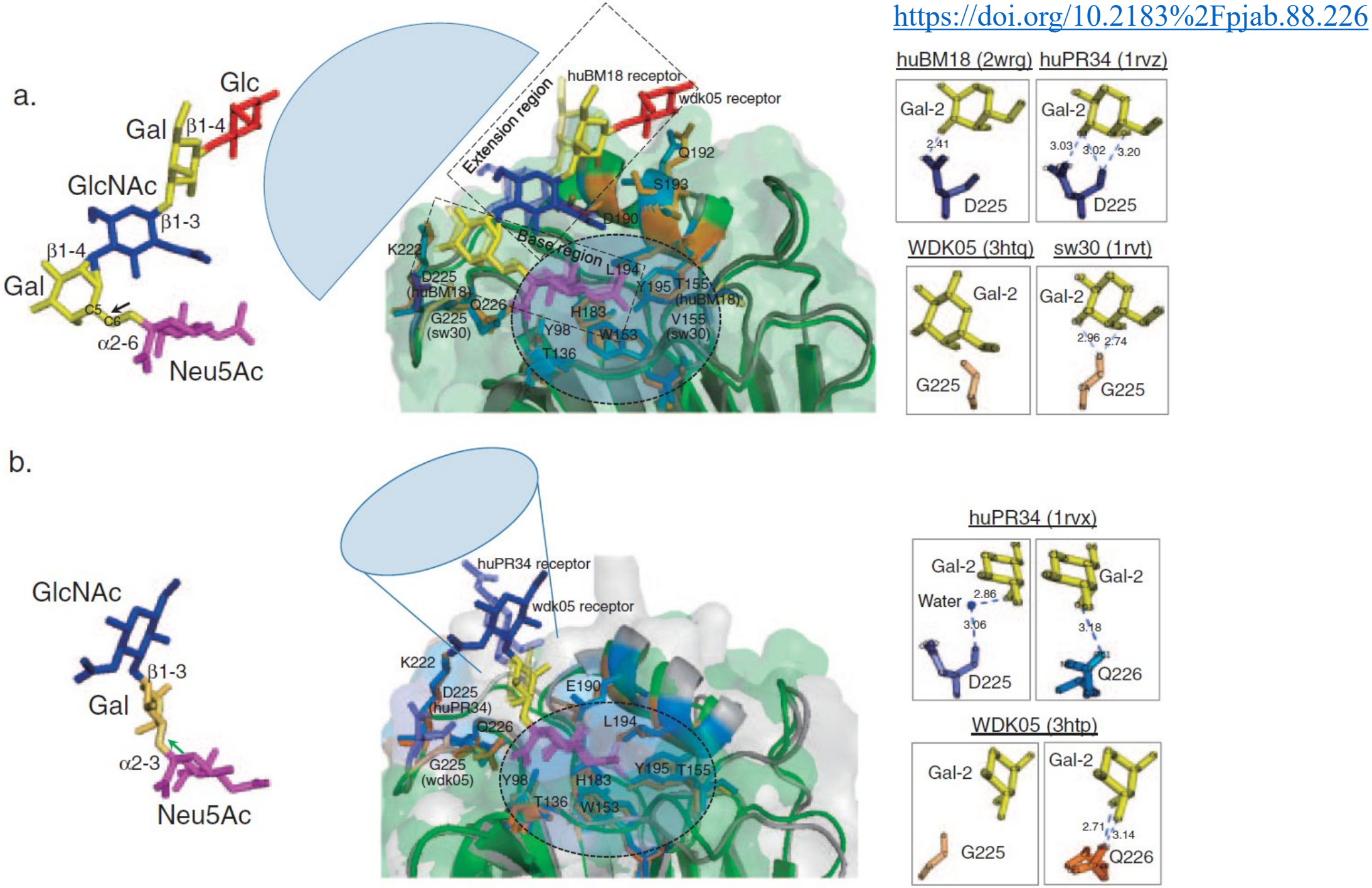

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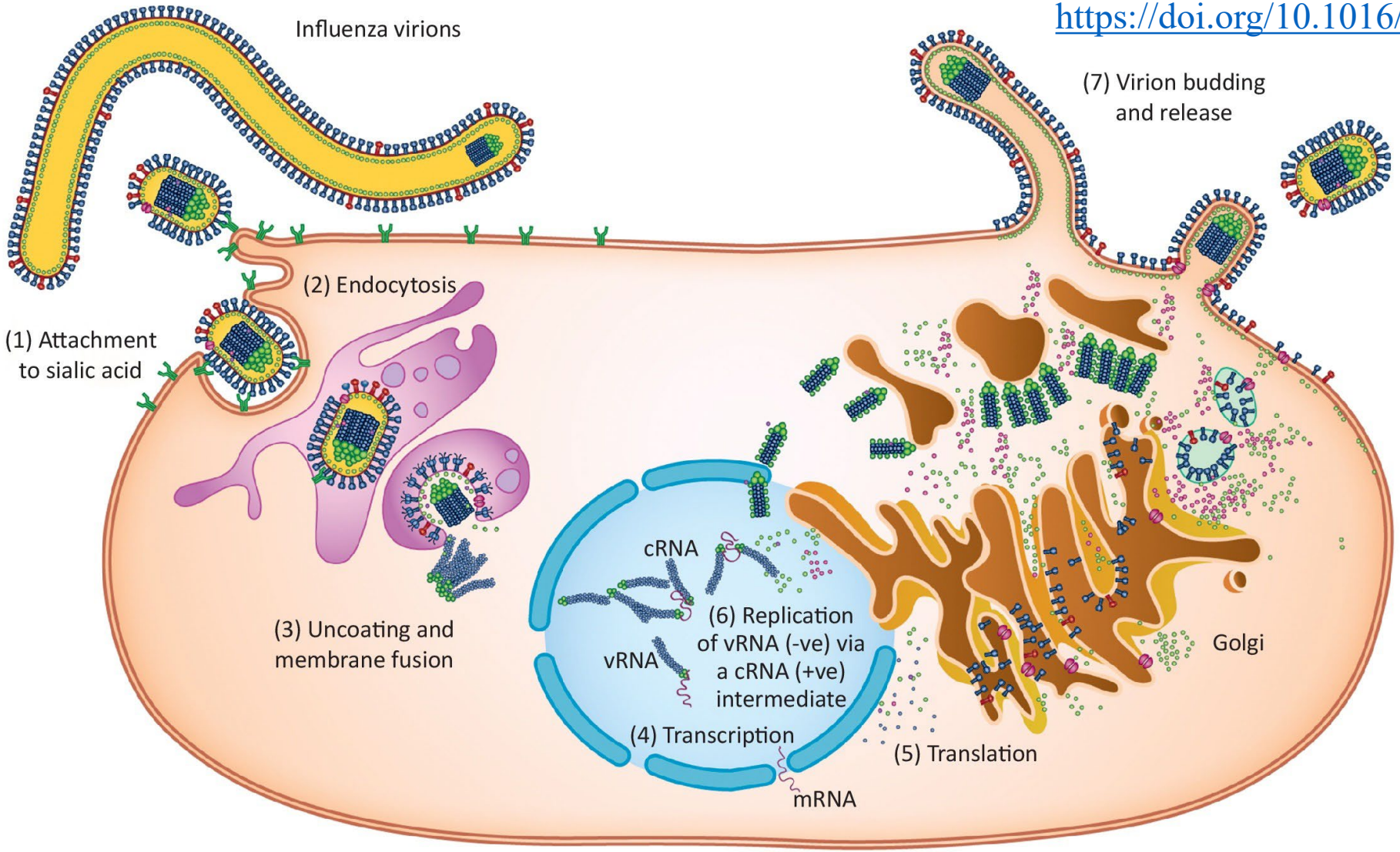

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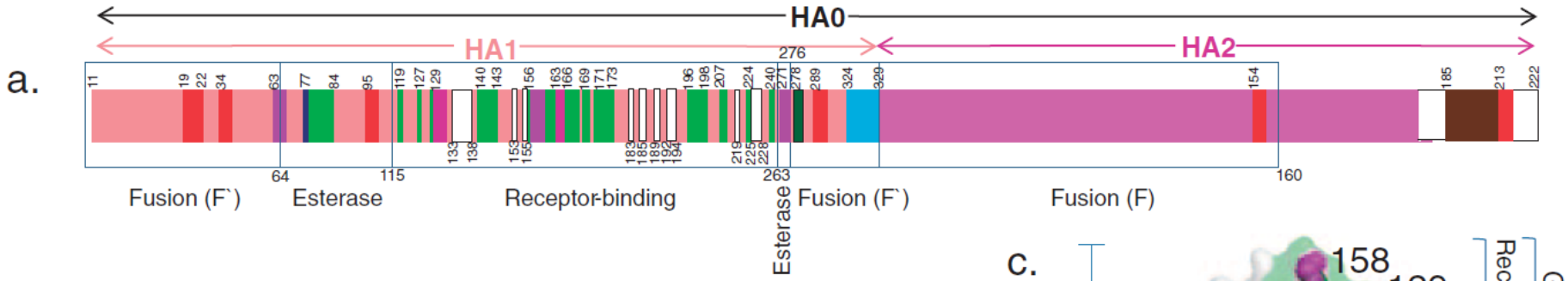
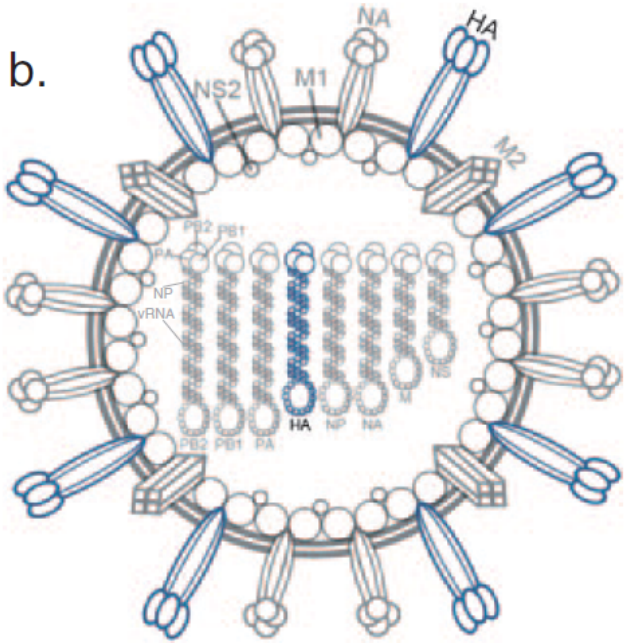


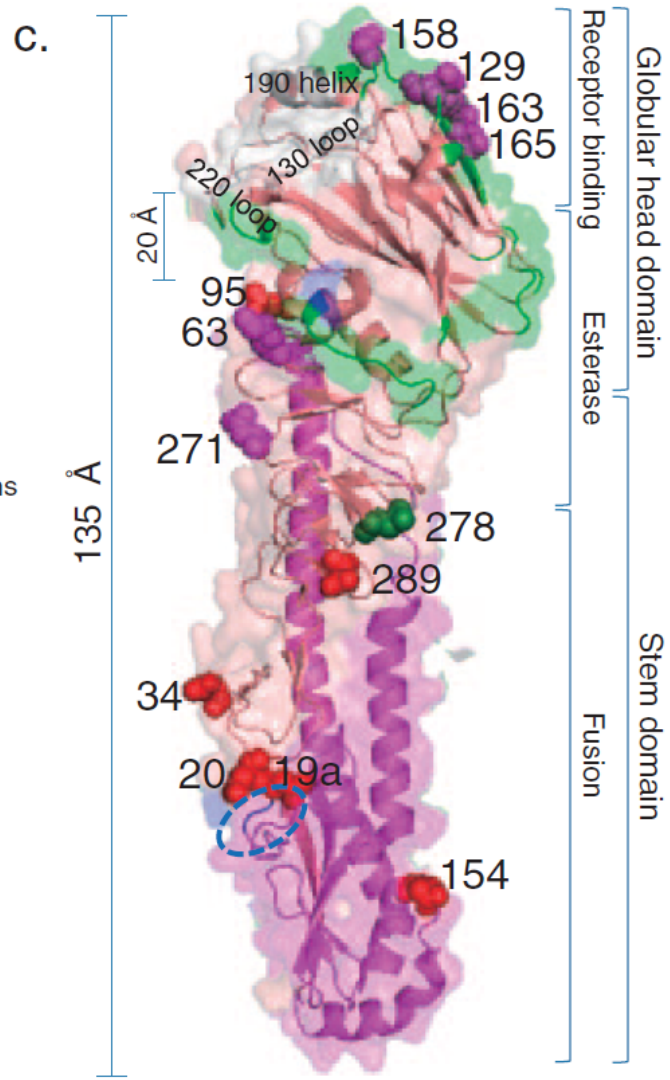


Eight ssRNA segments encode 12 proteins

Nine structural proteins:
Segment 1: PB2
Segment 2: PB1
Segment 3: PA
Segment 4: HA
Segment 5: NP
Segment 6: NA
Segment 7: M1 and M2
Segment 8: NS2 (NEP)

Three non-structural proteins:
Segment 2: PB1-F2 and N40
Segment 8: NS1

Note: N40 is a newly discovered protein that is still not completely understood.



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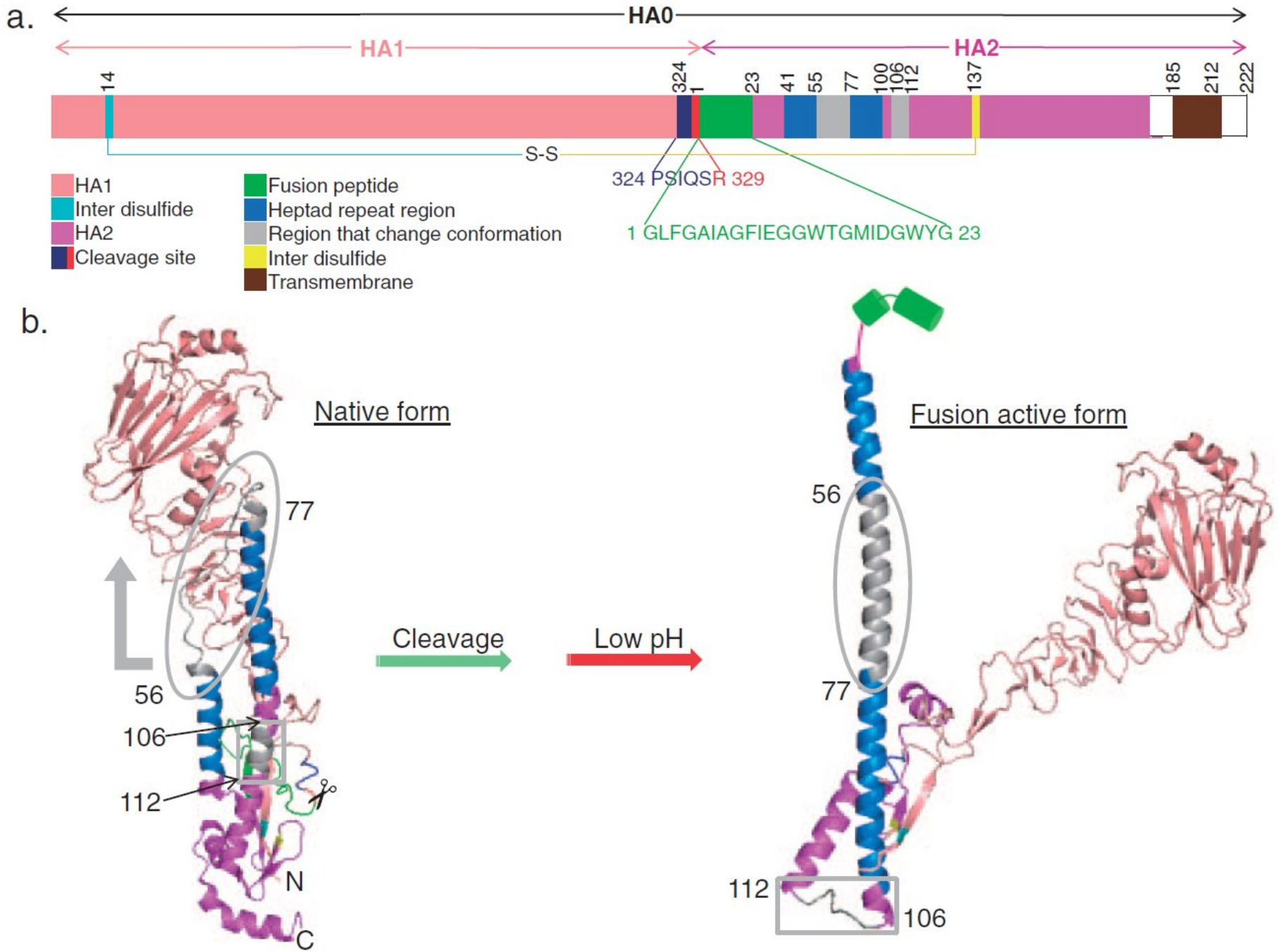

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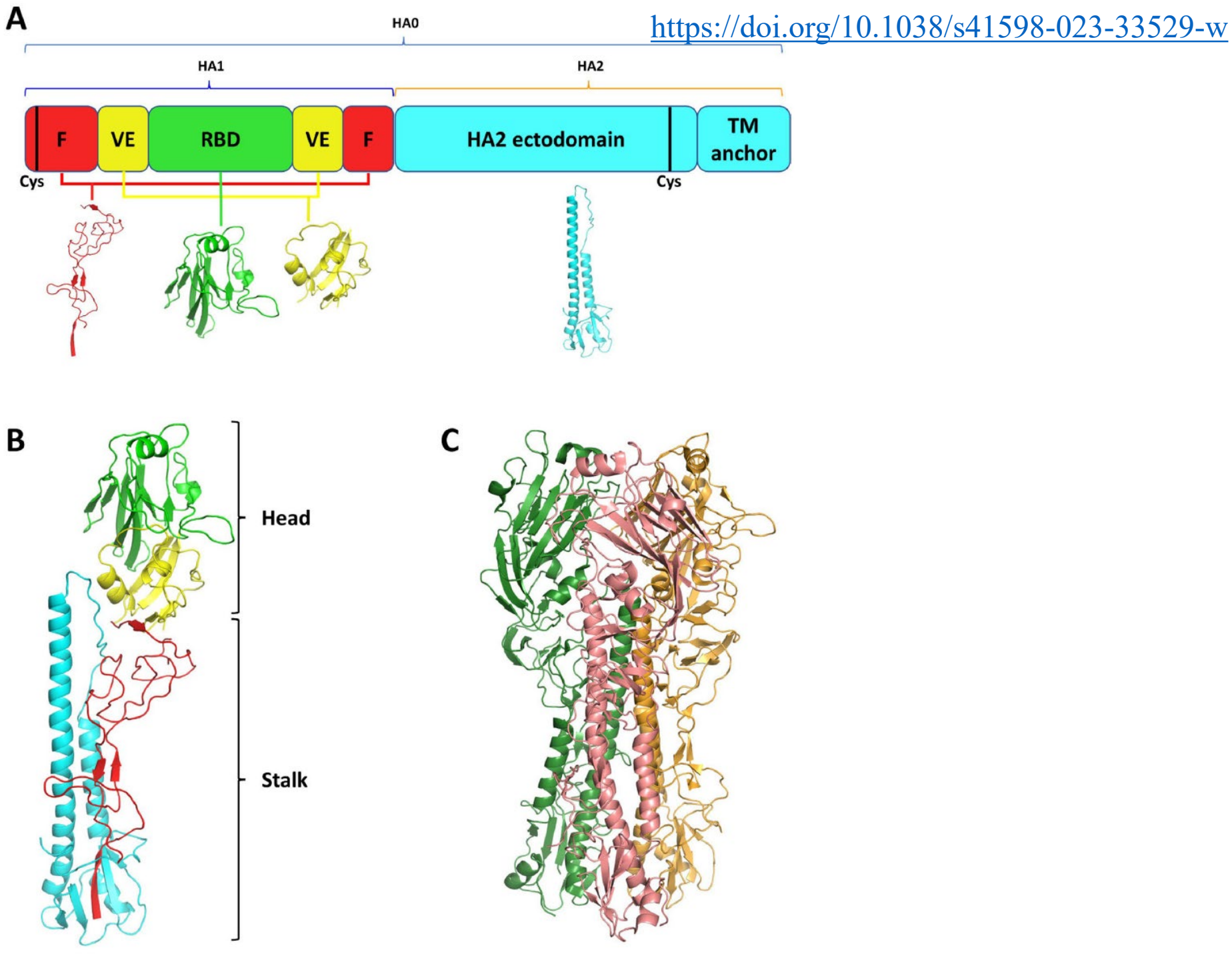

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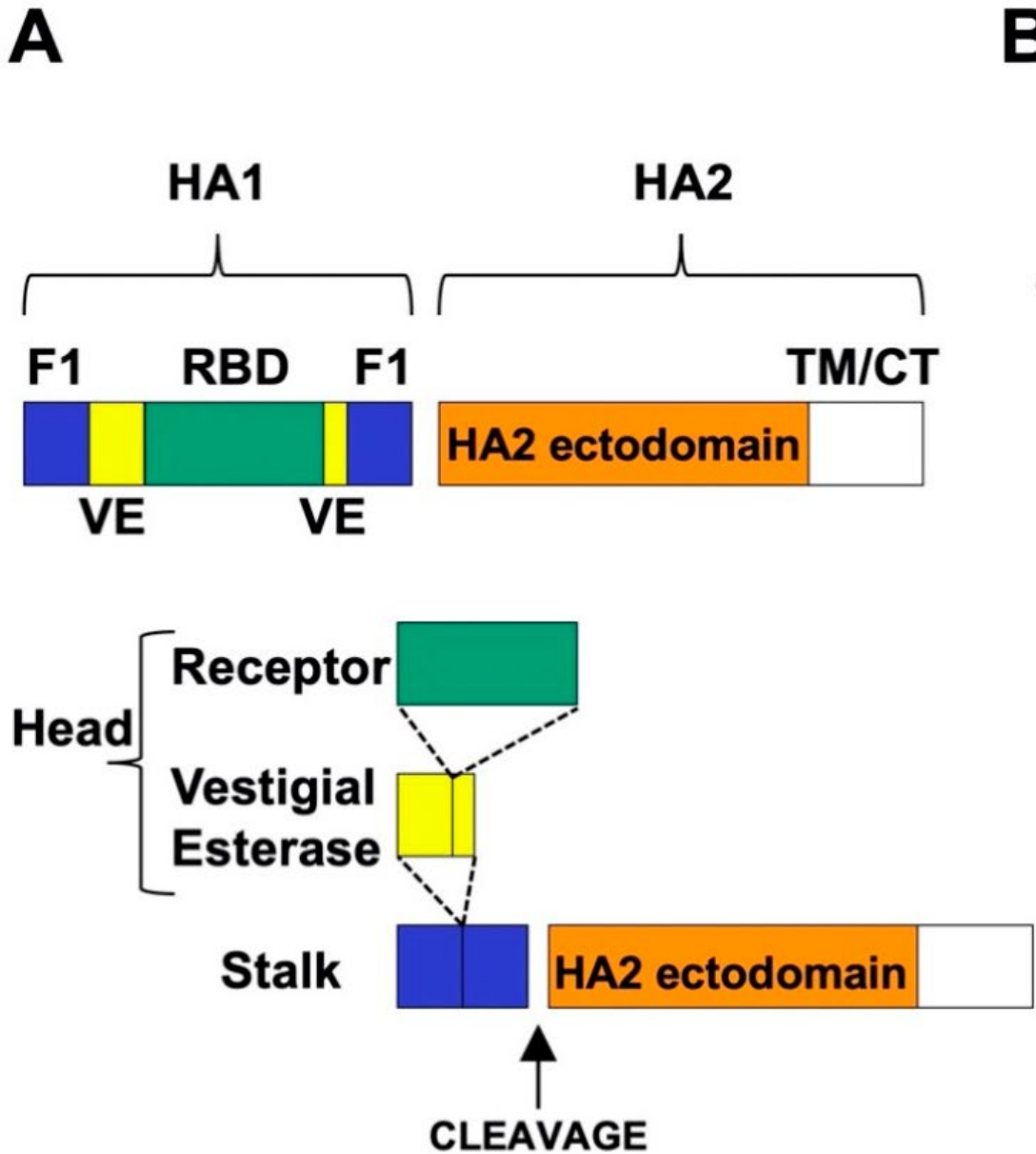

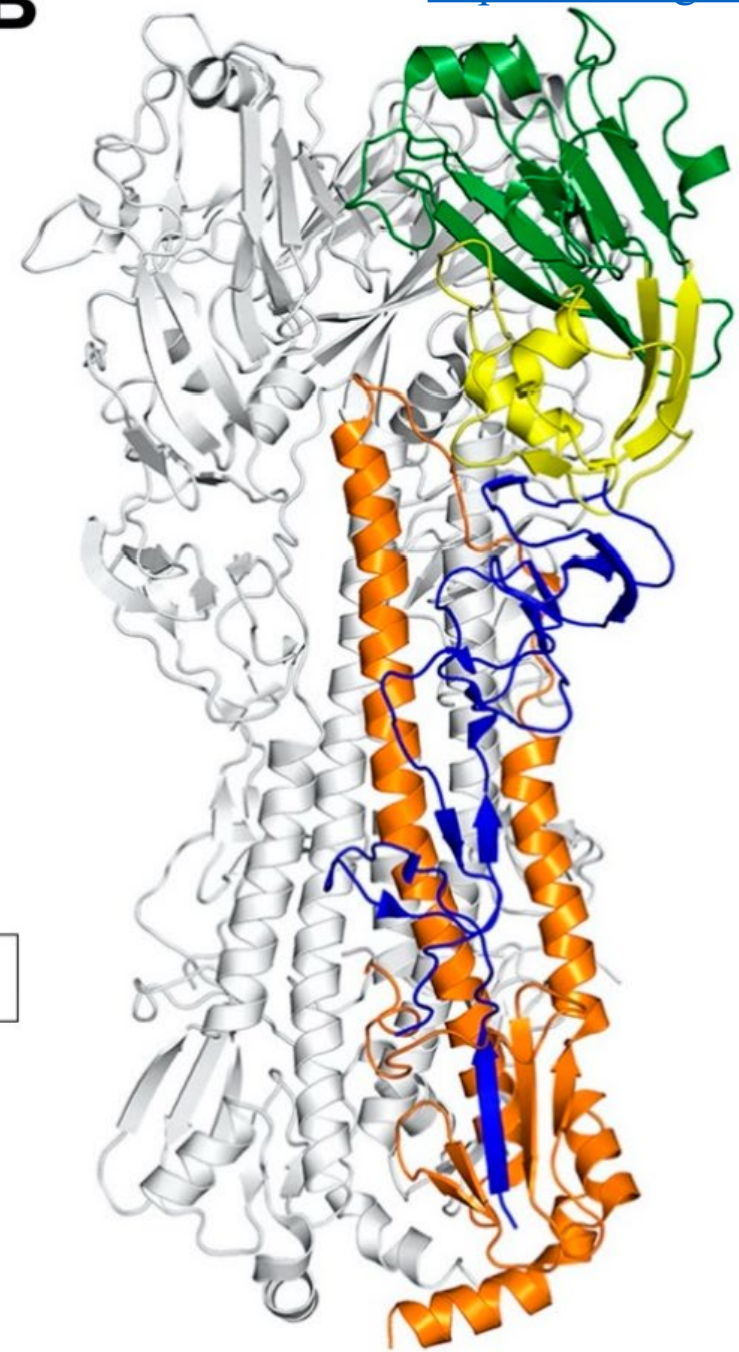

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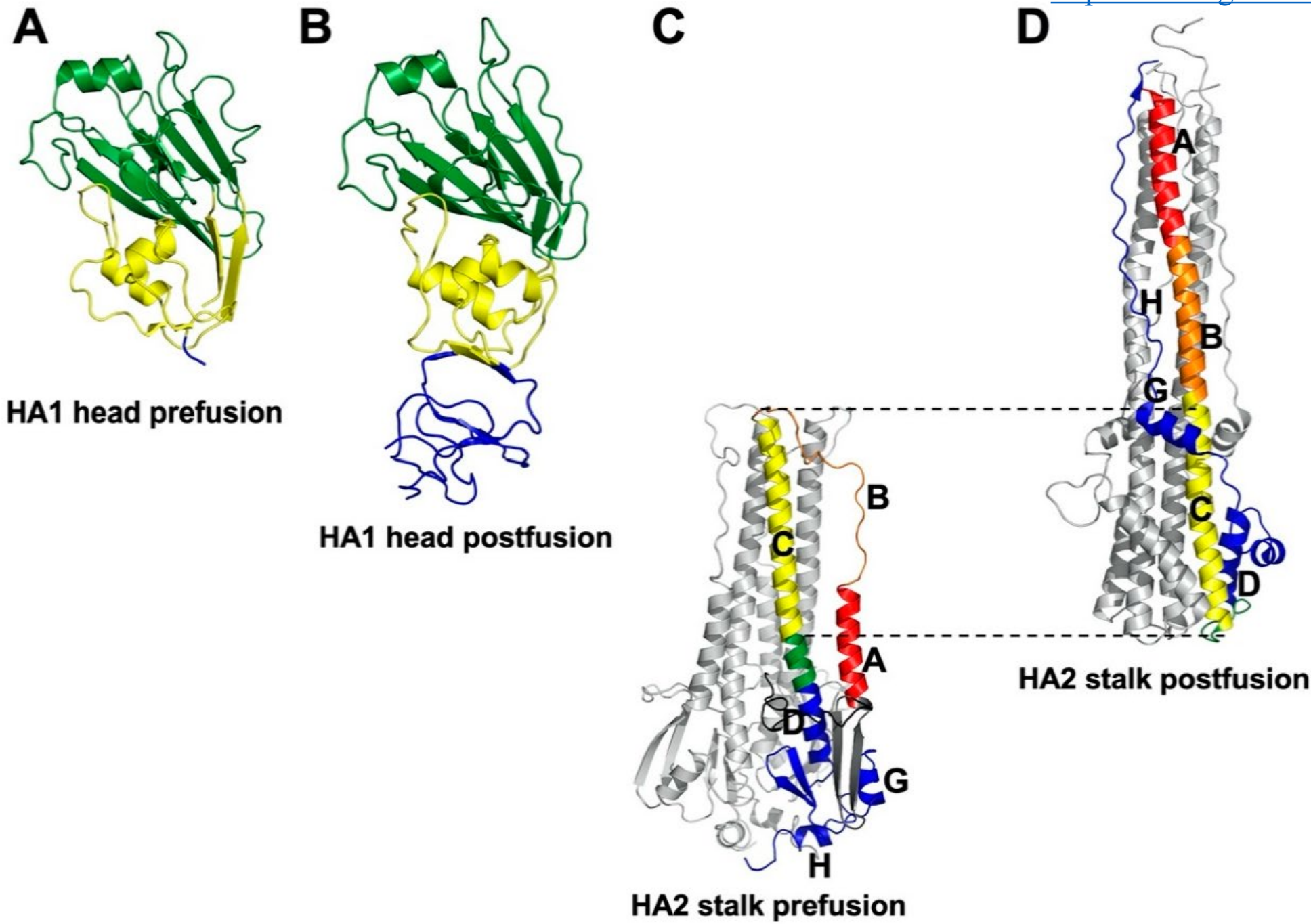

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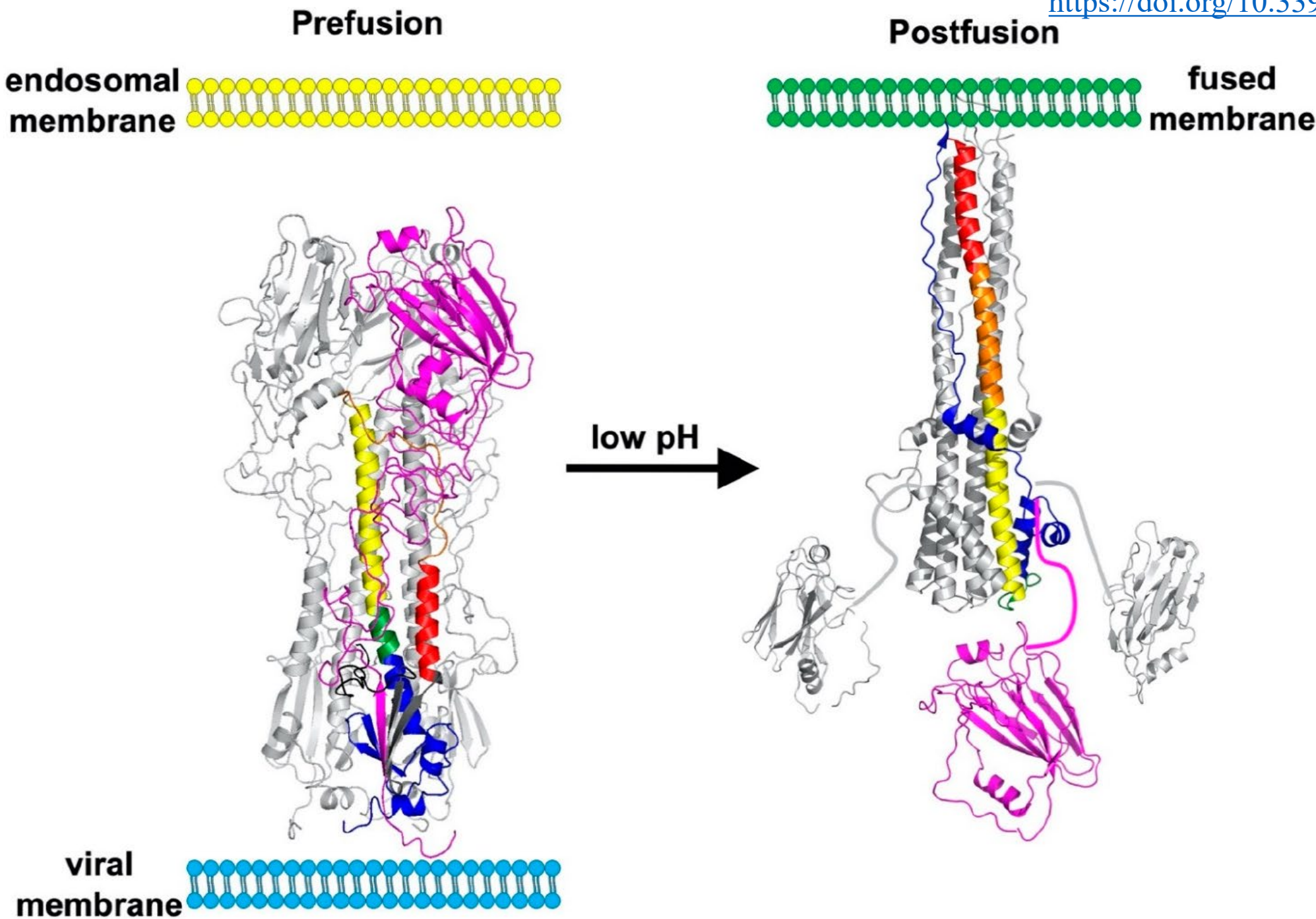

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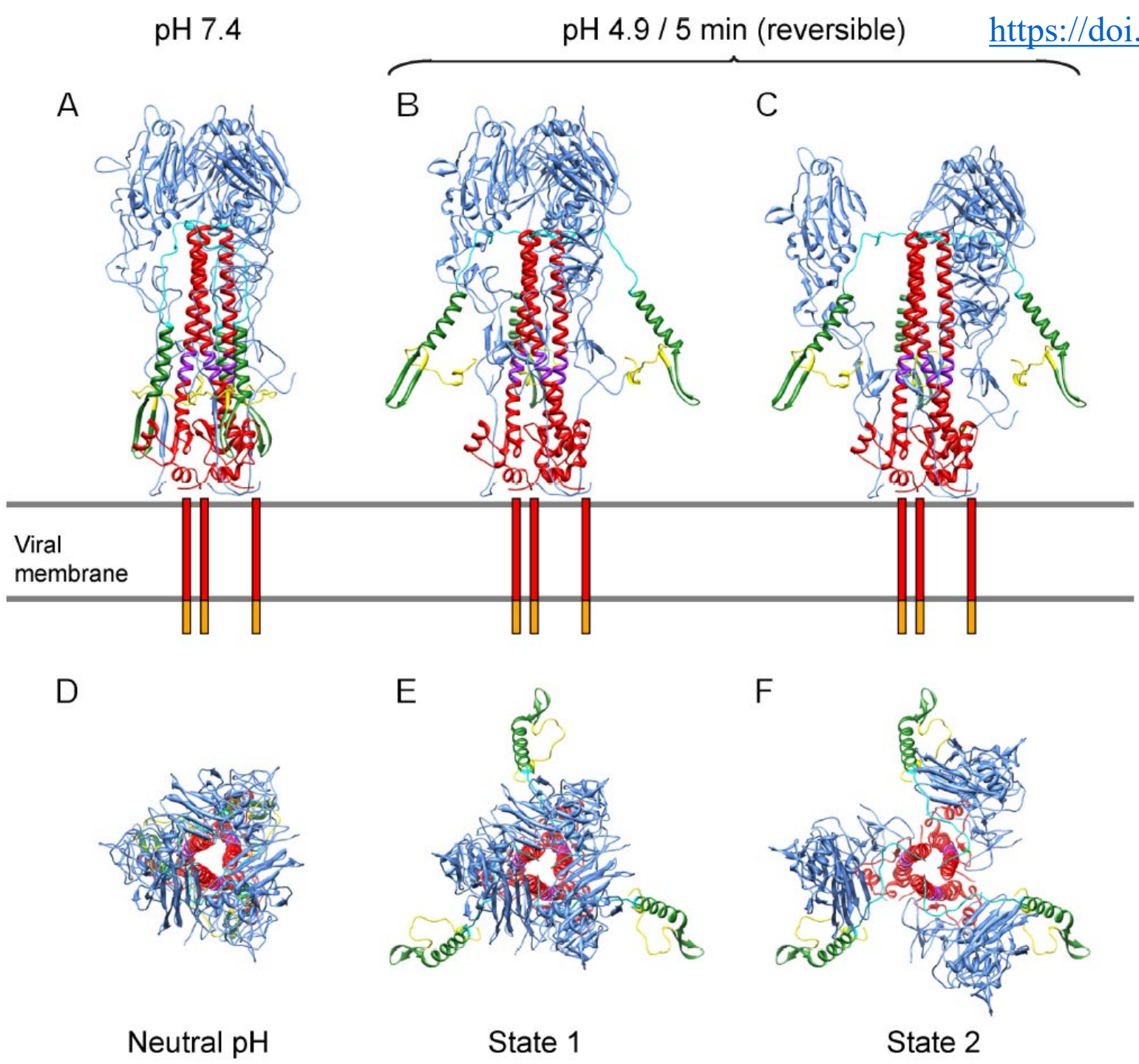

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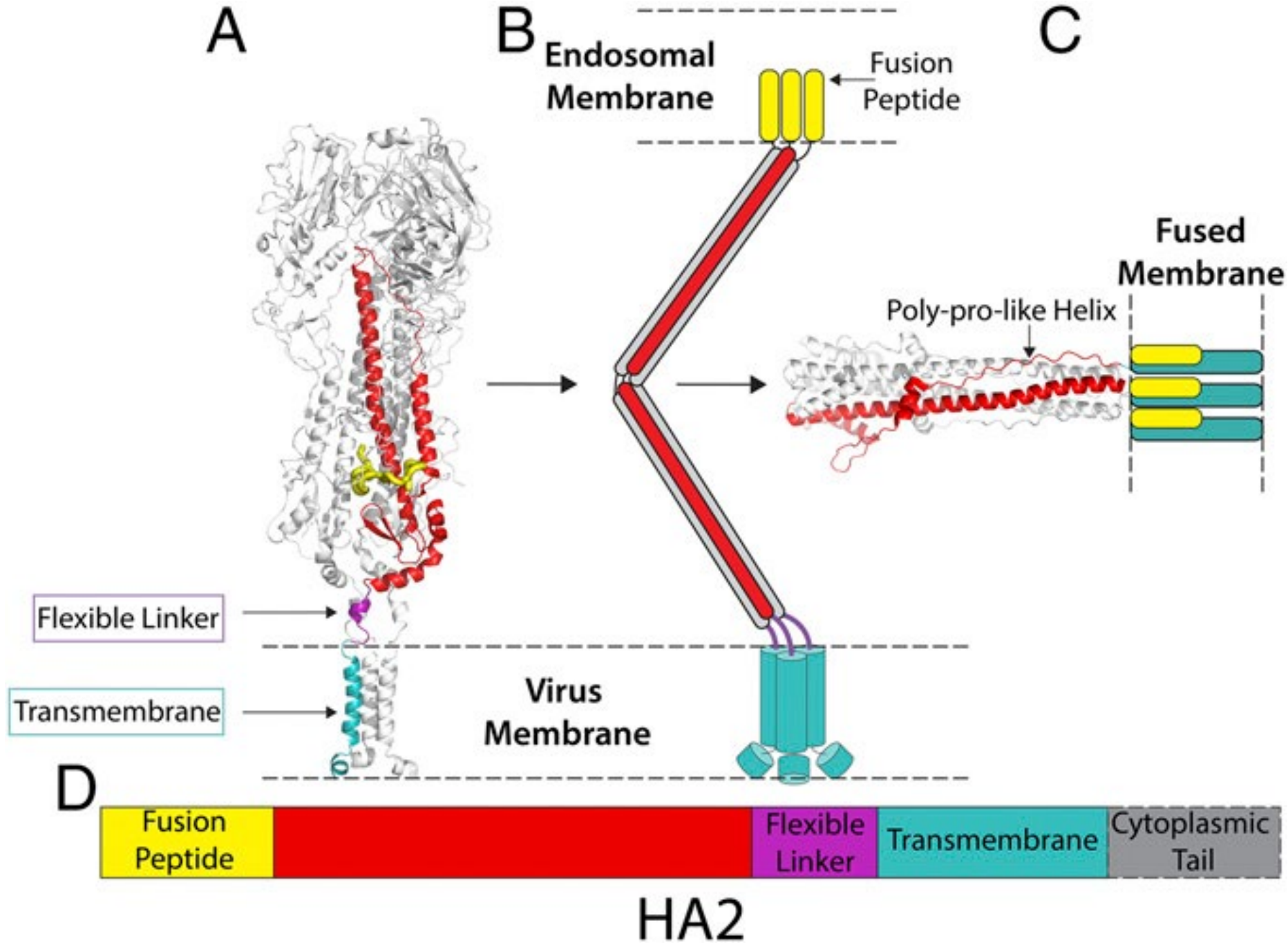
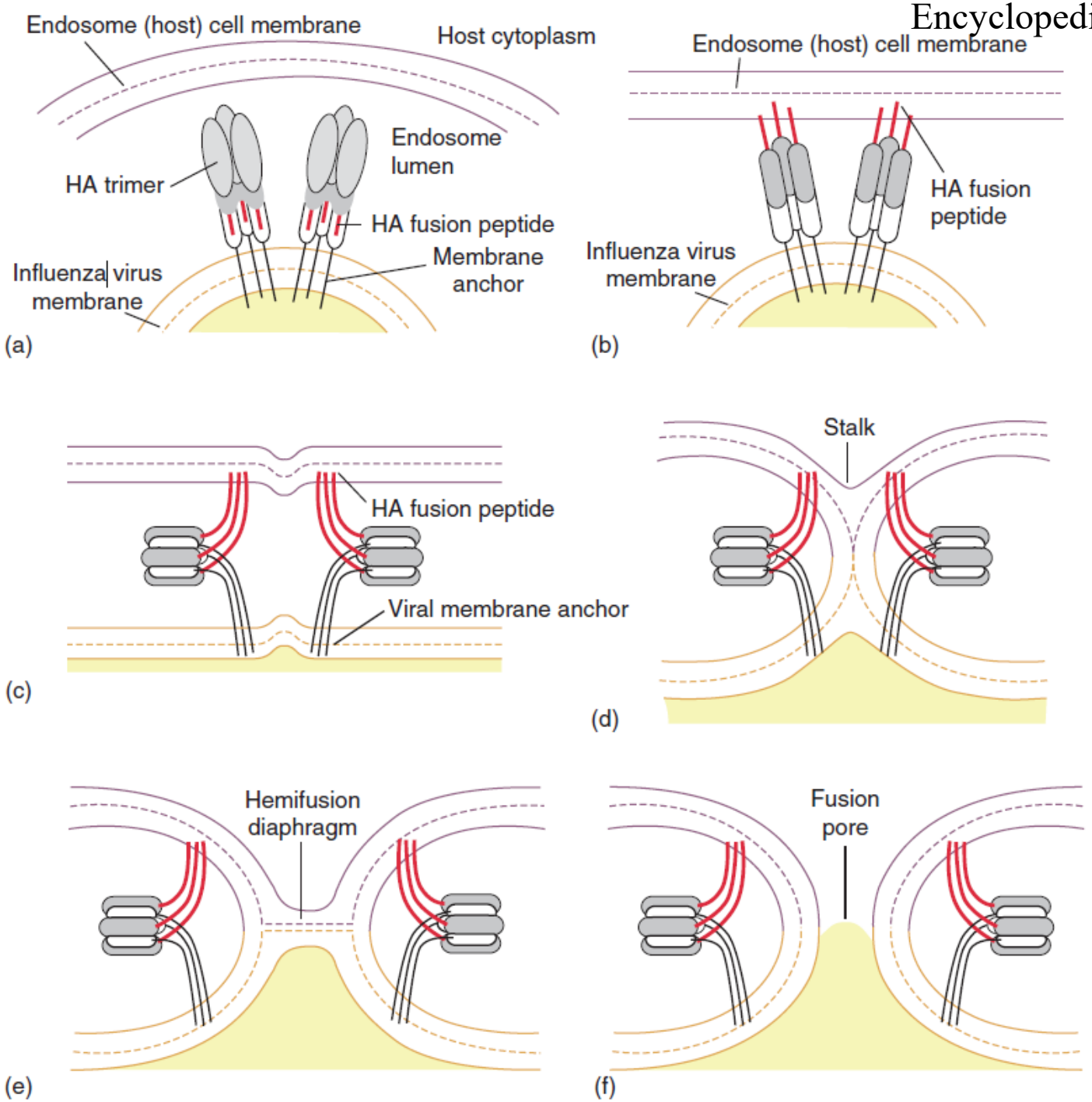



Endosome (host) cell membrane
Host cytoplasm
Endosome lumen
HA trimer
HA fusion peptide
Membrane anchor
Influenza virus membrane
(a)
Endosome (host) cell membrane
HA fusion peptide
Influenza virus membrane
(b)
HA fusion peptide
Viral membrane anchor
(c)
Stalk
(d)
Hemifusion diaphragm
(e)
Fusion pore
(f)

https://doi.org/10.1101%2Fcshperspect.a038620

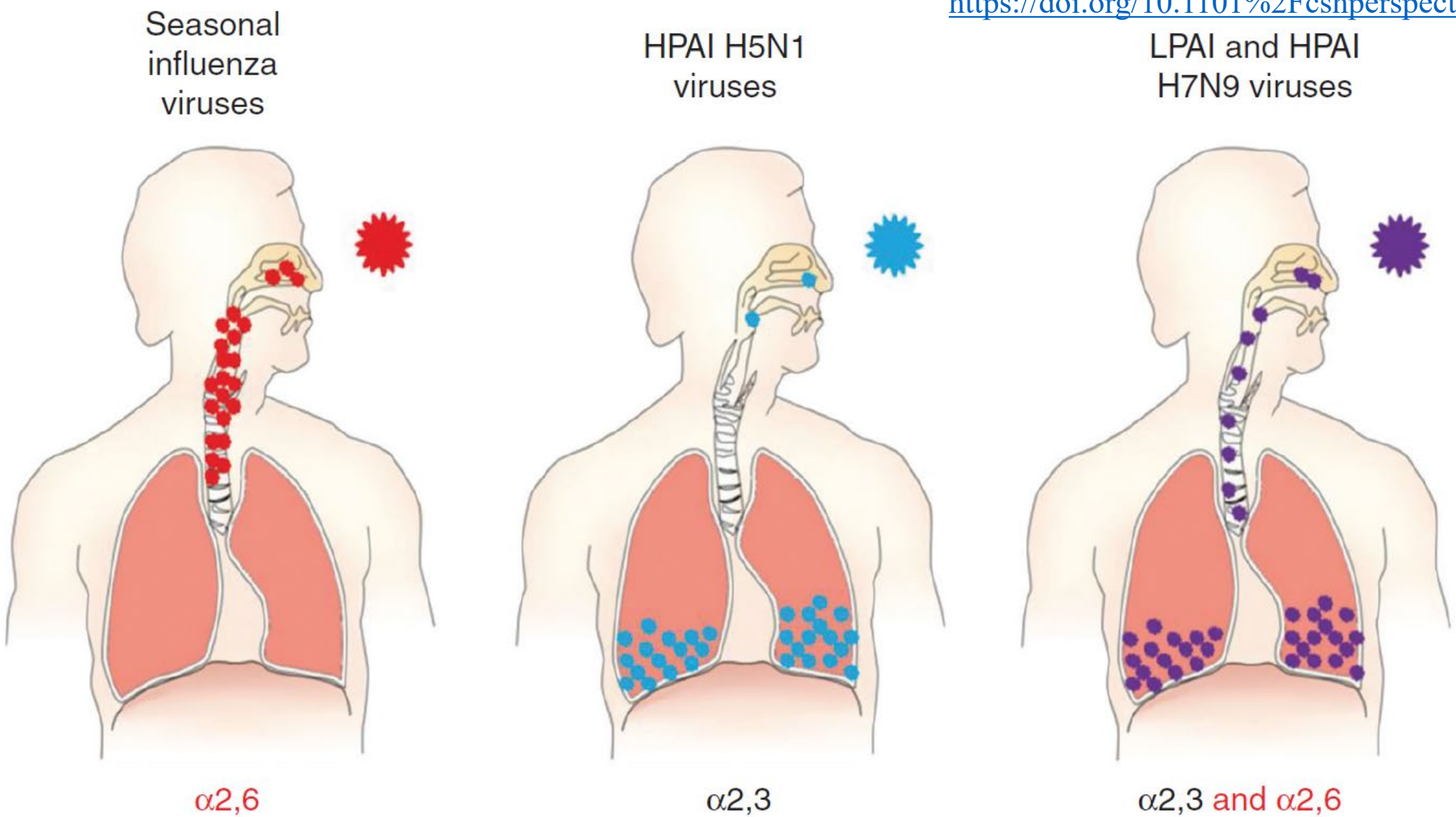


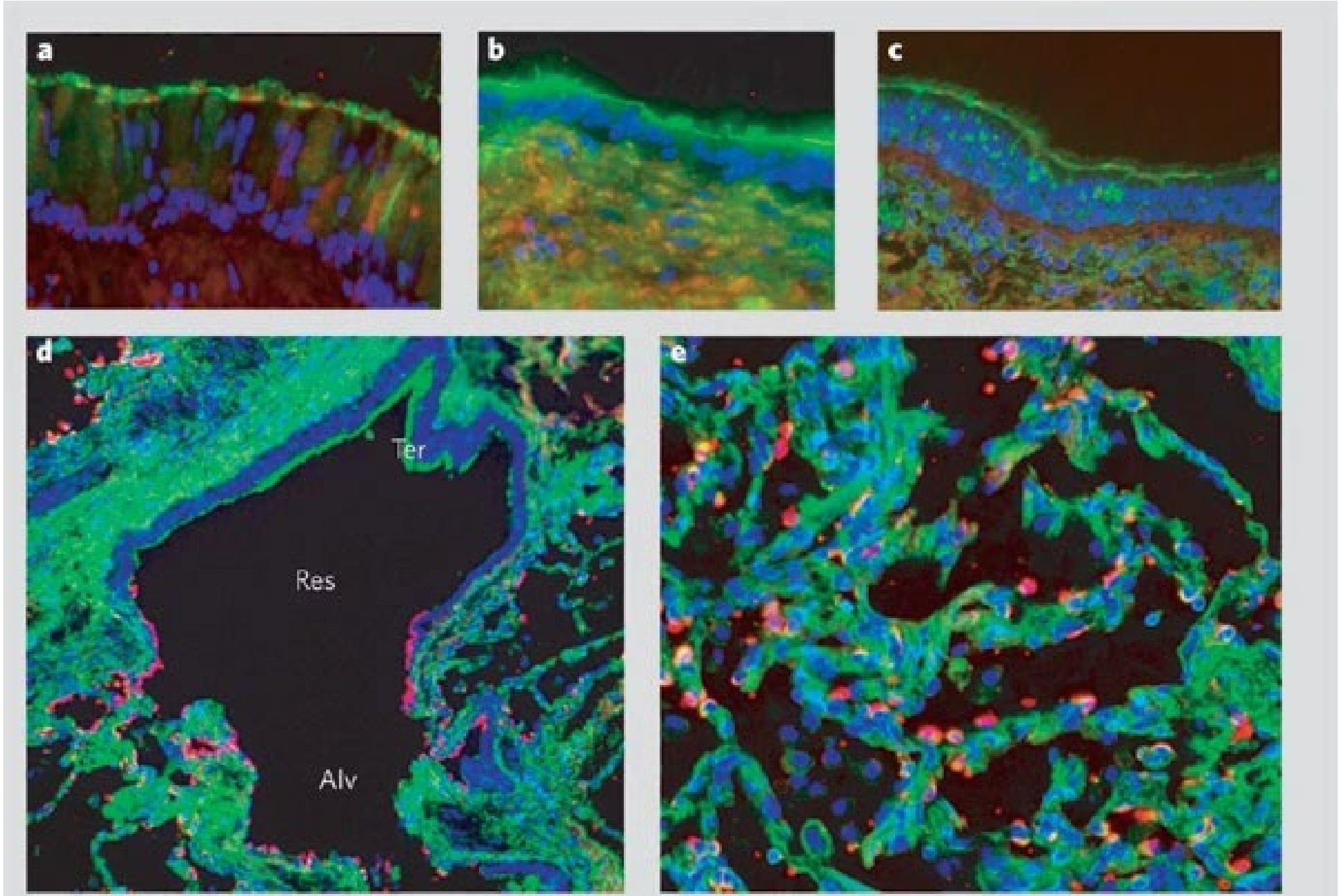
Figure 3. Airway tract tissue tropism illustration and the receptor-binding profiles of seasonal influenza viruses, avian H5N1 viruses, and influenza A(H7N9) viruses.

https://doi.org/10.3390%2Fv13020262

Table 1. Distribution of sialic acid receptors in different animal species.

Host	Distribution of SA α2,6-Gal	Distribution of SA α2,3-Gal	References
Humans	Ciliated and non-ciliated cells in respiratory tract; ileal epithelium	Ciliated cells in bronchioles and alveoli; colon epithelium; endothelial cells of blood vessels and inflammatory cells	[22,30,36,38–41,56]
Non-human primates	Goblet cells of submucosal glands and submucosal connective tissue; ciliated cells on epithelium in URT	Goblet cells of submucosal glands and submucosal connective tissue; Type II pneumocytes in lungs	[22,37,41,42]
Swine	Ciliated epithelia and goblet cells in trachea and bronchus; alveolar epithelium; duodenum; colon	Alveolar epithelium; duodenum; colon	[31,43–45]
Equines	Along nasal mucosa to bronchus; goblet cells	Ciliated nasal mucosa; trachea; bronchus; goblet cells	[49]
Bovines	Deficient in trachea;	Trachea	[45,47–49]
Camelidae	Not reported	Nasal respiratory epithelium; alveolar epithelial cells	[50]
Canines	Goblet cells and sub-epithelial regions of nasal mucosa and trachea; lamina propria; large intestine	Nasal mucosa; trachea; bronchi; alveoli; goblet cells and sub-epithelial regions of nasal mucosa and trachea; large intestine	[51,52]

https://www.nature.com/articles/440435a



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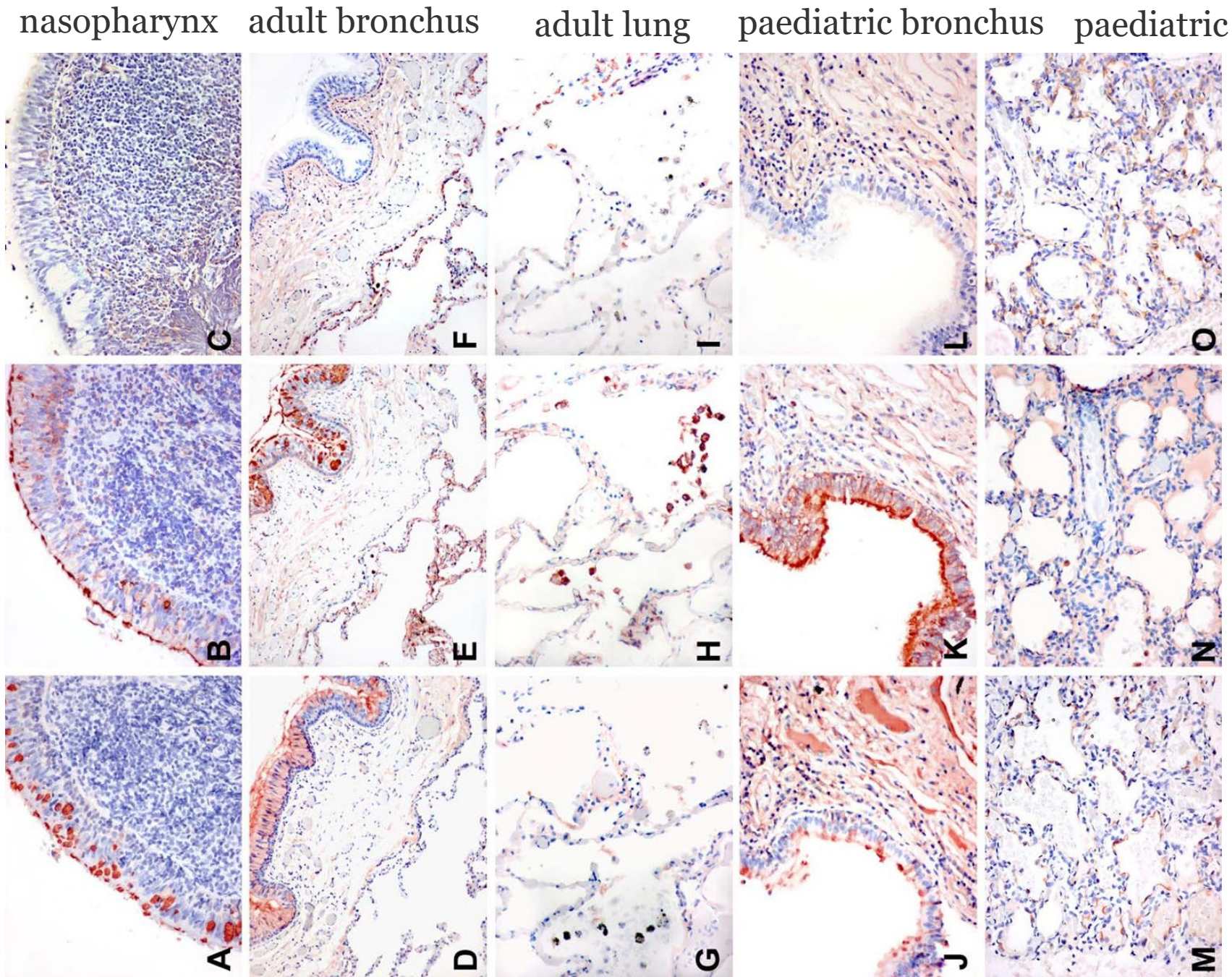

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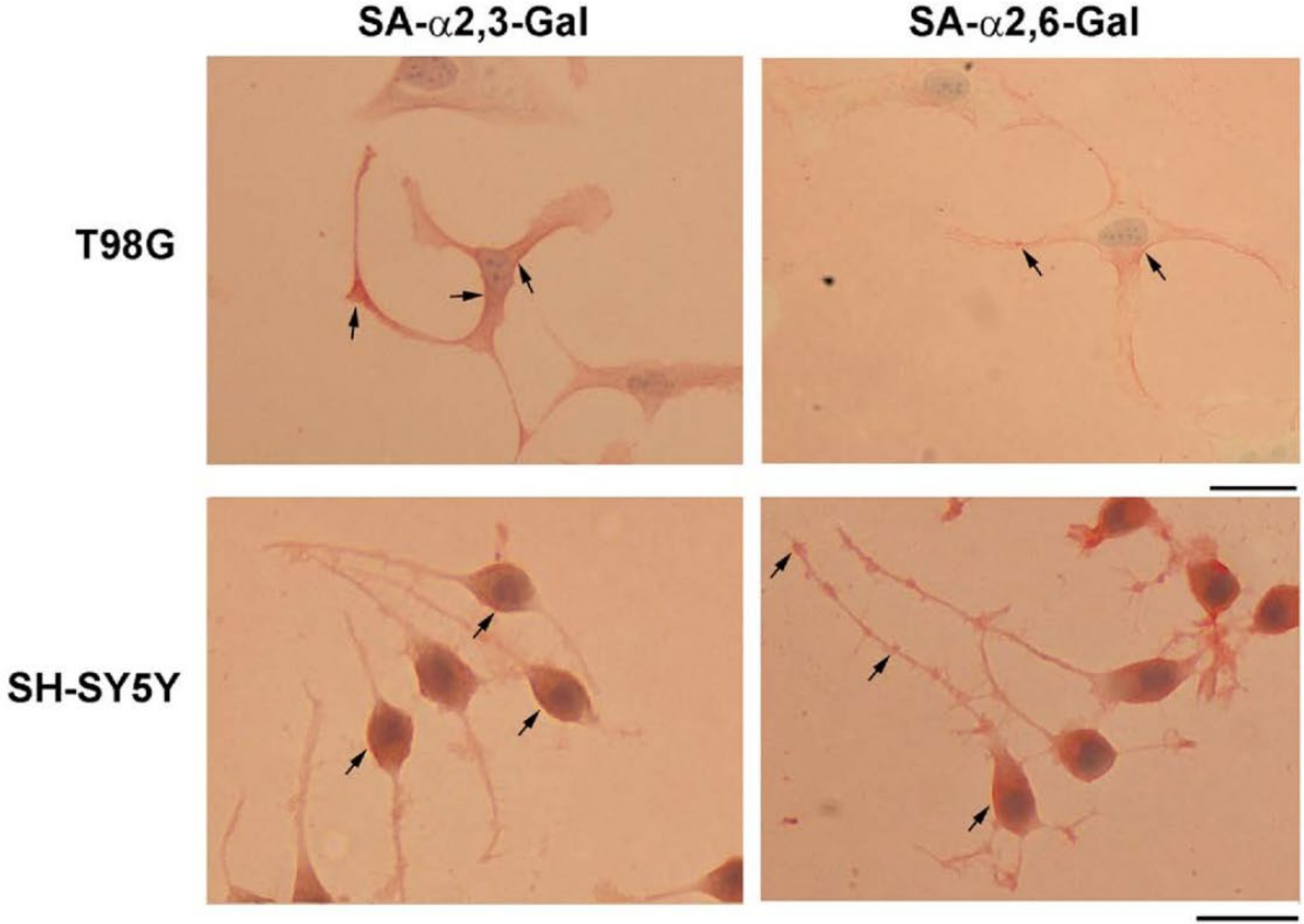

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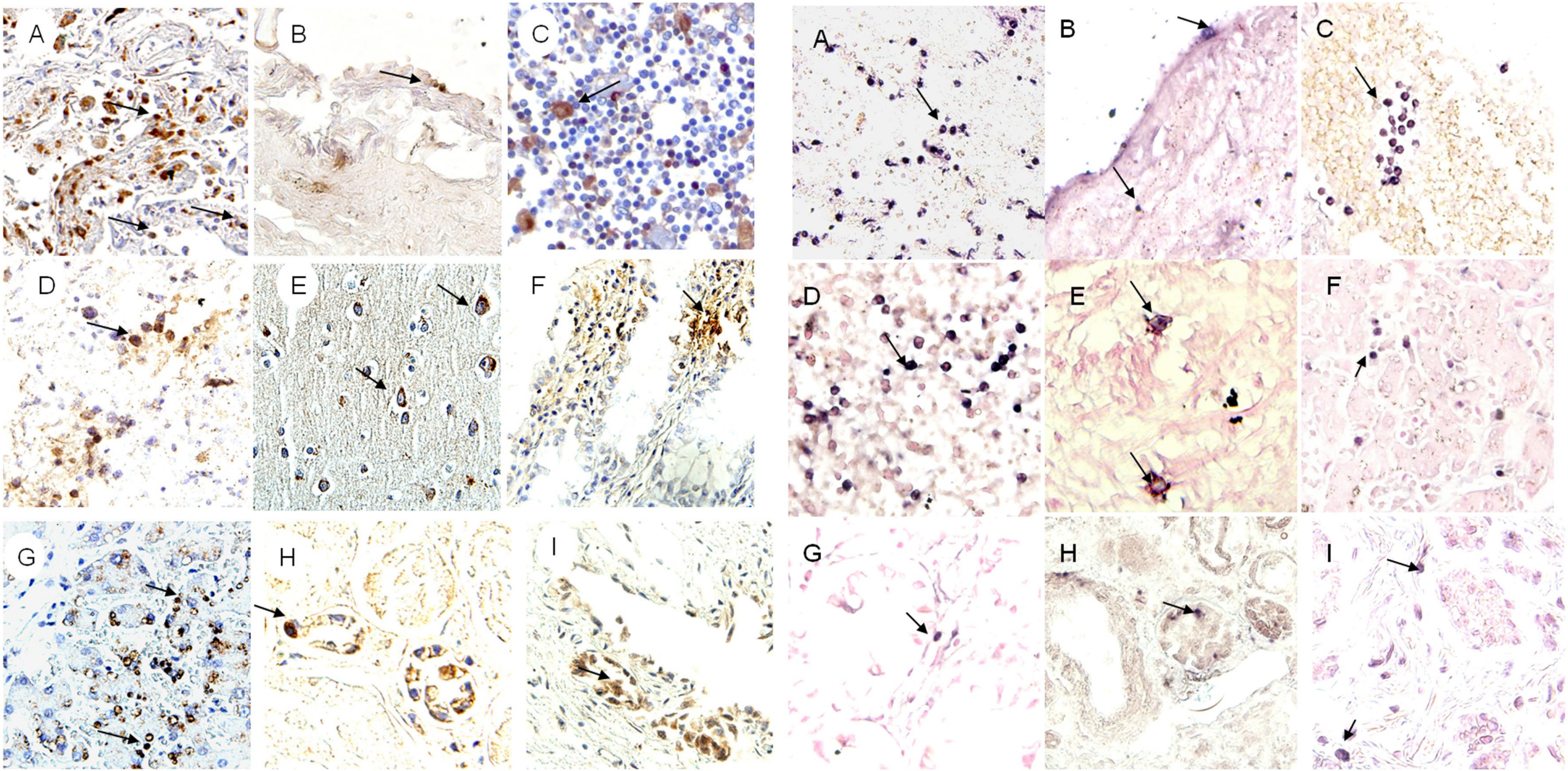

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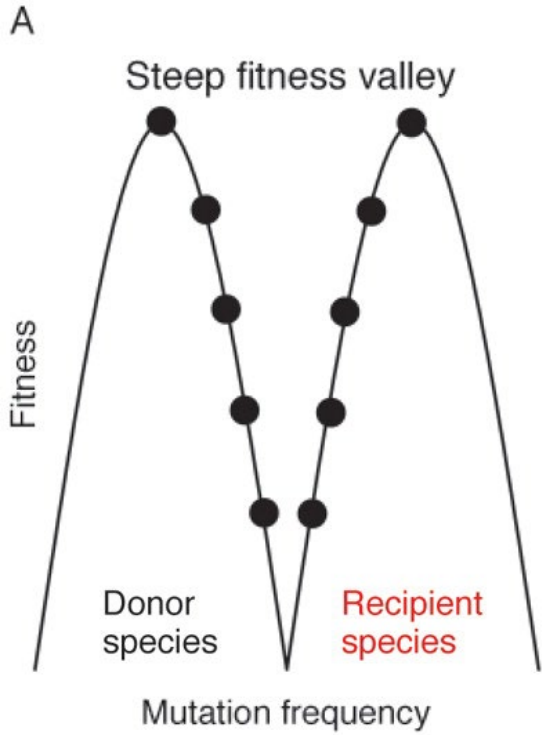
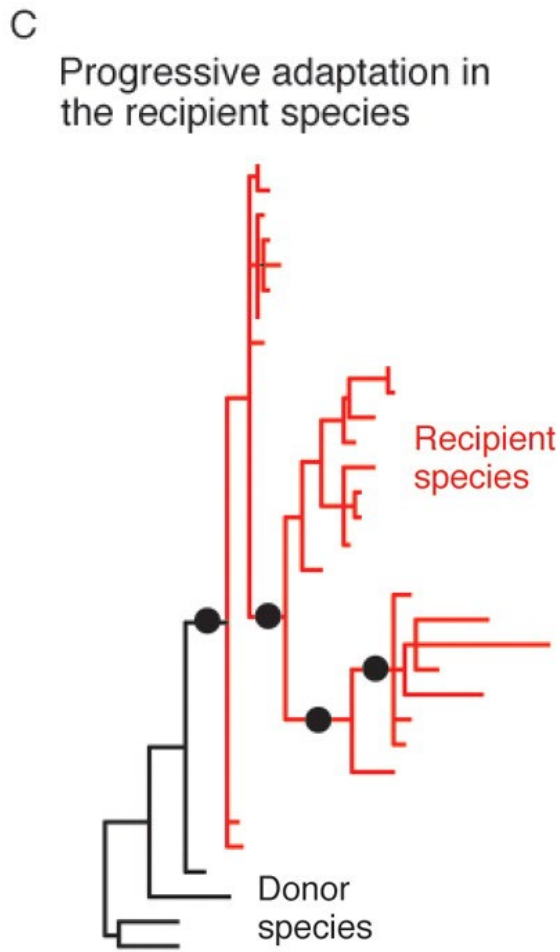
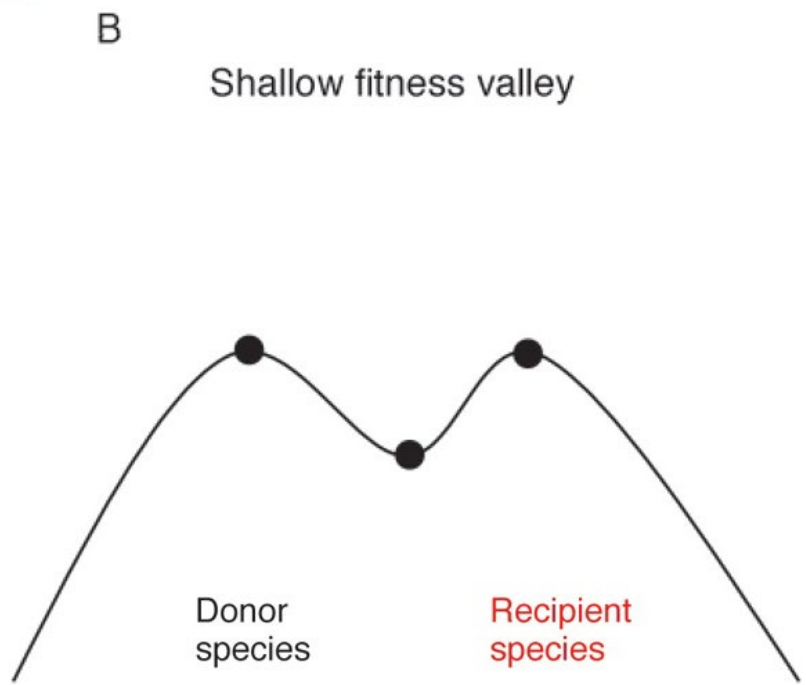
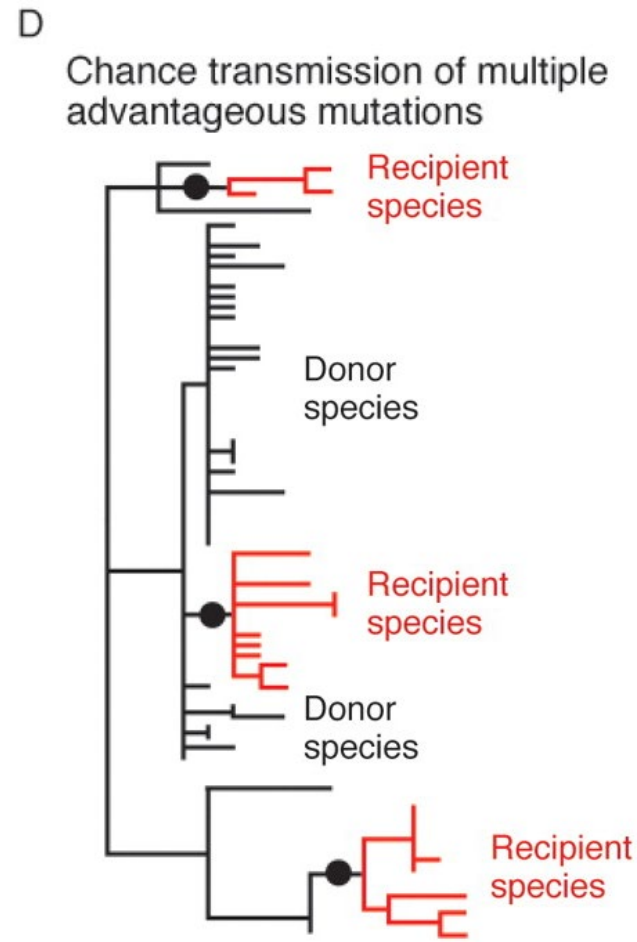
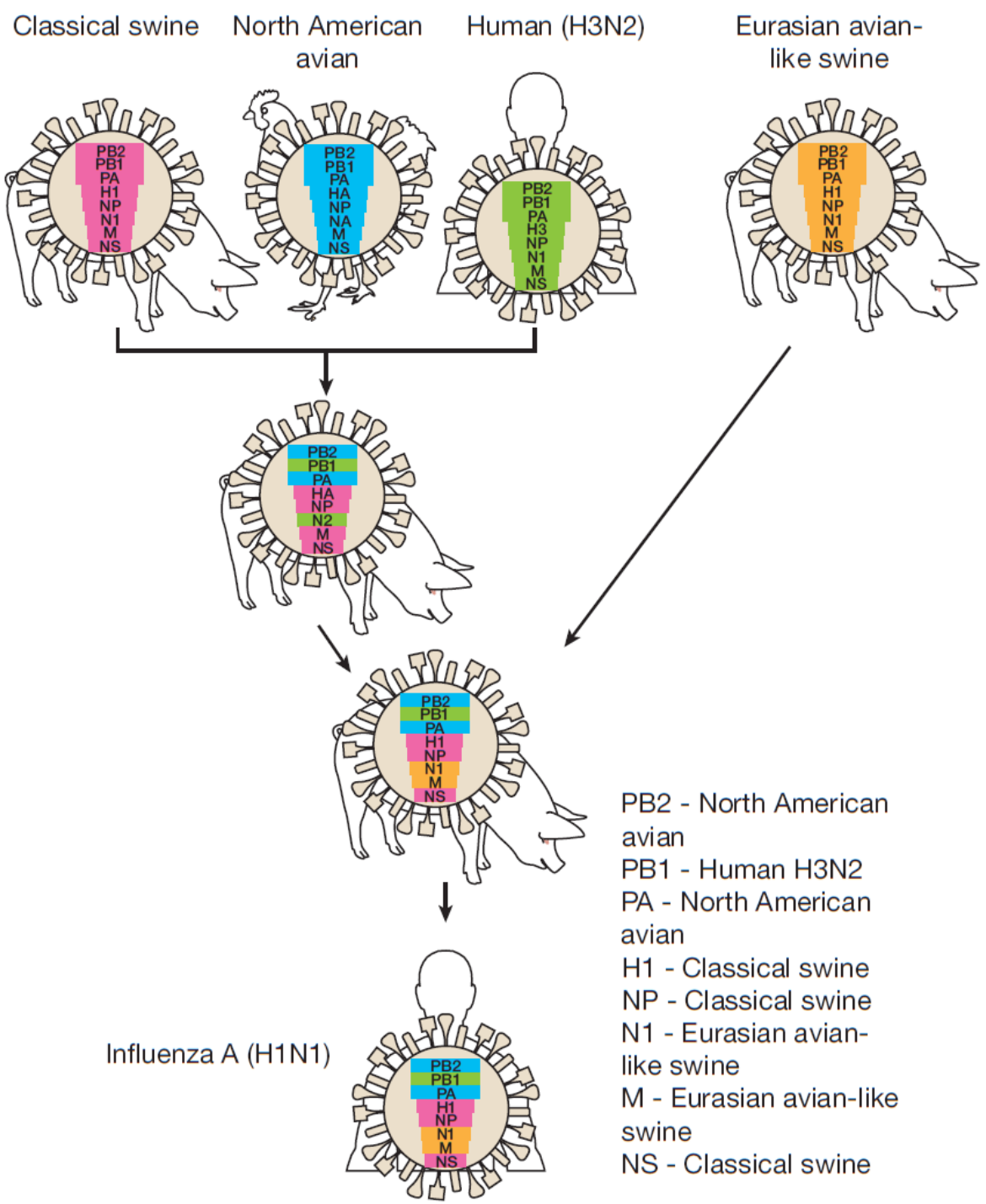


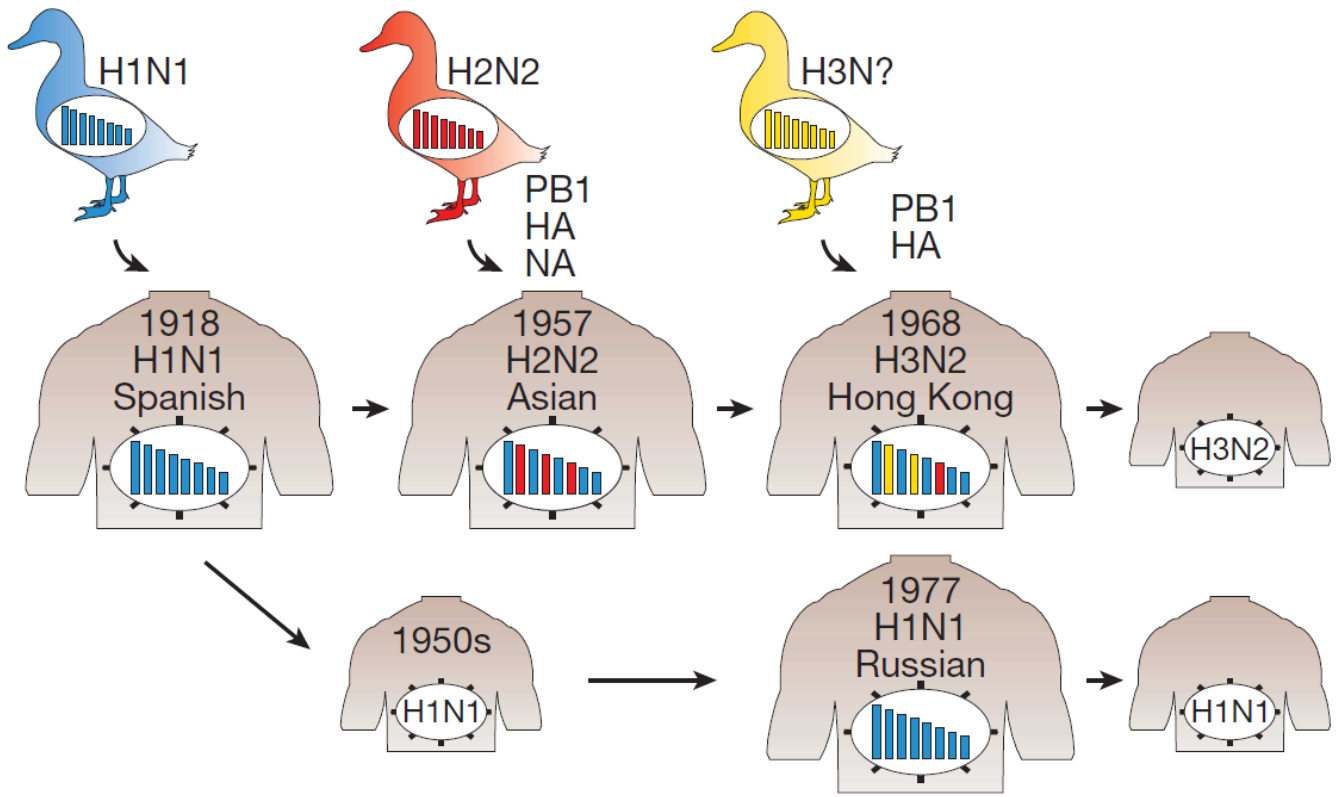






https://doi.org/10.1038/nature08157





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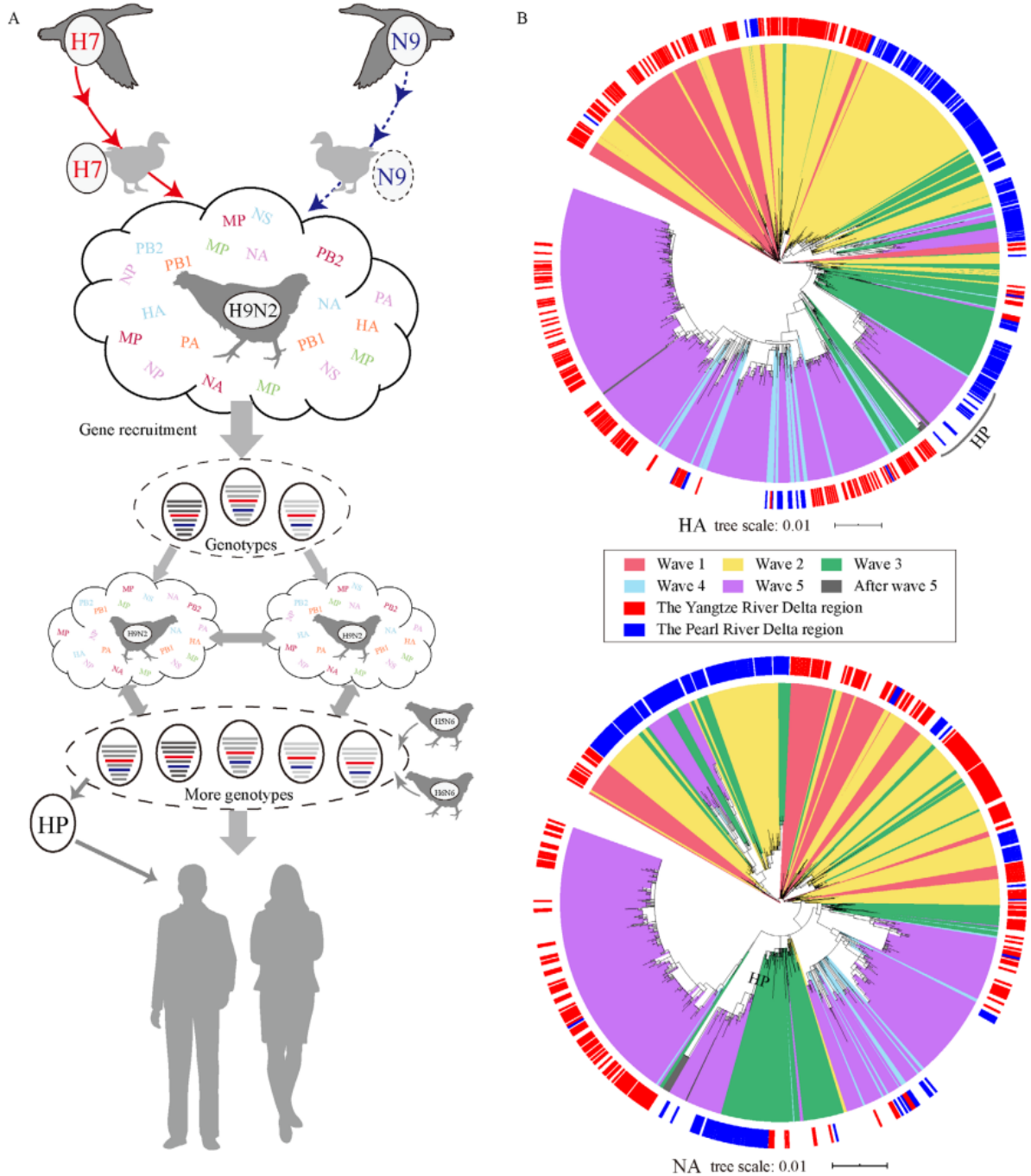

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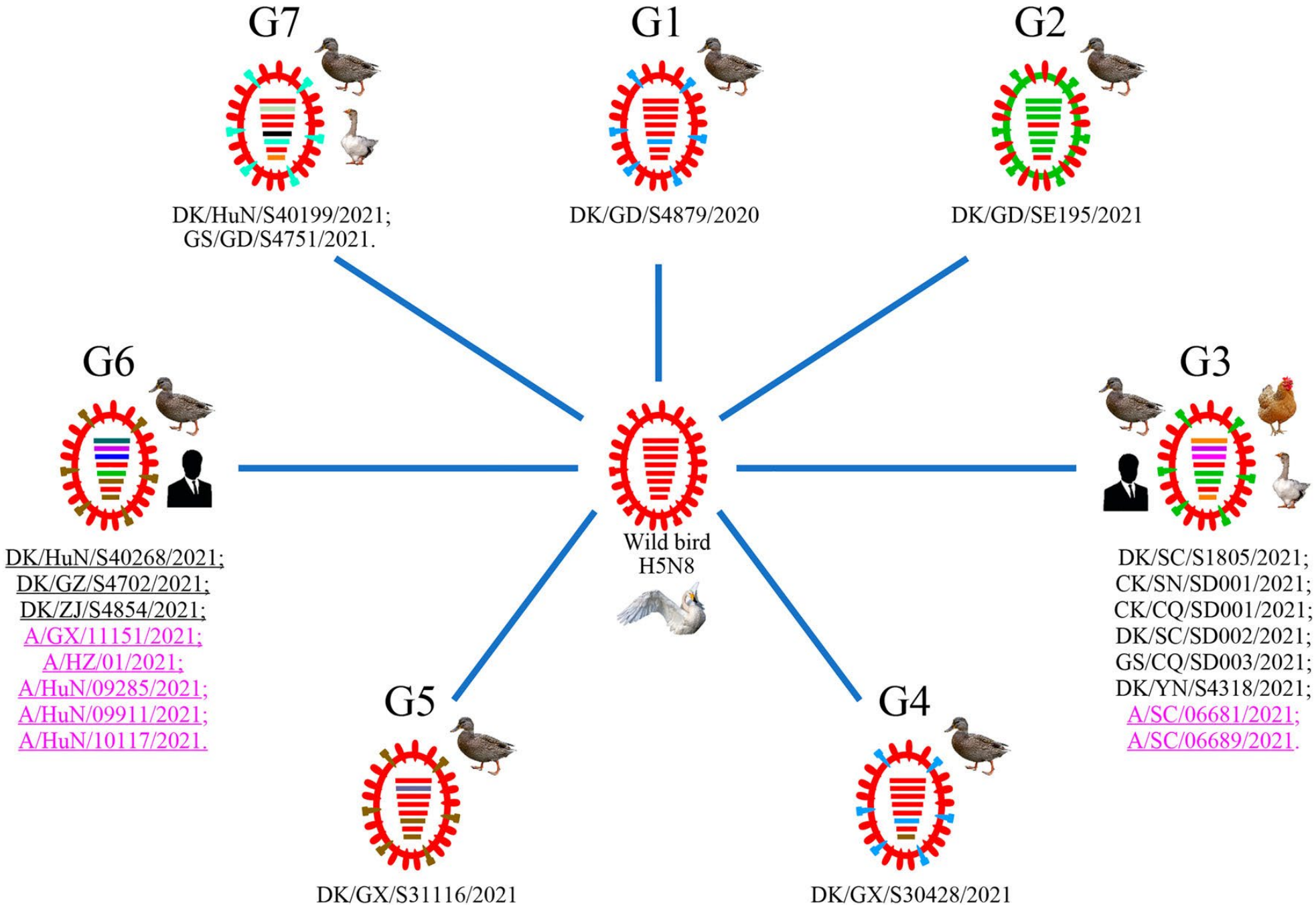

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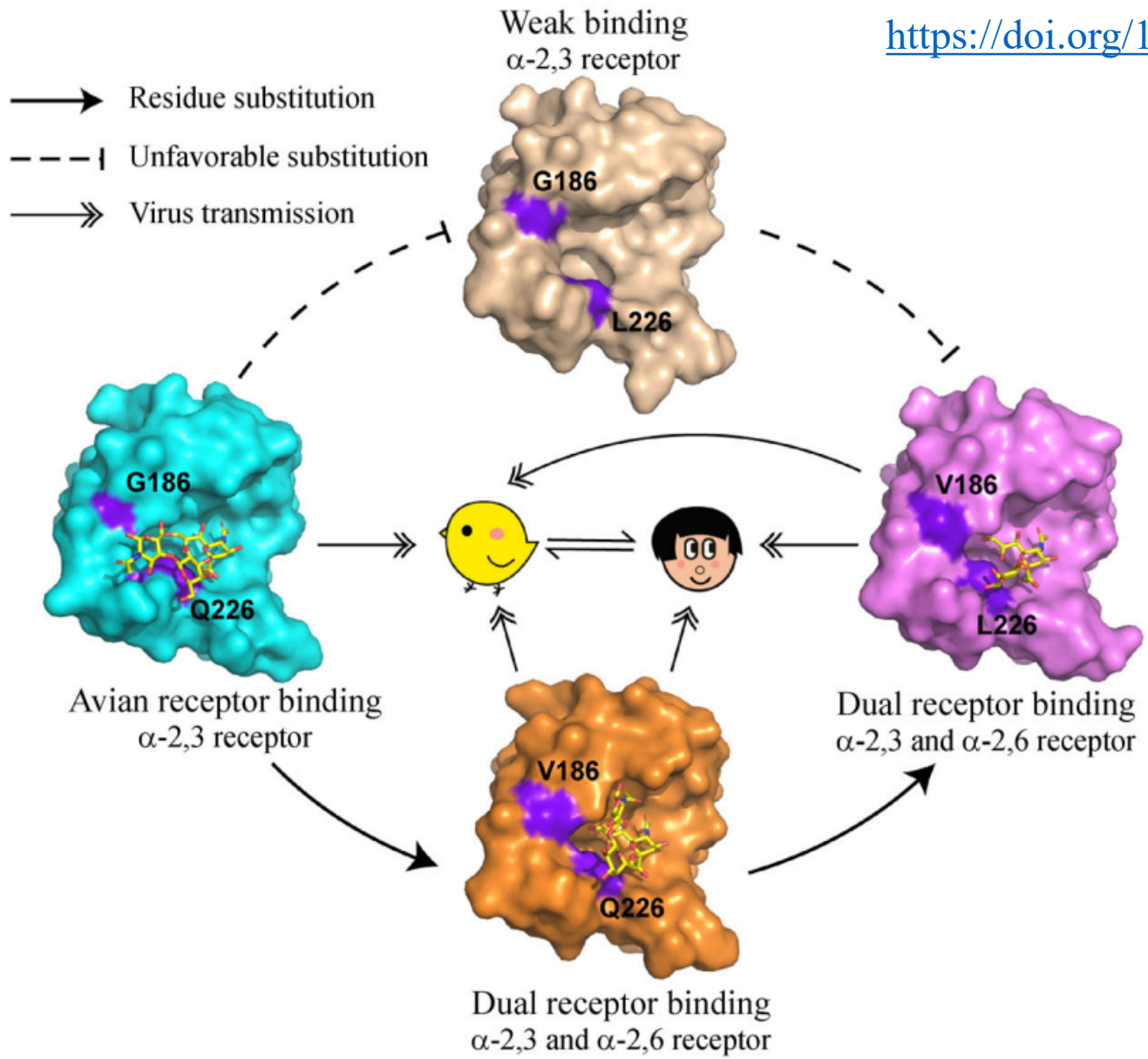


Fig. 3 Diagram of the evolutionary routes of H7N9 HA. H7 HA with different residue combinations at receptor binding sites (G186/Q226, V186/L226, G186/L226, and V186/Q226) are represented by surface sheets and colored cyan, violet, wheat, and orange. SA receptor analogs are shown as sticks and colored on the basis of elements (carbon, yellow; oxygen, red; nitrogen, blue). The positions of residues 186 and 226 are highlighted in purple.

https://doi.org/10.1007%2Fs11684-020-0814-5

Table 2 Critical amino acid residues in H7N9 proteins associated with viral virulence in mammals

Protein	Amino acid position	Potential biological functions
HA[a]	S138A	Responsible for the acquisition of human receptor binding capacity [70]
	T221P	
	G186V	Responsible for the acquisition of human receptor binding capacity [70,72]
	Q226L	Critical for binding the α-2,6-linked receptor and enables transmission in mammals [70,72,174,175]
	Insert-KRTA-at the HA cleavage site	Contributes to disease in mice [176]
	HA2-K64E	Reduces viral stability and replication in mice [176]
NA	19- to 20-amino-acid deletion in the NA stalk	Enhances virulence in mice [60]
PB2	T271A	Enhances viral replication in mammalian cells *in vitro* [175]
	K526R	Enhances viral replication in mammalian cells and in mice [56]
	A558V	Promotes mammalian adaptation [58]
	E627K	Associates with increased virulence of AIVs in mammals [33,175,177–179]
	Q591K	Increases pathogenicity in mice [177,178]
	D701N	
NP	V41I and/or D210E	Promotes the replication capability of H7N9 viruses at low temperature and thus might contribute to viral transmissibility [180]
	A286V	Attenuates the virulence of H7N9 viruses in mice [181]
	T437M	
NS1	V178I	Promotes viral replication in mice [182]
	P212S	

[a]H3 numbering.

https://doi.org/10.1093%2Fve%2Fveaa021

Table 2. Genetic comparison of HA molecules from different H7N9 isolates.

Viral strains	Collection date	Host	Cleavage peptide	Pathogenic	138aa	186aa	221aa	226aa[a]
A/Shanghai/1/2013	March, 2013	Human	PEIPKGR/GL	LP	S	G	T	Q
A/Anhui/1/2013	February, 2013	Human	PEIPKGR/GL	LP	A	V	P	L
A/Kunming/KMCDC-YHY/2017	March, 2017	Human	PEIPKGR/GL	LP	A	V	P	L
A/chicken/Yunnan/SD210/2017	November, 2017	Chicken	PEVPKRKRTAR/GL	HP	A	V	P	Q
A/China/LN/2017	December, 2017	Human	PEVPKRKRTAR/GL	HP	A	I	P	Q
A/chicken/Hunan/SD083/2017	February, 2017	Chicken	PEVPKRKRTAR/GL	HP	A	I	P	Q
A/chicken/Hunan/SD130/2017	March, 2017	Chicken	PEVPKRKRTAR/GL	HP	A	I	P	Q
A/Guangdong/17SF039/2017	February, 2017	Human	PEVPKRKRTAR/GL	HP	A	I	P	Q
A/Guangxi/18910/2017	March, 2017	Human	PEVPKRKRTAR/GL	HP	A	I	P	Q
A/Hunan/25351/2017	April, 2017	Human	PEVPKRKRTAR/GL	HP	A	I	P	H
A/Beijing/28707/2017	June, 2017	Human	PEIPKGR/GL	LP	A	I	P	L

[a]H3 numbering.
HP, highly pathogenic; LP, low pathogenic.

https://doi.org/10.7717%2Fpeerj.14419

Table 1 **Analysis for genetic determinants of HPAI H5N1 HA and NA compared to the H5N1 genetic change inventory (*Centers for Disease Control and Prevention, 2012*).**

Protein	Amino acid observed in Thai HPAI H5N1 isolates	Amino acid mutation previously reported	Association and function
HA[a]	190E (100%) and 225G (100%)	D190E and D225G	190D and 225D - human receptor preference 190E and 225G - avian receptor preference
	226Q (100%) and 228G (100%)	Q226L and G228S	226Q and 228G - receptor binding site for avian receptors 226L and 228S - receptor binding site for human receptors
	RE RRRKKR↓GLF (81%) RE KRRKKR↓GLF (10%) IE RRRKKR↓GLF (4%) RE RKRKKR↓GLF (3%) RE RRRKR↓GLF (1%) RE RRRKR↓GLF (1%)	RRRKK (329–333)	Polybasic amino acid insertion at HA cleavage site: RRRKK - indicator for HPAI and systemic infection
NA[b]	20-amino acid deletion at stalk region (100%)	20-amino acid deletion at stalk region[c]	Contributes to the high pathogenicity of H5N1 viruses
	274H (100%)	274H	Oseltamivir sensitive
		274Y	Oseltamivir resistance

Notes.

[a]Amino acid position on HA based on H3 numbering.

[b]Amino acid position on NA based on N2 numbering.

[c]NA of A/goose/Guangdong/1/96 (H5N1) contained CNQSIITYENNTWVNQTYVN at stalk region, but it was not present in NA of HPAI H5N1 Thailand isolates.

https://doi.org/10.3201/eid2907.221149

Appendix 2 Table 5. Mutations detected in the clade 2.3.4.4b H5N1 viruses that contributed to increased binding to human-type receptors and virulence in mammals

		Amino acids in HA that may increase the affinity to human-type receptor (H3 numbering)				Mutations in different genes that may increase virulence in mice						
						PB1-F2	M1			NS1		
Virus	Genotype	S137A	N158D	T160A	T192I	N66S	N30D	I43M	T215A	P42S	L103F	I106M
MD/HLJ/HL-1/2021	G07	A	N	A	I	N	D	M	A	S	F	M
MD/HLJ/HL-2/2021	G07	A	N	A	I	N	D	M	A	S	F	M
WS/SX/14/2021	G10	A	D	A	I	S	D	M	A	S	F	M
WS/SX/20/2021	G10	A	D	A	I	S	D	M	A	S	F	M
WS/SX/601/2021	G10	A	D	A	I	S	D	M	A	S	F	M
WS/SX/608/2021	G10	A	D	A	I	S	D	M	A	S	F	M
WS/HeN/2/2021	G10	A	D	A	I	S	D	M	A	S	F	M
WS/HeN/6/2021	G10	A	D	A	I	S	D	M	A	S	F	M
WS/HeN/8/2021	G10	A	D	A	I	S	D	M	A	S	F	M
WS/HeN/14/2021	G10	A	D	A	I	S	D	M	A	S	F	M
WS/HeN/15/2021	G10	A	D	A	I	S	D	M	A	S	F	M
WS/HeN/28/2021	G10	A	D	A	I	S	D	M	A	S	F	M
WS/HeN/44/2021	G10	A	D	A	I	S	D	M	A	S	F	M
WS/HeN/45/2021	G10	A	D	A	I	S	D	M	A	S	F	M
WS/HeN/46/2021	G10	A	D	A	I	S	D	M	A	S	F	M
WS/HeN/424/2021	G10	A	D	A	I	S	D	M	A	S	F	M
MD/HeN/426/2021	G10	A	D	A	I	S	D	M	A	S	F	M

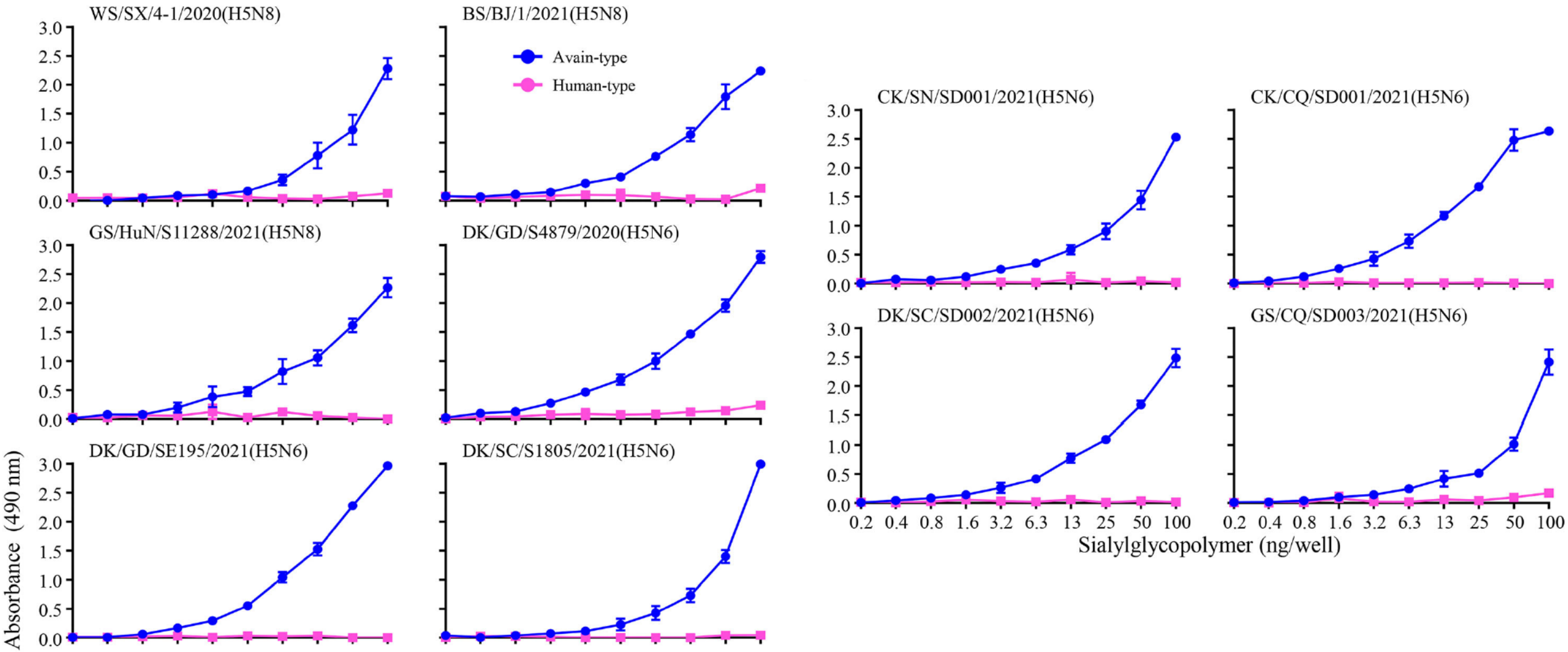
https://doi.org/10.1080%2F22221751.2022.2063076

Table 2. Mutations detected in the H5N6 viruses that contribute to the increased binding to human-type receptors and virulence in mammals.

		Amino acids in HA that increase affinity to human-type receptors (H3 numbering)		Amino acids that increase the replication and virulence of avian influenza viruses in mammals					
				HA	PB2		PB1	M1	NS1
Virus	Genotype	137/158/160/186	192	225	89/309/389 /598	292	622	30/43/215	42/106
DK/GD/S4879/2020	G1	A/N/A/N	I	G	V/D/R/T	V	G	D/M/A	S/M
DK/GD/SE195/2021	G2	A/N/A/N	I	G	V/D/R/T	V	G	D/M/A	S/M
DK/SC/S1805/2021	G3	A/N/A/N	I	G	V/D/R/T	/[b]	G	D/M/A	S/M
CK/SN/SD001/2021	G3	A/N/A/N	I	G	V/D/R/T	/	G	D/M/A	S/M
CK/CQ/SD001/2021	G3	A/N/A/N	I	G	V/D/R/T	/	G	D/M/A	S/M
DK/SC/SD002/2021	G3	A/N/A/N	I	G	V/D/R/T	/	G	D/M/A	S/M
GS/CQ/SD003/2021	G3	A/N/A/N	I	G	V/D/R/T	/	G	D/M/A	S/M
DK/YN/S4318/2021	G3	A/N/A/N	I	G	V/D/R/T	/	G	D/M/A	S/M
A/SC/06681/2021[a]	G3	A/N/A/N	I	G	V/D/R/T	/	G	D/M/A	S/M
A/SC/06689/2021[a]	G3	A/N/A/N	I	G	V/D/R/T	/	G	D/M/A	S/M
DK/GX/S30428/2021	G4	A/N/A/N	I	G	V/D/R/T	V	G	D/M/A	S/M
DK/GX/S31116/2021	G5	A/N/A/N	I	G	V/D/R/T	V	G	D/M/A	S/M
DK/HuN/S40268/2021	G6	A/N/A/N	I	G	V/D/R/T	/	G	D/M/A	S/M
DK/GZ/S4702/2021	G6	A/N/A/N	I	G	V/D/R/T	/	G	D/M/A	S/M
DK/ZJ/S4854/2021	G6	A/N/A/N	/	G	V/D/R/T	/	G	D/M/A	S/M
A/GX/11151/2021[a]	G6	A/N/A/N	I	G	V/D/R/T	/	G	D/M/A	S/M
A/HZ/01/2021[a]	G6	A/N/A/N	I	G	V/D/R/T	/	G	D/M/A	S/M
A/HuN/09285/2021[a]	G6	A/N/A/N	I	G	V/D/R/T	/	G	D/M/A	S/M
A/HuN/09911/202[a]	G6	A/N/A/N	I	G	V/D/R/T	/	G	D/M/A	S/M
A/HuN/10117/2021[a]	G6	A/N/A/N	I	G	V/D/R/T	/	G	D/M/A	S/M
DK/HuN/S40199/2021	G7	A/N/A/N	/	G	V/D/R/T	V	G	D/M/A	S/M
GS/GD/S4751/2021	G7	A/N/A/N	I	G	V/D/R/T	V	G	D/M/A	S/M

[a]Sequences of human H5N6 viruses were downloaded from the GISAID.
[b]No such mutation.

https://doi.org/10.1080%2F22221751.2022.2063076



https://www.cdc.gov/flu/avianflu/h5n1/inventory.htm

Protein	Amino acid position/motif[a]	Phenotypic consequences[b]	H5N1 virus tested[c]	References[d]	PMID[e]
HA	Asp94Asn	Increased virus binding to α2-6; enhanced virus fusion	A/chicken/Fujian/1042/05	Su et al., 2008	19020946
	Ser121Asn	Increased virus binding to α2-6	A/Vietnam/1203/2004	Wang et al., 2010	20427525
	Ser133Ala	Increased psuedovirus binding to α2-6	A/Thailand/KAN-1/2004	Yang et al., 2007	17690300
	Ala134Val	Increased infectivity in SIAT Cells ; emerged in the course of virus replication in a patient (fatal case)	A/Cambodia/408008/2005 & A/Thailand/KAN-1/2004	Naughtin et al., 2011; Kongchanagul et al., 2008	21343450; 18632950
	Gly139Arg	Increased virus binding to α2-6	A/Vietnam/1194/2004	Yamada et al., 2006	17108965
	Ser155Asn	Increased virus binding to α2-6	A/Vietnam/1203/2004	Wang et al., 2010	20427525
	Thr156Ala	Increased virus binding to α2-6 and increased transmission in guinea pigs	A/Vietnam/1203/2004 & A/duck/Guangxi/35/2001 & A/bar-headed goose/Qinghai/3/2005	Wang et al., 2010; Gao et al., 2009	20427525
	Asn182Lys/Asn182Asp	Increased virus binding to α2-6 ; emerged in the course of virus replication in a patient (fatal case)	A/Vietnam/1194/2004 & A/Indonesia/05/2005 & A/Thailand/KAN-1/2004	Yamada et al., 2006 ; Chutinimitkul et al., 2010 ; Kongchanagul et al., 2008	17108965; 20392847
	Asp183Gly	Increased virus binding to α2-6	A/Vietnam/1203/2004	Chen et al., 2012	22056389
	Glu186Gly	Increased virus binding to α2-6	A/Vietnam/1203/2004	Chen et al., 2012	22056389
	Thr188Ile	Increased psuedovirus binding to α2-6	A/Thailand/KAN-1/2004	Yang et al.2007	17690300
	Lys189Arg	Increased virus binding to α2-6	A/Vietnam/1203/2004	Wang et al., 2010	20427525
	Gln192Arg	Increased virus binding to α2-6	A/Vietnam/1194/2004 & A/chicken/Indonesia/N1/2005 & A/Vietnam/1203/2004	Yamada et al., 2006 ; Chen et al., 2012	17108965; 22056389
	Gln192His	Increased virus binding to α2-6	A/duck/Egypt/D1Br12/2007	Watanabe et al., 2011	21637809
	Asn193Lys	Increased virus binding to α2-6	A/Vietnam/1194/2004 & A/chicken/Indonesia/N1/2005	Yamada et al., 2006	17108965
	Val210Ile	Increased virus binding to α2-6	A/duck/Egypt/D1Br12/2007	Watanabe et al., 2011	21637809
	Lys218Glu	Altered pathogenicity and tissue tropism in mice, emerged in the course of virus replication in a patient (fatal case)	A/Thailand/KAN-1/2004	Manz et al., 2010 ; Kongchanagul et al., 2008	20519408; 18632950
	Gln222Leu	Increased virus binding to α2-6	A/Vietnam/1203/2004 & A/Hong Kong/156/1997 & A/Indonesia/05/2005	Chutinimitkul et al., 2010	20392847
	Ser223Asn	Increased virus binding to α2-6, emerged in the course of virus replication in a patient (fatal case)	A/Hong Kong/212/2003 & A/Hong Kong/213/2003 & A/Vietnam/1203/2004 & A/Indonesia/05/2005	Gambaryan et al., 2006; Shinya et al., 2010; Chutinimitkul et al., 2010; Chen et al., 2012; Kongchanagul et al., 2008	16226289; 20130132; 20392847; 22056389; 18632950
	Gly224Ser	Increased virus binding to α2-6	A/Vietnam/1203/2004 & A/Hong Kong/156/1997 & A/Indonesia/05/2005	Stevens et al., 2006 ; Chutinimitkul et al., 2010; Wang et al., 2010	16543414; 20392847; 20427525

https://www.cdc.gov/flu/avianflu/h5n1/inventory.htm

Protein	Amino acid position/motif[a]	Phenotypic consequences[b]	H5N1 virus tested[c]	References[d]	PMID[e]
HA	Pro235Ser	Increase in SAα2,6Gal binding	A/duck/Egypt/D1Br12/2007	Watanabe, 2011	21637809
	Glu251Lys	Increased virus binding to α2-6	A/Vietnam/1203/2004	Chen et al., 2012	22056389
	323 to 330 (R-X-R/K-R)	Polybasic cleavage motif sequence required for high pathogenicity of H5N1 avian influenza viruses	All H5N1 viruses [g]	Bosch et al., 1981 ; Perdue et al., 1997 ; Webster & Rott 1987 ; Subbarao et al., 1998 ; Horimoto & Kawaoka 1994 ; Schrauwen et al., 2012 ; Sugitan et al., 2012 ; Zhang et al., 2012	7023022; 9213392; 3304656; 9430591; 8151777; 22278228; 22205751; 22496231
	Lys388Ile (Lys58Ile in HA2)	Decreased pH of fusion, increased HA stability, increased replication efficiency in mice	A/Vietnam/1203/2004	Reed et al., 2009 ; Krenn et al., 2011	19193808; 21490925
	Glu435Lys	Decreased pH of fusion	A/chicken/Vietnam/C58/2004	Reed, 2009	19193808
	Asn444Lys	Increased pH of fusion	A/chicken/Vietnam/C58/2004	Reed, 2009	19193808
	Glu75Lys/Ser123Pro [f]	Increased virus binding to α2-6	A/Vietnam/1194/2004	Yamada et al., 2006	17108965
	Glu75Lys/Ser123Pro/Arg497Lys [f]	Increased virus binding to α2-6	A/Vietnam/1194/2004	Yamada et al., 2006	17108965
	Glu75Lys/Ser123Pro/Asn193Lys/Arg497Lys [f]	Increased virus binding to α2-6	A/Vietnam/1194/2004	Yamada et al., 2006	17108965
	Glu75Lys/Asn193Lys [f]	Increased virus binding to α2-6	A/Vietnam/1194/2004	Yamada et al., 2006	17108965
	Glu75Lys/Asn193Lys/Arg497Lys [f]	Increased virus binding to α2-6	A/Vietnam/1194/2004	Yamada et al., 2006	17108965
	Glu75Lys/Arg497Lys [f]	Increased virus binding to α2-6	A/Vietnam/1194/2004	Yamada et al., 2006	17108965
	His103Tyr, Thr156Ala, Gln222Leu, Gly224Ser [f]	H5 virus transmissible among ferrets	A/Indonesia/05/2005	Herfst et al., 2012	22723413
	Ser123Pro/Asn193Lys [f]	Increased virus binding to α2-6	A/Vietnam/1194/2004	Yamada et al., 2006	17108965
	Ser123Pro/Asn193Lys/Arg497Lys [f]	Increased virus binding to α2-6	A/Vietnam/1194/2004	Yamada et al., 2006	17108965
	Ser123Pro/Arg497Lys [f]	Increased virus binding to α2-6	A/Vietnam/1194/2004	Yamada et al., 2006	17108965
	Leu129Val, Ala134Val [f]	Increased virus binding to α2-6	A/Thailand/676/2005	Auewarakul et al., 2007	17626098
	Leu129del, Ile151Thr [f]	Increased virus binding to α2-6	A/duck/Egypt/D1Br12/2007	Watanabe et al., 2011 ; Auewarakul et al., 2007	20427525; 17626098
	Ser133Ala/Thr188Ile [f]	Increased psuedovirus binding to α2-6	A/Thailand/KAN-1/2004	Yang et al.2007	17690300
	Gly139Arg, Asn182Lys [f]	Increased virus binding to α2-6	A/Vietnam/1194/2004 & A/Indonesia/05/2005	Yamada et al., 2006; Chutinimitkul et al., 2010	17108965; 20392847
	Asn154Asp, Asn220Lys, Gln222Leu, Thr315Ile [f]	H5 HA virus transmissible among ferrets	A/Vietnam/1203/2004 HA in H1N1p background (A/California/04/09)	Imai et al., 2012	22722205
	Asn154Ser, Gln222Leu [f]	Increased virus binding to α2-6	A/Vietnam/1203/2004	Ilyushina et al., 2008	18404209
	Asn154Ser, Gln222Leu, Asn244Asp [f]	Increased virus binding to α2-6	A/Vietnam/1203/2004	Ilyushina et al., 2008	18404209

https://www.cdc.gov/flu/avianflu/h5n1/inventory.htm

Protein	Amino acid position/motif[a]	Phenotypic consequences[b]	H5N1 virus tested[c]	References[d]	PMID[e]
HA	Ser155Asn, Thr156Ala [f]	Increased virus binding to α2-6	A/Vietnam/1203/2004	Wang et al., 2010	20427525
	Ser155Asn, Thr156Ala, Ser223Asn [f]	Increased virus binding to α2-6, reduced lethality and systemic spread in mice	A/Vietnam/1203/2004	Yen et al., 2009	19116267
	Thr156Ala, Gln222Leu [f]	Increased virus binding to α2-6	A/Vietnam/1203/2004	Wang et al., 2010	20427525
	Thr156Ala, Gln222Leu, Gly224Ser [f]	Increased virus binding to α2-6	A/Vietnam/1203/2004 & A/Indonesia/05/2005	Stevens et al., 2008 ; Wang et al., 2010	18672252; 20427525
	Thr156Ala, Ser223Asn [f]	Increased virus binding to α2-6	A/Vietnam/1203/2004	Wang et al., 2010	20427525
	Asn182Lys, Gln192Arg, Gln222Leu, Ser223Asn, Gly224Ser [f]	Increased virus binding to α2-6	A/Indonesia/05/2005	Chutinimitkul et al., 2010	20392847
	Asn182Lys, Gln222Leu, Ser223Asn, Gly224Ser [f]	Increased virus binding to α2-6	A/Indonesia/05/2005	Chutinimitkul et al., 2010	20392847
	Asn182Lys, Gln222Leu, Gly224Ser [f]	Increased virus binding to α2-6	A/Indonesia/05/2005	Chutinimitkul et al., 2010	20392847
	Glu183Gly, Glu186Asp, Lys189Ser, Gln222Leu, Gly224Ser [f]	Increased virus binding to α2-6	A/Hong Kong/486/1997	Maines et al., 2011	21397290
	Glu183Gly, Gln222Leu ,Gly224Ser [f]	Increased virus binding to α2-6	A/Egret/Egypt/1162/NAMRU-3/2006	Chen et al., 2012	22056389
	Asp183Gly, Ser223Asn [f]	Increased virus binding to α2-6	A/Vietnam/1203/2004	Chen et al., 2012	22056389
	Glu186Gly, Gln222Glu, Gly224Ser [f]	Increased virus binding to α2-6	A/Egret/Egypt/1162/NAMRU-3/2006	Chen et al., 2012	22056389
	Lys189Arg, Gln222Leu, Gly224Ser [f]	Increased virus binding to α2-6	A/Vietnam/1203/2004	Stevens et al., 2008 ; Maines et al., 2011	18672252; 21397290
	Gln192Arg, Gln222Leu, Ser223Asn, Gly224Ser [f]	Increased virus binding to α2-6	A/Indonesia/05/2005	Chutinimitkul et al., 2010	20392847
	Gln192Arg, Gln222Leu, Gly224Ser [f]	Increased virus binding to α2-6	A/Egret/Egypt/1162/NAMRU-3/2006 & A/Indonesia/05/2005	Chutinimitkul et al., 2010; Chen et al., 2012	20392847; 22056389
	Gln192Arg, Ser223Asn [f]	Increased virus binding to α2-6	A/Vietnam/1203/2004 & A/Vietnam/1194/2004 & A/Indonesia/05/2005	Chutinimitkul et al., 2010; Chen et al., 2012	20392847; 22056389
	Asn193Lys/Arg497Lys [f]	Increased virus binding to α2-6	A/Vietnam/1194/2004	Yamada et al., 2006	17108965
	Gln222Leu, Ser223Asn, Gly224Ser [f]	Increased virus binding to α2-6	A/Indonesia/05/2005	Chutinimitkul et al., 2010	20392847
	Gln222Leu, Gly224Ser [f]	Increased virus binding to α2-6; decreased antiviral response in host; reduced tissue tropism in guinea pigs	A/Vietnam/1203/2004 & A/Indonesia/05/2005 & A/Egret/Egypt/1162/NAMRU-3/2006 & A/Hong Kong/156/1997 & A/Hong Kong/486/1997 & A/duck/Guangxi/35/2001 & A/Vietnam/1194/2004	Harvey et al., 2004; Stevens et al., 2006; Stevens et al., 2008; Ilyushina et al., 2008; Maines et al., 2011; Wang et al., 2010; Chutinimitkul et al., 2010; Ramos et al., 2011; Chen et al., 2012; Gao et al., 2009; Ayora-Talavera et al., 2009	14671130; 16543414; 18672252; 18404209; 21397290; 20427525; 20392847; 21345953; 22056389; 20041223; 19924306

Table 2. Equivalent amino acid numbering for subtypes currently circulating in humans or have pandemic potential. https://doi.org/10.1371/journal.pone.0112302

Mutation	H1pdm	H3	H5	H7	H9	Phenotype	Reference
Tyr → His	7	17	7	7	7	Increase in fusion pH	[13]
His → Gln	8	18	8	8	8	Decrease in fusion pH; increased stability	[13]
Asn → Any	11	21	11	11	11	Loss of N-glycosylation; increased virulence	[14]
Glu→Lys	75	83	75	73	75	Increased virus binding to α2-6 glycans	[15]
His → Tyr	103	110	103	100	103	Increased stability	[2]
Ser→ Asn	122	126	121	116	121	Increased virus binding to α2-6 glycans	[16]
Ser→Pro	124	128	123	118	123	Increased virus binding to α2-6 glycans	[15]
Ala → Δ	130	Δ	129	Δ	Δ	Increased virus binding to α2-6 glycans	[17–18]
Ser → Ala	134	137	133	127	131	Increased virus binding to α2-6 glycans	[19]
Ala→ Val	135	138	134	128	132	Increased infectivity in SIAT Cells	[20]
Gly→Arg	140	143	139	132	Δ	Increased virus binding to α2-6 glycans	[15]
Ile→ Thr	152	155	151	144	145	Increased virus binding to α2-6 glycans	[17–18]
Asn→ Asp	155	158	154	147	148	Loss of N-glycosylation; increased binding and transmission	[2]
Thr→ Ala	157	160	156	151	150	Loss of N-glycosylation; increased binding and transmission	[1]
Asn→Lys	183	186	182	177	176	Increased virus binding to α2-6 glycans	[15,21]
Asp→Gly	184	187	183	178	177	Increased virus binding to α2-6 glycans	[22]
Glu→Gly	187	190	186	181	180	Increased virus binding to α2-6 glycans	[22]
Thr→Ile	189	192	188	183	182	Increased virus binding to α2-6 glycans	[19]
Lys→Arg	190	193	189	184	183	Increased virus binding to α2-6 glycans	[16]
Gln→Arg/His	193	196	192	187	186	Increased virus binding to α2-6 glycans	[15,18,22]
Asn→Lys	194	197	193	188	187	Increased virus binding to α2-6 glycans	[15]
Val → Ile	211	214	210	205	204	Increased virus binding to α2-6 glycans	[18]
Gln→Leu	223	226	222	217	216	Increased virus binding to α2-6 glycans	[21]
Ser→Asn	224	227	223	218	217	Increased virus binding to α2-6 glycans	[21–23]
Gly→Ser	225	228	224	219	218	Increased virus binding to α2-6 glycans	[14–15,24]
Pro→Ser	236	239	235	230	229	Increased virus binding to α2-6 glycans	[18]
Glu→Lys	252	255	251	246	245	Increased virus binding to α2-6 glycans	[22]
Thr→Ile	316	318	315	309	309	Increase in fusion pH	[1]
Insertion of Arg or Lys	327	329	326	321	320	Poly-basic cleavage; increased pathogenicity	[25]
Lys → Ile	385	387	384	379	378	Increase in fusion pH; increased stability	[13,26]
Asn → Lys	441	443	440	435	434	Increase in fusion pH; decreased stability	[13]
Asn → Asp	444	446	443	438	437	Increase in fusion pH	[27]
Arg → Lys	494	496	493	488	487	Increased virus binding to α2-6 glycans	[15]

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Avian Influenza A (H5N1) in 10 Patients in Vietnam

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Table 1. Epidemiologic Data.

Patient No.	Location in Vietnam	Occupation	Epidemiologic Information
1	Ha Nam	Student	Family members are farmers who do not keep poultry, but many chickens in neighborhood unexpectedly died in the preceding 2 wk; mother died of influenza A (H5N1) Jan. 9, 2004; father and younger sibling healthy.
2	Nam Dinh	Not available	No information available on exposure to sick poultry; 7-yr-old sister died of acute respiratory illness on Dec. 29, 2003; parents and two other siblings healthy.
3	Bac Ninh	Student	Family members are farmers who kept chickens, which died unexpectedly 5 days before onset of illness; parents and older sibling healthy.
4	Ha Tay	Student	Family members are farmers who kept chickens, which died 2 wk before onset of illness; chickens died in patient's house and neighbors' houses during week before onset of illness; parents and 7 other siblings healthy.
5	Ho Chi Minh City	Student	Patient bought duckling as pet and cared for it in her house for 5 days; duck had diarrhea and died, patient buried it, dug it up a day later and reburied it; both patient and brother handled duck; patient also ate barely cooked eggs (Vietnamese delicacy) 2 days before onset of illness; neighbors kept 40 chickens, but no illness reported in these birds; fever developed in patient 3 days after she bought duck; no other poultry or animals at home; no other household members or relatives sick.
6	Ho Chi Minh City	Student	Frequently attended cockfights, held roosters and chickens; no illness reported in the chickens or in 20 people involved in cockfighting; patient walked through live-poultry market 50 m from house on his way to school.
7	Soc Trang	Student	Extensive exposure, including handling of 10 dead or dying chickens in patient's homestead; father and patient prepared dead chickens for eating (removed feathers, washed, cut meat) 3 days before onset of illness; no other household members or relatives sick; no other poultry or animals at home.
8	Lam Dong	Farmer	Direct handling of 50 chickens, including dead chickens, at home (which was also a restaurant); patient and father prepared chickens for eating; no other household members or relatives sick; no other poultry or animals at home.
9	Lam Dong	Farmer	Direct handling of chickens in patient's homestead 3 days before onset of illness; he prepared dead chickens for eating; no one else in family sick.
10	Lam Dong	Farmer	Direct handling of sick ducks and chickens in patient's home; many sick poultry in the district; no other illness in family.

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Table 2. Clinical Characteristics of the Patients on Admission.

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Days between exposure to poultry and onset of illness	—	—	—	—	3	2	3	4	3	3
Days since onset of illness	3	7	7	5	8	6	5	6	5	7
Sex	Female	Male	Male	Female	Female	Male	Female	Male	Male	Male
Age (yr)	12	5	10	8	8	13	16	18	24	23
Cough	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dyspnea	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sputum	No	No	No	No	Yes	No	Yes	Yes	Yes	Yes
Diarrhea	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Rash	No	No	No	No	No	No	No	No	No	No
Myalgia	No	No	No	No	No	No	No	No	No	No
Conjunctivitis	No	No	No	No	No	No	No	No	No	No
Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Temperature (°C)	39.5	38.8	39.0	38.5	38.5	39.6	40.0	40.0	39.5	38.7
Blood pressure (mm Hg)	90/60	112/54	105/80	80/40	104/64	110/70	110/60	100/60	110/60	120/80
Respiratory rate (breaths/min)	65	70	64	60	40	40	40	60	50	28
Crackles	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Wheeze	No	No	No	No	No	Yes	No	No	No	No
Other	Enlarged liver	—	—	Bleeding gums	—	—	—	—	—	—

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Table 3. Laboratory Values at Presentation.*

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Hemoglobin (g/dl)	13.4	12.6	12.4	12.3	11.3	13.4	11.9	14.5	15.8	17.6
Leukocyte count (per mm³)	2,100	3,400	2,800	1,900	1,200	2,700	3,000	1,700	1,900	2,100
Lymphocyte count (per mm³)	1,100	710	860	250	300	900	500	500	800	700
Neutrophil count (per mm³)	850	2,410	1,900	780	700	1,300	2,500	1,100	1,100	1,300
Platelet count (per mm³)	45,000	174,000	135,000	91,000	117,000	81,000	70,000	69,000	62,000	62,000
CD4:CD8 ratio	NA	NA	NA	NA	0.71	NA	0.62	0.75	0.59	1.08
ALT level (U/liter)	53.7	NA	NA	265	354	254	47	NA	NA	89
AST level (U/liter)	278	NA	NA	1,217	320	1,058	20	NA	NA	110
Serum creatinine (μmol/liter)	50	64	NA	27	34	14	71	89	43	121
Serum glucose (mmol/liter)	NA	NA	NA	NA	NA	NA	19.0	13.5	11.7	4.9
Oxygen saturation during receipt of 40% oxygen (%)	50	70	86	50	95	85	67	81	80	90
Day of illness on which PCR for H5N1 performed	5	7	9	6	12	6	5	6	5	7
Viral culture	+	+	NA	NA	Pending	Pending	Pending	Pending	Pending	Pending
Influenza antigens	NA	NA	NA	NA	+	–	–	+	–	–
Blood culture	–	–	–	–	–	–		–	–	–
Outcome	Died (day 6)	Died (day 17)	Died (day 14)	Died (day 7)	Recovered	Died (day 9)	Died (day 14)	Died (day 9)	Died (day 6)	Recovering

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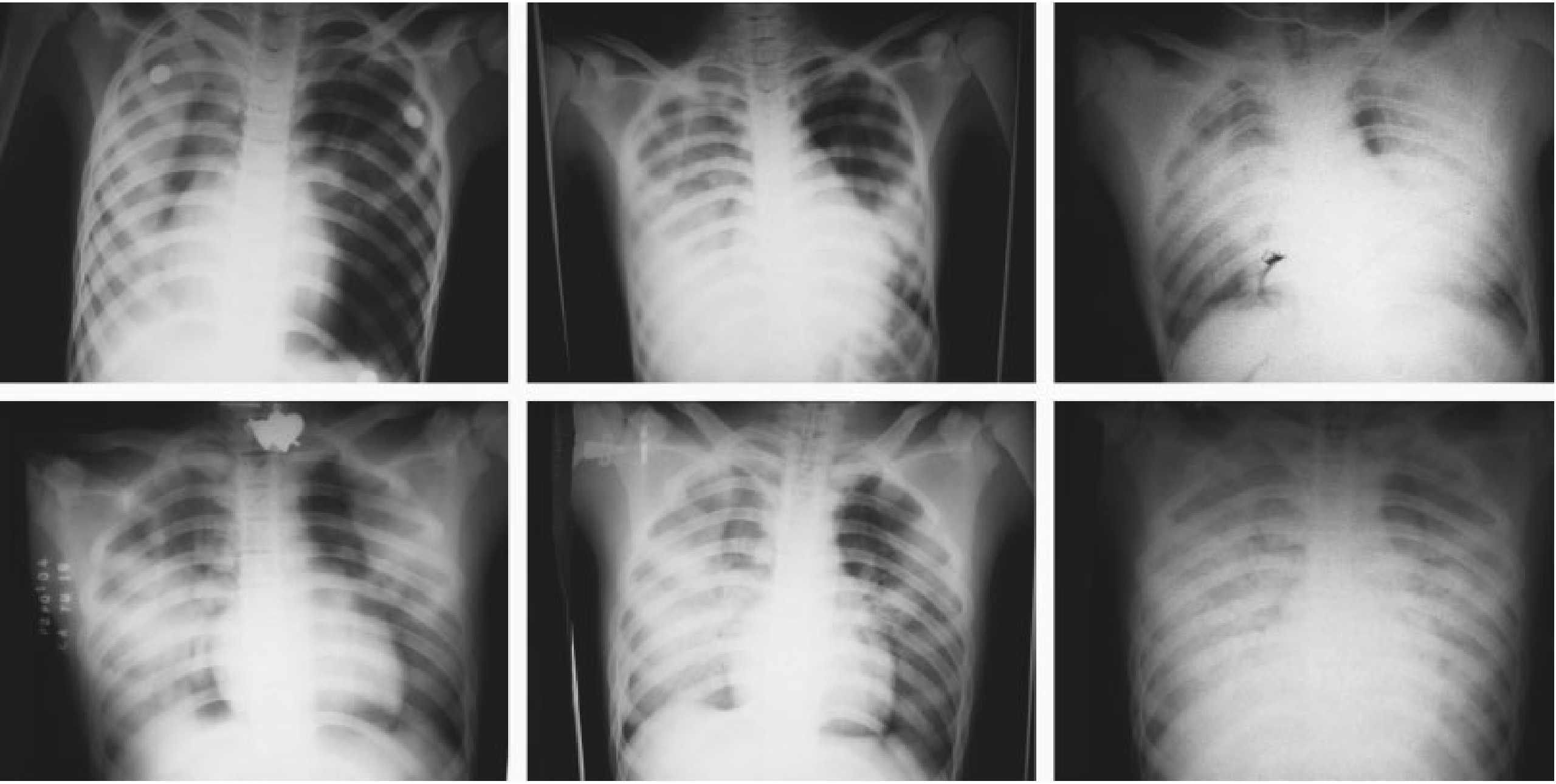

https://doi.org/10.3201%2Feid1102.041061

Table 1. Characteristics of 12 confirmed, 21 suspected, and 577 excluded human cases of avian influenza A (H5N1) in Thailand, 2004

Characteristic	Confirmed	Suspected	Excluded
No.	12	21	577
Median age (y) (range)	12 (2–58)	33 (1–67)	12 (1–92)
Sex (% male)	67	71	59
Poultry contact (%)	58	52	48
Adequate* specimen (%)	100	90	81
Death (%)	67	38	4

*Adequate was defined as a respiratory specimen obtained 2–14 days after onset of fever.

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Table 2. Characteristics and clinical findings of confirmed avian influenza A (H5N1) cases in Thailand, 2004*

Characteristics	Patient no. 1	2	3	4	5	6	7	8	9	10	11	12	%
Age (y), sex	2, M	27, F	31, M	46, F	5, M	6, M	6, M	6, M	7, M	13, M	39, F	58, F	67 (M)
Symptoms													
Fever	+	+	+	+	+	+	+	+	+	+	+	+	100
Rhinorrhea	–	+	–	–	+	+	+	–	–	–	–	–	33
Cough	+	+	+	+	+	+	+	+	+	+	+	+	100
Sore throat	+	+	–	+	+	–	+	+	+	+	–	+	75
Myalgia	–	+	+	+	–	–	–	+	–	–	+	–	42
Dyspnea	+	+	+	+	+	+	+	+	+	+	+	+	100
Diarrhea	+	–	+	–	+	–	–	+	–	–	+	–	42
Abdominal pain	–	–	–	–	+	–	+	–	–	–	–	–	17
Conjunctivitis	–	–	–	–	–	–	–	–	–	–	–	–	0
Vomiting	–	–	–	–	–	–	–	+	–	+	+	–	25
Laboratory values													
Hematocrit (vol%)	30	39	38	46	39	32	39	40	41	37	33	38	
Total leukocyte count	4,200	13,600	4,660	7,360	5,600	1,200	2,200	4,900	4,100	2,000	3,300	5,680	
Total lymphocyte count	2,646	3,400	513	2,429	2,296	624	638	1,763	1,435	580	660	454	
Platelet count ($x10^3$)	214	306	171	272	94	89	140	111	304	150	380	185	
Treatment													
Oseltamivir	+	–	+	–	+	+	–	+	+	+	–	–	58
Corticosteroids	+	–	+	–	–	+	+	+	+	+	+	–	67
Outcome													
ARDS	–	–	+	–	+	+	+	+	+	+	+	+	75
Inotropic support	–	–	–	–	+	–	–	+	+	+	–	+	42
Peak AST (U)	129	18	74	NA	70	790	175	280	120	34	394	NA	
Peak ALT (U)	57	23	41	NA	47	150	43	50	52	47	106	NA	
Peak BUN (mg/dL)	NA	8	10.7	NA	12	NA	14	22	10	132	37	39	
Peak creatinine (mg/dL)	NA	0.8	1.07	NA	0.7	NA	1.7	1.1	0.7	8.1	3.6	2.3	
Survival (day of death)	+	+	+	+	– (13)	– (20)	– (18)	– (8)	– (29)	– (16)	– (13)	– (8)	33

*M, male; f, female; +, yes, –, no, NA, not applicable; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen.

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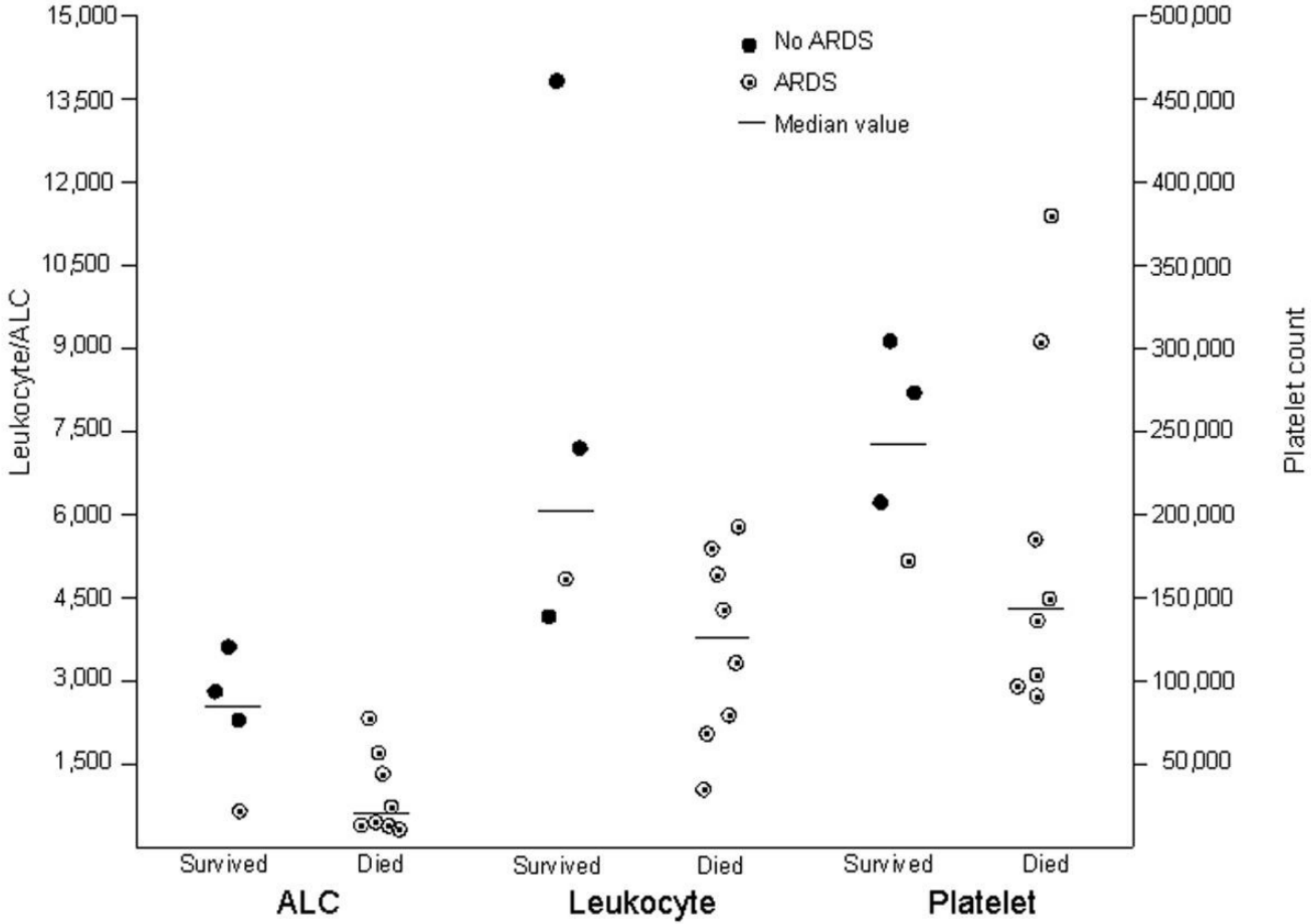

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ORIGINAL ARTICLE

Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection

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Table 1. Demographic and Epidemiologic Characteristics of 111 Patients Infected with H7N9 Virus in China.

Characteristic	Value
Age	
Median (range) — yr	61 (3–88)
Subgroup — no. (%)	
0–4 yr	1 (0.9)
5–14 yr	1 (0.9)
15–49 yr	28 (25.2)
50–64 yr	34 (30.6)
≥65 yr	47 (42.3)
Female sex — no. (%)	35 (31.5)
Coexisting condition — no. (%)	
Any	68 (61.3)
Hypertension	51 (45.9)
Diabetes	18 (16.2)
Coronary heart disease	11 (9.9)
Immunosuppression*	10 (9.0)
Chronic obstructive pulmonary disease	8 (7.2)
Cancer†	6 (5.4)
Cerebrovascular disease	4 (3.6)
Hepatitis B infection‡	4 (3.6)
Chronic renal disease	2 (1.8)
Pregnancy	2 (1.8)
Current smoker — no. (%)	27 (24.3)
Exposure to live poultry	
In previous 14 days — no. (%)	62 (55.9)
Median incubation time since exposure (interquartile range) — days	5 (2–8)
Hospitalization — no. (%)	109 (98.2)

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Table 2. Clinical Characteristics and Selected Laboratory Abnormalities of 111 Patients Infected with H7N9 Virus *

Characteristic	Value
Fever	
Any — no. (%)	111 (100.0)
Maximal temperature — °C	39.2±0.8
Subgroup — no. (%)	
37.3–38.0°C	11 (9.9)
38.1–39.0°C	43 (38.7)
>39.0°C	57 (51.4)
Fatigue — no. (%)	40 (36.0)
Conjunctivitis — no. (%)	0
Cough — no. (%)	100 (90.1)
Sputum production — no. (%)	62 (55.9)
Hemoptysis — no. (%)	27 (24.3)
Shortness of breath — no. (%)	62 (55.9)
Diarrhea or vomiting — no. (%)	15 (13.5)
White cells	
Median — per mm³	4450
Interquartile range — per mm³	2900–6230
Subgroup — no. (%)	
>10,000 per mm³	5 (4.5)
<4000 per mm³	51 (45.9)
Lymphocytes — per mm³	
Median	460
Interquartile range	320–700
Lymphocytopenia — no. (%)	98 (88.3)
Hemoglobulin — g/dl	12.9±3.1
Platelets — per mm³	
Median	115,500
Interquartile range	82,000–149,500
Thrombocytopenia — no. (%)	81 (73.0)
C-reactive protein >10 mg/liter — no. (%)	85 (76.6)
Procalcitonin >0.5 ng/ml — no. (%)	28 (37.3)
Aspartate aminotransferase >40 U/liter — no. (%)	73 (65.8)
Creatinine >133 μmol/liter (1.5 mg/dl) — no. (%)	10 (9.0)
Lactate dehydrogenase >250 U/liter — no. (%)	91 (82.0)
Creatine kinase >200 U/liter — no. (%)	49 (44.1)
Myoglobulin >80 μg/ml — no. (%)	16 (55.2)
PaO_2:FiO_2	
Median	144.0
Interquartile range	107.1–226.9
Potassium — mmol/liter	3.8±0.5
Sodium — mmol/liter	136.8±6.0
D-dimer >0.5 mg/liter — no. (%)	47 (90.4)
Chest radiologic findings — no. (%)	
Involvement of both lungs	60 (54.1)
Ground-glass opacity	62 (55.9)
Consolidation	99 (89.2)

* Plus–minus values are means ±SD. A complete list of ranges of laboratory measures in this table is provided in Table S4 in the Supplementary Appendix. Lymphocytopenia was defined as a lymphocyte count of less than 1500 per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 150,000 per cubic millimeter. Procalcitonin was measured in 75 patients, myoglobulin was measured in 29 patients, and total D-dimer was measured in 52 patients. PaO_2:FiO_2 denotes the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.

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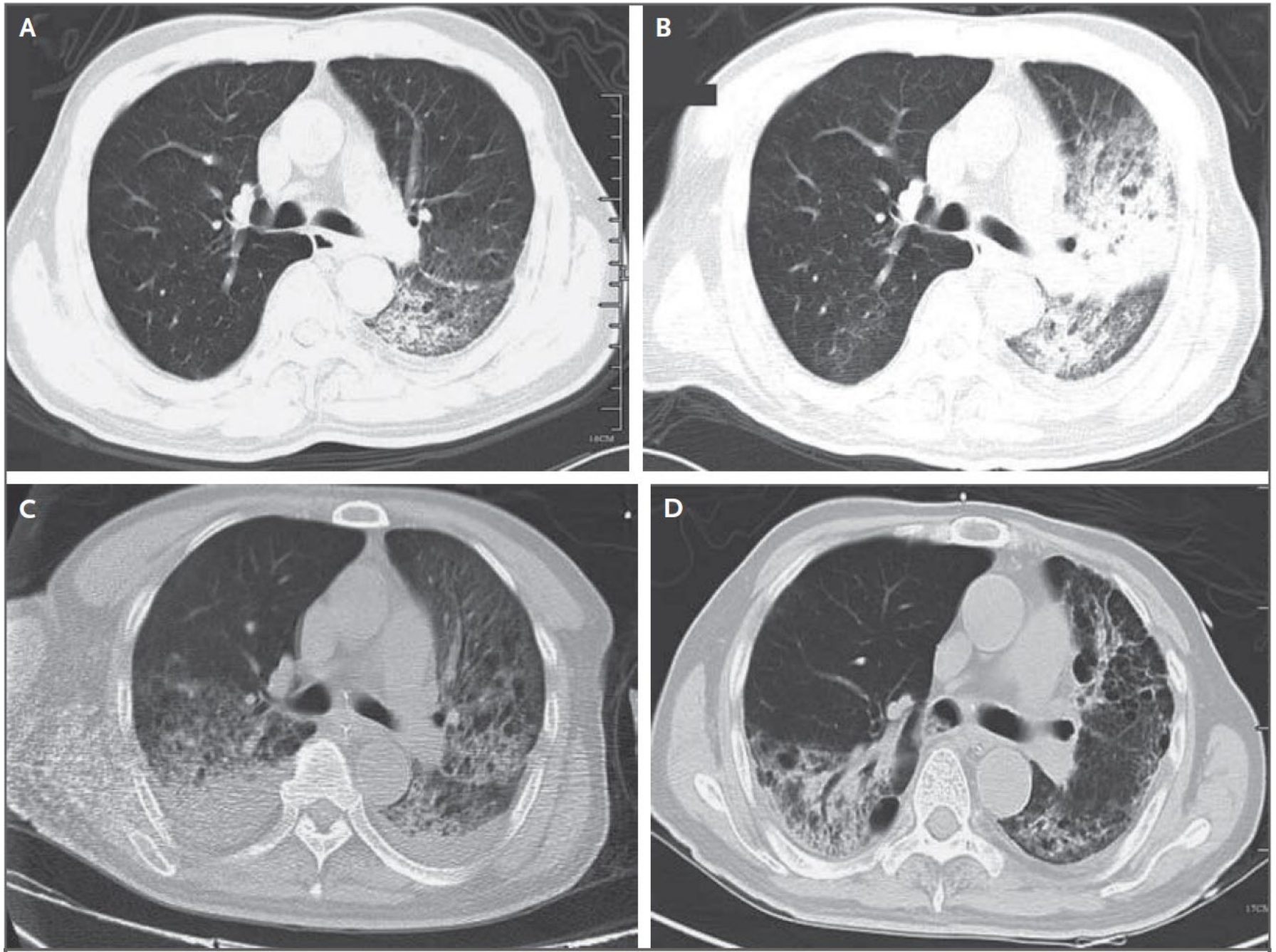


Table 3. Complications, Treatment, and Clinical Outcomes in 111 Patients Infected with H7N9 Virus.*

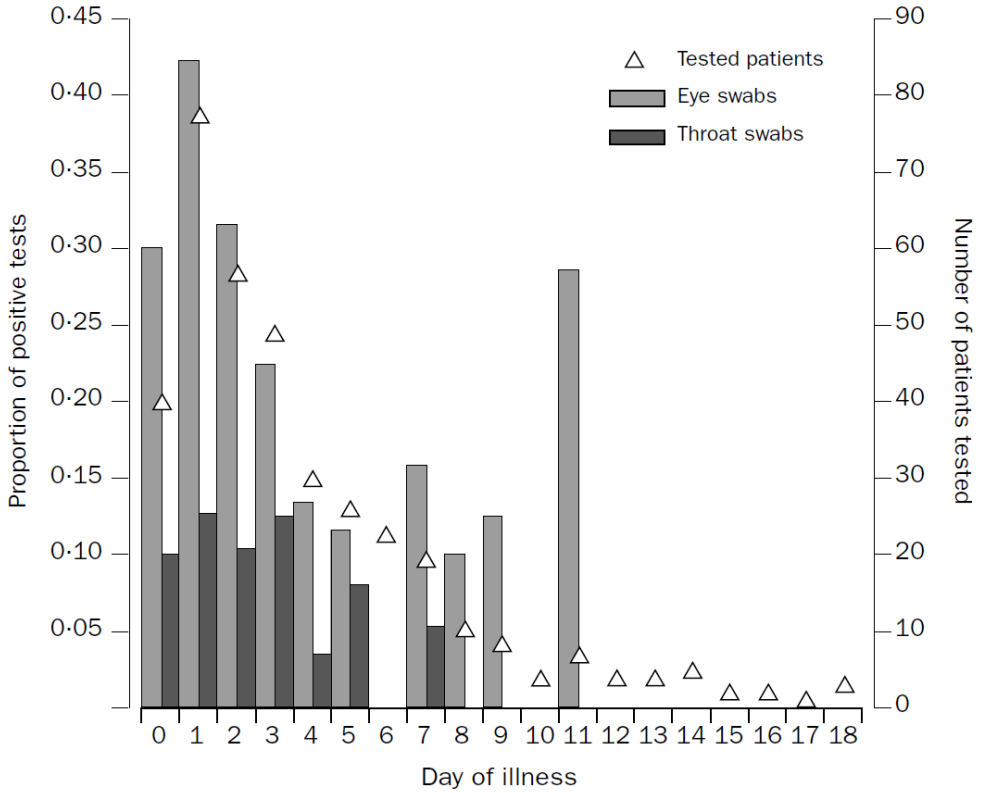
Variable	Value
	no. of patients (%)
Complications	
Pneumonia	108 (97.3)
Acute respiratory distress syndrome	79 (71.2)
Shock	29 (26.1)
Acute kidney injury	18 (16.2)
Rhabdomyolysis	11 (9.9)
Treatment	
Bacteria isolation from culture	29 (26.1)
Administration of oseltamivir or peramivir	108 (97.3)
Timing from onset of illness to administration of antiviral therapy	
0–2 days	11 (9.9)
3–5 days	32 (28.8)
≥6 days	65 (58.6)
Oxygen therapy	111 (100)
Mechanical ventilation	
Noninvasive	31 (27.9)
Invasive	65 (58.6)
Admission to an intensive care unit	85 (76.6)
Extracorporeal membrane oxygenation	20 (18.0)
Continuous renal-replacement therapy	29 (26.1)
Artificial-liver-support-system therapy*	17 (15.3)
Antibiotics	79 (71.2)
Antifungal drugs	1 (0.9)
Glucocorticoids	69 (62.2)
Intravenous immune globulin	59 (53.2)
Clinical outcome	
Death	30 (27.0)
Cause of death	
Refractory hypoxemia	22 (73.3)
Shock	1 (3.3)
Acute heart failure	2 (6.7)
Secondary bacterial or fungal infection	3 (10)
Arrhythmia	2 (6.7)
Discharge from hospital†	49 (44.1)

https://doi.org/10.1016/S0140-6736(04)15589-X

	Conjunctivitis	Conjunctivitis+ILI	Conjunctivitis total	ILI only	Other	Total
Final laboratory results						
Negative	198 (63·1%/66·9%)	39 (12·4%/73·6%)	237 (75·5%/67·9%)	27 (8·6%/72·9%)	50 (15·9%/74·6%)	314 (100%/69·3%)
A/H3 positive	2 (33·3%/0·7%)	3 (50·0%/5·7%)	5 (83·3%/1·4%)	1(16·7%/2·7%)	0	6 (100%/1·3%)
A/H7 positive	78 (87·6%/26·4%)	5 (5·6%/9·4%)	83 (93·3%/23·8%)	2 (2·2%/5·4%)	4 (4·5%/6·0%)	89 (100%/19·6%)
Influenza A positive, no subtyping data	8 (57·2%/2·7%)	2 (14·3%/3·8%)	10 (71·4%/2·9%)	2 (14·3%/5·4%)	2 (14·3%/3·0%)	14 (100%/3·1%)
Not tested	10 (33·3%/3·4%)	4 (13·3%/7·5%)	14 (46·7%/4·0%)	5 (16·7%/13·5%)	11 (36·7%/16·4%)	30 (100%/6·6%)
Total	296 (65·3%/100%)	53 (11·7%/100%)	349 (77·0%/100%)	37 (8·2%/100%)	67 (14·8%/100%)	453 (100%/100%)*

ILI=influenza-like illness. Data are n (% of row total/% of column total). *322 men, 128 women, data missing for 3.

Table 1: **Results of laboratory testing for influenza in people possibly exposed to HPAI A/H7 in the Netherlands, grouped by presenting symptoms**



https://doi.org/10.1038%2Fnm1477

Table 3 Levels of chemokines and cytokines in the peripheral blood

						H5N1		
	H5N1[a] ($n = 16$)	P^b	H3/H1 ($n = 6$)	P^c	Controls ($n = 15$)	Fatal ($n = 11$)	Not fatal ($n = 5$)	P
IP-10	5.1 (3.5–6.3)	0.005	3.8 (3.4–4.6)	0.001	2.7 (2.4–3.8)	5.4 (3.5–6.3)	4.2 (4.0–5.0)	0.031
MCP-1	2.4 (1.5–4.0)	0.083	1.9 (und.–2.4)	0.045	1.4 (und.–2.0)	2.8 (2.0–4.0)	1.8 (1.5–2.3)	0.015
MIG	4.3 (3.1–5.2)	0.013	3.2 (2.9–3.9)	0.002	2.6 (2.2–3.3)	4.6 (3.3–5.2)	3.3 (3.1–4.2)	0.011
IL-8	2.0 (0.7–3.2)	0.001	0.8 (0.4–1.5)	0.34	0.7 (und.–1.0)	2.4 (1.1–3.2)	1.7 (0.7–1.9)	0.020
IL-10	1.5 (und.–2.8)	0.002	–1.0 (und.–0.4)	0.85	–1.0 (und.–1.0)	1.6 (und.–2.8)	0.8 (und.–2.2)	0.6
IL-6	2.1 (und.–3.7)	0.001	–0.2 (und.–0.7)	0.30	–1.0 (und.–1.0)	2.2 (1.5–3.7)	1.0 (und.–2.4)	0.054
IFN-γ	2.0 (und.–4.2)	0.029	0.1 (und.–2.4)	0.42	–1.0 (und.–1.4)	2.3 (1.0–4.2)	2.0 (und.–2.6)	0.2

Levels of chemokines and cytokines in the peripheral blood of patients with influenza H5N1 and H3N2 or H1N1. Levels are given as median $\log_{10}$ pg per ml (range).
[a]Plasma levels of chemokines and cytokines in H5N1 patients were all higher than in healthy controls at <0.001 significance levels. [b]Comparison between H5N1 and H3/H1 patients. [c]Comparison between H3/H1 patients and healthy controls. und., undetectable.

インフルエンザの合併症

- 心筋炎
- インフルエンザ肺炎
- 二次性細菌性肺炎 ⇦ 高齢者
- インフルエンザ脳症 ⇦ 子ども

・
・
・

インフルエンザ脳症って何？

インフルエンザの感染後に意識障害、けいれん

異常言動・異常行動などの症状を引き起こす

重篤な脳の病気

主に５歳以下
1-2歳がピーク

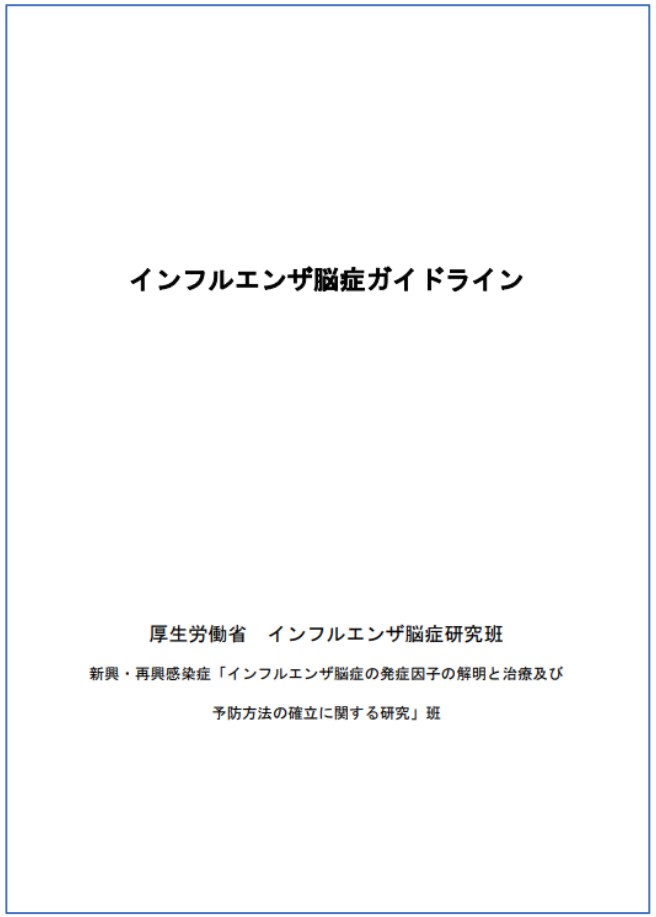
インフルエンザ脳症のヤバさ

- 日本における報告　　1990年代半ば
- 1997-98　　日本で多発　（推定500例）　→　100-200例
- 高い致死率（約30％）　→　7-8％
- 後遺症率　（約25％）　→　約15％

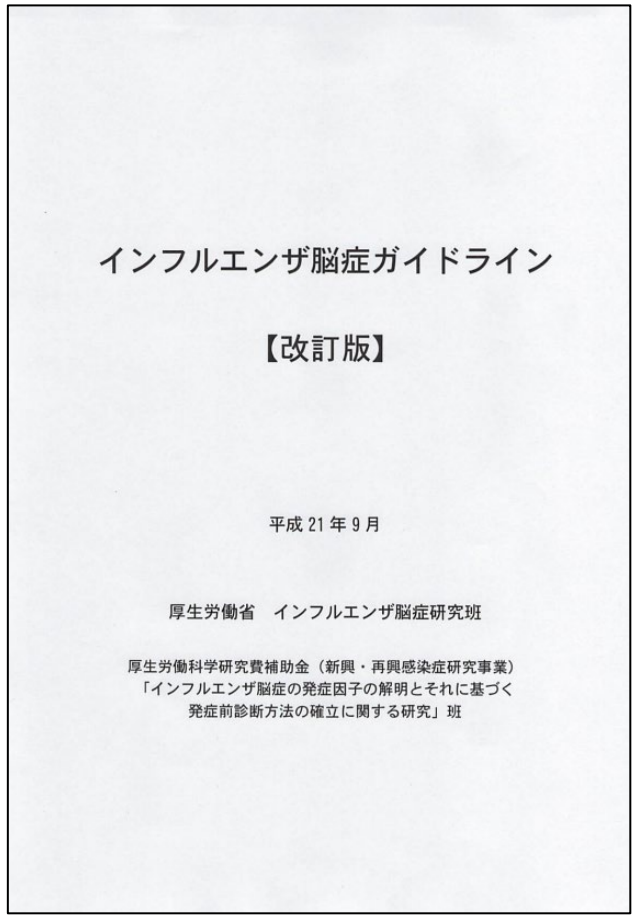
インフルエンザ脳症の診療戦略

厚生労働省　インフルエンザ脳症研究班

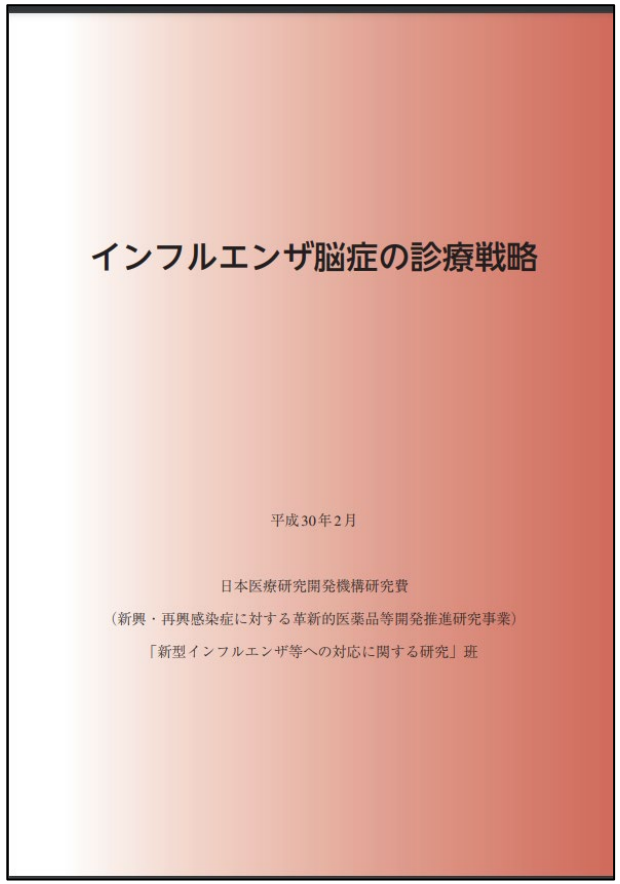
2005



2009



2018



脳炎なの？　脳症なの？

脳炎

脳内に直接ウイルスが浸潤し

炎症が起きる

脳症

脳内にウイルスが検出されず

過剰な免疫応答が見られる

インフルエンザ脳症の発生機序（仮説）

ウイルスの感染と鼻粘膜での増殖

↓

免疫系の障害（暴走）

↓

高サイトカイン血症

↓

脳細胞が障害

- けいれん
- 意識障害
- 異常行動

↓

多くの細胞が障害

- 血管炎
- 多臓器不全

インフルエンザ脳症の診断

インフルエンザの診断

けいれん

意識障害

一時間以上の
意識障害

繰り返す
左右非対称

表4　インフルエンザ脳症における前駆症状としての異常言動・行動の例

①両親がわからない，いない人がいると言う（人を正しく認識できない）．
②自分の手を噛むなど，食べ物と食べ物でないものとを区別できない．
③アニメのキャラクター・象・ライオンなどが見える，など幻視・幻覚的訴えをする．
④意味不明な言葉を発する，ろれつがまわらない．
⑤怯え，恐怖，恐怖感の訴え・表情．
⑥急に怒り出す，泣き出す，大声で歌い出す．

（子どもを亡くした家族の会「小さないのち」アンケート調査より）

JCS20以上の意識障害が24時間以上続く

CT等の画像診断で特異的所見

インフルエンザ脳症

インフルエンザ脳症の治療戦略より

インフルエンザ脳症の種類

インフルエンザ脳症は単一の脳の疾患ではなく

意識障害などを起こす複数の症候群の集合体

① 急性壊死性脳症（ANE）

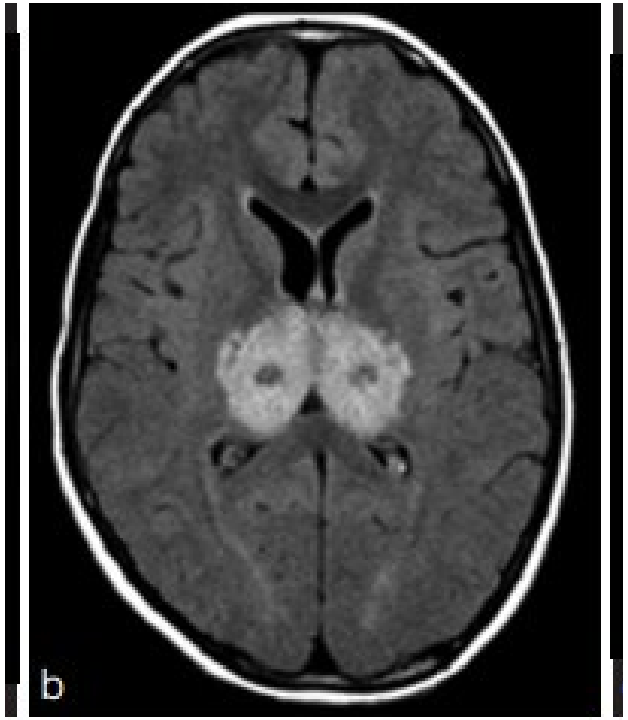
② 可逆性脳梁膨大部病変を有する軽症脳炎・脳症（MERS）

③ けいれん重積型（二相性）急性脳症（AESD）

① 急性壊死性脳症（ANE）

びまん性脳浮腫に両側対称性視床病変を伴う

ウイルス性脳症．東アジアの幼児に多い．



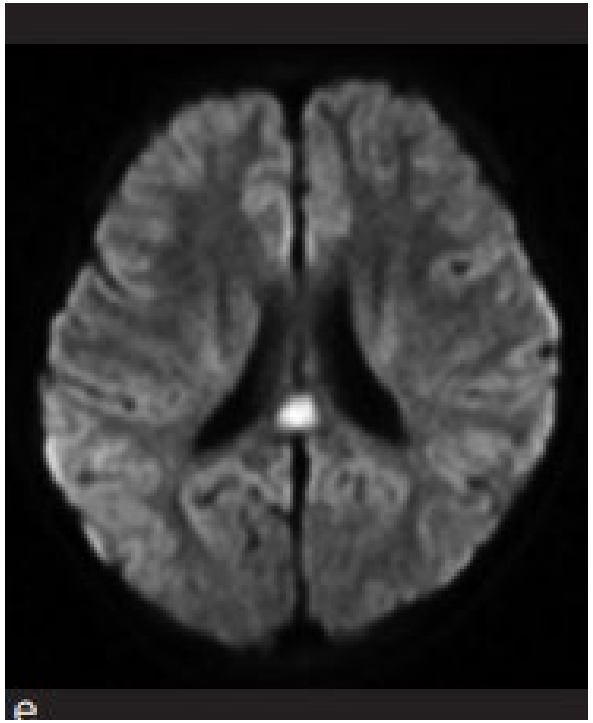
病理：過剰な炎症性サイトカインの産生
血管内皮障害と、広範な臓器のアポトーシス

予後悪い

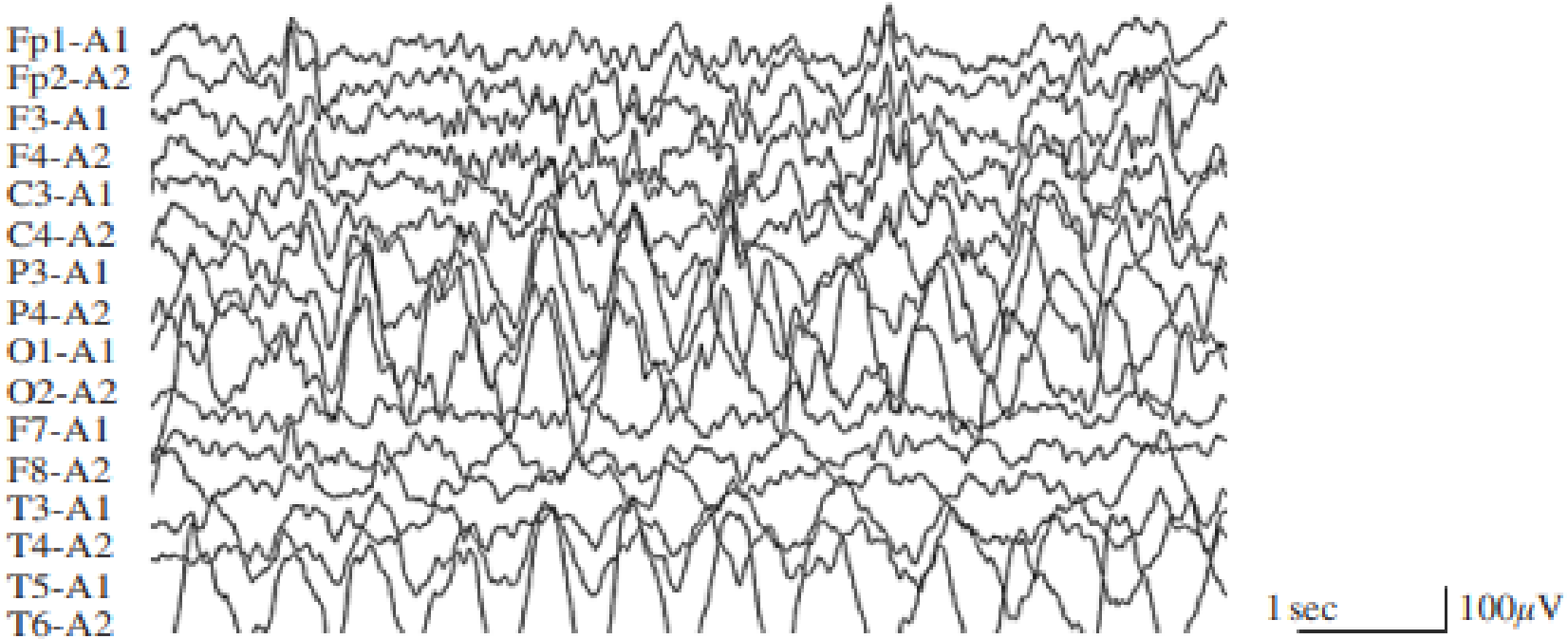
② 可逆性脳梁膨大部病変を有する軽症脳炎・脳症（MERS）

MRI拡散強調画像での脳梁膨大部の可逆性病変が特徴.

神経症状が軽傷で予後良好.



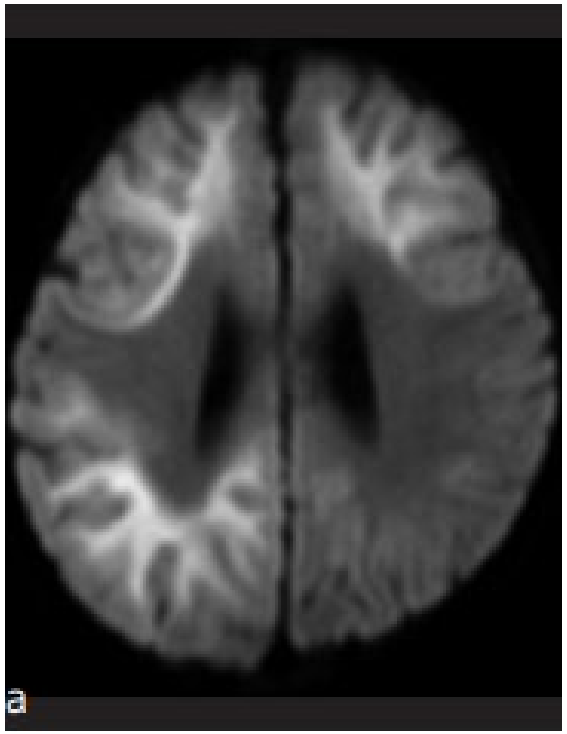
c：局在性高振幅徐波（3歳，MERS，第1病日）



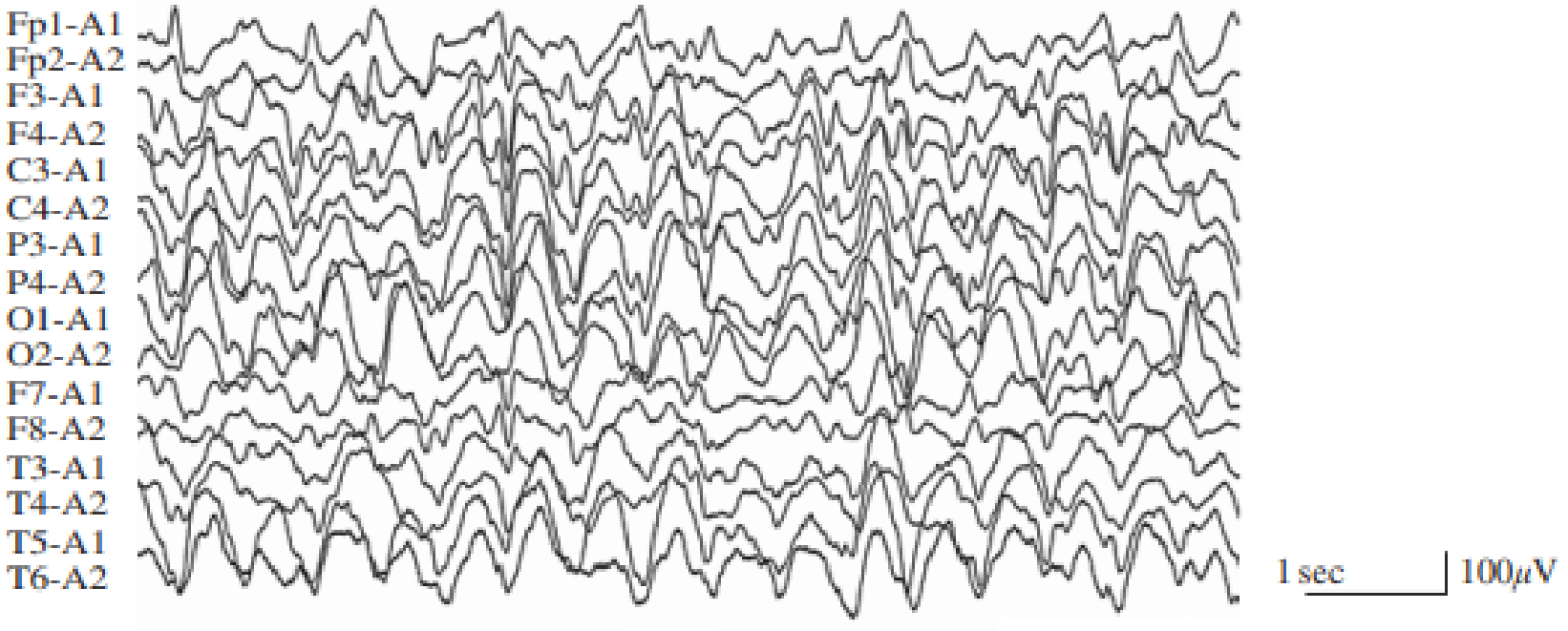
③ けいれん重積型（二相性）急性脳症（AESD）

発熱後のけいれん重積で発症．その後、症状改善傾向．

第3-7病日に反復するけいれん．意識障害憎悪。



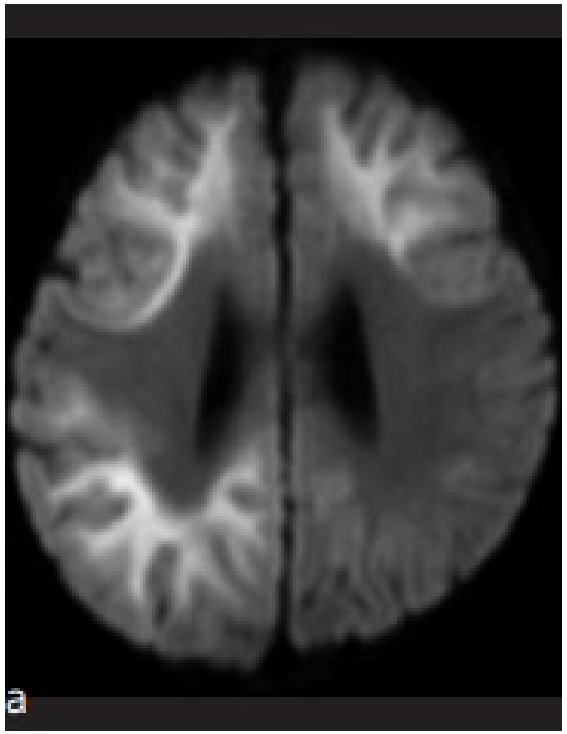
a：全般性高振幅徐波（1歳，AESD，第2病日）

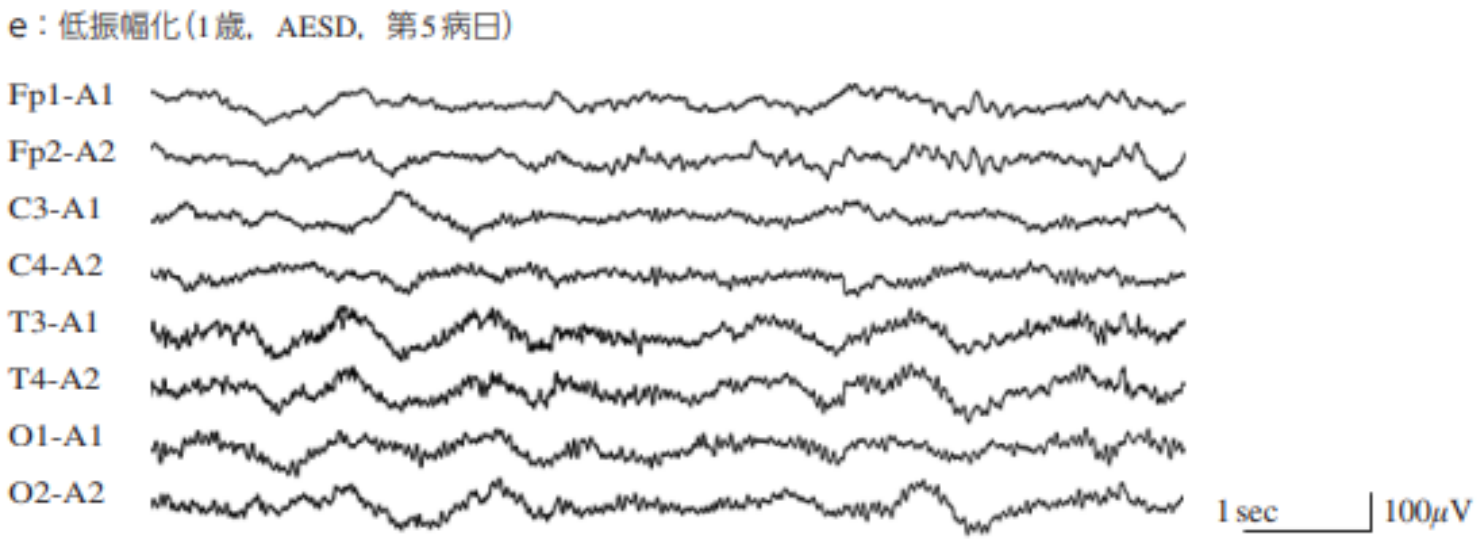


③ けいれん重積型（二相性）急性脳症（AESD）

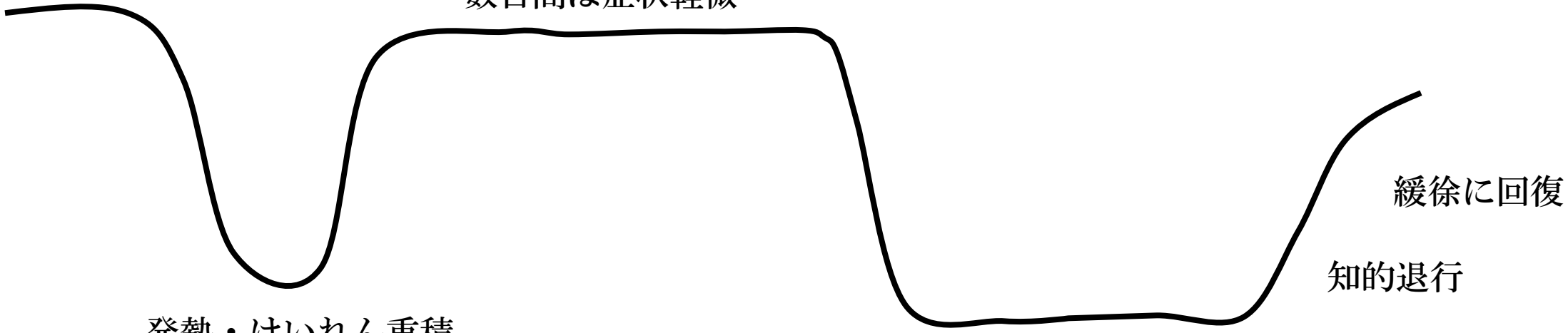
発熱後のけいれん重積で発症．その後、症状改善傾向．

第3-7病日に反復するけいれん．意識障害憎悪。





③ けいれん重積型（二相性）急性脳症（AESD）



発症初期は、熱性

早期診断のための

Yokochi[37]らの臨床スコア	
項目	スコア
1) 入院時pH＜7.014	1
2) 入院時の血清ALT≧28 IU/L	2
3) 入院時の血糖≧228 mg/dL	2
4) 覚醒するまでの時間≧11時間	2
5) 入院時の血清Cr≧0.3 mg/dL	1
6) 入院時のアンモニア≧125 μg/dL	2

上記スコアの合計が4以上だと，AESD予測感度93%，特異度91%．

持続脳波モニタリングが有用

インフルエンザ脳症の治療

支持療法：解熱、抗けいれん薬、鎮静（全身管理）

特異的治療：　抗ウイルス薬、ガンマグロブリン大量療法

ラピアクタ（注射薬）
タミフル（内服薬）
リレンザ・イナビル（吸入薬）
ゾフルーザ（新薬）

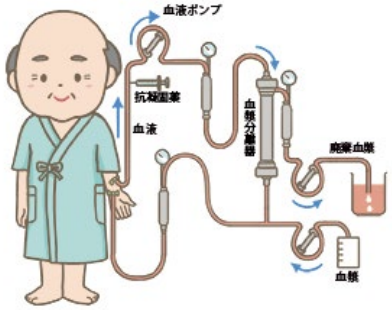
インフルエンザ脳症に対する特殊な治療

脳低温療法

体温を33.0-35.0℃

過剰な免疫反応や代謝を抑制し
神経障害の拡大を阻止する

血漿交換療法



5%アルブミン液で
血漿交換

高サイトカイン血症を改善し
細胞障害の進行を阻止

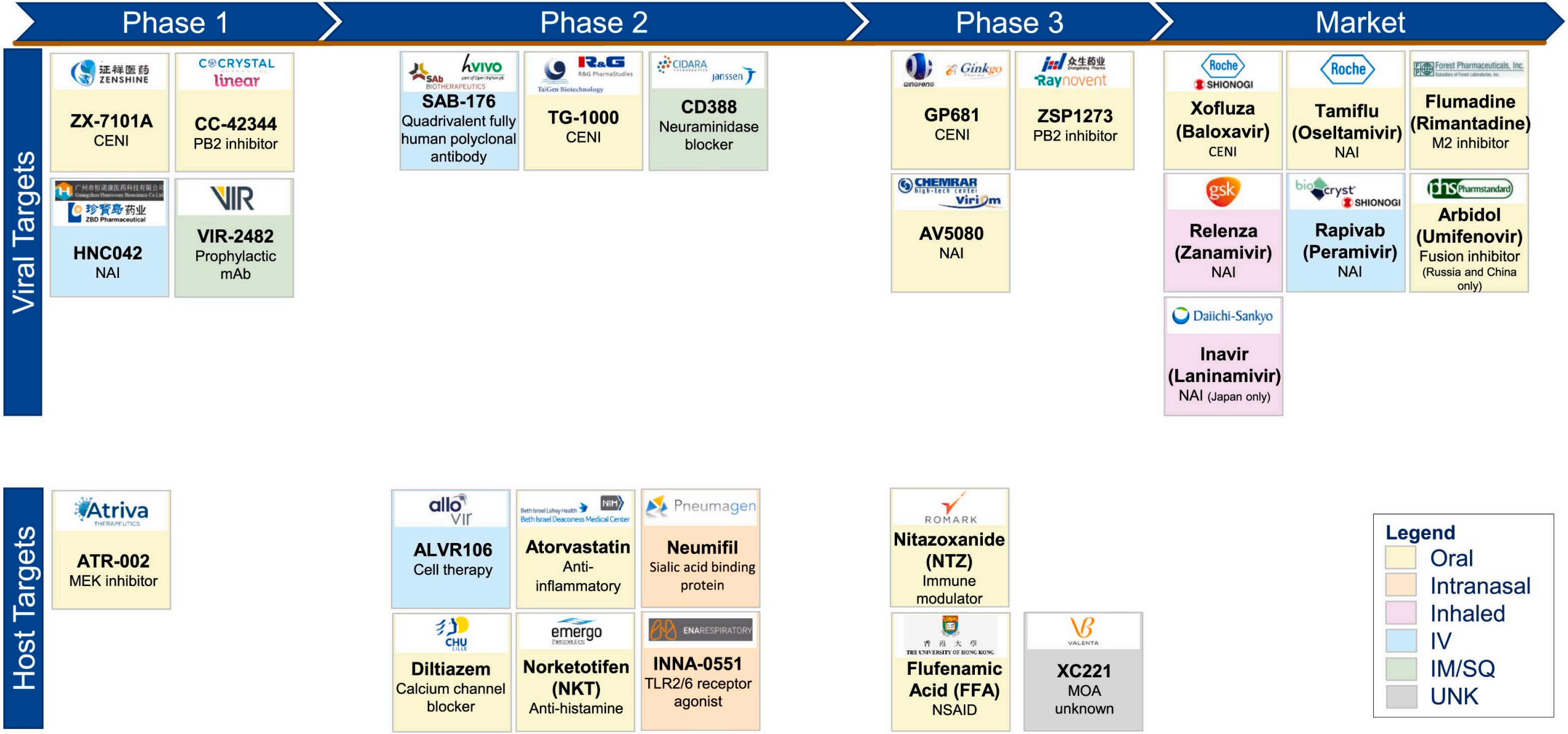
ミトコンドリア カクテル

ビタミンB1, ビタミンC, ビオチン,
ビタミンE, コエンザイムQ10,
L-カルニチンを経口投与

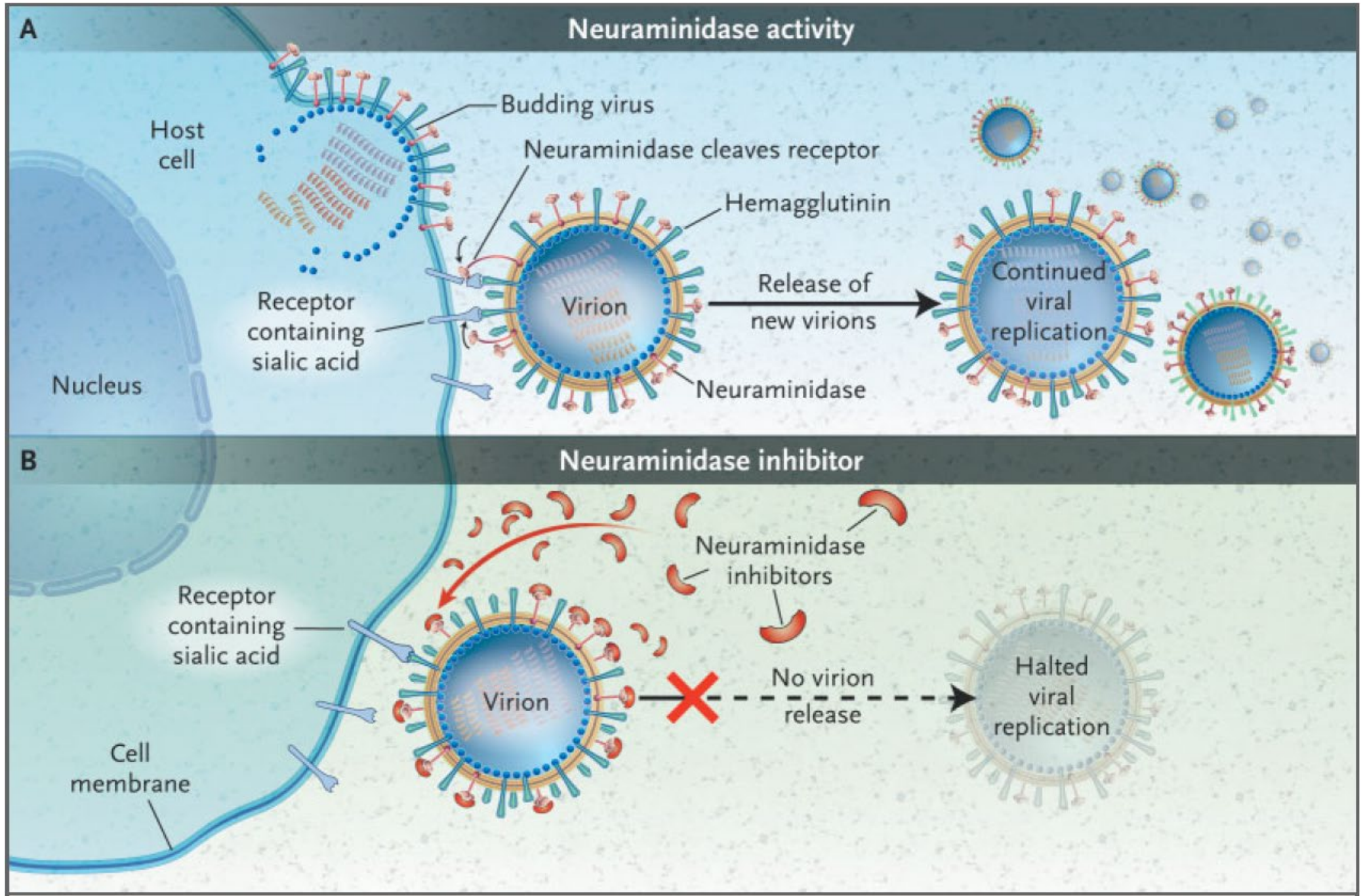
インフルエンザ脳症に伴う
ミトコンドリア機能異常を改善し
脳障害を軽減する

https://doi.org/10.1016/j.antiviral.2022.105499

Influenza Therapeutic Landscape

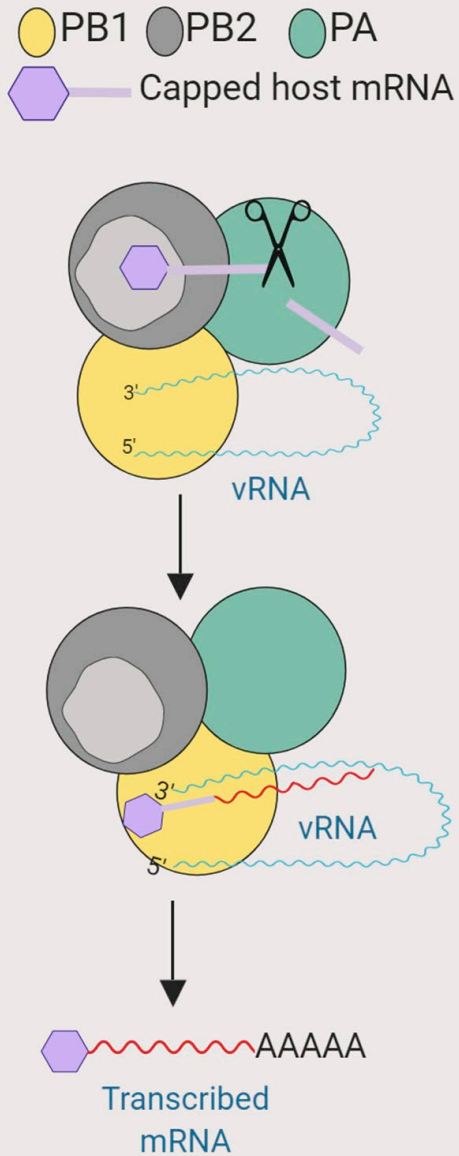


https://doi.org/10.1056/nejmra050740



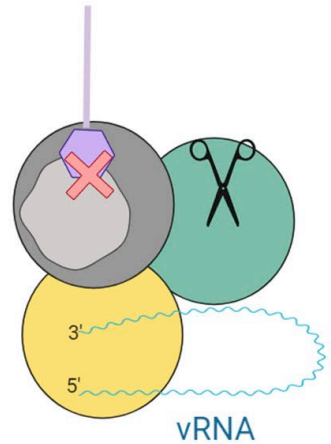
https://doi.org/10.1016/j.antiviral.2019.104545

Normal cap snatching and transcription



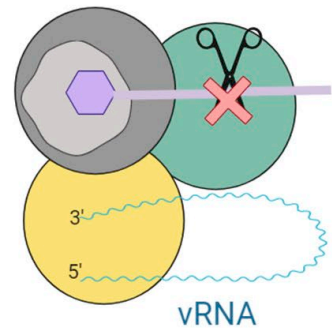
Antiviral inhibition of viral polymerase

Pimodivir



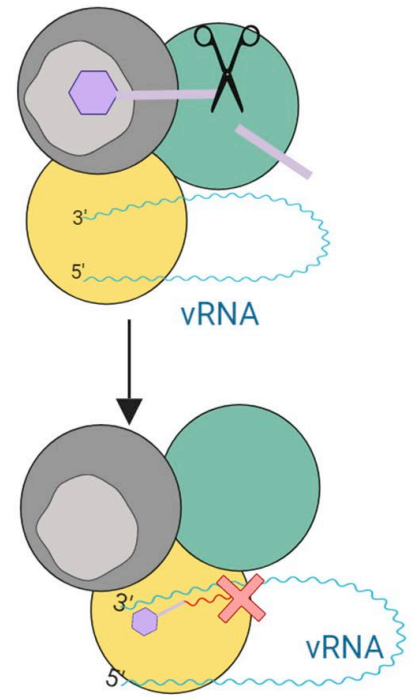
Inhibition of binding capped host mRNA

Baloxavir & AL-794



Inhibition of endonuclease activity

Favipiravir



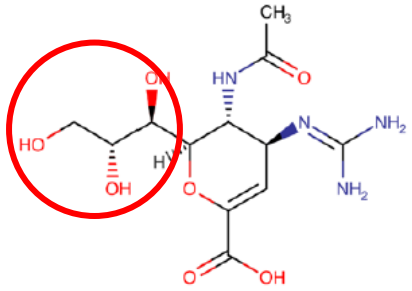
Inhibition of correct mRNA elongation

https://doi.org/10.3390%2Fijms232012244

ZANAMIVIR

IUPAC Name
(2R,3R,4S)-3-acetamido-4-(diaminomethylideneamino)-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid

Chemical Formula



Strains	Year/Period of Time	Mutations Conferring Resistance	Region of the World	Ref.
A(H1N1)	N/D	E119V, H126N, Q136K	N/D	[39]
H3N2	N/D	E119V	N/D	[4]
A(H1N1)pdm09	2012–2022	Q136L/R/K	Asia–Pacific region	[45]
A(H3N2)	2013–2022	Q136L/K	Asia–Pacific region	
A(H1N1)	2006–2008	Q136K	Australasia, Southeast Asia	[46]
A(H7N9)	2013	R292K	China	[40]
A(H1N1)pdm09	2014	I223R	Denmark	[47]
A(H1N1)pdm09	2014–2015	I223R	Bolivia	[48]
A(H3N2)	2014–2015	Q136K(NA)N142S(NA)	Western Pacific, Europe,USA	[48]
Influenza B viruses	2004–2005	R371K	Hong Kong	[49]
Influenza B viruses	2014–2015	D197N(NA)I221T(NA)	Australia, USA, China, Ukraine, Japan, Russia	[48]
Influenza B viruses	2018–2020	T146K	Philippines	[50]
		T146P, N169S, G247D, I361V, G108E, H101L, A200T, H439P	Malaysia	

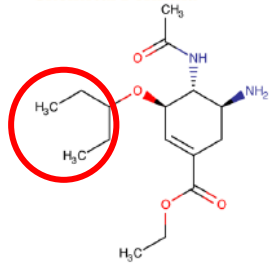
N/D: no data.

https://doi.org/10.3390%2Fijms232012244

OSELTAMIVIR

IUPAC Name
ethyl (3R,4R,5S)-4-acetamido-5-amino-3-pentan-3-yloxycyclohexene-1-carboxylate

Chemical Formula



Strains	Year/Period of Time	Mutations Conferring Resistance	Region of the World	Ref.
A(H1N1)	2005–2008	H274Y	Germany	[51]
A(H3N2)		E119V, R292K, N294S		
A(H5N1)		H274Y		
A(H1N1)	2009	I223V	USA	[52]
A(H1N1)	2007–2008	H274Y	Oceania, South Africa, South East Asia	[53]
A(H1N1)	2007–2008	H275Y	Europe, Asia, USA	[39]
A(H1N1)pdm09	2009–2016	H275Y	Germany	
A(H3N2)	2012	R292K	Germany	
A(H1N1)pdm09	2013–2014	H275Y	China, Japan, USA	
A(H1N1)pdm09	2014	H275Y, H275Y/G147R, I223R	Denmark	[47]
A(H1N1)pdm09	2014–2015	H275Y(NA)I223R(NA)	Australia, Hawaii, Ukraine, France, Bolivia	[46]
A(H3N2)	2014–2015	I222T/S331R E119V(NA) R292K(NA), G320E(NA) N142S(NA)	Western Pacific, Americas, Europe USA	[48]
A(H1N1)pdm09	2009–2010	H275Y(NA)	Greece	[54]
A(H7N9)	2013	R292K	China	[40]
Influenza B viruses	2004–2005	R371K	Hong Kong	[49]
Influenza B viruses	2011	H273Y	Canada	[55]
Influenza B viruses	2014–2015	I221T(NA) K152M(NA) D197N(NA) I221T(NA)	Honduras Bangladesh Australia, USA, China, Ukraine Japan, Russia, China	[48]
A(H3N2)	2011–2013	Q136L, Q136K	Asia–Pacific region	[45]
Influenza B viruses	2016–2019	T146K, T146P, T146P, N169S, G108E, A200T	Asia	[50]

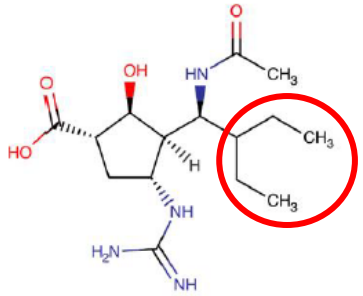
N/D: no data.

https://doi.org/10.3390%2Fijms232012244

PERAMIVIR

IUPAC Name
(1S,2S,3S,4R)-3-[(1S)-1-acetamido-2-ethylbutyl]-4-(diaminomethylideneamino)-2-hydroxycyclopentane-1-carboxylic acid

Chemical Formula

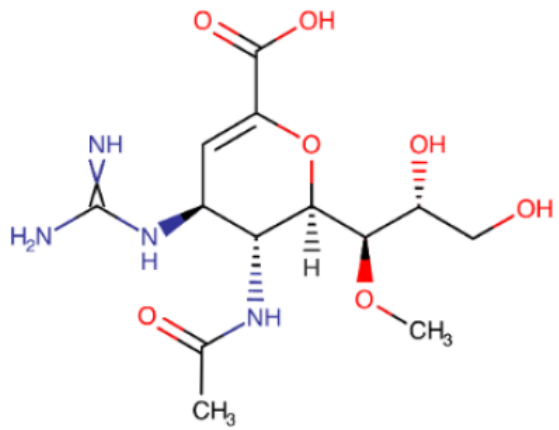


Strains	Year/Period of Time	Mutations Conferring Resistance	Region of the World	Ref.
A(H1N1)	2006–2008	Q136K(NA)	Australasia, Southeast Asia	[46]
A(H1N1)pdm09	2011–2012	Q136R(NA), Q136K(NA)	Asia–Pacific region	[45]
A(H1N1)pdm09	2014	H275Y/G147R	Denmark	[47]
A(H1N1)pdm09	2014–2015	H275Y(NA)	Australia, Hawaii, Ukraine, France	[48]
A(H3N2)	2014–2015	E119V(NA), R292K(NA) N142S(NA)	Japan USA	[48]
Influenza B viruses	2014–2015	T106P, G104R/G, G145E I221T(NA) D197N(NA) I221T(NA)	Japan Honduras Australia, USA, China, Ukraine Japan, Russia, China	[48]
A(H1N1)pdm09	2009–2012	H275Y(NA)	Asia, Africa, Oceania	[40]
Influenza B viruses		I221T, A245T, K360E, A395E, D432G, G145R + Y142H		
Influenza B viruses	2011	H273Y	Canada	[40]
A(H7N9)	2013	R292K	China	[55]
Influenza B viruses	2016–2020	T146K, T146P, N169S, G247D, I361V, G108E, H101L, A200T, D432G, H439P	Asia	[50]

https://doi.org/10.3390%2Fijms232012244

LANINAMIVIR

Chemical Formula



IUPAC Name
(2R,3R,4S)-3-acetamido-4-(diaminomethylideneamino)-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid

Strains	Year/Period of Time	Mutations Conferring Resistance	Region of the World	Ref.
A(H1N1)pdm09	2011–2012	Q136R/K	Asia–Pacific region	[45]
H3N2 wt	E119G	N/D	N/D	[50]
A(H3N2)	2014–2015	N142S(NA)	USA	[48]
Influenza B viruses	2019	T146P(NA), N169S(NA) T146K	Malaysia	[50]
	2018	T146K	Philippines	
	2019	A200T	Malaysia	

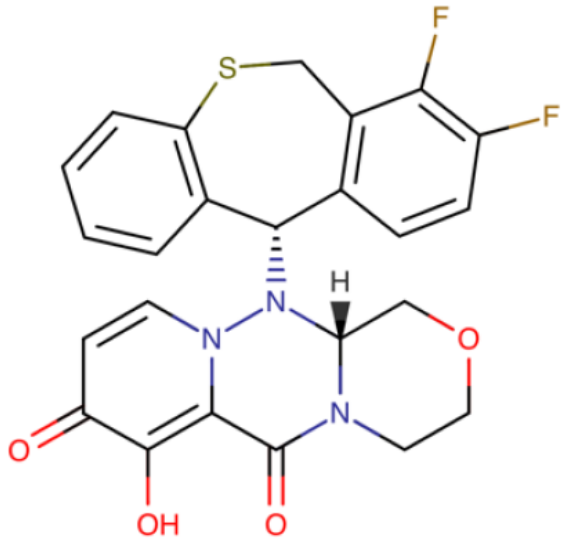
N/D: no data.

https://doi.org/10.3390%2Fijms232012244

BALOXAVIR MARBOXIL

IUPAC Name
[(3R)-2-[(11S)-7,8-difluoro-6,11-dihydrobenzo[c][1]benzothiepin-11-yl]-9,12-dioxo-5-oxa-1,2,8-triazatricyclo[8.4.0.03,8]tetradeca-10,13-dien-11-yl]oxymethyl methyl carbonate

Chemical Formula



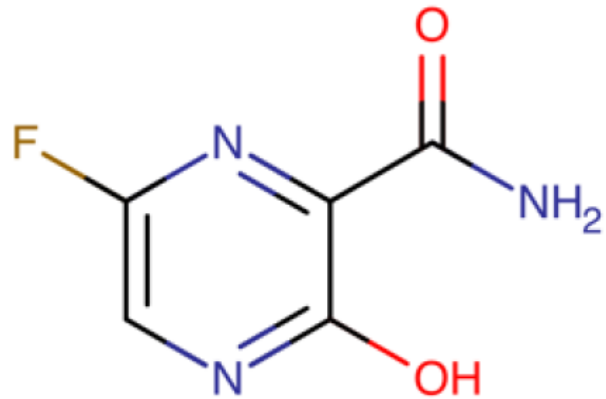
Strains	Year/Period of Time	Mutations Conferring Resistance	Region of the World	Ref.
A(H1N1)pdm09	2018	PA-I38T, PA-I38F, PA-I38M	USA	[84]
A(H3N2)	2018/2019 2018	PA-I38T PA-I38M, PA-I38F	Japan	[87,88]
Influenza B viruses	2020	PA-I38T, PA-I38M	Reported only in vitro	[89]

https://doi.org/10.3390%2Fijms232012244

FAVIPIRAVIR

IUPAC Name
5-fluoro-2-oxo-1H-pyrazine-3-carboxamide

Chemical Formula



Strains	Year/Period of Time	Mutations Conferring Resistance	Region of the World	Ref.
A(H1N1)pdm09 A(H3N2), A(H7N9)	2018	K229R P653L	Reported only in vitro	[93]

Table 1. Overview of influenza polymerase inhibitors

https://doi.org/10.1101%2Fcshperspect.a038687

	Favipiravir	Pimodivir	Baloxavir marboxil
Alternative name	T-705	JNJ-63623872, VX-787	S-033188
Molecular formula	$C_5H_4FN_3O_2$	$C_{20}H_{19}F_2N_5O_2$	$C_{27}H_{23}F_2N_3O_7S$
Molecular weight	157.1	399.4	571.6
Active form	Favipiravir-RTP	–	Baloxavir acid
Target protein	PB1	PB2	PA
Target influenza viruses	Types A, B, C, D	Type A	Types A, B, C, D
Current status	Approved in Japan for influenza pandemic preparedness	In Phase III clinical trials	Approved in several countries (Japan, USA, etc.)
Route of administration	BID oral dose for 5 d	BID oral dose for 5 d	Single oral dose
Inhibition of M2 inhibitor–resistant viruses	Yes	Yes	Yes
Inhibition of NA inhibitor–resistant viruses	Yes	Yes	Yes
Emergence of variants with reduced susceptibility in vitro	Yes	Yes	Yes
Emergence of variants with reduced susceptibility in clinical trials	No	Yes	Yes

(Favipiravir-RTP) Favipiravir-ribofuranosyl-5′-triphosphate, (PB1) polymerase basic protein 1, (PB2) polymerase basic protein 2, (PA) polymerase acidic protein, (BID) twice daily, (M2) matrix protein 2, (NA) neuraminidase.

https://doi.org/10.1016/j.antiviral.2022.105499

Table 1
Antiviral drugs for treating influenza virus infection.

Inhibitor	Trade name	Drug class	Viral protein target	Mechanism of action	Clinically relevant resistance (influenza A viruses)
Amantadine Rimantadine	Amantadine: Symmetrel Rimantadine: Flumadine	Adamantane	M2 (influenza A only)	Interferes with virion and endosomal acidification. Inhibits downstream HA conformation change, endosomal fusion, and release of viral genomes into the cytoplasm	M2 protein: S31N (predominant), L26F, V27A, A30T, G34E
Oseltamivir phosphate	Tamiflu	Neuraminidase inhibitor	NA (influenza A and B)	Blocks NA enzymatic cleavage of host cell sialic acid receptors. Inhibits progeny virus budding	NA protein: E119D/G/I/V, I222R, S246N, H274Y, R292K, N294S
Zanamivir	Relenza				NA protein: E119D/G, I222R, S246 G/R, R292K, E119G + H274Y
Peramivir	Rapivab/ Rapiacta/ PeramiFlu				NA protein: S246 G/R, H274Y, R292K, G147R + H274Y
Laninamivir	Inavir			A longer-lasting formulation of this class of drug	NA protein: G147R + H274Y
Favipiravir	Avigan	Nucleoside analogue	PB1 (influenza A and B)	Preferentially incorporated by PB1 into viral RNA. Leads to chain elongation termination and/or lethal mutagenesis	N/A
Baloxavir marboxil	Xofluza	Cap-dependent endonuclease inhibitor	PA (influenza A and B)	Blocks PA endonuclease activity necessary to cleave PB2-bound, capped host mRNAs. Halts viral mRNA transcription	PA protein: I38T (predominant), I38M/F/L/N/S, E23G/K, A37T, E199G

N2 NA numbering.
N/A, not applicable.

https://doi.org/10.7883/yoken.jjid.2021.751

Table 1. Antiviral susceptibilities of avian influenza A viruses isolated in Japan

Subtype	Isolate name	GISAID isolate ID	Neuraminidase inhibitor[1]				Polymerase inhibitor[2]	
			IC_{50} (nM)				IC_{50} (nM)	IC_{50} (μM)
			Oseltamivir	Peramivir	Zanamivir	Laninamivir	Baloxavir	Favipiravir
Representative avian influenza viruses[3]								
A(H5N1)	A/duck/Hyogo/36/2001	EPI_ISL_3697081	2.22	0.08	0.42	0.26	0.41	1.72
A(H5N2)	A/chicken/Ibaraki/1/2005	EPI_ISL_360	0.13	0.22	1.20	1.31	0.53	0.79
A(H7N7)	A/duck/Fukui/2/2004	EPI_ISL_3707554	0.34	0.23	1.85	2.88	0.36	0.92
A(H7N9)	A/duck/Gunma/466/2011	EPI_ISL_4105027	0.40	0.12	0.77	1.12	0.64	1.44
A(H9N1)	A/duck/Fukui/3/2005	EPI_ISL_3707749	2.05	0.10	0.20	0.21	0.43	1.62
A(H9N2)	A/chicken/Japan/AQ-HE28-28/2016	EPI_ISL_280895	0.09	0.11	0.71	1.24	0.73	2.05
Recently isolated avian influenza viruses								
A(H5N8)	A/chicken/Kagawa/11C/2020 (Clade 2.3.4.4b)	EPI_ISL_681286	0.44	0.06	0.15	0.13	0.26	0.59
A(H5N8)	A/chicken/Miyazaki/E3T/2020 (Clade 2.3.4.4b)	EPI_ISL_4105028	0.53	0.04	0.16	0.10	0.32	0.59
A(H5N8)	A/swan/Niigata/151118/2020 (Clade 2.3.4.4b)	EPI_ISL_4105052	0.31	0.05	0.33	0.33	0.25	0.57
A(H9N2)	A/chicken/Japan/AQ-HE31-26/2020	EPI_ISL_700743	0.11	0.10	0.72	1.15	0.39	1.00
Reference human influenza viruses								
A(H1N1)pdm09	A/KANAGAWA/AC1926/2019 (NA H275Y mutant)[4]	EPI_ISL_408551	236.53	19.13	0.24	0.86	2.22	1.27
	A/KANAGAWA/IC1890/2019 (PA I38T mutant)[5]	EPI_ISL_345217	0.29	0.07	0.33	0.30	60.18	0.89
	A/KANAGAWA/ZC1931/2019 (Wild-type)	EPI_ISL_403549	0.24	0.09	0.24	0.19	2.35	1.60
	Mean IC_{50} values[6] (Wild-type)		0.36 ± 0.16	0.09 ± 0.03	0.31 ± 0.12	0.44 ± 0.23	5.90 ± 2.22	1.08 ± 0.42

https://doi.org/10.1093%2Fcid%2Fciq183

Table 1. Characteristics of Pediatric Influenza Patients Studied

Table 2. Summary of Influenza Viruses Possessing a Neuraminidase (NA) Substitution

Virus ID	Amino acid substitution in NA	Subtype of virus	Age of patient, years	Date of sampling (day after beginning of treatment)	Proportion of viruses with substituted NA, %[a]	IC_{50} for oseltamivir,[b] nM	
						Parental virus	Mutant virus
1	Arg292Lys	H3N2	5	3	0	0.21	33,390
				5	25	0.21	33,390
2	Arg292Lys	H3N2	9	3	0	NT[c]	NT
				5	50	NT[c]	NT
3	Arg292Lys	H3N2	13	4	8	NT	NT
4	His274Tyr	H1N1	4	5	8	1.63	1115
				7	75	1.63	1115
5	His274Tyr	H1N1	9	4	16	NT	NT
6	Glu119Val	H3N2	5	4	41	0.43	230

[a] For each virus isolate, we analyzed the nucleotide sequences of the NA genes of at least 12 molecular clones and calculated the proportion of cDNA clones encoding substituted NAs.

[b] Median inhibitory concentration (IC_{50}) values are the mean of duplicate reactions.

[c] NT indicates samples not tested because infectious viruses were not isolated from the corresponding specimens.

No. (%) of patients with vaccination history	30 (42)	27 (38)	.61

https://doi.org/10.1289%2Fehp.0900930

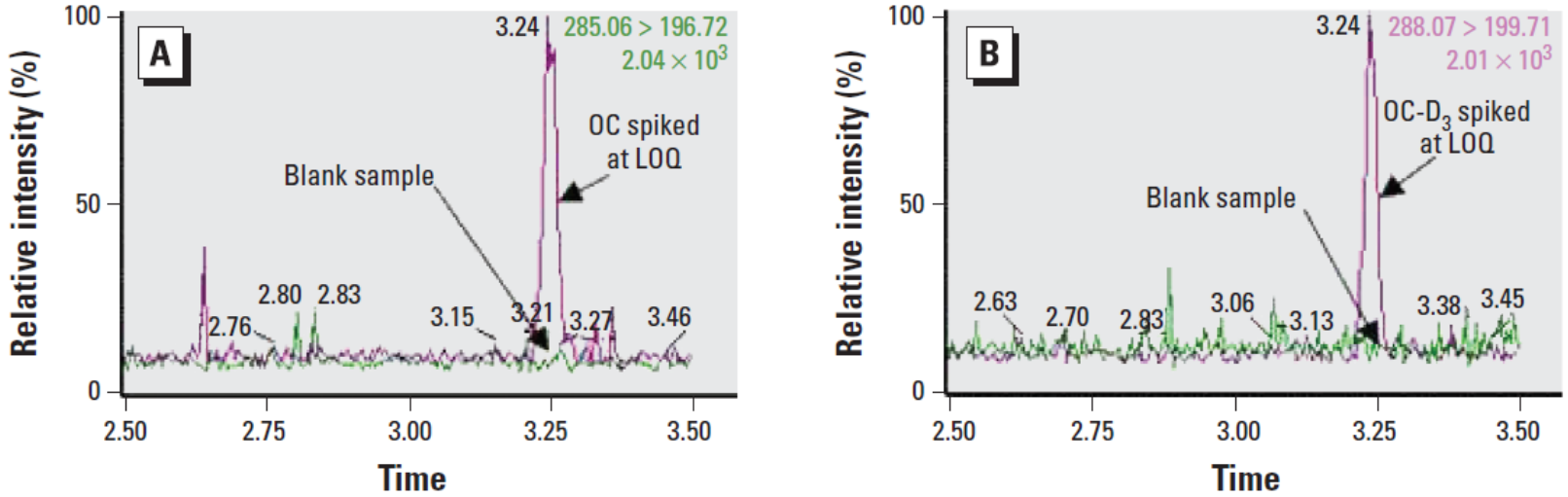
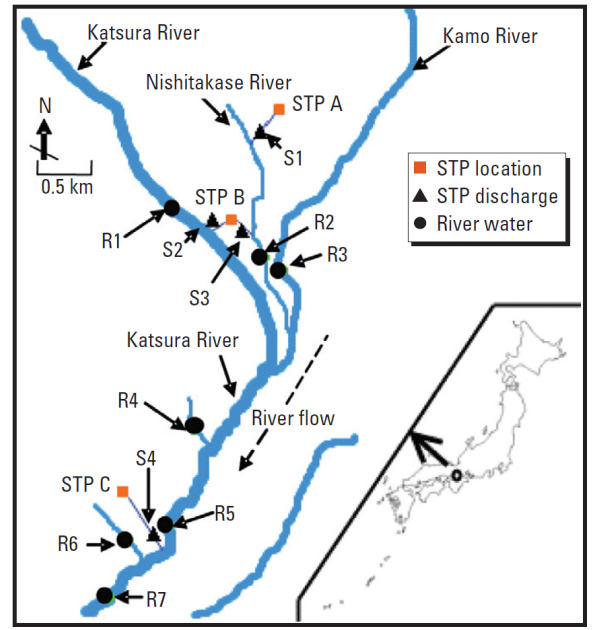


Figure 3. Representative total ion chromatograms of (*A*) a blank sewage discharge sample (OC-free) and spiked OC at the LOQ and (*B*) a blank sewage discharge sample and spiked OC-D_3 at the LOQ of OC.



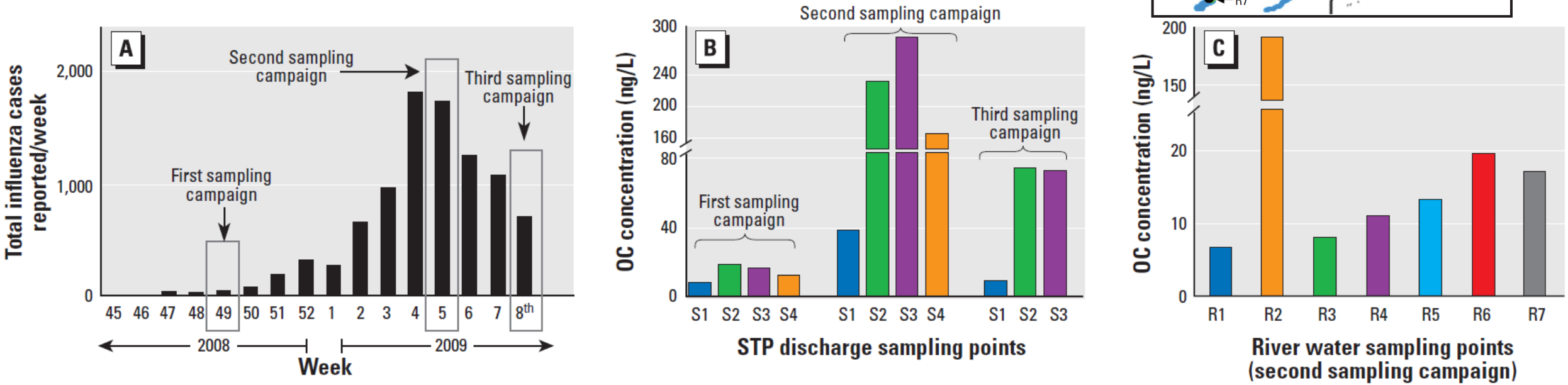
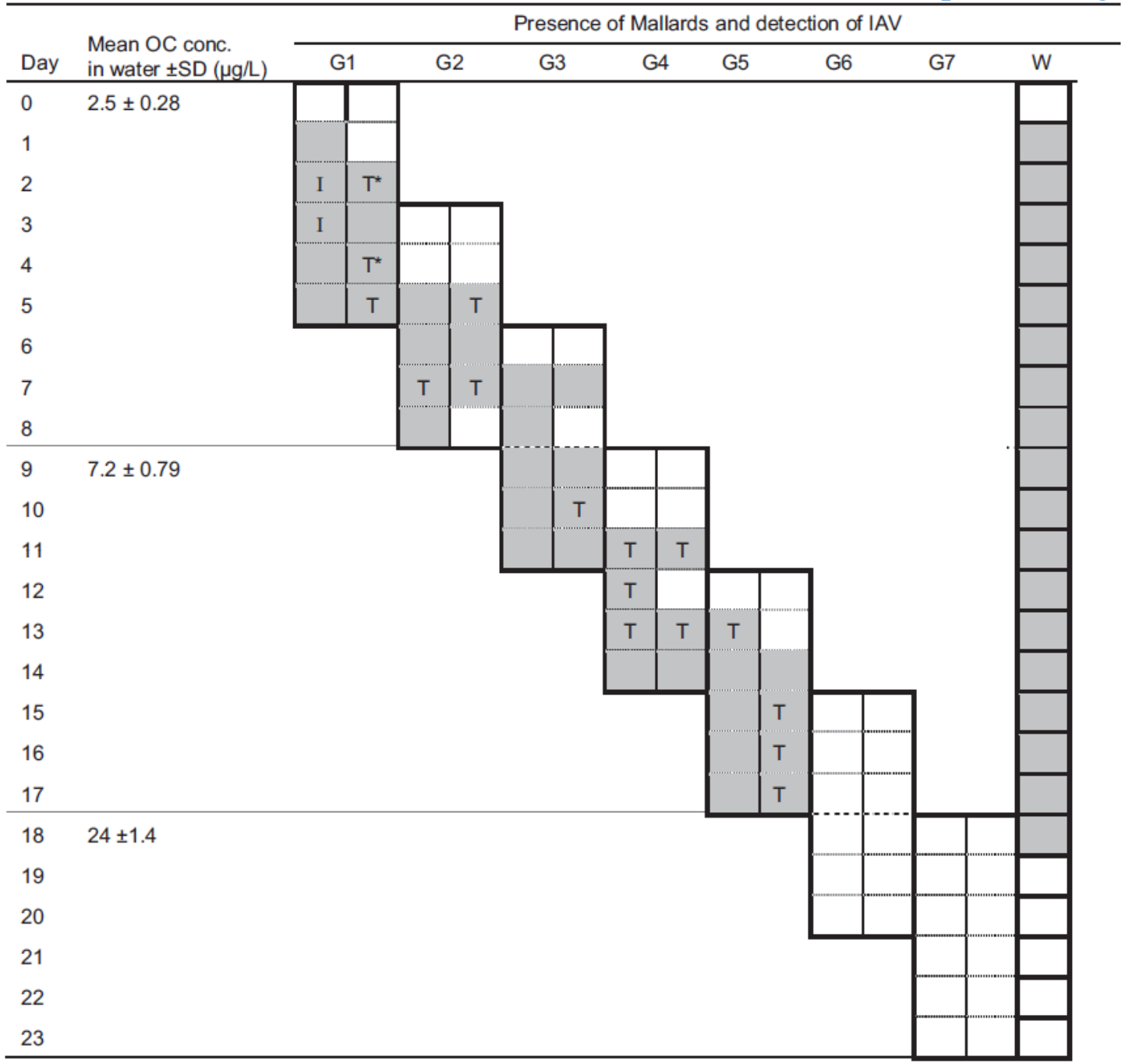


Figure 4. (*A*) Total number of influenza cases reported per week during the 2008–2009 influenza outbreak in Kyoto City during three sampling campaigns. (*B*) OC concentrations at STPs during three sampling campaigns (no sample was collected at S4 during the third campaign). (*C*) OC concentrations in river water during the second campaign. OC was detected in river water only during the second sampling campaign; no sample was collected at R2 during the first and third campaigns.

https://doi.org/10.1128%2FAAC.00886-15



https://www.fda.gov/vaccines-blood-biologics/audenz

AUDENZ

Vaccines, Blood & Biologics

Infectious Disease Tests

Fecal Microbiota Products

Allergenics

Blood & Blood Products

Blood Donor Screening

Cellular & Gene Therapy Products

Development & Approval Process (CBER)

Guidance, Compliance & Regulatory Information (Biologics)

International Activities

News & Events (Biologics)

STN: 125692
Proper Name: Influenza A (H5N1) Monovalent Vaccine, Adjuvanted
Tradename: AUDENZ
Manufacturer: Seqirus, Inc.
Indication:

- AUDENZ is an inactivated vaccine indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. AUDENZ is approved for use in persons 6 months of age and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.

Product Information

- Package Insert - AUDENZ
- Demographic Subgroup Information - AUDENZ
  Refer to Section 1.1 of the Clinical Review Memo for information about participation in the clinical trials and any analysis of demographic subgroup outcomes that is notable.

Supporting Documents

- November 17, 2021 Approval Letter - AUDENZ
- October 29, 2021 Approval Letter - AUDENZ
- January 31, 2020 Summary Basis for Regulatory Action - AUDENZ

Content current as of:
11/29/2021

https://doi.org/10.12688%2Fgatesopenres.13171.1

Table 5. Desired attributes of AI vaccines addressing the smallholder segment.

Desired attribute	Current situation
Inexpensive	Current cost for inactivated AIV vaccine: $0.03–0.10/dose plus cost of administration ($0.05–0.07 per dose for individual handling and injection)
Use in multiple avian species	Most vaccines are used in meat, layer and breeder chickens although a large number of doses also used in ducks; minor amounts in turkeys, geese, quail, etc.
Single dose protection	Most situations require a minimum of 2 doses; prime-boost scenario is optimal with revaccination in long-lived birds at 6–12-month intervals
Mass application	95.5% is inactivated vaccine administered by handling and injecting individual birds and 4.5% as vectored vaccine given by mass spray vaccination
Identify infected birds in vaccinated population (DIVA)	Serological differentiation tests are available, but only minor use. Most vaccine applied without using a serological DIVA strategy for surveillance
Overcome maternal antibody interference	Maternal antibody to AIV hemagglutinin or virus vector inhibits primary immune response. Initial vaccination must be timed for declining maternal antibody titers to allow optimal primary immune response
Given at 1 day of age in hatchery or *in ovo*	Inactivated vaccine provides poor protection when given at 1 day of age. Vectored vaccines can be given at 1 day of age, but generally require a boost with inactivated vaccine 10 days or more later
Universal vaccine	The majority of inactivated whole AIV vaccines use reverse genetic generated vaccine seed strains to antigenically match field viruses. The vaccinal strain of virus should also be a strong immunogen
Thermostable	Killed AI vaccines, rNDV-AI and rFPV-AI vaccines require refrigeration and rHVT-AI vaccine must be stored in liquid nitrogen

https://doi.org/10.3201/eid2907.221149

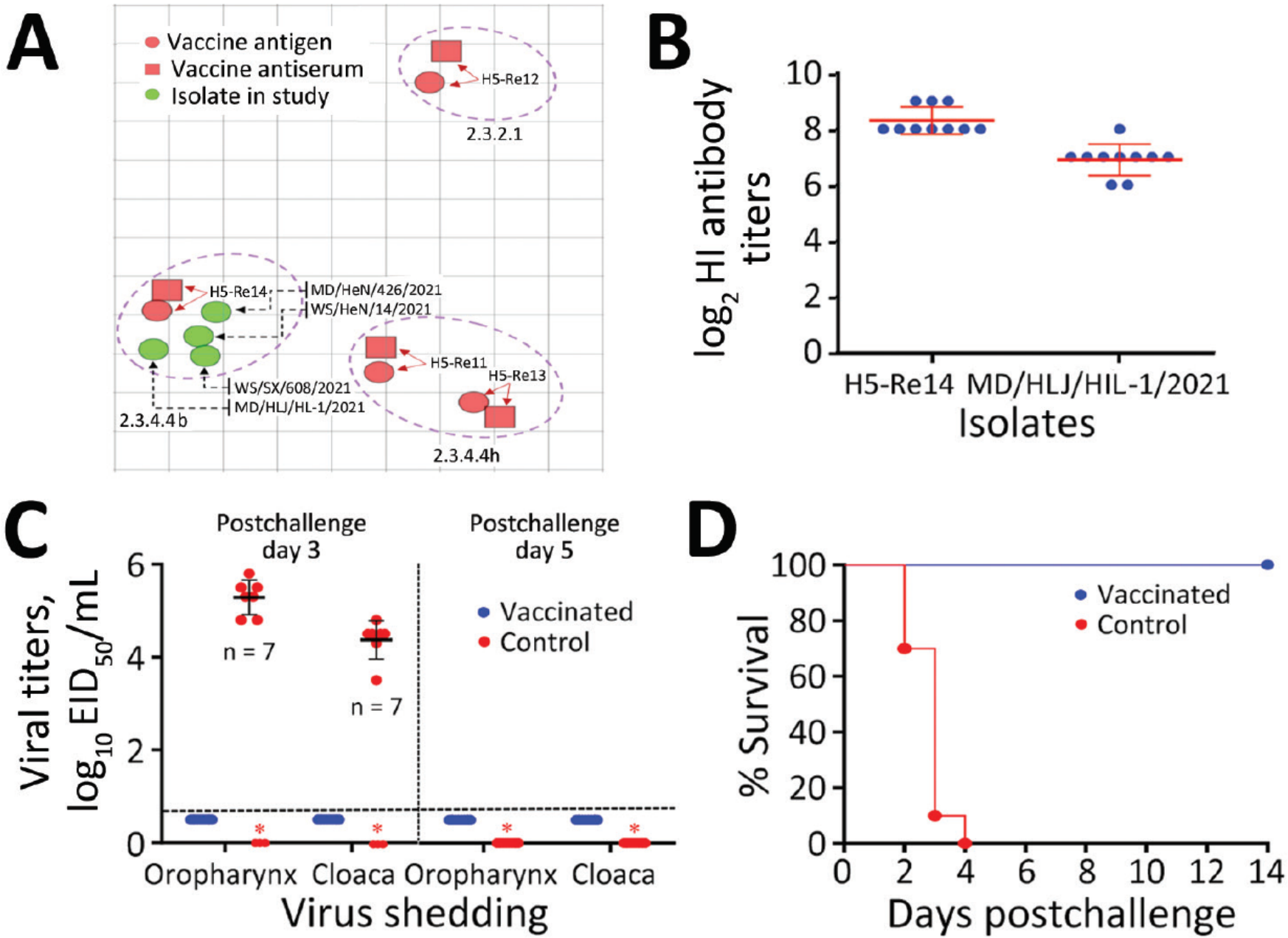


Figure 3. Antigenic difference of avian influenza (H5N1) virus isolates with H5 vaccine strains and protective efficacy of H5 vaccine against the challenge of H5N1 virus. A) Antigenic cartography of H5N1 viruses. The map was generated by using Antigenic Cartography software (https://acmacs-web.antigenic-cartography.org); 1 unit (grid) represents a 2-fold change in the HI assay results (Appendix 2 Table 7, https://wwwnc.cdc.gov/EID/article/29/7/22-1149-App2.pdf). B) HI antibody titers of vaccinated chickens against the vaccine seed virus and the challenge strain. C) Virus shedding from chickens on postchallenge days 3 and 5. D) Survival patterns of chickens in the vaccinated and control groups after challenge with the indicated H5N1 virus. EID_{50}, 50% egg infectious dose; HI, hemagglutination inhibition.

https://doi.org/10.1016/S2666-5247(21)00333-5

Supplementary Table 1. Virucidal effects of disinfectants on AIV H7N9 and H5N8

Disinfectant (Working concentration)	Virus titer (Log $TCID_{50}$/mL)					
	H7N9			H5N8		
	2 min	5 min	8 min	2 min	5 min	8 min
Household bleach (50mg/L)	U	U	U	U	U	U
Ethanol (75%)	U	U	U	U	U	U
Hand soap solution (1:49)	2.20±0.19	U	U	2.43±0.07	U	U
Peracetic acetic acid (0.015%)	U	U	U	U	U	U
Lactic acid (0.5%)	2.10±0.10	U	U	2.40±0.10	U	U
Acetic acid (1%)	U	U	U	U	U	U

Note: U, undetectable. Each data shows the means ±SD of three triplicates.

https://doi.org/10.1016/S2666-5247(21)00333-5

Supplementary Table 2. Stability of chicken-attached H7N9 AIV at 4 ° C,25 ° Cand -20 ° C.

	Virus titer (Log $TCID_{50}$/ml)														
Day	25℃					4℃					-20℃				
	Sample 1	Sample 2	Sample 3	Mean	±SD	Sample 1	Sample 2	Sample 3	Mean	±SD	Sample 1	Sample 2	Sample 3	Mean	±SD
1	4.61	4.50	4.50	4.54	0.06	5.00	4.81	4.70	4.84	0.15	5.11	5.00	5.23	5.11	0.12
2	4.21	4.71	4.30	4.41	0.27	4.23	4.23	4.00	4.15	0.13	4.67	4.67	4.29	4.54	0.22
3	3.71	3.39	3.19	3.43	0.26	3.88	3.30	3.30	3.49	0.34	3.80	3.88	4.10	3.93	0.16
4	2.28	2.10	U	2.19	0.13	3.11	2.80	3.00	2.97	0.16	3.24	3.61	3.20	3.35	0.23
5	U	U	U			2.71	2.70	2.50	2.64	0.12	3.00	2.61	2.29	2.63	0.36
6	U	U	U			2.50	2.50	2.40	2.47	0.06	2.42	2.77	2.29	2.49	0.25
7	U	U	U			2.20	2.00	2.00	2.07	0.12	2.25	2.41	2.40	2.35	0.09
8	U	U	U			U	U	U			2.39	2.35	2.00	2.24	0.22
9	U	U	U			U	U	U			2.20	U	2.42	2.31	0.16
10	U	U	U			U	U	U			U	U	U		

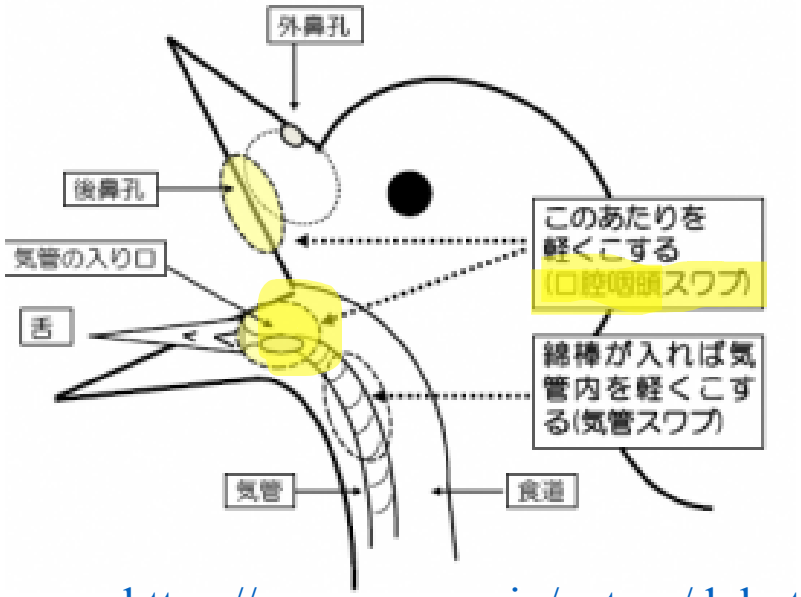
Note: U, undetectable. The detection limit of a typical $TCID_{50}$ assay is 100 $TCID_{50}$/mL.

使用する検体

推奨　　推奨

- 人：咽頭拭い液、鼻腔ぬぐい液、肺胞洗浄液
  気管支吸引液など

- 鳥：口腔咽頭スワブ、クロアカスワブ、糞便



ウイルス量
気管＞糞便

https://www.env.go.jp/nature/dobutsu/bird_flu/manual/pdf/3tyousa.pdf

検体保存

細胞培養液（MEM培地または199培地）またはPBS(-)を使用する

生理食塩水はpHが不安定となるため使用しない

採取後は**4℃**、長期保存する場合は**-70℃以下**に保存することが望ましい

RNA抽出

QIAamp Viral RNA Mini Kit（QIAGEN）

https://www.qiagen.com/jp/spotlight-pages/ias/automated-qpcr-workflow/purification/qiaamp-viral-rna-mini-qiacube-kit/

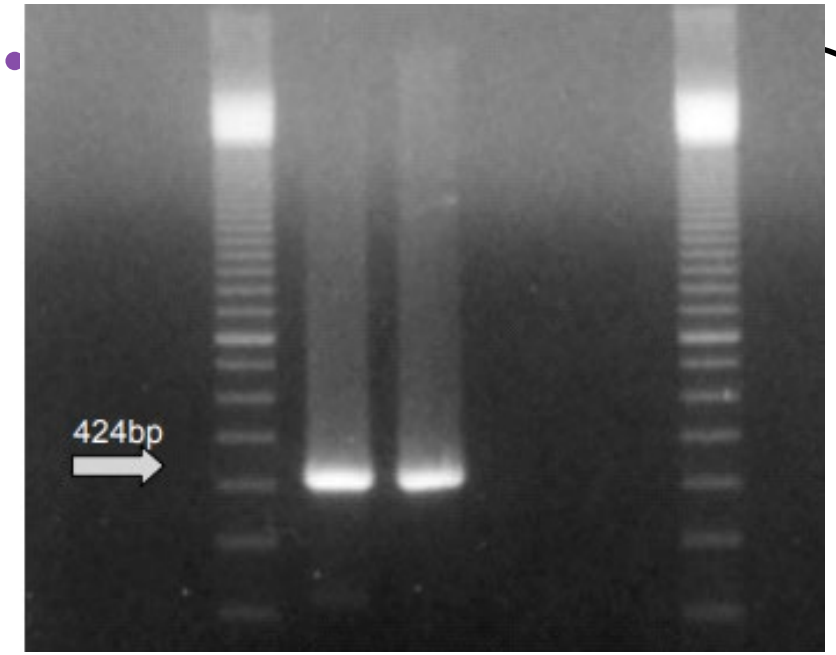
Maxwell® RSC Viral Total Nucleic Acid Purification Kit（プロメガ）

https://www.promega.jp/products/nucleic-acid-extraction/viral-rna-extraction-viral-dna-extraction/maxwell-rsc-viral-total-nucleic-acid-purification-kit/?catNum=AS1330

鳥インフルエンザウイルス亜型遺伝子検査法

- コンベンショナルPCR法(RT-PCR法)
- リアルタイムPCR法
- マルチプレックスPCR法
- LAMP法

コンベンショナルPCR法(RT-PCR法)

- 逆転写酵素によりRNAを鋳型としてcDNAを合成して
  PCRを行う
- 

ベを

東京都健康安全研究センター研究年報 (tokyo.lg.jp)

(A 型同定用)

Type A/M 遺伝子検出用プライマー:

Type A/M30F2/08	5'-ATGAGYCTTYTAACCGAGGTCGAAACG
Type A/M264R3/08	5'-TGGACAAANCGTCTACGCTGCAG

PCR 産物の長さ: 244bp

(H5 亜型同定用)

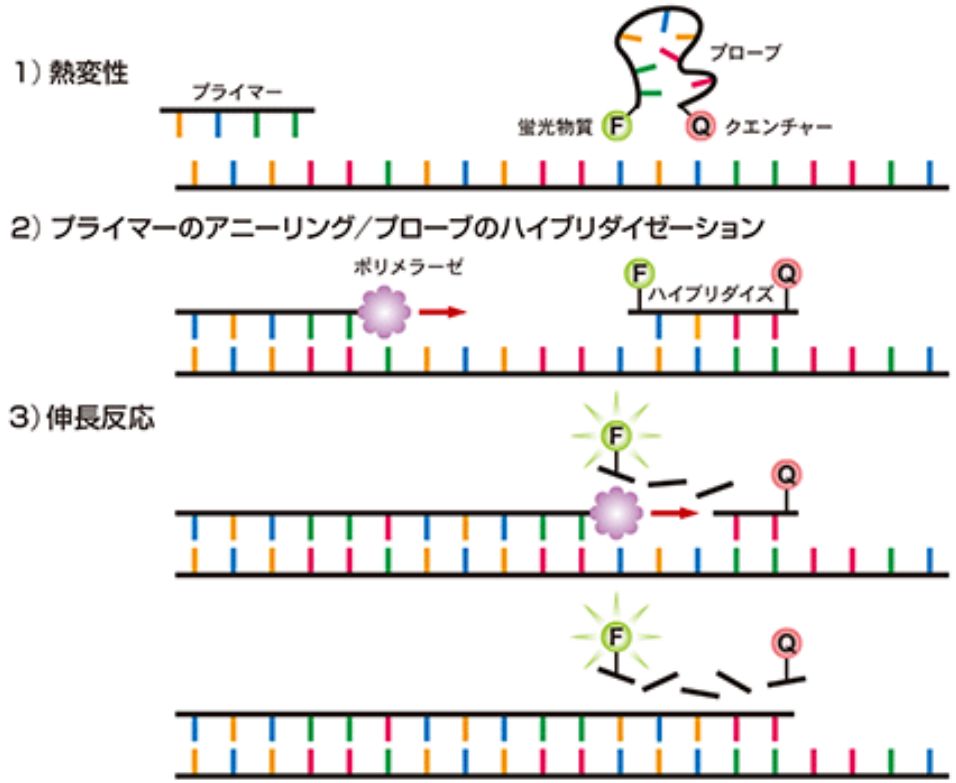
H5 HA 遺伝子検出用プライマー:

H5/ 248-270F	5'- GTGACGAATTCATCAATGTRCCG
H5/ 671-647R	5'- CTCTGGTTTAGTGTTGATGTYCCAA

PCR 産物の長さ: 424bp

https://www.niid.go.jp/niid/images/lab-manual/avian_influenza_2003.pdf

リアルタイムPCR法

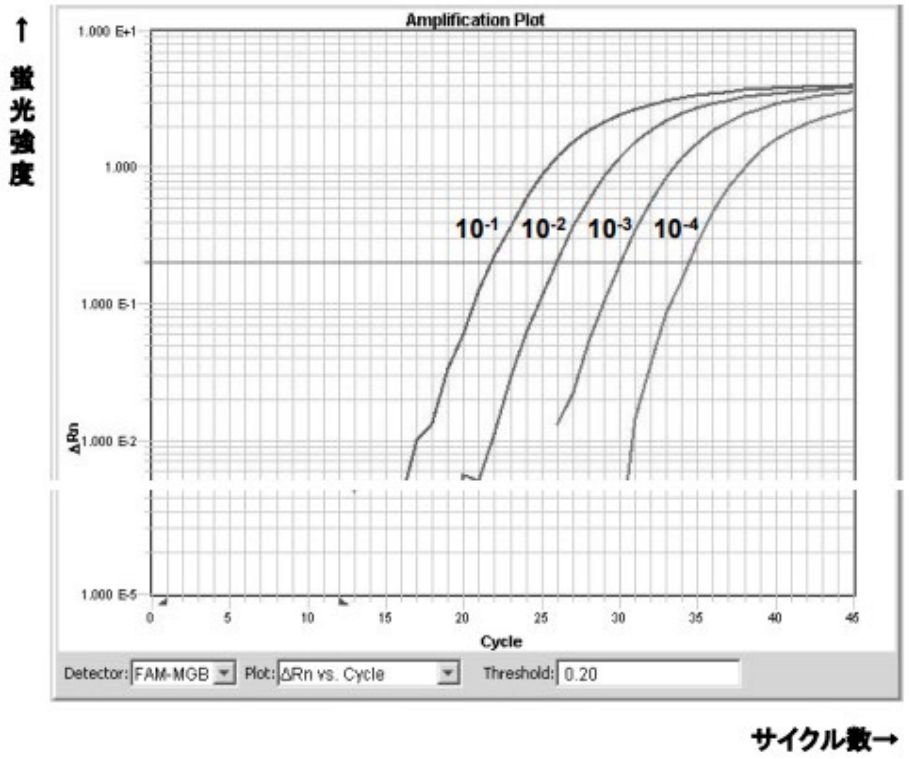


PCRの増幅量をリアルタイムでモニターし解析する方法。電気泳動が不要で迅速性と定量性に優れる

5′末端を蛍光物質（FAMなど）で、　3′末端をクエンチャー物質（TAMRAなど）で修飾したオリゴヌクレオチド（プローブ）を使用する

遺伝子検査技術/遺伝子分析化学認定テキスト/改訂第２版

リアルタイムPCR法



[東京都健康安全研究センター研究年報 (tokyo.lg.jp)]

鳥インフルエンザウイルスの遺伝子配列を基にプライマー、プローブを設計

反応チューブ内の蛍光強度が上昇し、判定ラインを通過した検出曲線が得られたものを陽性とする

リアルタイムPCR法

２種類のプライマーに１種類のプローブを用いて標的遺伝子の検出を迅速に行える

標的遺伝子検出系の設計の自由度が大きく、プライマー、プローブの設計が比較的容易

検出感度が高く、広範な型の検出にも対応可能

リアルタイムPCR法

・LAMP法、リアルタイムPCR法、Nested-PCR法、コンベンショナルPCR法の比較
・H5N1ウイルス抗原液から抽出したRNAを10倍段階希釈した溶液を使用

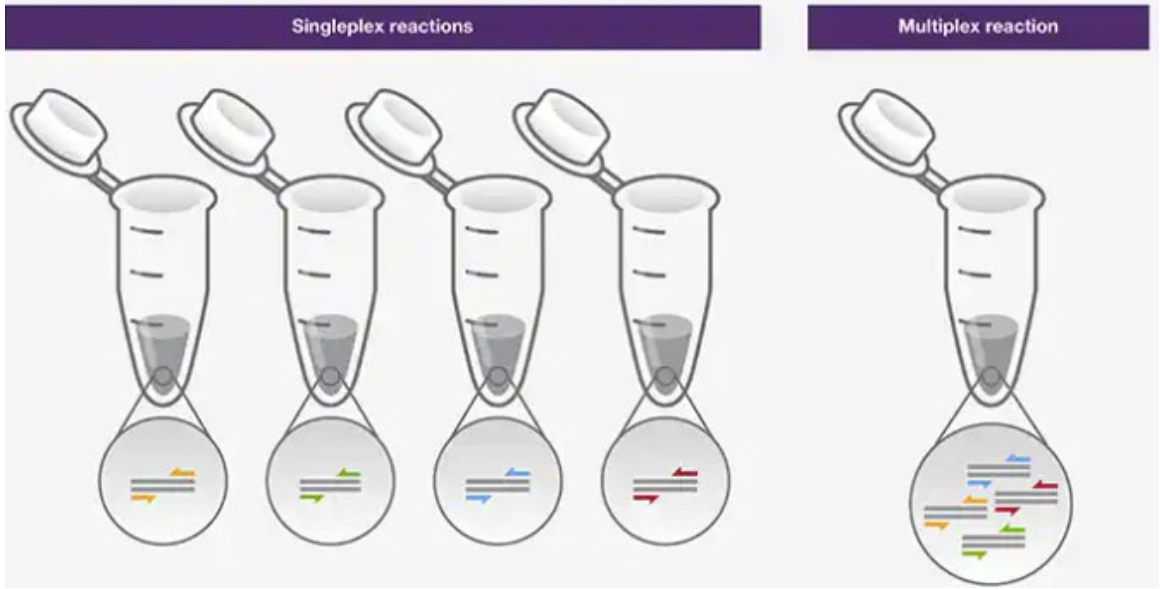
表４．H5型ウイルスを用いた各検査法の感度比較

	× 1	$\times 10^{-1}$	$\times 10^{-2}$	$\times 10^{-3}$	$\times 10^{-4}$
LAMP法	(＋)	(＋)	(＋)	(－)	(－)
Real-time PCR法					
FAM-TAMRA (RT-H5-1607N-F/1688N-R)	(＋)	(＋)	(＋)	(＋)	(－)
FAM-MBG (RT-H5-272F/342R)	(＋)	(＋)	(＋)	(＋)	(＋)
Nested-PCR法	(＋)	(＋)	(－)	(－)	(－)
RT-PCR法 (H5-515f-N/H5-1220R-N)	(－)	(－)	(－)	(－)	(－)
RT-PCR法 (H5-248-270/H5-671-647)	(＋)	(＋)	(＋)	(－)	(－)

(＋) ：検出
(－) ：非検出

東京都健康安全研究センター研究年報 (tokyo.lg.jp)

マルチプレックスPCR法



1つの反応系に対して、複数のプライマーセットを同時に使ってPCRを行う

非特異的な増幅、PCR効率が低下する可能性がある。非特異的な増幅を最小限に抑えるプライマー設計が極めて重要

PCRメソッド—トップ10の方法 | Thermo Fisher Scientific - JP

マルチプレックスPCR法

・H1,2,3,5,6,7,9,10（人に感染する亜型）の８種類を同時に検出

Serotype	No. of samples testing positive via:			
	GeXP assay	RRT-PCR	Sequencing	Coincidence rate
H1	2	2	2	100%
H2	1	1	1	100%
H3	8	8	8	100%
H5	2	2	2	100%
H6	14	14	14	100%
H7	5	5	5	100%
H9	14	14	14	100%
H10	1	1	1	100%
Mix	20	20	20	100%
Total	66	66	66	100%

単一測定と同等の
感度で検出

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5906657/

マルチプレックスPCR法

・H5,N1,N2,N6,N8を同時に検出
　Ｈ５Ｎ1、Ｈ５Ｎ２、Ｈ５Ｎ６、Ｈ５N8を一回の反応で検査

ウイルス分離	鳥インフルエンザウイルス陰性サンプル		鳥インフルエンザウイルス陽性検体						
	RRT-PCR	GeXPアッセイ	RRT-PCR	GeXPアッセイ					
				M	H5	N1	N2	N6	N8
H5N1	29/30	29/30	1/30	1/30	1/30	1/30	0/30	0/30	0/30
H5N2	29/30	28/30	1/30	2/30	2/30	0/30	2/30	0/30	0/30
H9N2	39/42	38/42	3/42	4/42	0/42	0/42	4/42	0/42	0/42
H6N2	34/35	34/35	1/35	1/35	0/35	0/35	1/35	0/35	0/35
H6N6	41/43	41/43	2/43	2/43	0/43	0/43	0/43	2/43	0/43

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4746555/

LAMP法

- １種類の酵素を使用して等温で増幅反応を行う

- ６領域を認識する４種類のプライマーを使用する

[Loopamp H5亜型インフルエンザウイルス検出試薬キット｜（Loopamp製品（臨床検査分野））｜Eiken Genome Site]

[Loopamp プライマーセット Avian Flu H7｜（Loopamp製品（産業・研究分野））｜Eiken Genome Site]

LAMP法

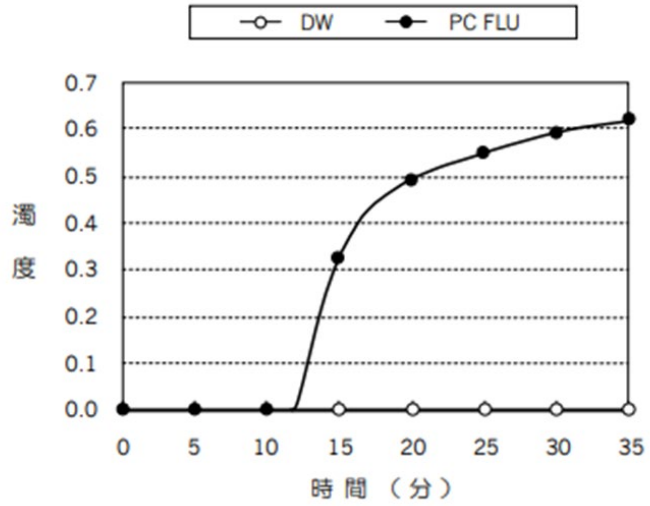
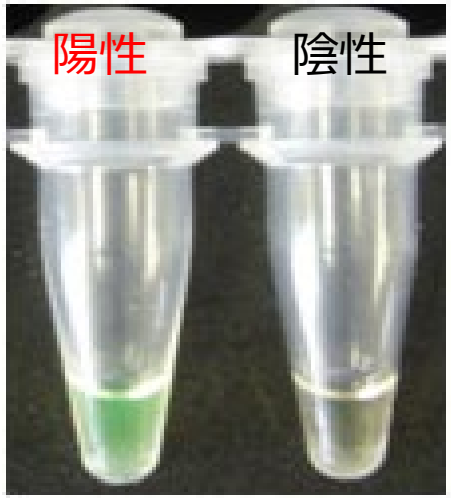


図. Positive Control Flu（PC FLU）の増幅曲線パターン※2
（使用装置：Loopamp リアルタイム濁度測定装置）



増幅反応の副産物のピロリン酸マグネシウムの濁度を測定することにより、増幅の有無を確認

https://loopamp.eiken.co.jp/uploads/insert_h7.pdf

LAMP法

・RT-PCRやリアルタイムPCR法よりも短時間で結果が得られる

・使用するプライマーが６種類におよぶため、遺伝子変異しやすいウイルス遺伝子領域の増幅には適さない

	Virus isolate	H5 real-time RT-LAMP
Subtype	Name	Undiluted (min)
H5		
H5N1 hp	A/chicken/Indonesia/R60/05	10.6
H5N1 hp	A/chicken/Indonesia/R134/03	10.7
H5N1 hp	A/cat/Germany/R606/06	11.3
H5N1 hp	A/duck/Vietnam/AG40-02/05	13.0
H5N1 hp	A/duck/Vietnam/TG24-01/05	13.1
H5N1 hp	A/chicken/Vietnam/P78/05	13.5
H5N1 hp	A/chicken/GXLA/1204/04	14.3
H5N1 hp	A/turkey/Turkey/R11/06	15.4
H5N1 hp	A/Cygnus olor/Germany/R854/06	20.6
H5N1 hp	A/Cygnus cygnus/Germany/R65/06	24.2
H5N1 hp	A/chicken/Scotland/59	*50.5*
H2N3	A/mallard/Germany/Wv672/04	*59.4*
H6N5	A/turkey/Grub/R41/98	*49.7*

- 検出できないH5、H7分離株が認められた
- リアルタイムPCR法と比較し、感度が低い

６０分増幅で検出

非特異反応
非特異反応

https://doi.org/10.1177/1040638710022001 10

Subtype	Name	Undiluted (min)	
H7			
H7Nx	A/teal/Föhr/Wv180/05	11.2	
H7Nx	A/teal/Föhr/Wv177/05	17.8	
H7Nx	A/mallard/Föhr/Wv190/05	18.8	
H7Nx	A/alexandria tyrode/T145	29.5	
H7N1 hp	A/FPV/Rostock/45/34	Neg.	検出せず
H7N1 hp	A/chicken/Brescia/19/02	*36.2*	６０分増幅で検出
H7N1	A/turkey/Italy/472/99	10.5	
H7N1	A/mallard/NVP/41/04	15.8	
H7N3	A/duck/Italy/636/03	11.3	
H7N3	A/turkey/Italy/2043/03[*]	14.8	
H7N3	A/turkey/Italy/2043/03[*]	15.5	
H7N3	A/swan/Potsdam/64/81	*56.7*	６０分増幅で検出
H7N3	A/duck/Alberta/48/76	Neg.	検出せず

プライマー・プローブ設計部位

- A型：M遺伝子、NP遺伝子、NS遺伝子
- 亜型：HA遺伝子、NA遺伝子

H亜型が重要

Target	Oligonucleotide[a]	Sequence 5′→3′[b]
M	M1-f-245	CCAGTGAGCGAGGACTGCAG
	M1-r-332	GGATCCCCATTCCCATTGAG
H5	h5c-f-729	AGATCCAAAGTAAACGGGCAAA
	h5c-r-808	TCGAAGTTGATTGCATCATTCG
	ch5a-f-244	GGAAACCCAATGTGTGACGAA
	ch5a-r-318	ATTGGCTGGATTGGCCTTCT
H7	c2h7-f-520	CTGAGCAGCGGCTACAAAGA
	c2h7-r-609	GAAGACAAGGCCCATTGCAA

https://doi.org/10.1128%2FJCM.01090-08

混合塩基を含むプライマー・プローブ

混合塩基

記号	R	M	W	S	Y	K	H	B	D	V	N
塩基の種類	A,g	A,C	A,T	C,g	C,T	g,T	A,T,C	g,T,C	g,A,T	A,C,g	A,C,g,T

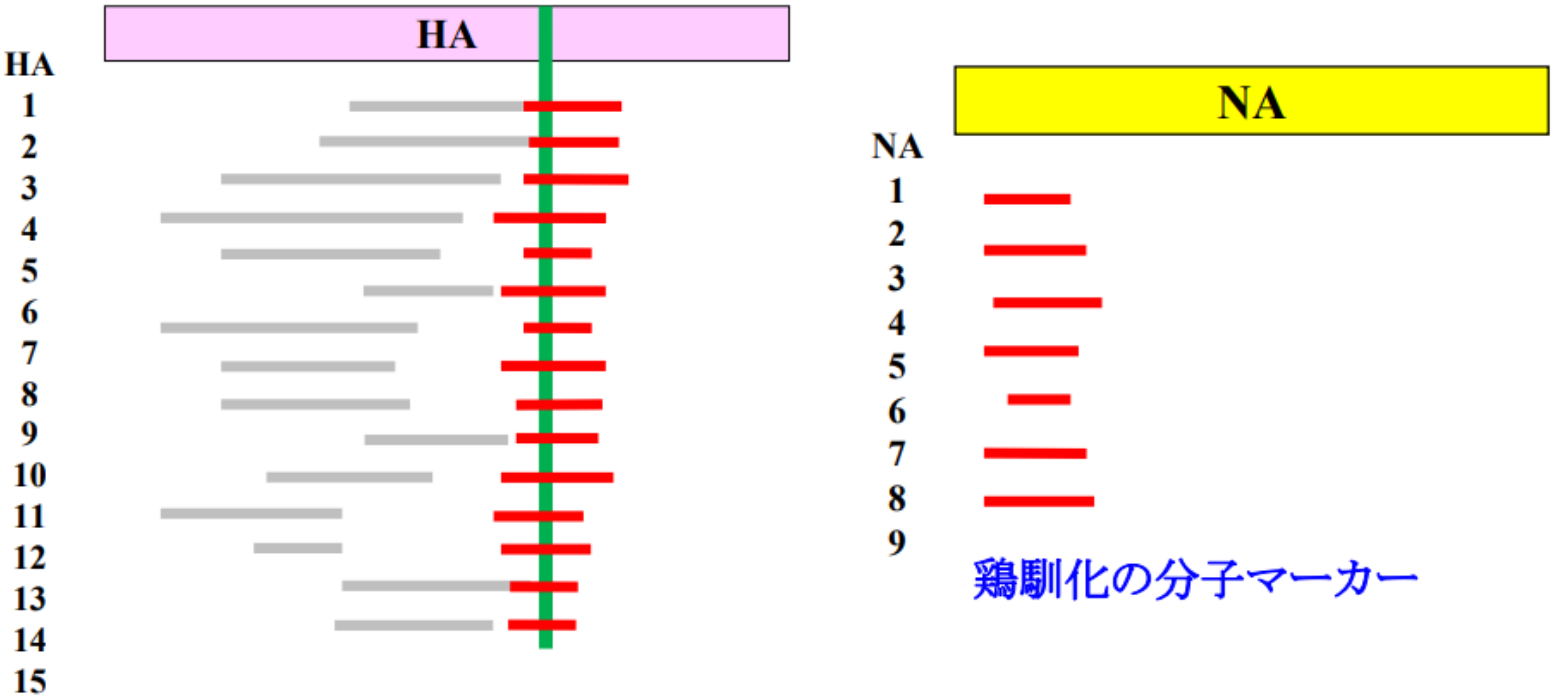
Gene	Primer identification no.	Primer or probe	Product size (bp)	Sequence[a]	No. of mixed bases	No. of genes used for design
H5	491	H5-918F	249	CCARTRGGKGCKATAAAYTC	5	1,439
	820	H5-1166R		GTCTGCAGCRTAYCCACTYC	3	1,439
	547	H5-Probe		FAM-ACCATKCCYTGCCAYCCYCCYTCT-BHQ	5	1,439

https://doi.org/10.1128%2FJCM.01264-10

Gene	No. of AIVs	No. of genes detected by use of[d]:																	
		Primer[a]						Probe[b]						Primer/probe set[c]					
		Without mixed bases			With mixed bases			Without mixed bases			With mixed bases			Without mixed bases			With mixed bases[e]		
		Early	Late	Neg.	Early	Late	Neg.	Early	Late	Neg.	Early	Late	Neg.	Early	Late	Neg.	Early	Late	Neg.
H5	20	9	7	4	20	0	0	19	1	0	20	0	0	5	9	6	19	1	0
H7	19	11	3	5	16[f]	2[f]	1[f]	14	2	3	19	0	0	10	2	7	16[f] (19)	3[f] (0)	0[f] (0)

https://doi.org/10.1128%2FJCM.01264-10

HA開裂部位　病原性の推定



https://doi.org/10.1128%2FJCM.02386-07

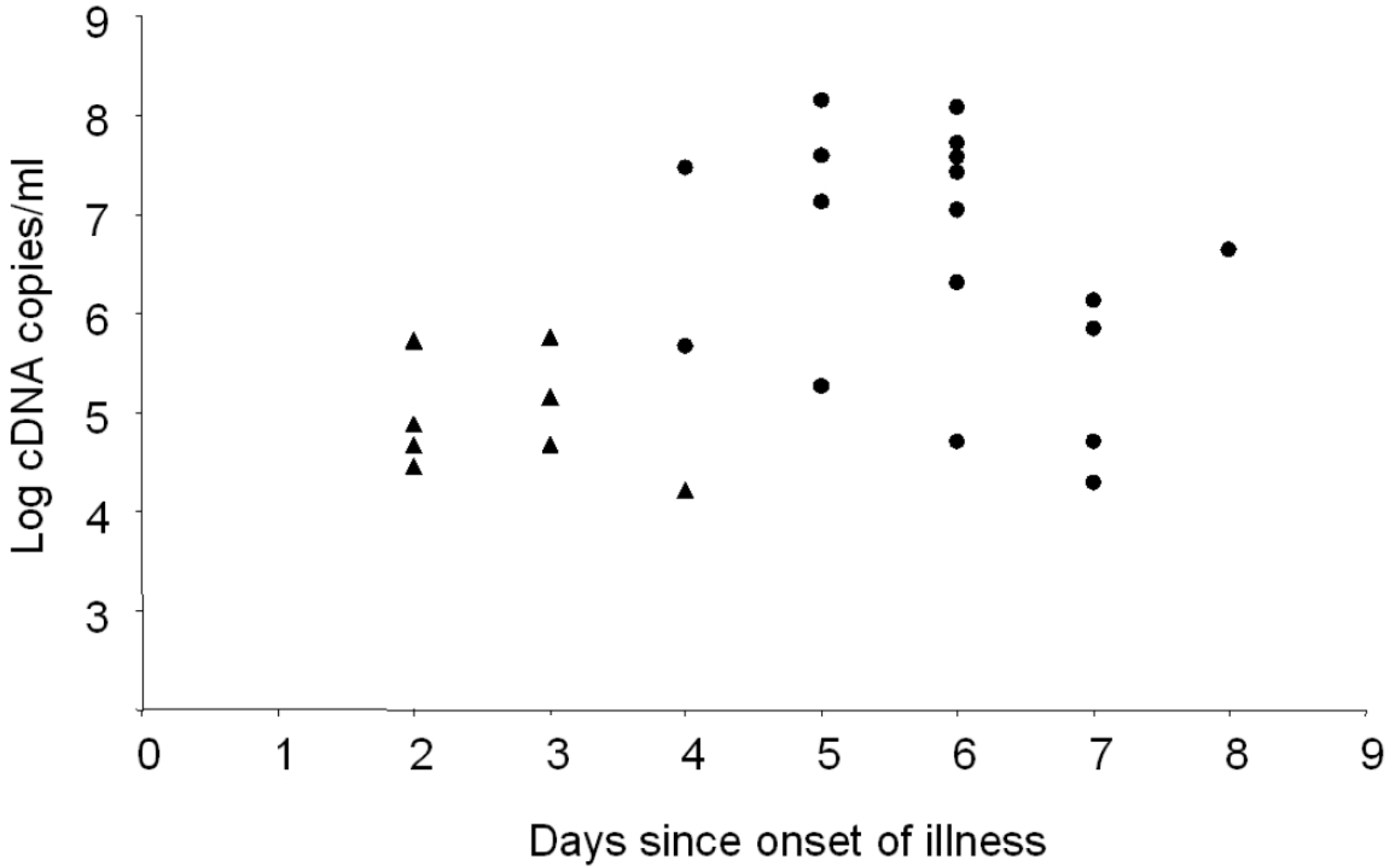
HA開裂部位　病原性の推定

ウイルス株	亜　型	HA開裂部位のアミノ酸配列	鶏病原性の分子推定
A/tk/MN/3689-1551/1981	H5N2	PQRETR/GLF	低
A/ck/Ibaraki/1/2005	H5N2	PQRETR/GLF	低
A/ck/Yamaguchi/7/2004	H5N1	PQRERRKKR/GLF	高
A/ck/Suphanburi/1/2004	H5N1	PQRERRRKKR/GLF	高
A/ck/Miyazaki/H358/2007	H5N1	PQGERRRKKR/GLF	高
A/ck/Pennsyl/21525/1983	H5N2	PQKKKR/GLF	高
A/ck/Puebla/8623-607/1994	H5N2	PQRKRKTR/GLF	高
A/ck/Italy/330/1997	H5N2	PQRRRKKR/GLF	高
A/tern/South Africa/1961	H5N3	PQRETRRQKR/GLF	高
A/ck/NY/119055-7/2001	H7N2	PEKPKPR/GLF	低
A/dk/Shimane/18/2006	H7N7	PEIPKGR/GLF	低
A/tk/Italy/4580/1999	H7N1	PEIPKGSRVRR/GLF	高
A/tk/England/1963	H7N3	PETPKRRRR/GLF	高
A/ck/Pakistan/447/1995	H7N3	PEIPKRKRKR/GLF	高
A/ck/Chile/184240-2/2002	H7N3	PEKPKTCSPLSRCRKTR/GLF	高
A/ck/Netherland/2586/2003	H7N7	PEIPKRRRR/GLF	高

https://doi.org/10.1128%2FJCM.02386-07

Supplementary Figure 1. Pharyngeal virus load in relation to onset of illness during H5N1 influenza and human influenza. Viral RNA loads were measured in throat swabs obtained at admission from 18 H5N1 patients (circle), and eight patients with H3N2 or H1N1 influenza (triangle).

https://doi.org/10.1038%2Fnm1477



https://doi.org/10.1038%2Fnm1477

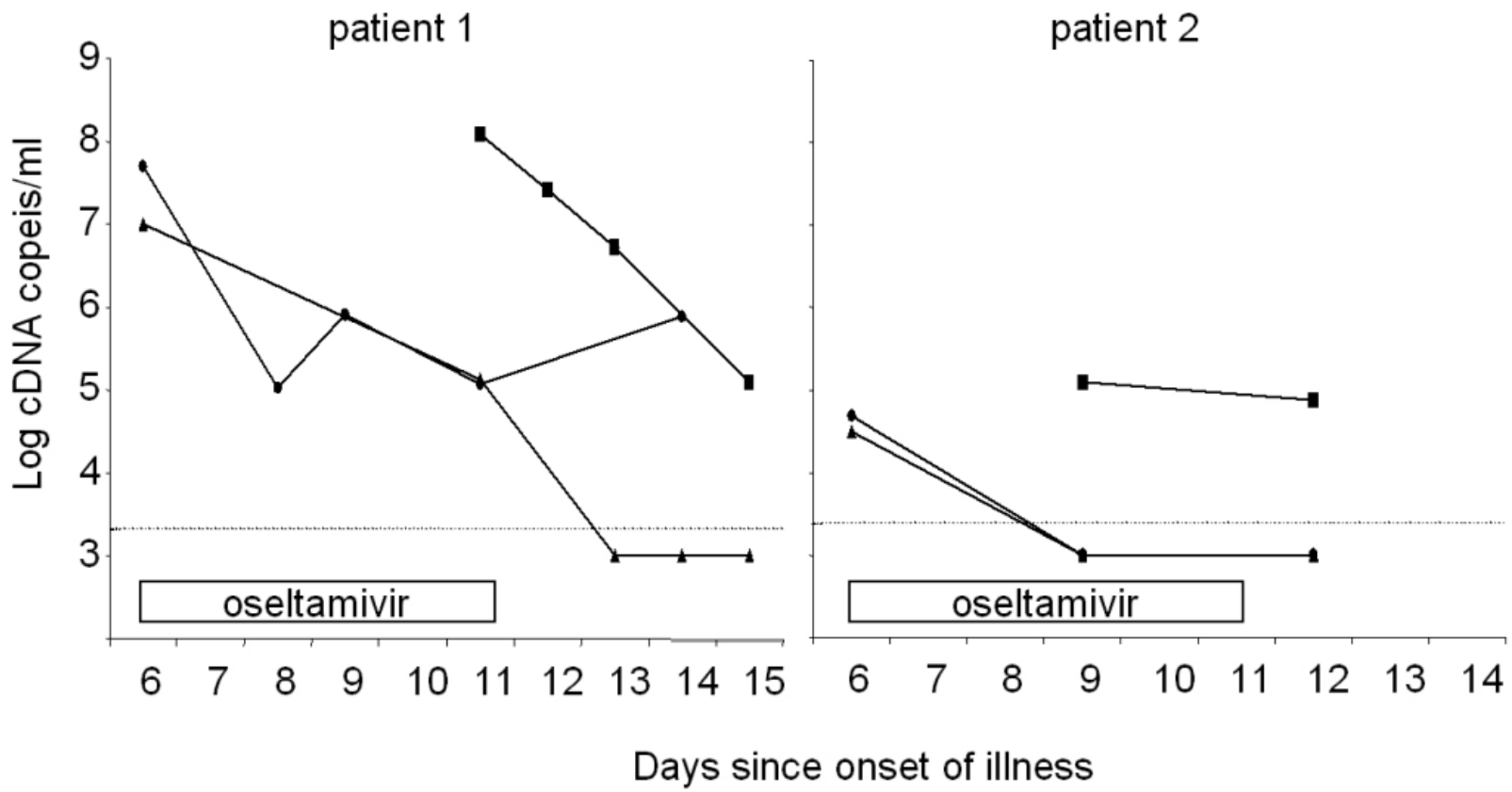
Table 2 Detection of influenza virus in respiratory and non-respiratory sites

					H5N1		
		H5N1	H3/H1	*P*	Fatal	Not fatal	*P*
Nasopharynx							
Virus isolation rate (positive/tested; %)		12/16[a] (75)	NA		8/12 (67)	4/4 (100)	
Detectable RNA (positive/tested; %)	Nose	13/17 (76)	6/8 (75)		10/12 (83)	3/5 (60)	
	Throat	18/18 (100)	8/8 (100)		13/13 (100)	5/5 (100)	
Viral load (median; range)	Nose	5.5 (und.–8.1)	4.5 (und.–7.7)	0.59	5.8 (und.–8.1)	4.5 (und.–6.4)	0.20
	Throat	7.0 (4.3–8.2)	4.8 (4.2–5.8)	0.003	7.5 (4.7–8.2)	5.9 (4.3–7.0)	0.058
	P	0.001	0.87				
Rectum[b]							
Virus isolation rate (positive/tested; %)		1/7 (14)	NA		1/7 (14)	NA	
Detectable RNA (positive/tested; %)		5/7 (71)	NA		5/7 (71)	NA	
Viral load (median; range)		4.8 (3.6–5.8)	NA		4.8 (3.6–5.8)	NA	
Blood[c]							
Virus isolation rate (positive/tested; %)		1/6 (17)	NA		1/6 (17)	NA	
Detectable RNA (positive/tested; %)		9/16 (56)	0/6 (0)	0.046	9/11 (82)	0/5 (0)	0.005
Viral load (median; range)		4.5 (3.2—5.7)	Und.		4.5 (3.2–5.7)	Und.	

Rates of virus isolation, detection of viral RNA and viral loads in nasopharyngeal, rectal and blood specimens of patients with influenza H5N1 and H3N2 or H1N1. Viral loads are given as $\log_{10}$ cDNA copies per ml of viral transport medium. Und., below detection limit; NA, not assessed.
[a]Virus isolation was not performed in two cases due to insufficient specimens. [b]Rectal swabs were obtained after 6–11 d (median 8) of illness. [c]Blood specimens were obtained after 5–9 d (median 7) of illness.

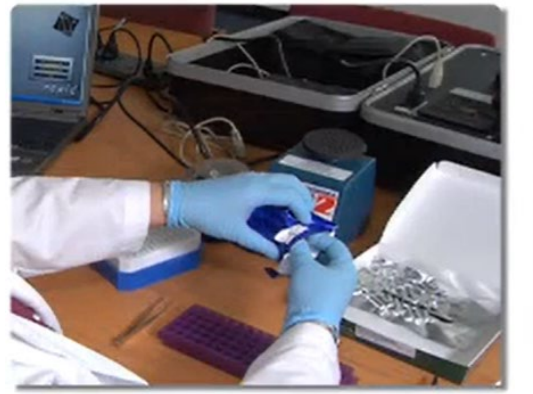
https://doi.org/10.1038%2Fnm1477

Supplementary Figure 2. Nasal, pharyngeal and tracheal virus load during the course of illness in two H5N1 patients. Viral RNA loads were measured in nasal swabs (triangle), throat swabs (circle) and tracheal aspirates (square) from two H5N1 patients and revealed higher viral RNA loads and more prolonged detection of viral RNA in tracheal specimens compared to nasal and pharyngeal specimens. Both patients received a five-day course of oseltamivir upon admission. The dashed horizontal line signifies the lower limit of detection of viral RNA.



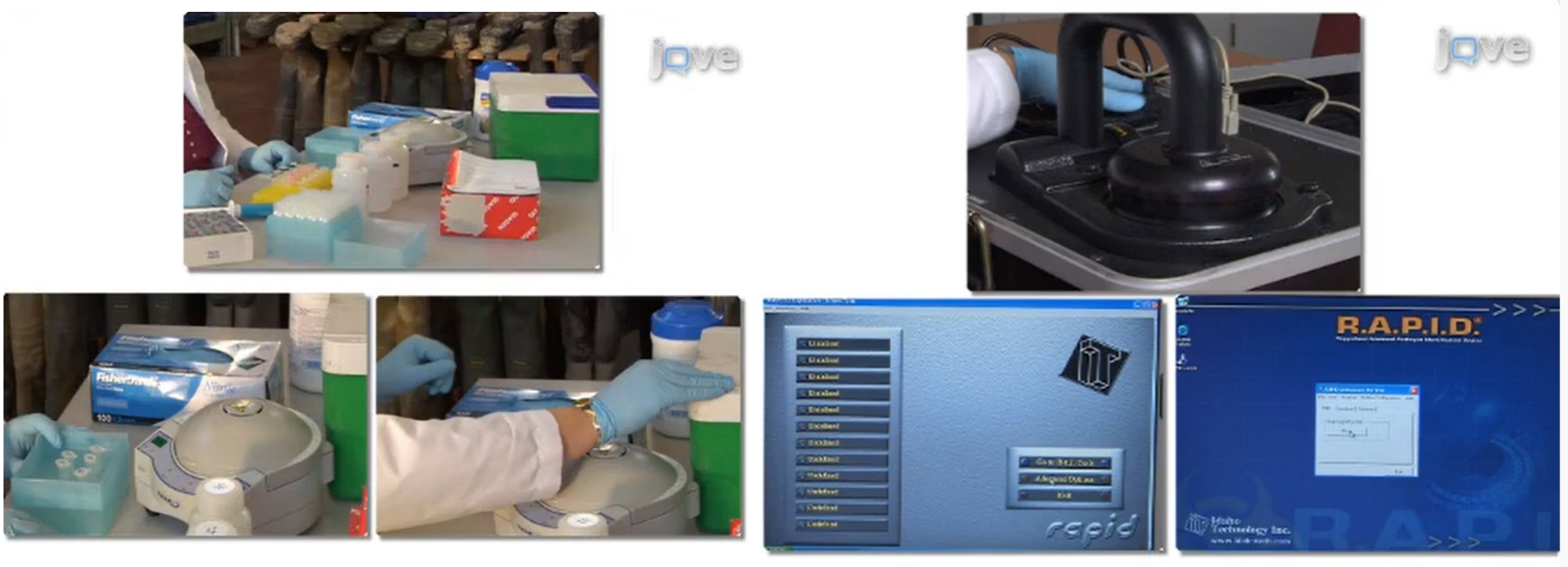
野外現場での鳥インフルエンザ検査

- ポータブルリアルタイムPCR装置と凍結乾燥試薬で
  野外現場にてスクリーニング検査可能



https://dx.doi.org/10.3791/2829

野外現場での鳥インフルエンザ検査



https://dx.doi.org/10.3791/2829

当院の遺伝子検査室で実施するなら

- LAMP法
- リアルタイムPCR法

当院の遺伝子検査室で実施するなら
LAMP法

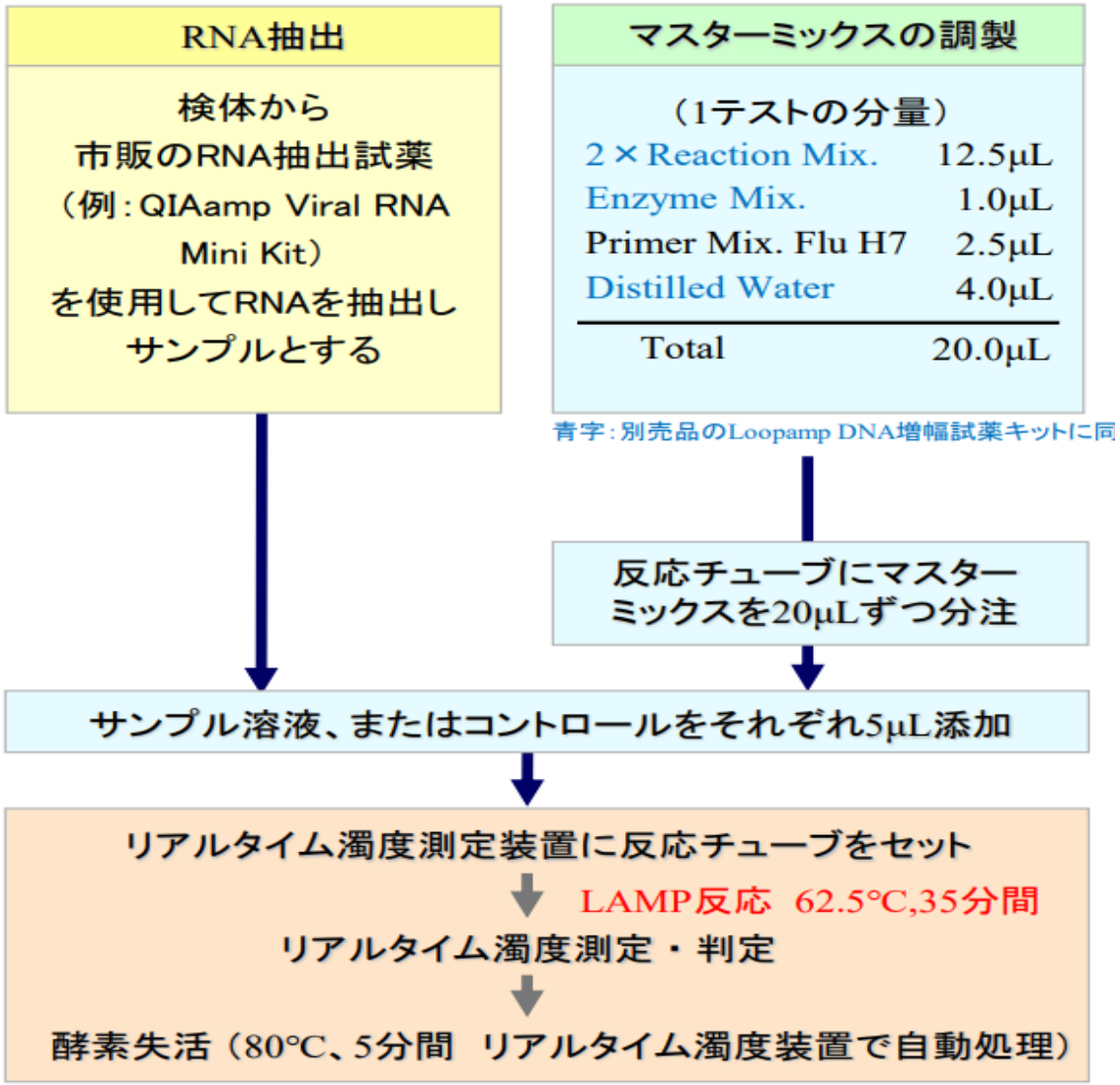
Loopamp RNA増幅試薬キット(RT-LAMP)

[Loopamp H5亜型インフルエンザウイルス検出試薬キット]

[Loopamp プライマーセット Avian Flu H7]

※これは個人の見解であり、所属する組織の公式見解ではありません。

当院の遺伝子検査室で実施するならLAMP法



https://loopamp.eiken.co.jp/uploads/insert_h7.pdf

※これは個人の見解であり、所属する組織の公式見解ではありません。

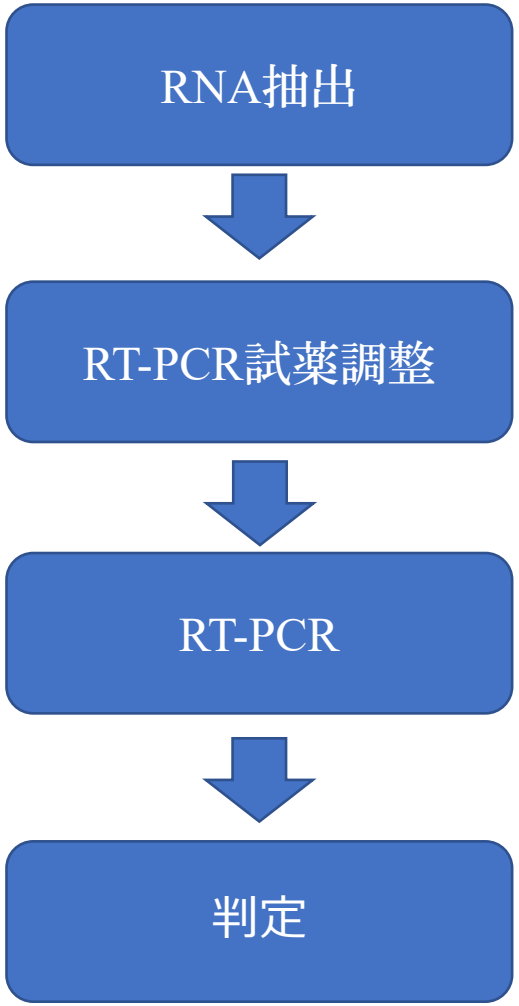
当院の遺伝子検査室で実施するなら
リアルタイムPCR

・遺伝子配列をもとにプライマーおよびプローブ
　を設計

・PCR試薬(QuantiTect Probe RT-PCR Kit
　（キアゲン）

※これは個人の見解であり、所属する組織の公式見解ではありません。

当院の遺伝子検査室で実施するなら
リアルタイムPCR



Type A M 遺伝子検出用プライマーおよびプローブ：

MP-39-67For	5'-CCMAGGTCGAAACGTAYGTTCTCTCTATC
MP-183-153Rev	5'-TGACAGRATYGGTCTTGTCTTTAGCCAYTCCA
MP-96-75ProbeAs	5'-(FAM)ATYTCGGCTTTGAGGGGGCCTG(MGB)

PCR 産物の長さ：146bp

H1pdm09 HA 遺伝子検出用プライマーおよびプローブ：

NIID-swH1 TMPrimer-F1	5'-AGAAAAGAATGTAACAGTAACACACTCTGT
NIID-swH1 TMPrimer-R1	5'-TGTTTCCACAATGTARGACCAT
NIID-swH1 Probe2	5'-(FAM)CAGCCAGCAATRTTRCATTTACC(MGB)

PCR 産物の長さ：187bp

influenza20190116.pdf (niid.go.jp)
国立感染症研究所

※これは個人の見解であり、所属する組織の公式見解ではありません。

当院の遺伝子検査室で実施するならリアルタイムPCR

Light Cycler 480

	Analysis Mode	Cycle	Temperature (℃)	Time	Ramp Rate (℃/sec)	Acquisition Mode
RT	None	1	50	30min.	Max*	None
Denature	None		95	15min.	Max*	None
PCR	Quantification	45	94	15sec.	1.5	None
			56	75sec.	1	Single
Cooling	None		40	30sec.	Max*	None

Light Cycler480 反応条件

https://www.niid.go.jp/niid/images/lab-manual/avian_influenza_2003.pdf

※これは個人の見解であり、所属する組織の公式見解ではありません。

鳥インフルエンザAウイルス(H5N1)は、輸血によってフェレット間で感染する可能性がある

- ウイルス血症を起こすため、輸血により感染する。
- 哺乳類であるフェレット間で輸血によりH5N1ウイルスが伝播することが確認された。
- フェレット間での伝播が直接ヒトーヒト間の伝播を証明するものではない。

Highly pathogenic avian influenza A virus (H5N1) can be transmitted in ferrets by transfusion
Xue Wang et al. 2014 Apr 8.doi: 10.1186/1471-2334-14-192

鳥インフルエンザのパンデミックが血液の安全性と供給に及ぼす潜在的な影響

- パンデミックの発生により血液製剤の需要が急増し、供給不足や安全性の問題が生じる可能性がある。
- 無症候性感染症では輸血による感染の可能性は低い。

Potential Impact of Pandemic Influenza on Blood Safety and Availability
Shimian et al. Zou 2006 Jun 17. doi: 10.1016/j.tmrv.2006.03.001

回復期血漿を用いた鳥インフルエンザA(H7N9)感染症の治療に成功

- 同じウイルスに感染し回復期を迎えた患者から採取した血漿を投与して患者の状態が改善した。

Successful treatment of avian-origin influenza A (H7N9) infection using convalescent plasmaXiao Xin Wu et al. doi:https://doi.org/10.1016/j.ijid.2015.10.009

重症鳥インフルエンザA(H7N9)患者に対するECMOの使用症例

- H7N9鳥インフルエンザ感染症患者がARDSを発症し、通常の酸素療法や人工呼吸器だけでは対処できない場合に、ECMOが有効であった。
- ECMOの使用は、ヘパリンを同時に適用する必要があるため、患者に血小板減少症と凝固障害が必然的に発生します。

Extracorporeal membrane oxygenation for avian influenza A (H7N9) patient with acute respiratory distress syndrome: a case report and short literature review
Qi Nie et al. 2017 Feb 14. doi: 10.1186/s12890-017-0381-y