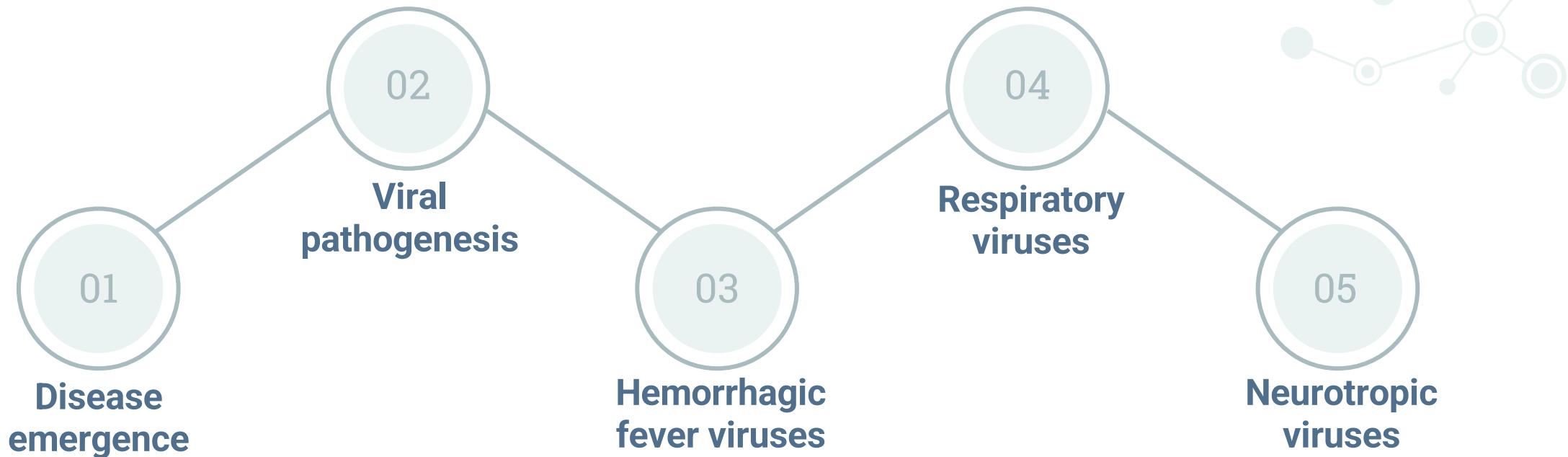


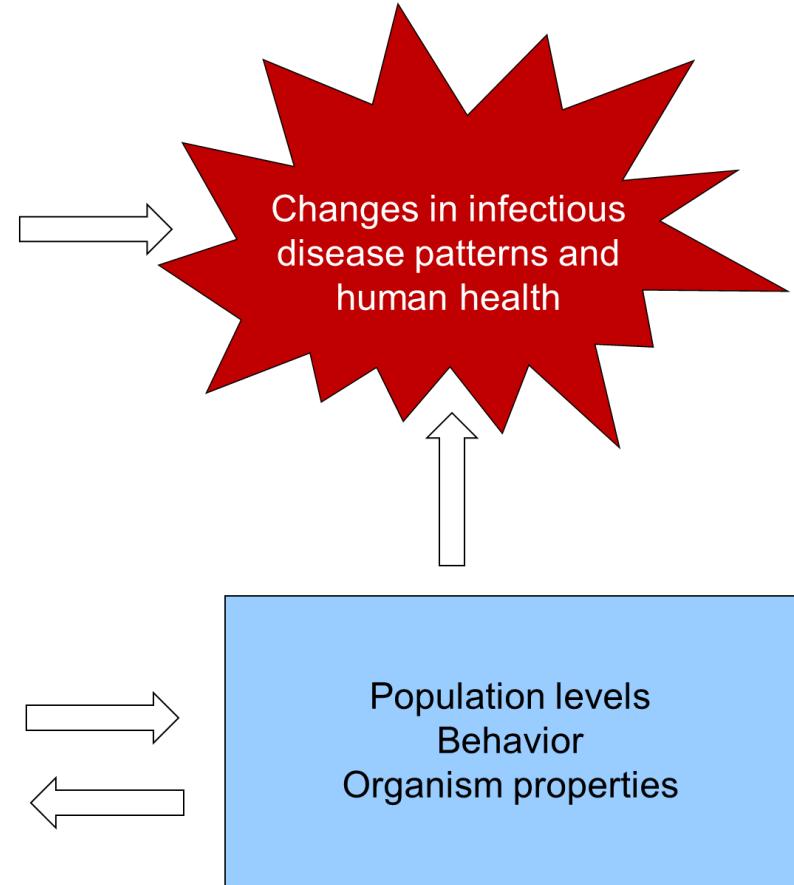
Pathogenesis of emerging viral diseases



Dustin R. Glasner, PhD
BIMM 114 - Virology
2024.02.08

Overview



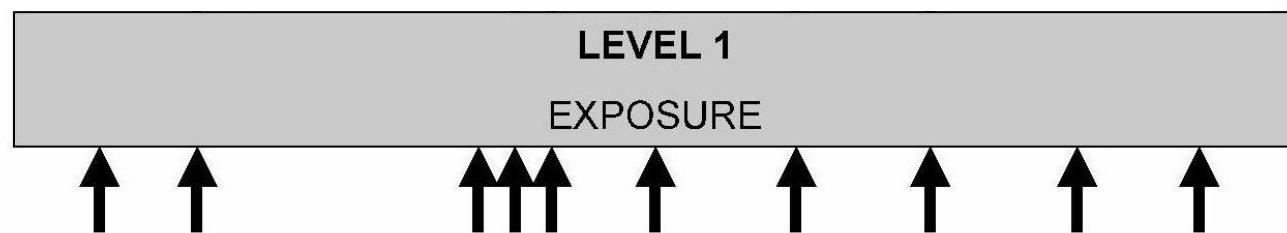


Drivers of disease emergence

- Since 1980, at least 90 novel human pathogens have been recognized
- Each has a specific and unique ecological origin
- Origins may be tied to several factors
- Human-induced changes may drive pathogen emergence in unique ways

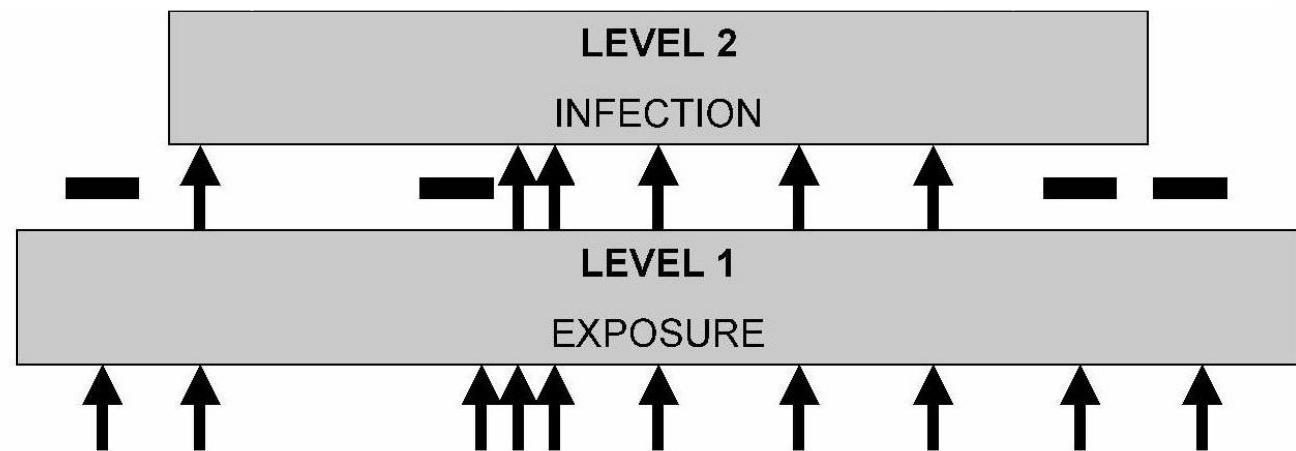


Disease emergence



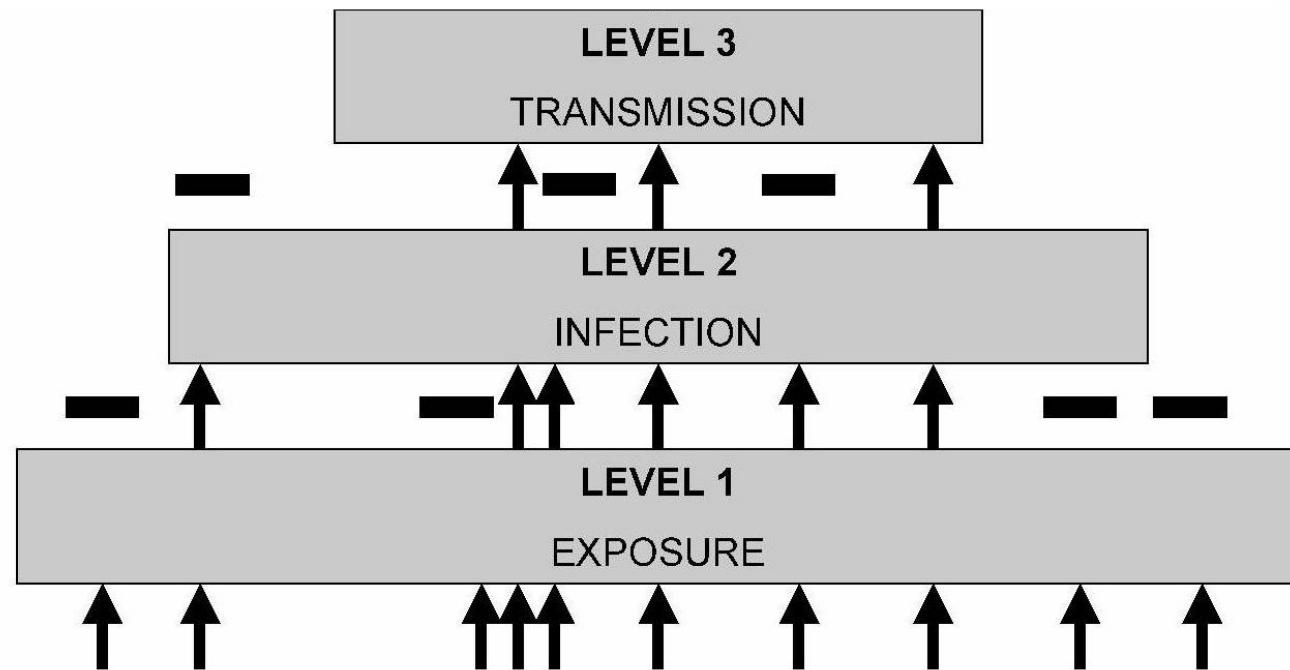


Disease emergence

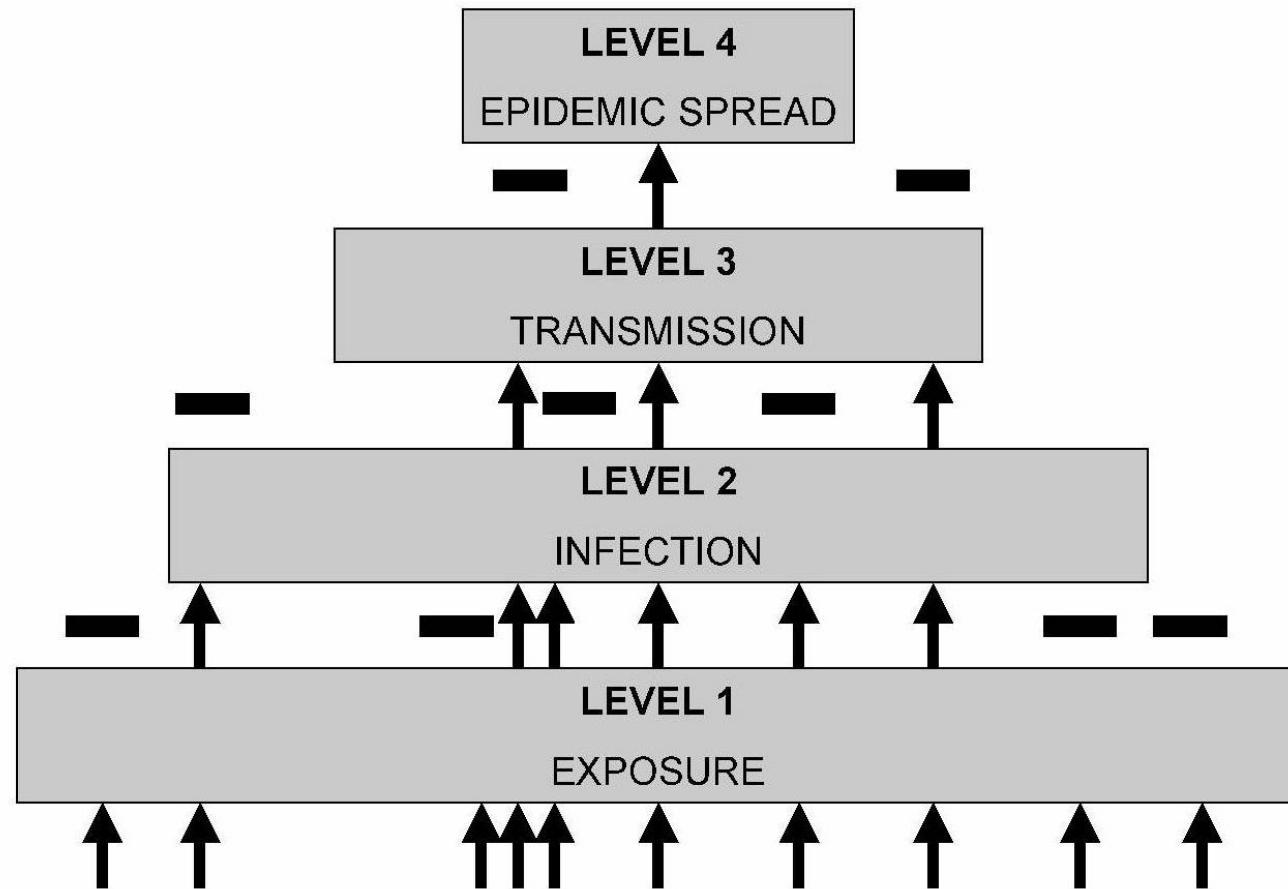


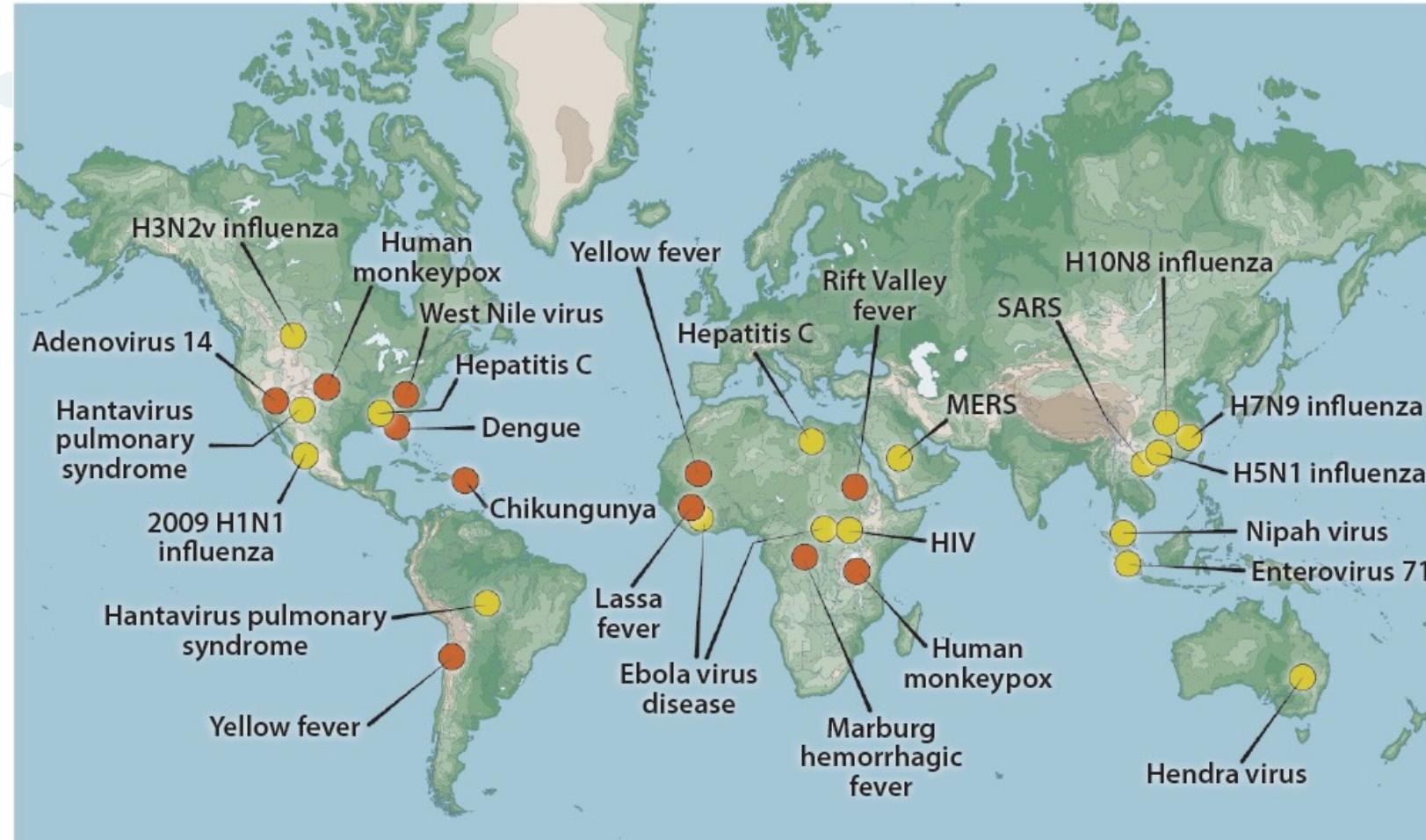


Disease emergence



Disease emergence





● Newly emerging

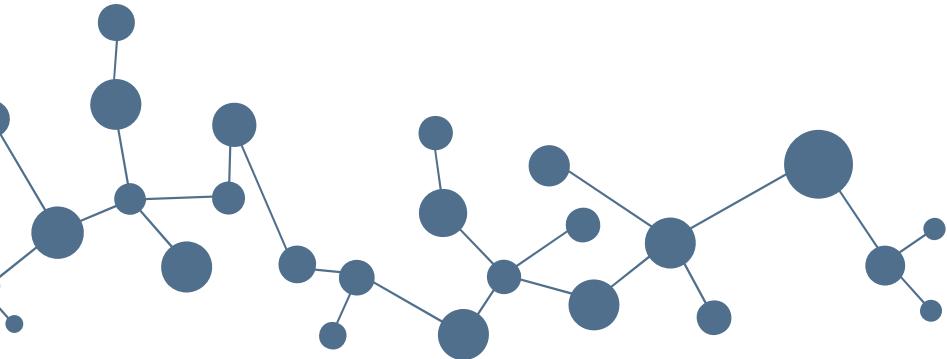
● Reemerging

Developments facilitating spread

- Commercial air travel
- Global trade
- Urbanization
- Unchecked population growth
- Climate change

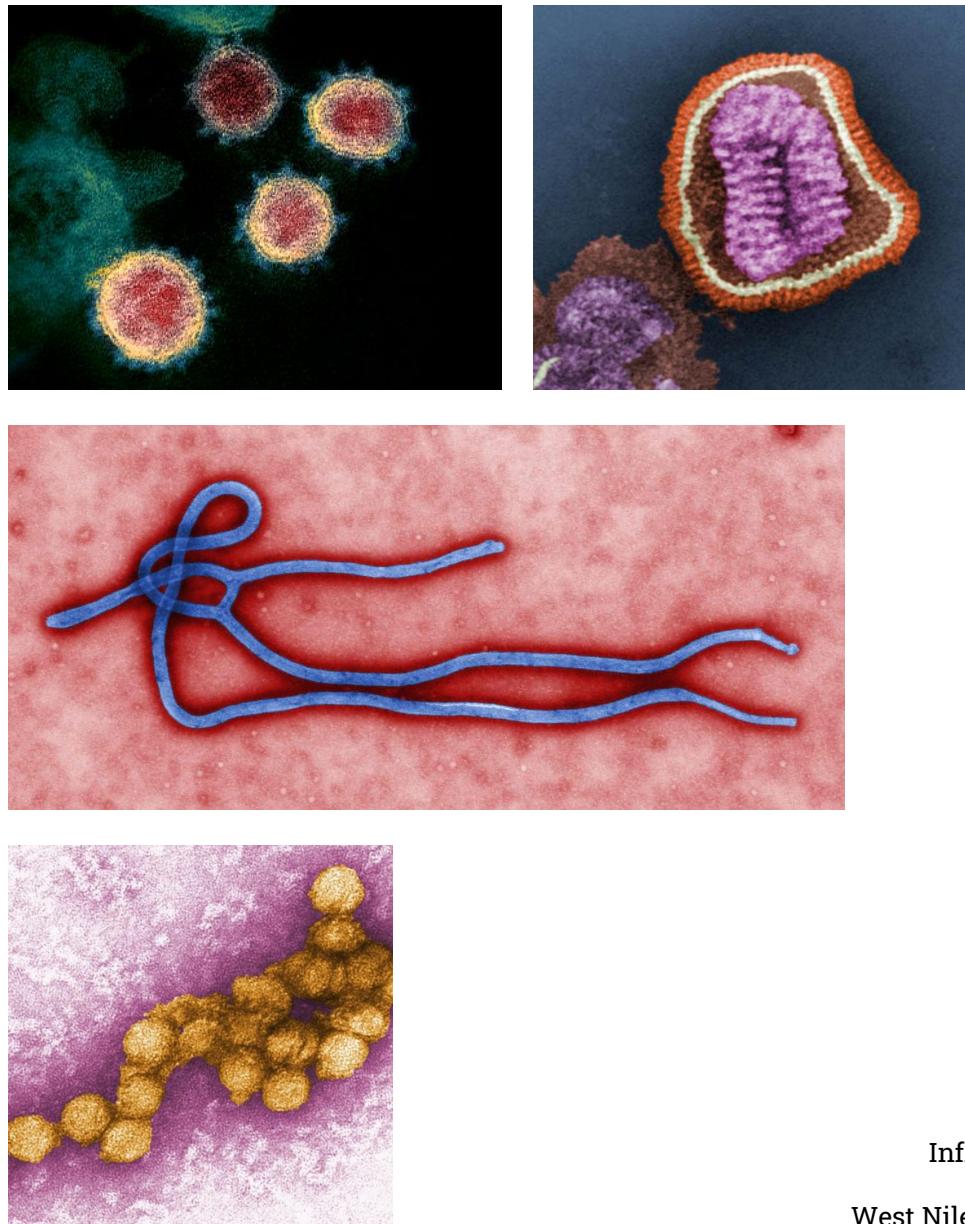
Advances facilitating control

- Genome sequencing to identify emerging viruses
- Global communication networks
- Rapid diagnostics
- New approaches to vaccine and therapeutic design

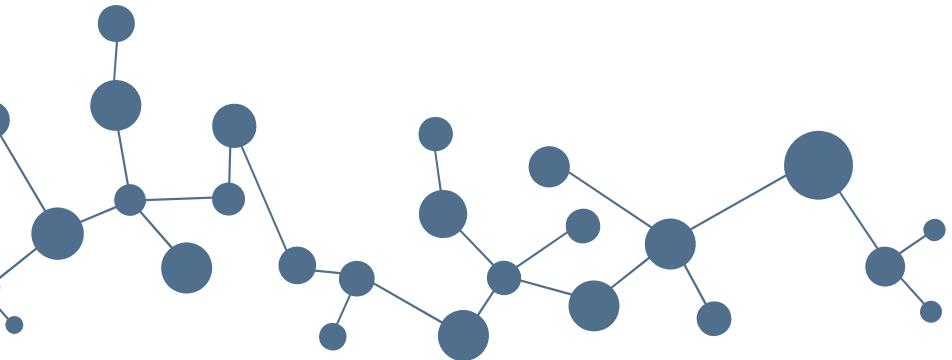


RNA viruses have mutation rates up to a million times higher than their hosts

This can lead to spillover of viruses from animal reservoirs into human populations, leading to emergence of novel human pathogens.

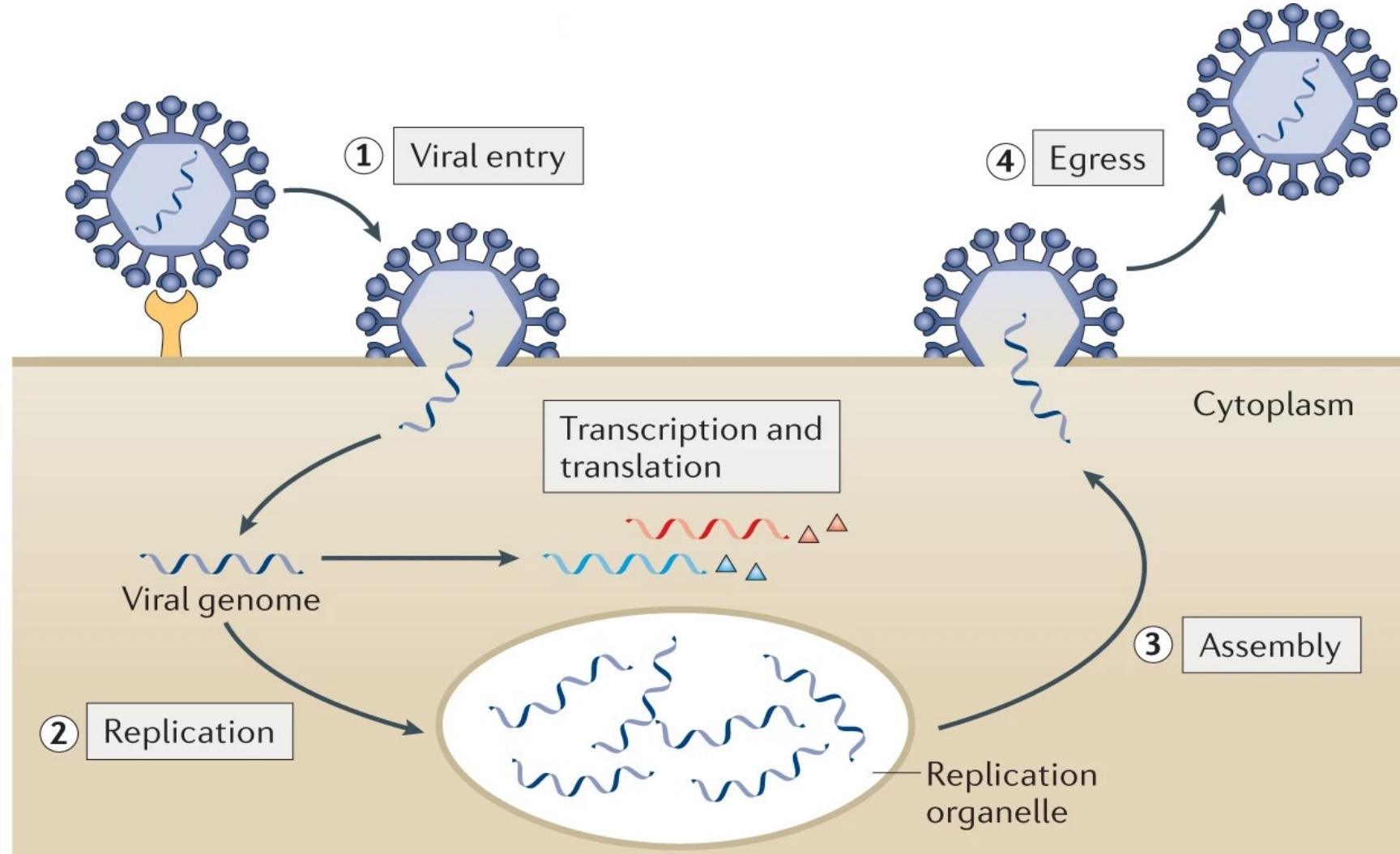


SARS-CoV-2: NIH NIAID/RML
Influenza: CDC/Cynthia Goldsmith
Ebola: CDC/Cynthia Goldsmith
West Nile Virus: CDC/Cynthia Goldsmith

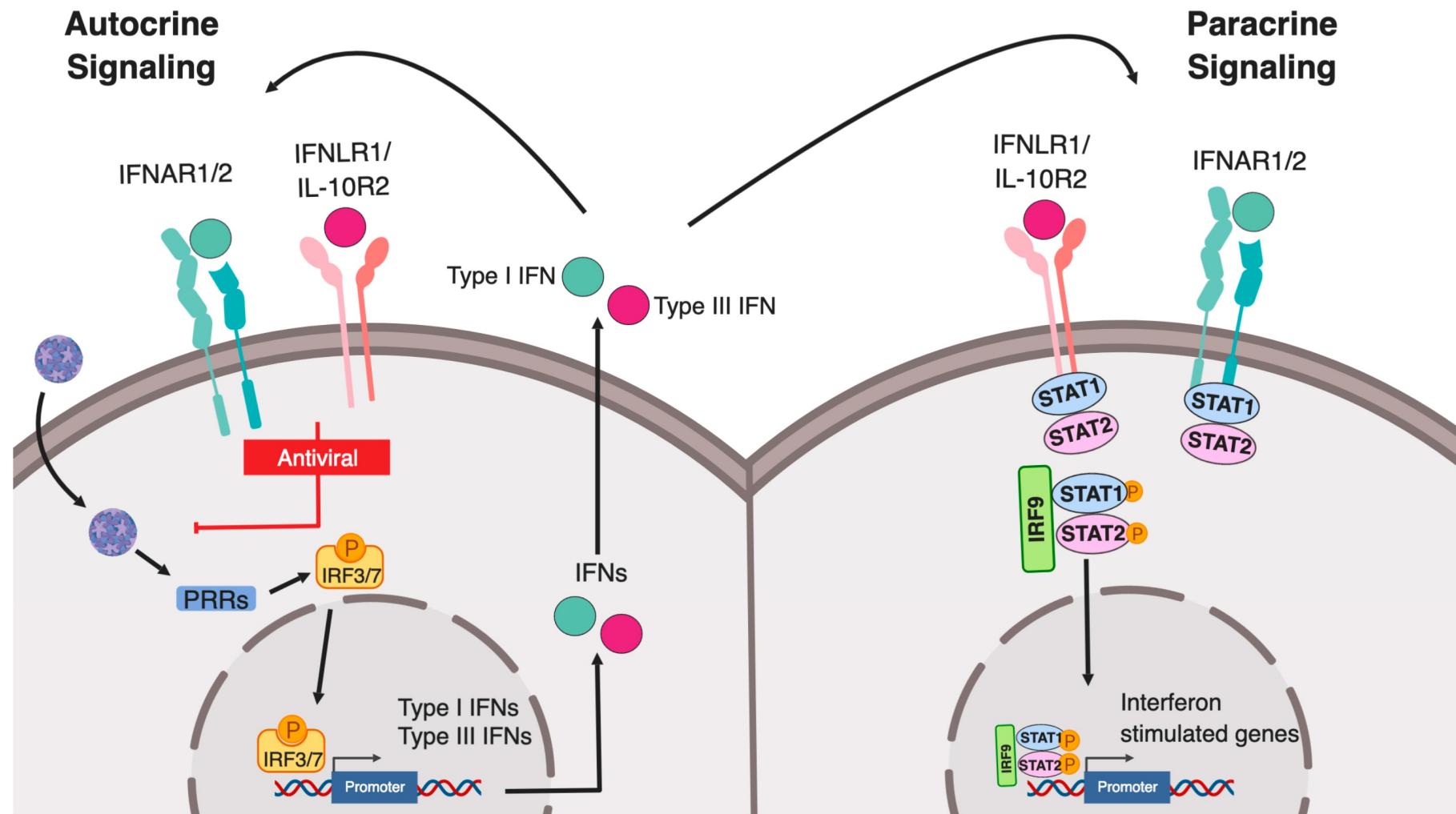


Viral pathogenesis

Viral replication cycle



Interferon signaling





What is viral pathogenesis?

The process by which viruses infect and cause disease in a host



Direct virus killing

- Cytotoxic effects
- Induction of cell death
- Lysis during viral release

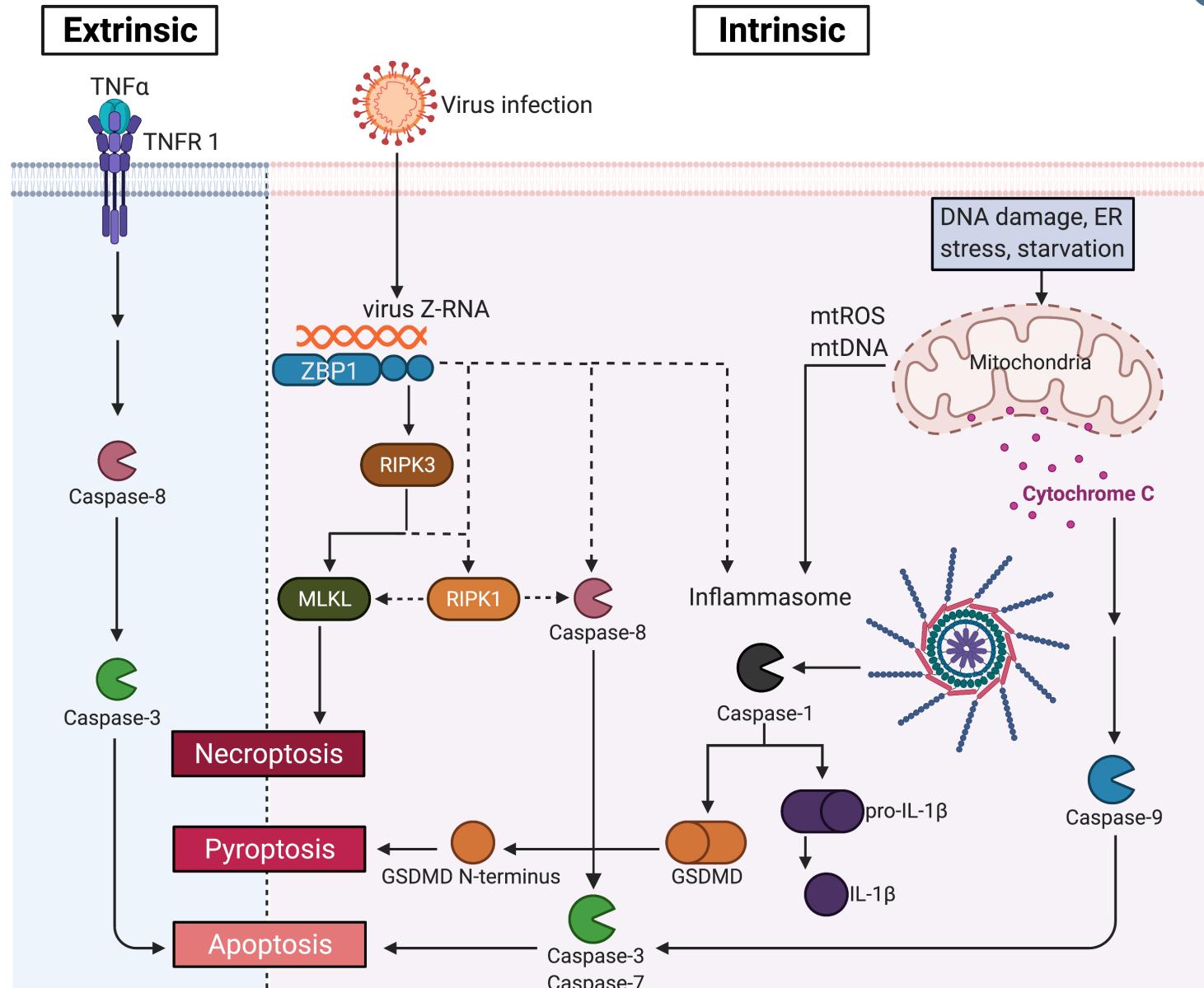


Immunopathology

- Overreaction or inappropriate immune responses
- Cytokines, complement, antibodies, T-cells, etc.

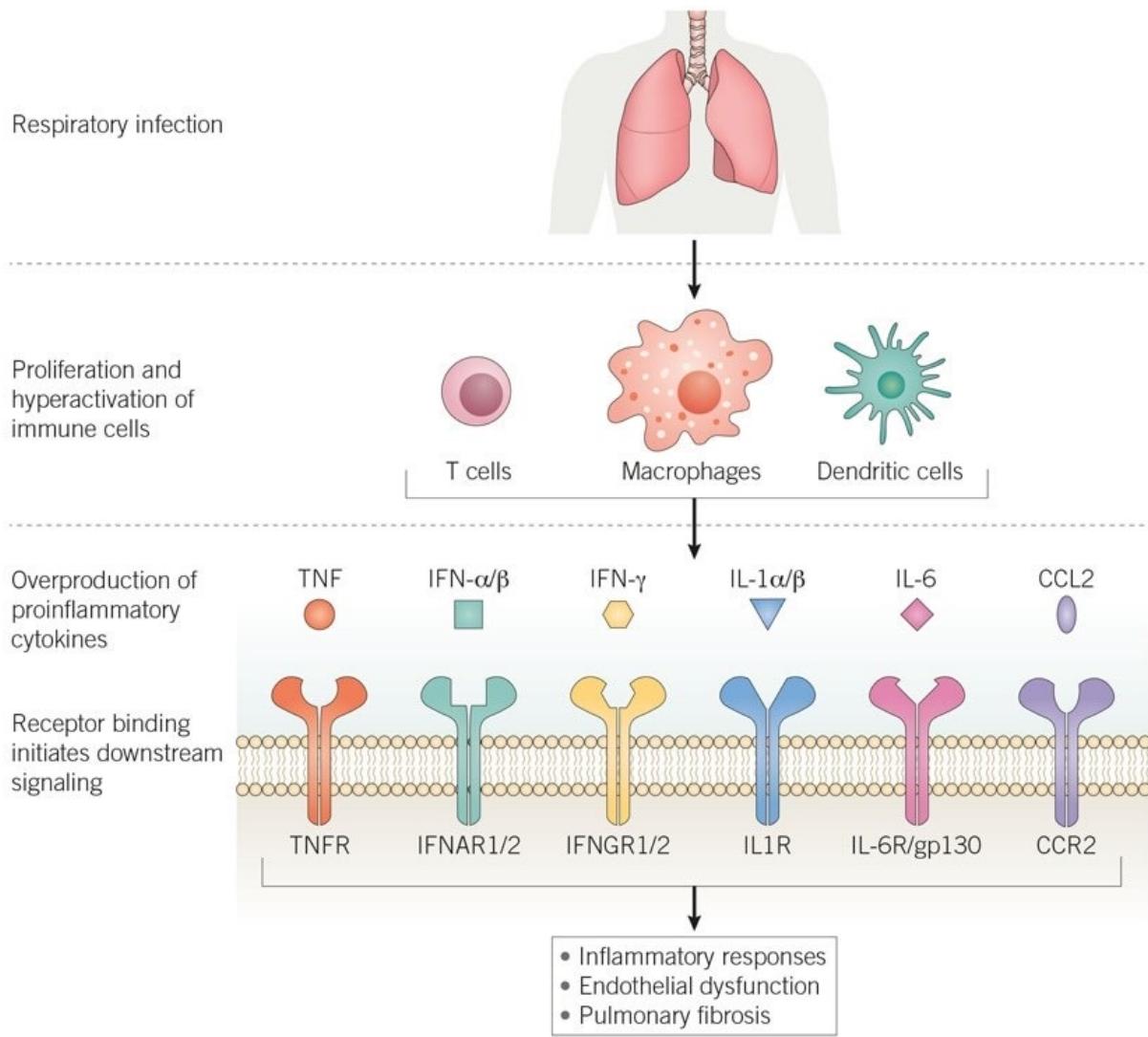
**Host and environmental factors play a contributing role as well*

Cell death

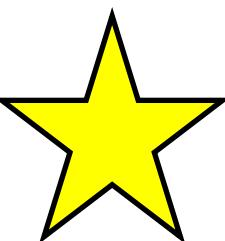


Courtesy of Dr. Liz Fay

Cytokine storm

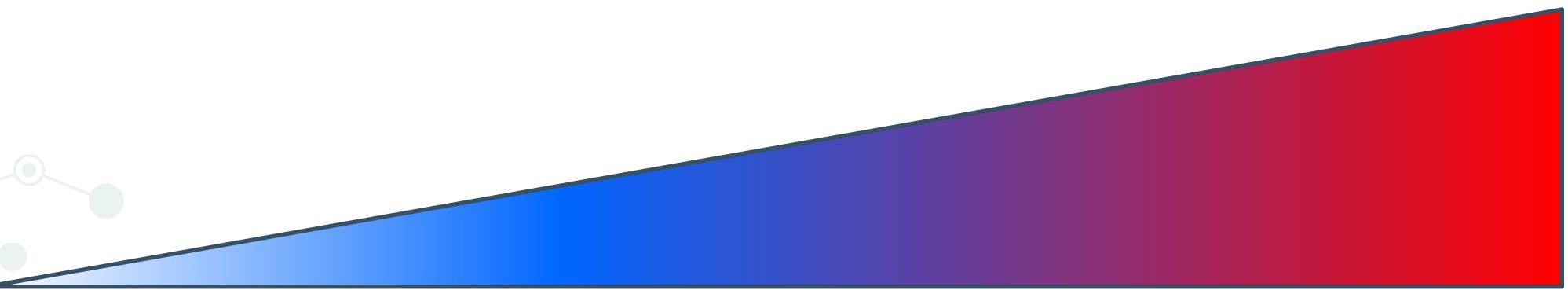
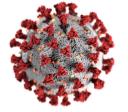


- Uncontrolled, excessive release of pro-inflammatory cytokines
- Results from both infectious and non-infectious causes
- Can lead to acute respiratory distress syndrome (ARDS), multi-organ failure, hyperinflammation syndrome, and death





A delicate balance during infection



Immune activation

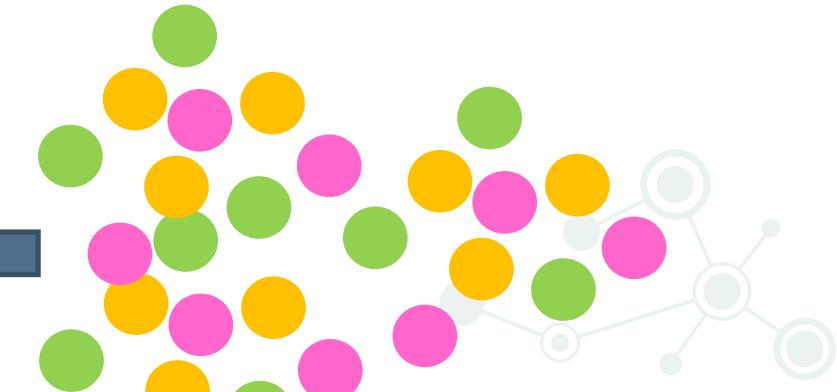
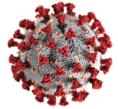
A delicate balance during infection

Cytokine storm

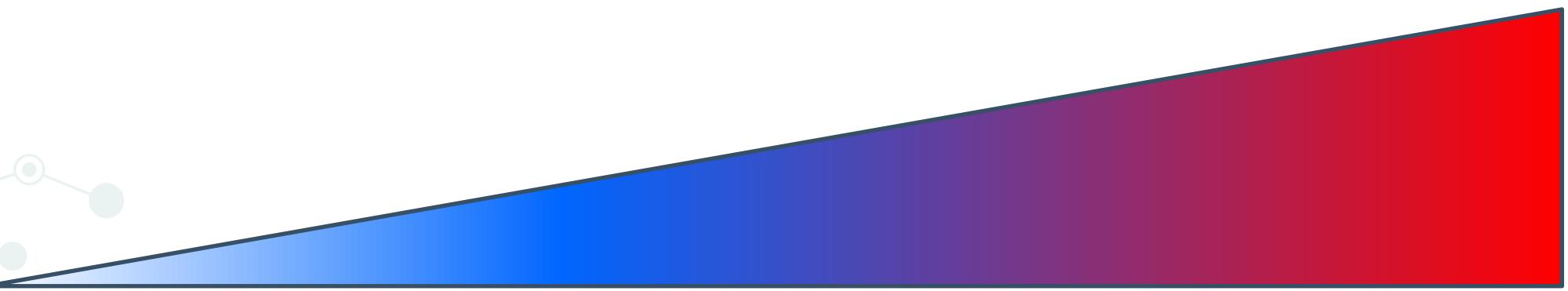
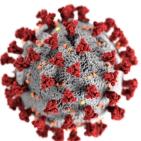


Hyper activation

Immune activation



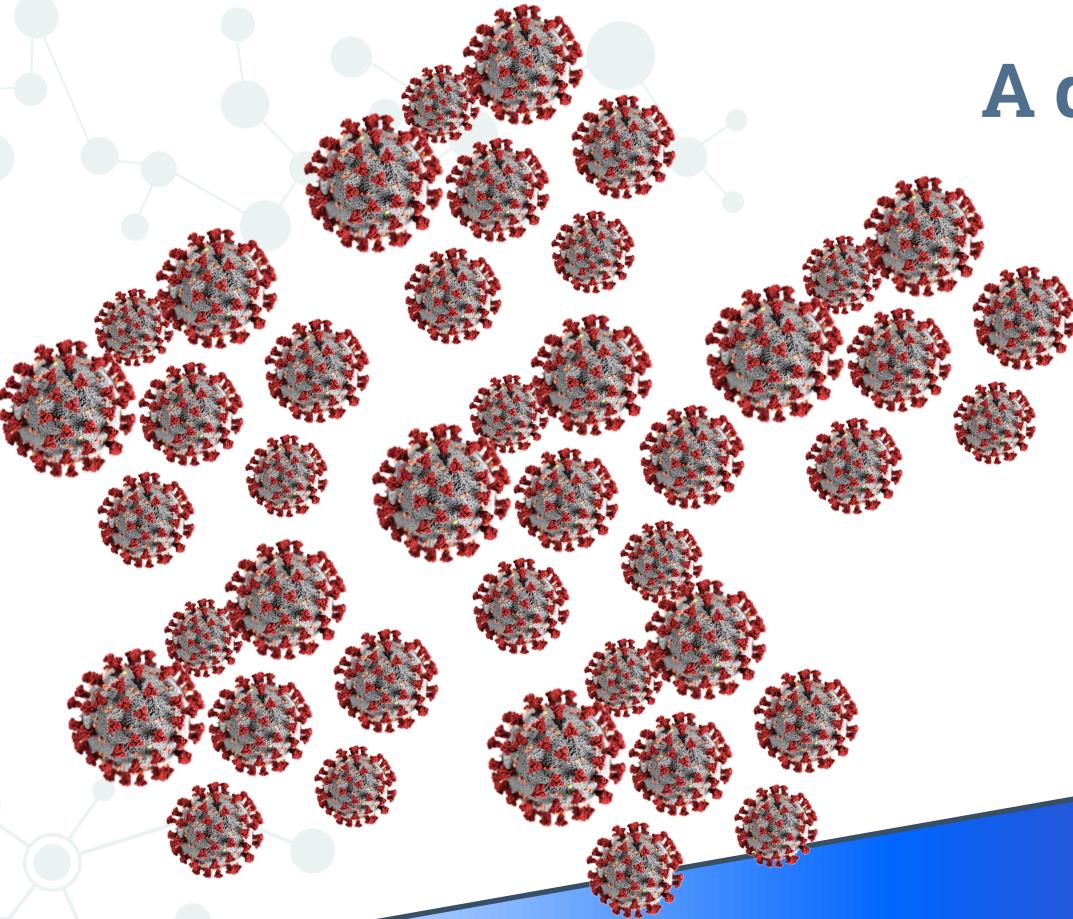
A delicate balance during infection



Immune activation



A delicate balance during infection



Unchecked viral
replication

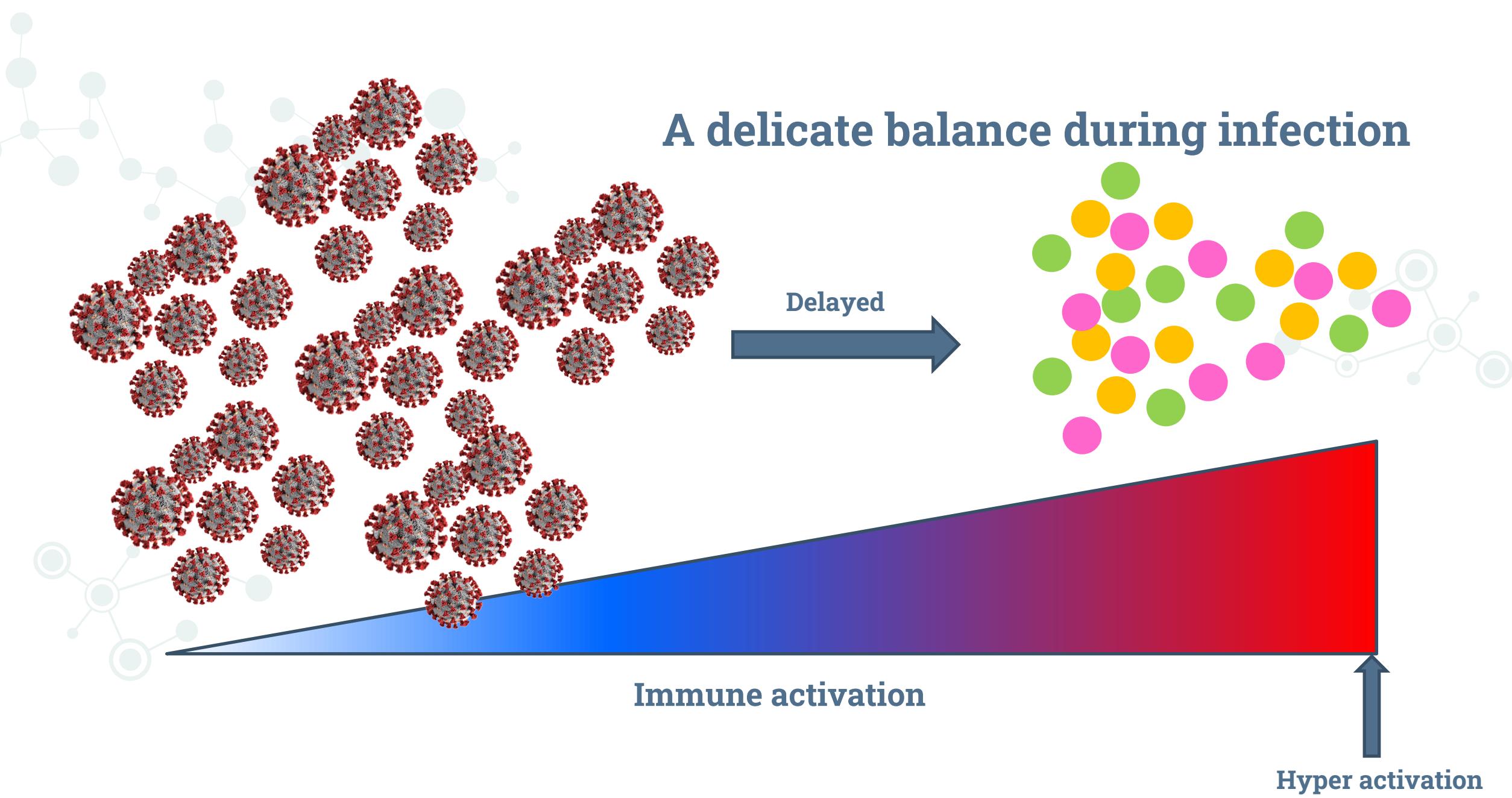


No activation

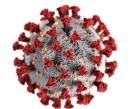
Immune activation



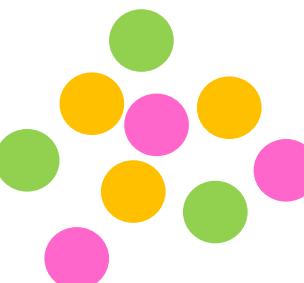
A delicate balance during infection



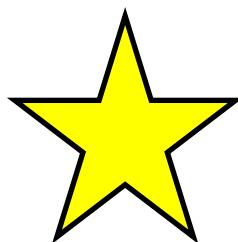
A delicate balance during infection



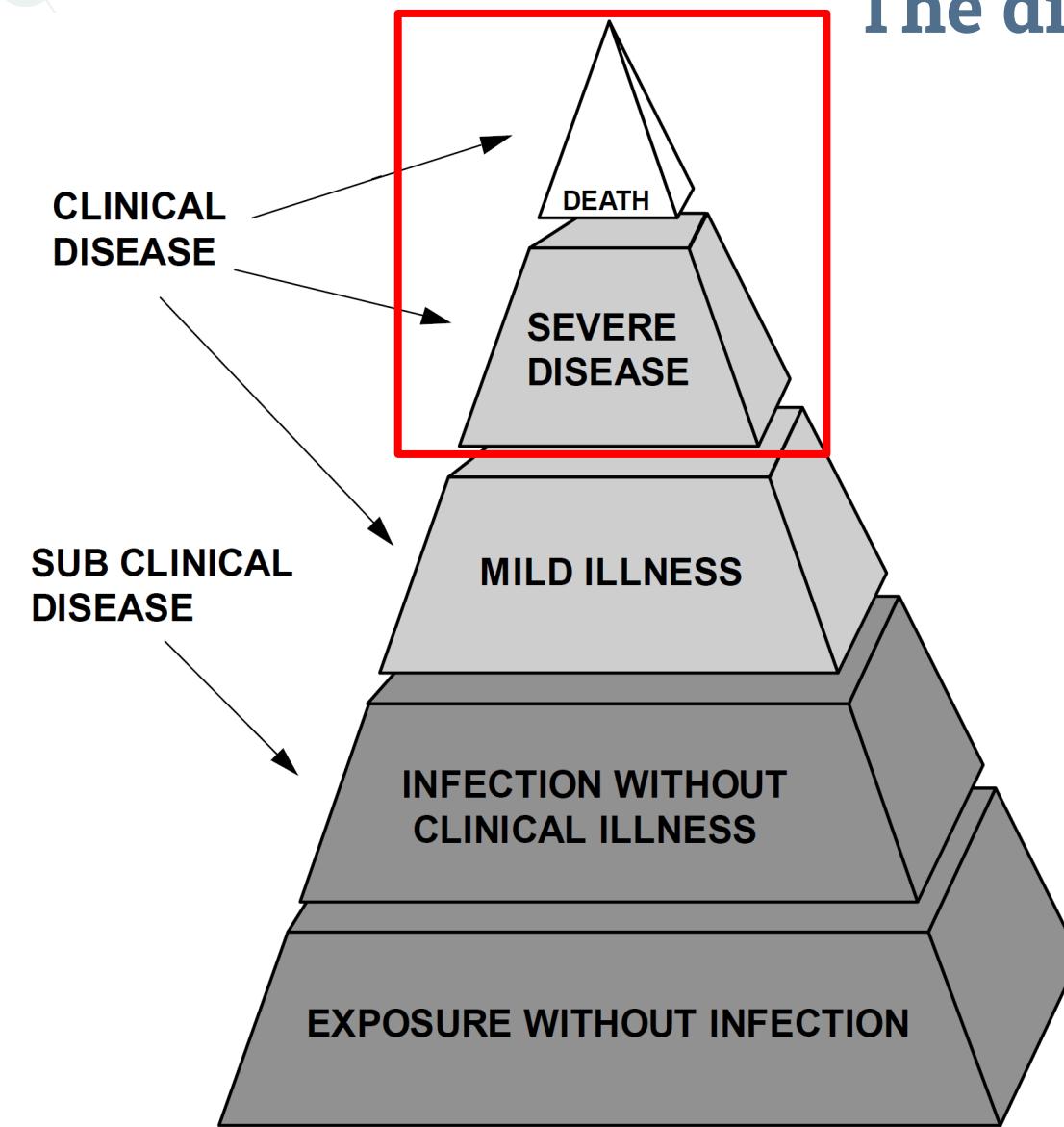
Control of viral replication
Limited immunopathogenesis

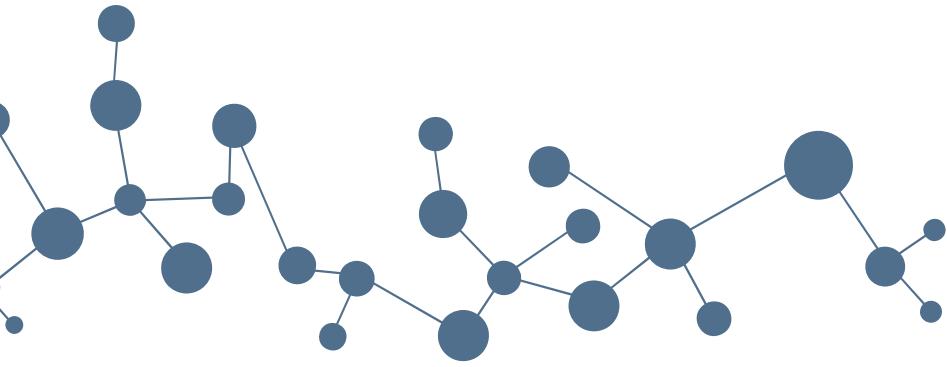


Immune activation
Immune regulation



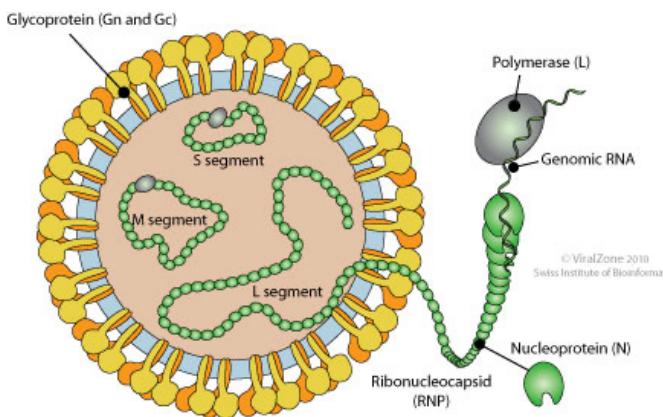
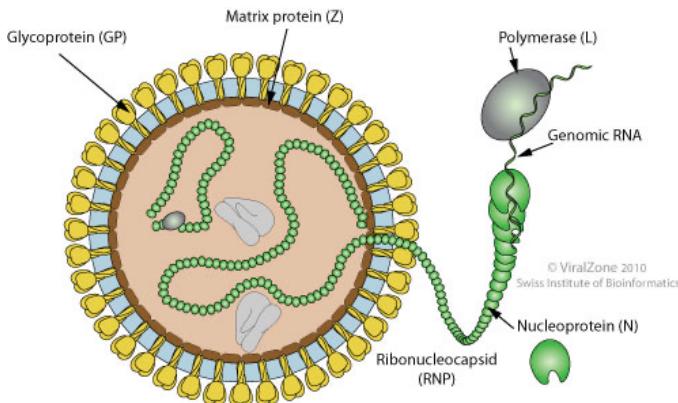
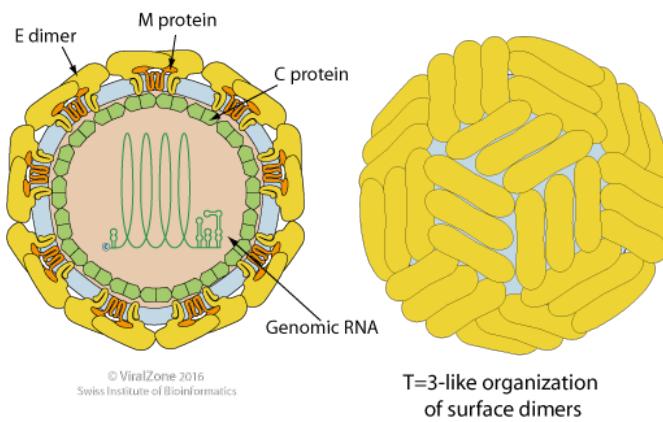
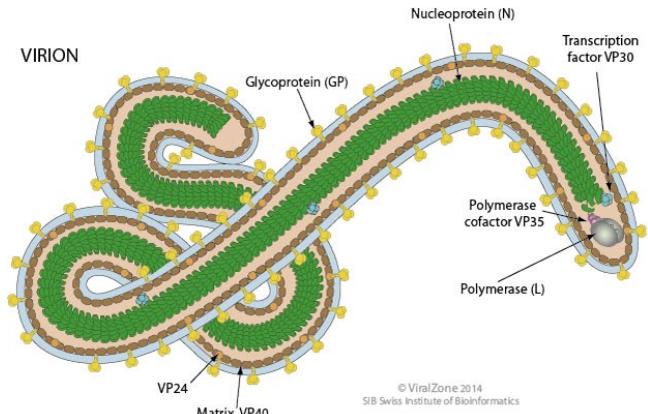
The disease pyramid





Hemorrhagic fever viruses

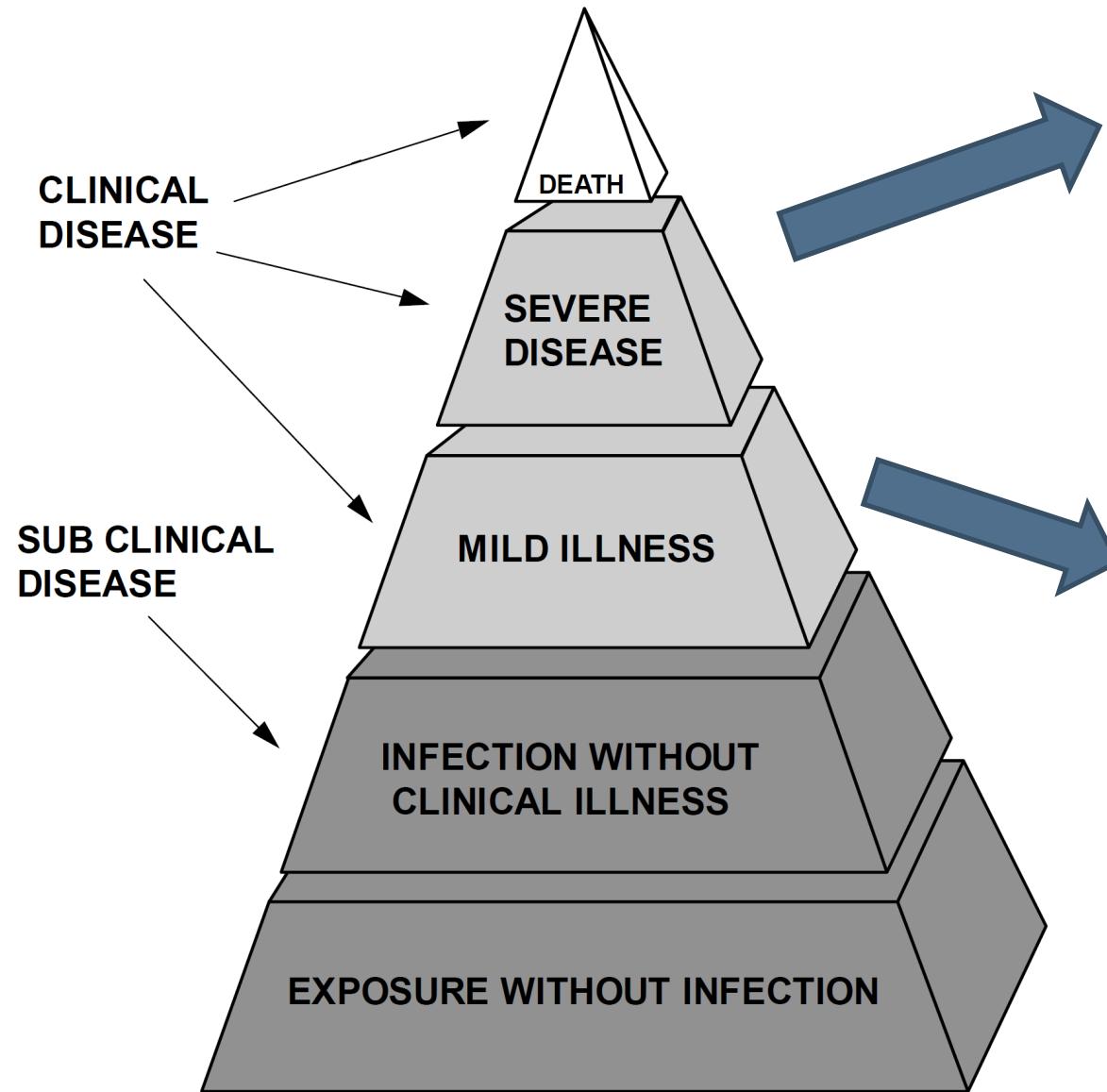
Hemorrhagic fever viruses



<https://viralzone.expasy.org/>

- Filoviridae
 - Ebola
 - Marburg
- Flaviviridae
 - Dengue
 - Yellow Fever
- Arenaviridae
 - Lassa
 - Lujo
- Nairoviridae
 - Crimean-Congo

Viral hemorrhagic fever

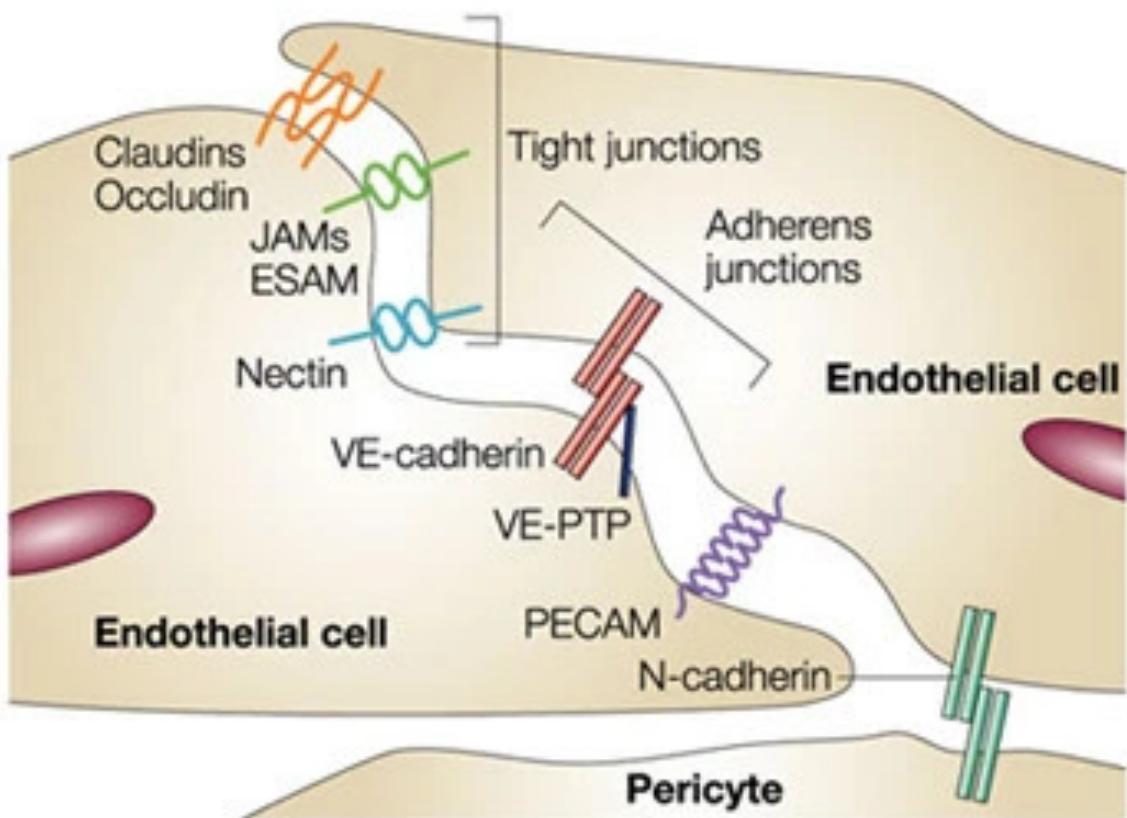


- Bleeding manifestations
- Clotting disorders
- Edema
- Shock
- Organ failure

- Fever
- Fatigue, weakness or general feeling of being unwell
- Dizziness
- Muscle, bone or joint aches
- Nausea and vomiting
- Diarrhea

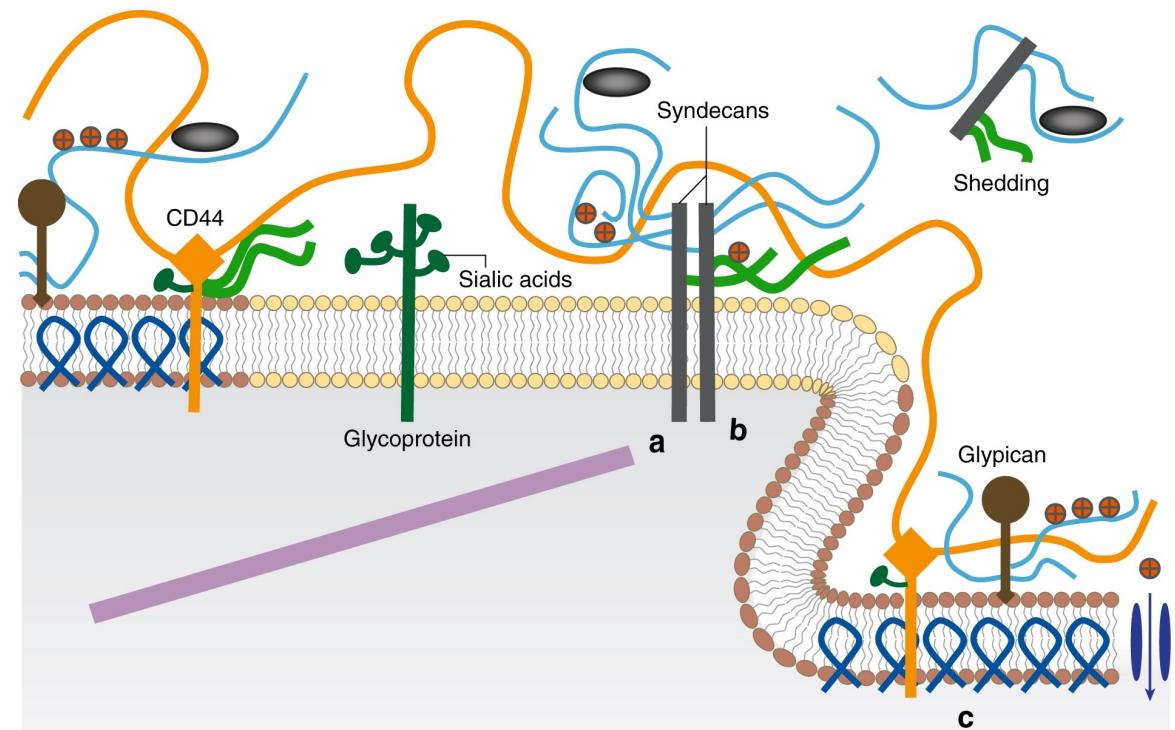
The endothelial barrier

Junctional complexes



Dejana E. *Nat Rev Mol Cell Biol* (2004). <https://doi.org/10.1038/nrm1357>

Endothelial glycocalyx

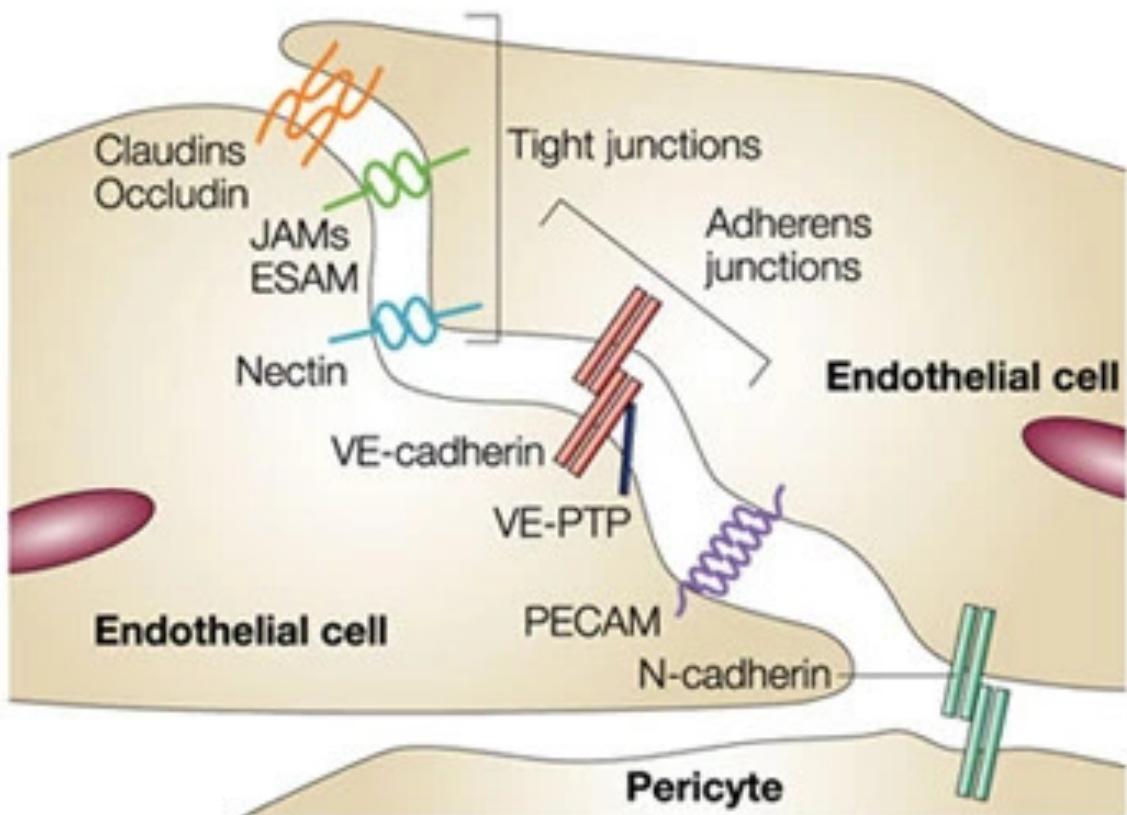


Weinbaum S et al. *Annu Rev Biomed Eng* (2007).
<https://doi.org/10.1146/annurev.bioeng.9.060906.151959>

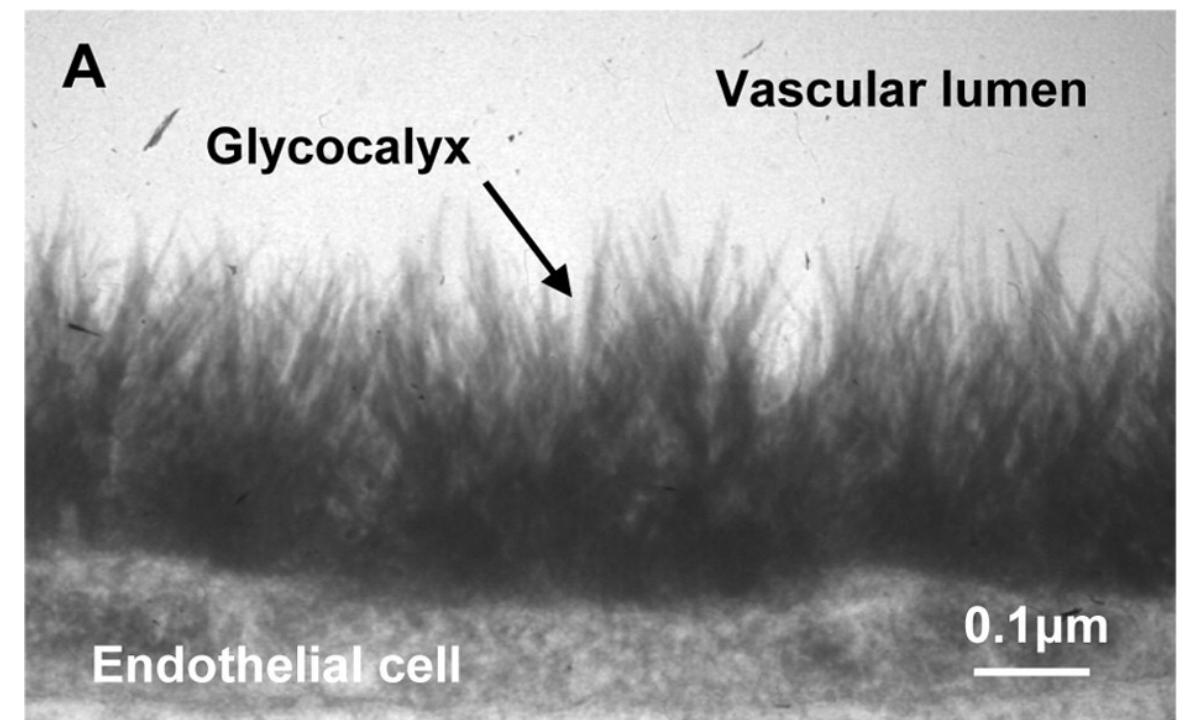
The endothelial barrier

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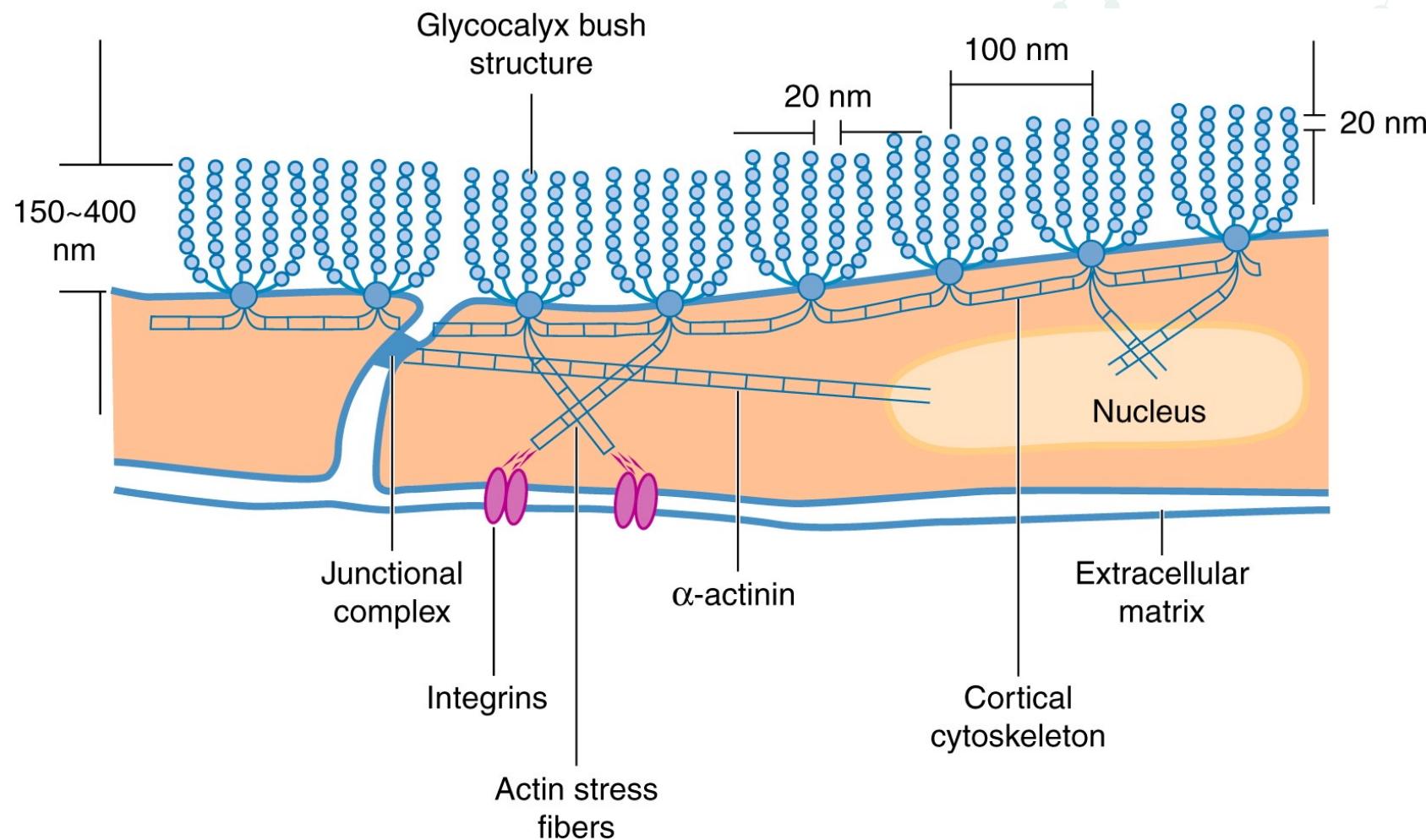


Dejana E. *Nat Rev Mol Cell Biol* (2004). <https://doi.org/10.1038/nrm1357>

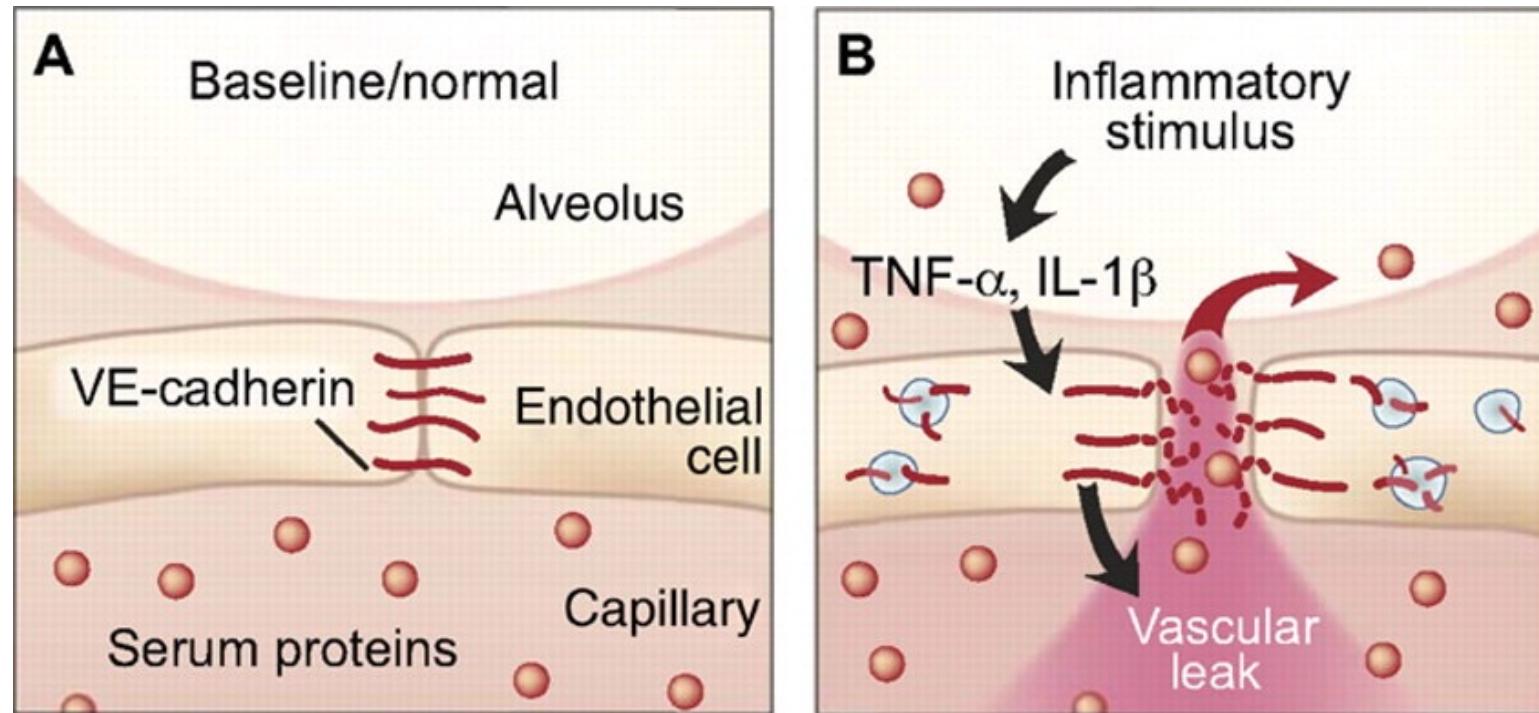


Chappell D et al. *Cardiovasc Res* (2009). <https://doi.org/10.1093/cvr/cvp097>

The endothelial barrier

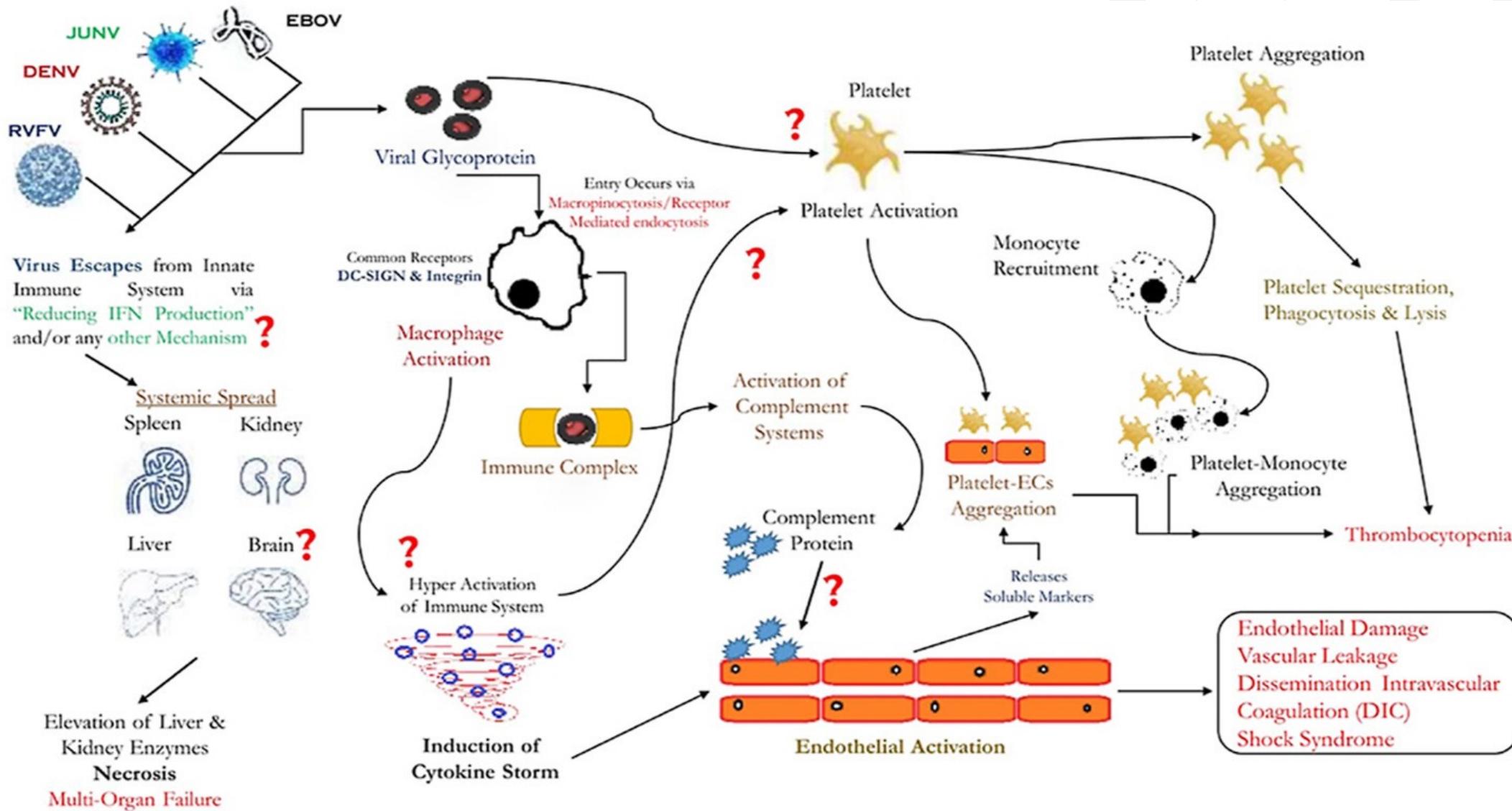


Vascular leak



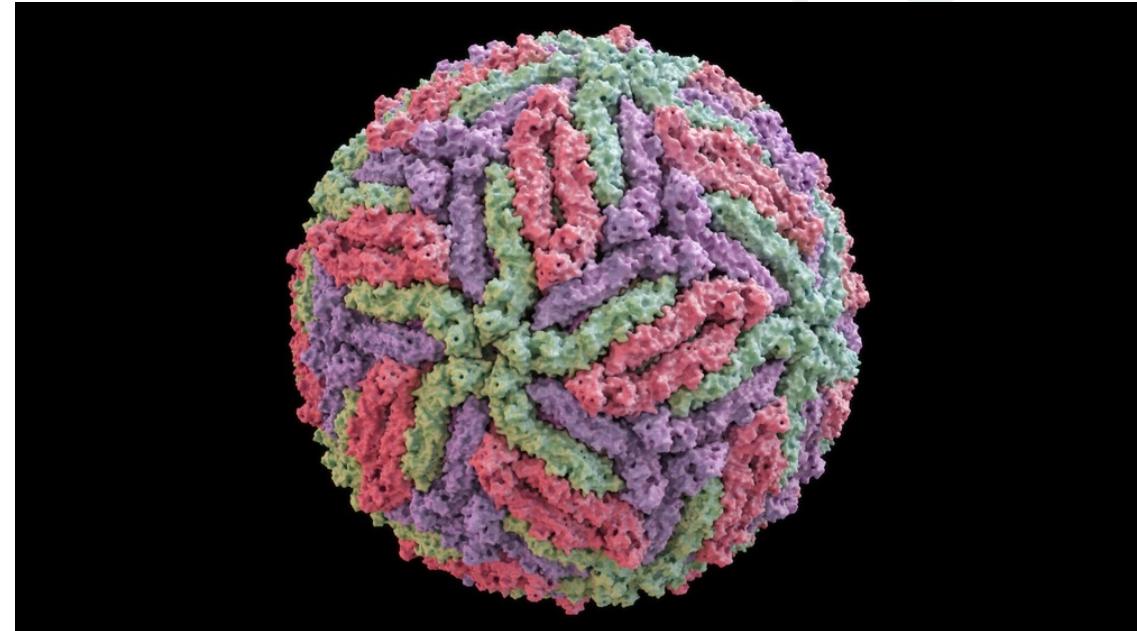
London NR et al. *Sci Transl Med* (2010). <https://doi.org/10.1126/scitranslmed.3000678>

How do hemorrhagic fever viruses cause vascular leak?



Dengue virus

- Family: Flaviviridae
- (+)ssRNA virus
- Is transmitted to people by mosquitoes



<https://thenativeantigencompany.com/products/dengue-virus-serotype-2-envelope-protein/>

Global burden of dengue



3.6 billion at risk for infection from DENV1-4
~400 million infections/year
~100 million dengue cases/year
250,000-500,000 cases of DHF/DSS/year
21,000 deaths attributed to dengue/year

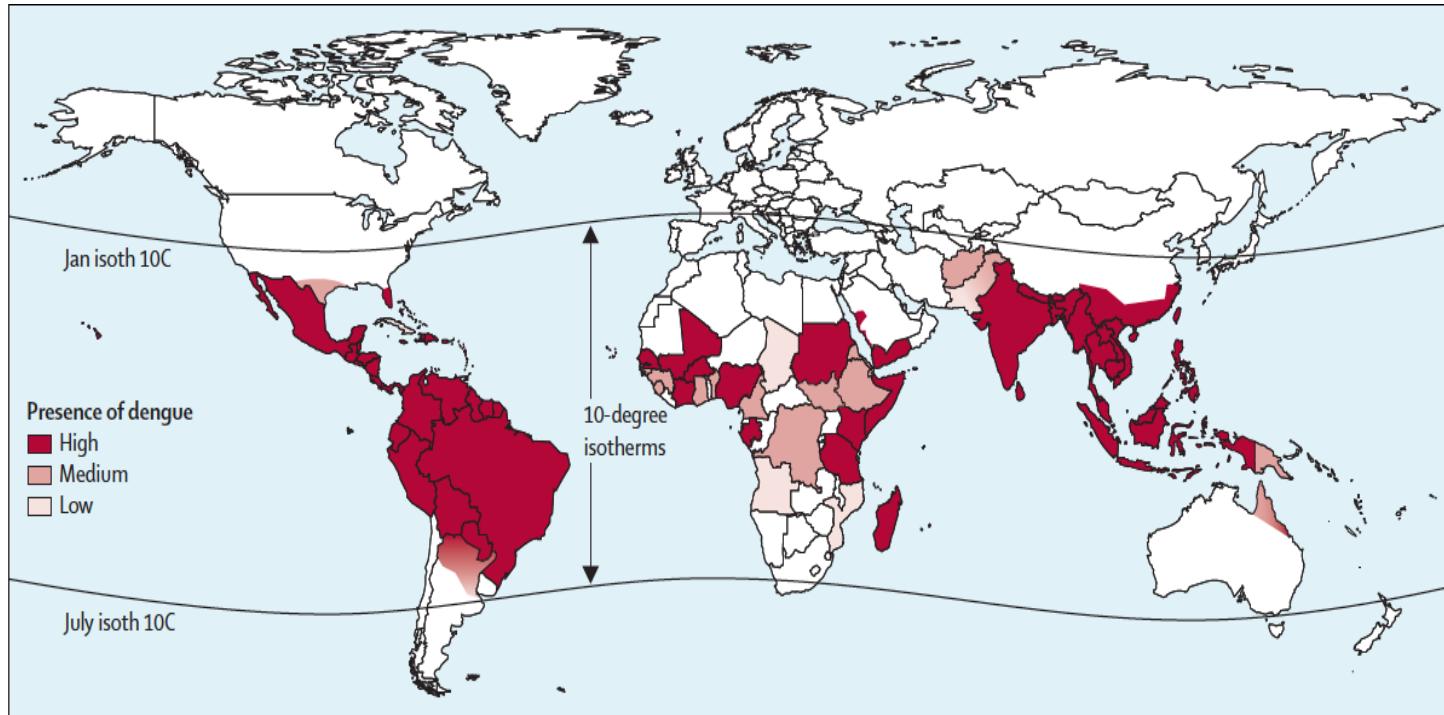


Figure 1: Global dengue burden, 2014

Data from Bhatt and colleagues,¹ Healthmap,² and WHO³ were integrated to indicate the relative amount of dengue globally according to best estimates.

Two Forms of Dengue Disease



Dengue Fever

High Fever
Muscle/Bone Pain
Retro-orbital pain
Fatigue
Rash
Nausea, vomiting



Two Forms of Dengue Disease



Dengue Fever

High Fever
Muscle/Bone Pain
Retro-orbital pain
Fatigue
Rash
Nausea, vomiting

Warning Signs

Persistent vomiting
Tender abdomen
Fluid accumulation
Lethargy
Bleeding



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Bleeding

DHF/DSS

Increased fluid leakage
Low platelet count
Hemorrhagic manifestations
Increased cytokines
Shock from low blood volume



Two Forms of Dengue Disease

Dengue Fever

High Fever
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Rash
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Tablets Manual

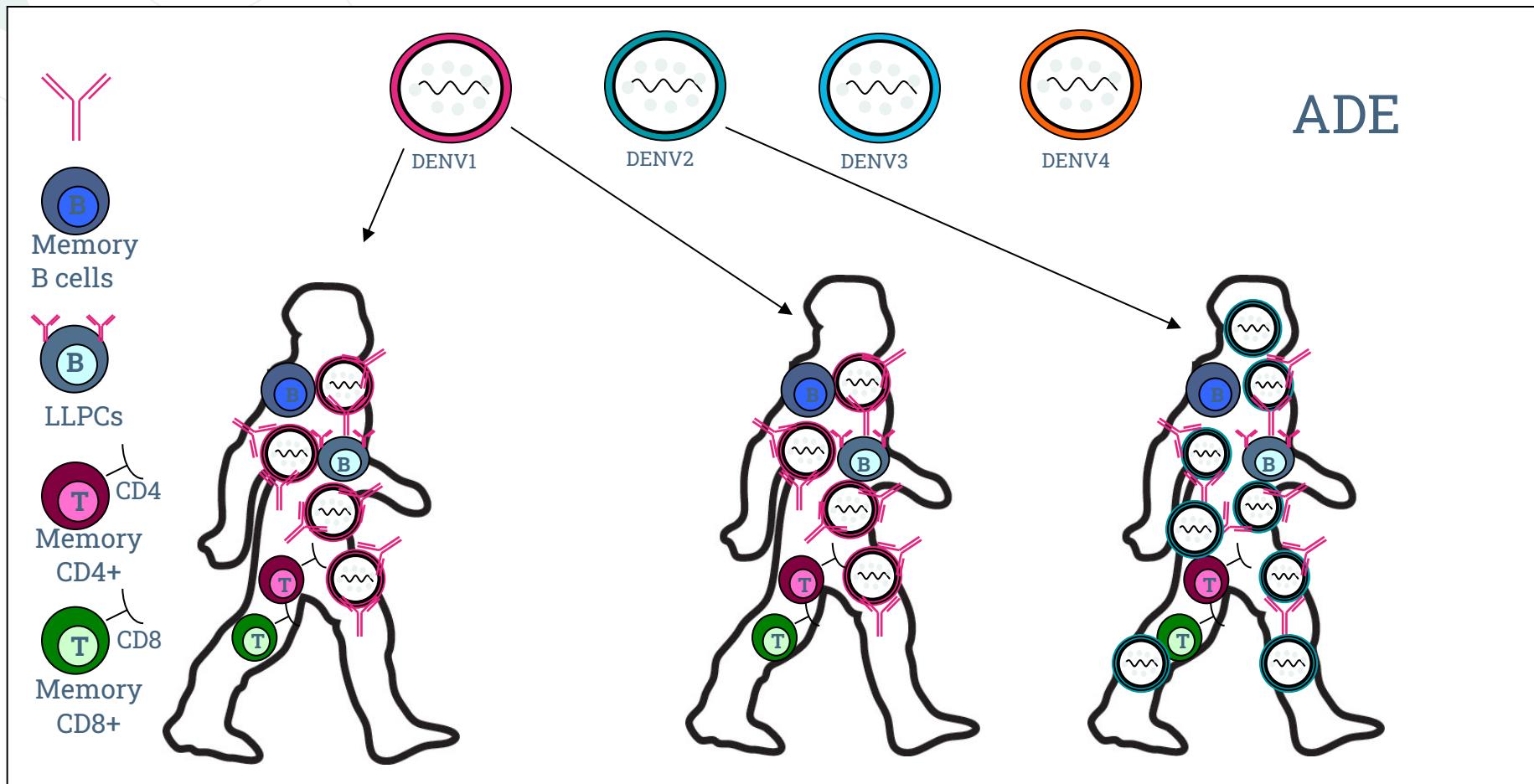


DHF/DSS

Increased fluid leakage
Low platelet count
Hemorrhagic manifestations
Increased cytokines
Shock from low blood volume



Sequential infection with different dengue serotypes can give rise to severe disease

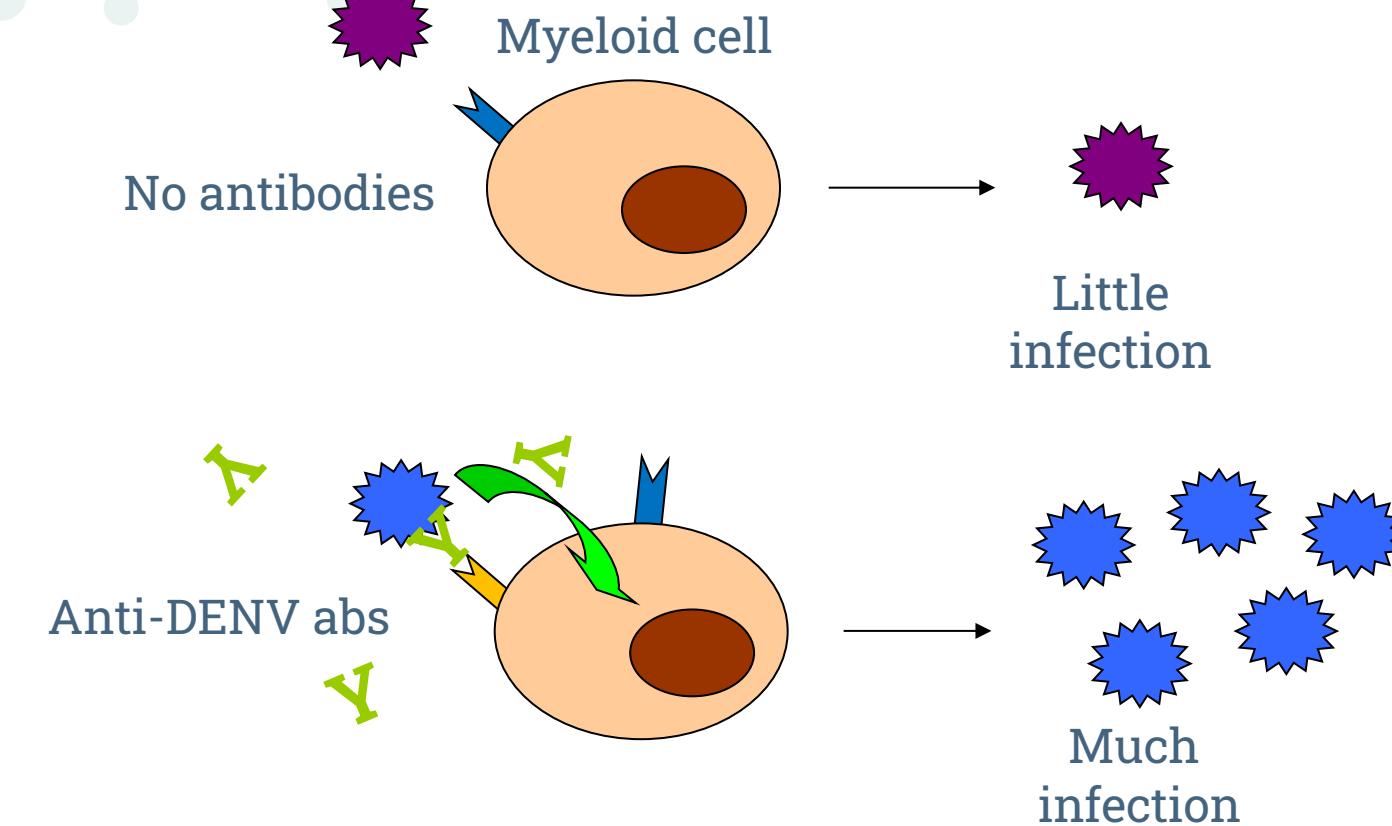


Primary Infection
Asymptomatic infection OR mild disease

Secondary Infection
Increased risk of severe dengue (DHF/DSS) disease

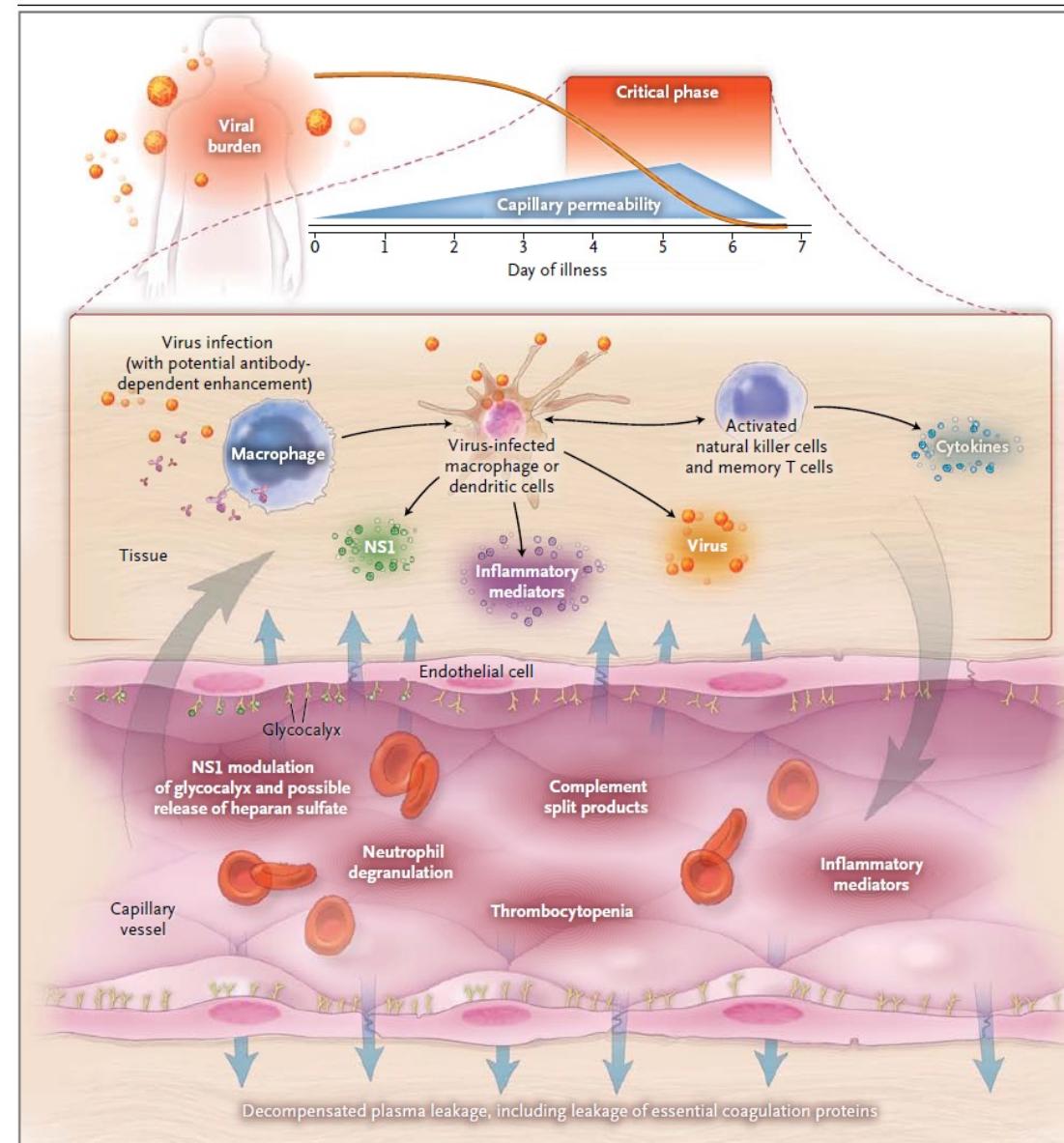
Courtesy of Dr. Eva Harris

Antibody-dependent enhancement (ADE)



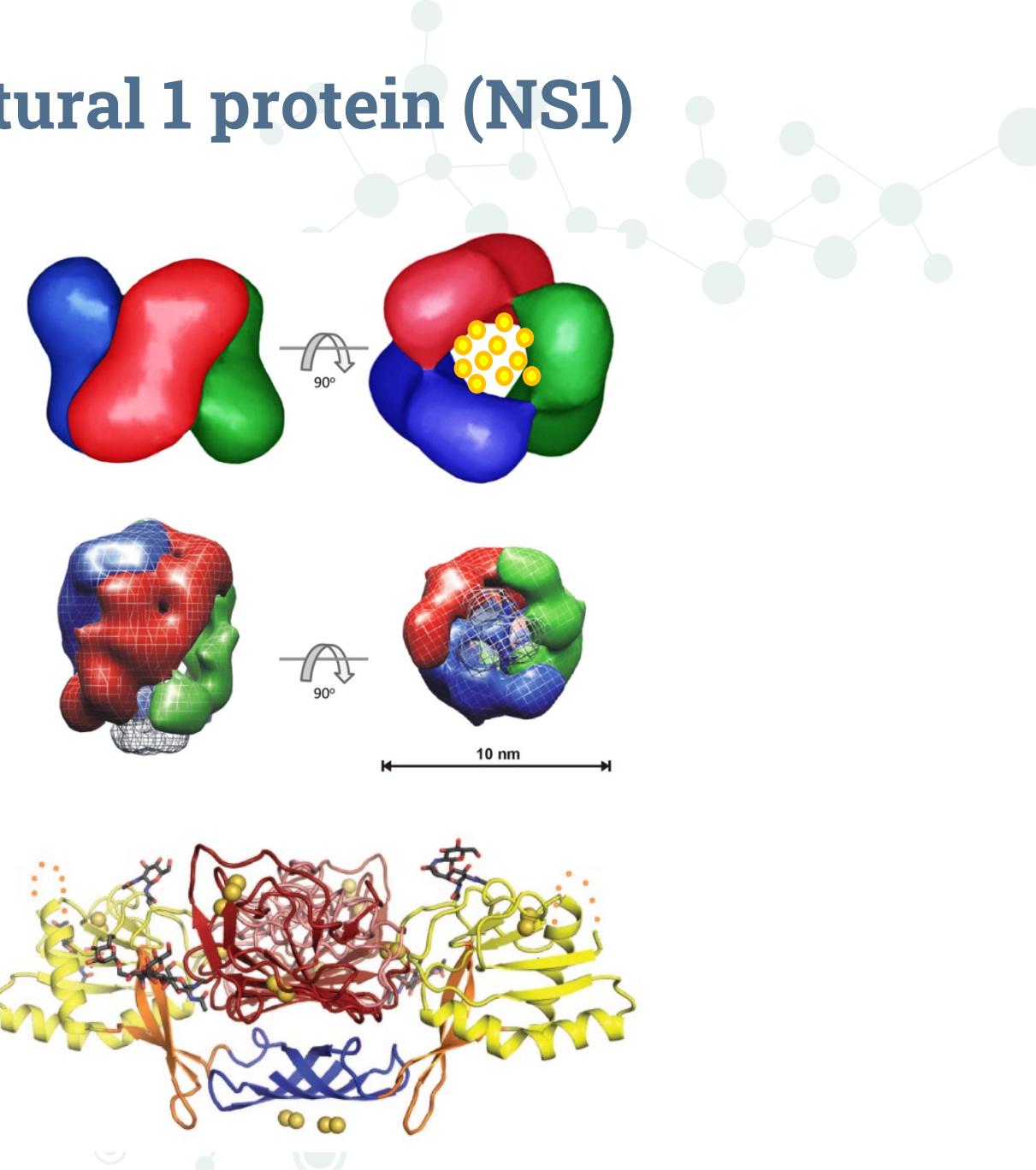
Courtesy of Dr. Eva Harris

Dengue immunopathogenesis

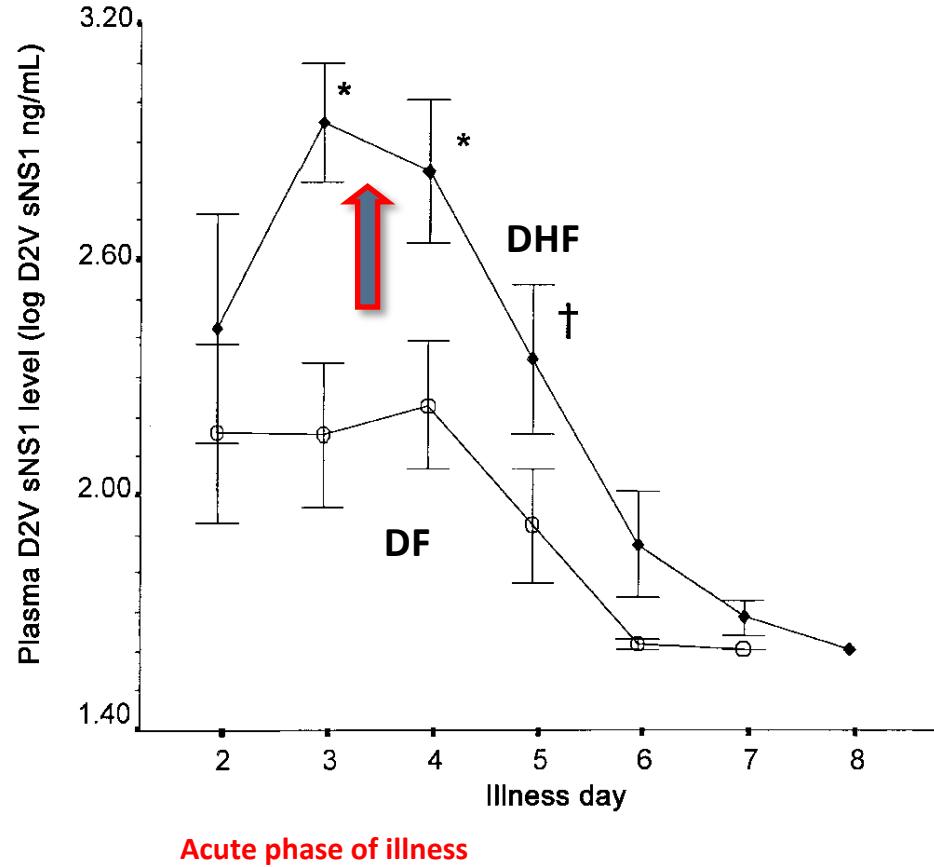


Dengue virus non-structural 1 protein (NS1)

- DENV NS1 is **secreted by infected cells**, found on the cell surface, and exists intracellularly in vesicles.
- NS1 can be in **monomeric (intracellular)**, **dimeric (intracellularly and cell surface)** or **hexameric (secreted) forms as a lipoparticle (lipid cargo)**.
- NS1 plays a **role in viral replication** and in **immune evasion (particularly in relation to complement pathways)** and is implicated in pathogenesis via activation of complement.

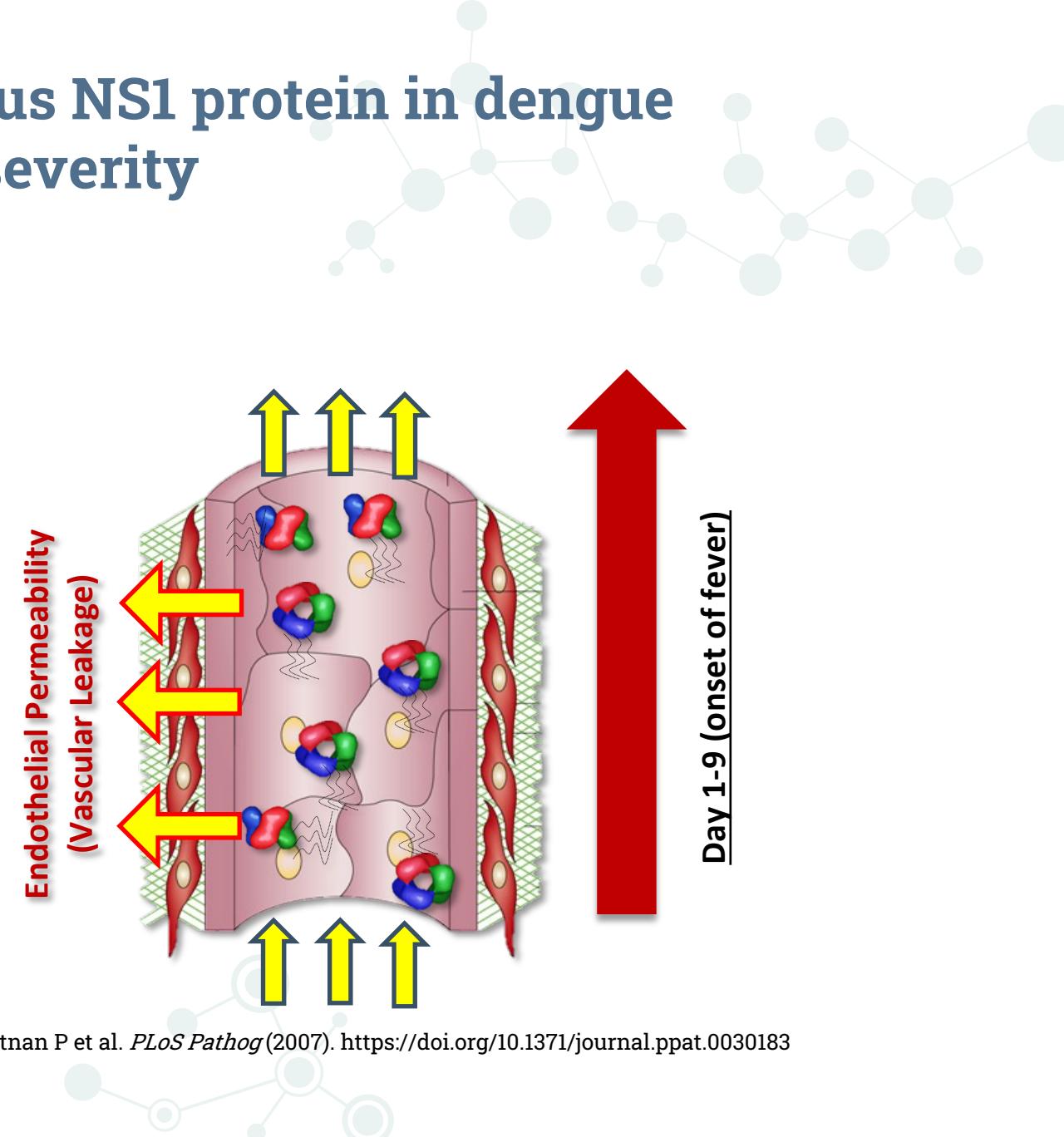


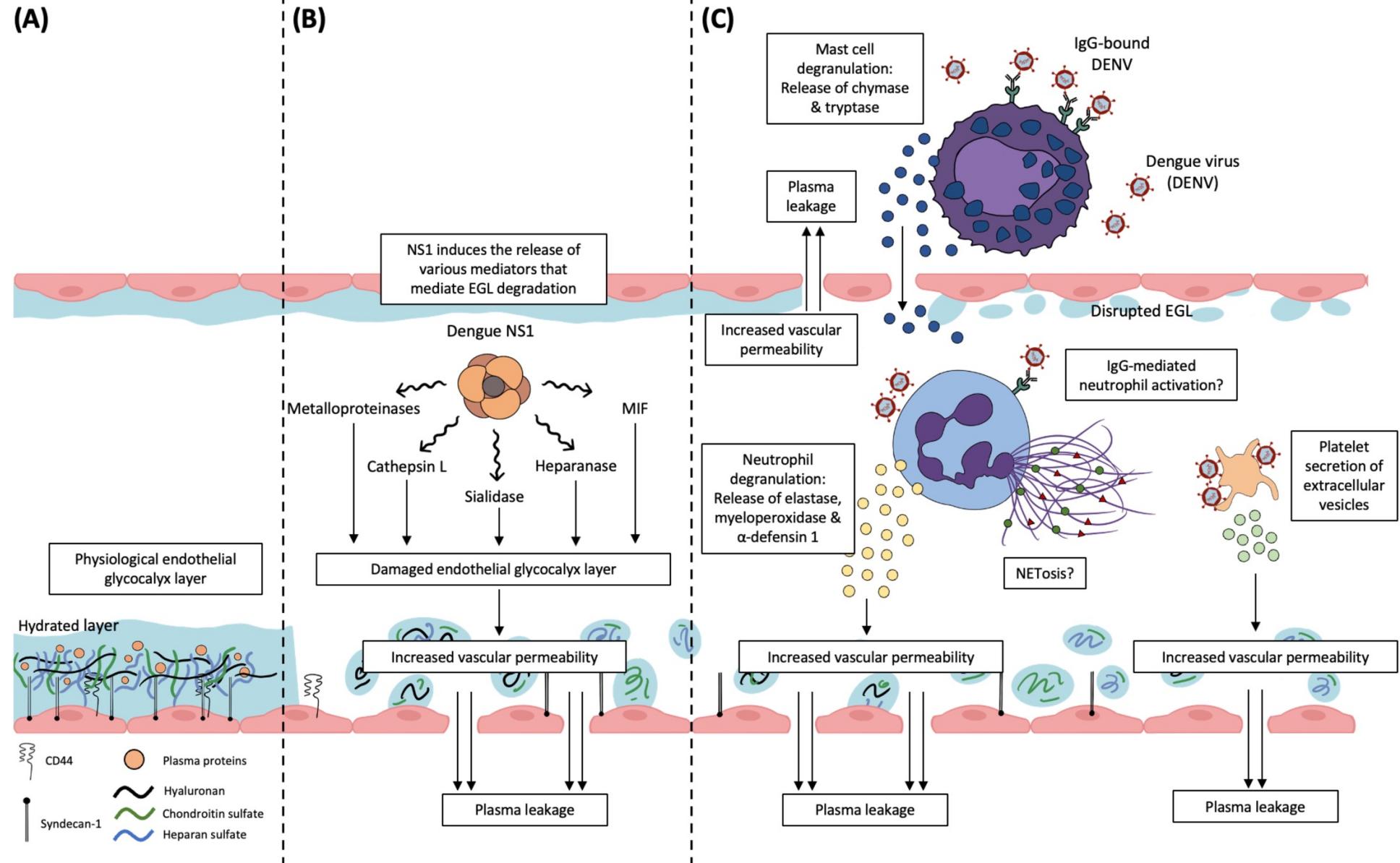
Circulating levels of dengue virus NS1 protein in dengue illness correlates with disease severity



Libratty DH et al. *J Infect Dis* (2002). <https://doi.org/10.1086/343813>

Avirutnan P et al. *PLoS Pathog* (2007). <https://doi.org/10.1371/journal.ppat.0030183>







What is viral pathogenesis?

The process by which viruses infect and cause disease in a host



Direct virus killing

- Cytotoxic effects
- Induction of cell death
- Lysis during viral release



Immunopathology

- Overreaction or inappropriate immune responses
- Cytokines, complement, antibodies, T-cells, etc.

**Host and environmental factors play a contributing role as well*



What is viral pathogenesis?

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Viral toxins

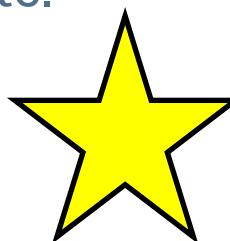
- Secreted or shed viral proteins that directly damage host cells or trigger immunopathology



Immunopathology

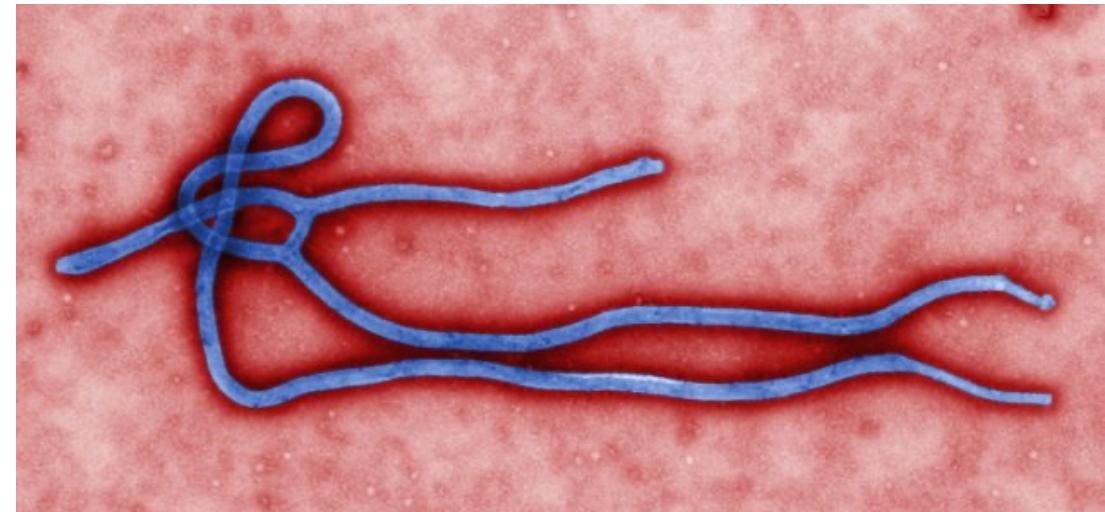
- Overreaction or inappropriate immune responses
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Ebola virus

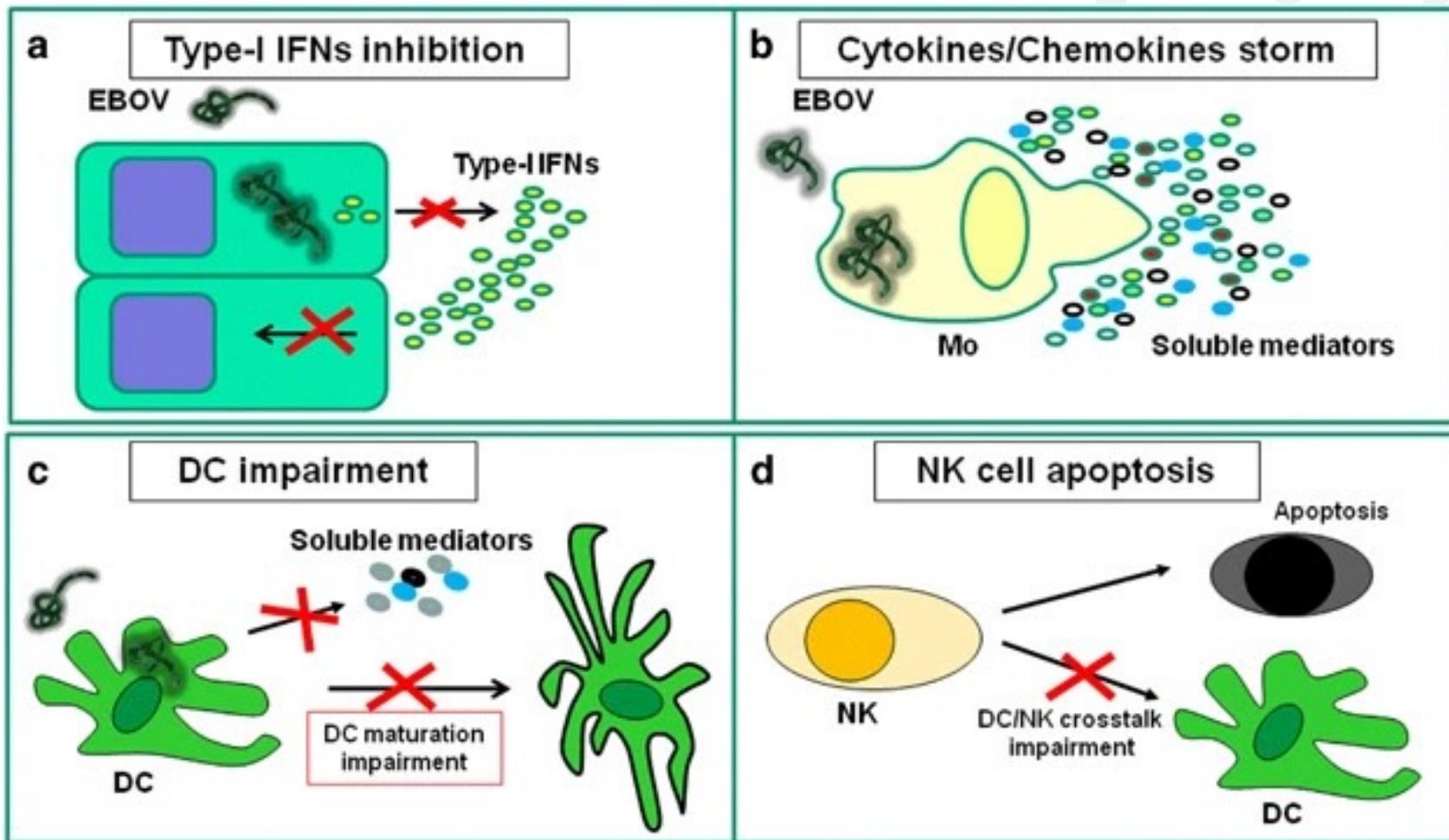
- Family: Filoviridae
- Is transmitted to people from wild animals and can spread human-to-human
- The average fatality rate is around 50% (ranges from 25% to 90%)
- Sporadic outbreaks occur but do not last long



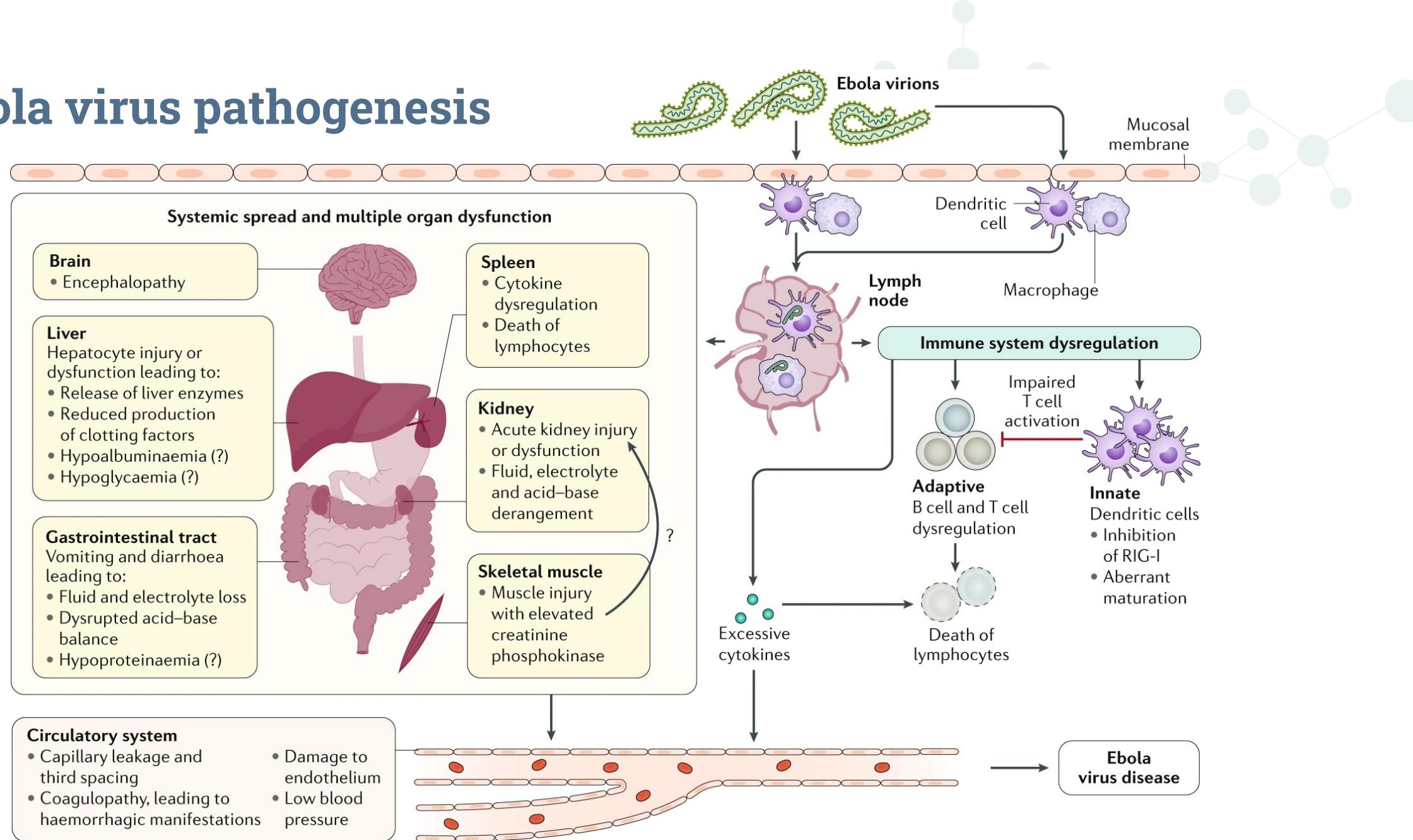
CDC.gov



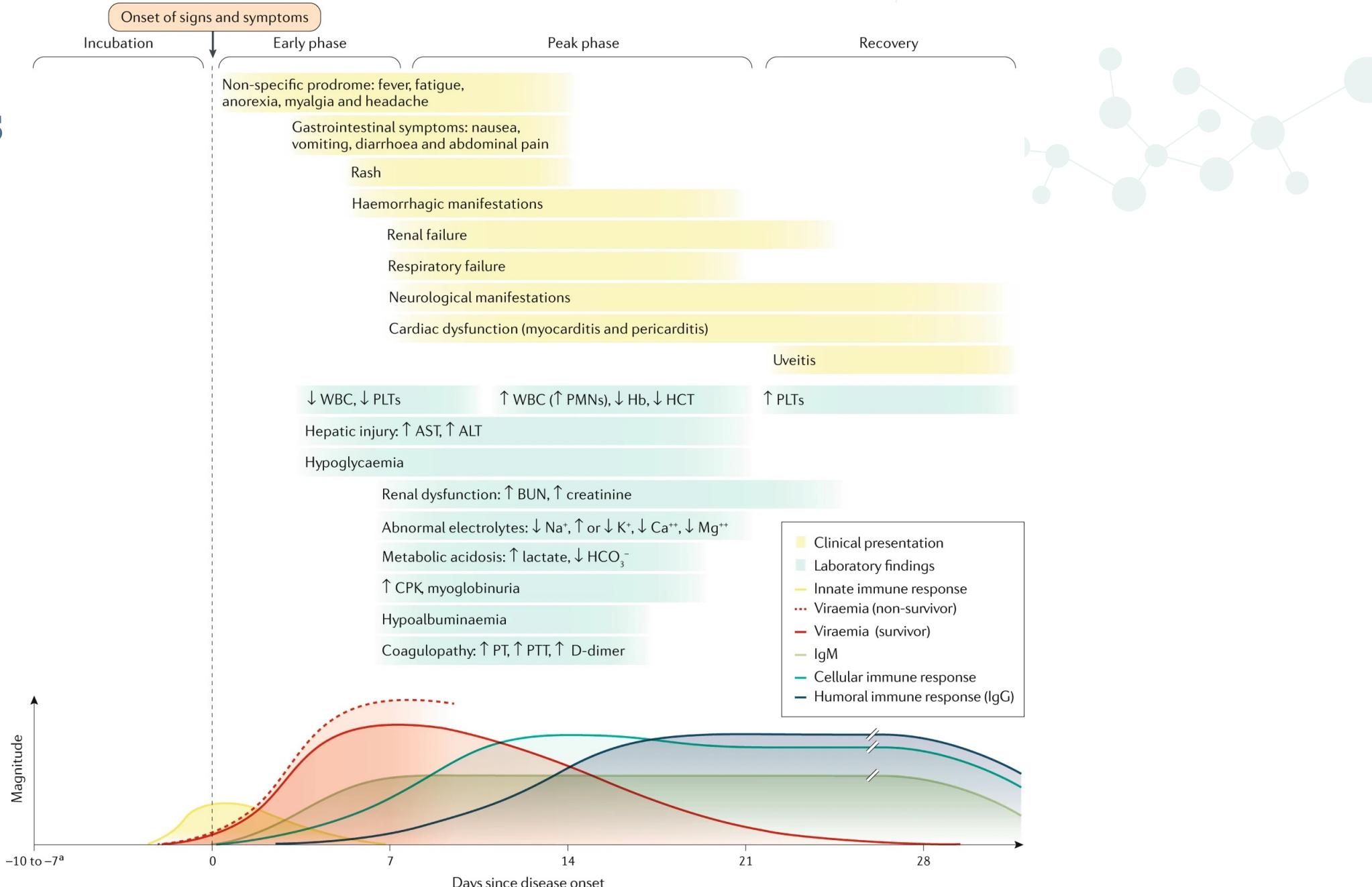
Ebola virus pathogenesis



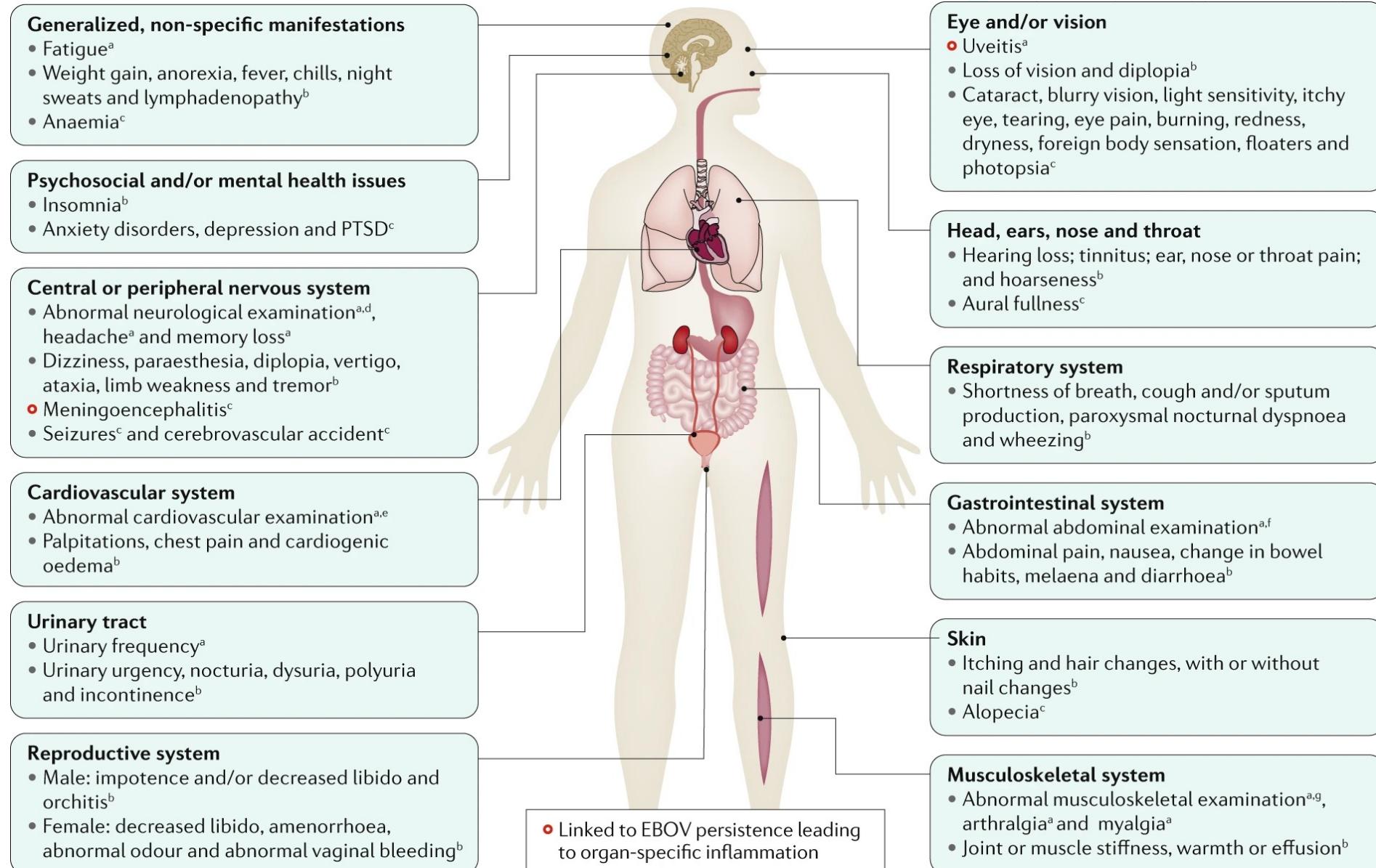
Ebola virus pathogenesis



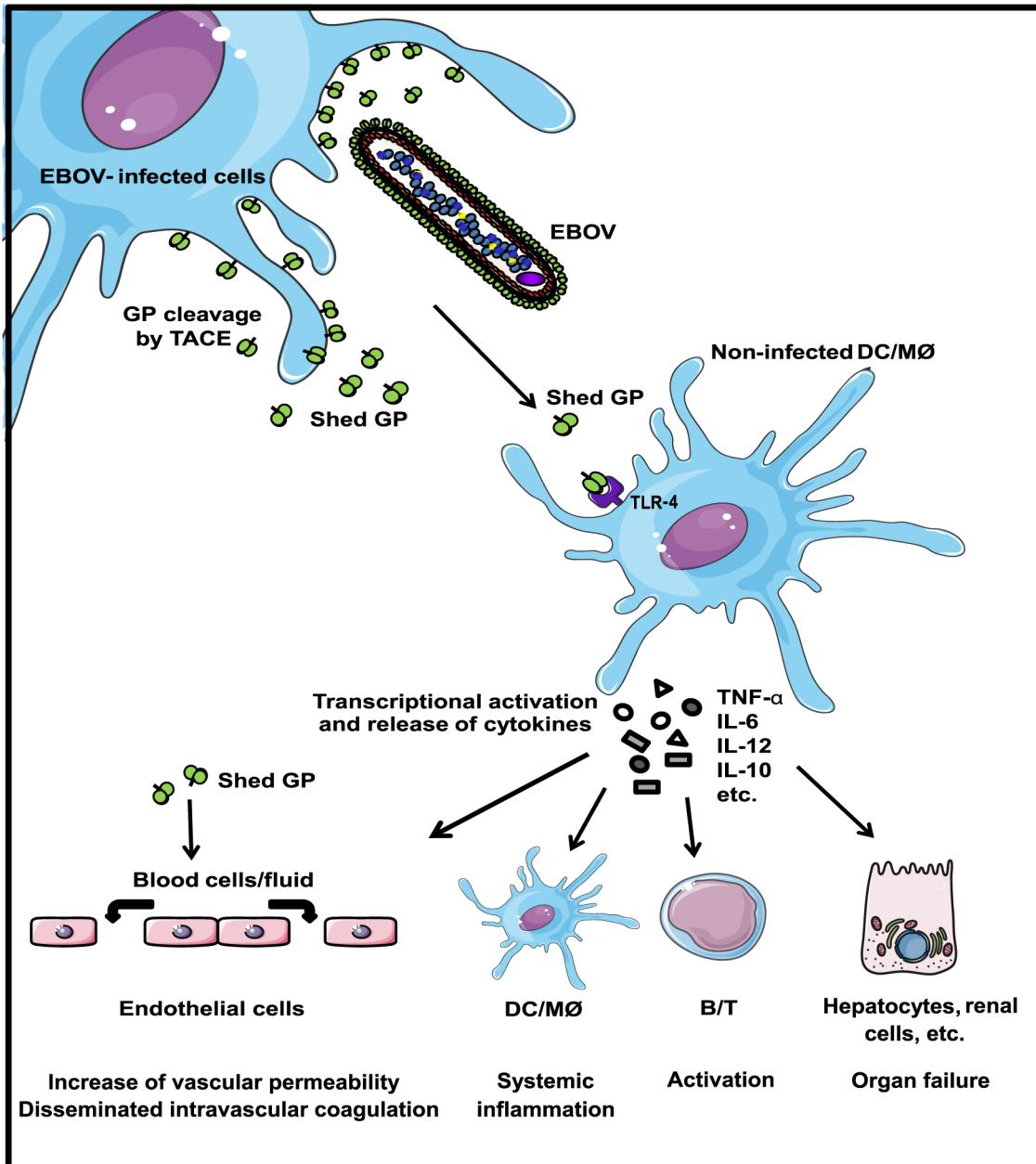
Kinetics of Ebola virus disease

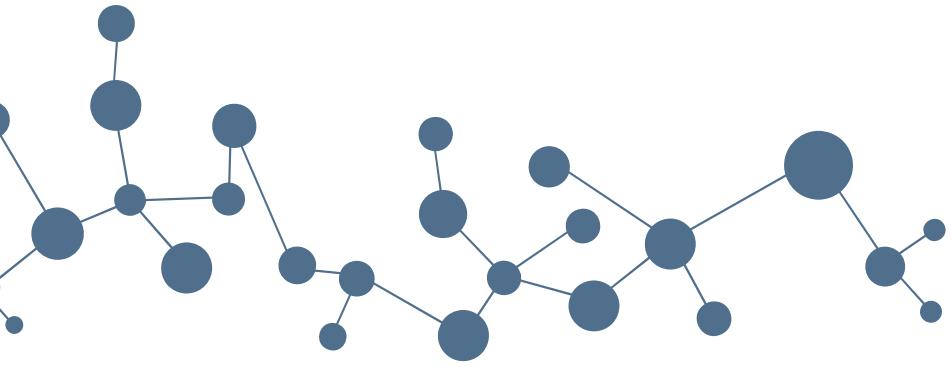


Sequelae of Ebola virus disease

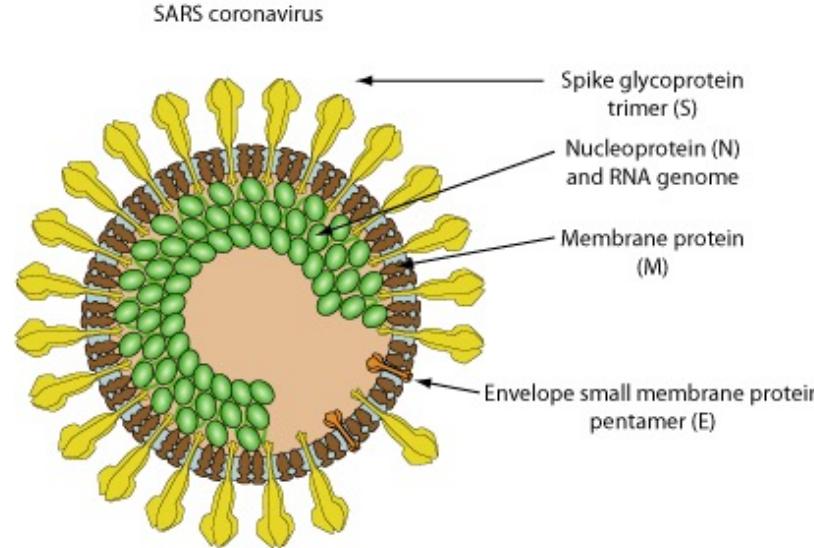


Ebola virus shed glycoprotein is a viral toxin

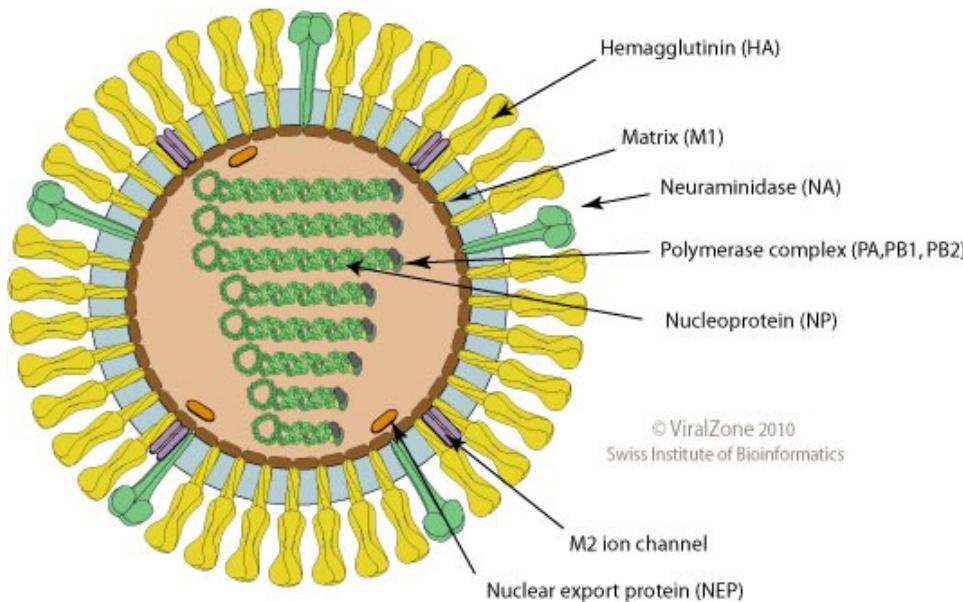




Respiratory viruses



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SIB Swiss Institute of Bioinformatics

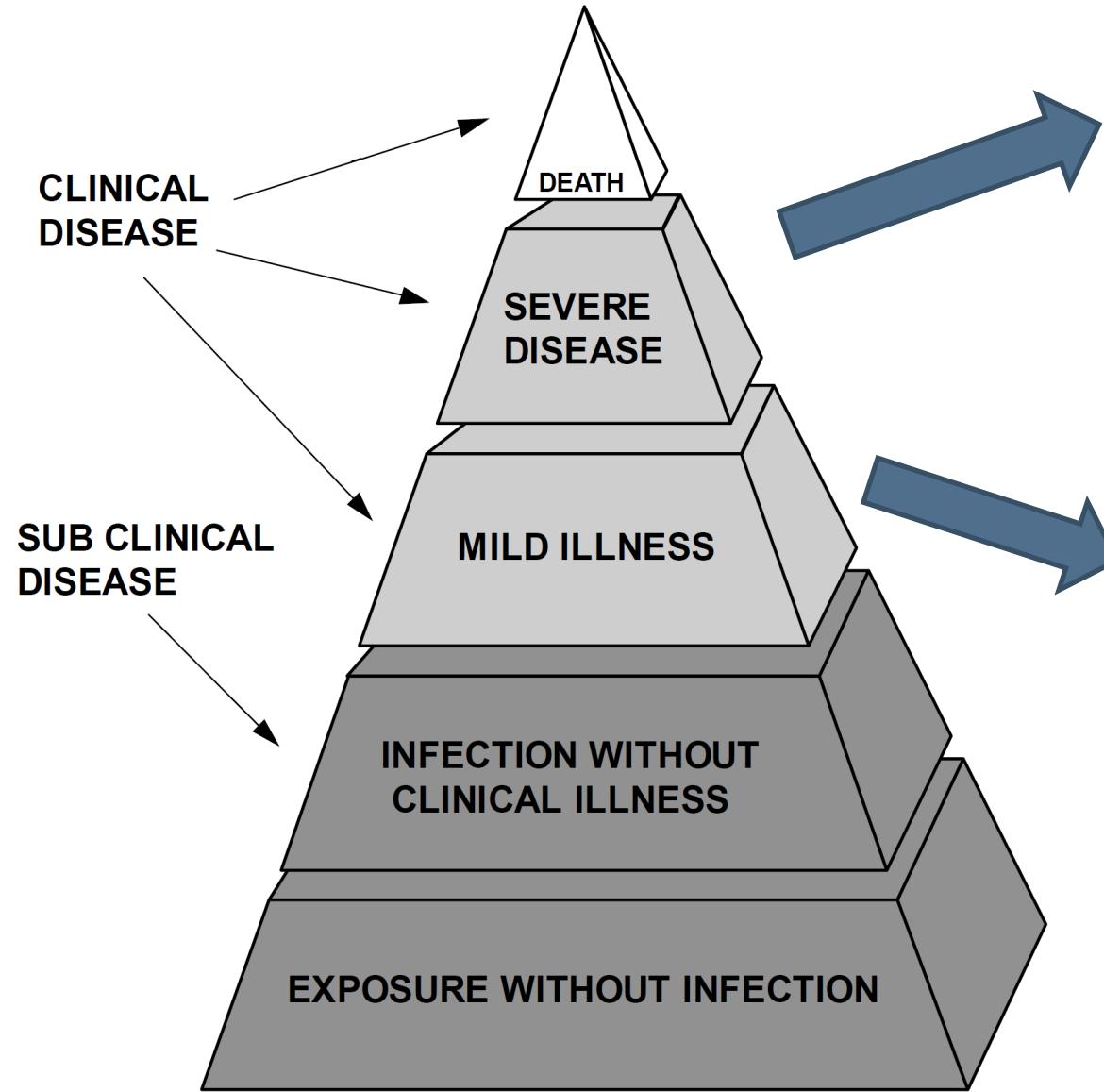


<https://viralzone.expasy.org/>

Emerging respiratory viruses

- Coronaviridae
 - SARS-CoV-1
 - SARS-CoV-2
 - MERS-CoV
- Orthomyxoviridae
 - H1N1
 - H5N1
 - H7N9

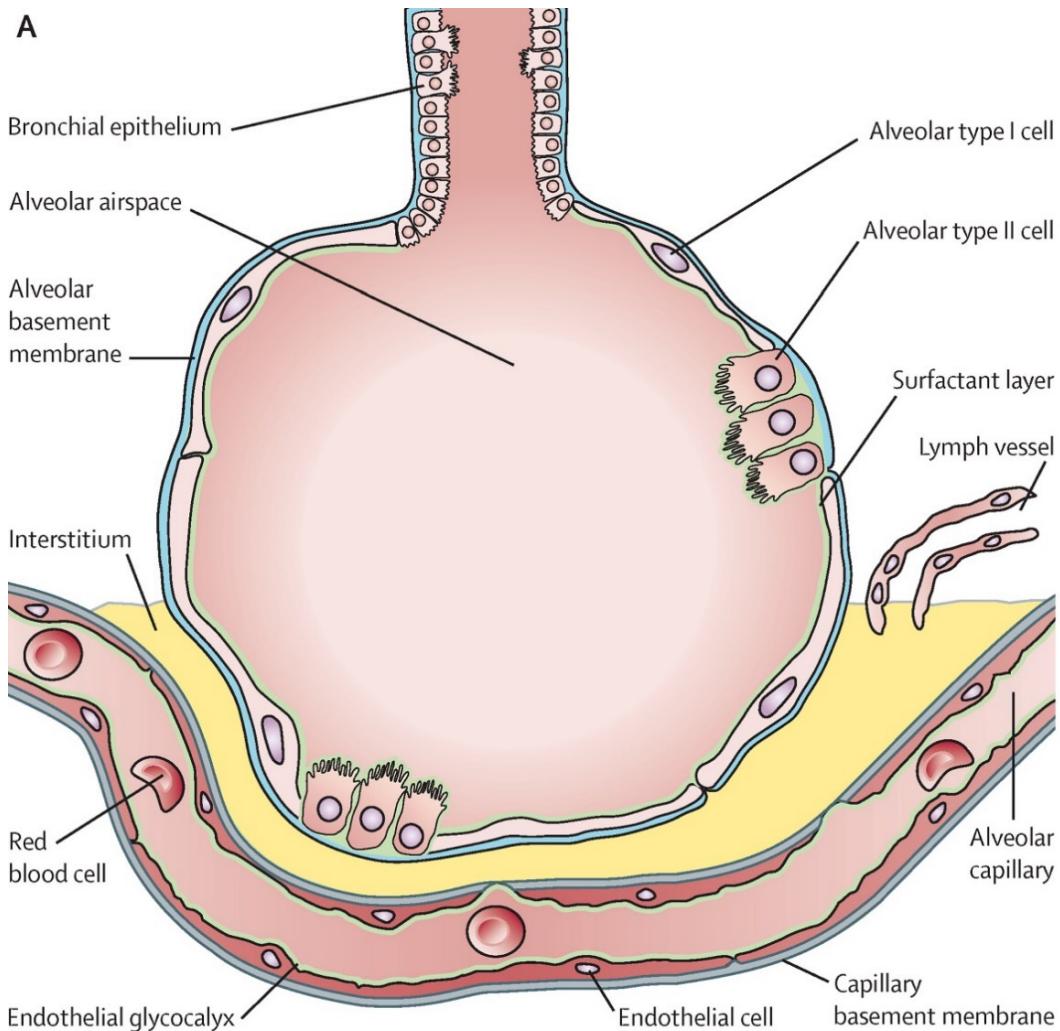
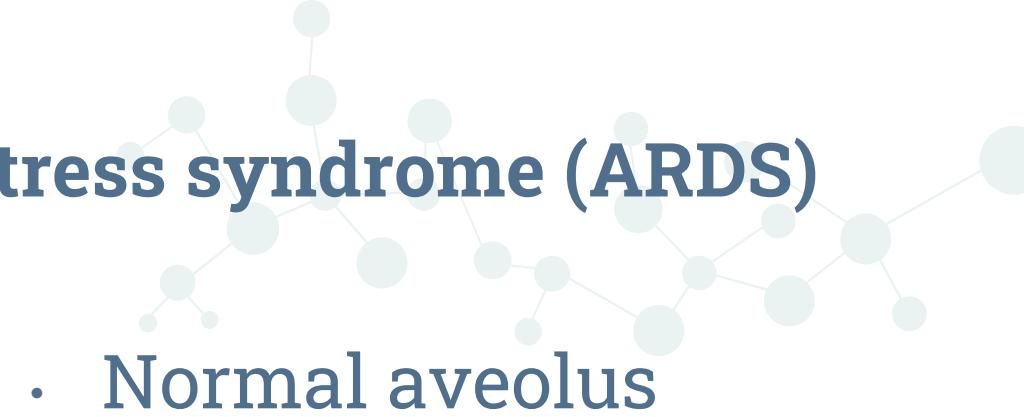
Respiratory disease



- Acute respiratory distress syndrome (ARDS)
 - Severe shortness of breath
 - Labored, unusually rapid breathing
 - Low blood pressure
 - Confusion and extreme tiredness

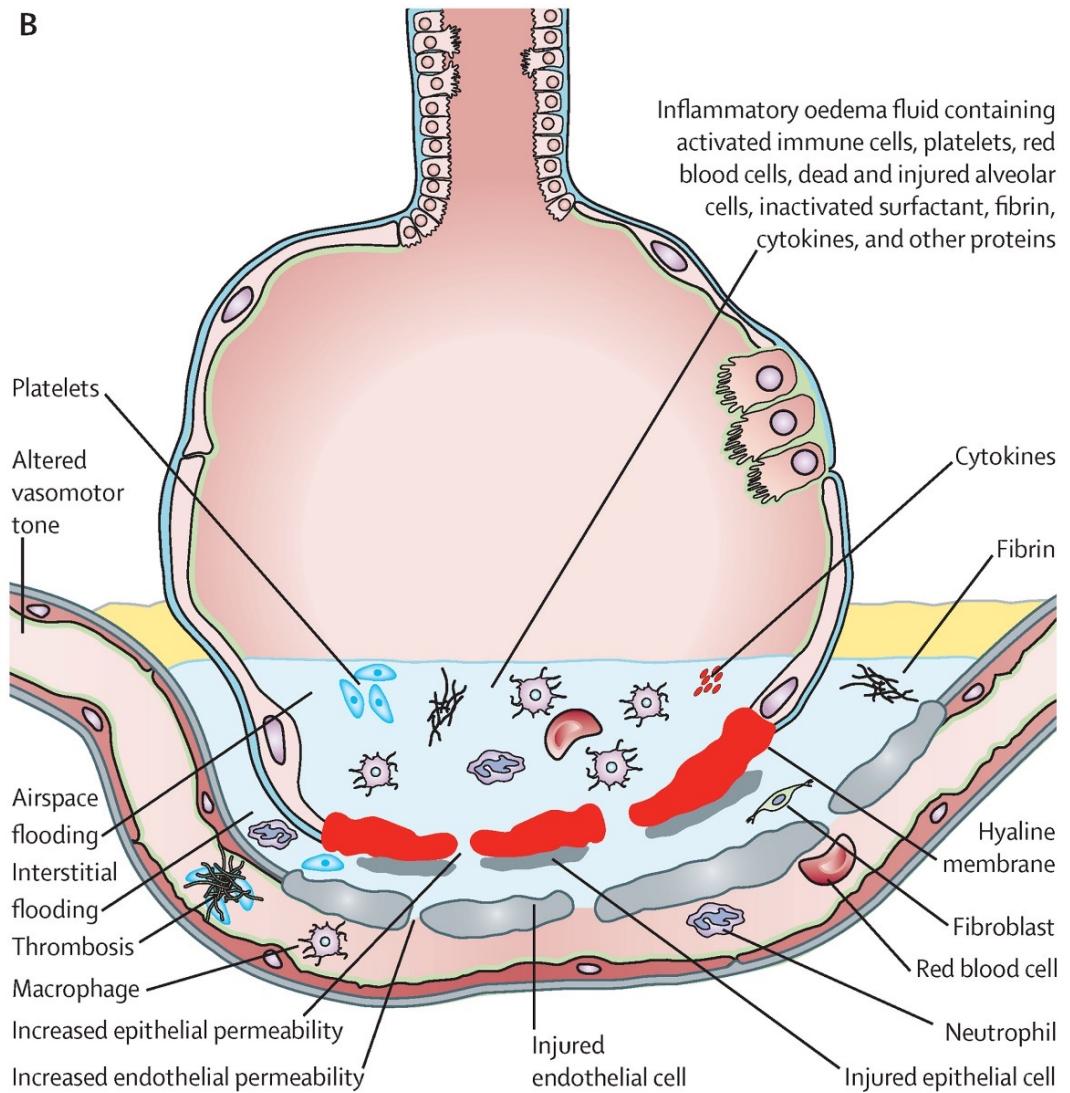
- Cough
- Fever
- Sneezing
- Runny nose
- Fatigue
- Sore throat
- Lymphadenopathy

Acute respiratory distress syndrome (ARDS)



Acute respiratory distress syndrome (ARDS)

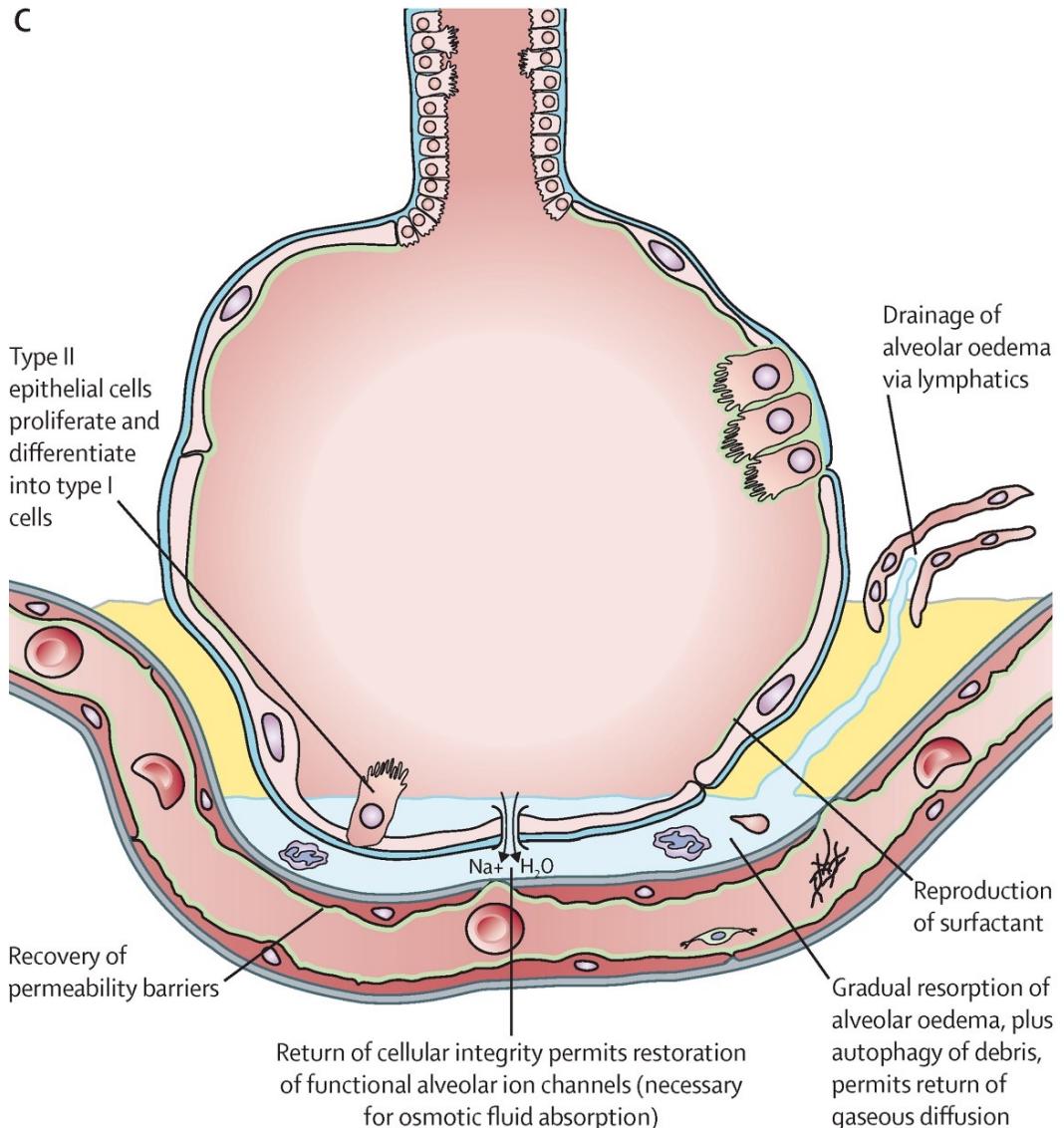
B



- Exudative phase
 - Immune cell-mediated destruction of alveolar barriers
 - Allows plasma, plasma proteins, and cellular content to flood the interstitium and airspace

Acute respiratory distress syndrome (ARDS)

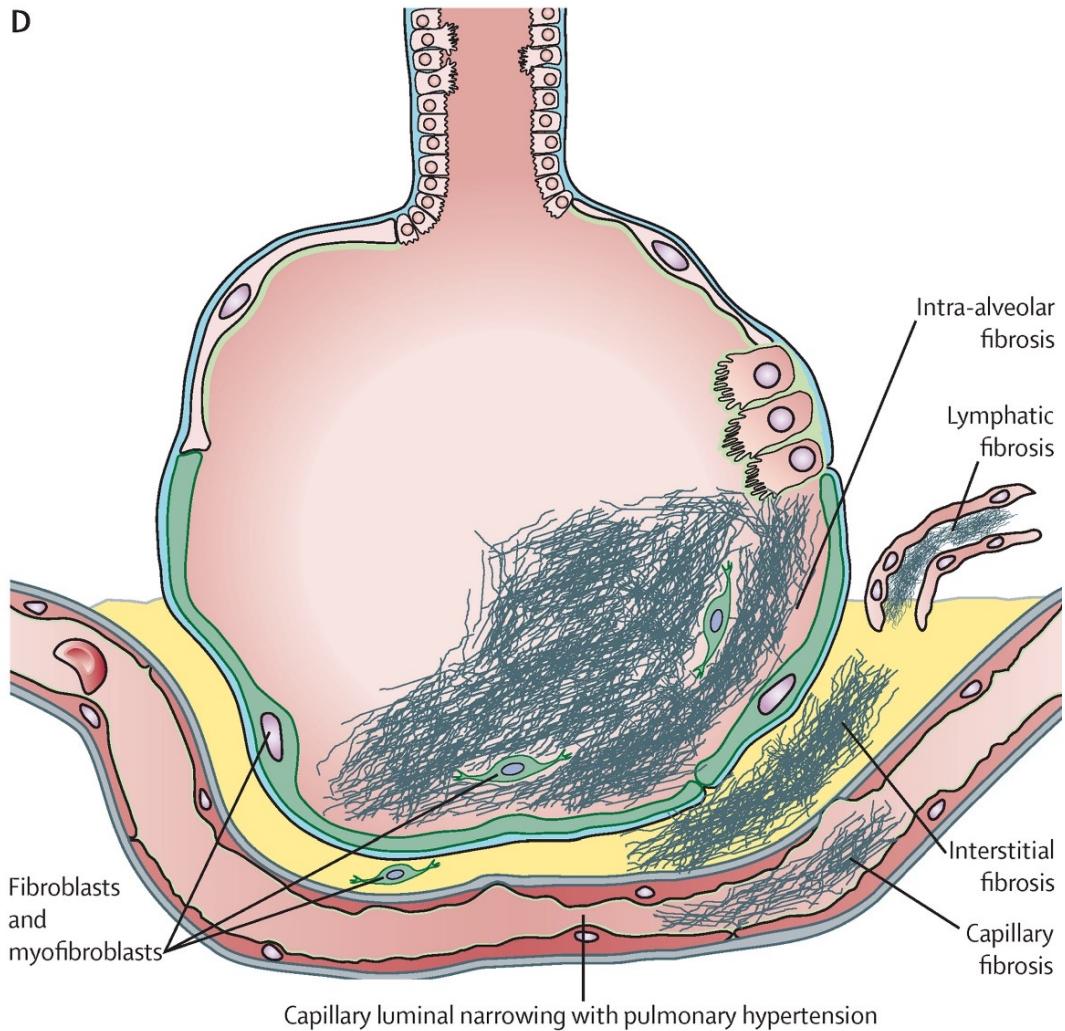
C



- Proliferative phase
 - Attempt at recovery
 - Restoration of cell populations and barrier function

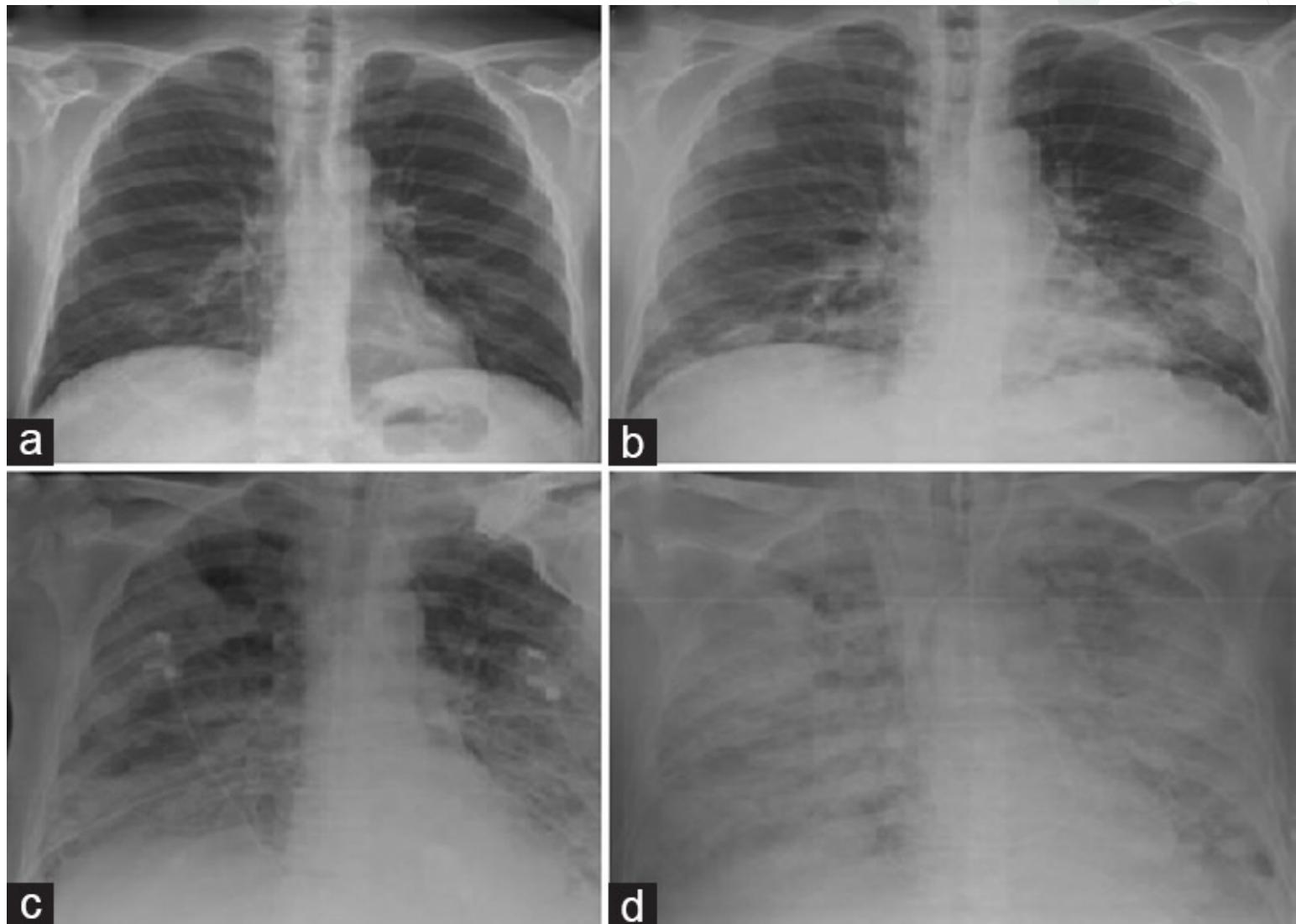
Acute respiratory distress syndrome (ARDS)

D



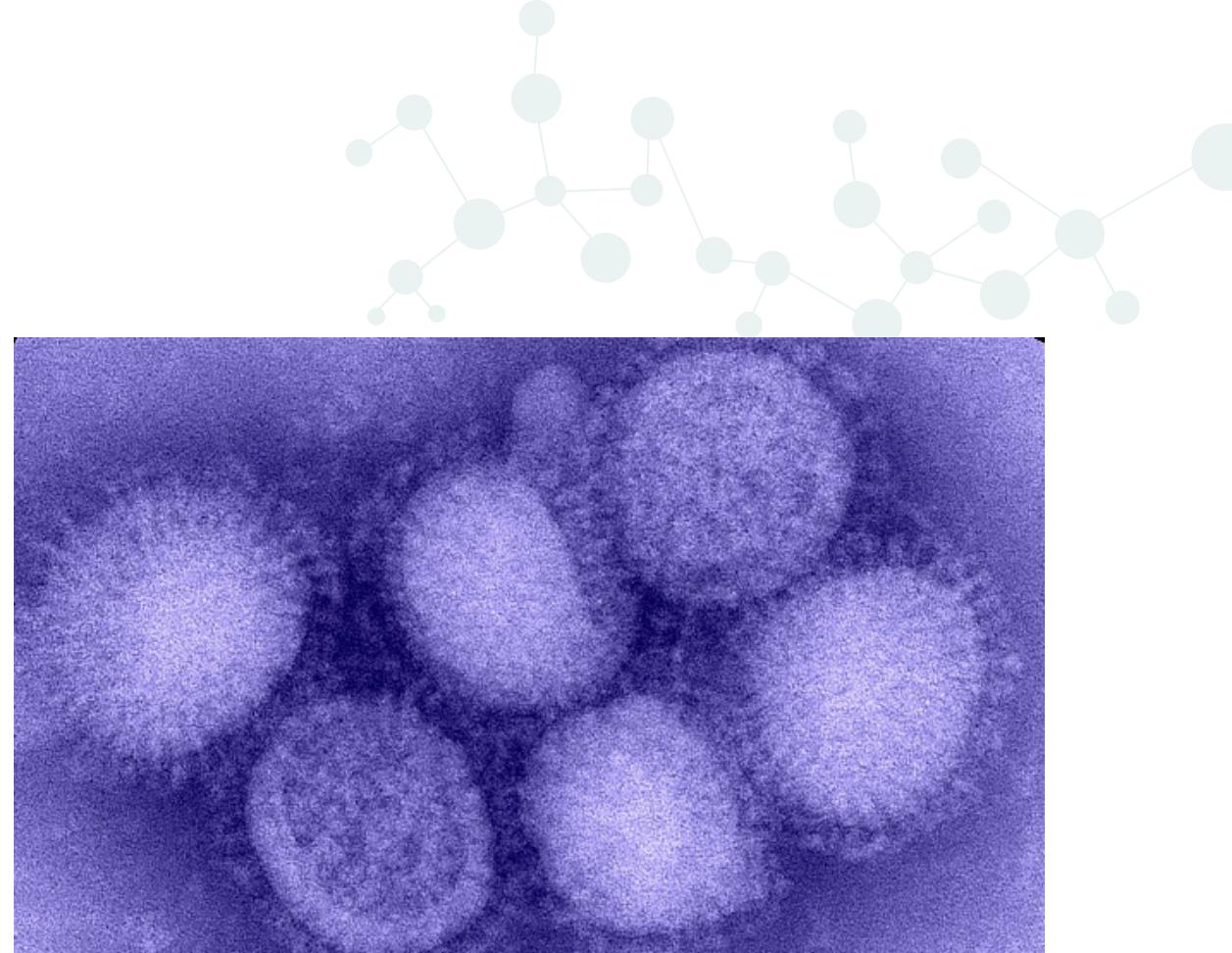
- Fibrotic phase
 - Failure of removal of alveolar collagen
 - Development of cystic changes
 - Limits functional recovery

Acute respiratory distress syndrome (ARDS)



Influenza virus

- Family: Orthomyxoviridae
- (-)ssRNA virus
- Segmented genome
- Transmitted person-to-person by respiratory droplets

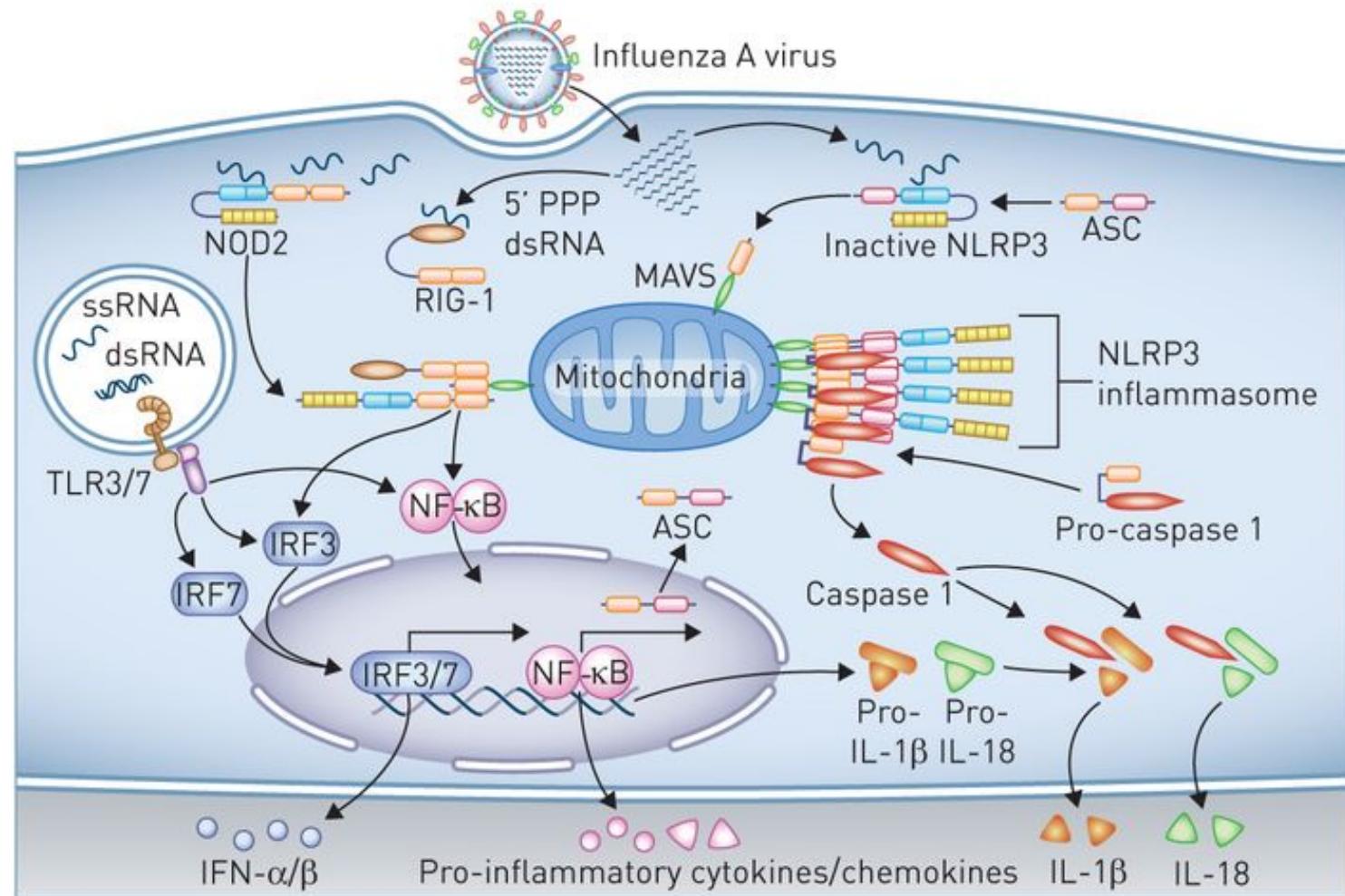


<https://www.cdc.gov/flu/pandemic-resources/index.htm>



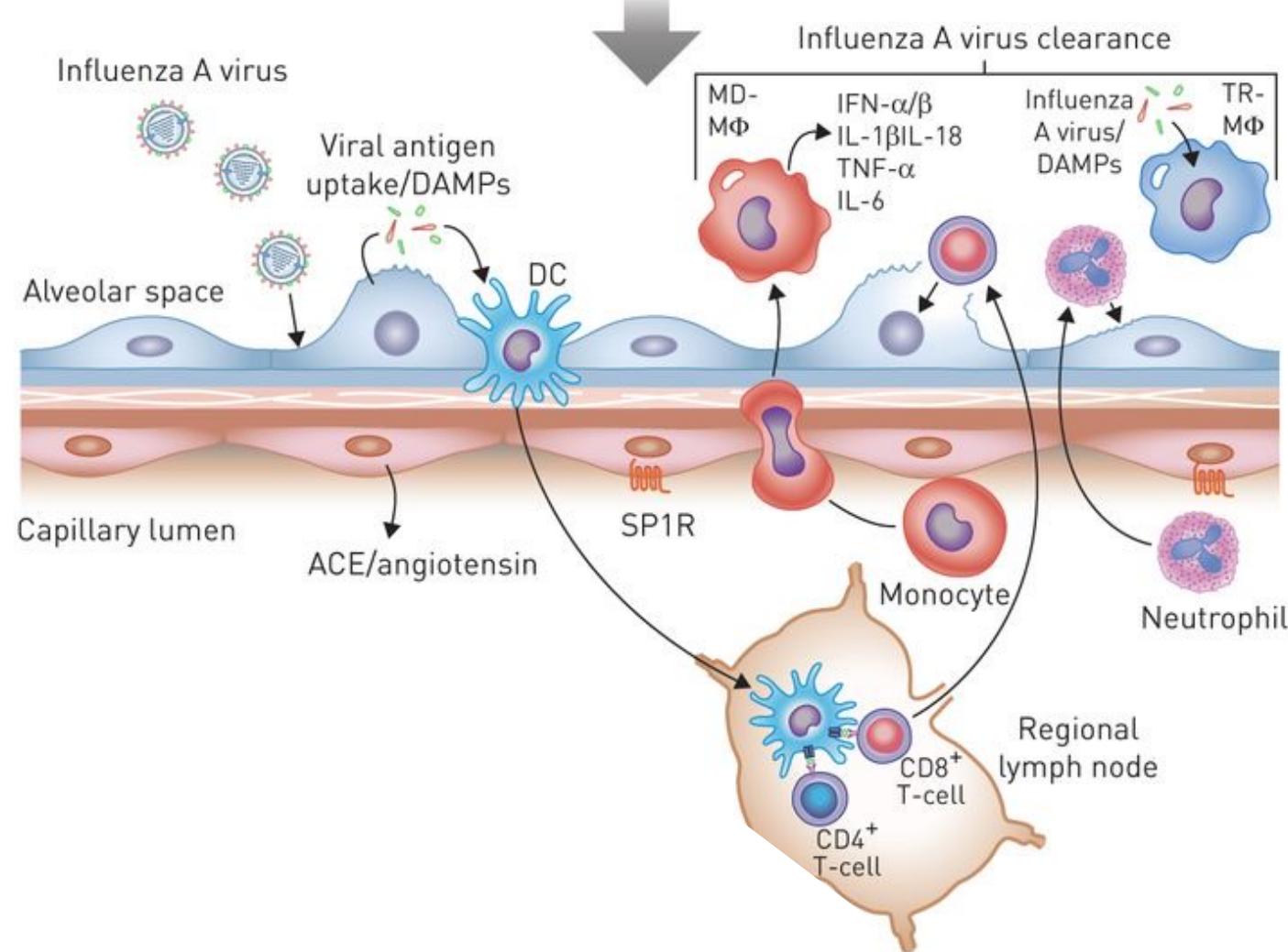
Influenza infection triggers the innate immune response

a)

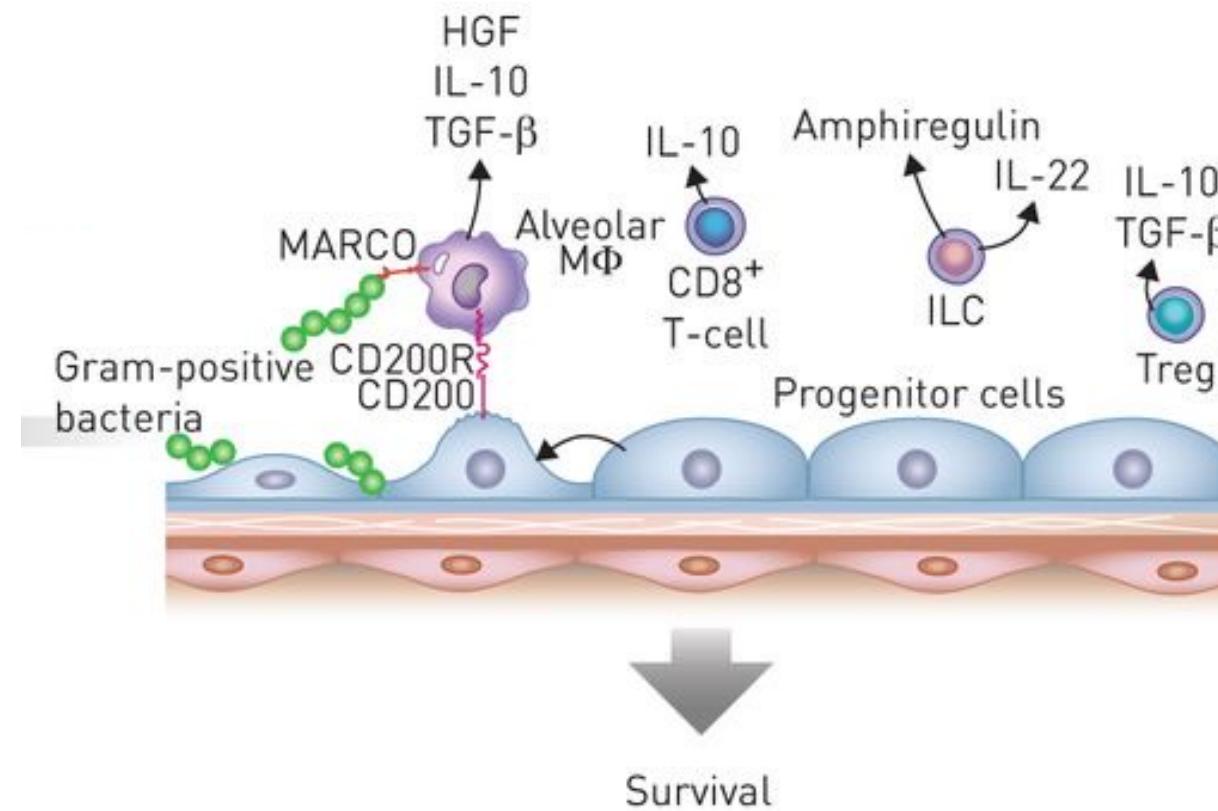


The adaptive immune response is activated and inflammation is amplified

b)

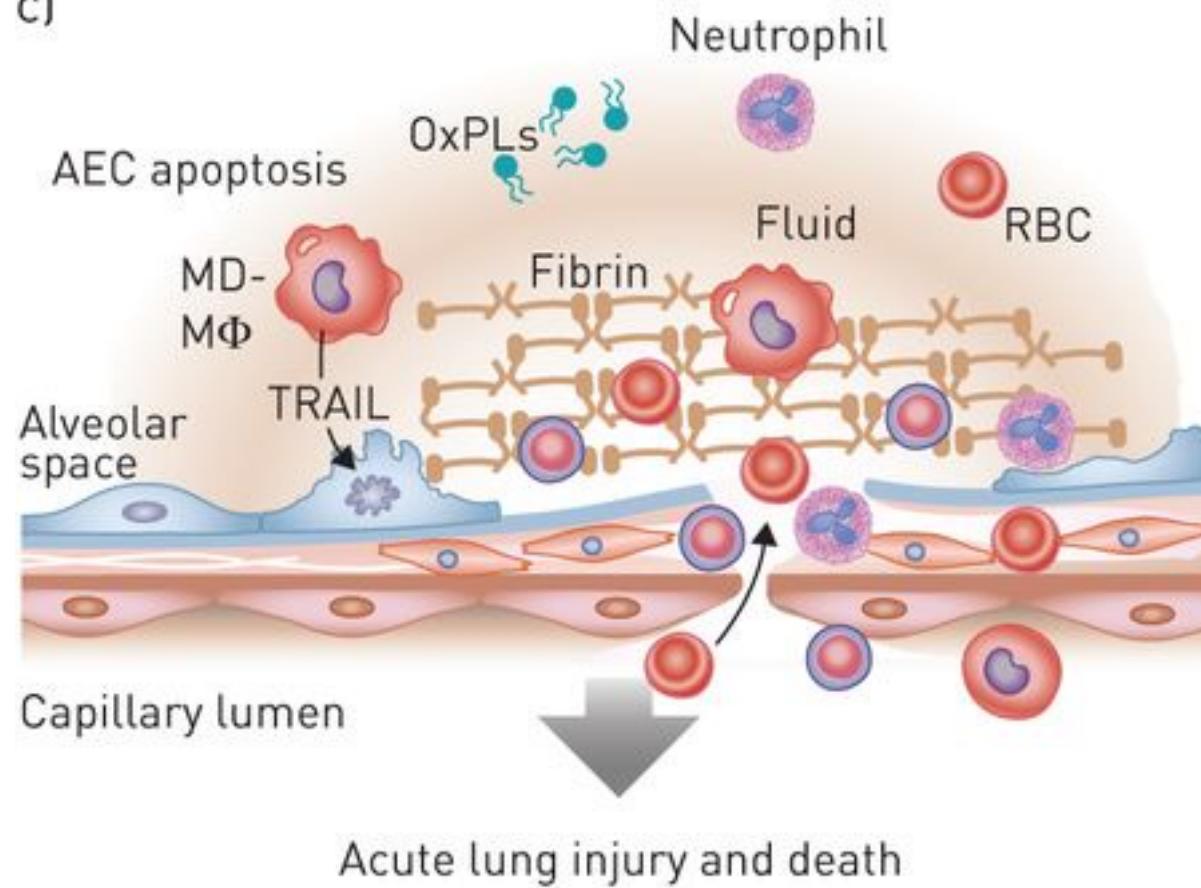


Regulation of inflammation leads to clearance of the virus, limited tissue damage, and host survival

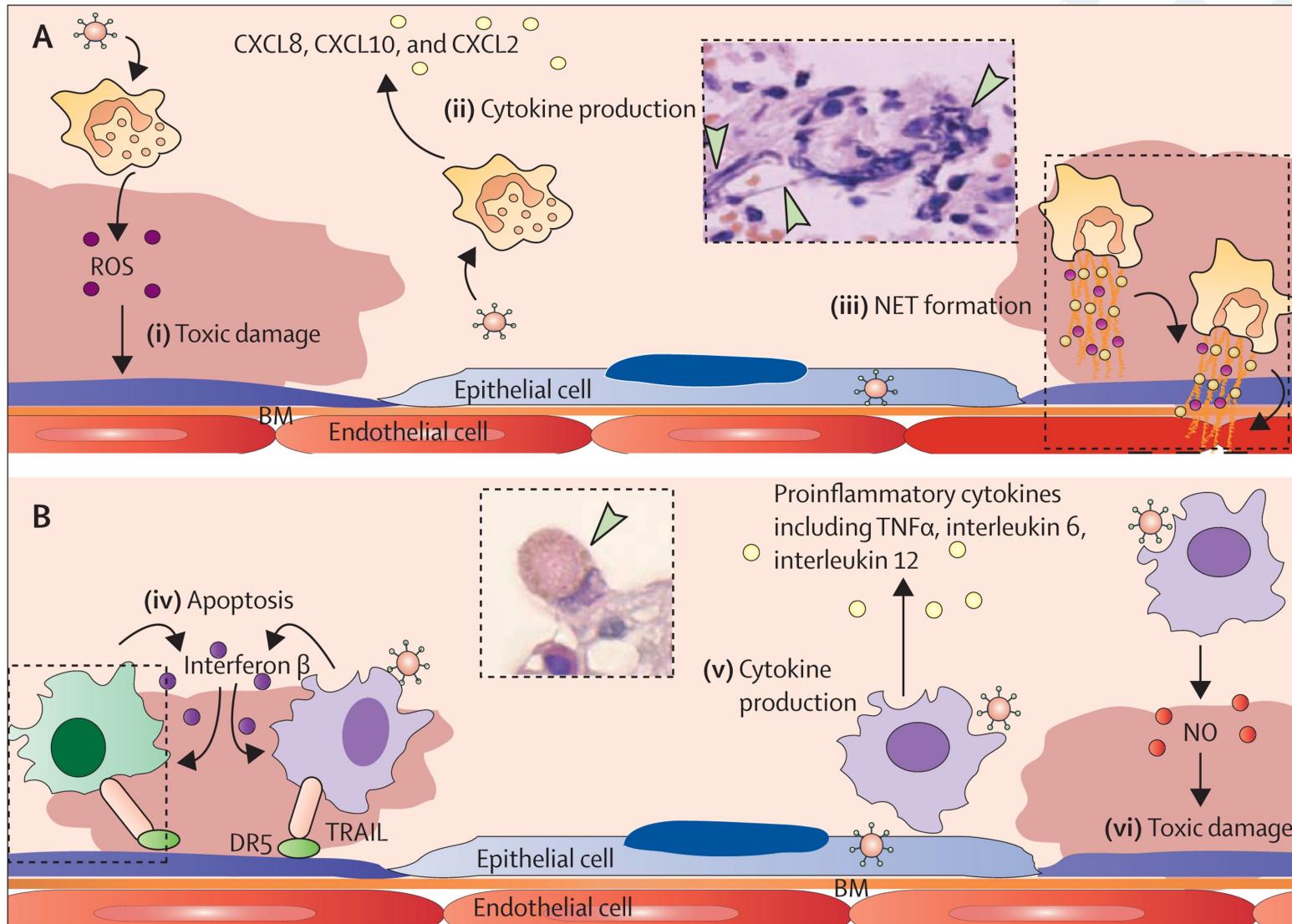


Dysregulated inflammation leads to lung injury and, potentially, death of the host

c)

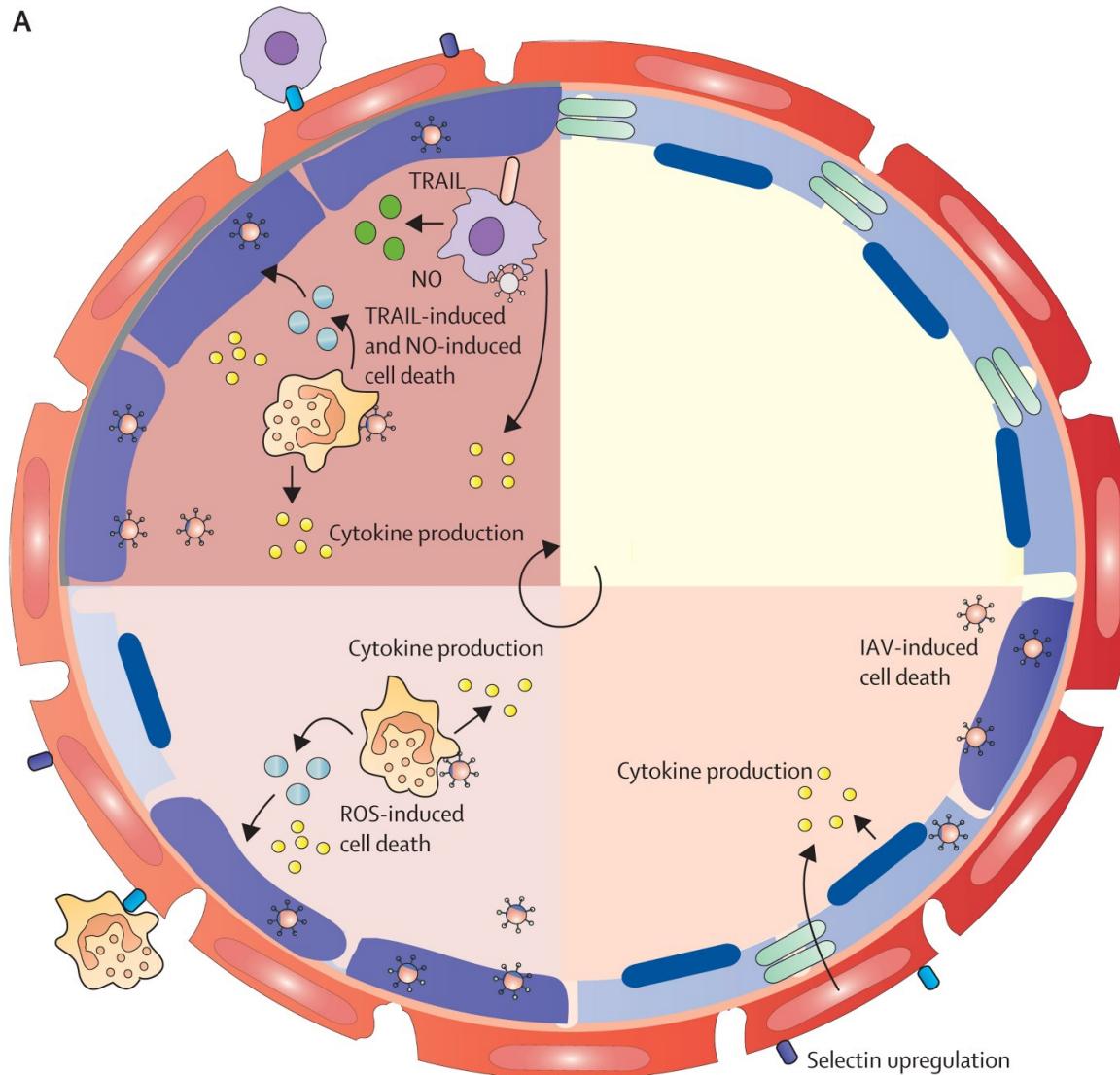


Neutrophils and macrophages play a key role in severe influenza pathogenesis

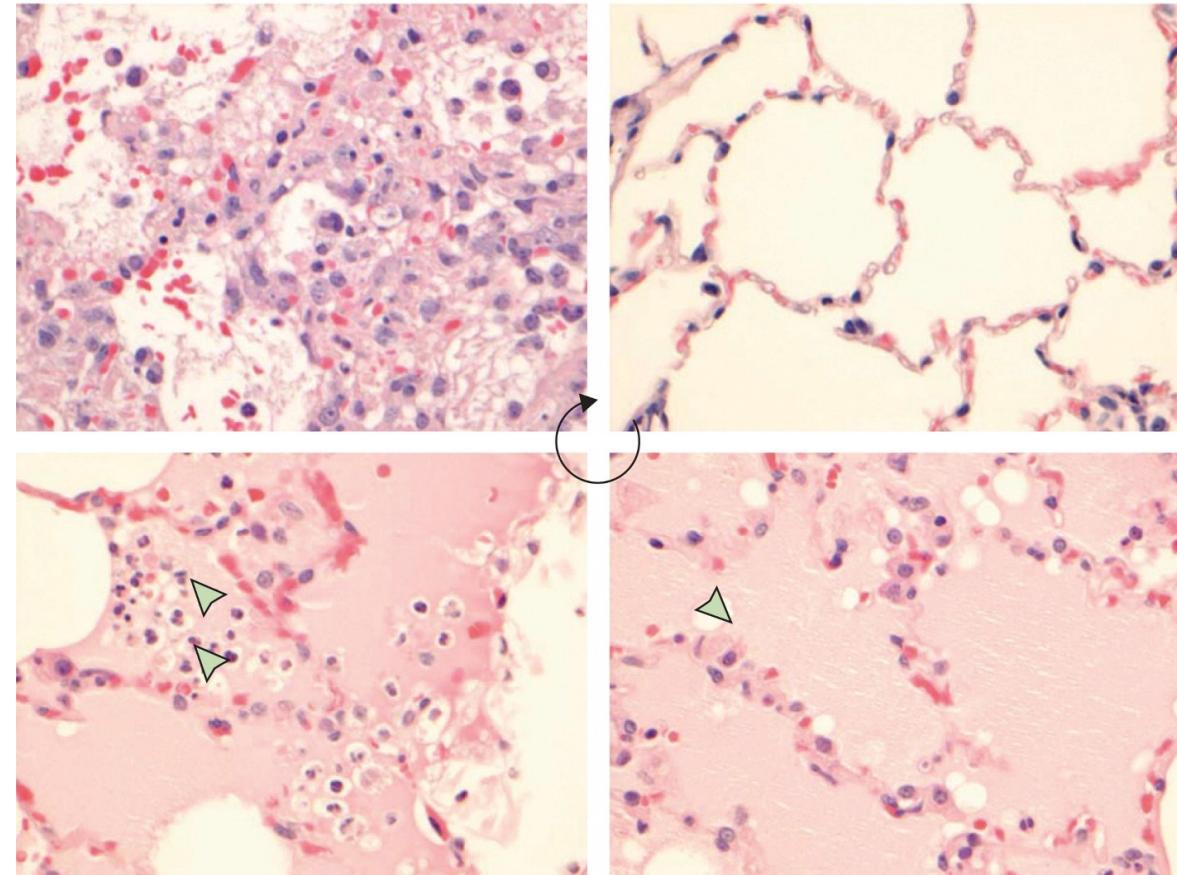


Influenza-induced ARDS

A

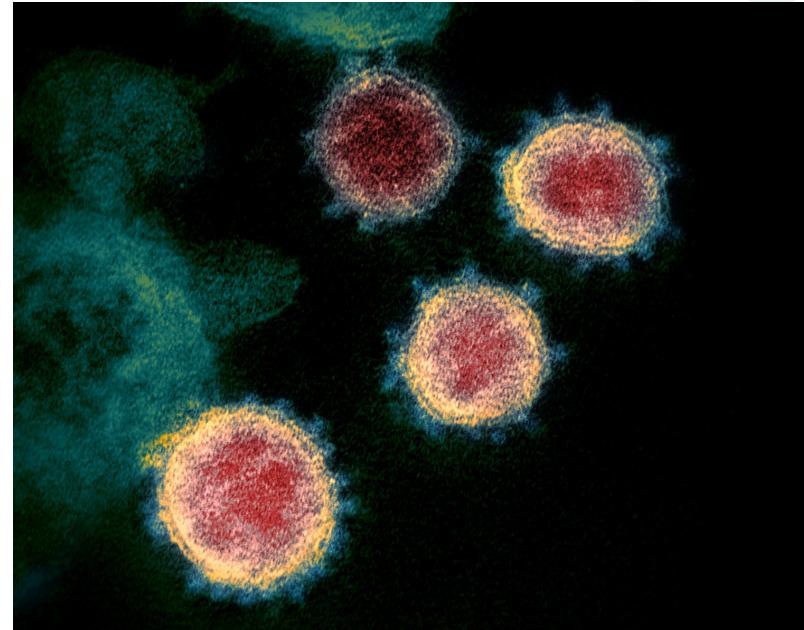


B



Severe acute respiratory syndrome coronavirus 2

- Family: Coronaviridae
- (+)ssRNA virus
- Among the largest genomes for RNA viruses
- Transmitted person-to-person by respiratory droplets

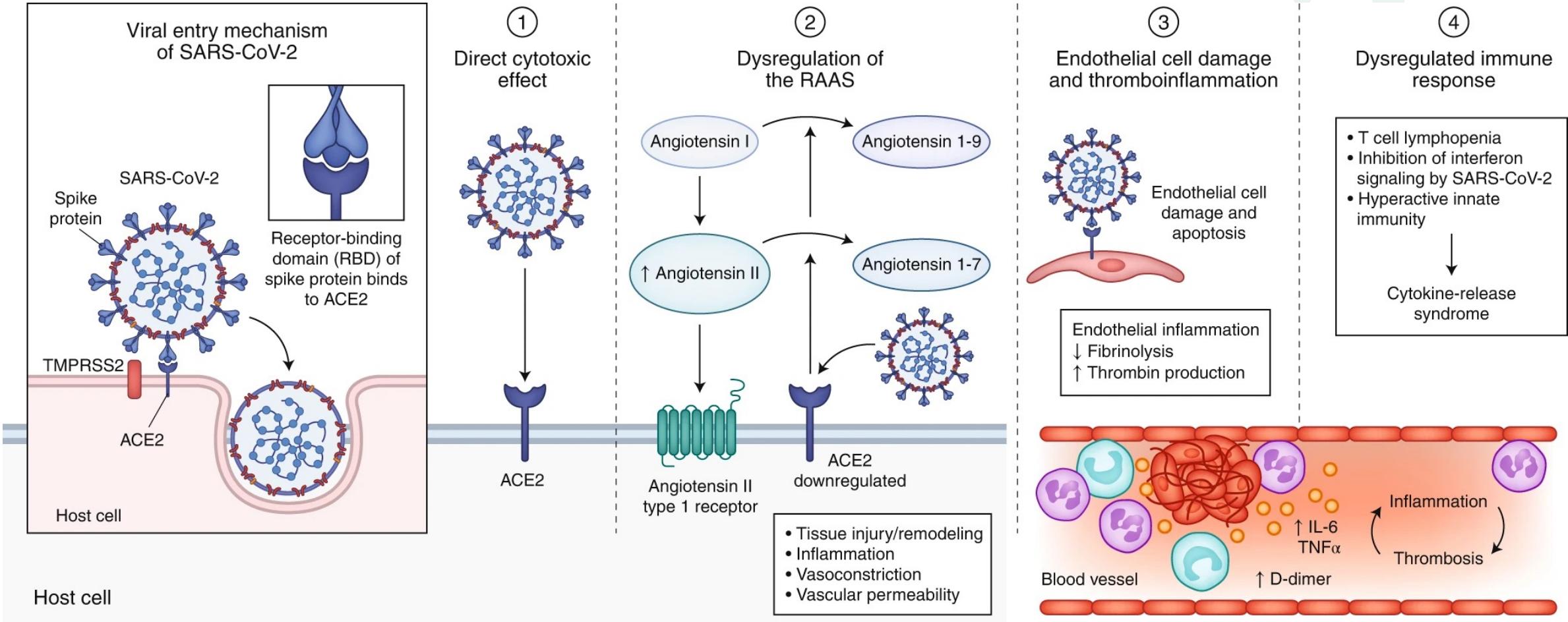


NIH NIAID/RML

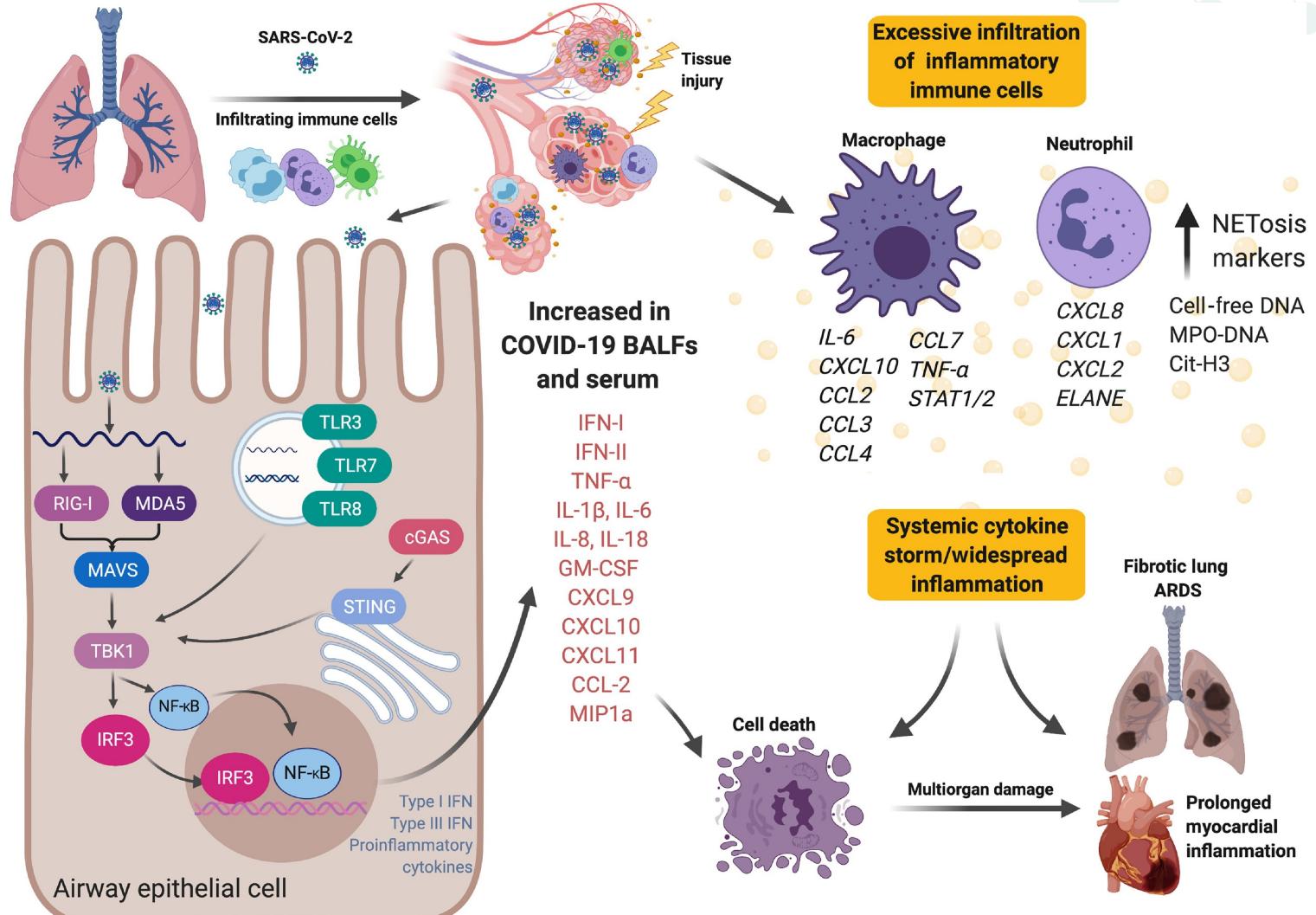
Comparison of clinical characteristics of human coronaviruses

HCoV	Clinical Symptoms	Case Fatality Rate	Incubation Period	Median Time to Death
229E	General malaise, headache, nasal discharge, sneezing, sore throat, fever and cough (10–20% of patients)	N/A	2–5 days	—
OC43	General malaise, headache, nasal discharge, sneezing, sore throat, fever and cough (10–20% of patients)	N/A	2–5 days	—
SARS-CoV	Fever, myalgia, headache, malaise, chills, nonproductive cough, dyspnea, respiratory distress, diarrhea (30–40% of patients)	9%	2–11 days	23 days
NL63	Cough, rhinorrhea, tachypnea, fever, hypoxia, obstructive laryngitis (croup)	N/A	2–4 days	—
HKU1	Fever, running nose, cough, dyspnea	N/A	2–4 days	—
MERS-CoV	Fever, cough, chills, sore throat, myalgia, arthralgia, dyspnea, pneumonia, diarrhea and vomiting (one-third of patients), acute renal impairment	36%	2–13 days	14 days
SARS-CoV-2	Cough, fever, dyspnea, myalgia, sore throat, anosmia/ageusia/dysgeusia, diarrhea, headache, malaise	~1.2%	2–14 days	14 days

SARS-CoV-2 may induce pathogenesis in a variety of ways

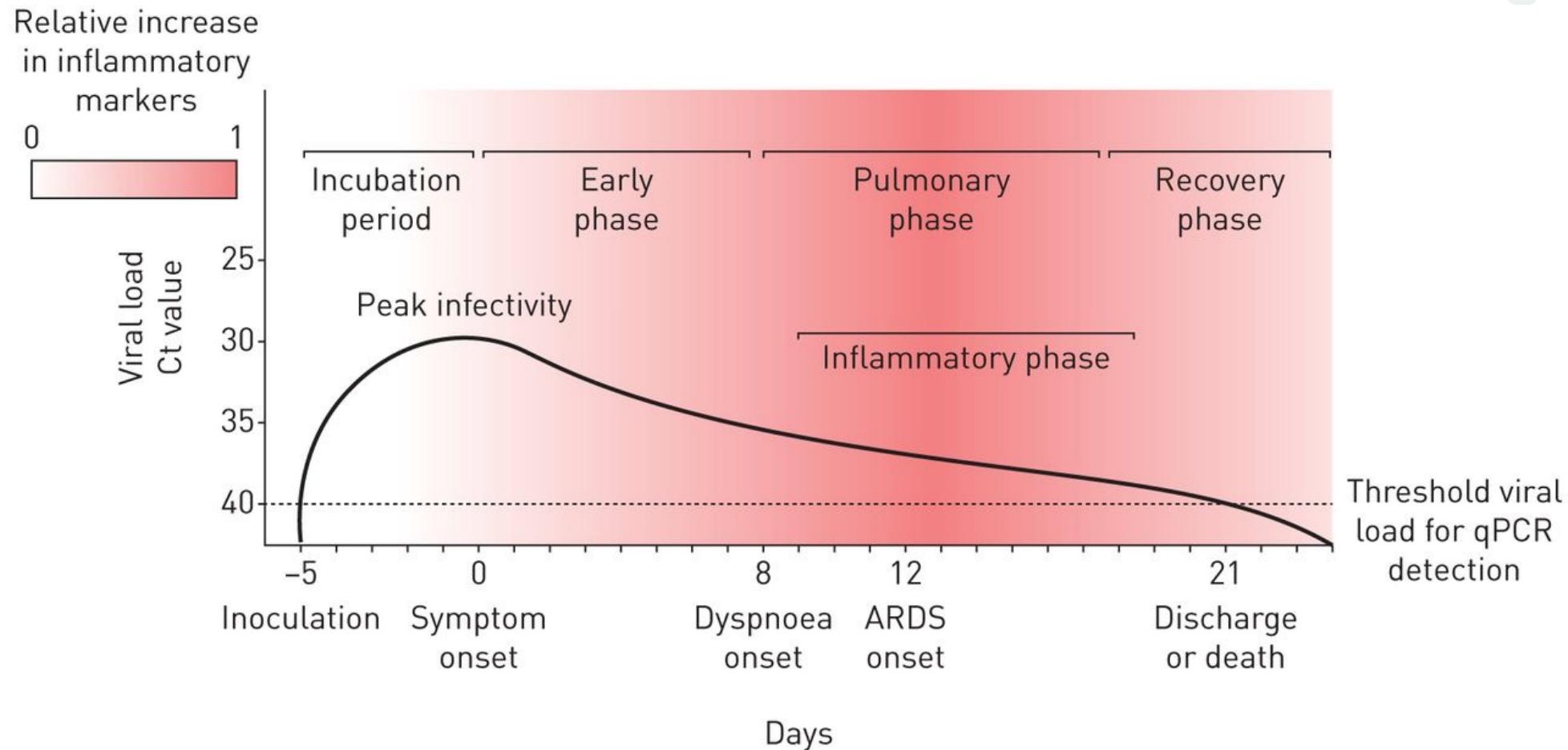


SARS-CoV-2

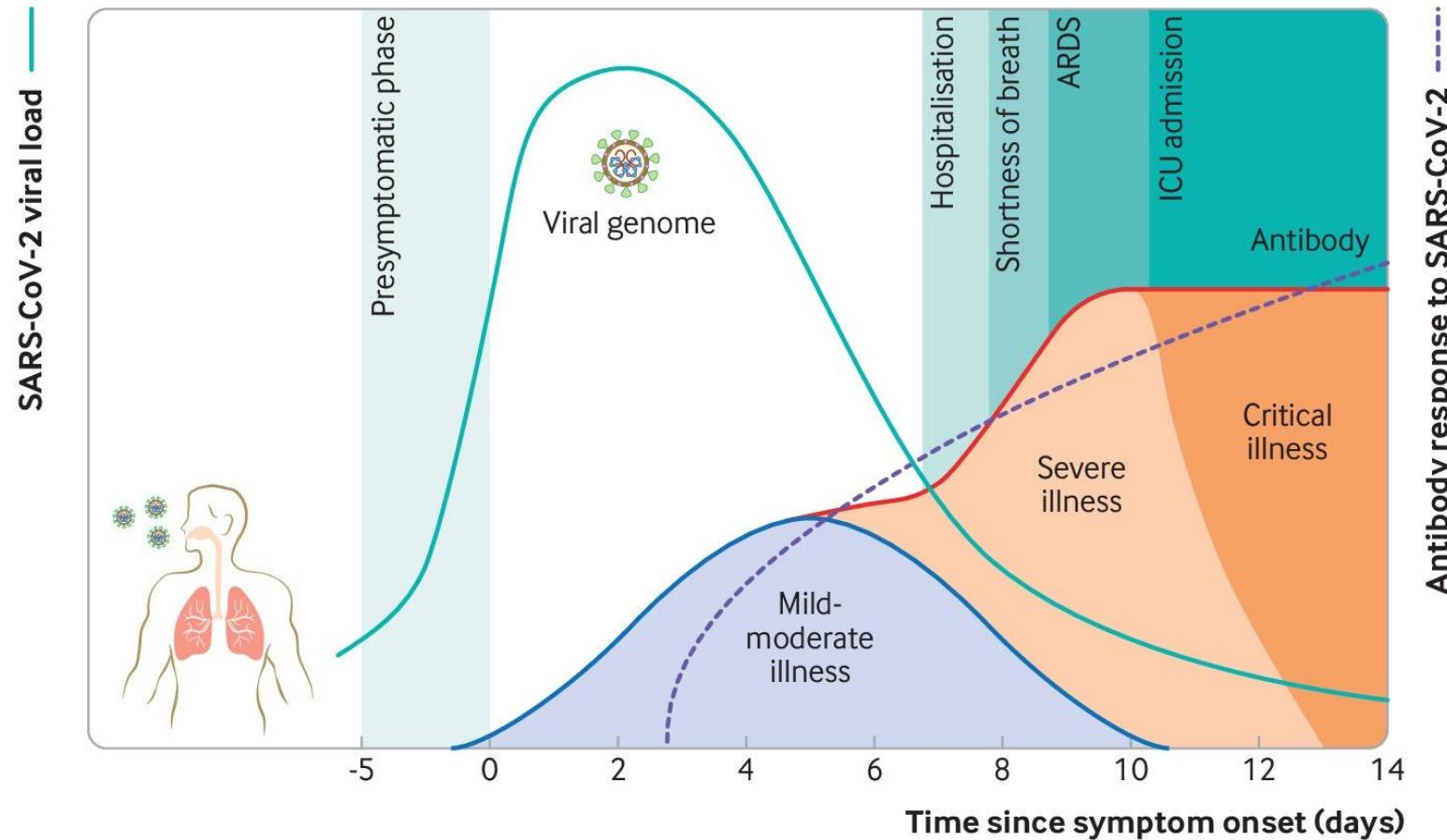


Trends in Immunology

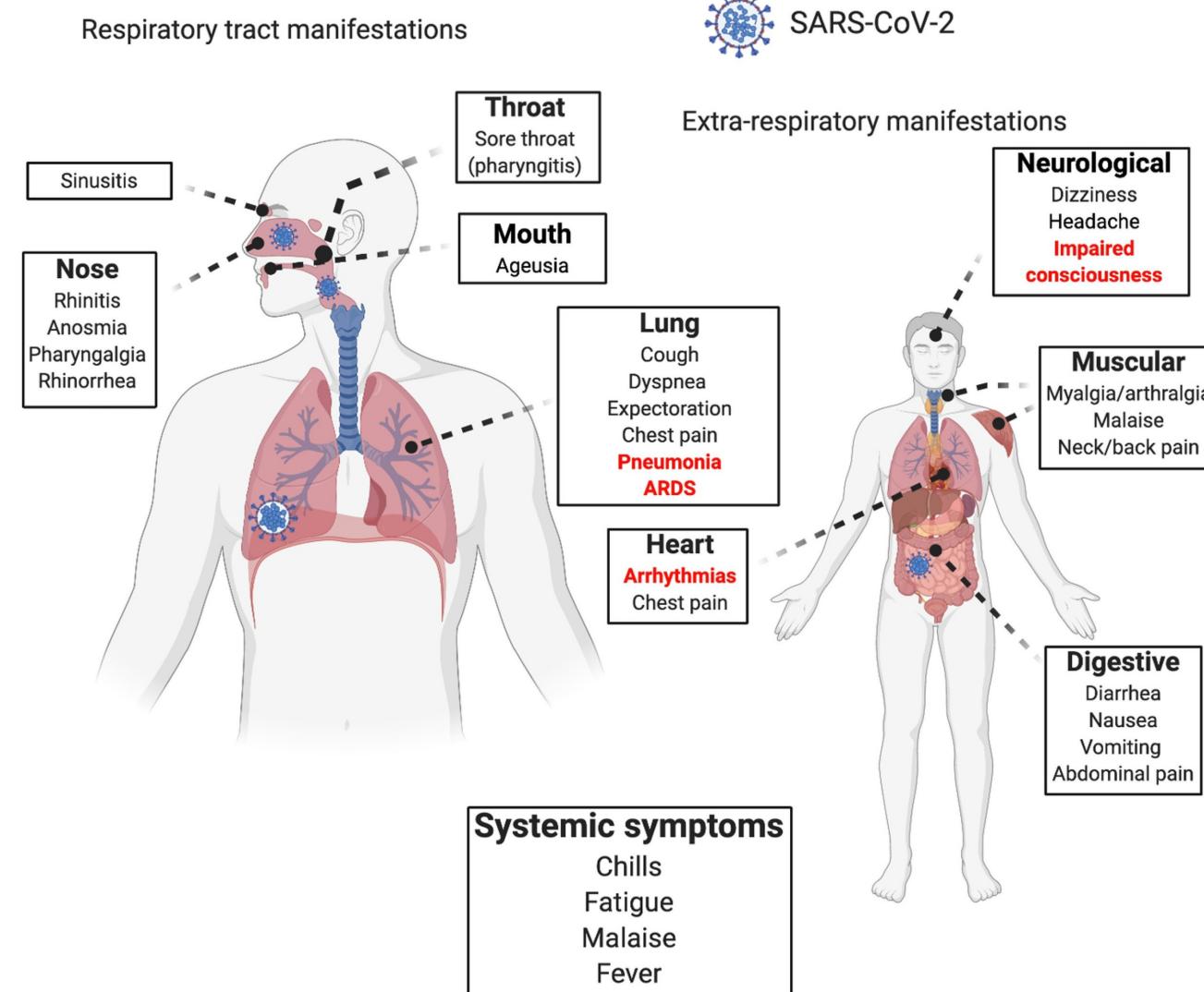
Timing and regulation of the immune response is critical in SARS-CoV-2 infection

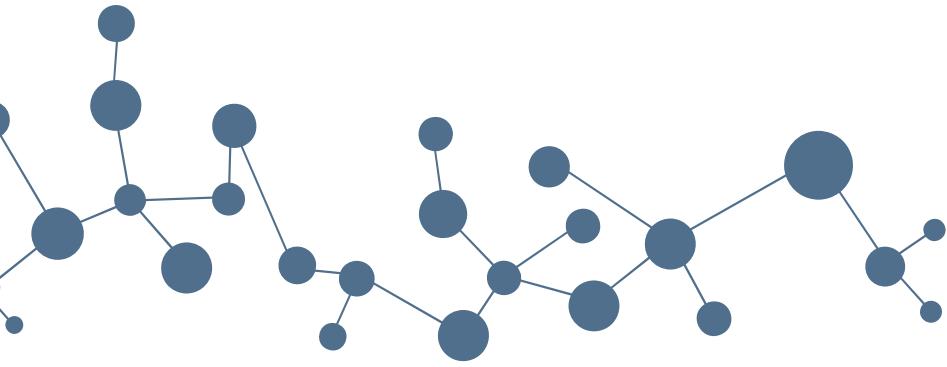


Timing and regulation of the immune response is critical in SARS-CoV-2 infection

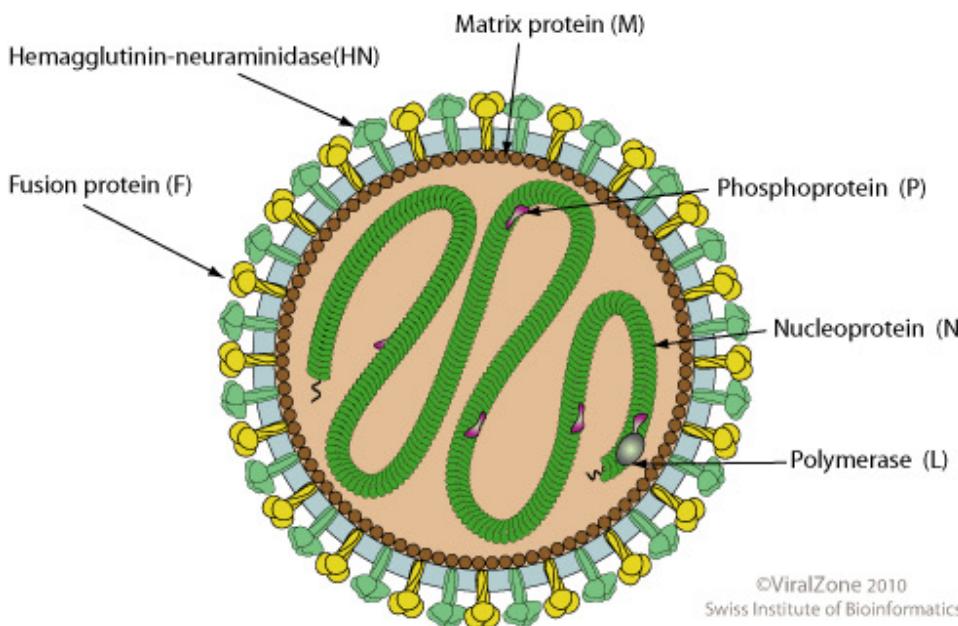
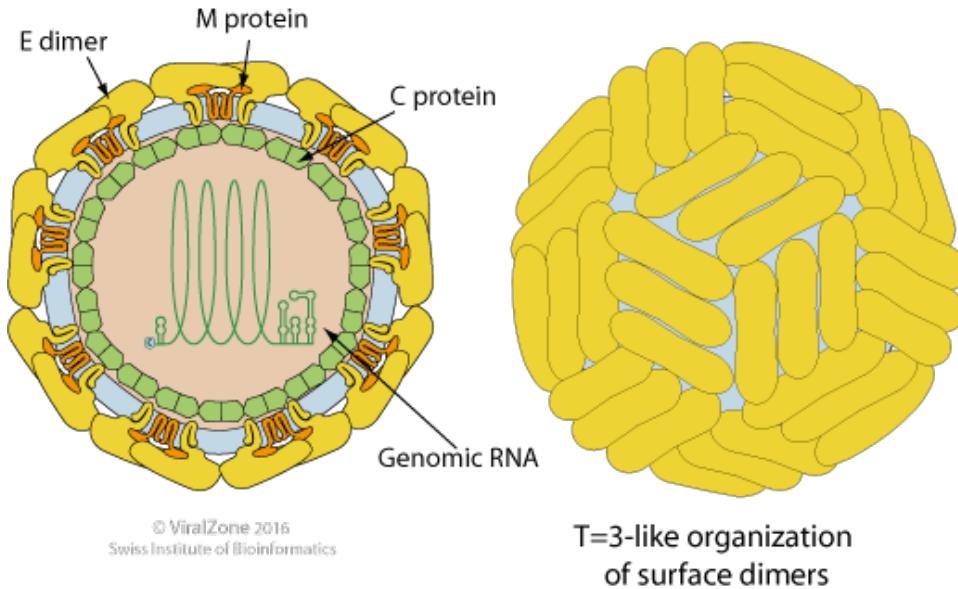


SARS-CoV-2 causes disease outside of the lung





Neurotropic viruses

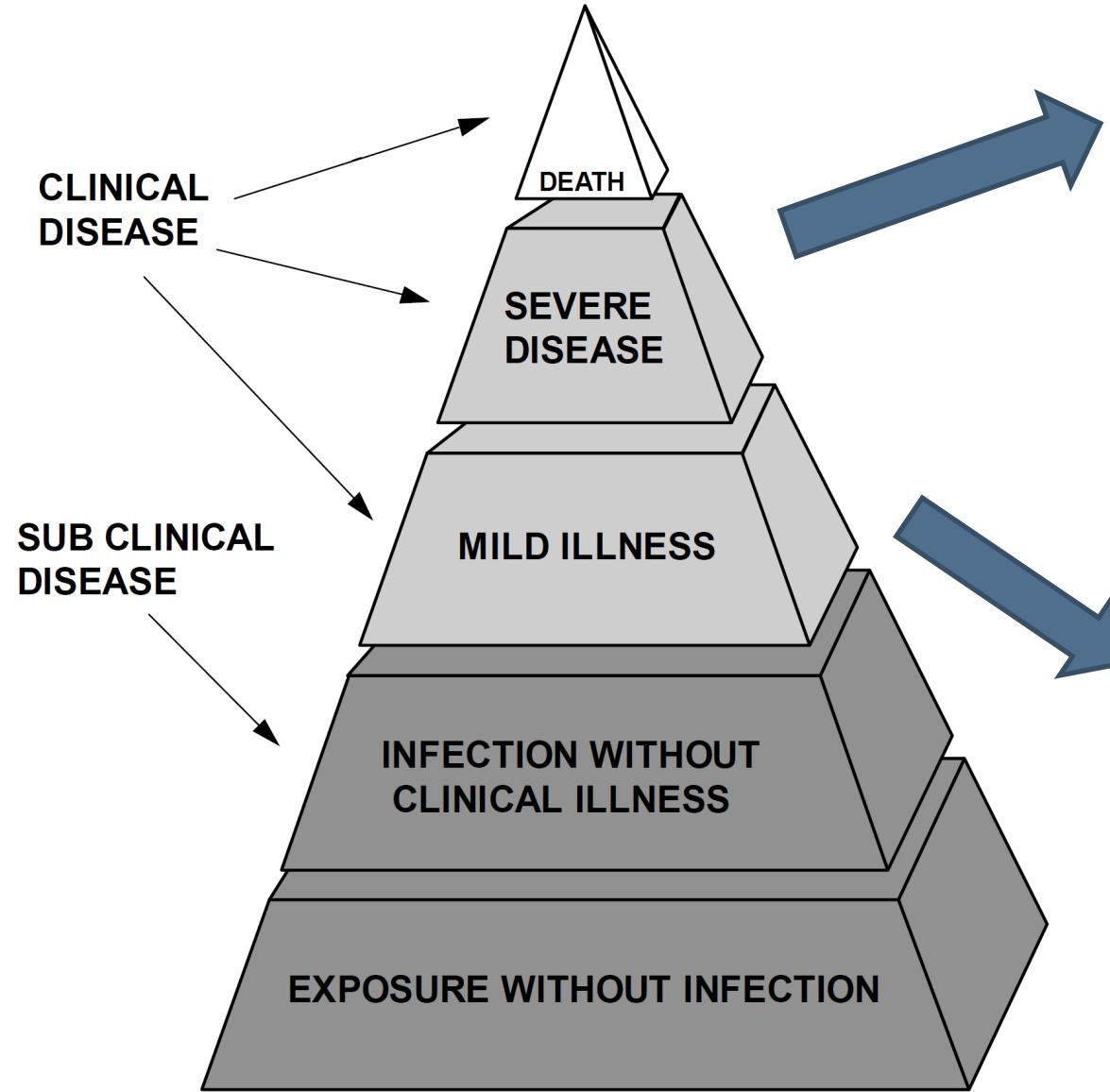


<https://viralzone.expasy.org/>

Emerging neurotropic viruses

- Flaviviridae
 - West Nile virus
 - Japanese encephalitis virus
 - Zika virus
- Paramyxoviridae
 - Nipah virus
 - Hendra virus

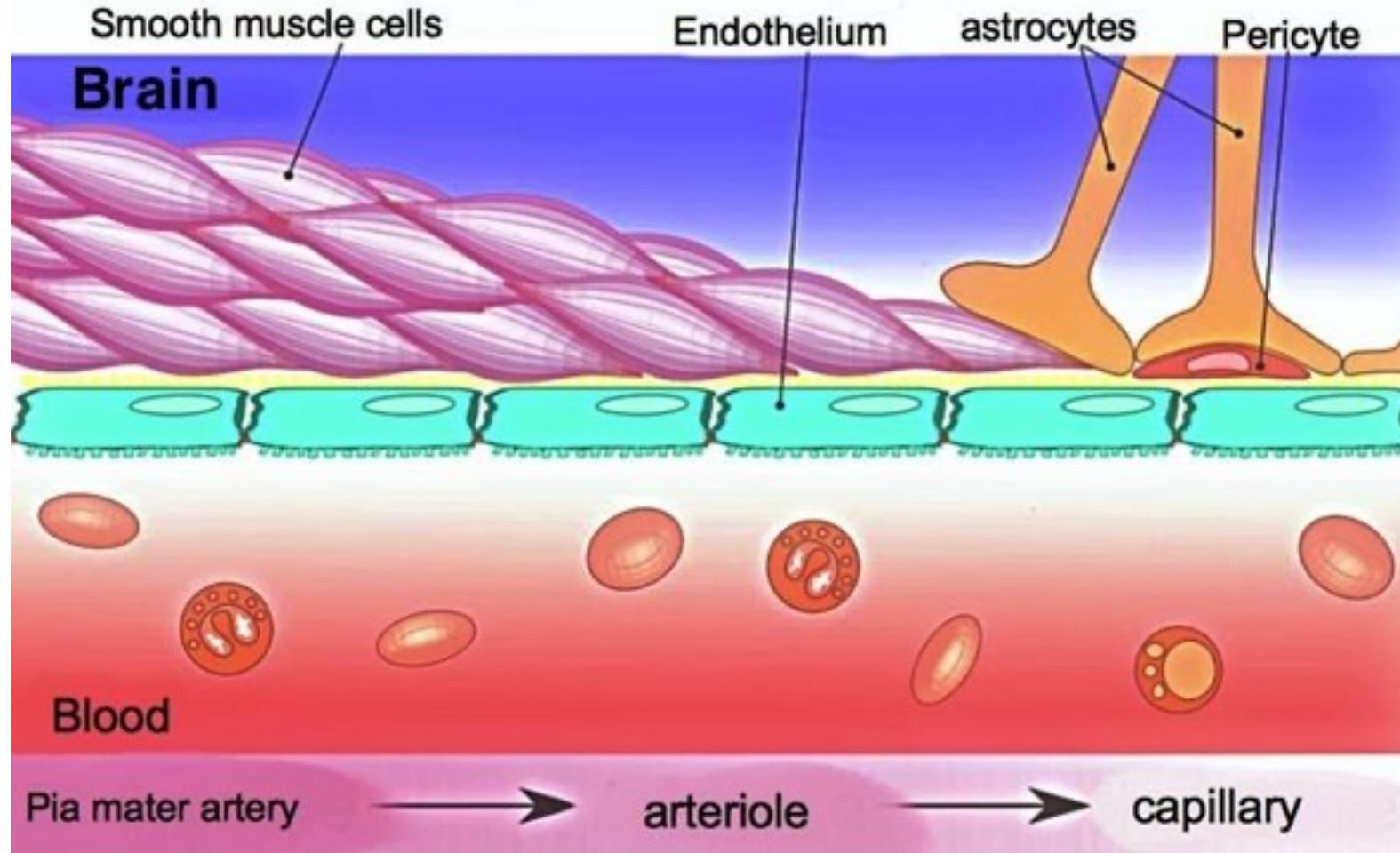
Neurotropic disease



- High fever
- Severe headache
- Stiff neck
- Disorientation or confusion
- Coma
- Tremors or muscle jerking
- Seizures
- Partial paralysis or muscle weakness
- Vision loss
- Numbness

- Fever
- Headache
- Body aches
- Vomiting
- Diarrhea
- Fatigue
- Skin rash

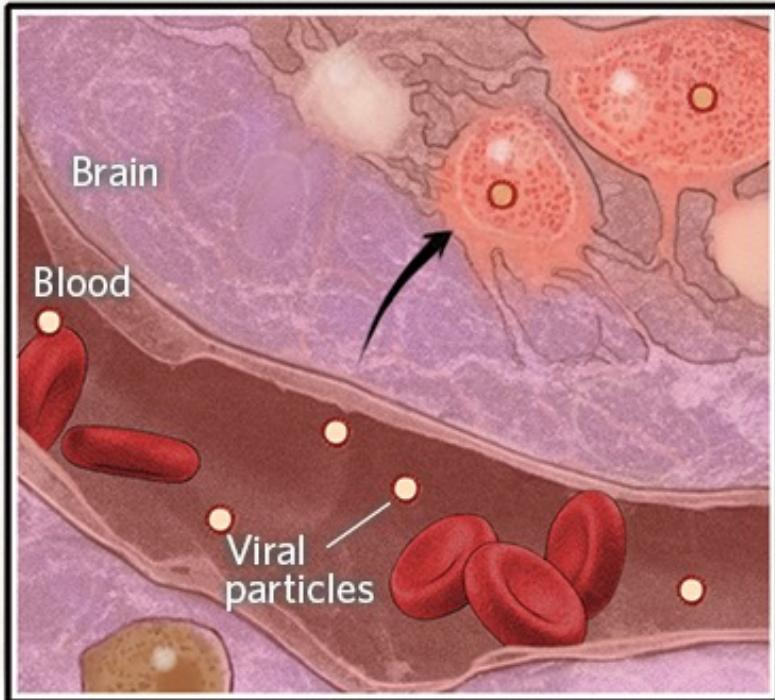
The blood-brain barrier maintains the brain as an immune privileged site



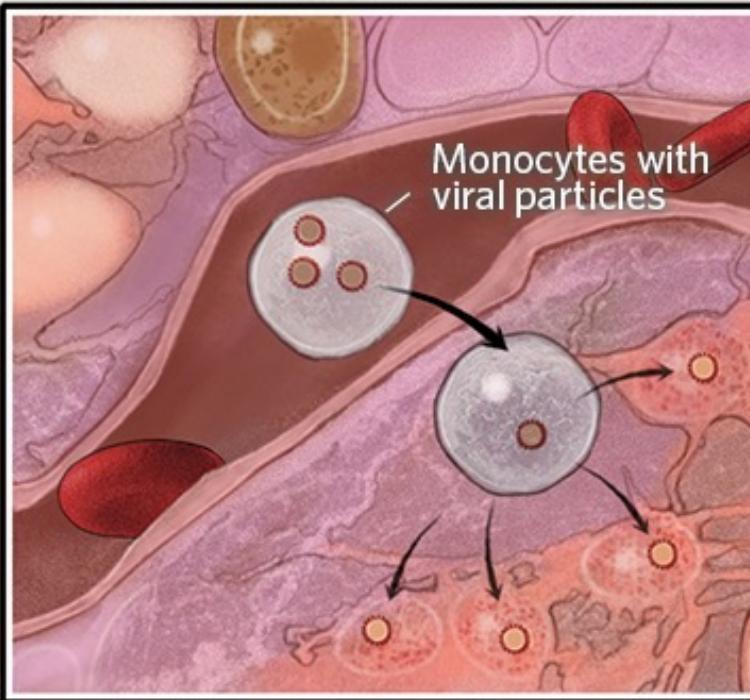
Viruses have multiple strategies to cross the BBB



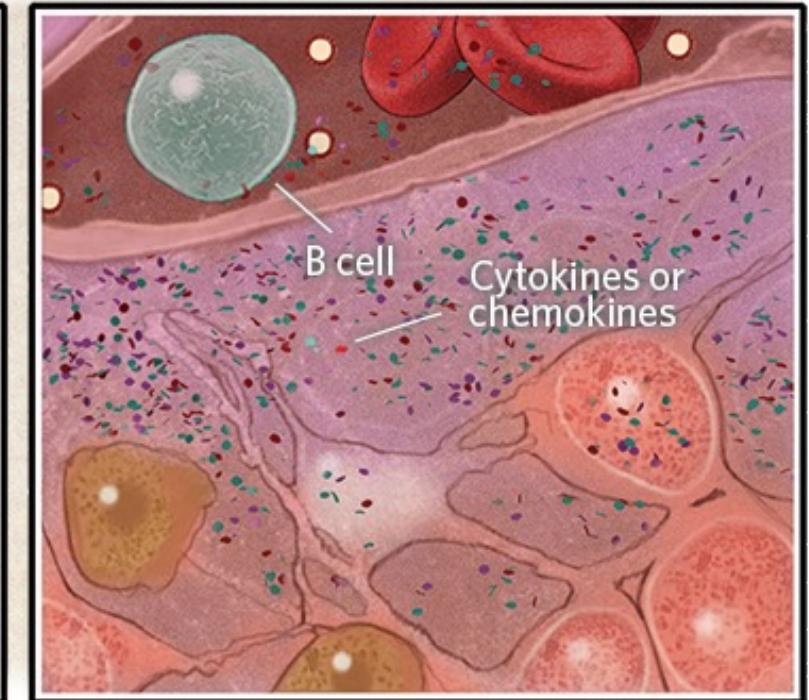
DIRECT CROSSING



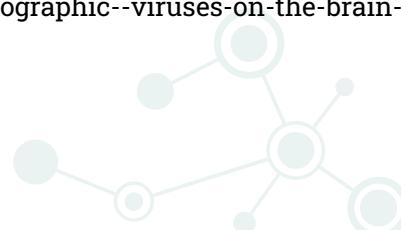
TROJAN HORSE



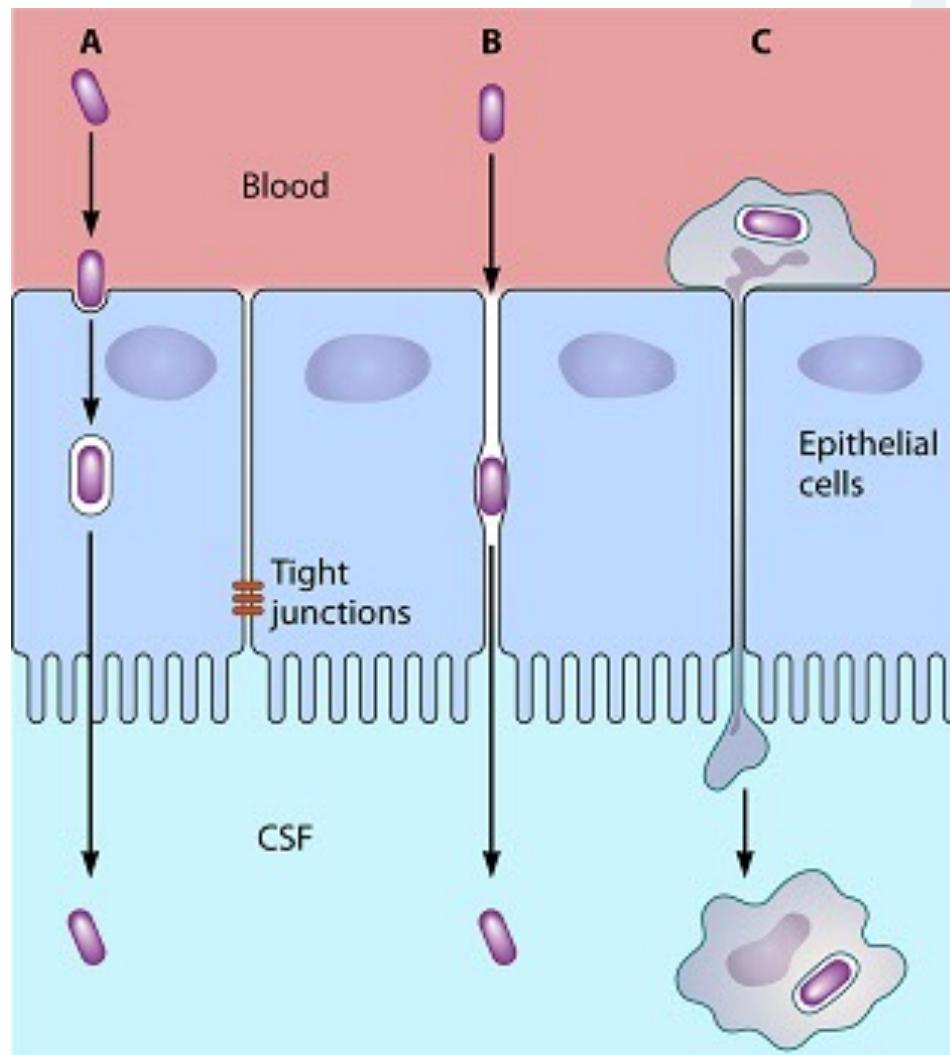
IMMUNE RESPONSE



<https://www.the-scientist.com/infographics/infographic--viruses-on-the-brain-65532>



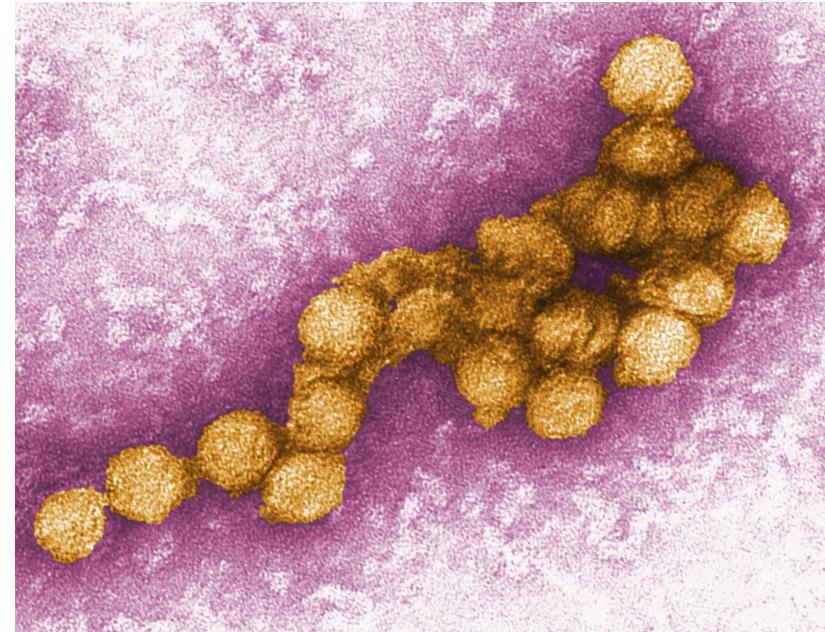
Viruses have multiple strategies to cross the BBB



<https://asm.org/Articles/2020/April/How-Pathogens-Penetrate-the-Blood-Brain-Barrier>

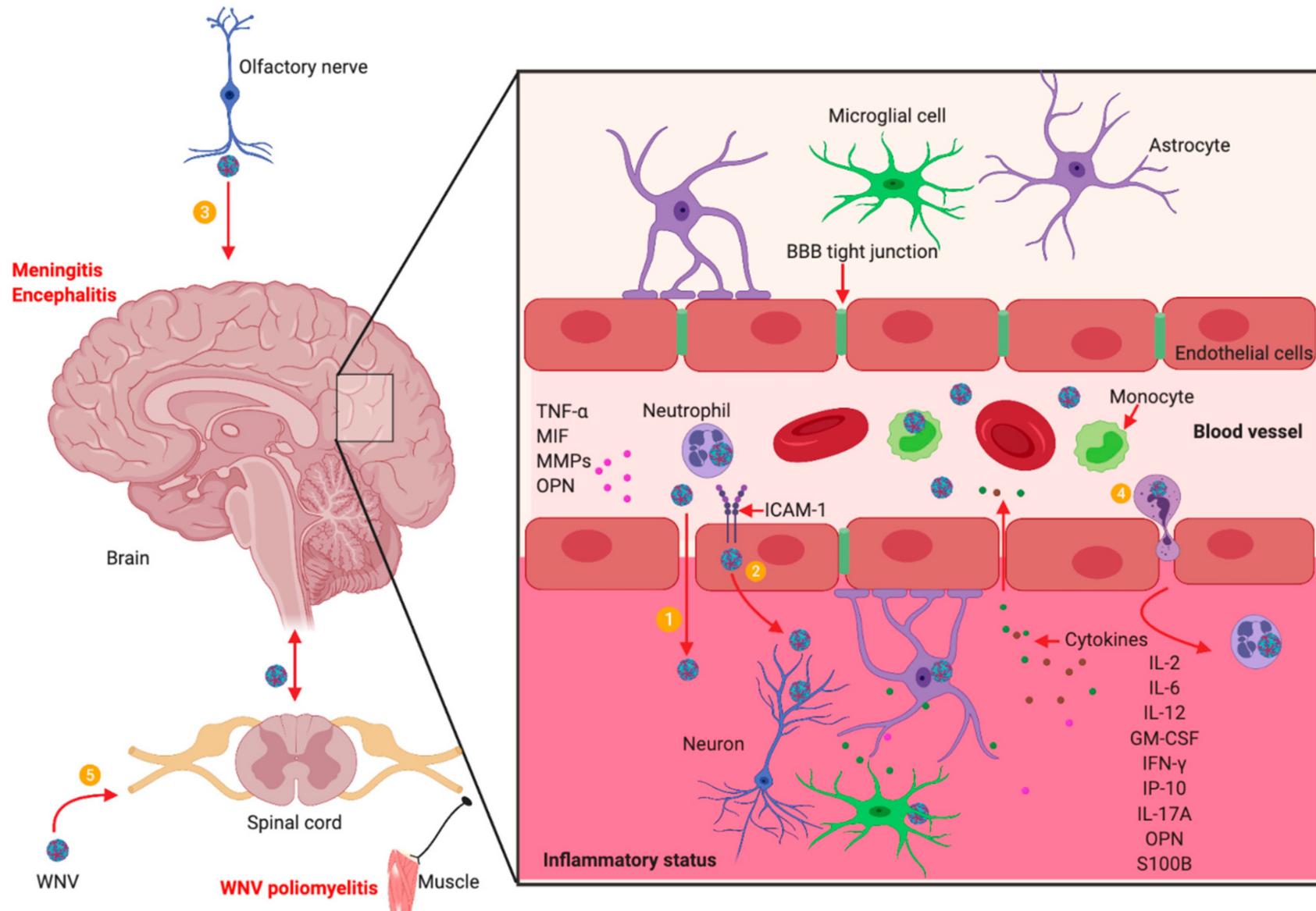
West Nile virus

- Family: Flaviviridae
- (+)ssRNA virus
- Is transmitted to people by mosquitoes
- Primary host is birds



<https://www.niaid.nih.gov/diseases-conditions/west-nile-virus>

Pathogenesis of West Nile encephalitis

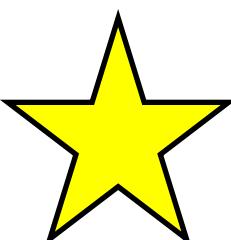




What is the overarching theme for all of these viruses and the diseases they cause?

Key takeaways

1. Severe viral disease is often driven by immunopathogenesis
2. Viral toxins are a potential driver of viral pathogenesis
3. Viral disease is often characterized by disruptions of barriers





A faint, large network graph is visible at the bottom left of the slide, consisting of numerous small, semi-transparent grey nodes connected by thin white lines.

Questions?

dglasner@ucsd.edu