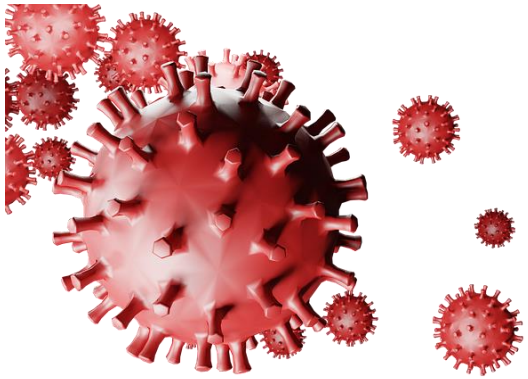
UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU



Subject: Virology
Topic: SARS-CoV-2 Coronavirus causing COVID-19

Academic Year 2023/2024

Faculty: Medicine
Field of study: Medicine
Level of study (unif. Master's):
Form of study (full time, part-time):
Year of study: II, III

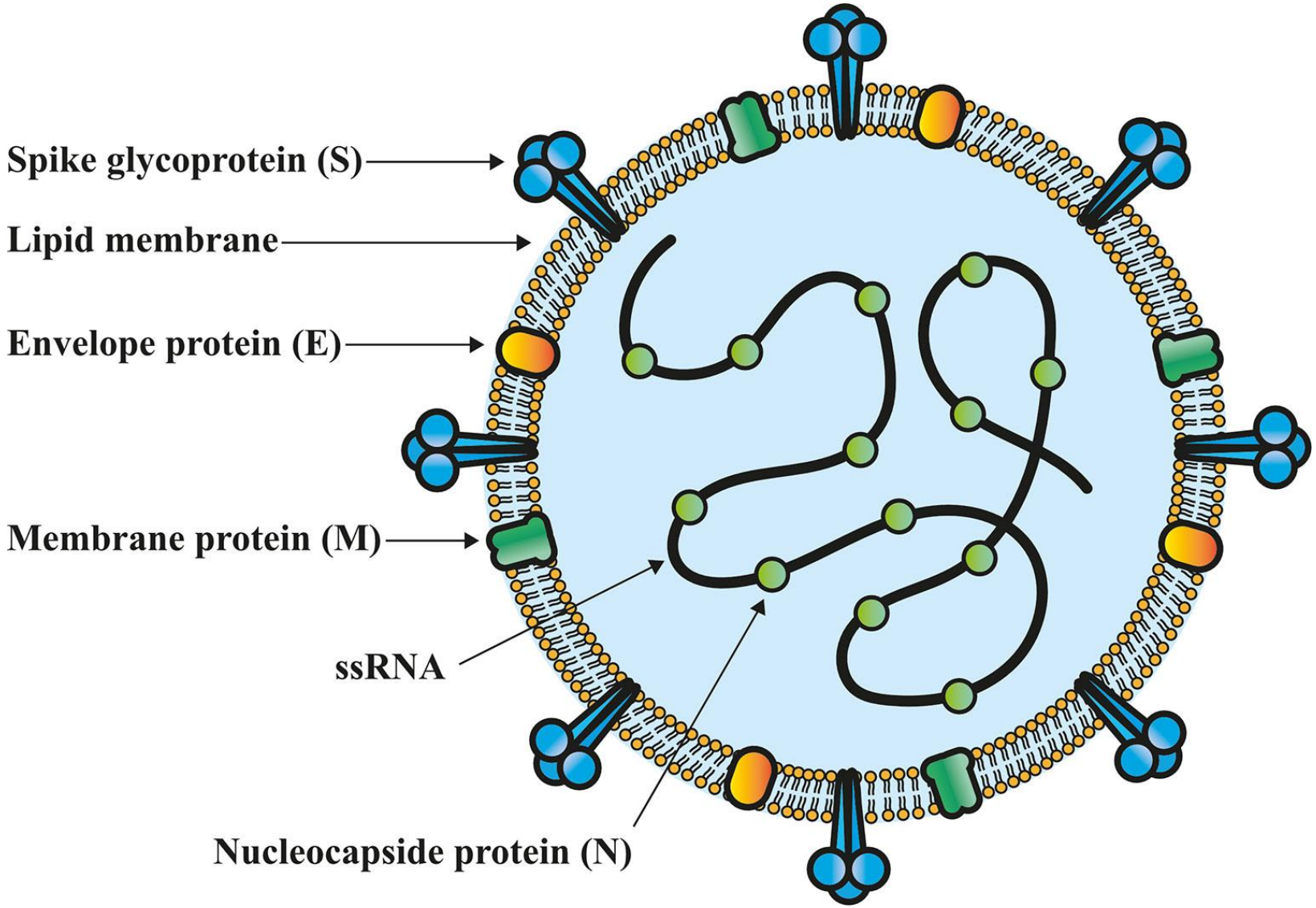
Academic title/professional title: prof. dr hab.
Name, last name of the lecturer: Beata Sobieszczańska
Position of person conducting classes: professor
Wroclaw Medical University

Coronavirus SARS-CoV-2

(+) ssRNA enveloped cytopathic virus

S protein:

- receptor recognition
- viral attachment
- viral entry into host cell



Nidovirales, Coronavirine family

Coronaviruses pathogenic to humans

Low pathogenic

HKU1, 229E,
NL63, OC43

Common cold
diarrhea

High pathogenic

SARS-CoV-1 2002
MERS-CoV 2012
SARS-CoV-2 2019

Modes of transmission

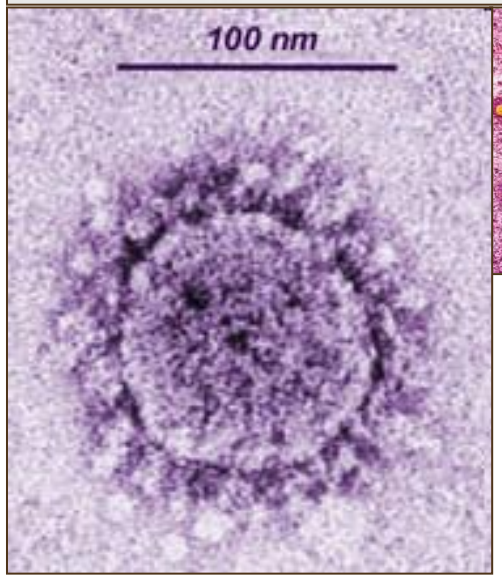
- droplet transmission, direct contact

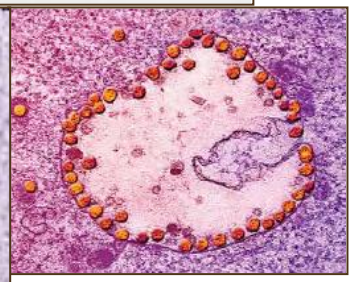
Infectivity – the ability of a virus to jump from one person to another

- SARS virus has low infectivity
  (it requires a large dose to pass on to the recipient)

Virulence – the property of the virus to cause damage to the host's organs

SARS virus has a high virulence





Severe **A**cute **R**espiratory **S**yndrome

CLINICAL COURSE OF SARS

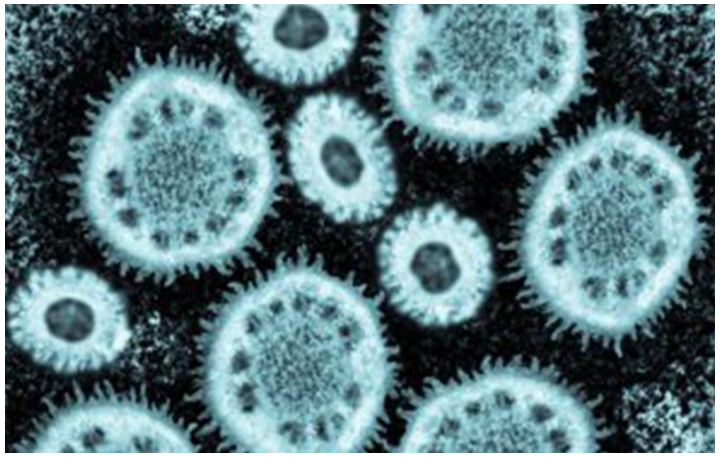
90%

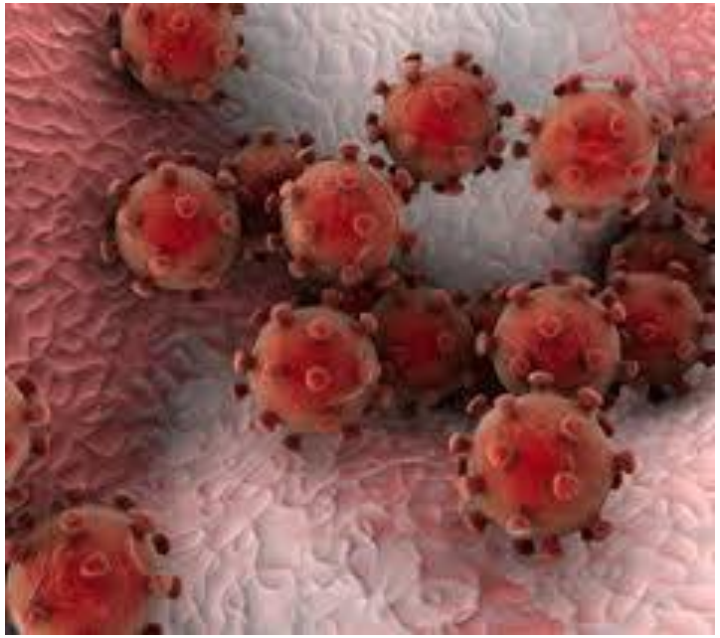
Death on 17-18 days

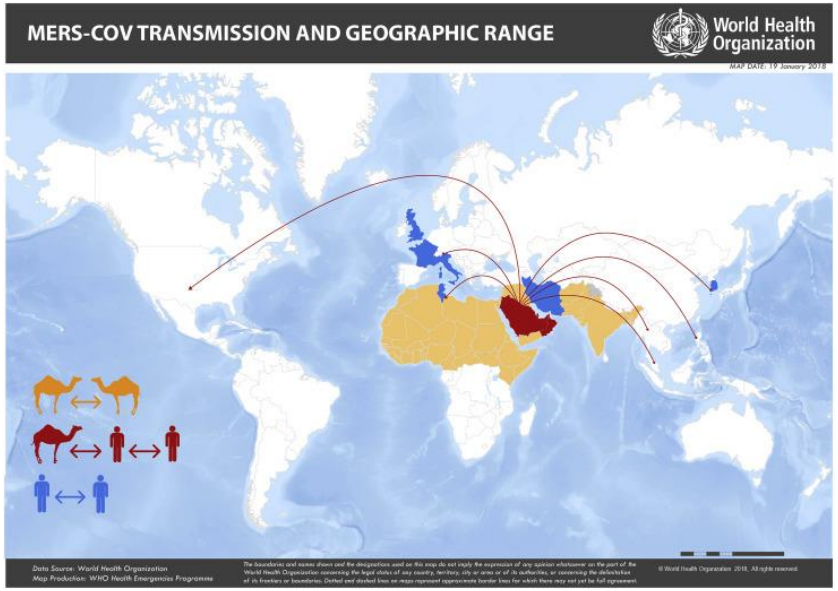
Middle East Respiratory Syndrome

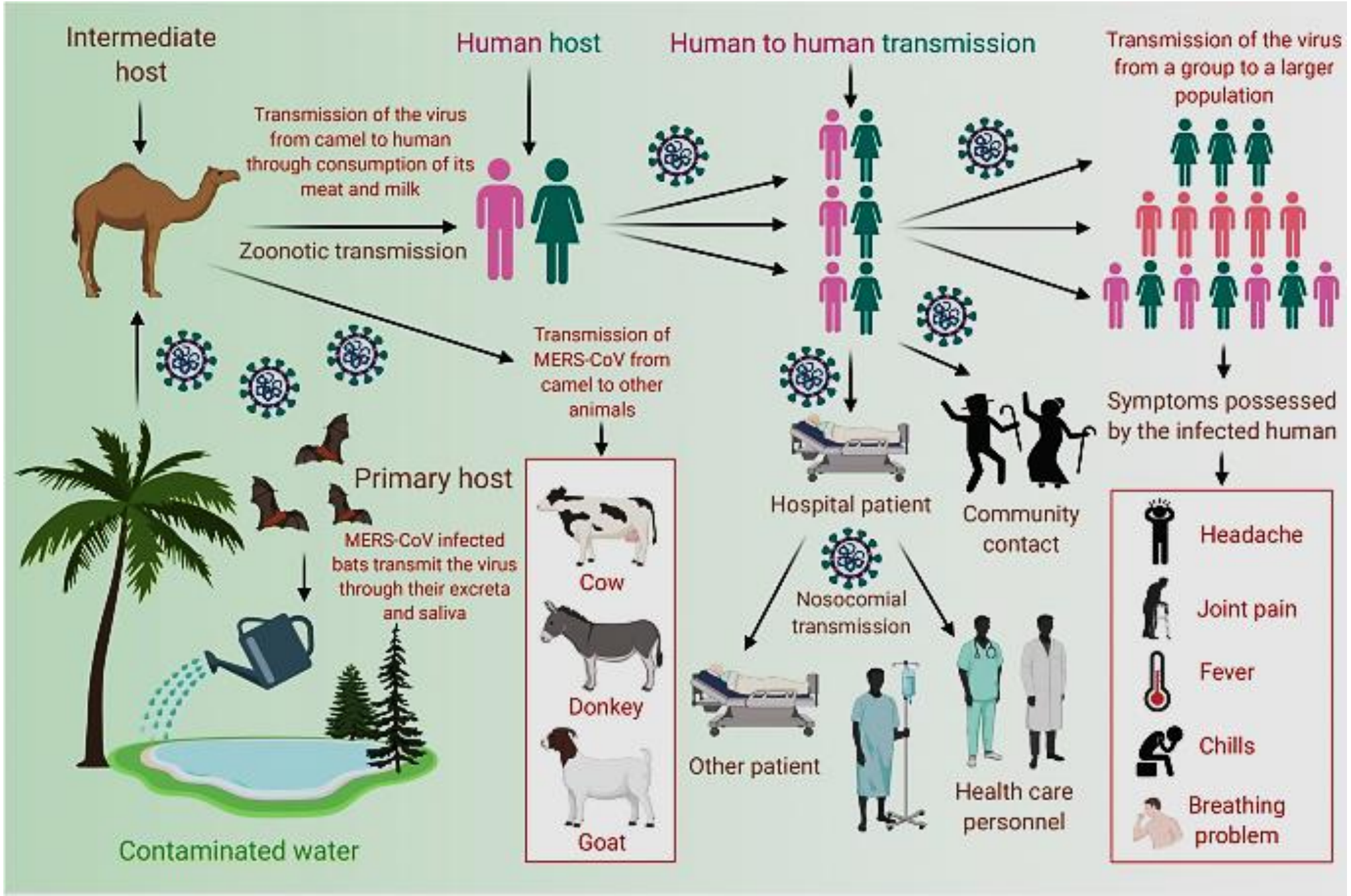
Modes of transmission

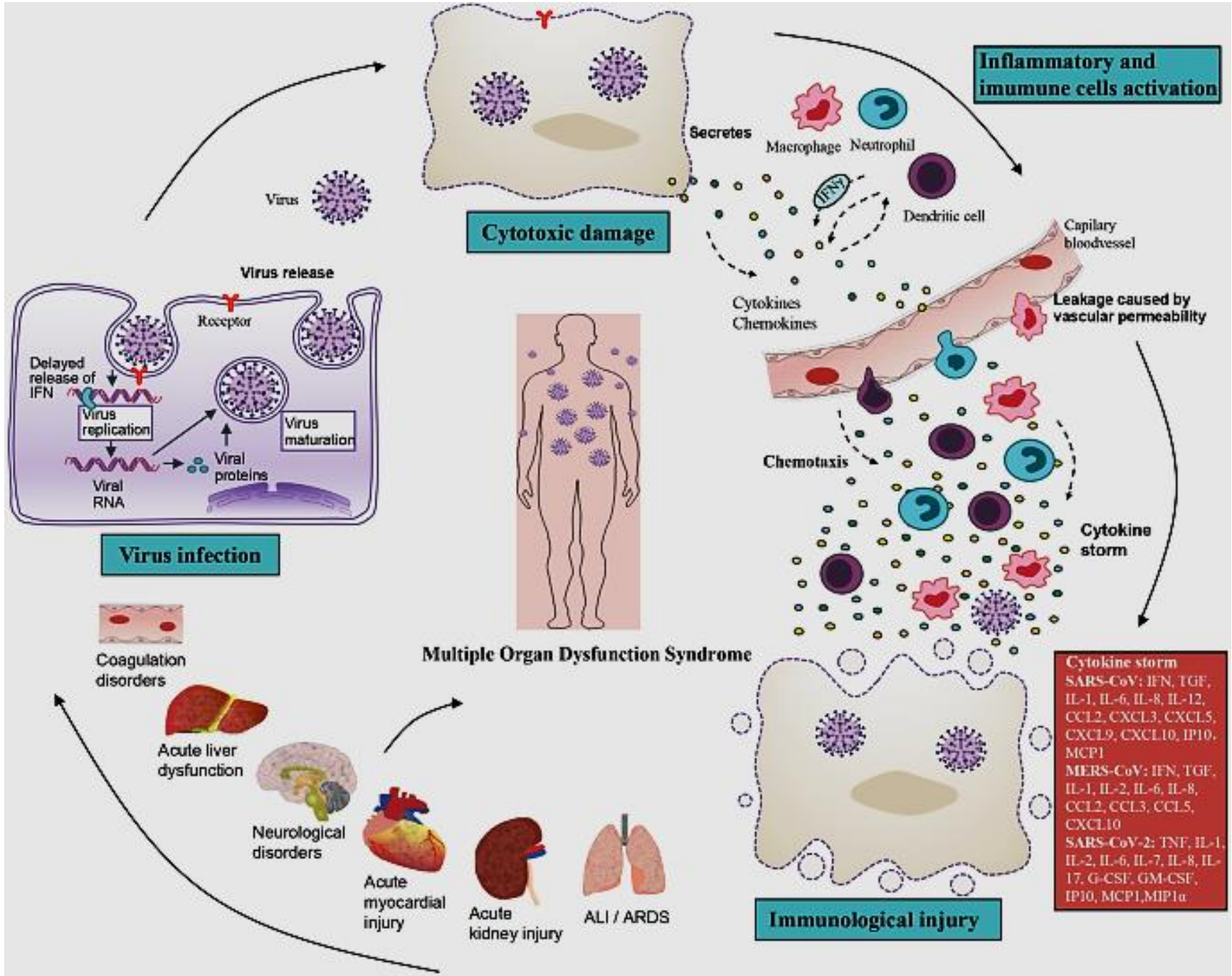
- droplet transmission, direct contact
- MERS virus has low infectivity but high virulence








Intermediate host
Human host
Human to human transmission
Transmission of the virus from a group to a larger population
Transmission of the virus from camel to human through consumption of its meat and milk
Zoonotic transmission
Transmission of MERS-CoV from camel to other animals
Primary host
MERS-CoV infected bats transmit the virus through their excreta and saliva
Contaminated water
Cow
Donkey
Goat
Hospital patient
Community contact
Nosocomial transmission
Other patient
Health care personnel
Symptoms possessed by the infected human
Headache
Joint pain
Fever
Chills
Breathing problem


Virus
Cytotoxic damage
Secretes
Macrophage
Neutrophil
IFNγ
Dendritic cell
Inflammatory and imumune cells activation
Capilary bloodvessel
Leakage caused by vascular permeability
Cytokines
Chemokines
Chemotaxis
Cytokine storm
Virus release
Receptor
Delayed release of IFN
Virus replication
Virus maturation
Viral proteins
Viral RNA
Virus infection
Multiple Organ Dysfunction Syndrome
Coagulation disorders
Acute liver dysfunction
Neurological disorders
Acute myocardial injury
Acute kidney injury
ALI / ARDS
Immunological injury
Cytokine storm
SARS-CoV: IFN, TGF, IL-1, IL-6, IL-8, IL-12, CCL2, CXCL3, CXCL5, CXCL9, CXCL10, IP10, MCP1
MERS-CoV: IFN, TGF, IL-1, IL-2, IL-6, IL-8, CCL2, CCL3, CCL5, CXCL10
SARS-CoV-2: TNF, IL-1, IL-2, IL-6, IL-7, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1,MIP1α

SARS/MERS case definitions

Clinical criteria:

- fever >38^{0}C & respiratory illness
- radiologic findings (pneumonia, RDS)
- autopsy findings (pneumonia, RDS)

Epidemiologic criteria:

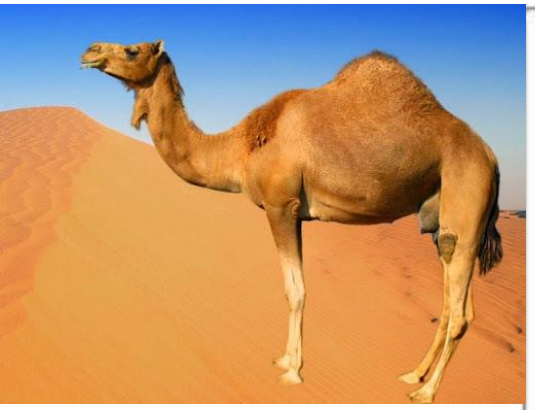
- travel history (10 days) to SARS/MERS-affected areas
- close contact with known or suspected patients

Laboratory criteria:

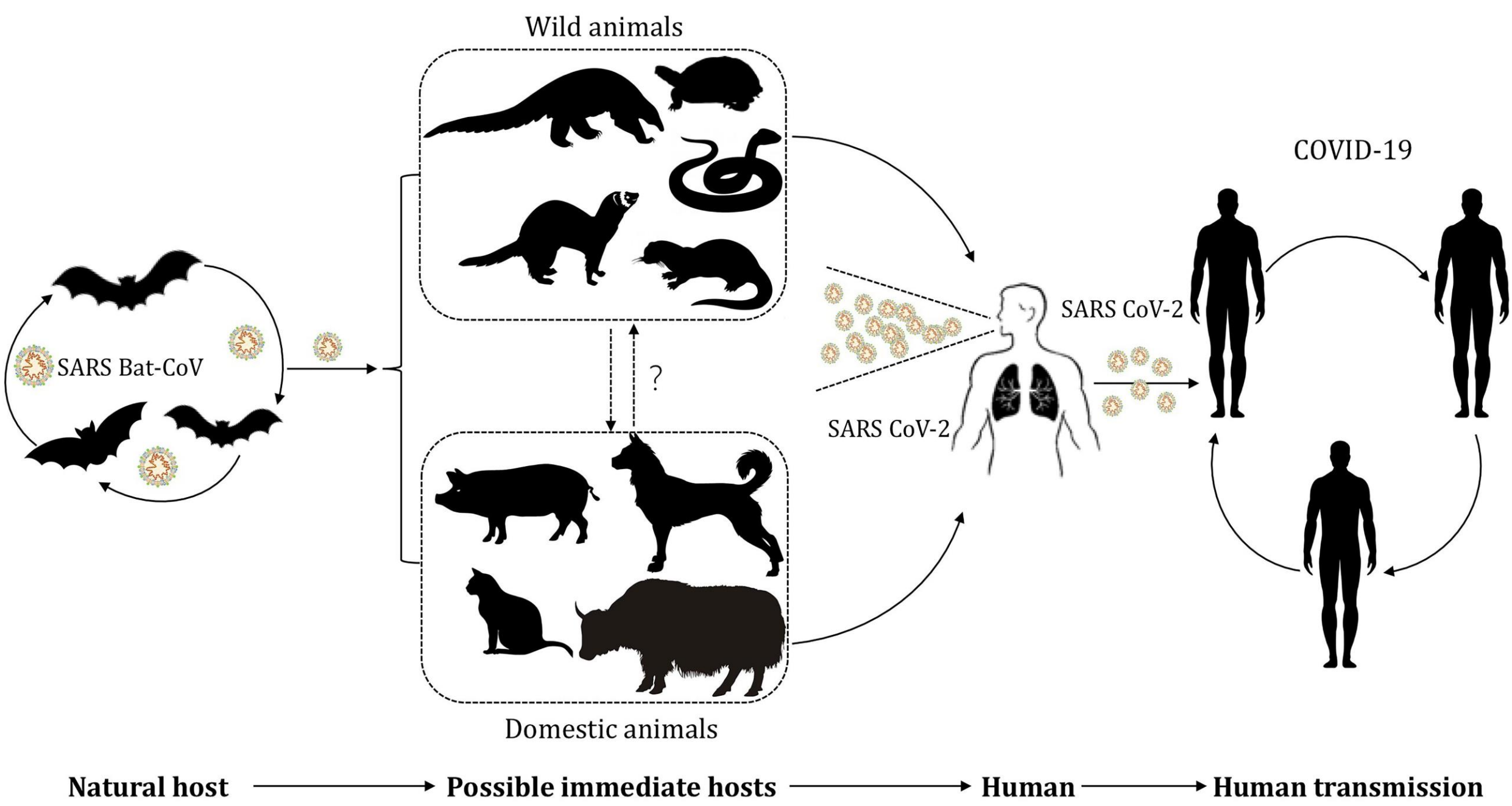
- antibodies specific to SARS-CoV/MERS-Cov
- RT-PCR

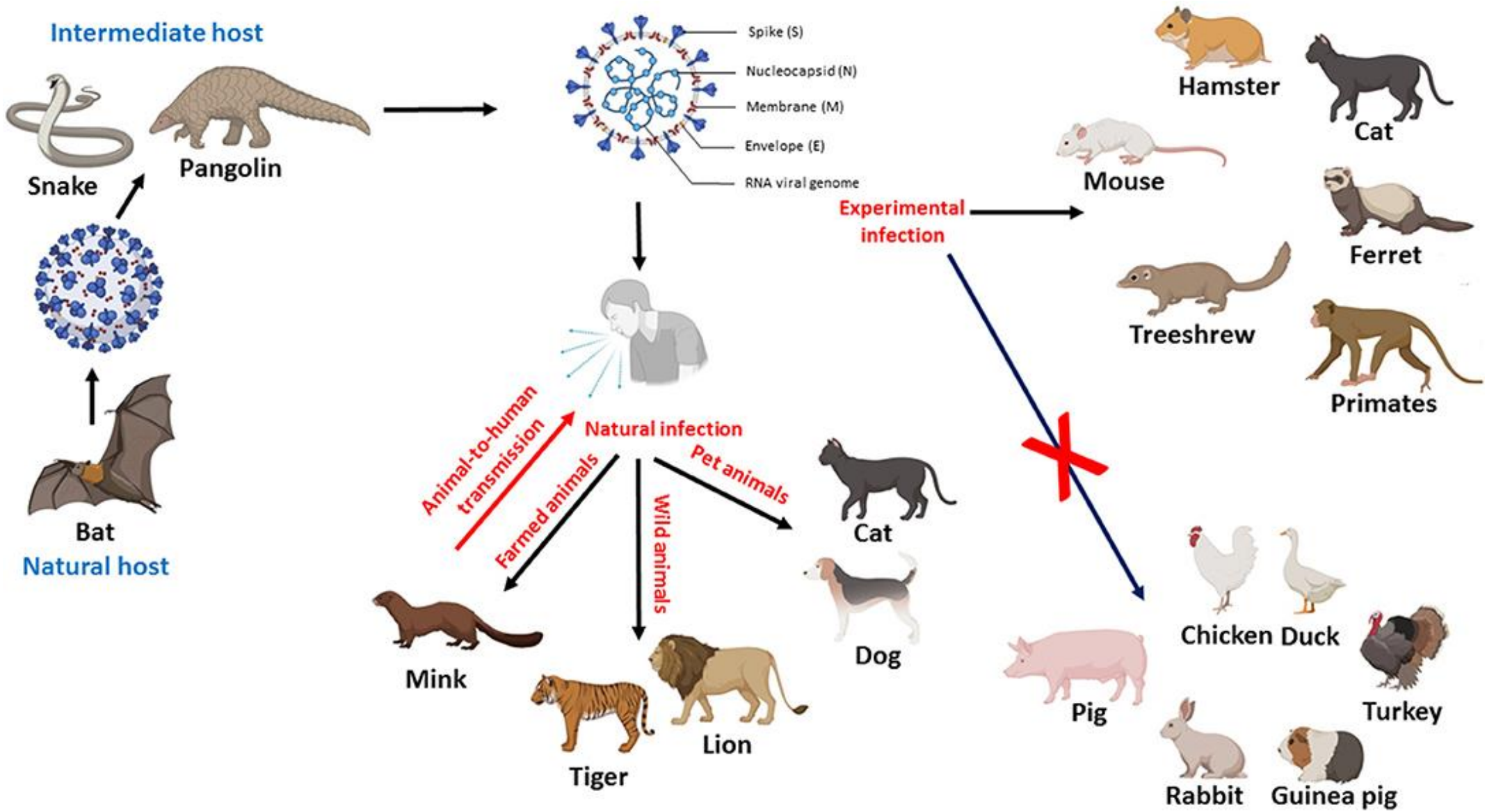
SARS endemic areas in Asia: China, Taiwan, Singapore, Hong Kong, Vietnam

MERS endemic areas: Saudi Arabia, United Arab Emirates, Republic of Korea



TYPE	SARS-CoV	MERS-CoV	COVID-19
SPECIES BARRIERS — Primary	BAT	BAT	BAT
SPECIES BARRIERS — Secondary/ Host reciever	Palm Civets and Racoon Dogs between Bats and Human	CAMEL	UNKNOWN
Out Break Year	2002	2012	2019
Place of Origin	Guangdong Province of CHINA	Arrabian Peninsula (Middle-East)	Wuhan City, CHINA


Wild animals
SARS Bat-CoV
?
SARS CoV-2
SARS CoV-2
COVID-19
Domestic animals
Natural host
Possible immediate hosts
Human
Human transmission


Intermediate host
Snake
Pangolin
Bat
Natural host
Spike (S)
Nucleocapsid (N)
Membrane (M)
Envelope (E)
RNA viral genome
Animal-to-human transmission
Natural infection
Farmed animals
Pet animals
Wild animals
Mink
Cat
Dog
Tiger
Lion
Experimental infection
Hamster
Cat
Mouse
Ferret
Treeshrew
Primates
Pig
Chicken
Duck
Turkey
Rabbit
Guinea pig

What are the differences between SARS-CoV-2 and SARS-CoV-1 and MERS-CoV?

Similarities with other SARS viruses:

- the same structure
- all produce RTI
- spread by respiratory droplets
- have similar stability in the environment
- can lead potentially to serious illness
- no seasonality

Differences:

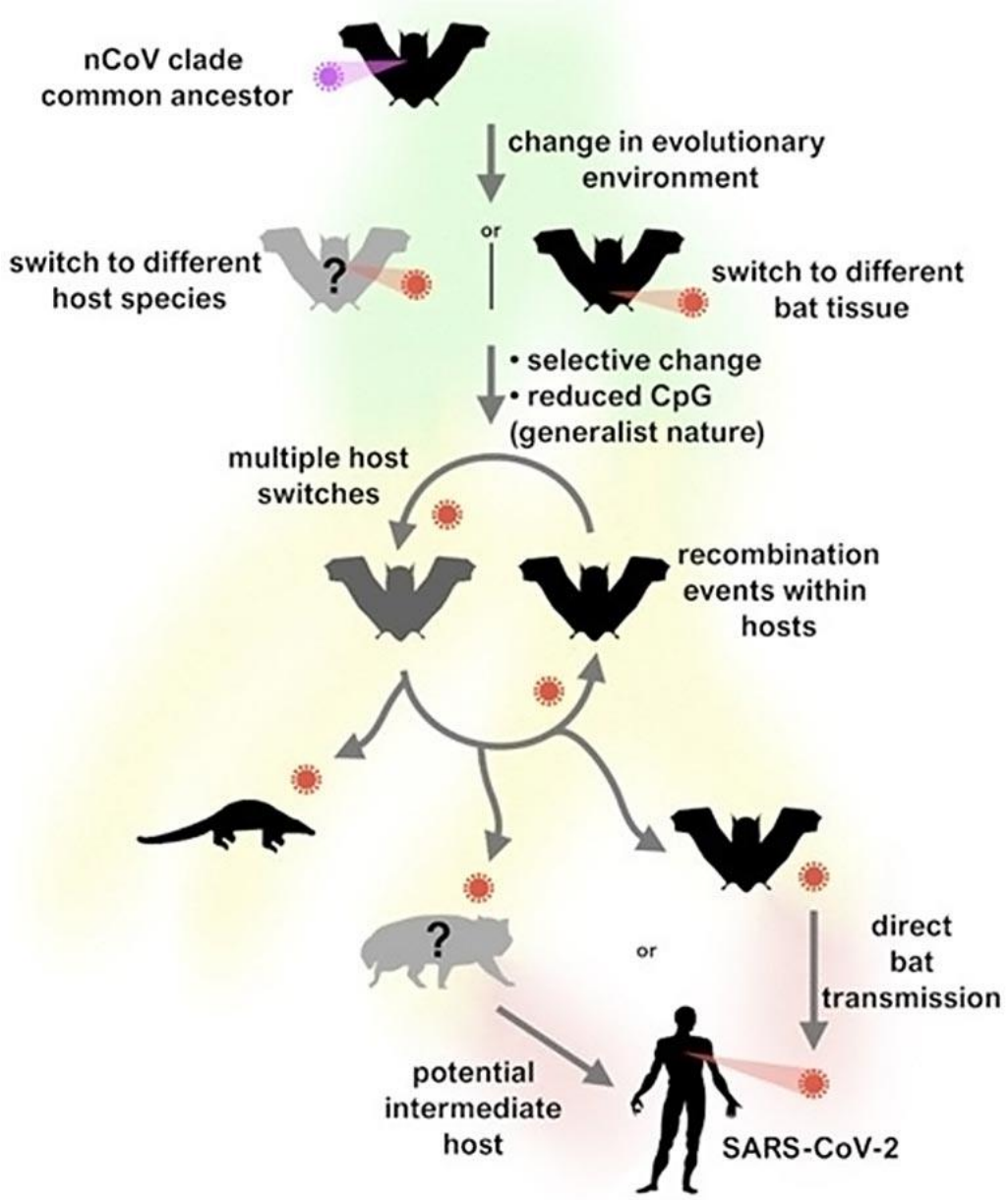
- SARS-CoV-2 is easily transmitted within communities = a lot more infectious and contagious than other Coronaviruses
- infected people shed the virus earlier in the course of disease = difficulties in the detection of infected people
- some differences in the symptoms of COVID-19 and SARS
- Mortality rate of MERS – 34%; SARS – 10%; Cov-2 – 15% (decline)

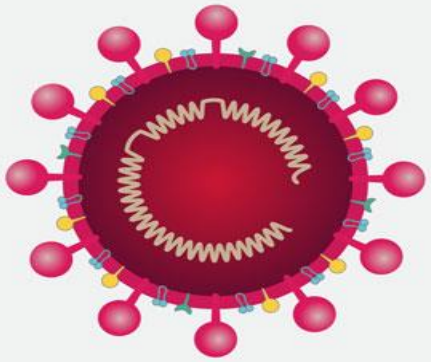
Mutations in SARS-CoV-2 that make it adapted to humans

- Transfer of the virus from animals (bats) to humans (zoonotic transmission) – not so easy and long process often many intermediated animal hosts (e.g., civet cats) are necessary

- Why?

- Lack of the virus-specific receptors in a new host – so virus must adapt to a new organism (multiple abortive infections of a new hosts – but often one effective is enough)





D614G
(China)

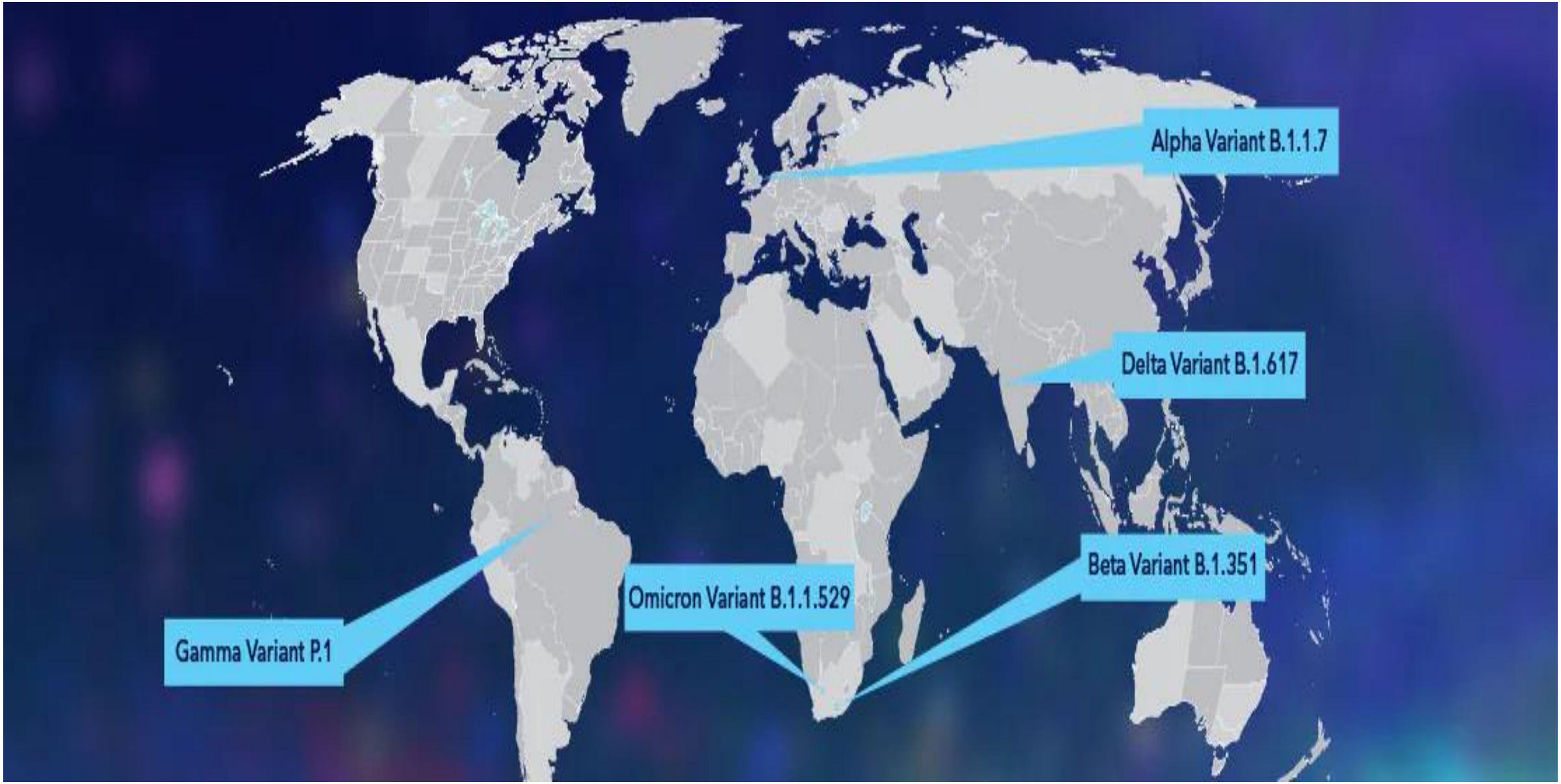
Variant of Concern (country where first detected)	Total Characteristic Mutations	Mutations in the S gene receptor binding domain
B.1.1.7 (United Kingdom)	18	N501Y
B.1.351 (South Africa)	8	N501Y, E484K, K417N
P.1 (Brazil)	21	N501Y, E484K

Possible functional changes

- More efficient transmission
- Reduced antibody binding and immune protection
- Reduced vaccine efficacy against B1.351 and P.1

New mutations: B.1.617.2 & B.1.1.529

General trend in mutations: enhance virus infectivity and immune escape


Alpha Variant B.1.1.7
Delta Variant B.1.617
Beta Variant B.1.351
Omicron Variant B.1.1.529
Gamma Variant P.1

Mutations in SARS-CoV-2 that make it adapted to humans

BUT

- New research suggests that SARS-CoV-2 had already evolved to be able to infect humans prior to the first reported case, making the initial transmission from bats to humans an easy one
- The researchers found that SARS-CoV-2 did, at one point, go through significant genomic changes, but that was before it made the jump to humans
- In 2021, French researchers isolated from Laos' bats three new viruses (BANAL-52, BANAL-103, and BANAL-236) that shared more than 95% of their genome with SARS-CoV-2

= sequences very close to those of early strains of SARS-CoV-2 existing in nature

COVID-19

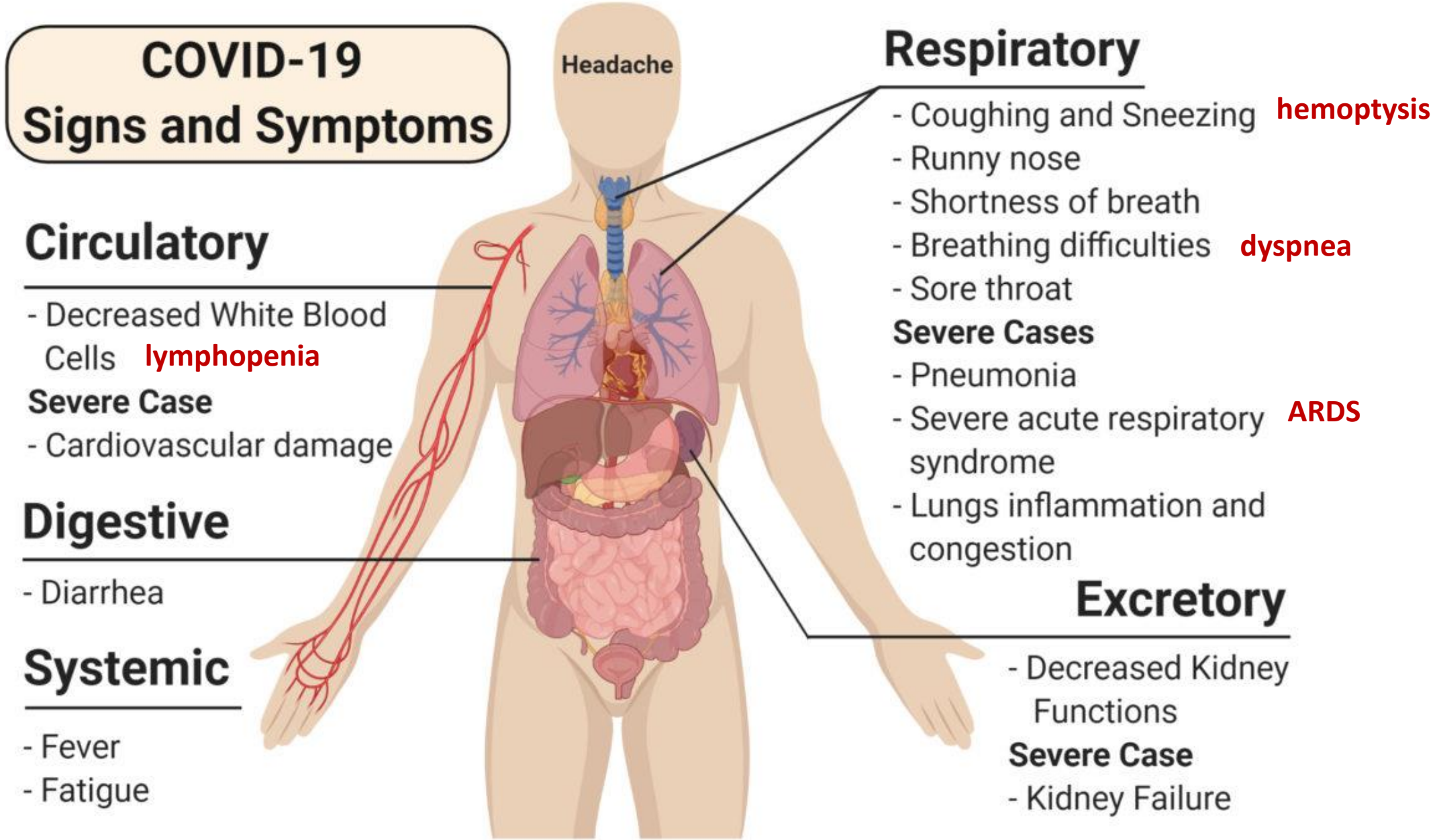
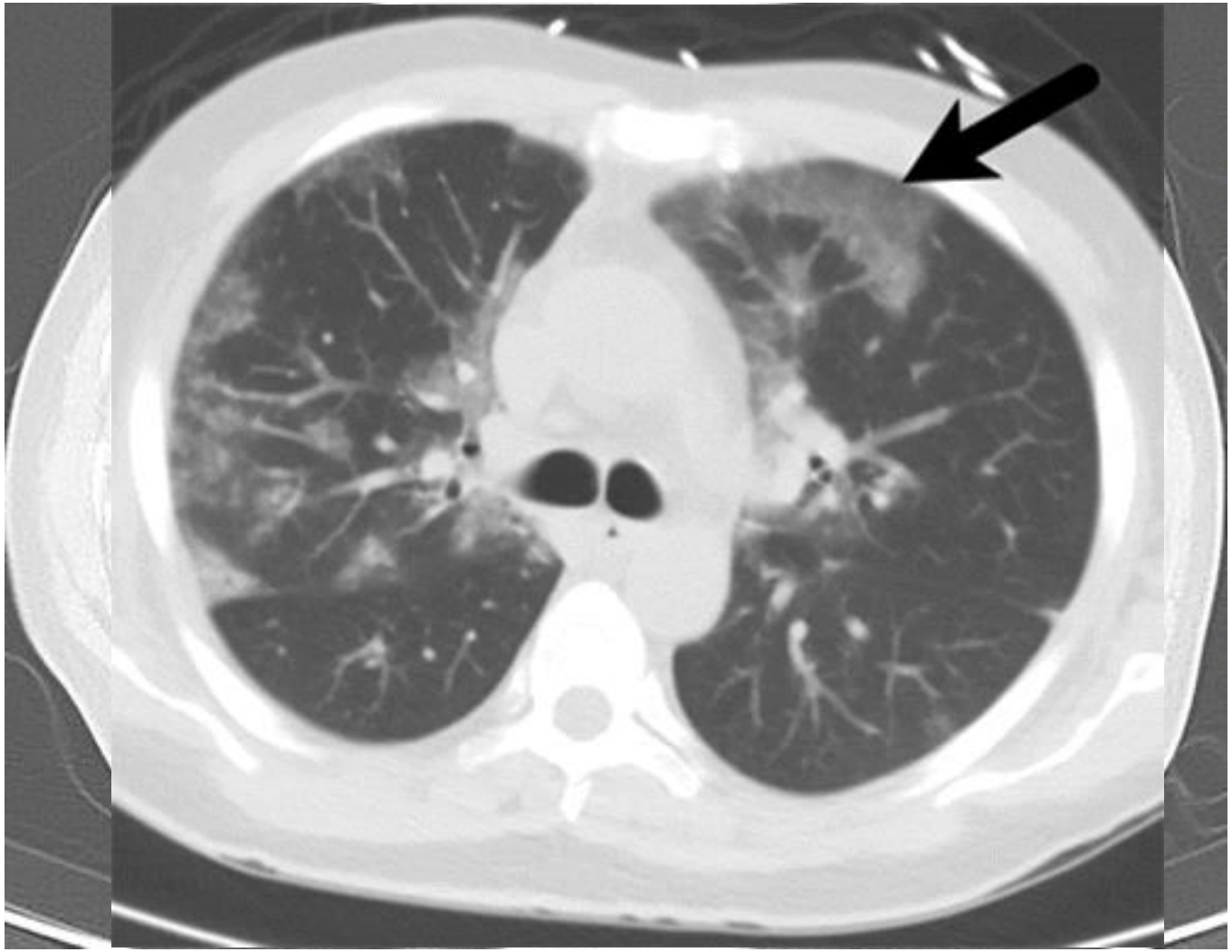


Figure: Symptoms of COVID-19 caused by Novel Corona Virus, SARS-CoV-2,

Grand-glass opacity (GGO) in subpleural regions (chest X-ray, CT scan)

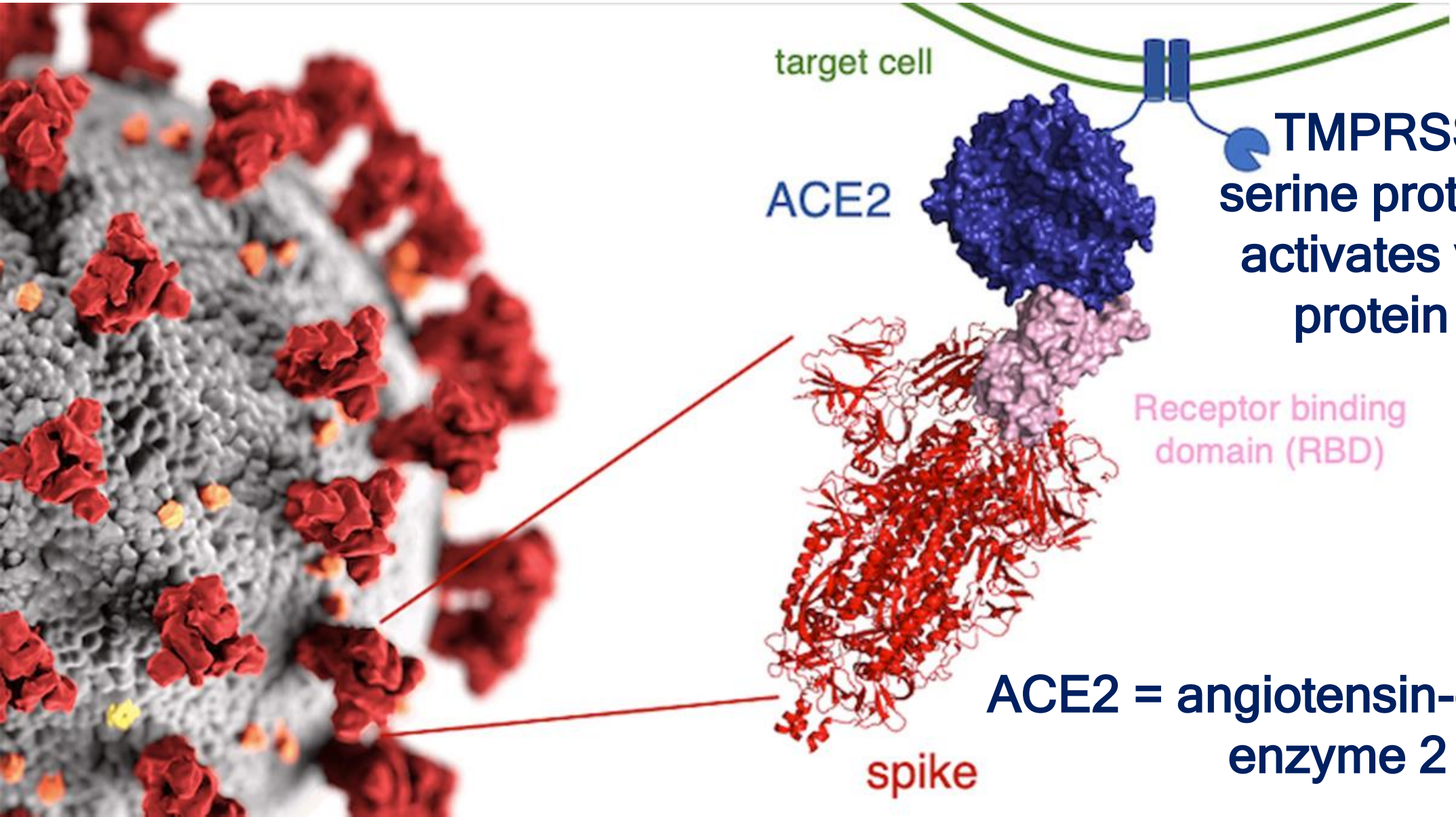
GGO = hazy grey areas that indicate increased density inside the lungs
= air displacement by fluid, airway collapse, fibrosis, neoplastic process



URT symptoms, diarrhea, acute cardiac injury are unique for Covid-19

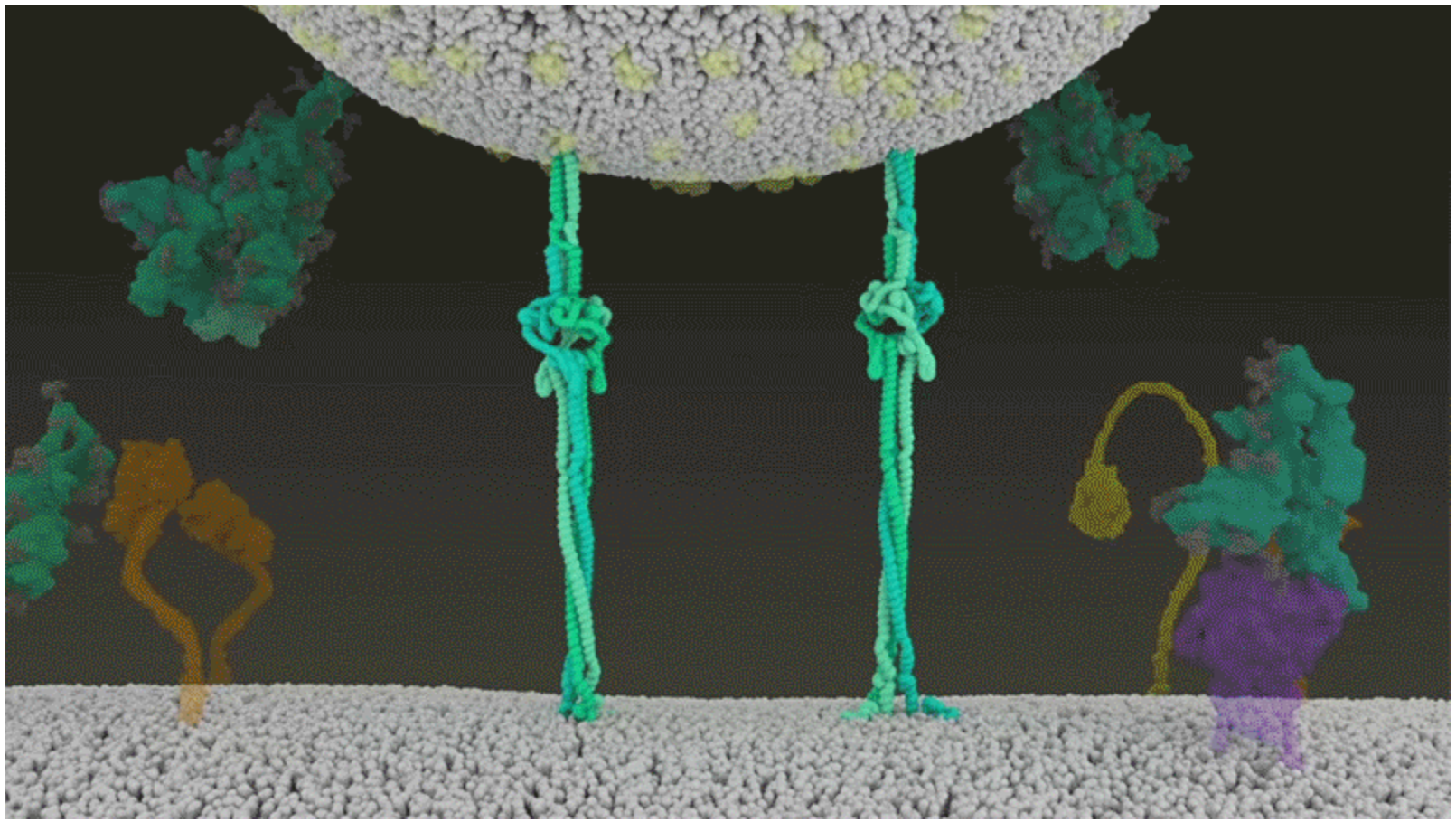
Bilateral GGO, fever, dry cough, dyspnea are shared with SARS

SARS-CoV-2 binding to the host cell



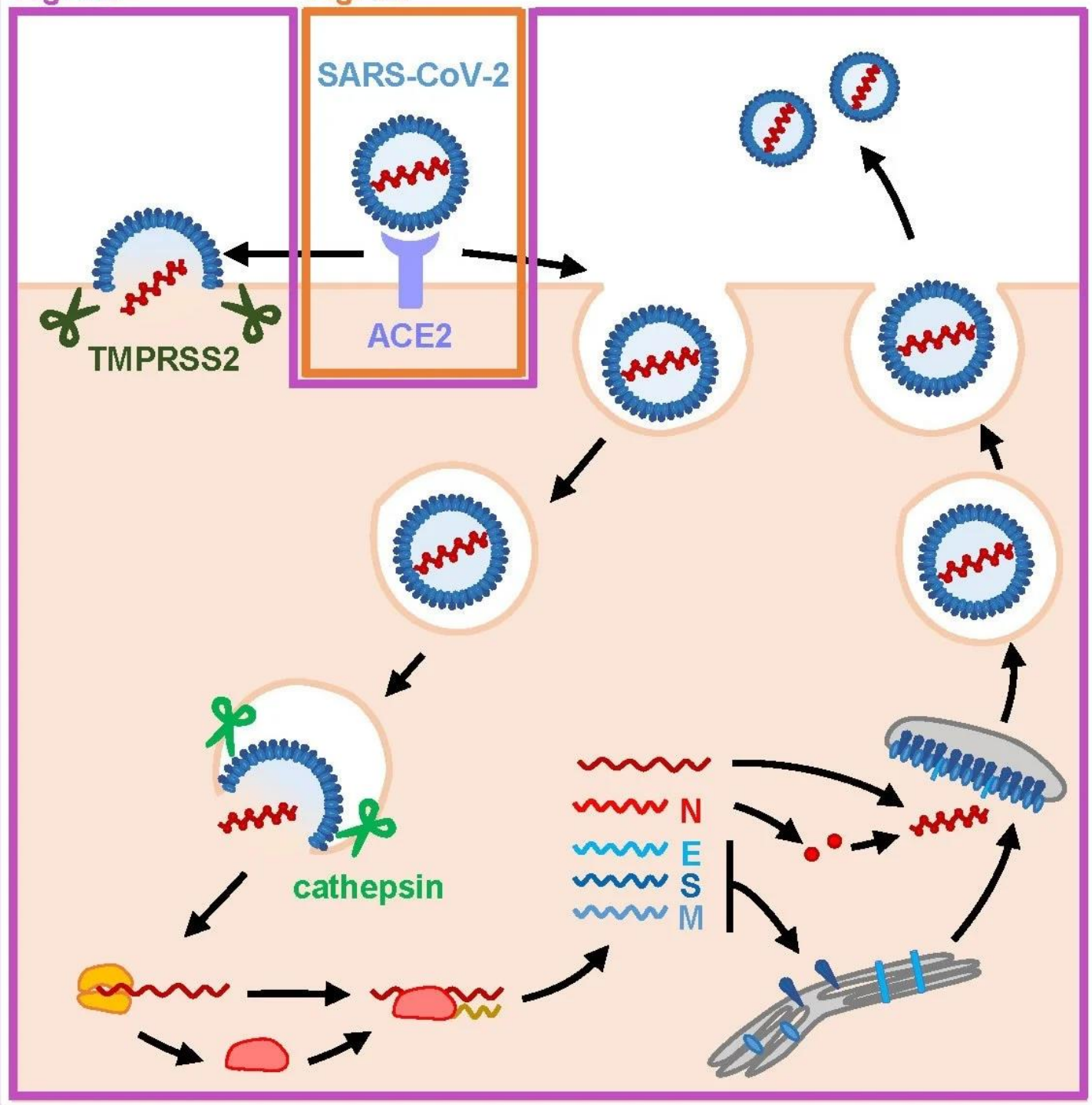
ACE2 = angiotensin-converting enzyme 2

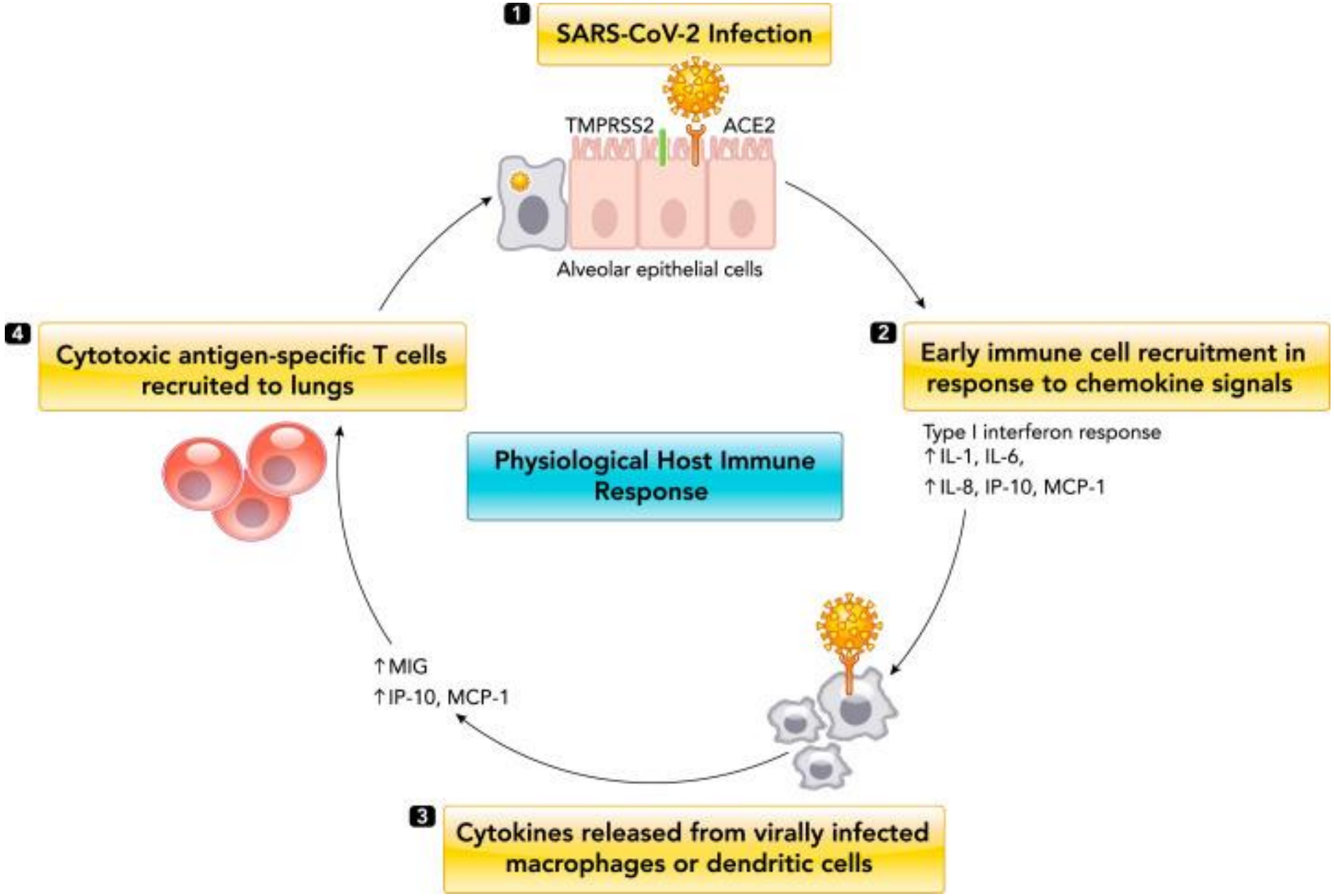
https://www.youtube.com/watch?v=Xuc9D4LVJdg

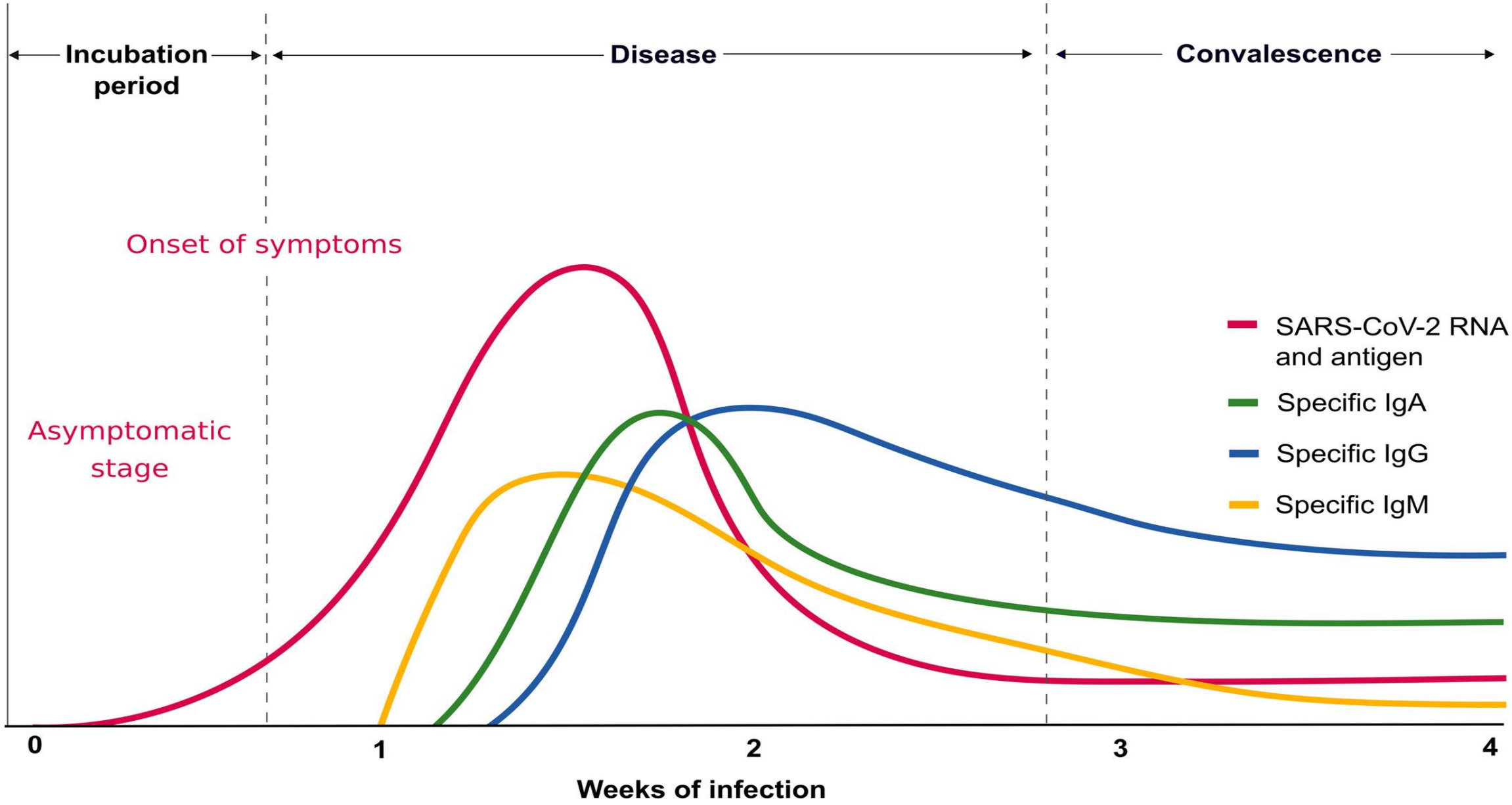


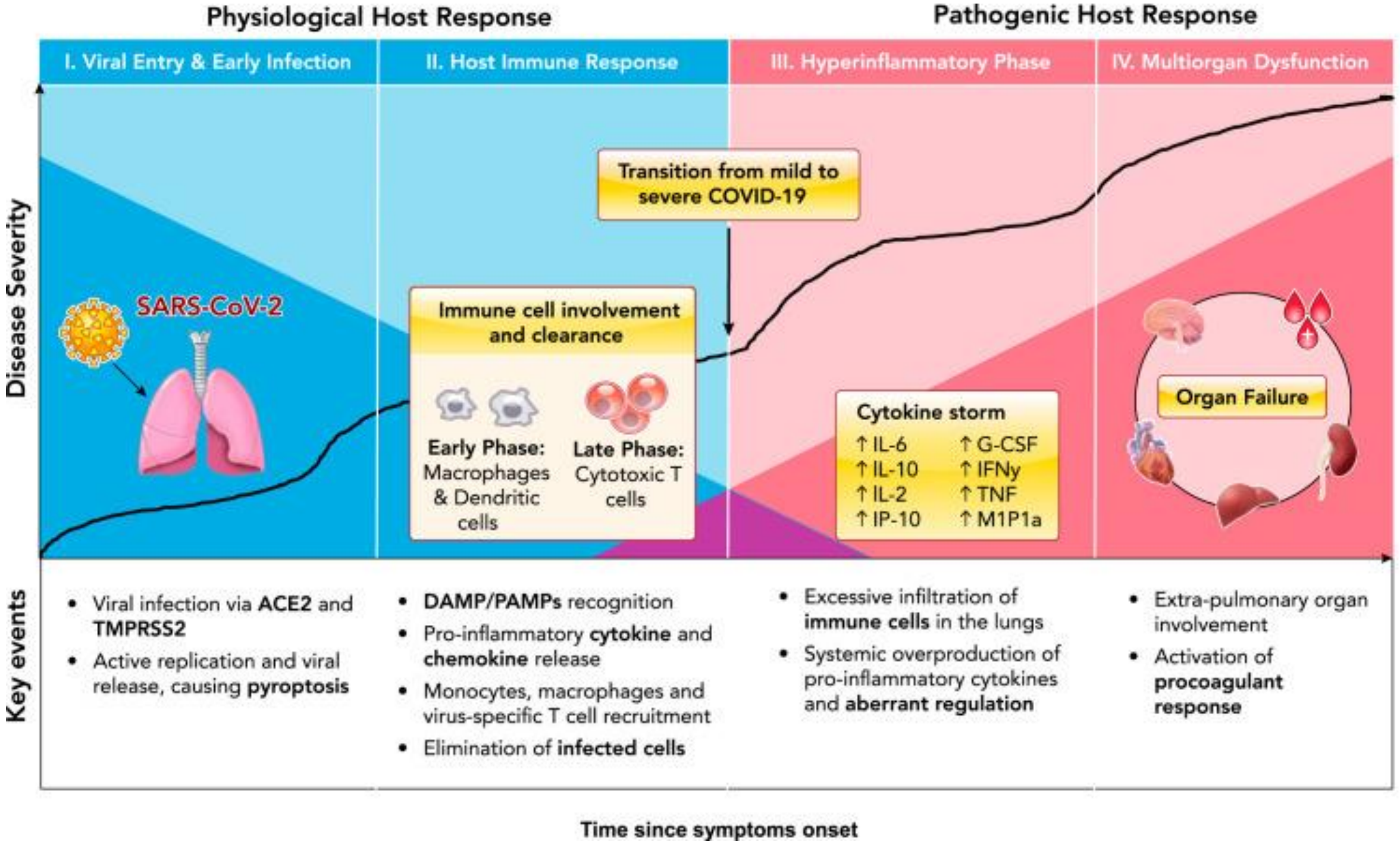
Pathomechanism of SARS-CoV-2 infection

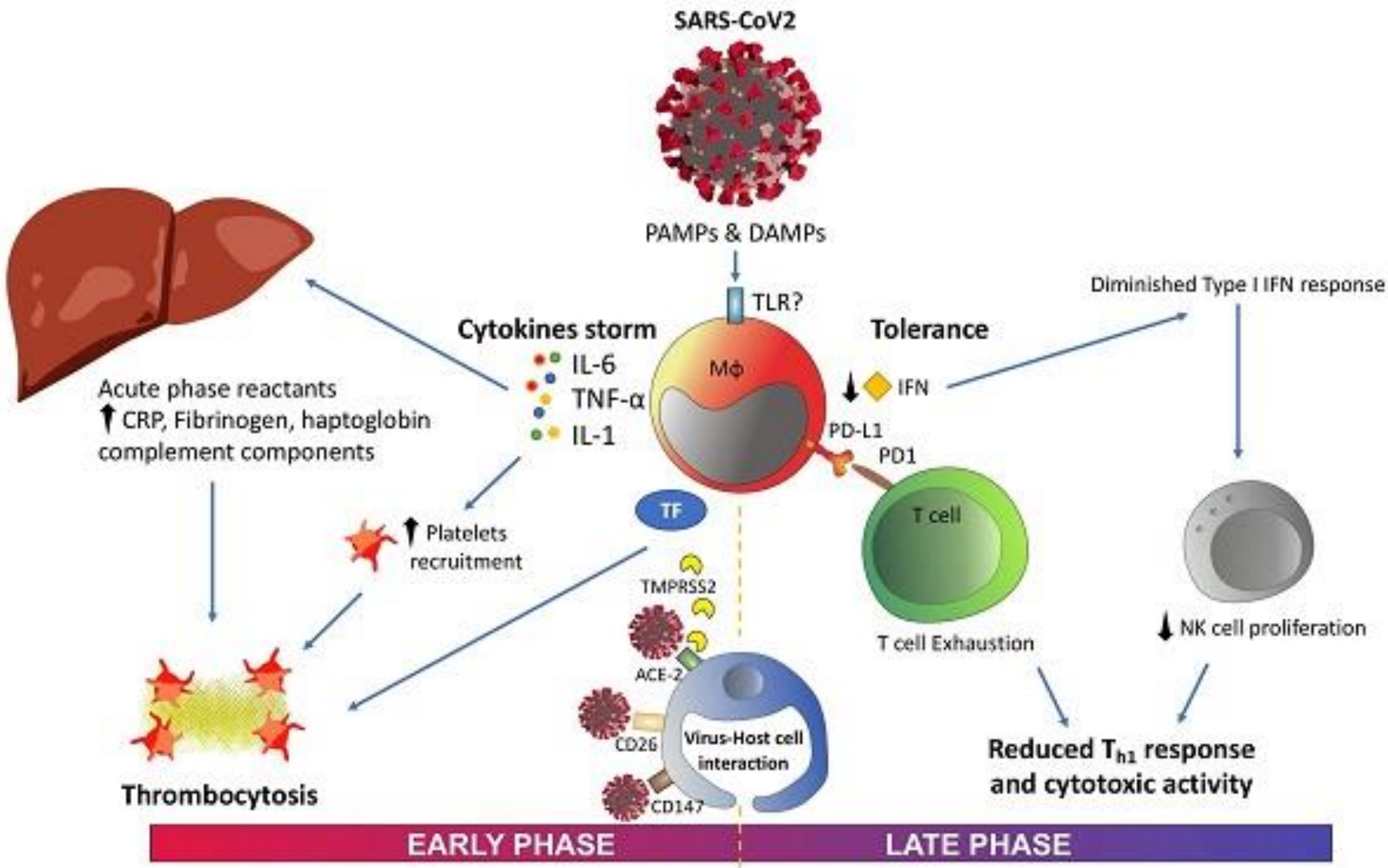
- Spike S protein determines the diversity of coronaviruses and host tropism
- SARS-CoV-2 has higher affinity for the ACE2 receptor than SARS-CoV-1
- ACE2 expression is high throughout the body (in lung, heart, ileum, kidney and bladder, adipose tissue, thyroid, testis, heart, blood vessels, neurons, neuroglia etc.)
- Transmembrane serine protease 2 (TMPRSS2) cleavages S protein to S1 and S2 subunits – step necessary for fusion
- Furin-like cleavage site in S viral protein – furin-like proteases are ubiquitous in human body and may contribute to the widened cell tropism and enhanced transmission of SARS-CoV-2

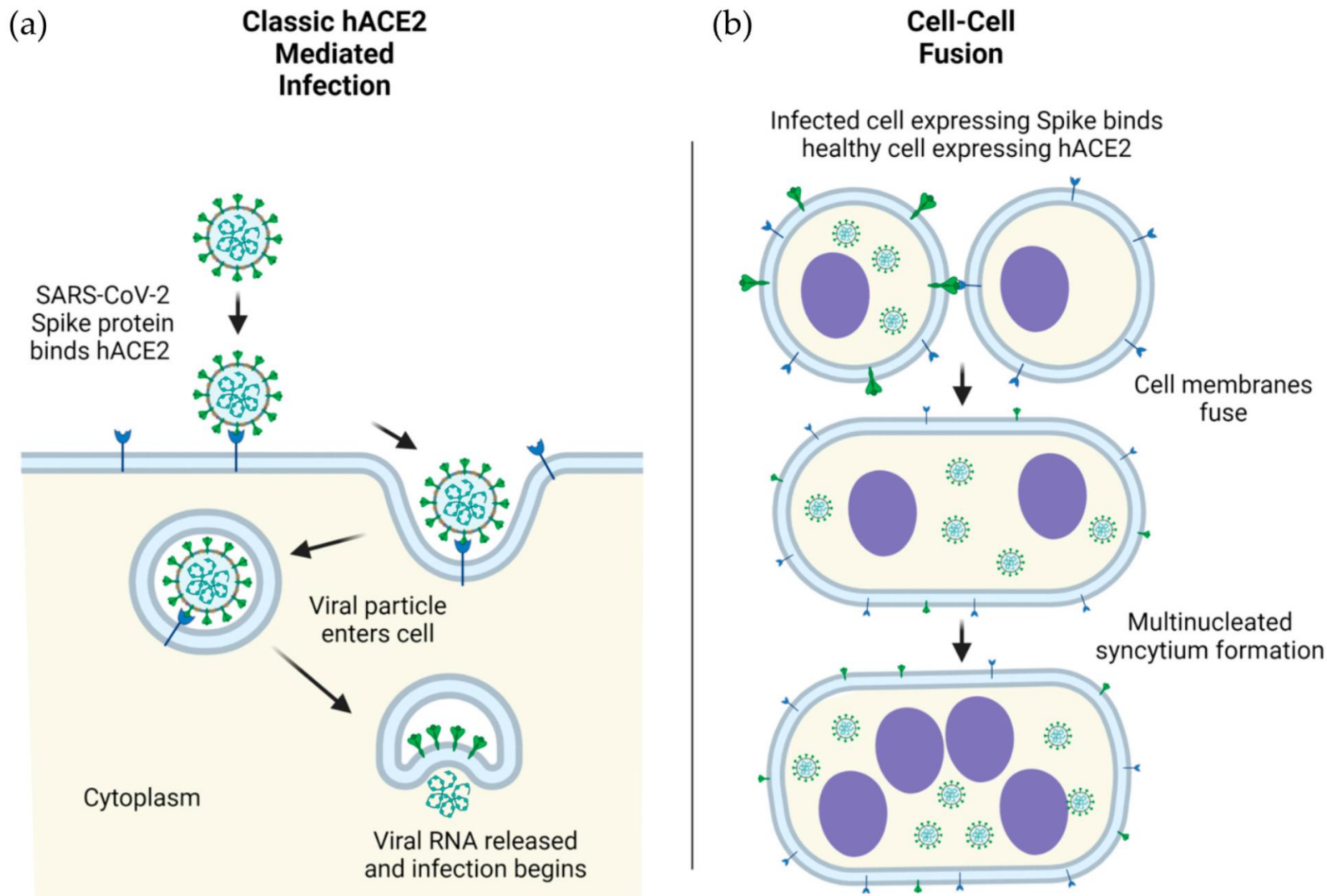

SARS-CoV-2
ACE2
TMPRSS2
cathepsin
N
E
S
M

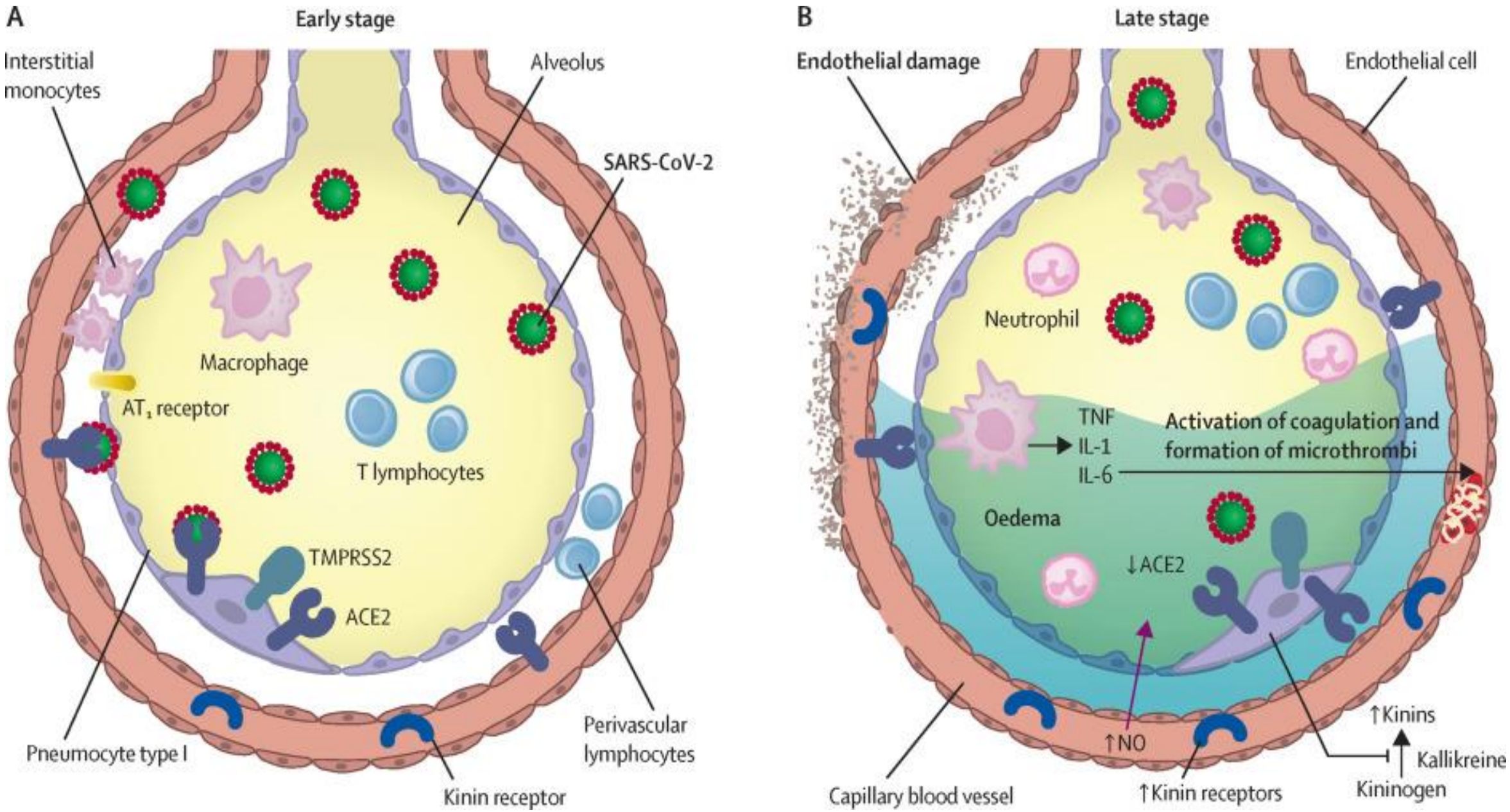

1
SARS-CoV-2 Infection
TMPRSS2
ACE2
Alveolar epithelial cells
2
Early immune cell recruitment in response to chemokine signals
Type I interferon response
↑IL-1, IL-6,
↑IL-8, IP-10, MCP-1
3
Cytokines released from virally infected macrophages or dendritic cells
↑MIG
↑IP-10, MCP-1
4
Cytotoxic antigen-specific T cells recruited to lungs
Physiological Host Immune Response

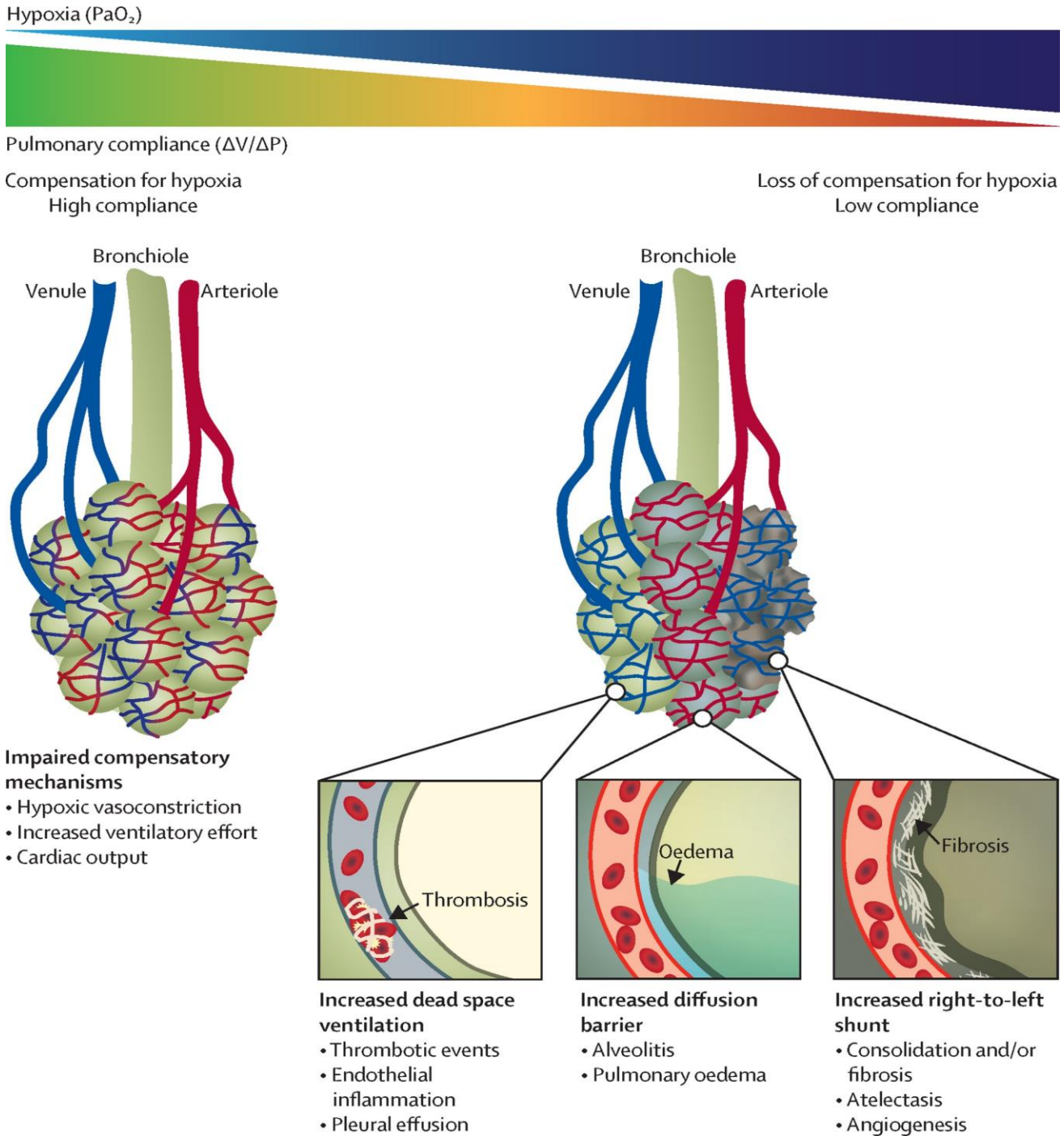

Incubation period
Disease
Convalescence
Onset of symptoms
Asymptomatic stage
SARS-CoV-2 RNA and antigen
Specific IgA
Specific IgG
Specific IgM
0
1
2
3
4
Weeks of infection

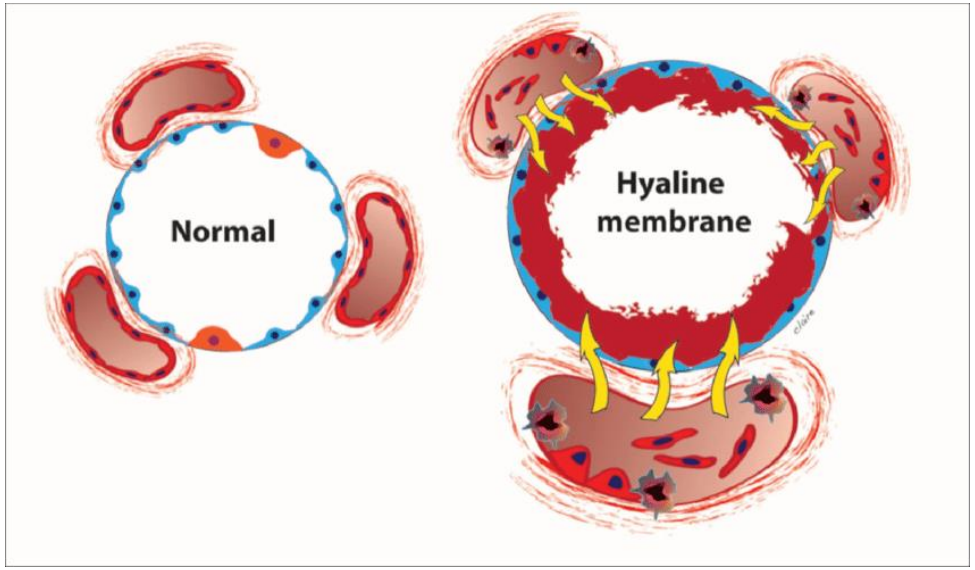

Physiological Host Response
Pathogenic Host Response
I. Viral Entry & Early Infection
II. Host Immune Response
III. Hyperinflammatory Phase
IV. Multiorgan Dysfunction
Disease Severity
SARS-CoV-2
Transition from mild to severe COVID-19
Immune cell involvement and clearance
Early Phase: Macrophages & Dendritic cells
Late Phase: Cytotoxic T cells
Cytokine storm
↑ IL-6
↑ IL-10
↑ IL-2
↑ IP-10
↑ G-CSF
↑ IFNγ
↑ TNF
↑ M1P1a
Organ Failure
Key events
• Viral infection via ACE2 and TMPRSS2
• Active replication and viral release, causing pyroptosis
• DAMP/PAMPs recognition
• Pro-inflammatory cytokine and chemokine release
• Monocytes, macrophages and virus-specific T cell recruitment
• Elimination of infected cells
• Excessive infiltration of immune cells in the lungs
• Systemic overproduction of pro-inflammatory cytokines and aberrant regulation
• Extra-pulmonary organ involvement
• Activation of procoagulant response
Time since symptoms onset


SARS-CoV2
PAMPs & DAMPs
TLR?
Cytokines storm
IL-6
TNF-α
IL-1
Mϕ
Tolerance
IFN
Diminished Type I IFN response
PD-L1
PD1
T cell
T cell Exhaustion
Acute phase reactants
CRP, Fibrinogen, haptoglobin
complement components
Platelets
recruitment
TF
TMPRSS2
ACE-2
CD26
CD147
Virus-Host cell
interaction
NK cell proliferation
Thrombocytosis
Reduced T_{h1} response
and cytotoxic activity
EARLY PHASE
LATE PHASE


(a)
Classic hACE2 Mediated Infection
SARS-CoV-2 Spike protein binds hACE2
Viral particle enters cell
Cytoplasm
Viral RNA released and infection begins
(b)
Cell-Cell Fusion
Infected cell expressing Spike binds healthy cell expressing hACE2
Cell membranes fuse
Multinucleated syncytium formation


A
Early stage
Interstitial monocytes
Alveolus
SARS-CoV-2
Macrophage
AT1 receptor
T lymphocytes
TMPRSS2
ACE2
Pneumocyte type I
Perivascular lymphocytes
Kinin receptor
B
Late stage
Endothelial damage
Endothelial cell
Neutrophil
TNF
IL-1
IL-6
Activation of coagulation and formation of microthrombi
Oedema
↓ACE2
↑NO
↑Kinins
Kallikreine
Kininogen
Capillary blood vessel
↑Kinin receptors


Hypoxia (PaO_2)
Pulmonary compliance (ΔV/ΔP)
Compensation for hypoxia
High compliance
Loss of compensation for hypoxia
Low compliance
Bronchiole
Venule
Arteriole
Bronchiole
Venule
Arteriole
Impaired compensatory mechanisms
• Hypoxic vasoconstriction
• Increased ventilatory effort
• Cardiac output
Thrombosis
Oedema
Fibrosis
Increased dead space ventilation
• Thrombotic events
• Endothelial inflammation
• Pleural effusion
Increased diffusion barrier
• Alveolitis
• Pulmonary oedema
Increased right-to-left shunt
• Consolidation and/or fibrosis
• Atelectasis
• Angiogenesis

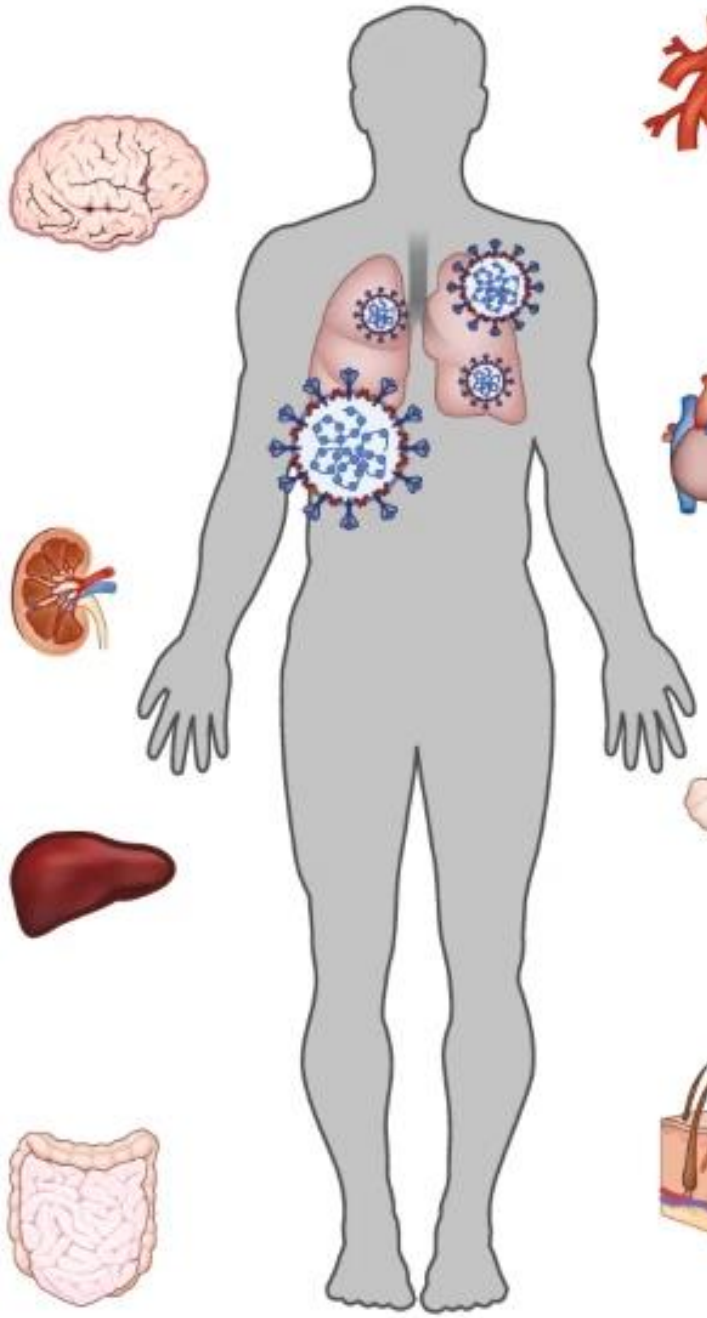

Normal
Hyaline membrane

Neurologic
Headaches
Dizziness
Encephalopathy
Guillain-Barré
Ageusia
Myalgia
Anosmia
Stroke

Renal
Acute kidney injury
Proteinuria
Hematuria

Hepatic
Elevated aminotransferases
Elevated bilirubin

Gastrointestinal
Diarrhea
Nausea/vomiting
Abdominal pain
Anorexia

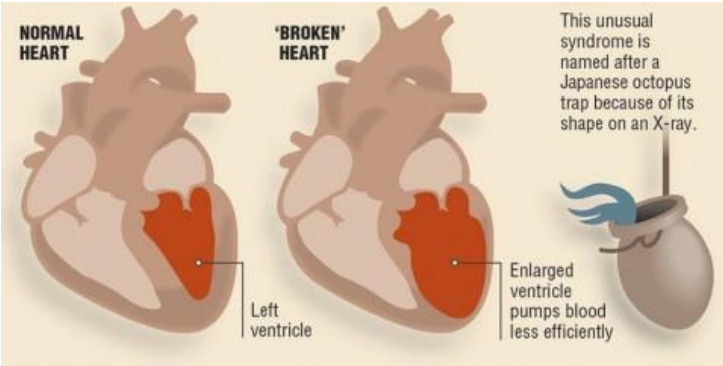


Thromboembolism
Deep vein thrombosis
Pulmonary embolism
Catheter-related thrombosis

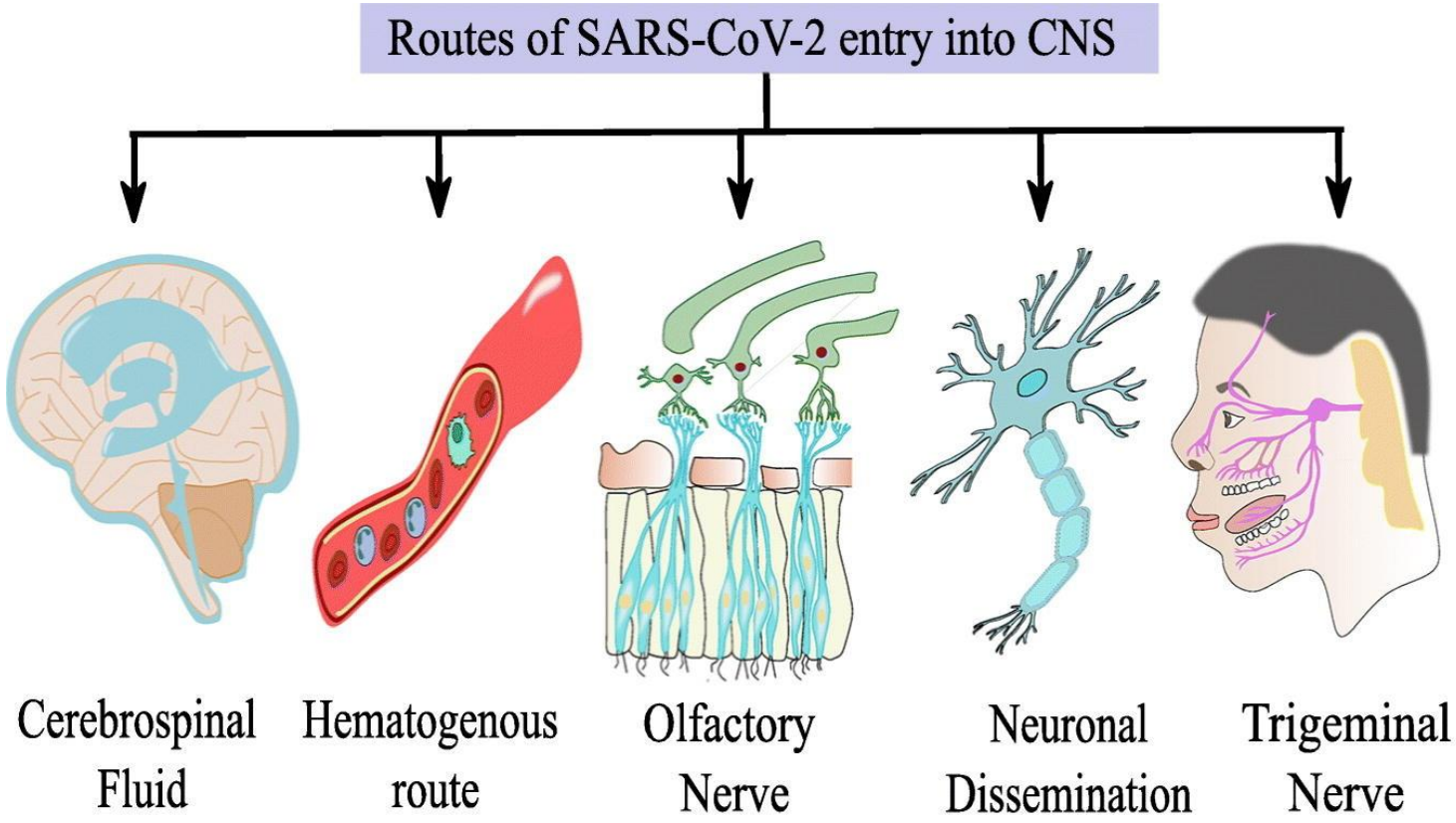
Cardiac
Takotsubo cardiomyopathy
Myocardial injury/myocarditis
Cardiac arrhythmias
Cardiogenic shock
Myocardial ischemia
Acute cor pulmonale

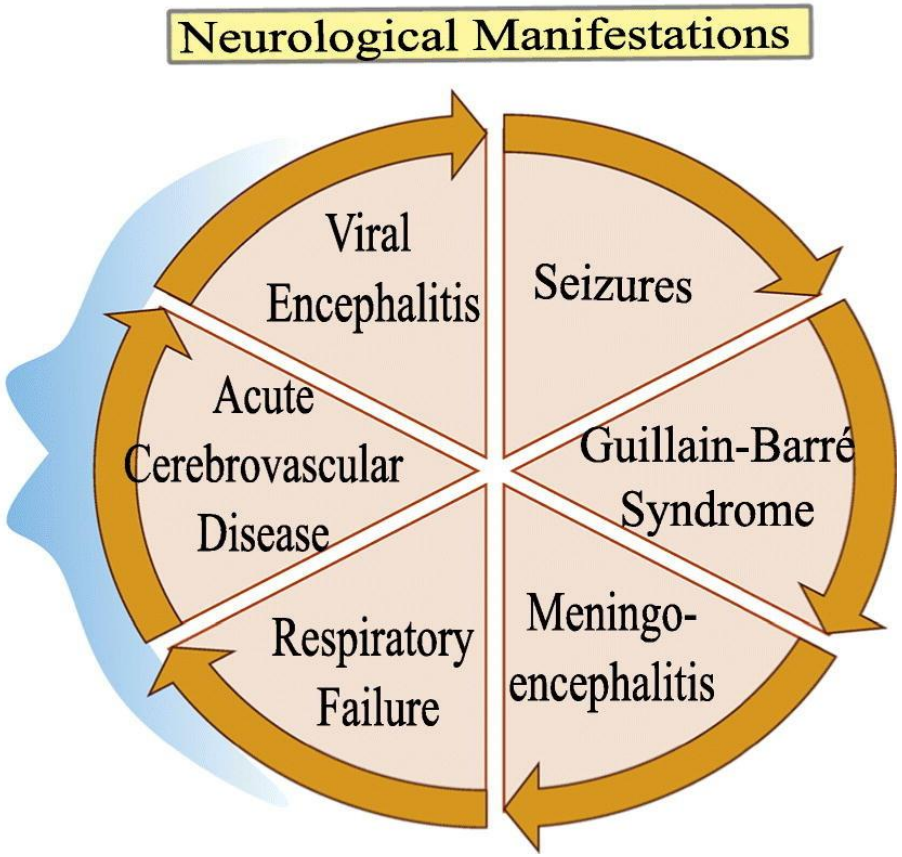
Endocrine
Hyperglycemia
Diabetic ketoacidosis

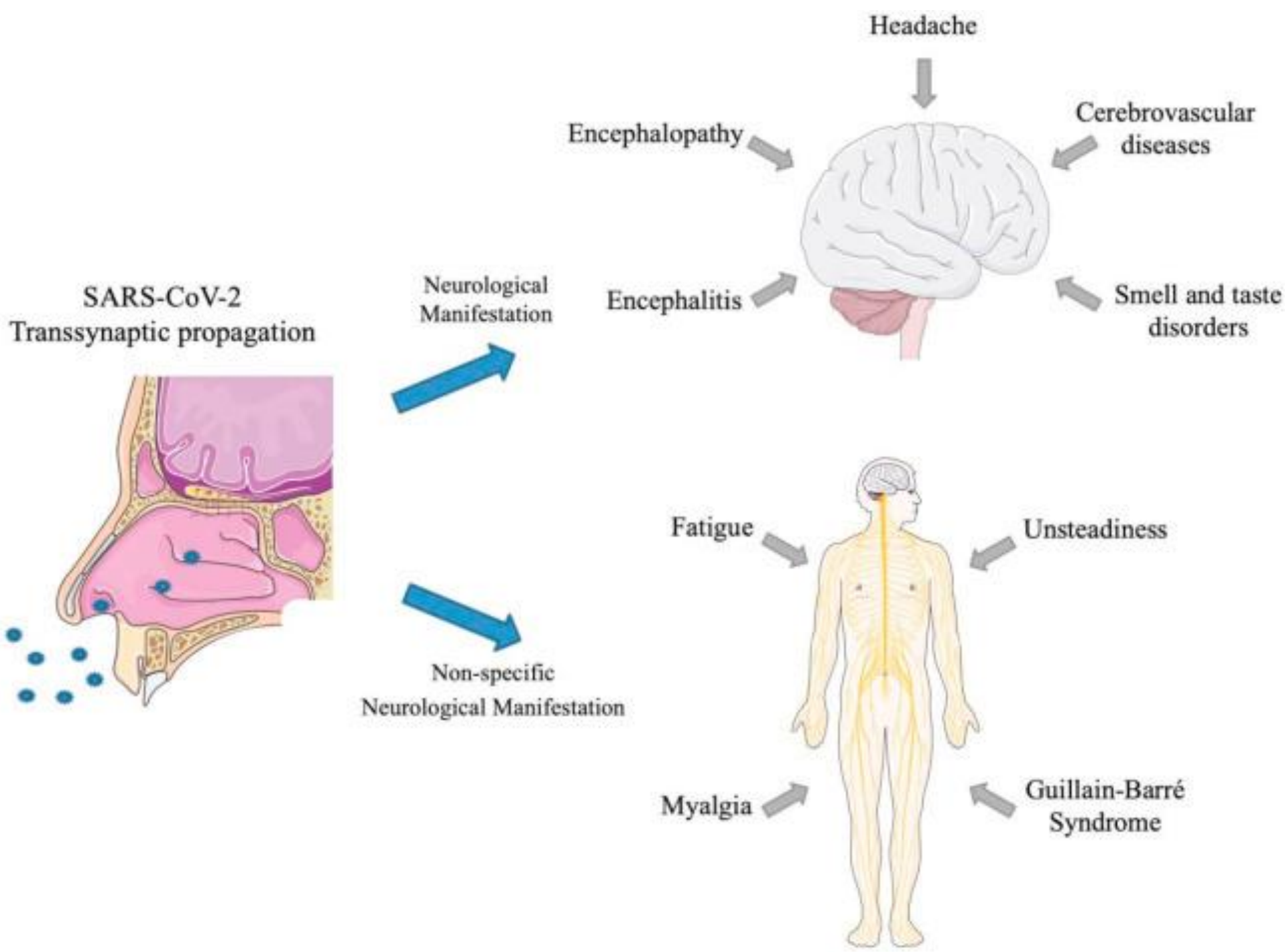
Dermatological
Petechaie
Livedo reticularis
Erythematous rash
Urticaria
Vesicles
Pernio-like lesions

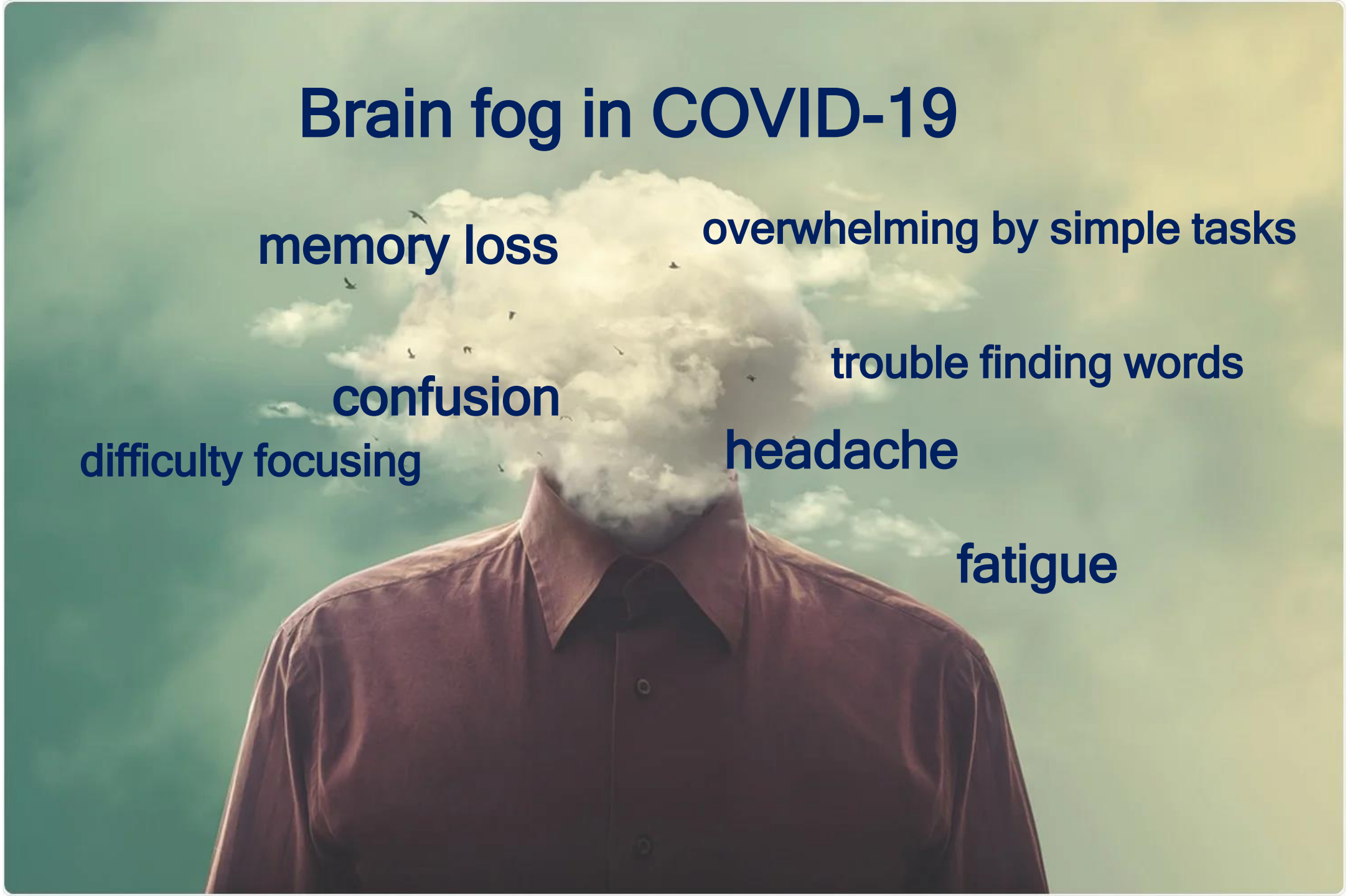


NeuroCovid-19






SARS-CoV-2
Transsynaptic propagation
Neurological Manifestation
Non-specific Neurological Manifestation
Headache
Encephalopathy
Cerebrovascular diseases
Encephalitis
Smell and taste disorders
Fatigue
Unsteadiness
Myalgia
Guillain-Barré Syndrome


Brain fog in COVID-19
memory loss
overwhelming by simple tasks
trouble finding words
confusion
difficulty focusing
headache
fatigue

Classification of COVID-19 patients

Asymptomatic	COVID nucleic acid test positive. Without any clinical symptoms and signs and the chest imaging is normal
Mild	Symptoms of acute upper respiratory tract infection (fever, fatigue, myalgia, cough, sore throat, runny nose, sneezing) or digestive symptoms (nausea, vomiting, abdominal pain, diarrhea)
Moderate	Pneumonia (frequent fever, cough) with no obvious hypoxemia, chest CT with lesions
Severe	Pneumonia with hypoxemia ($SpO_2 < 92\%$)
Critical	Acute respiratory distress syndrome (ARDS), may have shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction and acute kidney injury

Key variables that can influence the severity of COVID-19

1. Dosage – small number = asymptomatic or mild infection
2. Genetics – receptor protein on the host cells are unique to each person
3. Infection route – via nose or mouth through aerosolized droplets from cough or sneeze vs. indirect route through contaminated surfaces = differ immune responses
4. Virus virulence
5. Immune status – infection with new foe may thwart rapid immune response and allow the virus to do more damage; virus has the capability to switch off chemical warnings (IFNɣ)

Why COVID-19 is so severe in some individuals?

- LUNGS DAMAGE – SARS-CoV-2 kills lung cells and corrupts them too – cells have been fusing together into malfunctioning syncytia and lungs regeneration does not happen
- STICKY BLOOD – blood clotting goes strangely awry in COVID-19 - doctors are unable to get a line into a patient because it is immediately blocked with blood clots (blood-clotting chemicals in the blood are "200%, 300%, 400% higher" than normal in some patients)
- UNCONTROLLED INFLAMMATION – the virus can cause runaway inflammation in some patients, making the immune system go into overdrive, with damaging consequences for the rest of the body
- We are fatter than we should be – COVID-19 is worse in obese – generous waistline increases the risk of needing intensive care or death - this is unusual…..

Low-dose SARS-CoV-2 infection

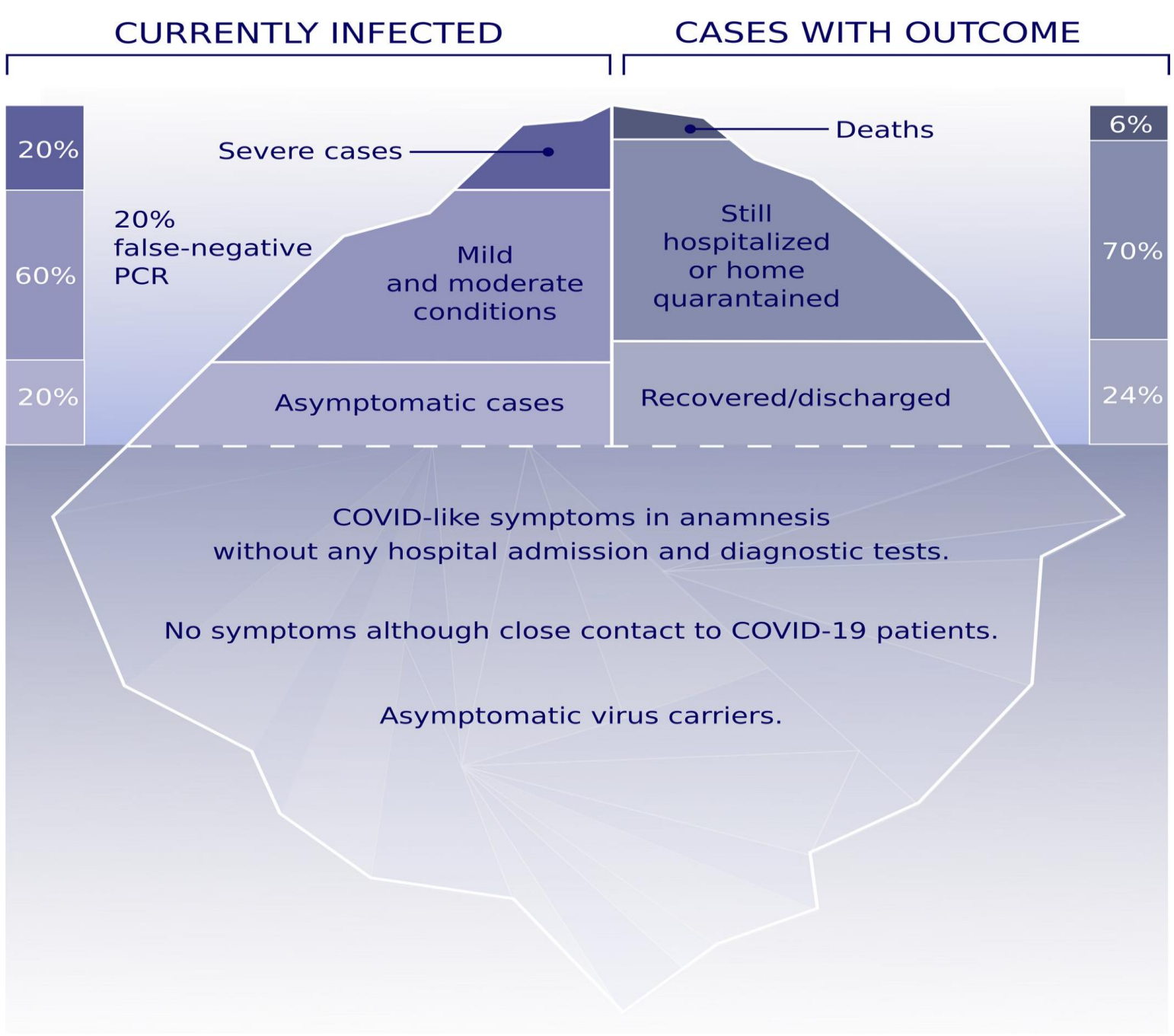
Effector T and B cell immune response and development of virus-specific neutralizing IgM, IgA, IgG antibodies

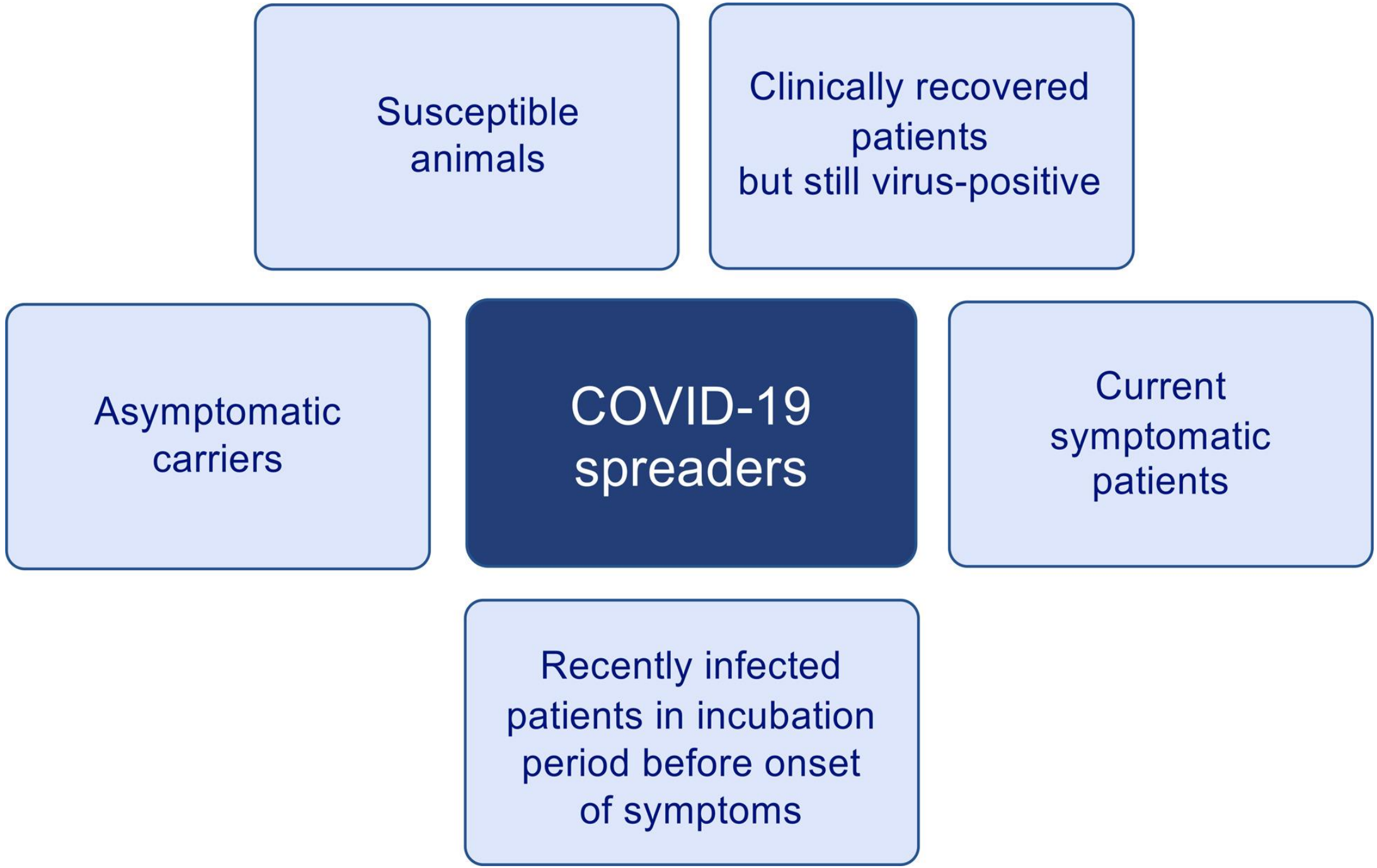
Rapid viral clearance + indolent disease

High-dose SARS-CoV-2 infection or risk factor comorbidities

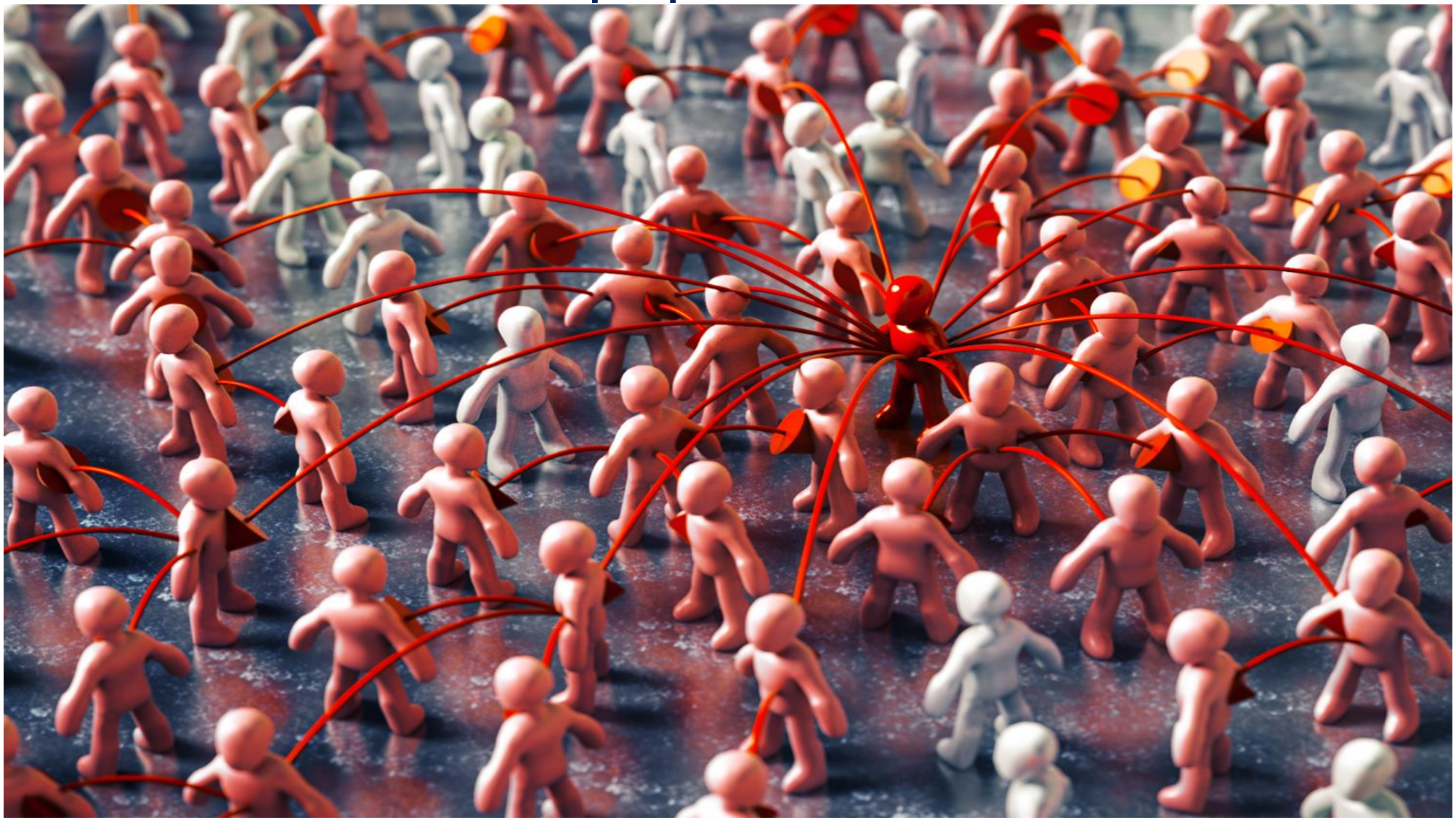
Lymphopenia
Immunosuppression
Inefficient T and B cell immunity
Cytokine storm
Destructive tissue inflammation

Severe disease
Prolonged viral clearance
Organ failure
DIC


CURRENTLY INFECTED
CASES WITH OUTCOME
20%
60%
20%
Severe cases
20%
false-negative
PCR
Mild
and moderate
conditions
Asymptomatic cases
Deaths
Still
hospitalized
or home
quarantained
Recovered/discharged
6%
70%
24%
COVID-like symptoms in anamnesis
without any hospital admission and diagnostic tests.
No symptoms although close contact to COVID-19 patients.
Asymptomatic virus carriers.


Susceptible animals
Clinically recovered patients but still virus-positive
Asymptomatic carriers
COVID-19 spreaders
Current symptomatic patients
Recently infected patients in incubation period before onset of symptoms

The study shows that events (crowding) where one person infects more than six other people are much more common



Why there is no effective treatment of COVID-19?

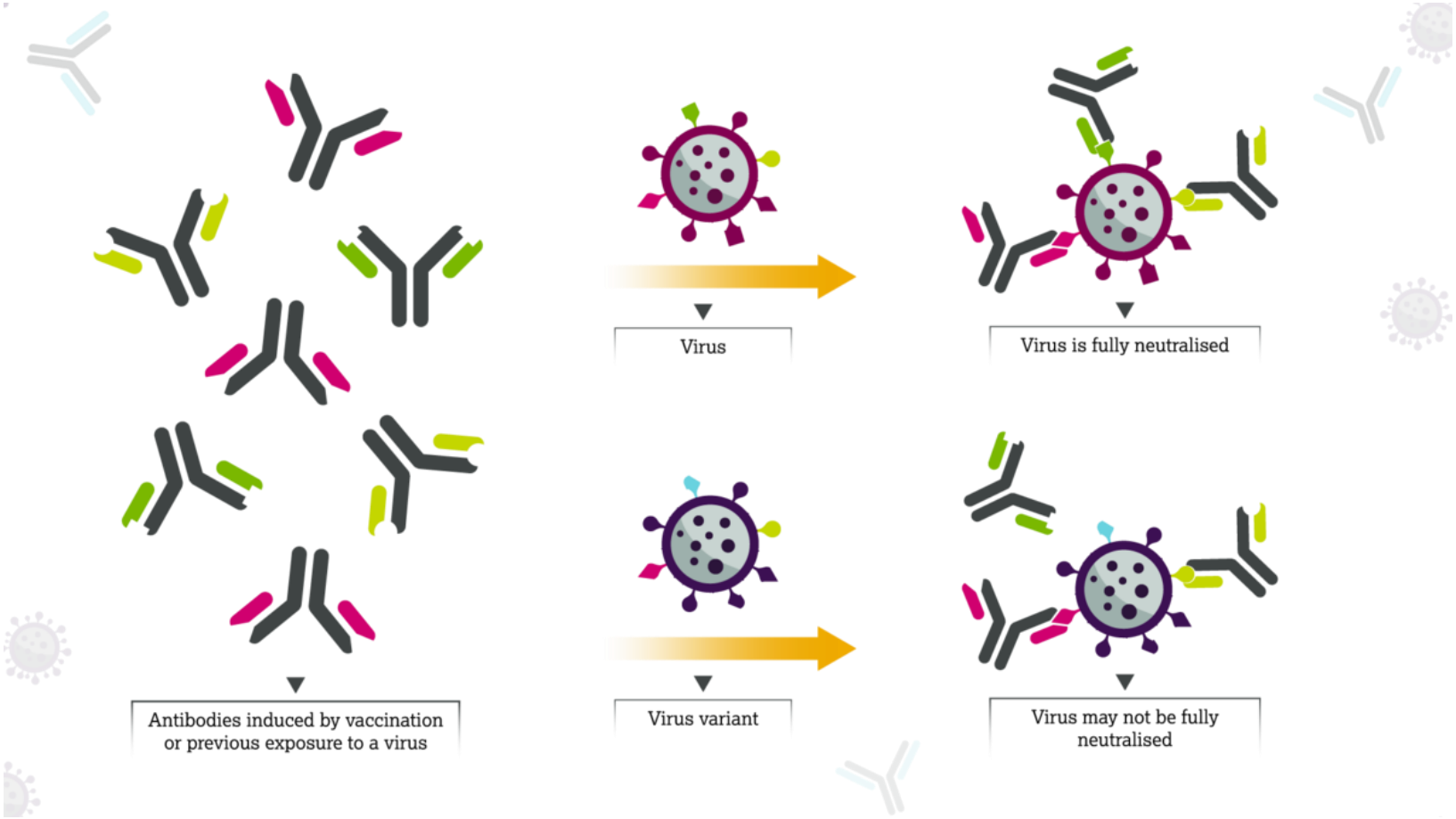
Examples only:

- Chloroquine, hydroxychloroquine
- Bevacizumab – recombinant monoclonal antibody against VEGF
- Protease inhibitors (lopinavir/ritonavir)
- Anticoagulants
- Inhibitors of viral entry
- Convalescent plasma with antibodies
- Inhibitors of cytokine storm (corticosteroids, sirolimus – prevents transplants rejection)
- Many others biologically tested or not approved yet
- Currently – remdesivir, dexamethasone, heparin, baricitinib, tofacitinib, tocilizumab, or sarilumab

Current clinical development of COVID-19 vaccines

Therapeutic agents	Properties	Organization/Company	Status
mRNA-1273	mRNA vaccine	Moderna and NIAID	Phase 2
BNT162	mRNA vaccine	BioNTech and Pfizer	Phase 1/2
INO-4800	DNA vaccine	Inovio Pharmaceuticals	Phase 1
AZD1222	Adenovirus vaccine	University of Oxford and AstraZeneca	Phase 2b/3
Ad5-nCoV	Adenovirus vaccine	CanSino Biologics	Phase 2
Unnamed	Inactivated virus	Wuhan Institute of Biological Products and Sinopharm	Phase 1/2
Unnamed	Inactivated virus	Beijing Institute of Biological Products and Sinopharm	Phase 1/2
PiCoVacc	Inactivated virus with adjuvant	Sinovac	Phase 1/2
Unnamed	Inactivated virus	Institute of Medical Biology and Chinese Academy of Medical Sciences	Phase 1
NVX-CoV2373	Protein subunit	Novavax	Phase 1/2

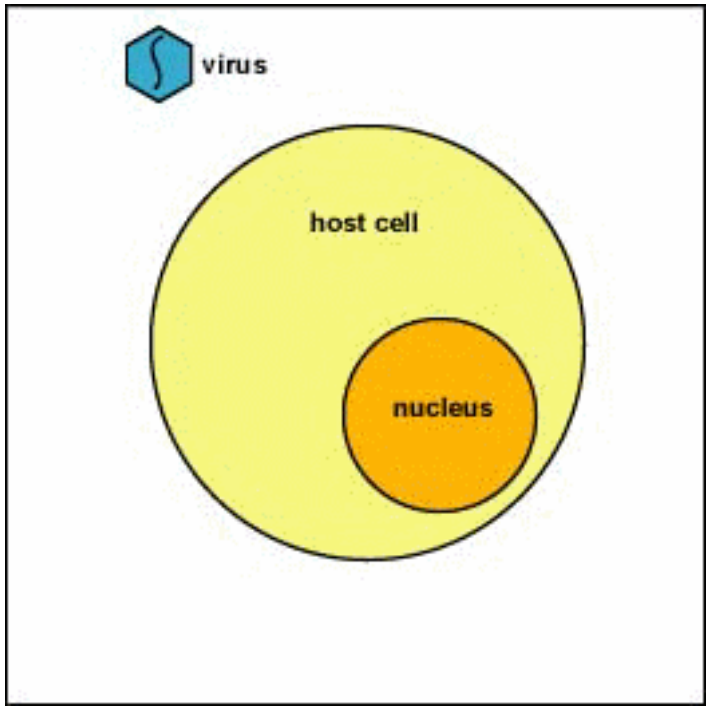
Why do vaccines against COVID-19 provide only short-lived immunity?



Clever virus

Brilliant cheater

it inhibits INFγ production so well you do not even know you are ill



It behaves like a „hit and run" killer

The amount of virus in human body begins to peak the day before someone begin to get sick… But it takes at least a week before COVID-19 progress to the overt disease – so, the virus spread on the next victims long before someone recover or die…..

…the virus doesn't care if you die

So new for humans' organism…

quite a shock to our immune system

It does peculiar and unexpected things to the body…

COVID-19 as a zoonotic disease that has already spread globally to several millions of humans and probably animals, will be practically impossible to eradicate

We have to learn how to live together with the virus and disease

A commonly observed phenomenon in infectious diseases is that pathogens become less virulent as they evolve in a human population

Protect yourself from Covid-19 !

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Thank you for your attention!

In order to get information on the presented content, please send messages to the e-mail address:

beata.sobieszczanska@umw.edu.pl