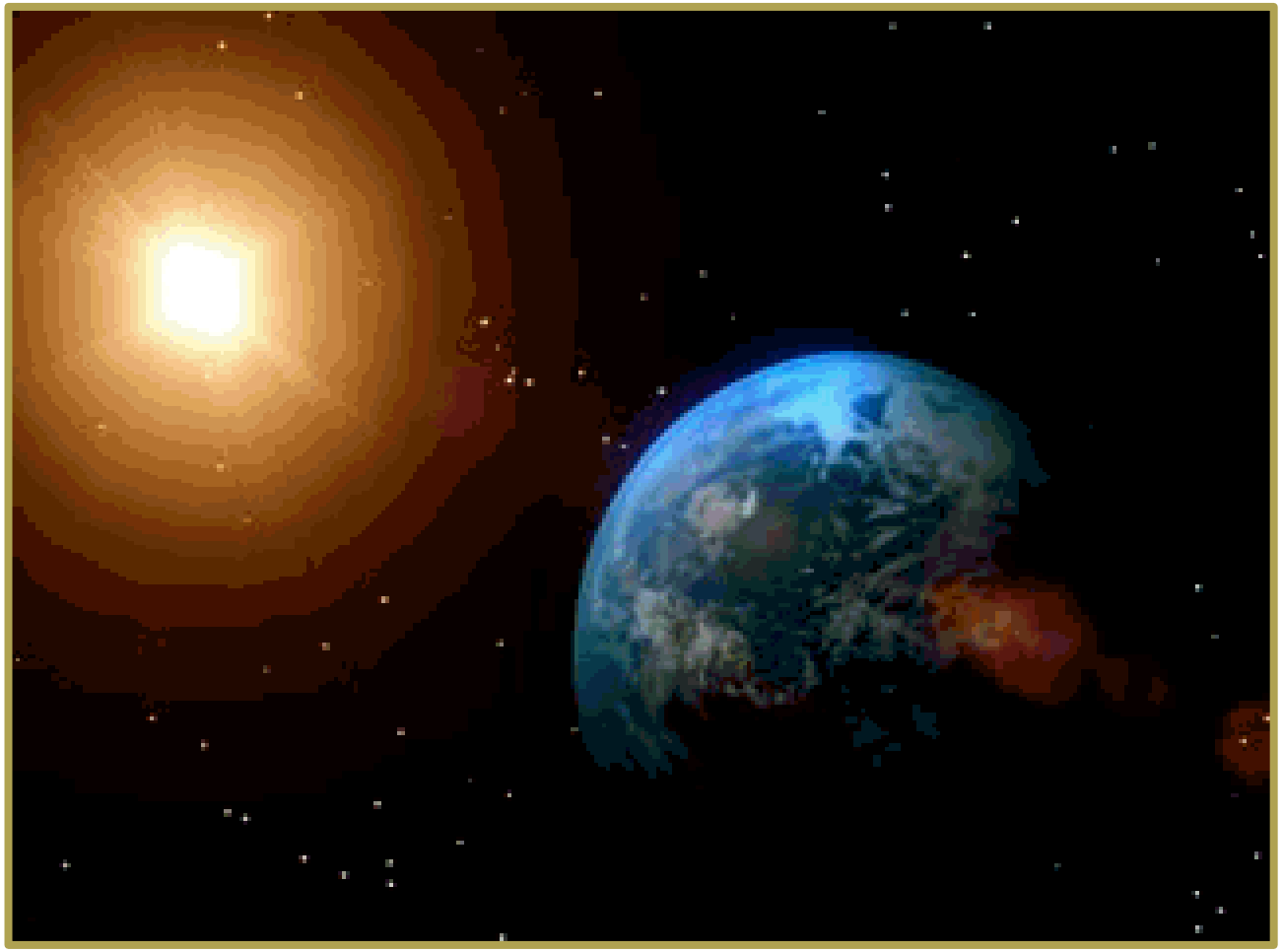
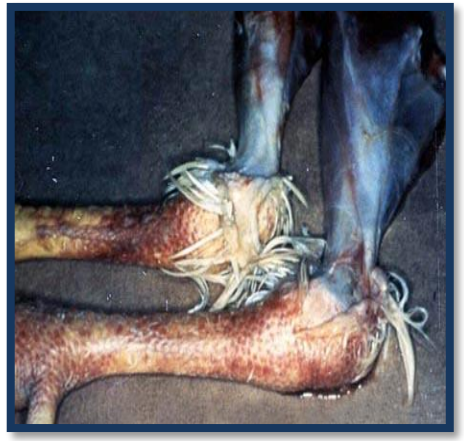
Influenza (and Highly Pathogenic Avian Influenza such as H5N1) What Emergency Managers Need to Know





Seasonal Influenza is a perennial problem for humans and other animals

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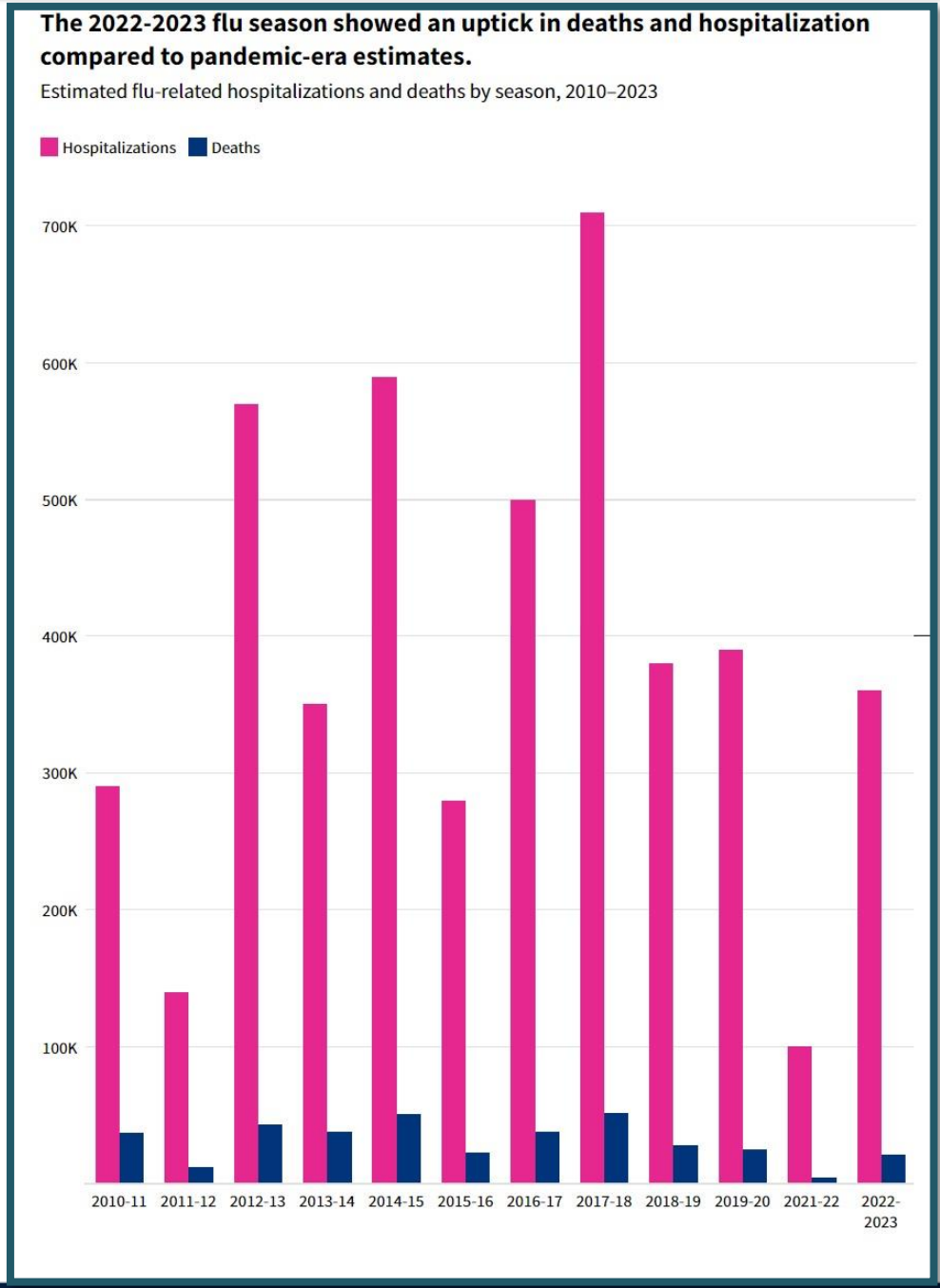
So far, all cases of Highly pathogenic AI have been from viruses with H5 or H7 surface antigens

While precise dates vary year to year, annual epidemics of seasonal influenza in the USA usually fall between October and May.

Seasonal Influenza is no Joke

Human-adapted Influenza A Virus (IAV) and Influenza B (IBV) Are highly contagious viruses that cause respiratory. They are characterized by their ability to undergo genetic reassortment and mutation, leading to the emergence of new strains.

- Over the last 100 years, influenza has been one of the most consistent public-health infectious threats.
- It routinely causes significant deaths, serious illness, and socioeconomic burdens annually worldwide.
  - Seasonal illness rate varies per year, ranging from 5% to 20%.
  - WHO estimates > 1 billion cases worldwide of seasonal influenza per year.
  - CDC data show the incidence of seasonal influenza in the USA has ranged from 9 million to 45 million cases annually, with 12,000 to 61,000 deaths each year

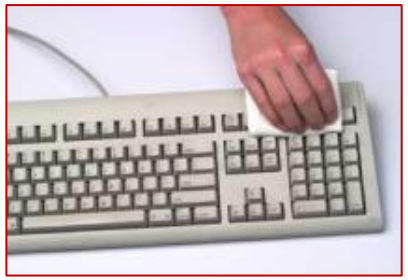


https://usafacts.org/articles/how-many-people-die-flu/

Incubation and Infectivity of Influenza Viruses

- Incubation (Adults): 1 to 3 days; average 2 days
- Contagious time frame
  - Adults: 1 day before symptoms to 5 day after manifesting symptoms
  - Children: 3 or 4 days before symptoms to 7^{+} days after manifesting symptoms
  - Immunocompromised persons: 2 days before symptoms, to 7 or more days after manifesting symptoms
- Influenza A viruses can persist and remain infectious on stainless steel surfaces for 7 days (consider all surfaces, phones, computers, fax machines, tables, etc.)






- Refusal of HCWs who have direct patient contact to be immunized against influenza implies **failure in their duty of care to patients**
  - Some people never manifest symptoms but can still spread virus to others. (More than half of HCW that test positive **have no symptoms**)
  - Influenza may be introduced by staff, visitors or new or transferred residents, leading to outbreaks of influenza

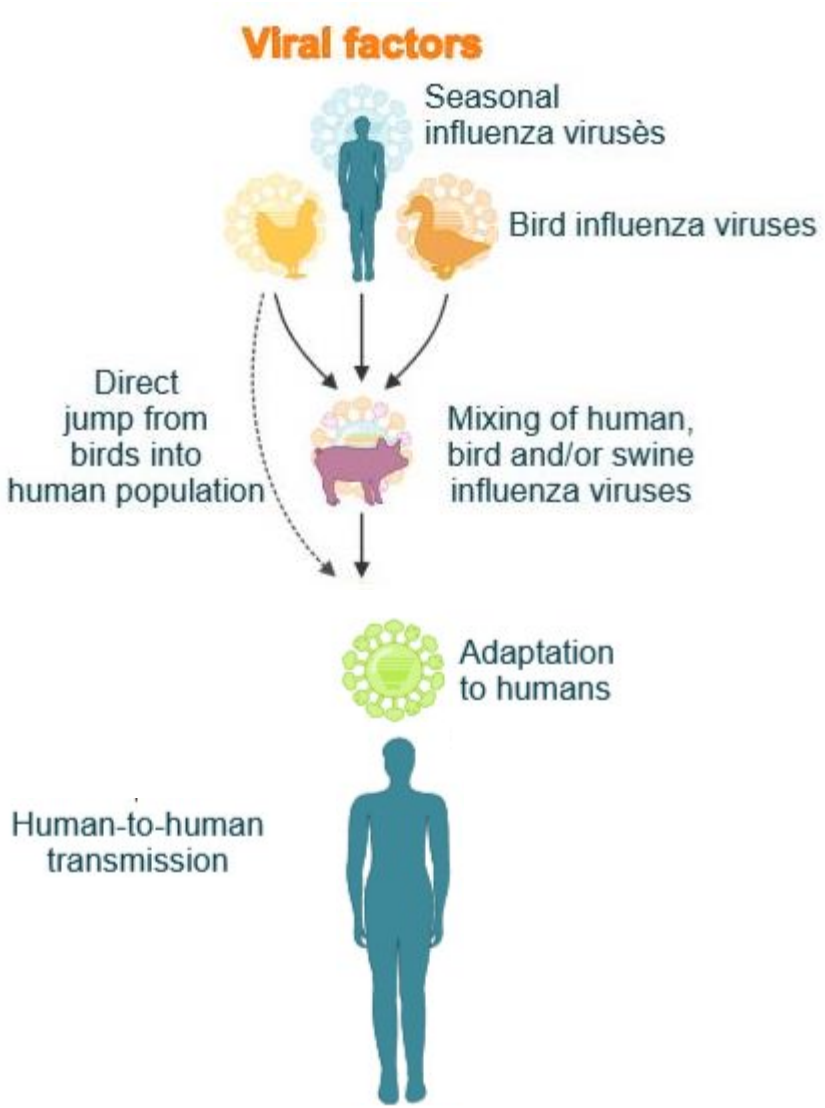
Why don't we do it in our Sleeves?
https://www.youtube.com/watch?v=CtnEwvUWDo0

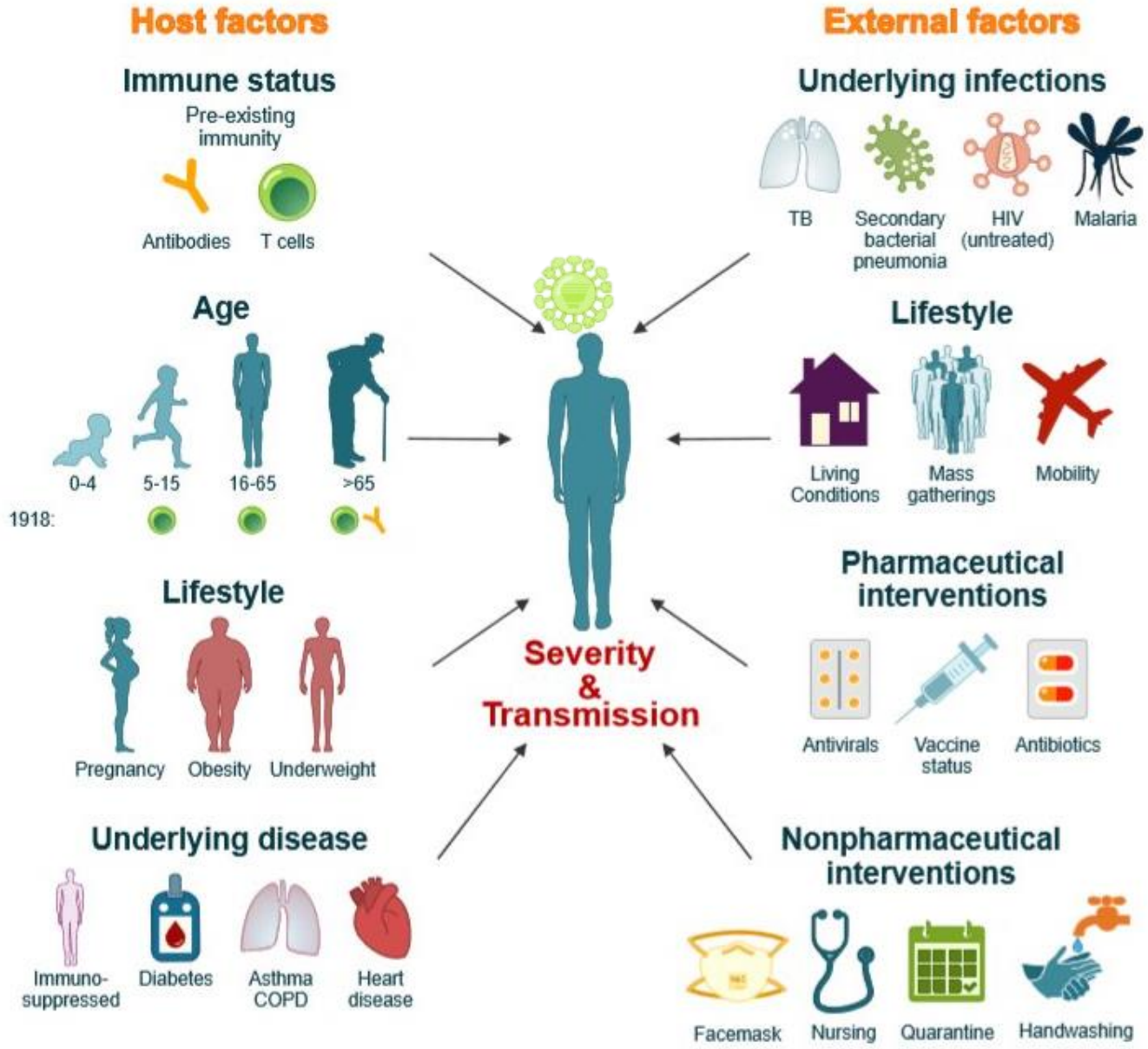
Typical Clinical Manifestations of Adult Influenza

Abrupt onset of:

- Fever* or feeling feverish/chills
- Sore throat
- Cough
- Runny or stuffy nose
- Muscle or body aches
- Headaches
- Fatigue (tiredness)
- Vomiting & diarrhea (rare in adults, not uncommon in children)

Many Factors Affect severity





Influenza Viruses

(1) Genus: *Influenzavirus A*

- Species: *Influenza A virus*

18 hemagglutinin subtypes
11 neuraminidase subtypes
(Hundreds of strains)

(2) Genus: *Influenzavirus B*

- Species: *Influenza B virus*

Two lineages *Victoria and Yamagata*
(*Multiple strains*)

(3) Genus: *Influenzavirus C*

- Species: *Influenza C virus*
  - *103 Subtypes known*

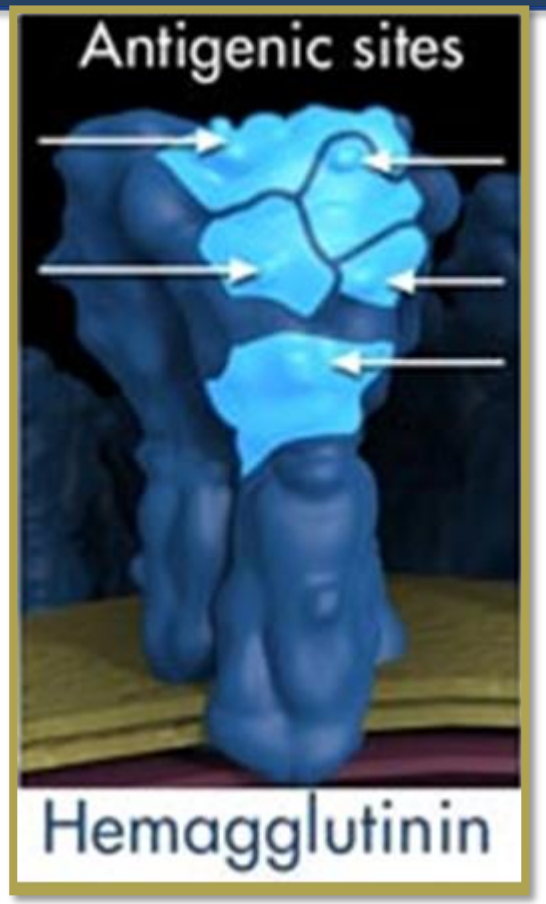
(4) Genus: *Influenzavirus D*

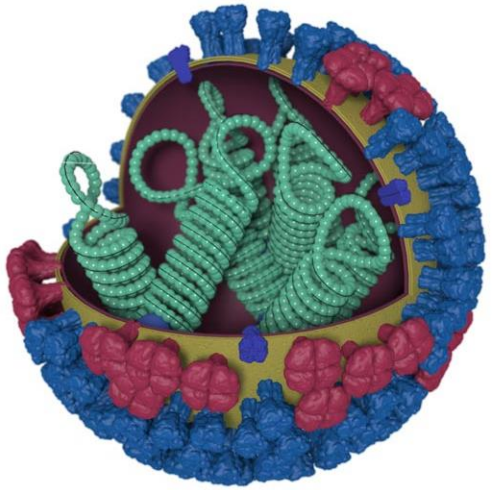
- Species: *Influenza D virus*
  - *Cattle pathogens*

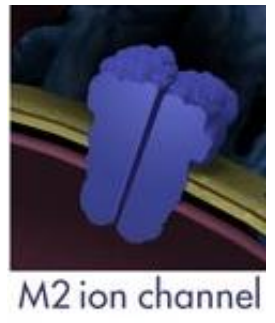
Flu A: severity asymptomatic to life-threatening; Affects all age groups
Infects humans, pigs, birds, other animals

Flu B: disease severity asymptomatic to life-threatening; Affects all age groups, some other animals e.g., Ferrets

Flu C: most cases subclinical



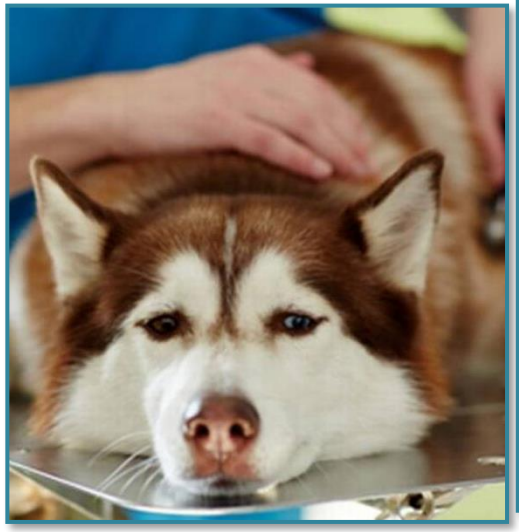




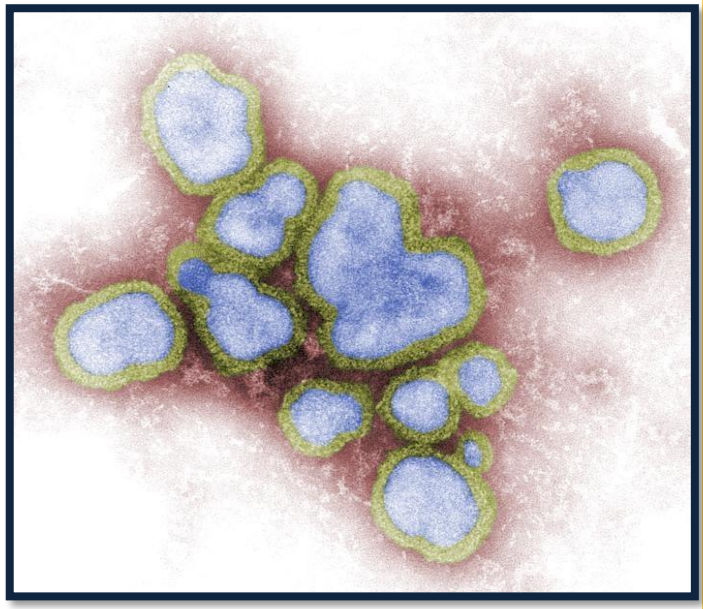
naming system: place strain first found, lab identification number, year of discovery, & in parentheses, type of HA & NA

Influenza A is a Highly Zoonotic Disease





InfluenzAvirus Surface Antigens

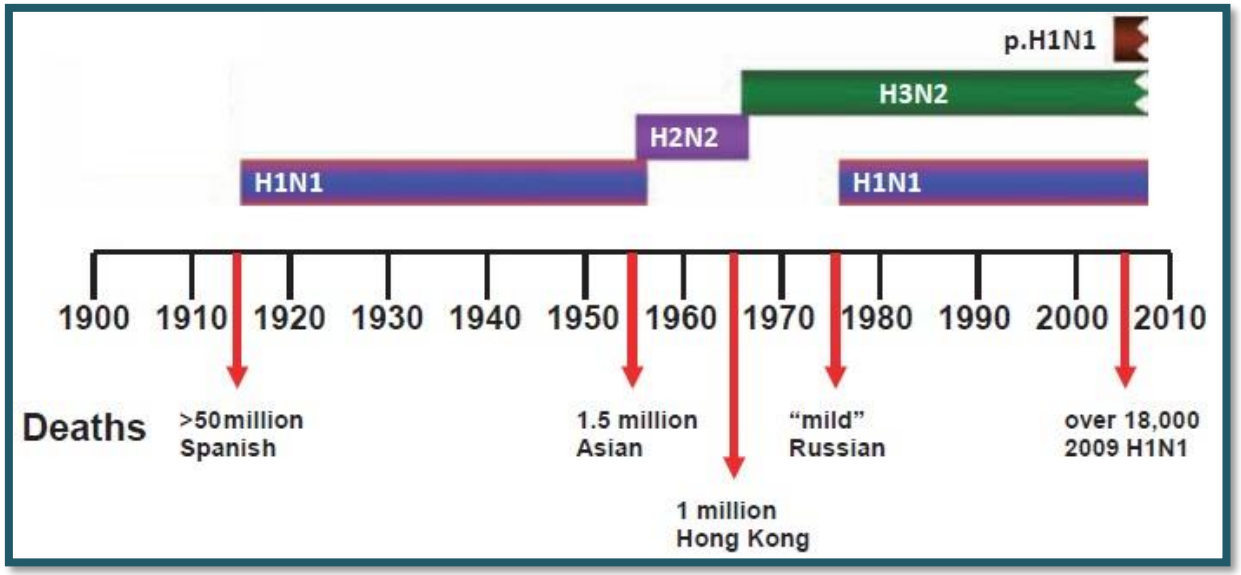
HA	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Avian	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Bats																	X	X
Humans	X	X	X		+/-	+/-	+/-		+/-	+/-								
Swine	X	+/-	X	X	X				X									
Canines			X															
Equines			X				X											
Seals			X	X	+/-	X	+/-			X								
Cetaceans	+												+					
Felines	+/-		X		+/-		X		+/-									
Mustelinae																		

"Bird Flu" is H_5N_1

But of course, H_7N_2 is also "Bird Flu," etc.

NA	1	2	3	4	5	6	7	8	9	10	11
Avian	X	X	X	X	X	X	X	X	X		
Bats										X	X
Humans	X	X				+/-	+/-	+/-	+/-		
Swine	X	X									
Canines		X						X			
Equines							X				

Seven Influenza Pandemics Since Germ Theory



1889: Started in Russia, not characterized

1918: Started in Kansas, USA, detected in Spain "Spanish flu,"

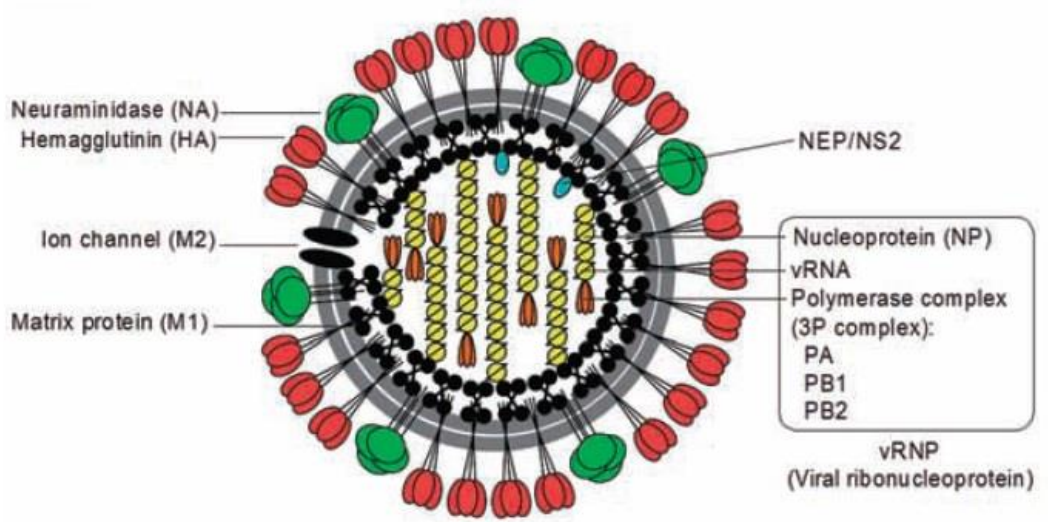
1957: Started in China, detected in Hong Kong

1968: Started in China, detected in Hong Kong

1976: Started in Fort Dix, NJ, USA

1977: Started in China, detected in Russia

2009: Started in the USA, detected in California and Mexico



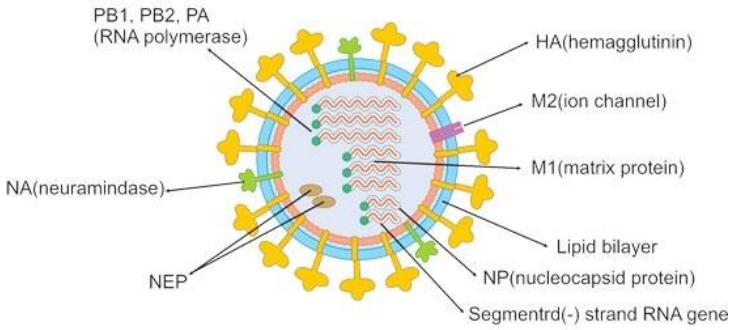
What does a Flu Virus need to have to cause a Pandemic?

1. An HA to which the human population is immunologically naive
2. Cause disease in humans
3. Cause sustained chains of human-to-human transmission.

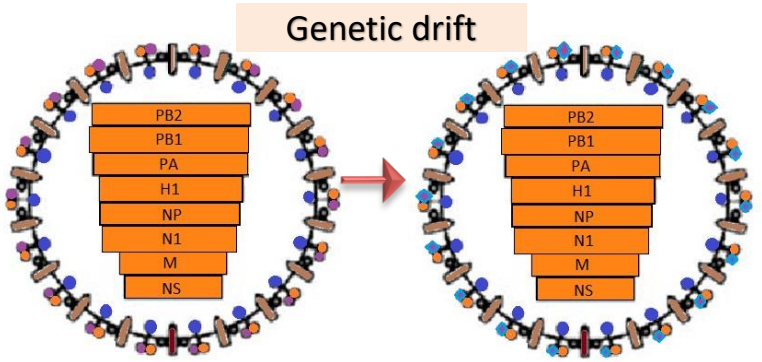
Each pandemic saw a shift in the ability of HA to bind to α2,6 sialic acid and additional shifts in other key influenza genes

Influenza Viruses

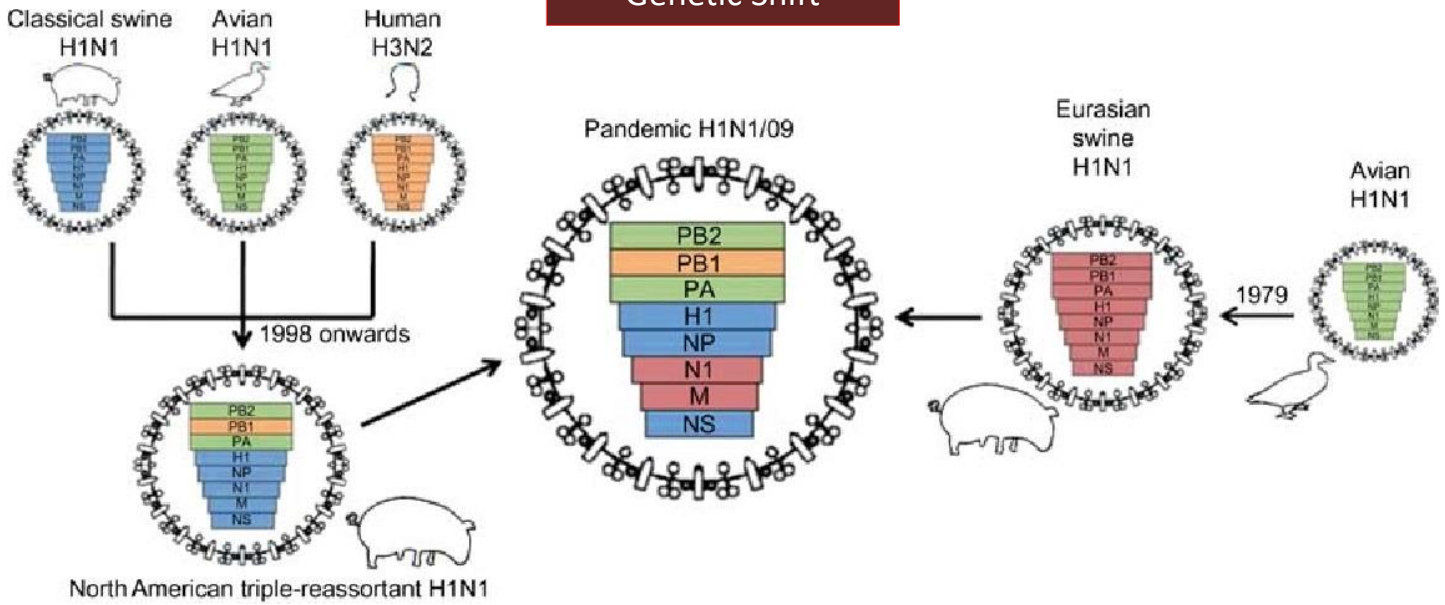
- Enveloped ssRNA virus; glycoprotein spikes of hemagglutinin (HA) and neuraminidase (NA) protrude from the envelope.
  - **HA** comprised of HA1 & HA2. HA1 binds the cell's receptor, and HA2 fuses the virus with the cell membrane
  - **NA** helps the virus exit the host cell, cleaves terminal sialic acid from cell surface glycoproteins & gangliosides



Genome: *Segmented*: **8 pieces of ssRNA coated** with nucleoprotein. RNA-dependent RNA polymerase (3 subunits PB1, PB2, PA) forms a ribonucleoprotein complex. Nuclear export protein is also within the virion



Genetic Shift



The RNA is in 8 segments that must be packaged in each new virion. Thus, if two flu viruses enter one host cell, the RNA segments from the two viruses can recombine. These recombinations led to the 2009 H1N1 pandemic.

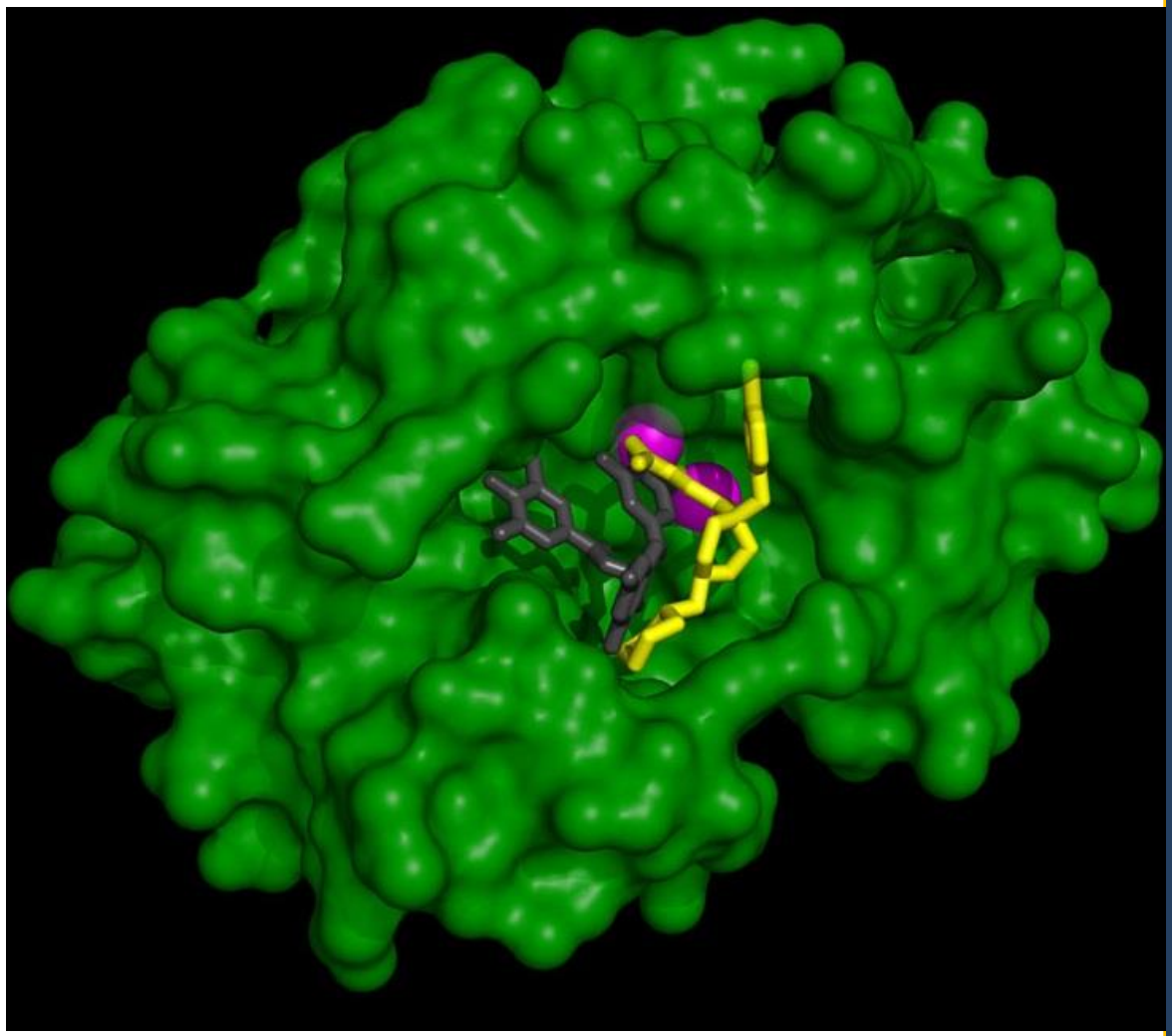
Maritz et al. Pandemic influenza A (H1N1) 2009: the experience of the first six months. Clin Chem Lab Med. 2010;48(1):11-21. doi: 10.1515/CCLM.2010.023. https://www.degruyter.com/document/doi/10.1515/CCLM.2010.023/html

https://www.cusabio.com/infectious-diseases/influenza-virus.html

Mutations in the Polymerase can provide Gain-Of-Function

- In human cells, the translation of mRNA strands into proteins requires a special " cap " structure at the beginning of each mRNA.
- The RNA polymerase complex is composed of 3 subunits: PA, PB1, and PB2. The PA unit of Influenza is the "Cap Snatcher"!
  - The endonuclease of the RNA polymerase subunit **PA "snatches"** a cap from the host cell mRNA.
  - Then, the viral RNA polymerase subunit **PB2 binds** the human cap to the viral mRNA.
  - Finally, the viral RNA polymerase subunit **PB1** is the viral RNA-dependent RNA polymerase, which uses the stolen cap as the starting point for synthesizing viral mRNA.
    - Thanks to the stolen cap, viral mRNA enters the host protein-production machinery to make viral proteins, which assemble into new viruses that will spread the infection.

Influenza viruses are unusual among negative-sense RNA viruses in that they transcribe and replicate their genomes in the nucleus



The active site of the endonuclease of the Viral RNA polymerase is shaped like a cave with two metal ions at the bottom.

The Evolving Menace of H5N1

1996 H5N1 Clade 0 in birds

1997, H5N1 **clade zero** caused 18 human cases with 6 deaths in Hong Kong.

It seemed to disappear, and a new threat SARS (the original) appeared

2003-2004 H5N1 Clade 1

2004: As the threat of SARS abated, human cases of H5N1 returned, with focal transmission from poultry, particularly in Indonesia, Vietnam, and Thailand

2006-2024 H5N1 Clade 2

2006: The H5N1 viruses in Egypt clustered in clade 2.2.1, with several new Sublineages emerging from 2007 to 2008. This clade was responsible for the initial outbreaks in poultry and subsequent human infections

Country	2003		2004		2005		2006		2007		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	0	0	0	0	0	0	8	5	0	0	8	5
Cambodia	0	0	0	0	4	4	2	2	1	1	7	7
China	1	1	0	0	8	5	13	8	3	2	25	16
Djibouti	0	0	0	0	0	0	1	0	0	0	1	0
Egypt	0	0	0	0	0	0	18	10	19	5	37	15
Indonesia	0	0	0	0	19	12	55	45	26	22	101	80
Iraq	0	0	0	0	0	0	3	2	0	0	3	2
Lao PDR	0	0	0	0	0	0	0	0	2	2	2	2
Nigeria	0	0	0	0	0	0	0	0	1	1	1	1
Thailand	0	0	17	12	5	2	3	3	0	0	25	17
Turkey	0	0	0	0	0	0	12	4	0	0	12	4
Viet Nam	3	3	29	20	61	19	0	2	0	0	95	42
Total	4	4	46	32	97	42	115	79	54	33	317	191

H5N1 has now diversified into multiple clades - 0, 1, 2.1, 2.2, 2.3.4, 3, 4, 5, 6, 7, 8, and 9

Data from 29 June 2007

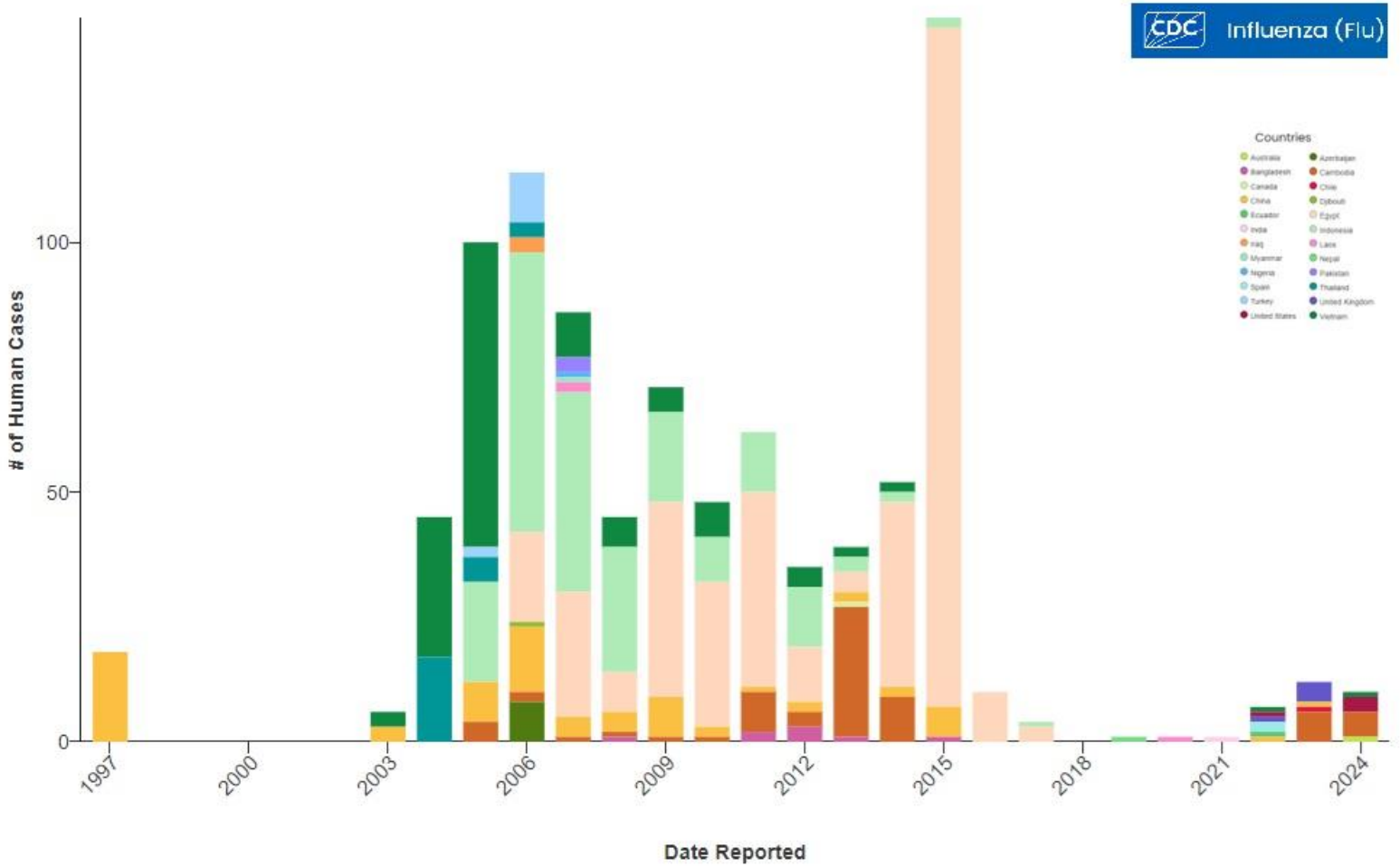
The total number of cases includes the number of deaths.
WHO reports only laboratory-confirmed cases.

Global Human Cases with Influenza A(H5N1) 1997 to 30 May 2024

Cases are not dramatically high, so why are we worried?

Unprecedented outbreak of HPAI H5N1 infection among dairy cows since Feb 2024 involving herds in Texas, Kansas, and New Mexico, raising the potential for cow-to-human transmission.

Three confirmed human cases in the USA, all farm workers, have been reported so far, with the third person presenting with respiratory symptoms.



https://www.cdc.gov/flu/avianflu/chart-epi-curve-ah5n1.html

The H5N1 Currently Causing a global **panzootic** is NOT the same one from 20 years ago!


Franklin's gull


Peruvian Pelican


Peruvian booby

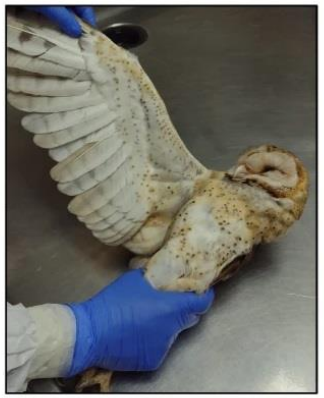

Belcher's gull


Humboldt penguin


Peregrin falcon


Harris's hawk


Guanay cormorant


Western barn owl


American kestrel

2010-11, H5N1 clade **2.3.4.4** emerged in China

2014, H5N1 the HA from clade 2.3.4.4 began pairing with different NA subtypes (NA1,NA2, NA5, NA6, and NA8). Migrating birds have spread these H5Nx viruses that carry clade 2.3.4.4 to nearly every continent on earth

2020, H5N1 2.3.4.4b subclade of 2.3.4.4 appeared and spread to all continents except Australia. It has devasted wild and domestic birds and infected at least 26 mammalian species,

Why is it in Dairy Cows?

The use of chicken litter as animal feed in the United States

POULTRY WORLD

Chicken litter as animal feed becoming trade issue

12-01-2018 | Uk | News

https://www.poultryworld.net/uk/chicken-litter-as-animal-feed-becoming-trade-issue/

In the USA, it is accepted practice to use chicken litter - a rendered down mix of chicken manure, dead chickens, feathers, and spilled feed) as animal feed. [its use for dairy cattle is only banned in California]

It is marketed as a cheap feed product, particularly for cattle.

We've been doing this for decades….but now, the chickens have H5N1…..

12 June 2024 WHO: *"Since our last update five weeks ago, the number of affected dairy herds has almost tripled to 92 in 12 [USA] states, the number of human cases has increased from 1 to 3, and the number of people being monitored has more than doubled to 500."*

But should we be worried?

Gain-of-Function Risk

- The HA gene is in segment 4 of the influenza A virus genome.
  - **Avian flu virus HA proteins** bind to α2,3-linked sialic acids
  - **Human flu virus HA** viruses need to bind α2,6-linked sialic.
- For Gain-of-function
  - *For H5 to adapt to human hosts, it must mute HA protein to enable binding to α2,6-linked sialic acids*

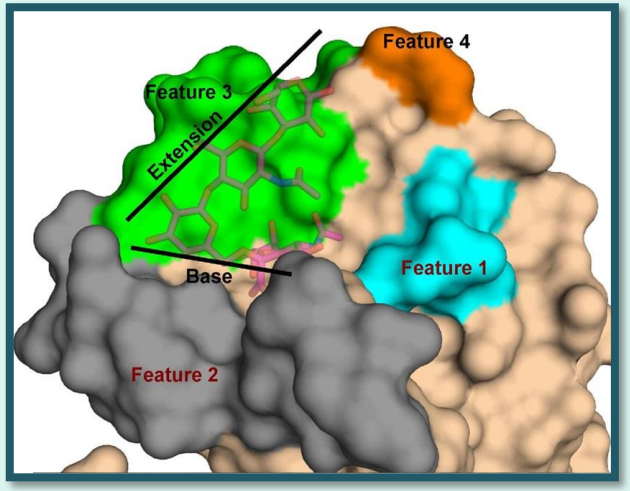
Only 2 nucleotide changes are needed for gain-of-function of H5 2.3.4.4b to become capable of human-to-human transmission. To achieve the Q226L and G228S mutations so that H5 can bind to α2,6-linked sialic:

Gln-226 → Leu (Q226L):

Original Codon: CAG (Gln)
Mutated Codon: CTG (Leu)
Nucleotide Change: CAG → C**T**G

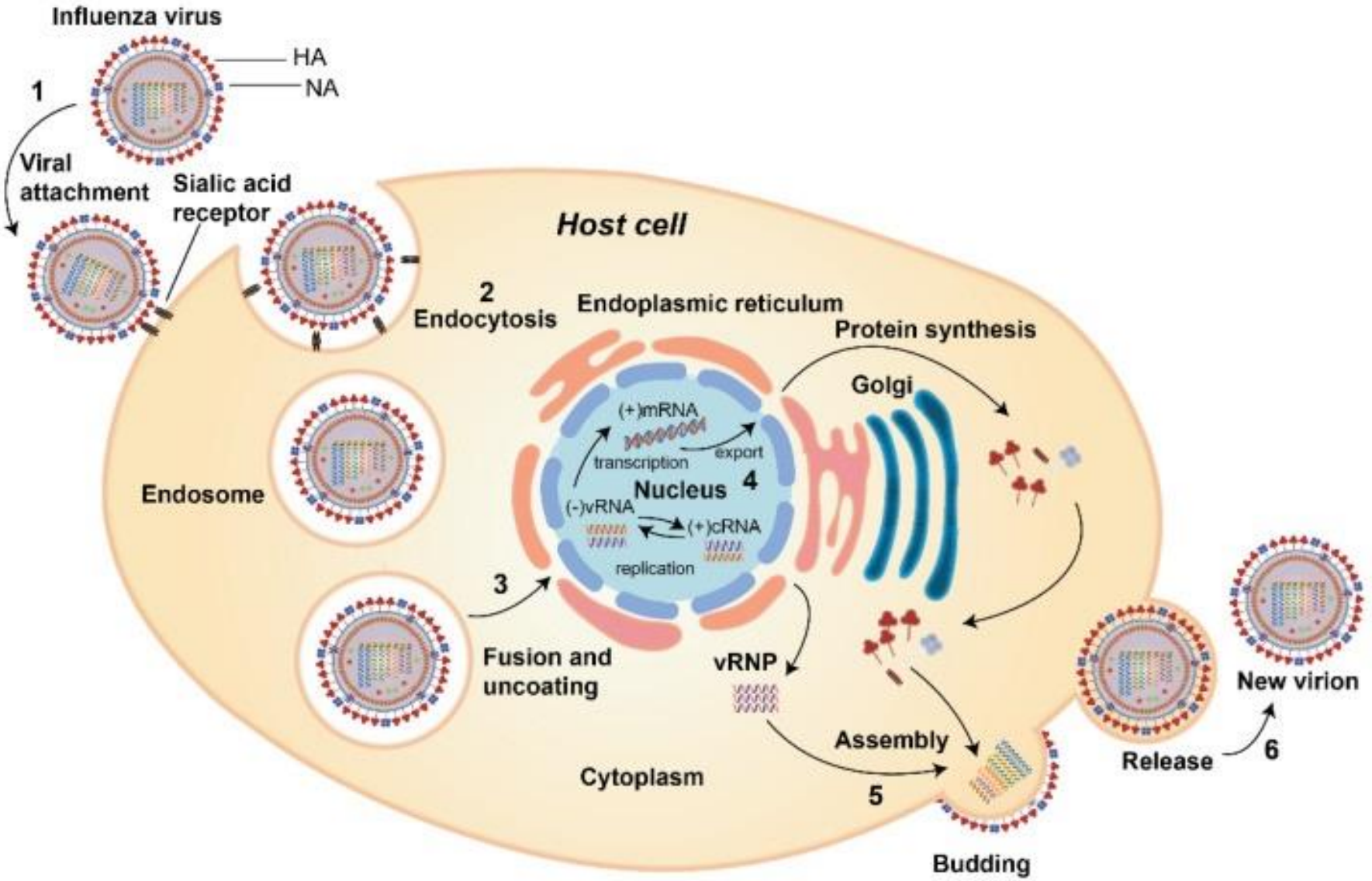
Gly-228 → Ser (G228S):

Original Codon: GGT (Gly)
Mutated Codon: AGT (Ser)
Nucleotide Change: GGT → **A**GT



Change in features 1 and 2 RBD of H5

Gain-of-Function also involves Other Segments that Enhance Reproduction and Protect from Immune System



- Segment 1 (PB2)
- Segment 2 (PB1 & PB1F2)
- Segment 3 (PA)
- Segment 4 (HA)
- Segment 5 (NP)
- Segment 6 (NA)
- Segment 7 (M1 & M2)
- Segment 8 (NS1 &NS2/NEP)

Nuwarda RF, Alharbi AA, Kayser V. An Overview of Influenza Viruses and Vaccines. Vaccines (Basel). 2021 Sep 17;9(9):1032. doi: 10.3390/vaccines9091032.

Key Gain-of-Function Changes in H5N1 Clade 2.3.4.4b that have increased pathogenicity in humans

1. **Hemagglutinin (HA)** Protein: (1) Mutation T392A (L131Q) increased antigenic variability in the H5N1 virus. And (2) Loss of Glycosylation Site at Positions 158-160, which increases the affinity for human receptors.
2. **Neuraminidase (NA)** Protein: NA: 22-AA Deletion in the NA Stalk Region increased virulence. Also, L269M and S339P: specific phenotypic effects are not well characterized.
3. **Polymerase Basic 2 (PB2)** Protein: Mutation E627K: Enhances the virus's polymerase activity at the lower temperatures of the mammalian respiratory tract.
4. **Polymerase Basic 1 (PB1)** Protein: Mutation D253N: Enhanced polymerase activity and replication in mammalian cells.
5. **Nucleoprotein (NP**) Protein: Mutation Y52N: Helps evade the human BTN3A3 protein, which is part of the host's immune response.
6. **Matrix (M) Protein**: Mutations 30D, 43M, and 215A in M1: These mutations have been associated with increased virulence in mammals.
7. **Nonstructural (NS)** Protein: Mutations 42S, 103F, and 106M in NS1: increased virulence and the ability to evade the host immune response.

Antiviral Treatment Options

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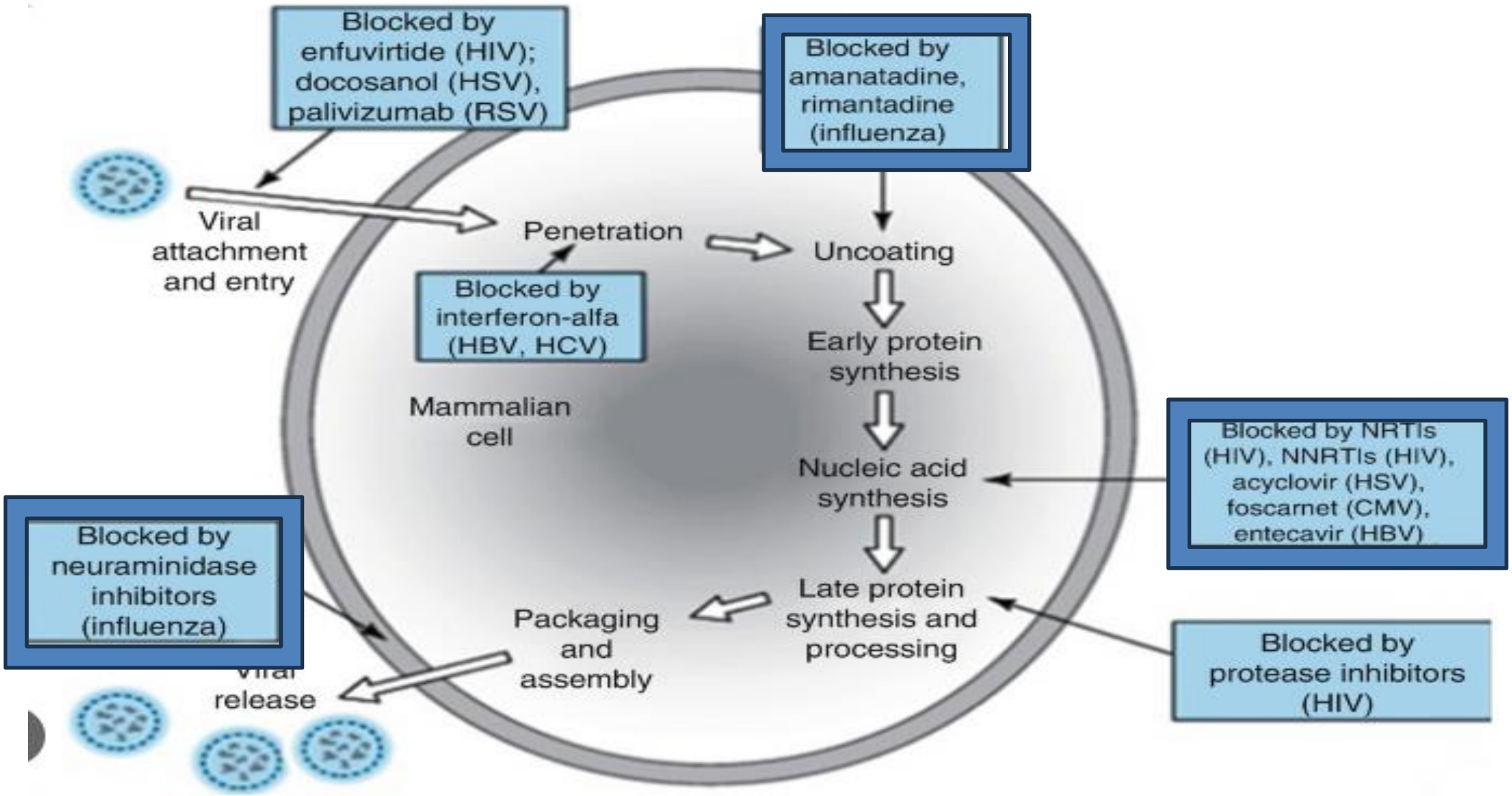
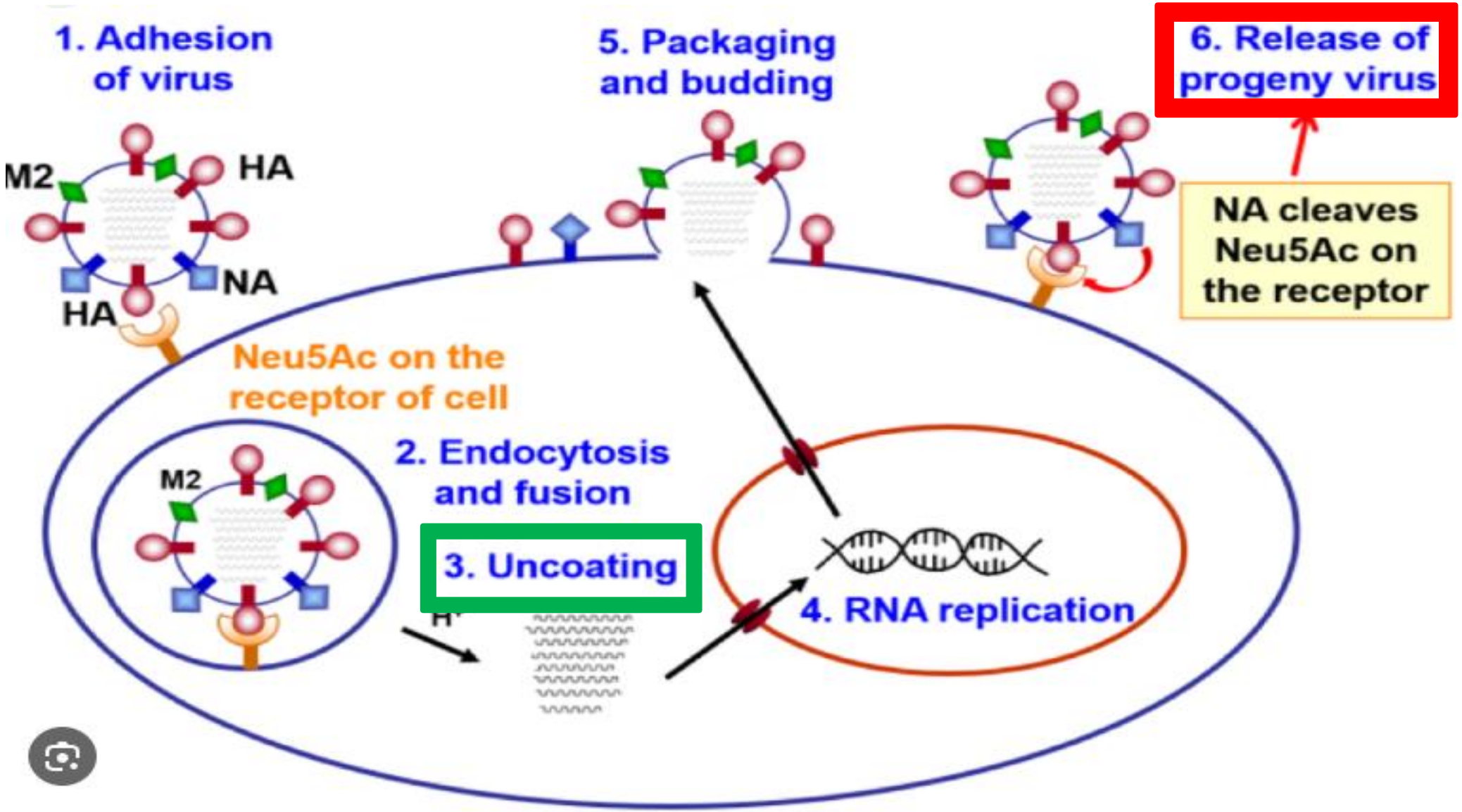
Influenza treatment options

- Antivirals
- Immunomodulators
- Monoclonal antibodies
- Vaccines

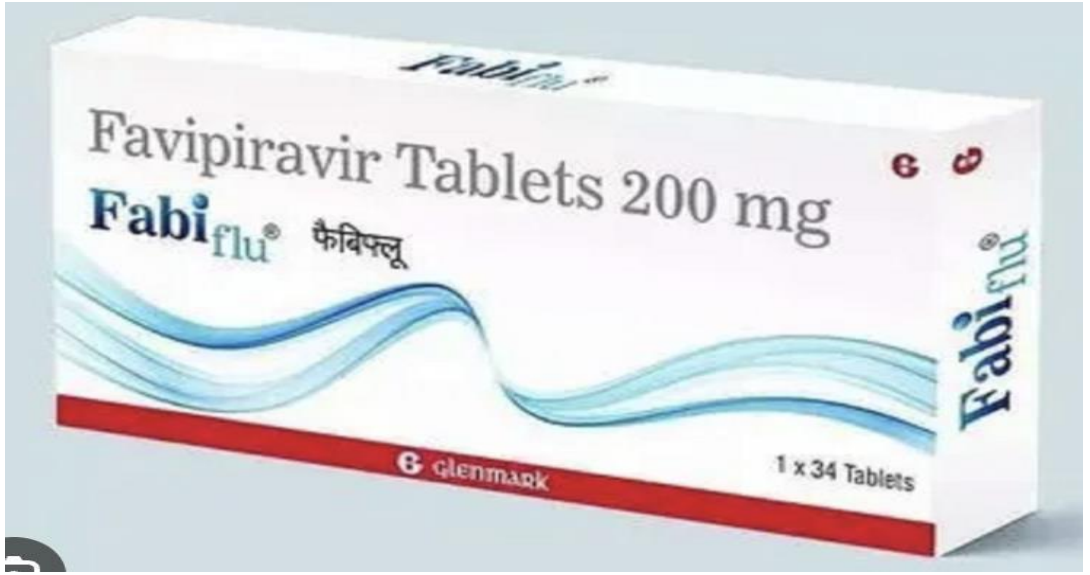
Influenza antivirals

Mechanisms	Medications
Viral Penetrator Inhibitors (Blocks M2 ion channel)	amantadine, rimantadine
Viral Release Inhibitor (Blocks NA)	oseltamivir zanamivir peramivir
Viral replication inhibitor	
Inhibits RNA-dependent RNA polymerase (binds and blocks PB1)	favipiravir (approved COVID)
Blocks Cap-snatcher (PA)	baloxavir


Blocked by enfuvirtide (HIV); docosanol (HSV), palivizumab (RSV)
Blocked by amanatadine, rimantadine (influenza)
Viral attachment and entry
Penetration
Uncoating
Blocked by interferon-alfa (HBV, HCV)
Early protein synthesis
Mammalian cell
Nucleic acid synthesis
Blocked by NRTIs (HIV), NNRTIs (HIV), acyclovir (HSV), foscarnet (CMV), entecavir (HBV)
Blocked by neuraminidase inhibitors (influenza)
Late protein synthesis and processing
Packaging and assembly
Blocked by protease inhibitors (HIV)
release


1. Adhesion of virus
M2
HA
NA
HA
Neu5Ac on the receptor of cell
2. Endocytosis and fusion
M2
3. Uncoating
H+
4. RNA replication
5. Packaging and budding
6. Release of progeny virus
NA cleaves Neu5Ac on the receptor

Favipiravir



The Journal of Infectious Diseases

MAJOR ARTICLE

Favipiravir Treatment of Uncomplicated Influenza in Adults: Results of Two Phase 3, Randomized, Double-Blind, Placebo-Controlled Trials

Frederick G. Hayden,[1] Robert P. Lenk,[2,a] Lucille Stonis,[2,b] Catherine Oldham-Creamer,[2] Lih Lisa Kang,[2,c] and Carol Epstein[2,d]

[1]Division of Infectious Diseases and International Health, Department of Medicine, University of Virginia School of Medicine, Charlottesville, Virginia, USA; and [2]Medivector, Inc, Boston, Massachusetts, USA

Favipiravir in influenza

- This favipiravir dosing regimen demonstrated significant antiviral efficacy but inconsistent illness alleviation in uncomplicated influenza.
- Studies of higher doses and antiviral combinations for treating serious influenza and other RNA viral infections are warranted.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(baloxavir marboxil) tablets
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Single dose
Contains 40 mg total dose
(2 x 20 mg tablets)
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Baloxavir marboxil (Xofluza)

- Antiviral drug
- Given as a pill in a single dose by mouth
- Approved on October 24, 2018, by the U.S. FDA

Baloxavir: Mechanism of action

- Inhibits the endonuclease activity of the polymerase acidic (PA) protein found in influenza virus to ultimately inhibit virus replication

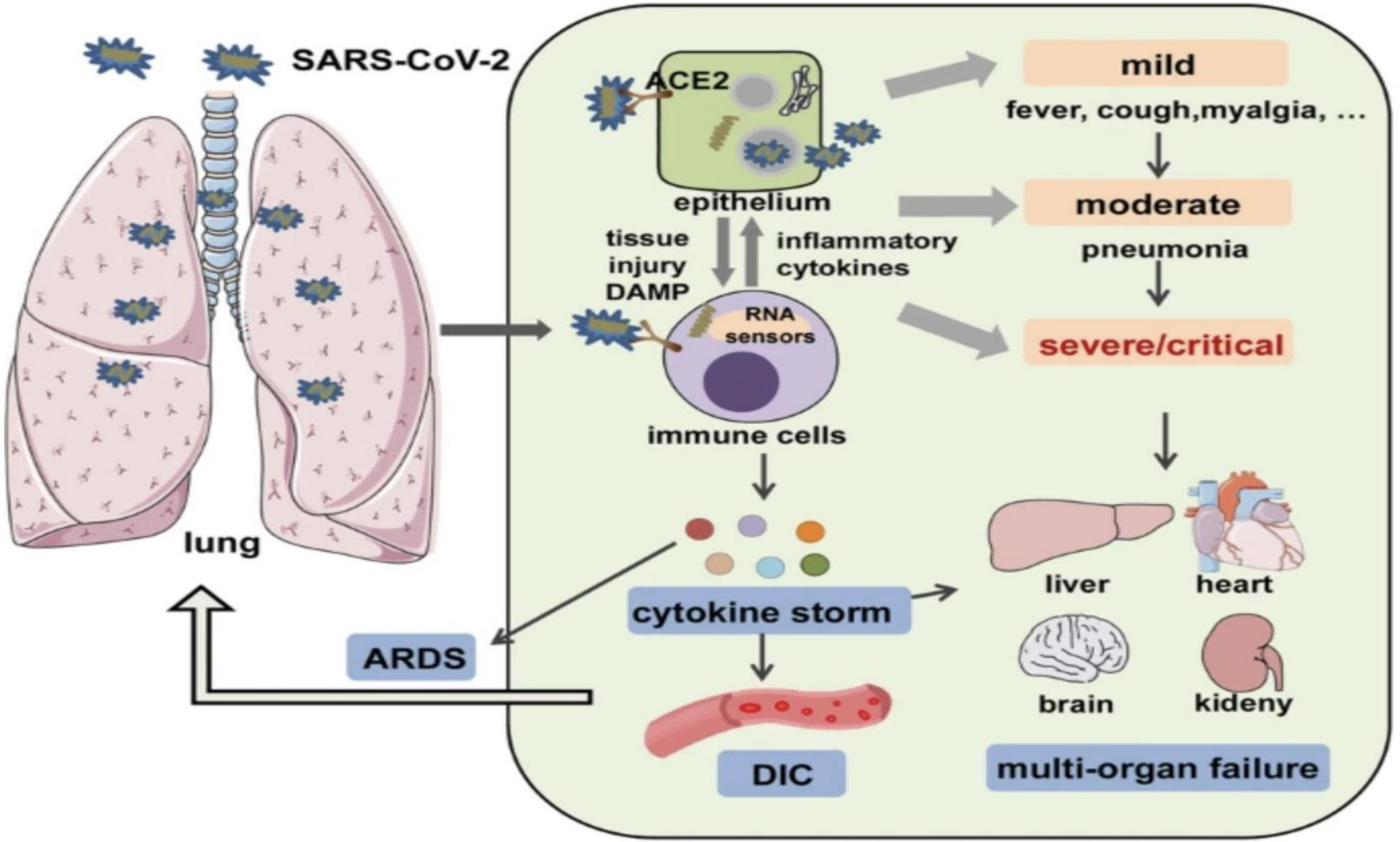
Baloxavir

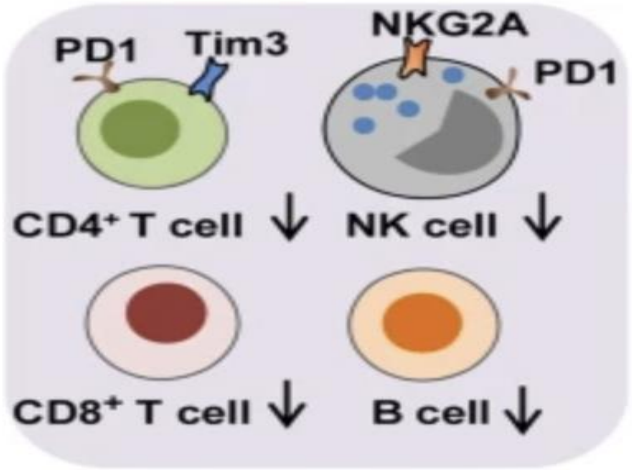
- treat the flu (influenza) in people 5 years of age and older who have flu symptoms for no more than 48 hours and who are otherwise healthy

- prevent the flu in people 5 years of age and older following contact with a person who has the flu (post-exposure prophylaxis).

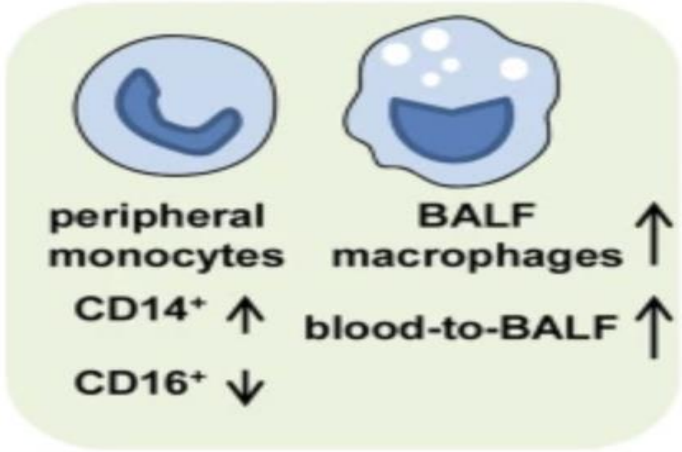
Cytokine storm
Lessons learned from COVID

1918 Flu pandemic

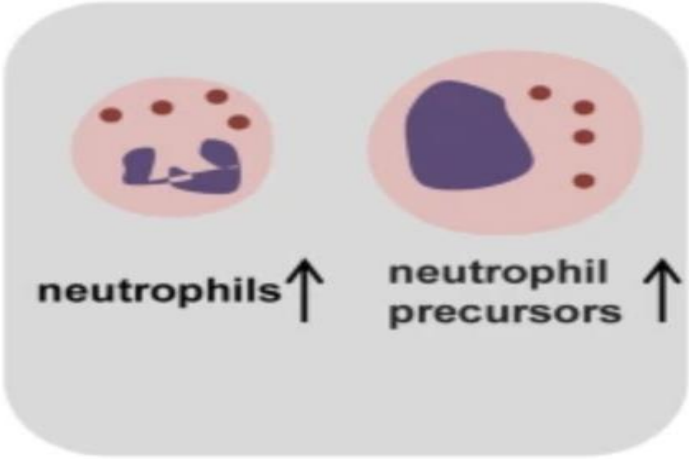

SARS-CoV-2
lung
ACE2
epithelium
tissue
injury
DAMP
inflammatory
cytokines
RNA
sensors
immune cells
mild
fever, cough,myalgia, …
moderate
pneumonia
severe/critical
liver
heart
brain
kideny
cytokine storm
ARDS
DIC
multi-organ failure



lymphopenia

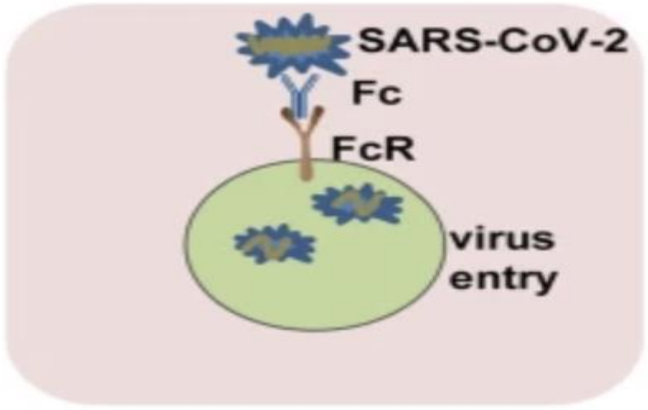


dysregulated monocytes and macrophages



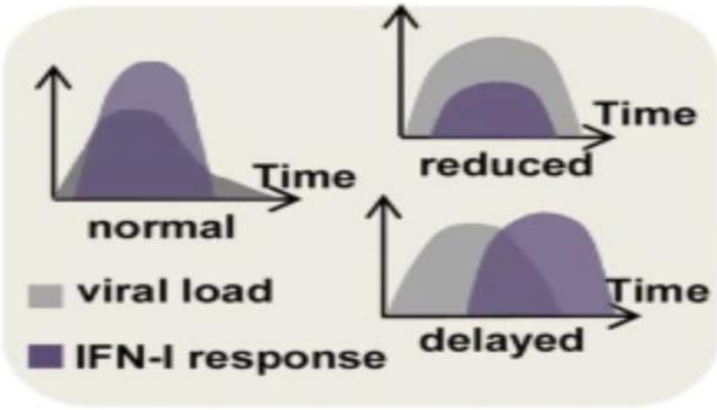
neutrophilia

The immunopathological manifestations of severe COVID-19

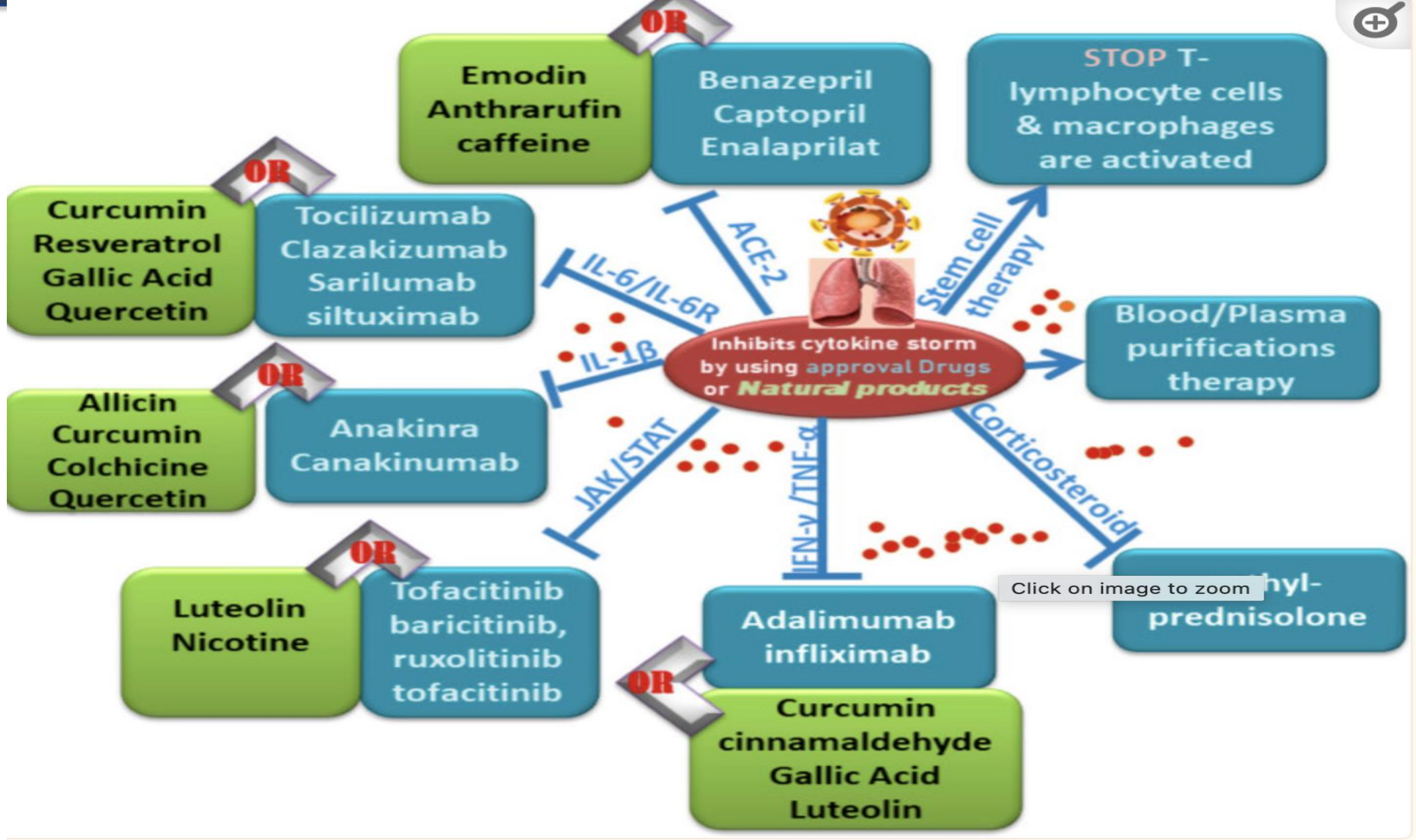


ADE effect

cytokine storm



reduced or delayed IFN-I response



Click on image to zoom

SUMMARY

- **Oseltamivir reduces symptoms in healthy adults and adolescents with influenza by up to 1 day**
- **IDSA recommends oseltamivir in eligible hospitalized patients**
- **For severely ill influenza patients**
- **Future may combine multiple antiviral agents**
- **For select patients, immunomodulators may prove useful, similar to COVID**

IDSA Clinical Guidelines 2018

- **Treatment**
- **IV. Which patients with suspected or confirmed influenza should be treated with antivirals?**

18. Clinicians should start antiviral treatment as soon as possible for adults and children with documented or suspected influenza, irrespective of influenza vaccination history, who meet the following criteria:
    18. **Persons of any age who are hospitalized with influenza**, regardless of illness duration prior to hospitalization *(A-II)*.
    19. **Outpatients of any age with severe or progressive ill**ness, regardless of illness duration *(A-III)*.
    20. **Outpatients who are at high risk of complications from influenza**, including those with chronic medical conditions and immunocompromised patients *(A-II)*.
    21. Children younger than 2 years and adults ≥65 years *(A-III)*.
    22. Pregnant women and those within 2 weeks postpartum *(A-III)*.

IDSA Clinical Guidelines 2018

- Clinicians can consider antiviral treatment for adults and children who are not at high risk of influenza complications, with documented or suspected influenza, irrespective of influenza vaccination history, who are either:
  19. Outpatients with illness onset ≤2 days before presentation *(C-I)*.
  20. Symptomatic outpatients who are household contacts of persons who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised *(C-III)*.
  21. Symptomatic healthcare providers who care for patients who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised *(C-III)*

IDSA Statement on Cochrane Reviews

- **Of particular importance, RCTs of NAI treatment in ambulatory patients with mild illness do not inform clinical practice regarding the treatment of patients with severe illness or persons at higher risk for influenza complications. No placebo-controlled RCTs are available for NAI treatment of hospitalized influenza patients.** Therefore, evidence from the many observational studies of hospitalized seasonal and pandemic 2009 H1N1 influenza patients should be considered despite the limitations of observational studies compared to RCTs. **These observational studies have consistently reported that NAI treatment of influenza in hospitalized patients reduces severe outcomes, including intensive care unit admission and death, especially when treatment is started within two days of illness onset.** These studies have also shown that later initiation of NAI treatment may still provide some clinical benefit. No RCT was powered to evaluate the effect of oseltamivir treatment of outpatients to reduce influenza-associated complications such as hospitalization or lower respiratory tract infections; both outcomes are rare in otherwise healthy individuals but more common in persons at higher risk for complications. Pooled data from RCTs have been used to try to assess the effect of outpatient treatment on subsequent complications. While too few hospitalizations were recorded from available RCTs to assess this outcome, published studies have demonstrated a reduction in clinician diagnosed lower respiratory tract infections requiring antibiotics.
- IDSA continues to recommend the use of neuraminidase inhibitors for the treatment of influenza and endorses the CDC statement that current antiviral recommendations for influenza remain unchanged [4].

Vaccines

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Influenza Strains are Currently Recommended for vaccines for the 2024-2025 Flu Season

CDC and WHO Recommendations for the 2024-2025 Flu Season

- Egg-based vaccines:
  - A/Victoria/4897/2022 (**H1N1**)pdm09-like virus
  - A/Thailand/8/2022 (**H3N2**)-like virus
  - B/Austria/1359417/2021 (B/Victoria lineage)-like virus
- Cell- or recombinant-based vaccines:
  - A/Wisconsin/67/2022 (**H1N1**)pdm09-like virus
  - A/Massachusetts/18/2022 (**H3N2**)-like virus
  - B/Austria/1359417/2021 (B/Victoria lineage)-like virus

Current Platforms

1. **Inactivated** Influenza Vaccines
   e.g., Fluzone, Fluarix
2. **Recombinant** Influenza Vaccines (HA is cloned into a baculovirus expression vector
   e.g., Flublok
3. **Live Attenuated** Influenza Vaccines
   e.g., FluMist

SANOFI PASTEUR

Recombinant

*For quadrivalent vaccines, the **WHO recommends adding the B/Phuket/3073/2013 (B/Yamagata lineage)**-like a virus as the second influenza B strain.*

CDC does not recommend quadrivalent since the B/Yamagata linage has not been detected since March 2020, and it is cheaper to make a trivalent vaccine.

Emerging influenza Vaccine Platforms

mRNA Vaccines:

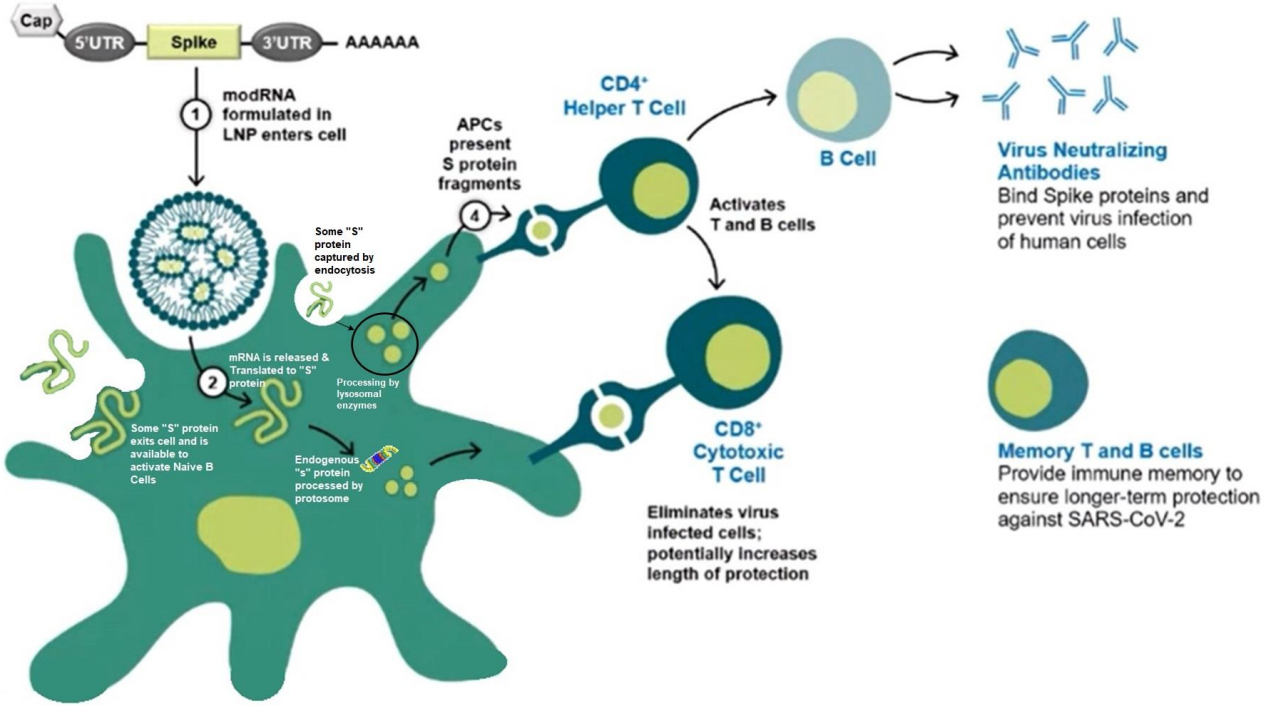
- Mechanism: These vaccines use messenger RNA to instruct cells to produce a protein that triggers an immune response.
  - Examples: **mRNA-1010** (Moderna's investigational flu vaccine) RNA for all 4 HA glycoproteins of four influenza strains recommended by the WHO
  - Moderna's **mRNA-1083**: Omicron XBB.1.5 with the same RNAs for HA as mRNA-1010

Protein-based Nanoparticles

- Mechanism: These vaccines use nanoparticles to deliver proteins that mimic the structure of the virus, prompting an immune response.
  - Examples: **Novavax's NanoFlu**

DNA Vaccines:

- Mechanism: These vaccines use DNA to encode antigens that are expressed in the body to elicit an immune response.
  - Examples: **INO-4800** (Inovio's investigational DNA vaccine for COVID-19, with potential applications for influenza) uses Plasmid: pGX9501, which encodes the entire SARS-CoV-2 spike protein.



Available H5N1 Vaccines

- Sanofi Pasteur's H5N1 Vaccine
  - Platform: Inactivated, egg-based
    - Clade 1 (A/Vietnam/1203/2004)
    - Clade 2 (A/Indonesia/05/2005)
  - License Date: April 2007
  - Approved by the US FDA for use in humans.
- GlaxoSmithKline's Q-Pan H5N1 Vaccine
  - Platform: Inactivated, split-virus with AS03 adjuvant
    - Clade 2.1.3.2 (A/Indonesia/5/2005)
  - License Date: November 2013
  - Approved by the US FDA for adults ≥ 18 years. The adjuvanted formulation allows for a smaller amount of antigen to be used
- Seqirus Inc's Audenz
  - Platform: Adjuvanted, inactivated monovalent
    - AA/turkey/Turkey/1/2005 (NIBRG-23), which is derived from clade 2.2.1
  - License Date: January 2020
  - Approved by the US FDA for active immunization against H5N1 in persons six months of age and older at increased risk of exposure.
- GlaxoSmithKline's Prepandrix
  - Platform: Inactivated, split-virus with AS03 adjuvant
    - Clade 1 (A/Vietnam/1194/2004)
  - License Date: May 2008
  - Approved by the European Medicines Agency (EMA) for use in humans. This vaccine uses an oil-in-water emulsion adjuvant to enhance the immune response
- CSL Limited's Panvax
  - Platform: Inactivated, egg-based
    - H5N1 strain A/Vietnam/1194/2004, which belongs to clade 1
  - License Date: June 2008
  - Approved by the Australian Therapeutic Goods Administration (TGA) for use in human
- CSL Seqirus' Prepandemic Vaccine
  - Platform: Inactivated, egg-based
    - AA/turkey/Turkey/1/2005 (NIBRG-23), which is derived from clade 2.2.1
  - Finland plans to use CSL Seqirus' prepandemic H5N1 vaccine. This vaccine is part of the proactive measures taken by European nations to secure vaccines for at-risk populations, including poultry workers and other high-risk groups

The END

THANK YOU!