

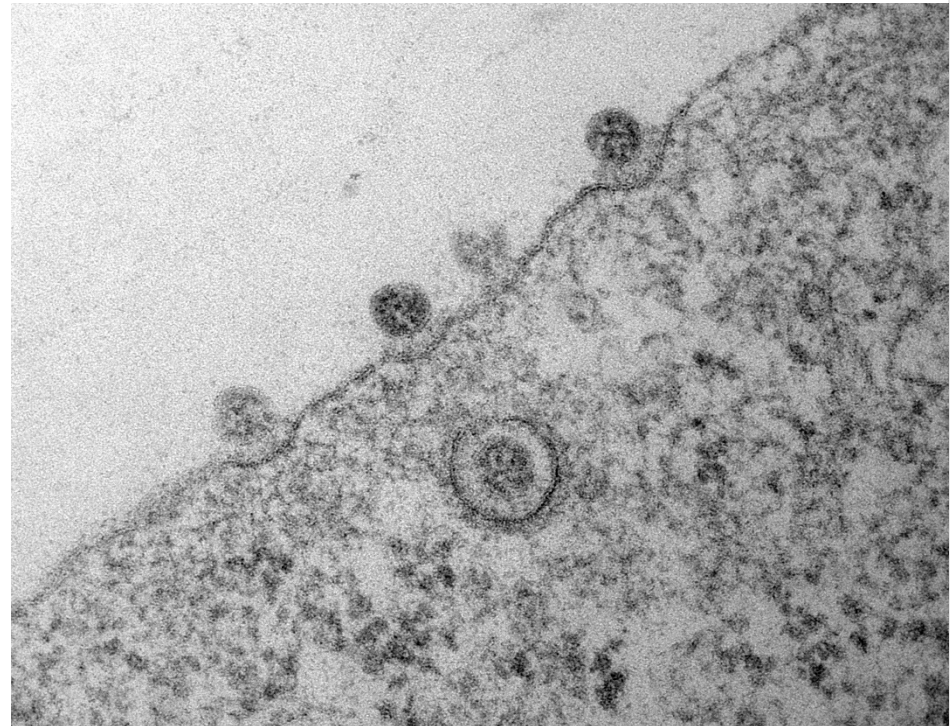
# Coronaviruses and SARS-CoV-2

Dr Richard J. P. Brown

Qu et al. (2024) *PNAS*  
<https://doi.org/10.1073/pnas.2407437121>

Department for Molecular &  
Medical Virology

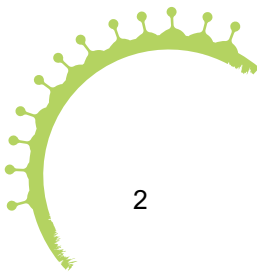
13.05.2026



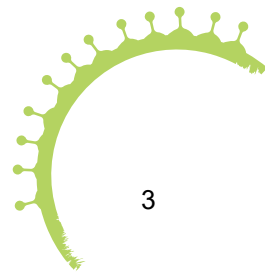
# Goals for today's lecture

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- Understanding the coronavirus replication cycle
- Overview of highly pathogenic coronaviruses - origins
- Update: SARS-CoV-2 and COVID-19

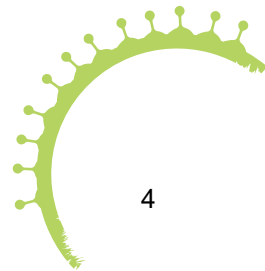
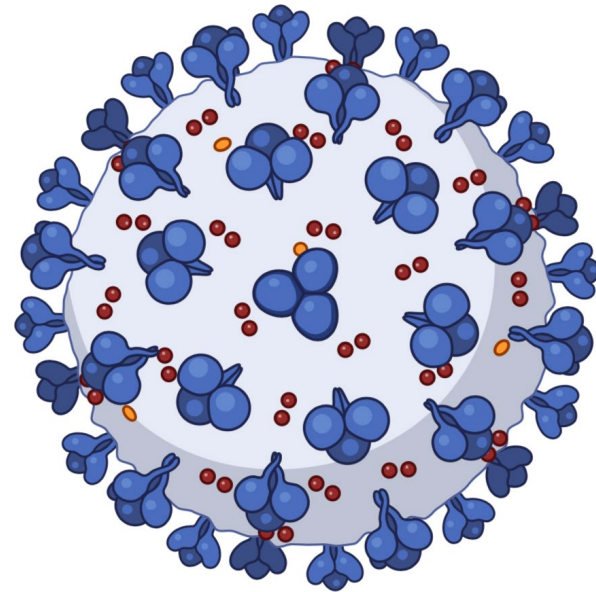


# Coronaviruses

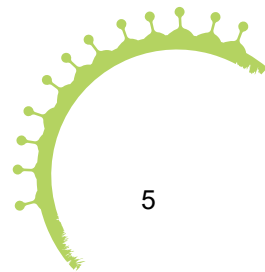
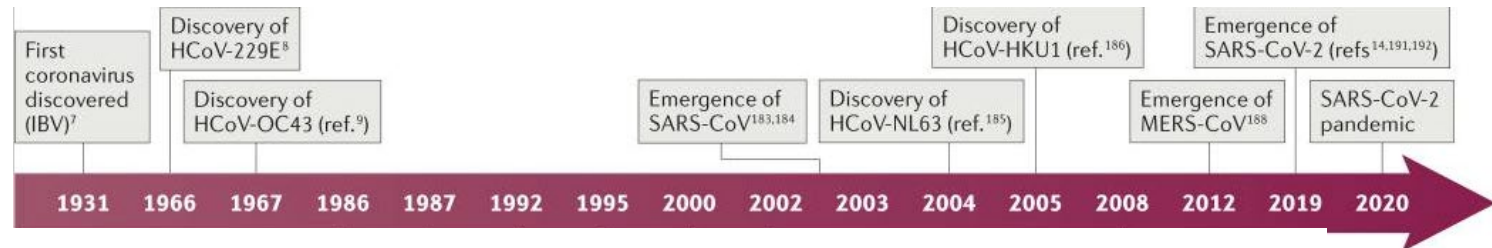
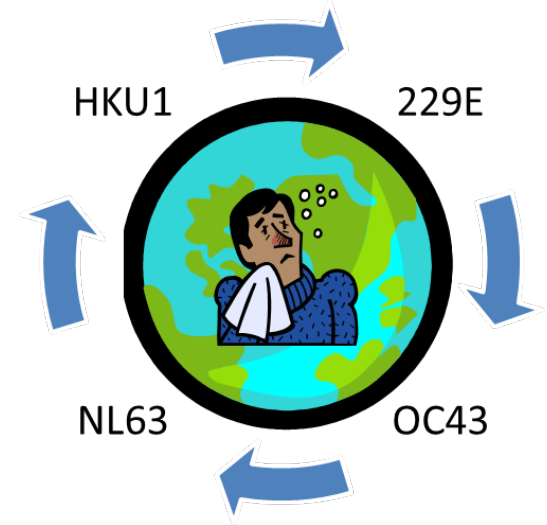


# Coronaviruses

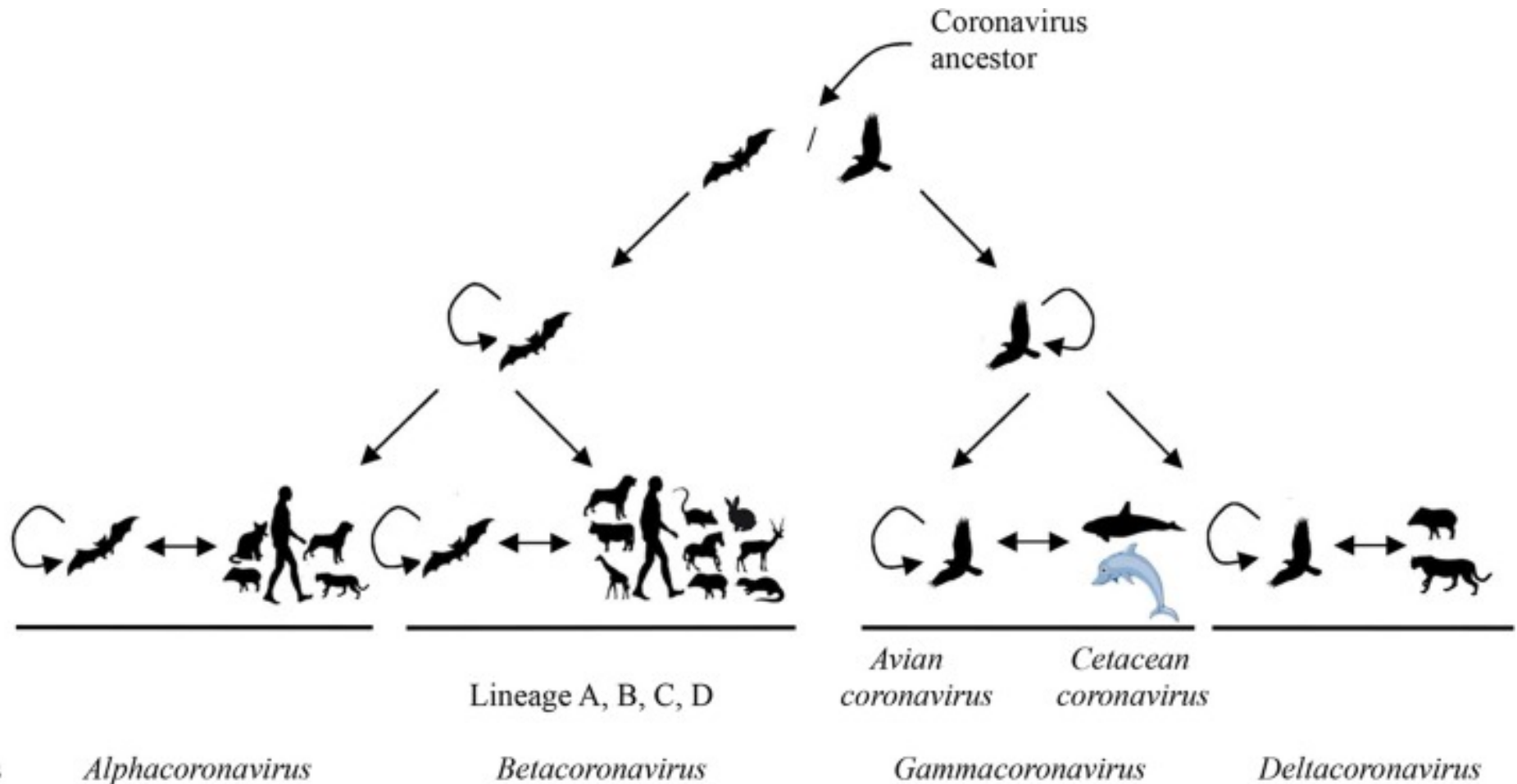
- Family: *Coronaviridae*
- Genus: Coronavirus
- Enveloped
- Size: 80 – 150 nm
- Genome: 27 – 32 kb
- ss (+) RNA



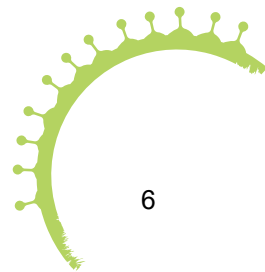
- Human Coronaviruses are endemic worldwide
- Cause approx. 15% of the yearly common colds
- Three pathogenic human Coronaviruses
  - SARS-CoV
  - MERS-CoV
  - SARS-CoV-2



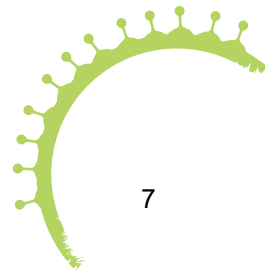
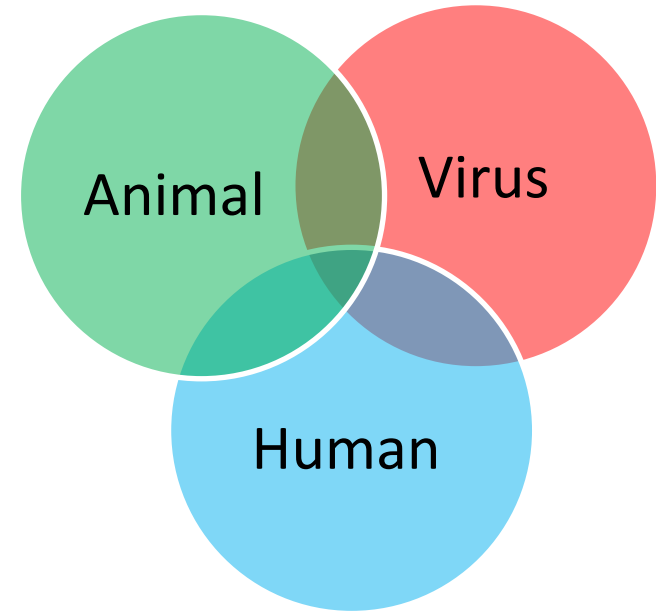
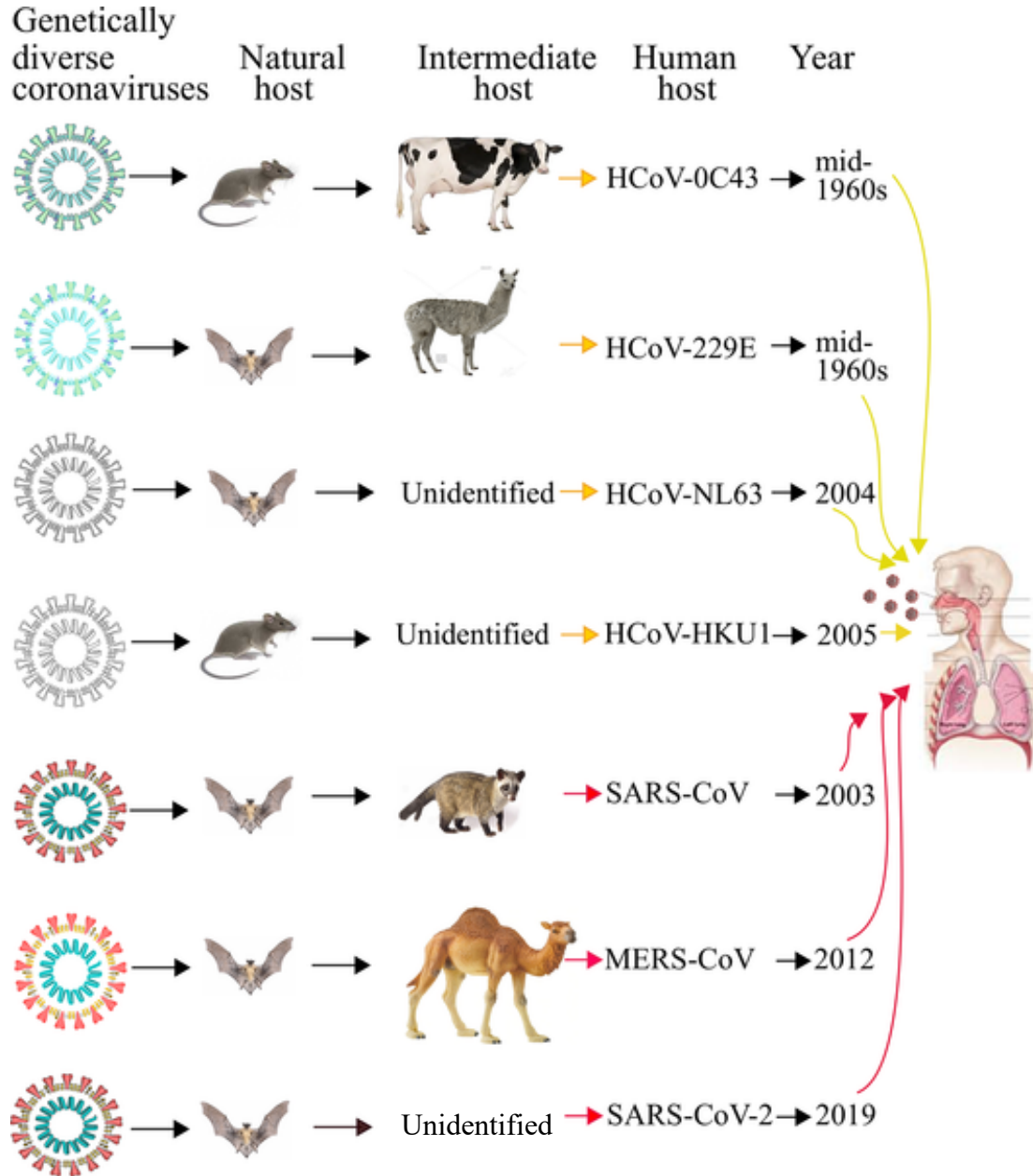
# Coronaviruses - Genera



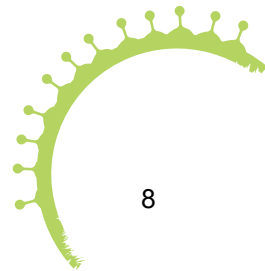
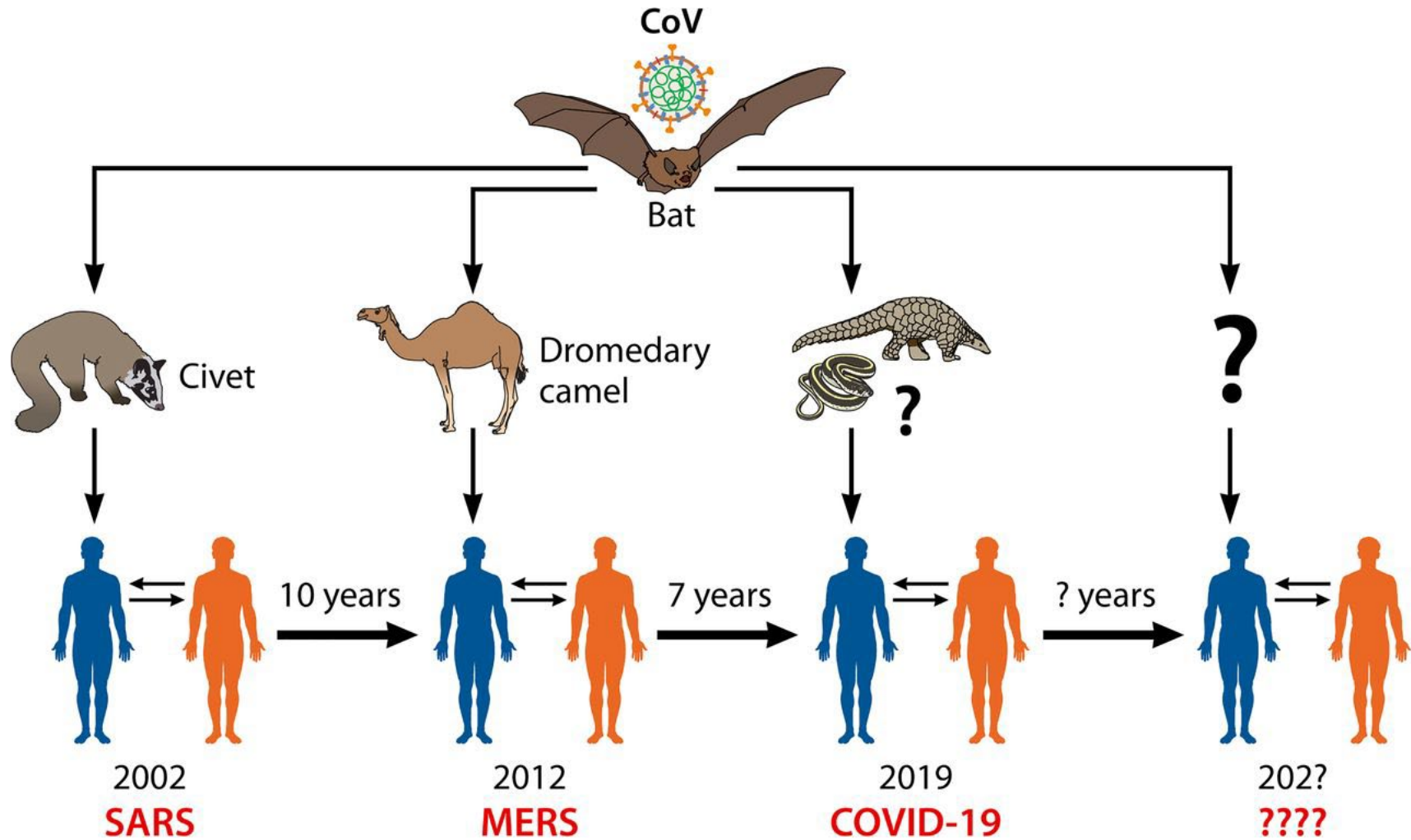
- 4 Genera (Alpha-, Beta-, Gamma-, Deltacoronaviren)
- Coronaviruses can infect many species
- A zoonotic origin is suspected for all human CoVs



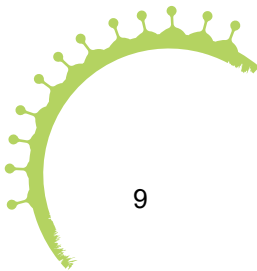
# Coronaviruses - Zoonosis



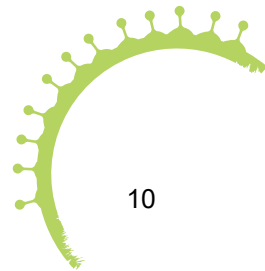
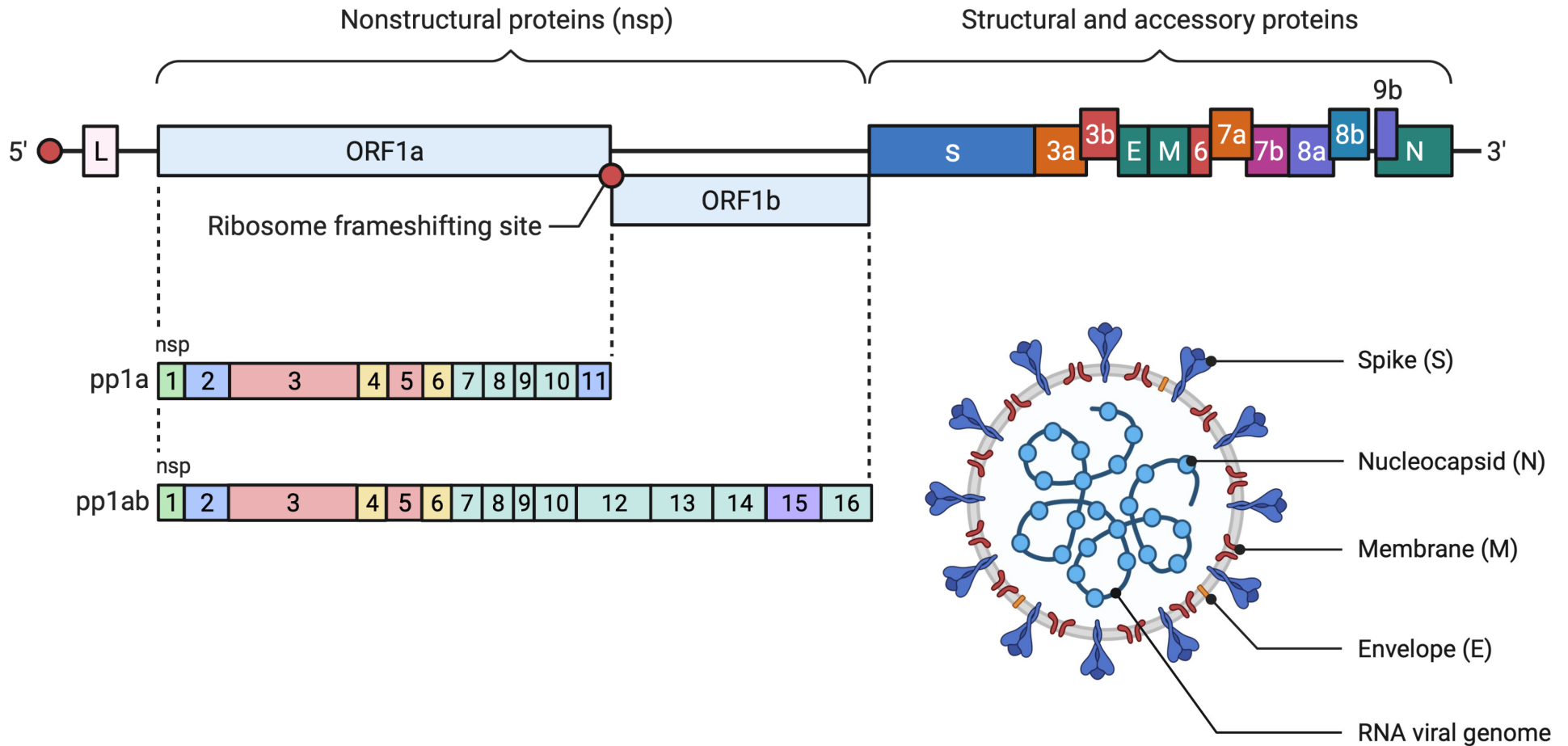
# Past – Present – Future?

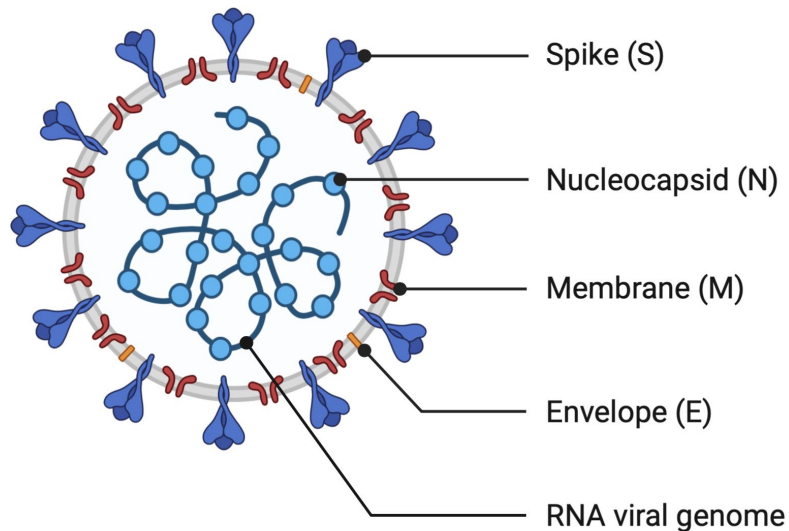


## Genomic Organization and Replication Cycle

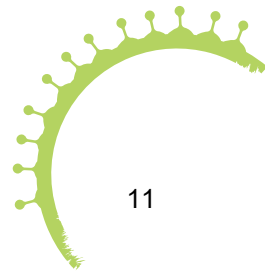


# Coronaviruses – Genomic organisation

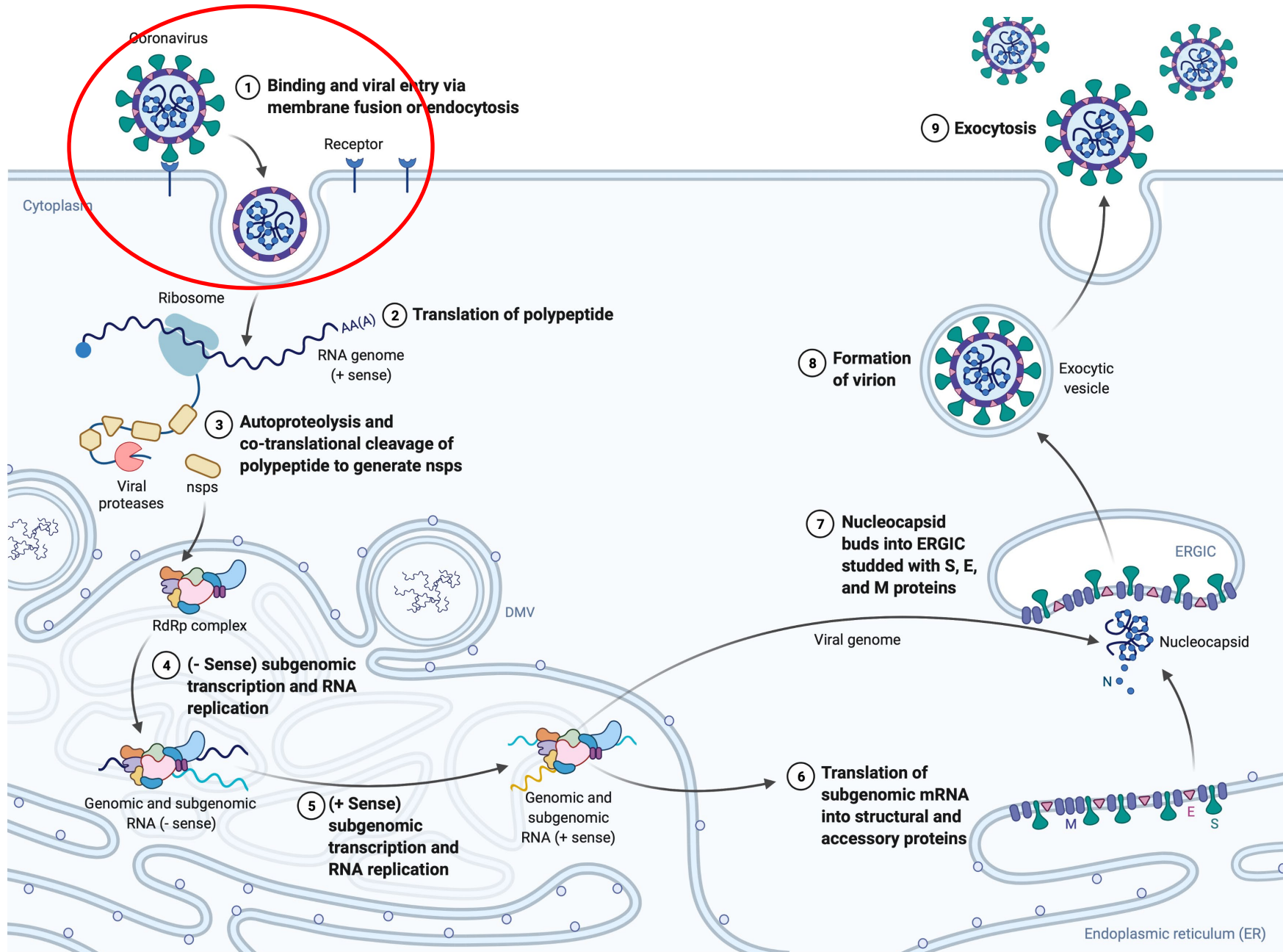




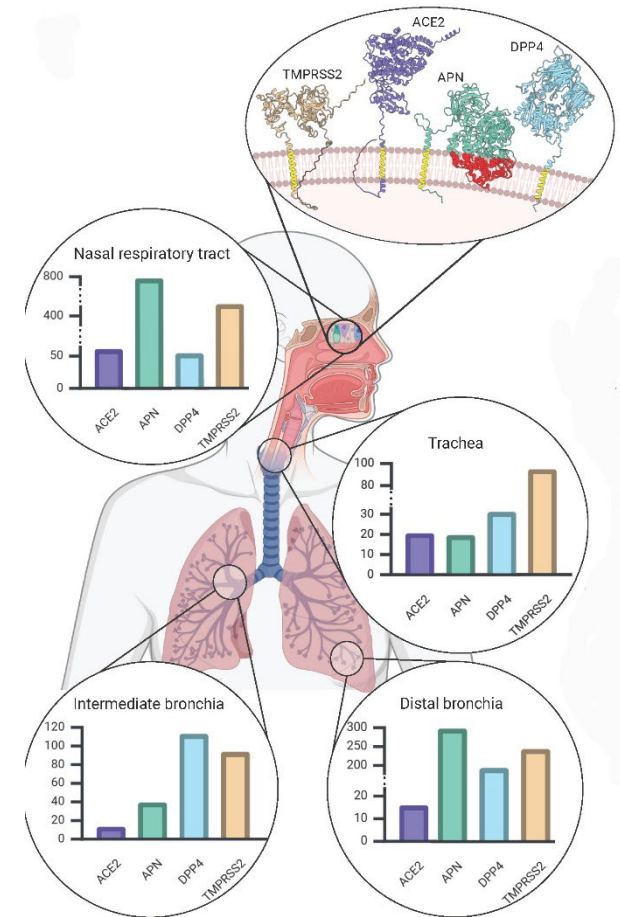
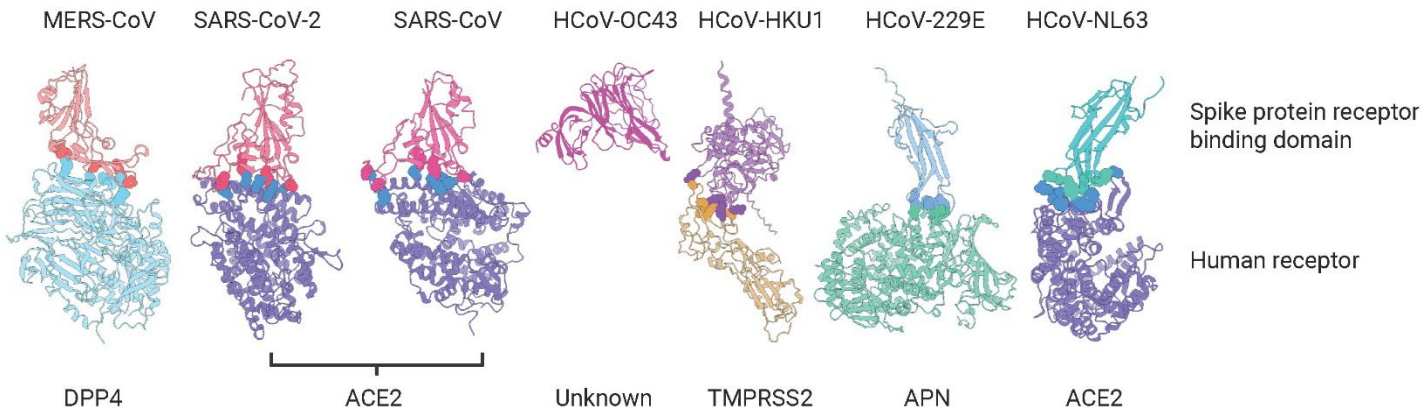
- Spike glycoprotein (S)
  - Binds receptor
  - Induces fusion
  - Target of neutralizing antibodies
- Nucleocapsid phosphoprotein (N)
  - Binds viral RNA
  - Target of cellular immunity
- Membrane glycoprotein (M)
  - Determines budding
  - Triggers virus assembly
- Envelope protein (E)
  - Involved in assembly and release



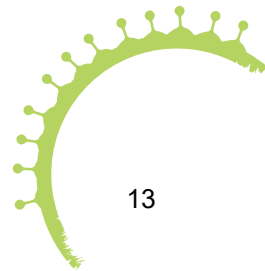
# Coronaviruses – Replication cycle



# Coronaviruses - Receptor

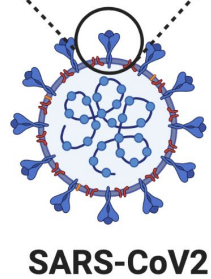
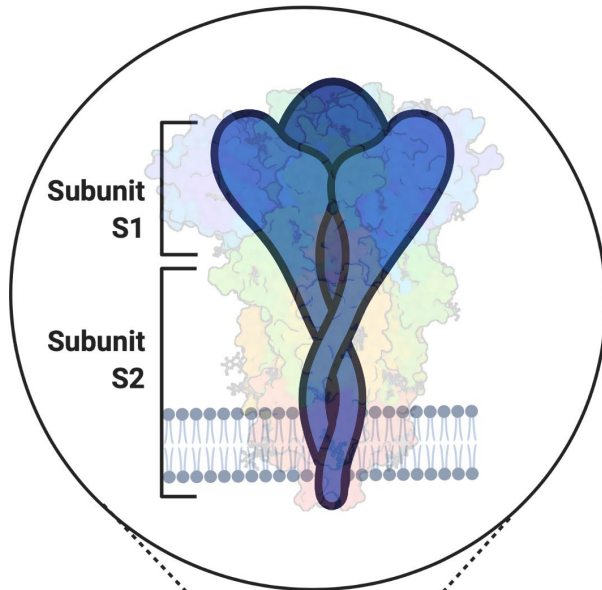


Westhoven et al (2025) *mBio*  
<https://journals.asm.org/doi/10.1128/mbio.02437-25>

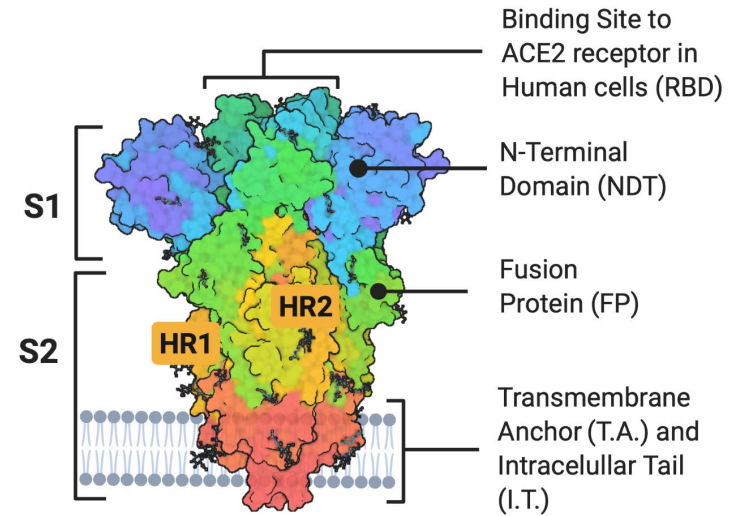


# Coronavirus - entry

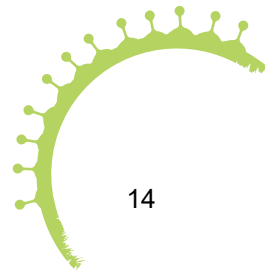
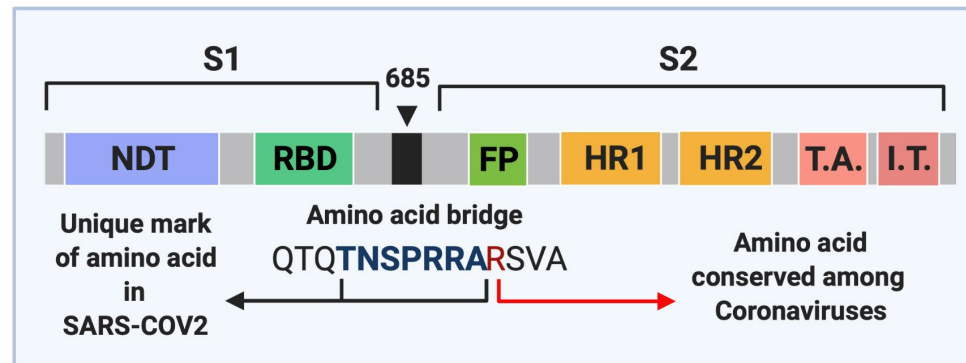
**Virus spike protein  
Diagram**



**Virus spike protein  
Crystallographic structure seen by electron microscopy  
(PDB ID: 6VXX-PDB)**



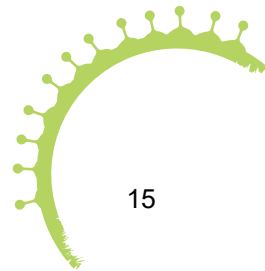
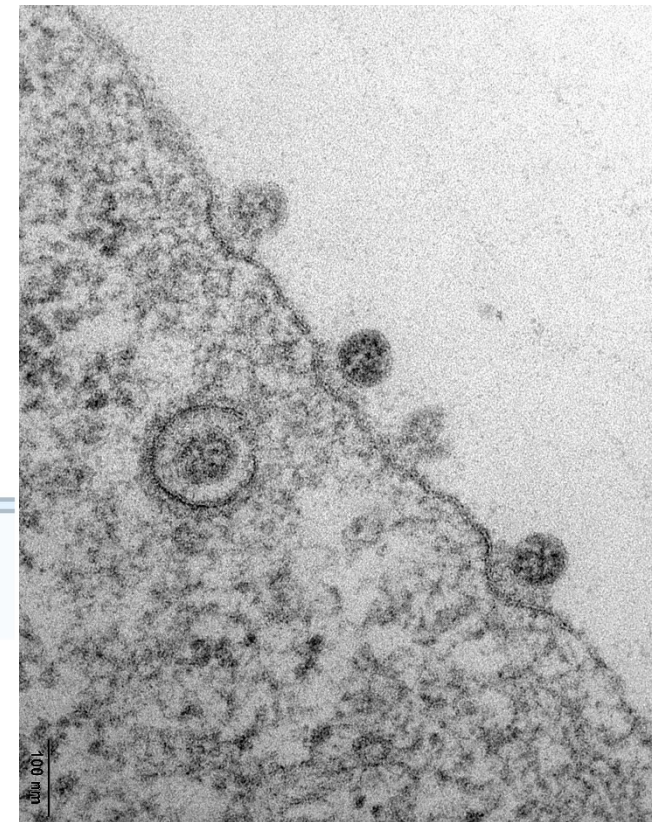
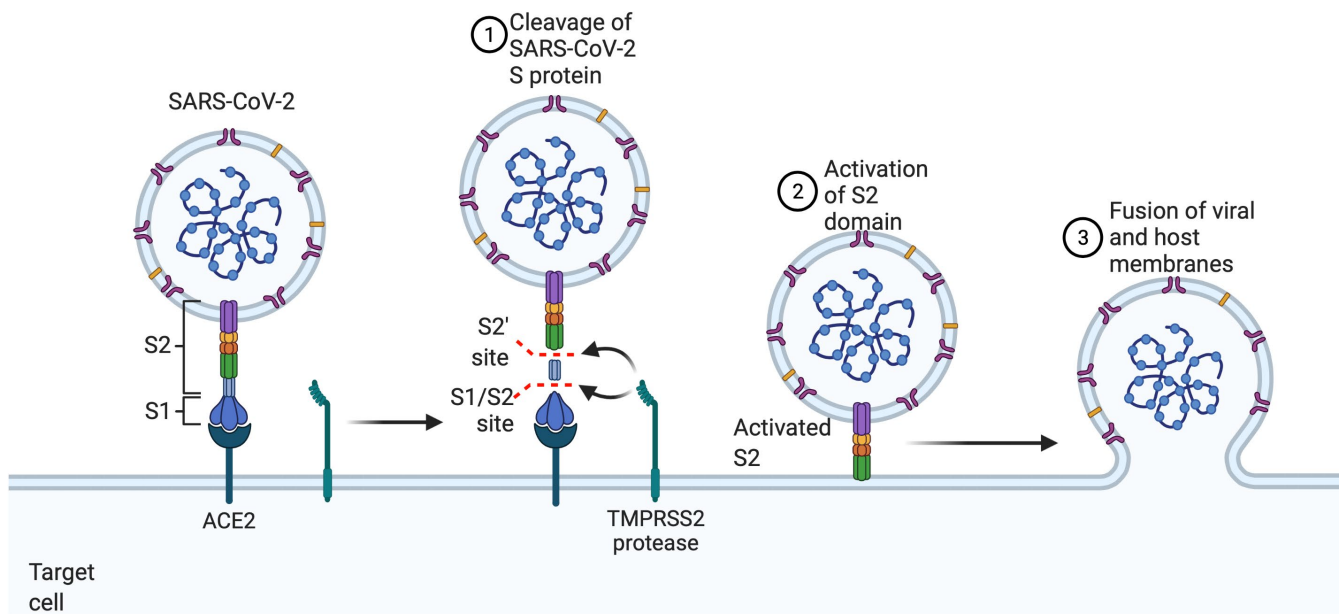
**Primary Structure**



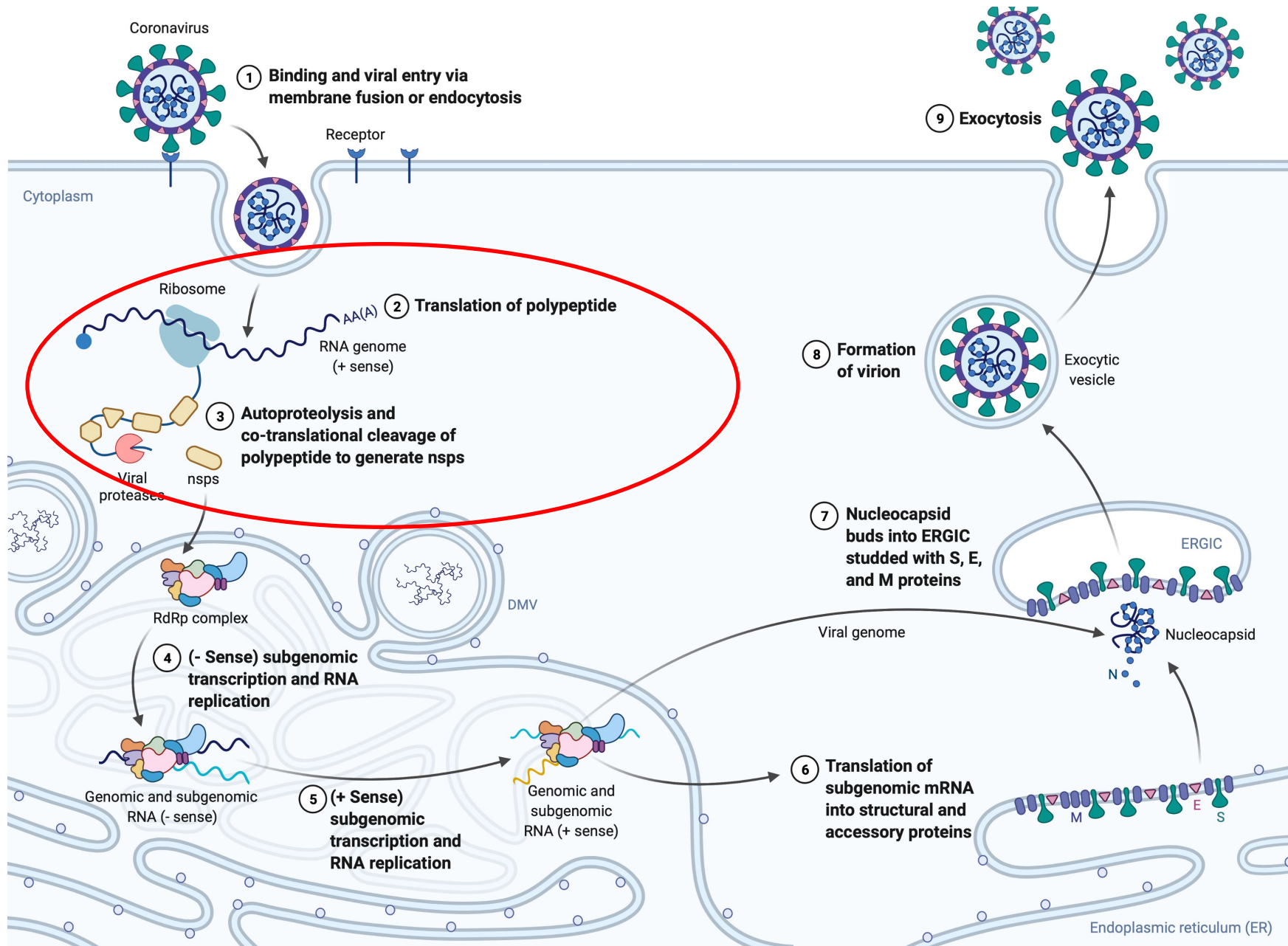
# Coronavirus - entry

Qu et al. (2024) *PNAS*

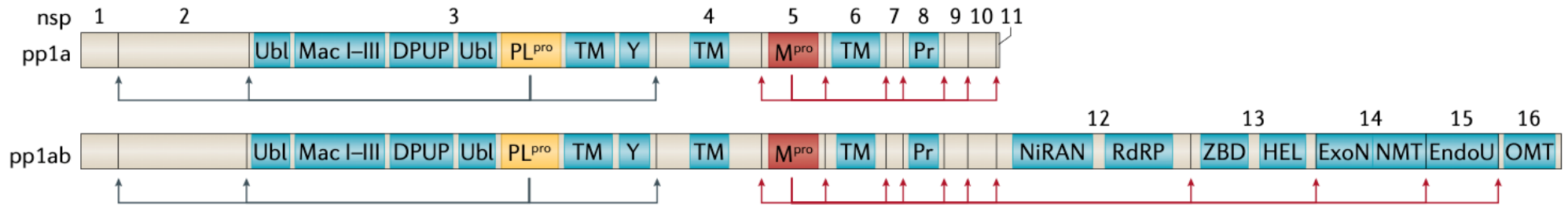
<https://doi.org/10.1073/pnas.2407437121>



# Coronaviruses – Replication cycle



# Coronaviruses - Polyprotein



nsp1 Host mRNA degradation, translation inhibition

nsp2 Unknown

nsp3 Ubl Mac I-III DPUP Ubl PL<sup>pro</sup> TM Y Polyprotein processing, de-ADP-ribosylation, deubiquitination, interferon antagonist, DMV formation

nsp4 TM DMV formation

nsp5 M<sup>pro</sup> Polyprotein processing, inhibition of interferon signalling

nsp6 TM DMV formation

nsp7 Cofactor for RNA-dependent RNA polymerase

nsp8 Pr Primase or 3'-terminal adenylyltransferase, cofactor for RNA-dependent RNA polymerase

nsp9 Binding of single-stranded RNA

nsp10 Cofactor for nsp14 and 16

nsp11 Unknown

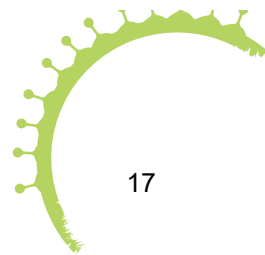
nsp12 NiRAN RdRP RNA-dependent RNA polymerase, nucleotidyltransferase

nsp13 ZBD HEL Helicase, RNA 5' triphosphatase

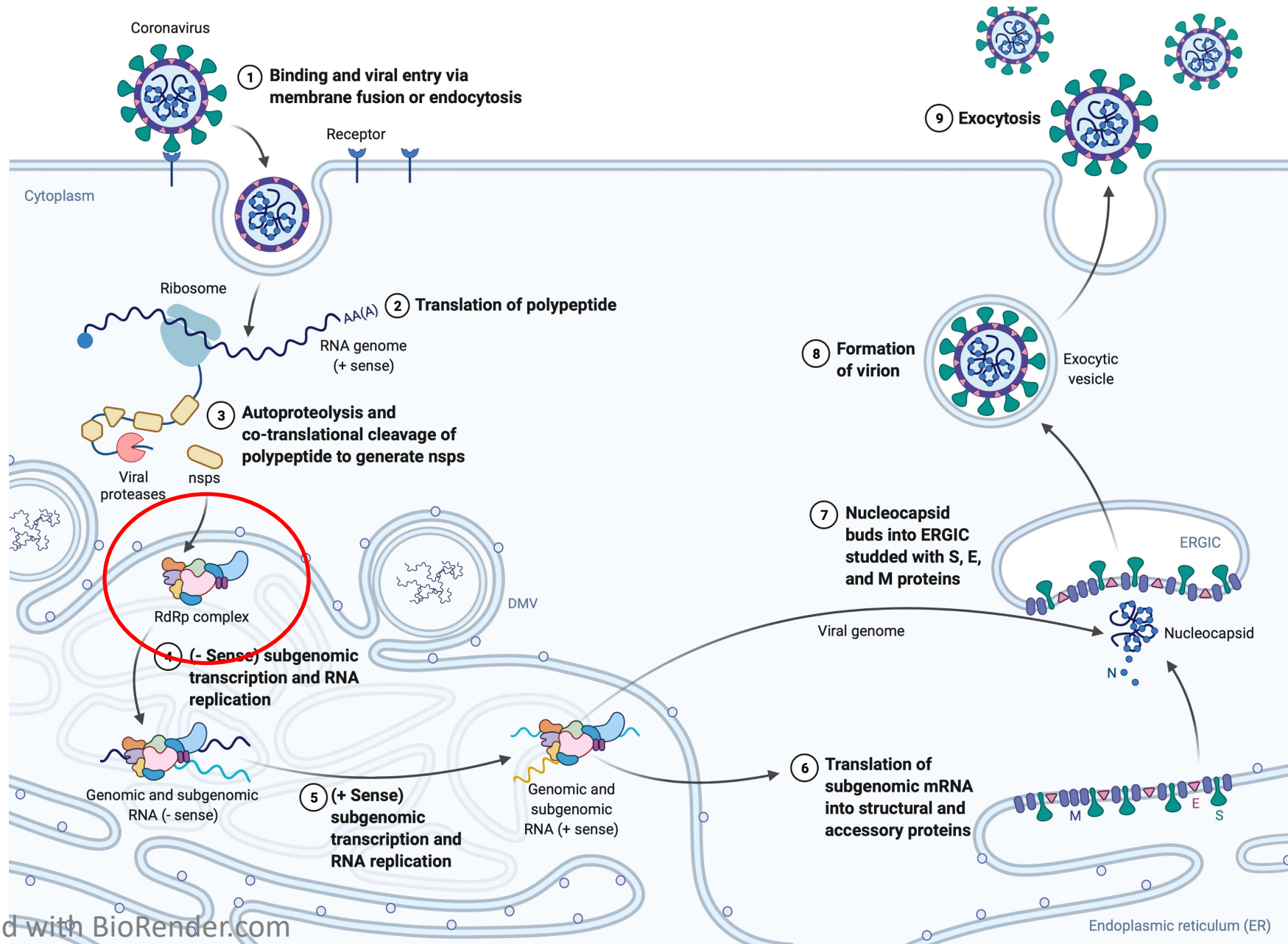
nsp14 ExoN NMT 3' to 5' exoribonuclease, proofreading, RNA cap formation, guanosine N7-methyltransferase

nsp15 EndoU Endoribonuclease, evasion of immune response

nsp16 OMT RNA cap formation, ribose 2'-O-methyltransferase

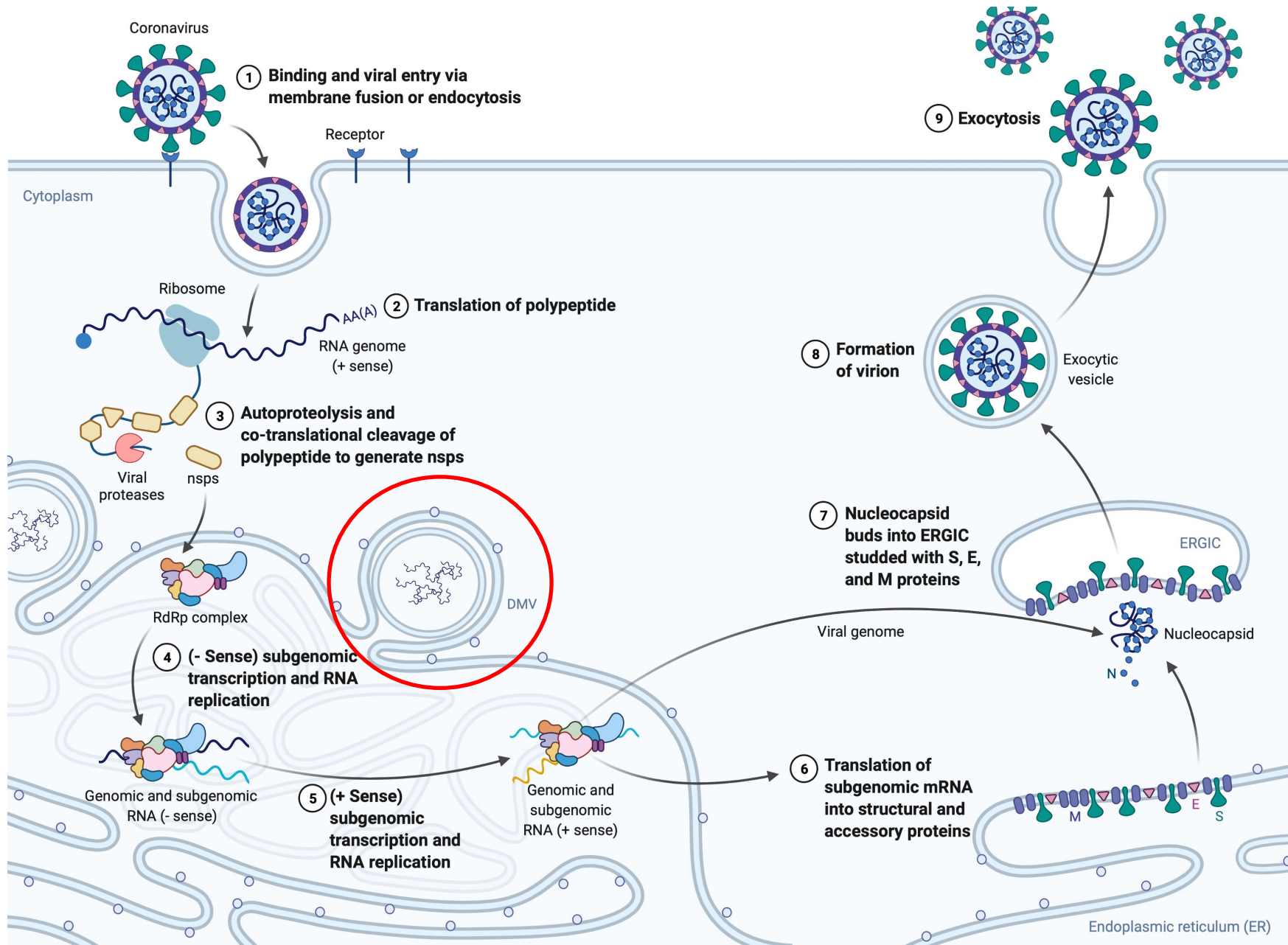


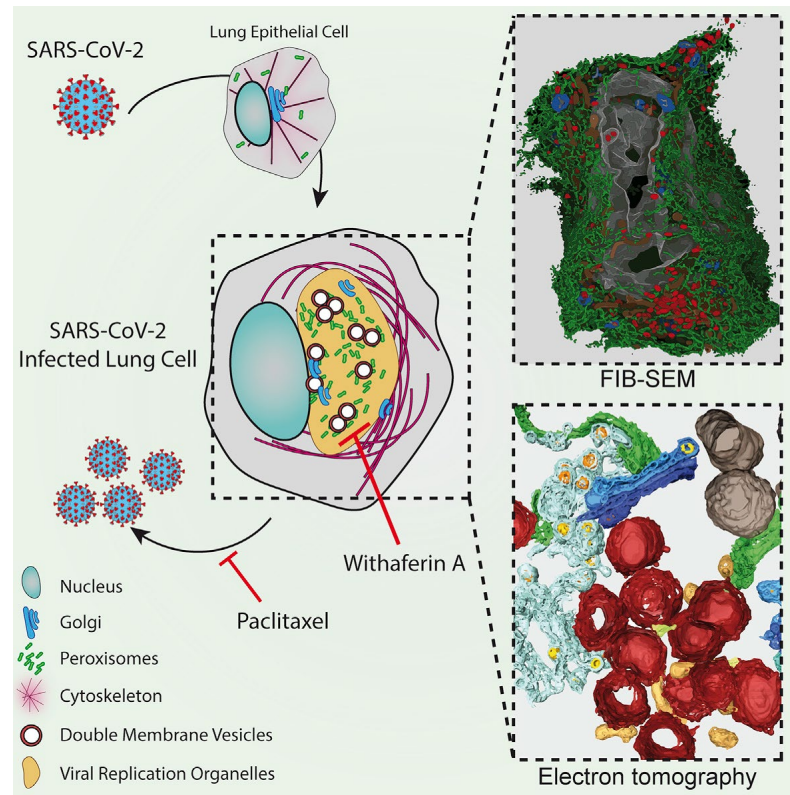
# Coronaviruses – Replication cycle



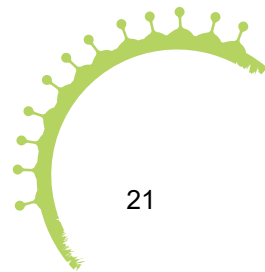


# Coronaviruses – Replication cycle

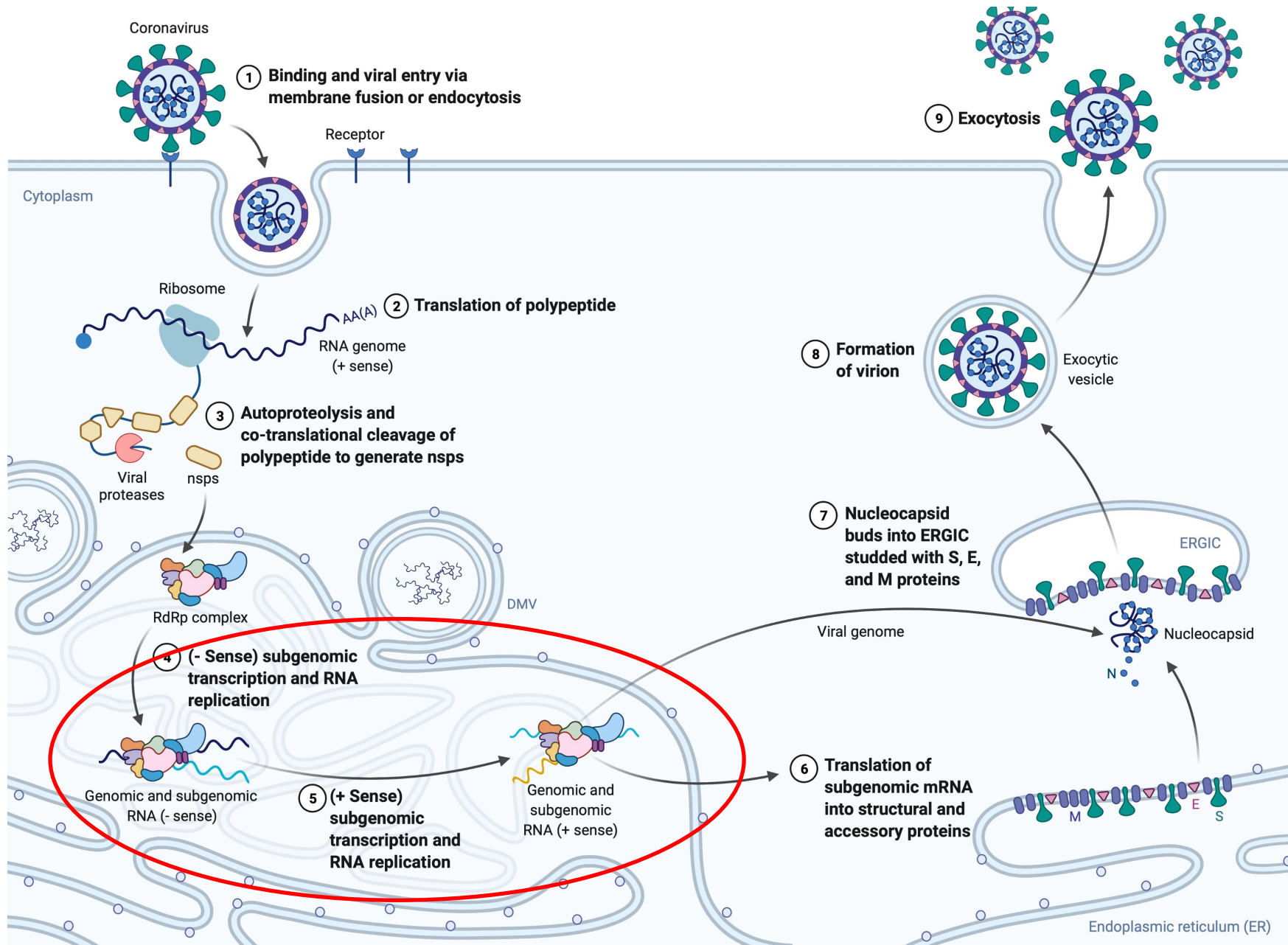




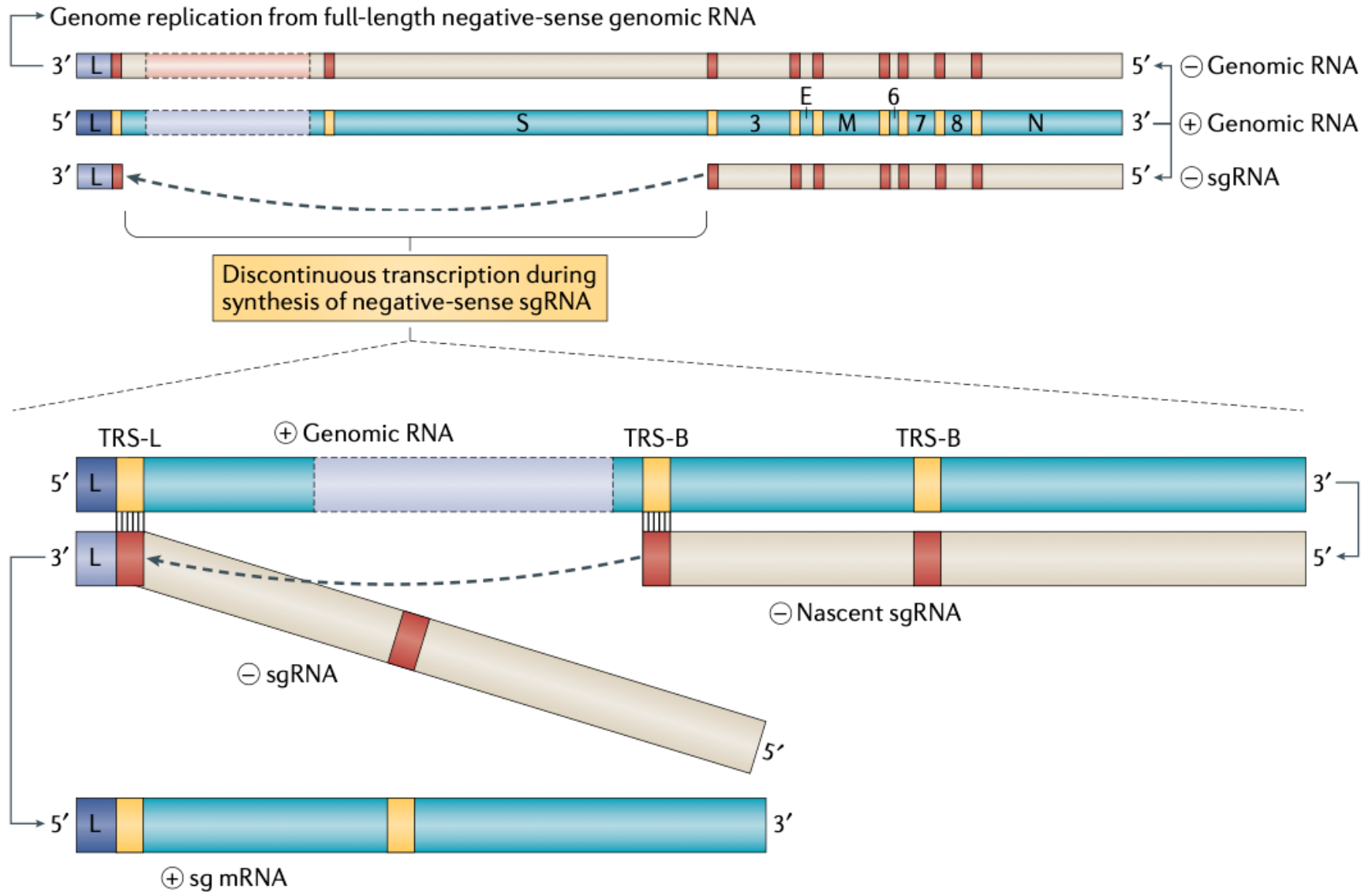
- Spatial compartment for replication and transcription
- Concentration of macromolecules
- “Hiding” of replication intermediates from cytosolic sensors



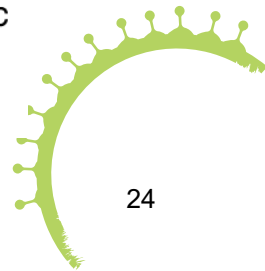
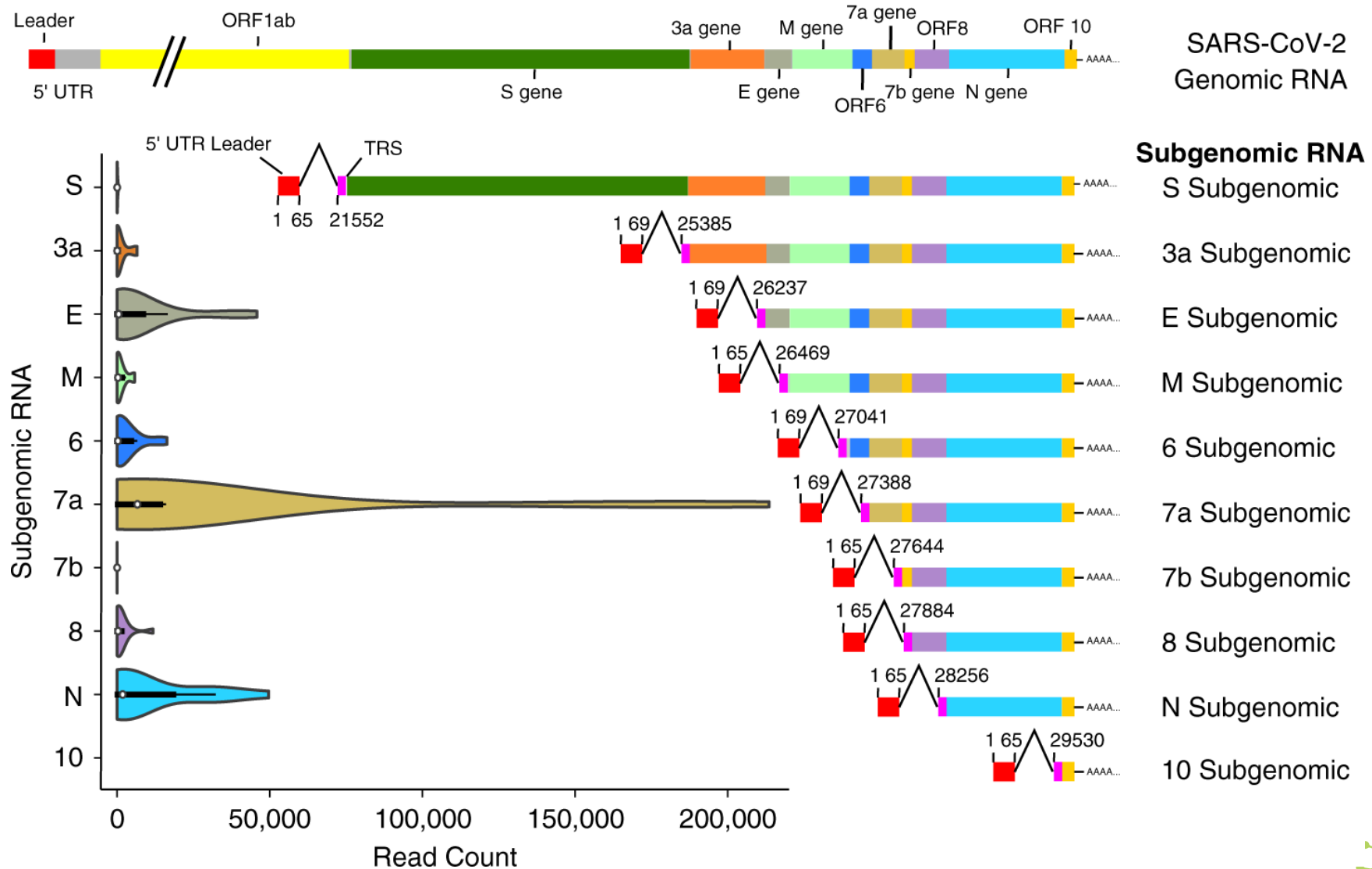
# Coronaviruses – Replication cycle



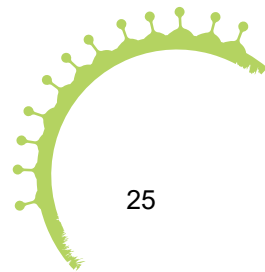
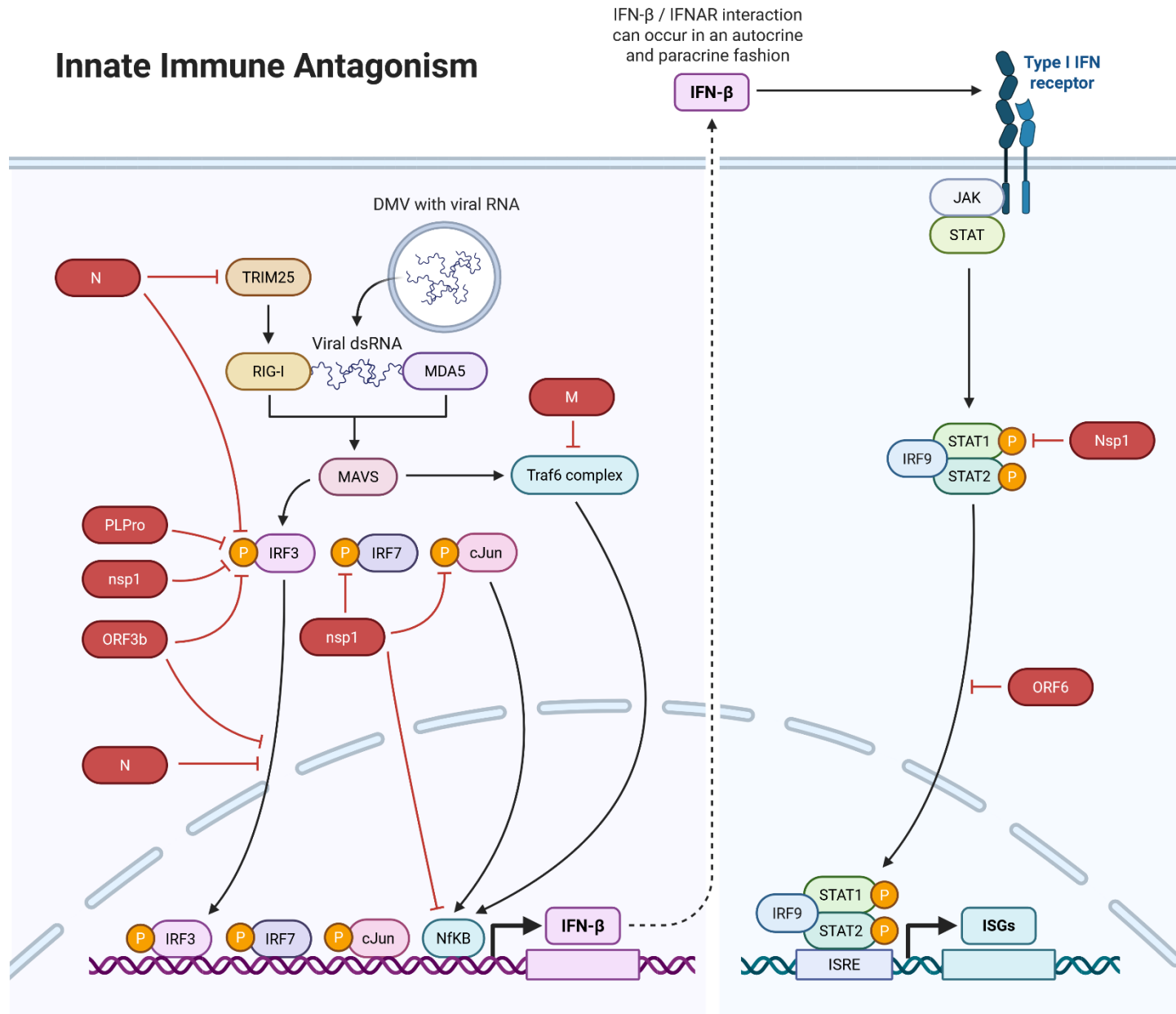
# Coronaviruses - Replication



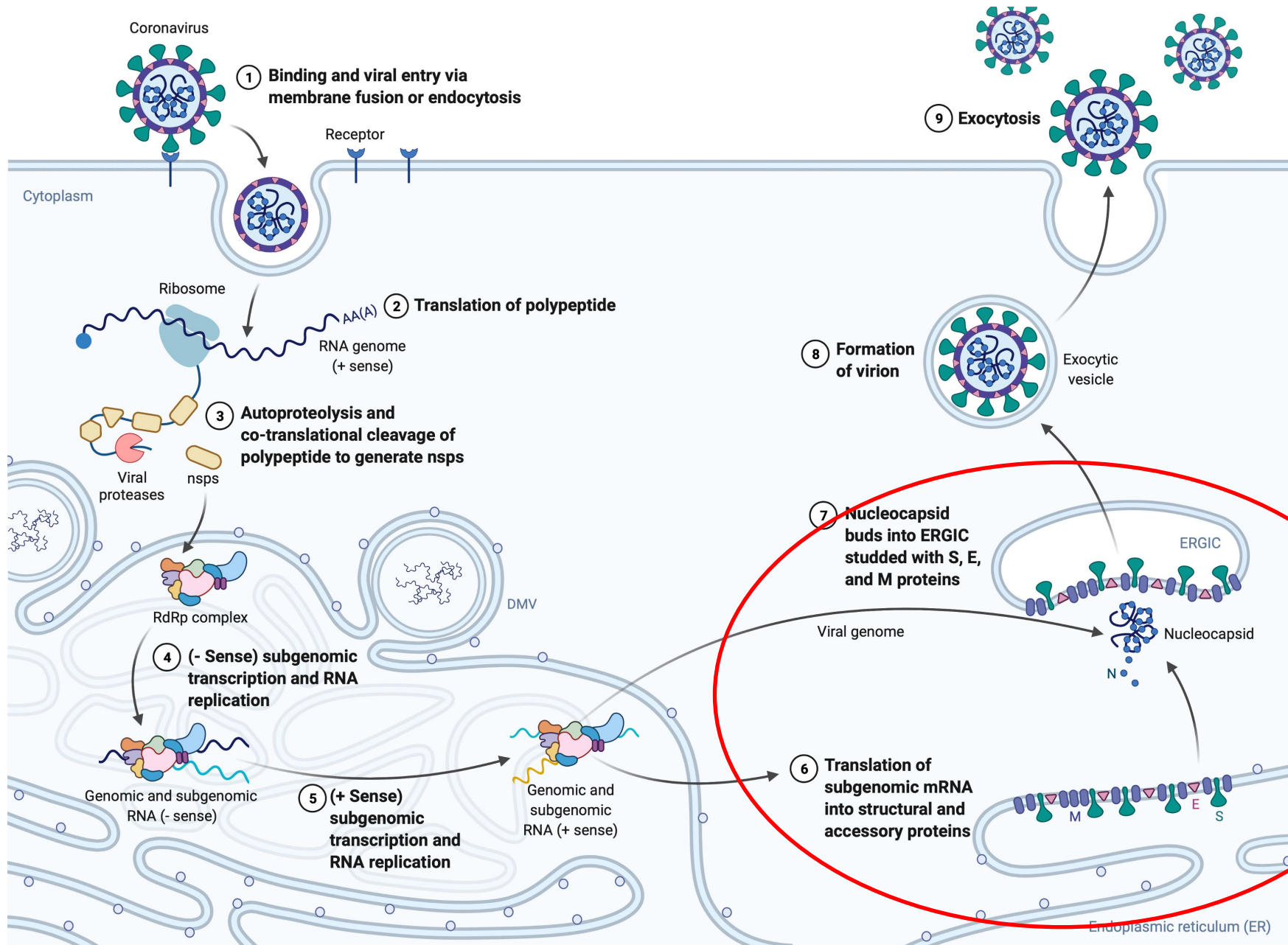
# Coronaviruses - Replication

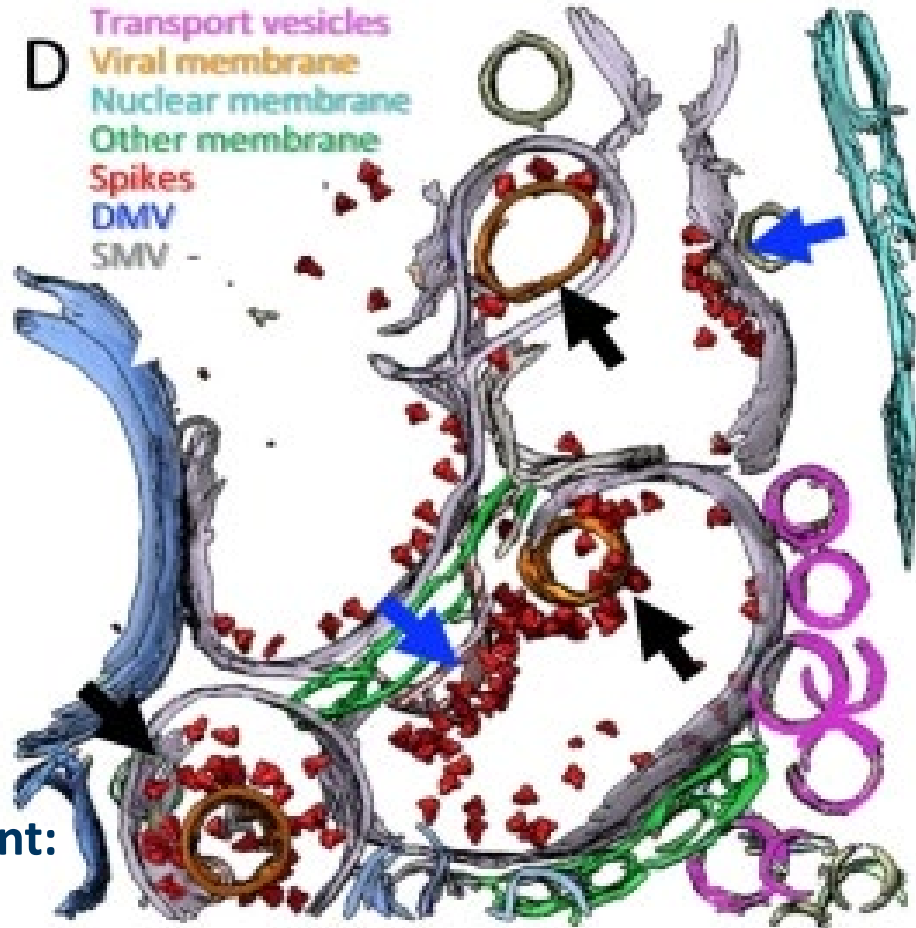
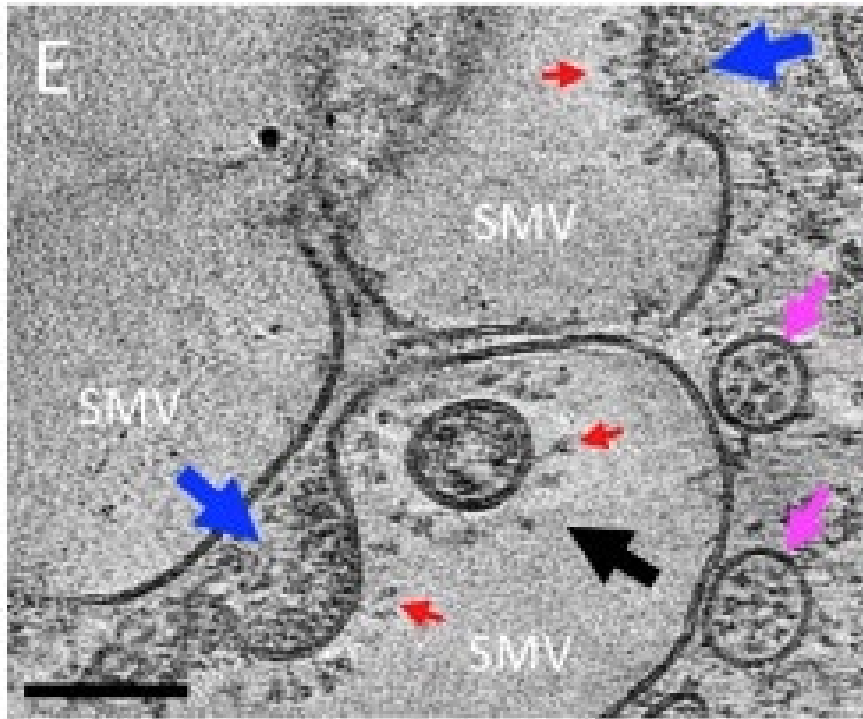


## Innate Immune Antagonism



# Coronaviruses – Translation/Assembly





**ER and ER-GOLGI Intermediate compartment:  
(ERGIC) Assembly and budding site**

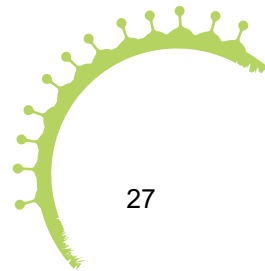
**Blue** arrows: SARS-CoV-2 assembly intermediates

**Pink** arrows: Transport vesicles

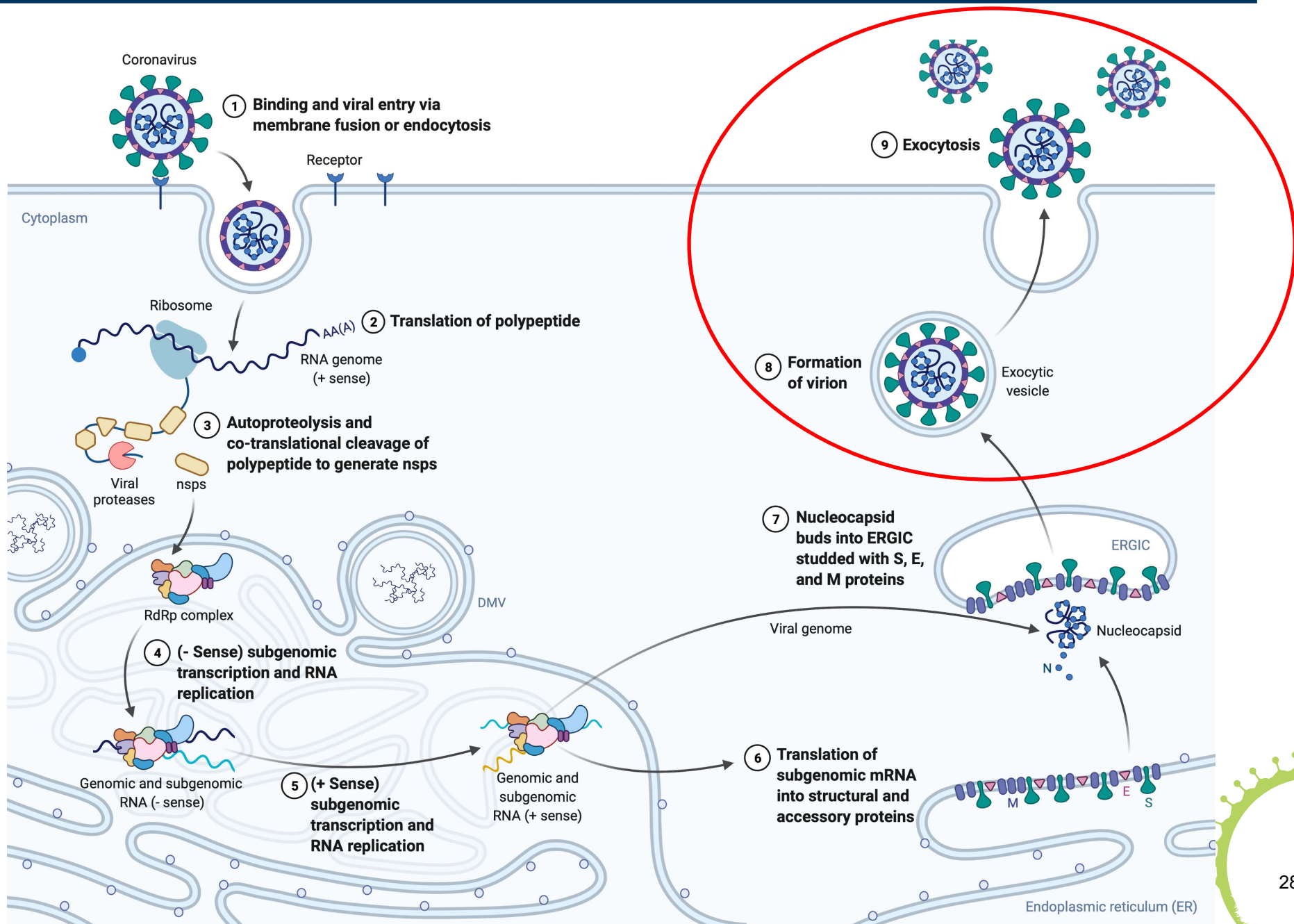
**Black** arrows: vesicles containing virus particles

*DMV: Double membrane vesicles*

*SMV: Single membrane vesicles*

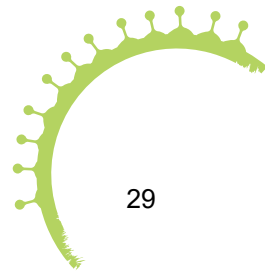
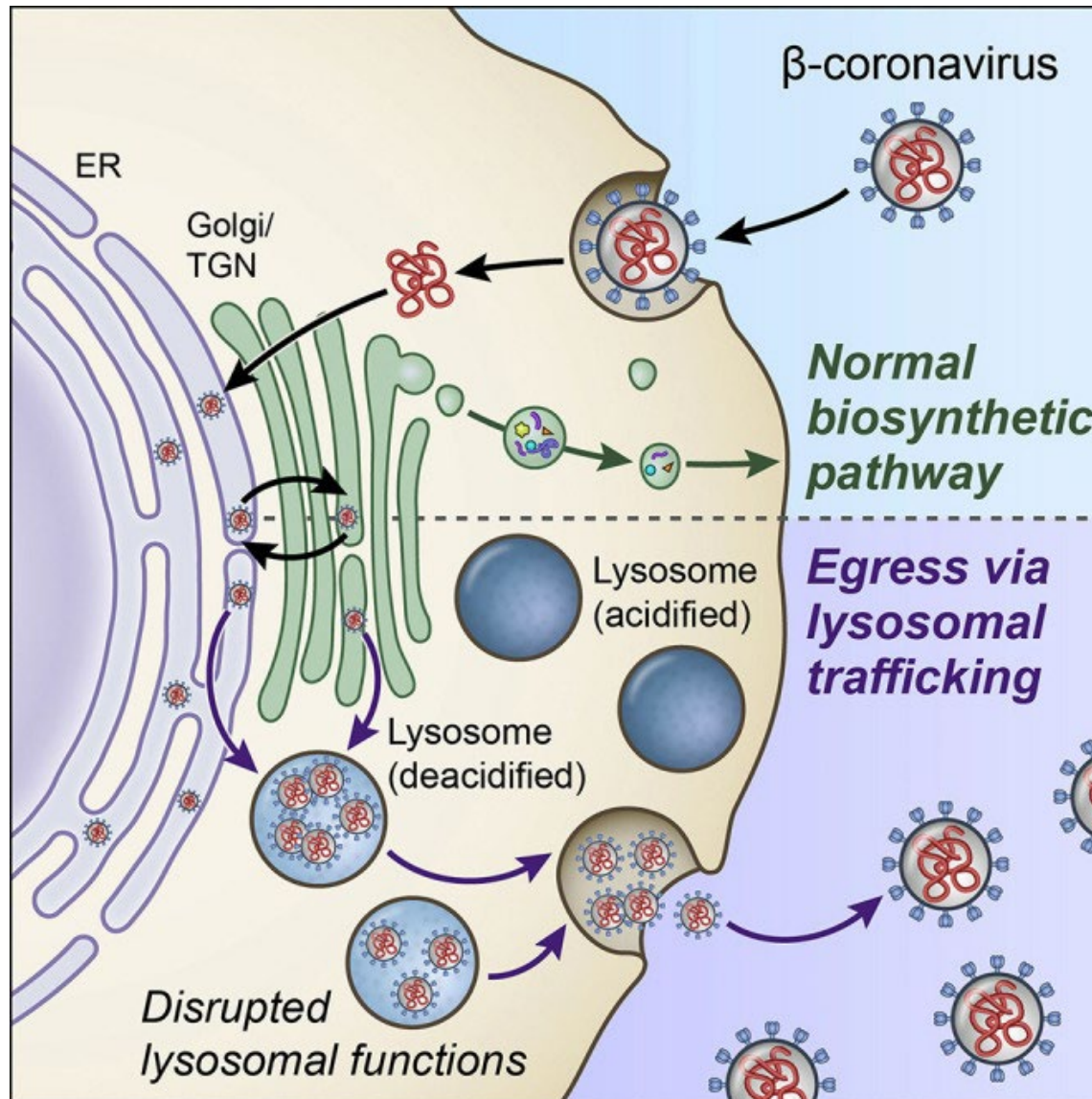


# Coronaviruses – Egress

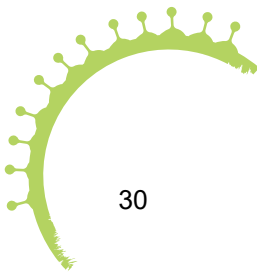


# Coronaviruses – Egress

Egress through exocytosis-like mechanism (main) or lysosomal trafficking (alternative)

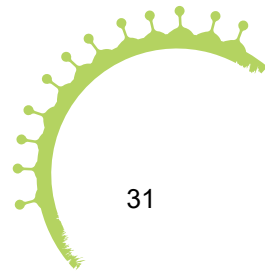


SARS-CoV  
MERS-CoV  
SARS-CoV-2



## SARS-CoV

Severe acute respiratory Coronavirus



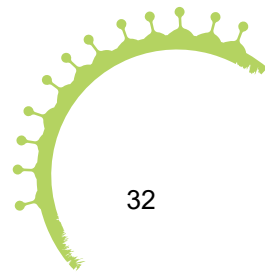
# SARS-CoV - Transmission

Friday,  
Feb 21 2003

Metropole Hotel  
Professor Liu  
checks into the  
9th floor

- Prof. Liu enters the hotel
- In the elevator he meets
  - Businessmen from the US
  - Lady from Toronto
- In the hallway:
  - Stewardesses from Singapur
- A couple of days later....

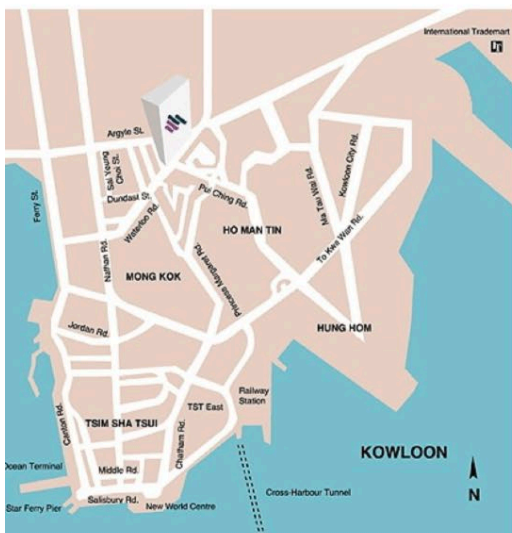
.... he dies!



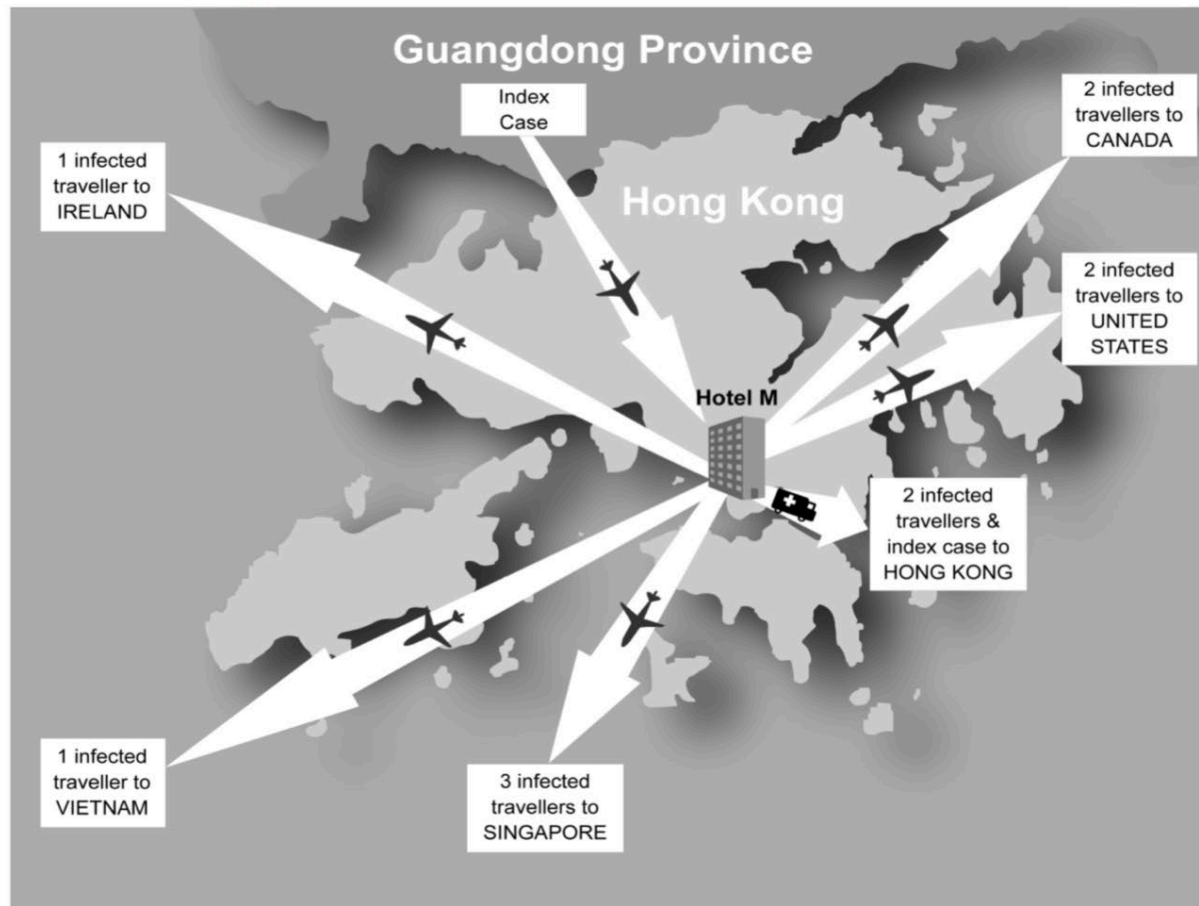
# SARS-CoV - Transmission

Friday,  
Feb 21 2003

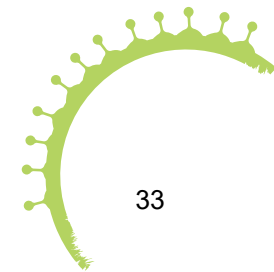
Metropole Hotel  
Professor Liu  
checks into the  
9th floor



Next days ...

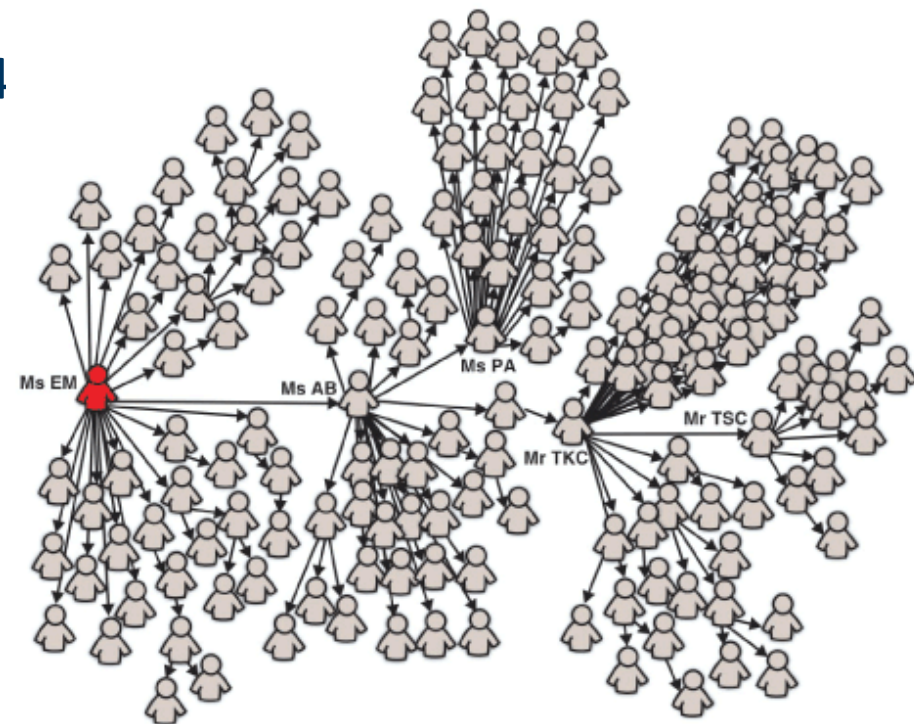
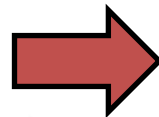
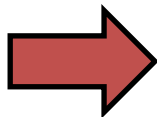


Finally ... 8'098 infected, ... 774 (9.6%) died



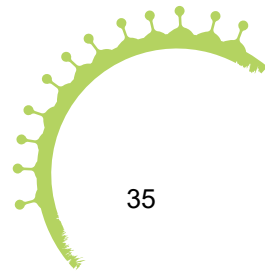
## 2002/2003 SARS

- Severe atypical pneumonia in Guangdong Province, China → 24 countries affected
- 20-30% of infected: ICU, external Respiration necessary
- 774 Deaths, ca. 8.000 infected → 10 % Mortality
- Droplets/Aerosols, „Superspreader“
- No new natural infections since 2004



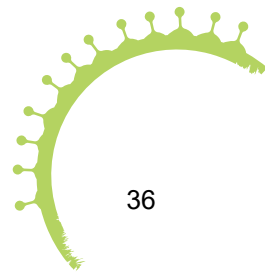
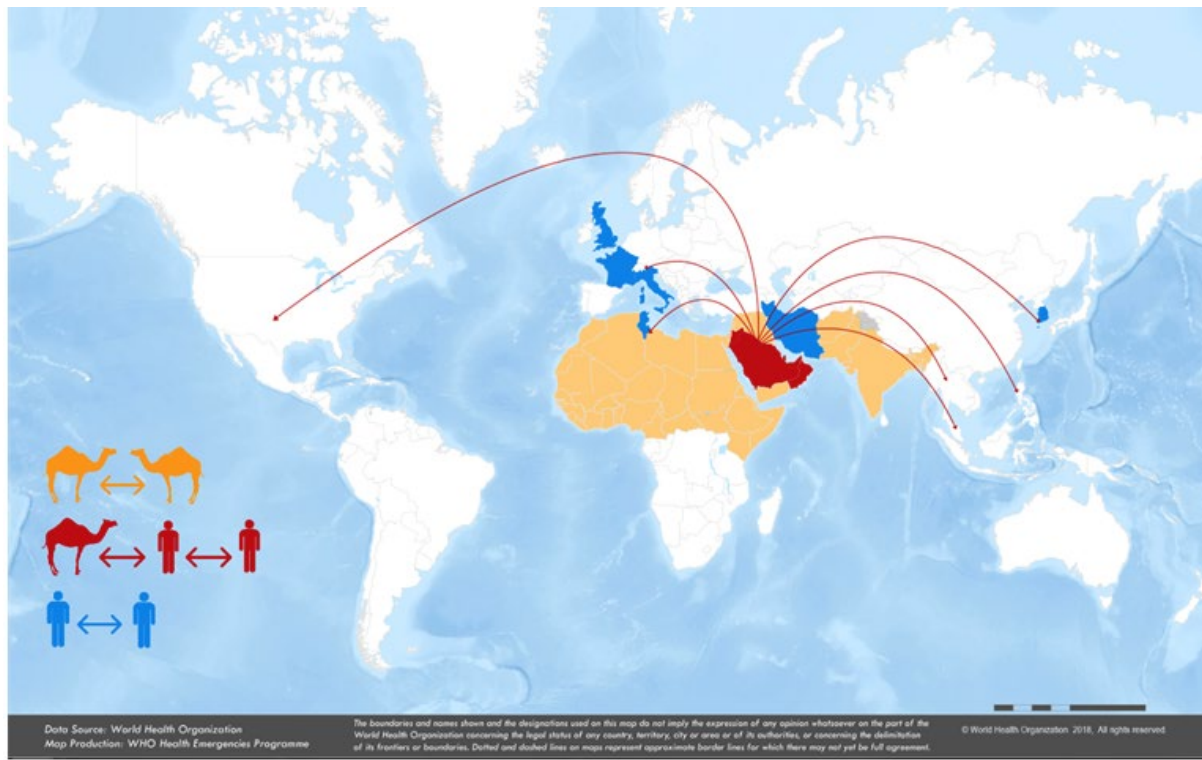
## MERS-CoV

### Middle East Respiratory Syndrome Coronavirus



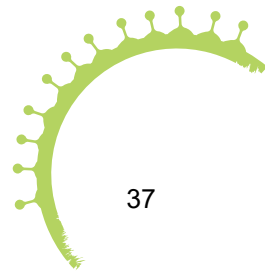
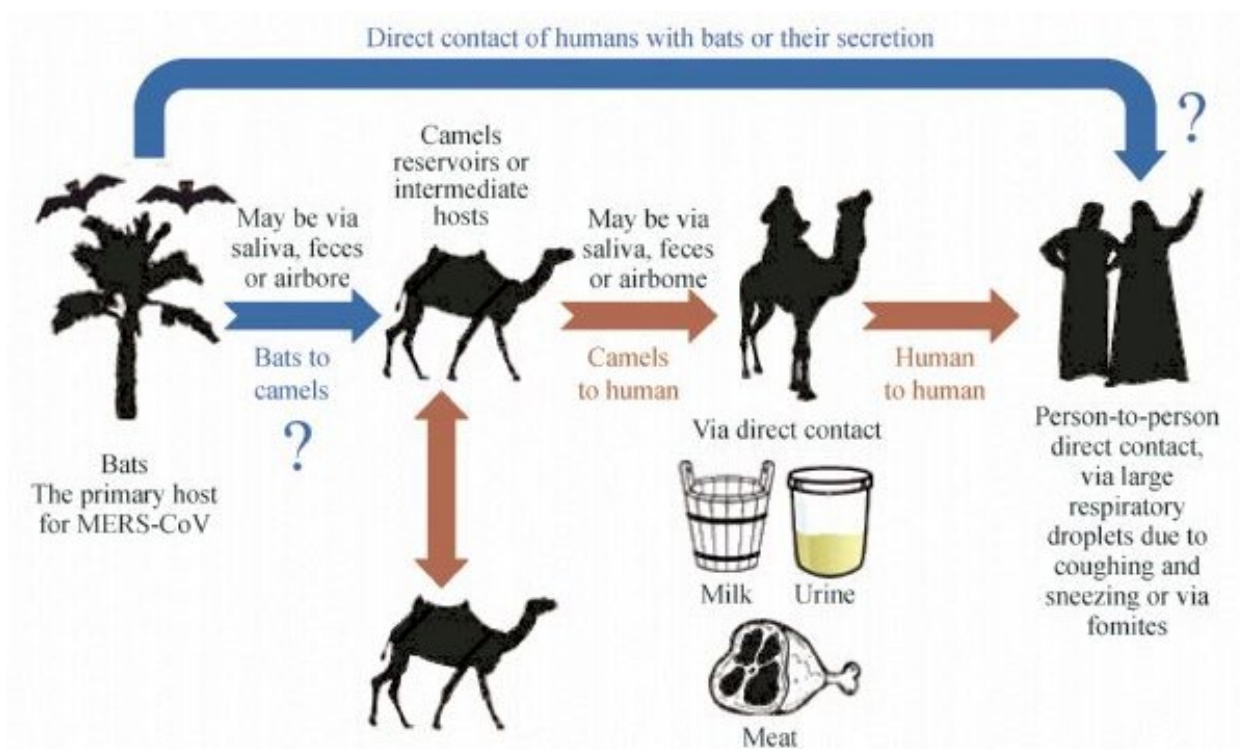
## 2012 MERS

- Identified in Saudi Arabia
- So far 2.589 laboratory confirmed cases in 27 countries (940 deaths)
- Acute respiratory syndrome, Pneumonia
  - Ca. 34.3% CFR



# MERS-CoV - Transmission

- Zoonotic transmission
  - Close contact to infected animal
  - Camels are zoonotic reservoir
- Human-to-human transmission  
(not very efficient)
- Aerosol/Droplet

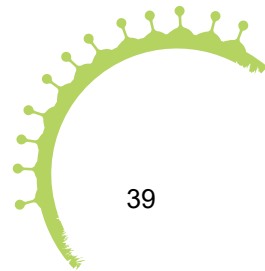
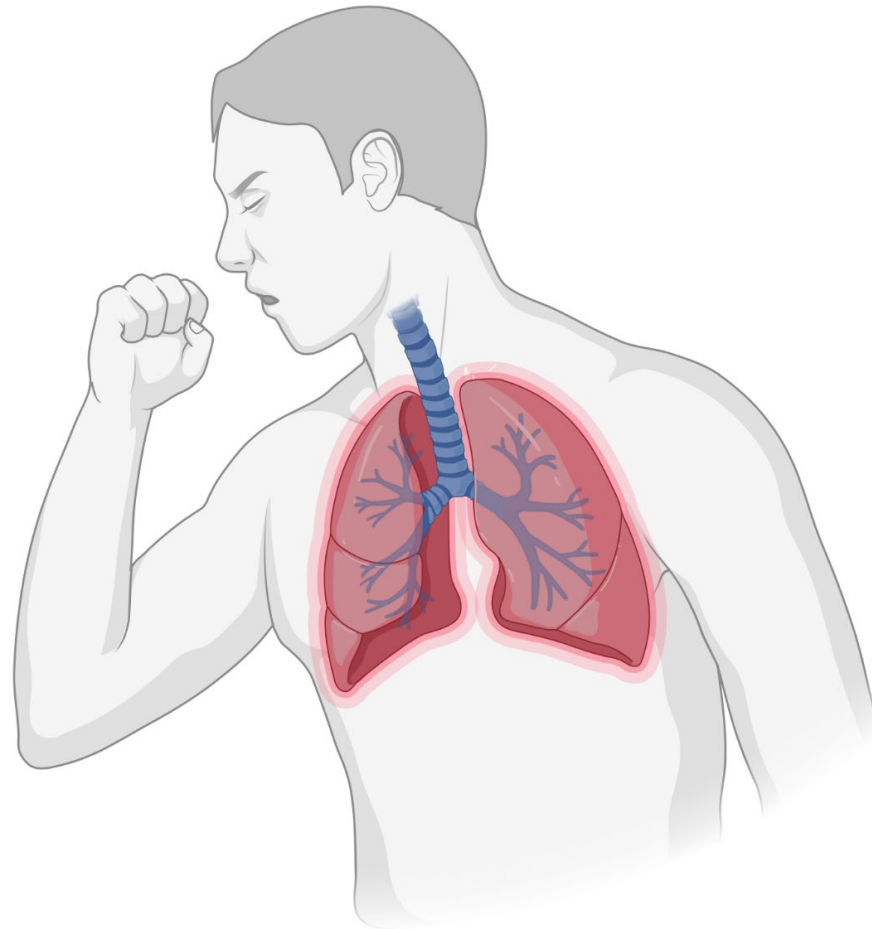


## SARS-CoV-2

### Severe Acute Respiratory Syndrome Coronavirus - 2

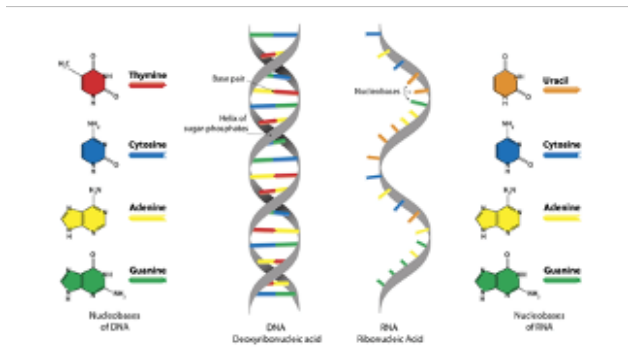


## A novel Disease breaks out

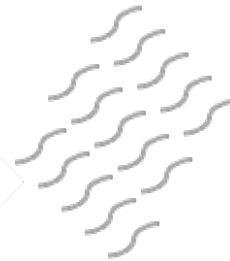


## Next Generation Sequencing:

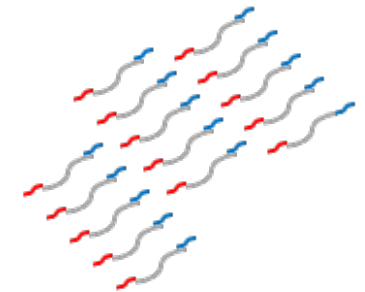
### Genom



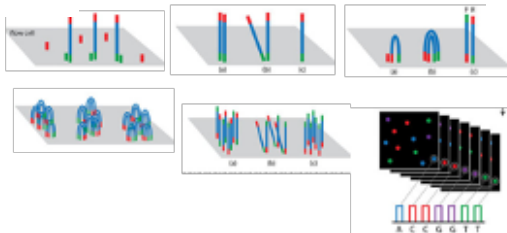
Fragmentation



Adapter Ligation



Cluster Amplification



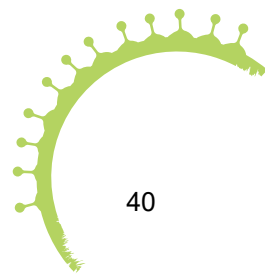
Assembly



Annotation



Identification



The NEW ENGLAND JOURNAL of MEDICINE

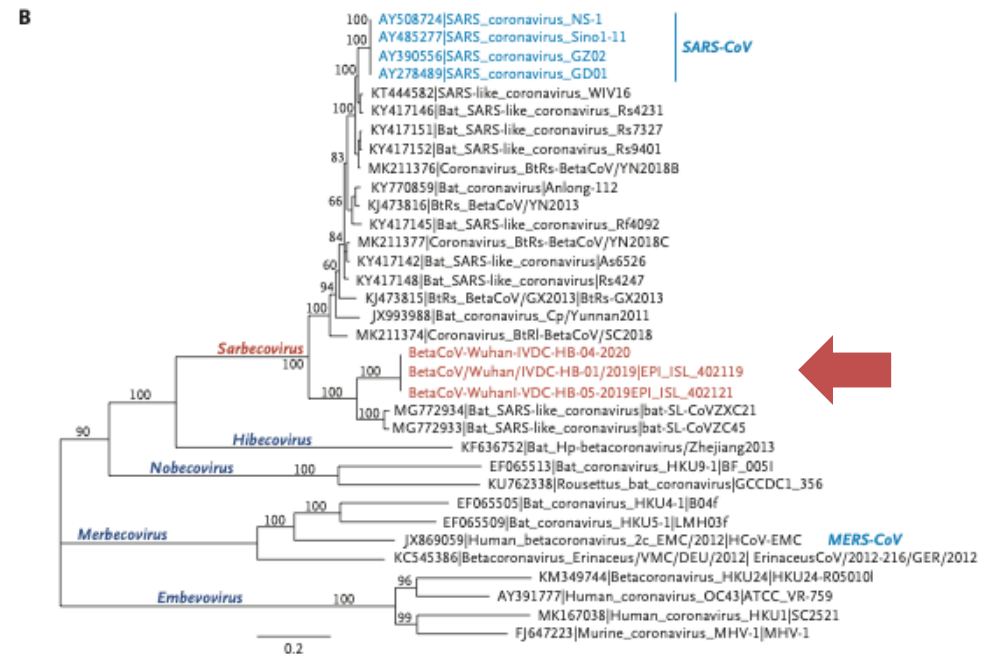
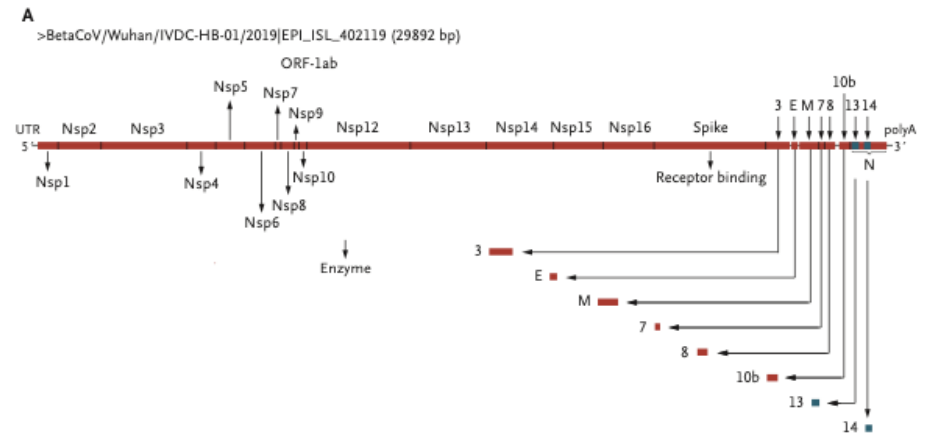
**BRIEF REPORT**

## A Novel Coronavirus from Patients with Pneumonia in China, 2019

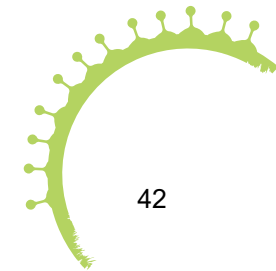
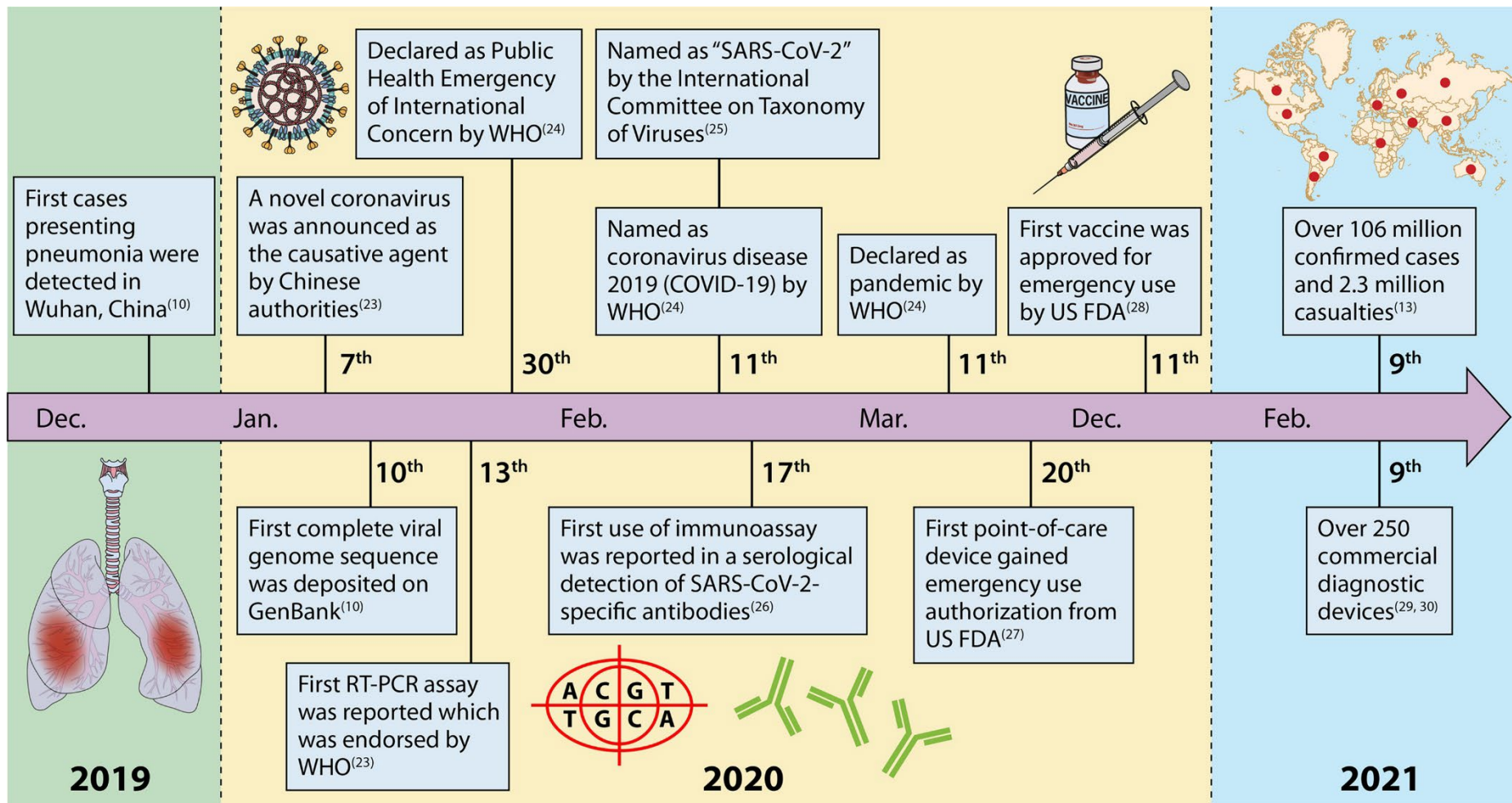
Na Zhu, Ph.D., Dingyu Zhang, M.D., Wenling Wang, Ph.D., Xingwang Li, M.D., Bo Yang, M.S., Jingdong Song, Ph.D., Xiang Zhao, Ph.D., Baoying Huang, Ph.D., Weifeng Shi, Ph.D., Roujian Lu, M.D., Peihua Niu, Ph.D., Faxian Zhan, Ph.D., Xuejun Ma, Ph.D., Dayan Wang, Ph.D., Wenbo Xu, M.D., Guizhen Wu, M.D., George F. Gao, D.Phil., and Wenjie Tan, M.D., Ph.D., for the China Novel Coronavirus Investigating and Research Team

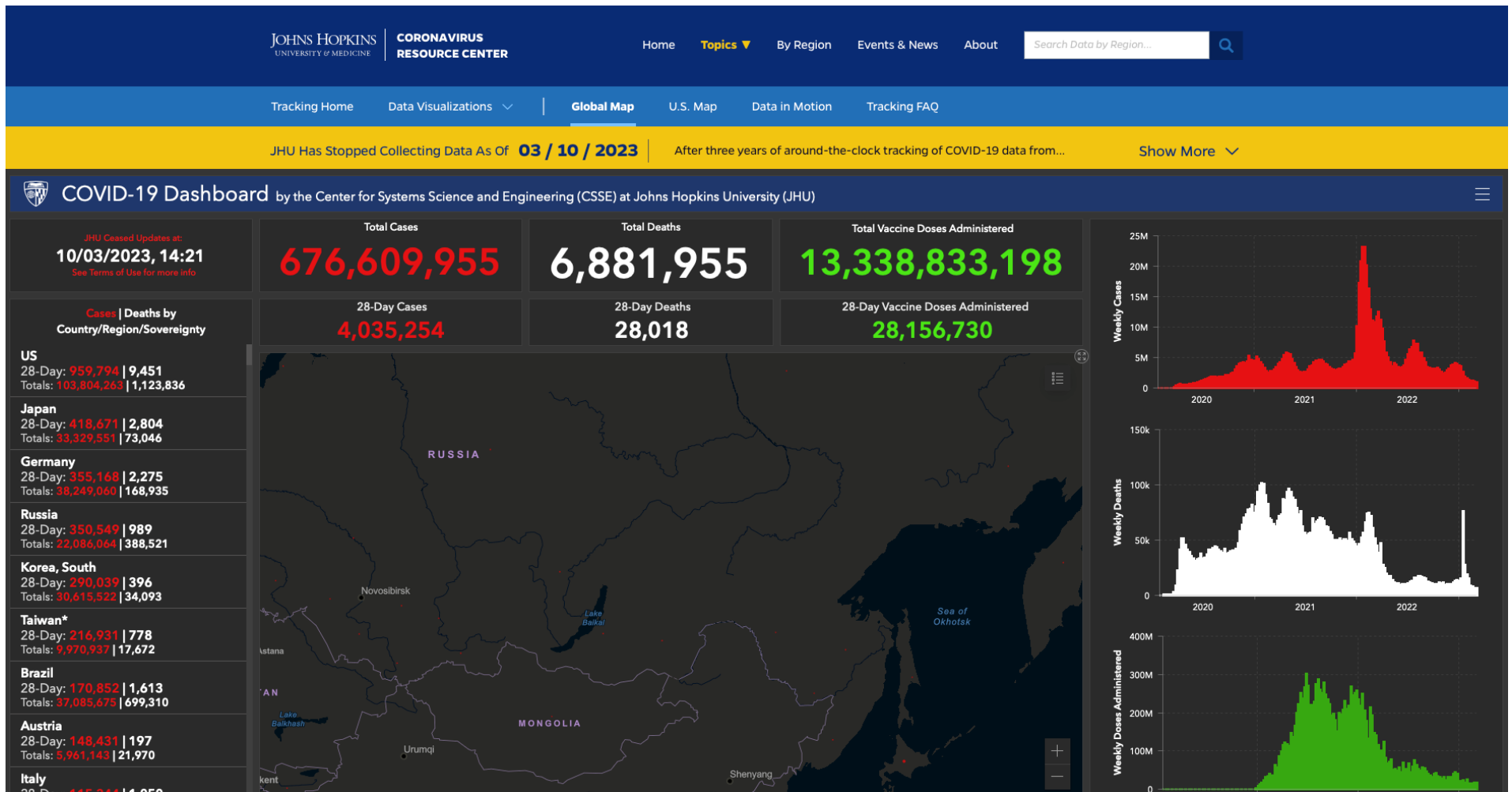
**SUMMARY**

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China. A previously unknown betacoronavirus was discovered through the use of unbiased sequencing in samples from patients with pneumonia. Human airway epithelial cells were used to isolate a novel coronavirus, named 2019-nCoV, which formed a clade within the subgenus sarbecovirus, Orthocoronavirinae subfamily. Different from both MERS-CoV and SARS-CoV, 2019-nCoV is the seventh member of the family of coronaviruses that infect humans. Enhanced surveillance and further investigation are ongoing. (Funded by the National Key Research and Development Program of China and the National Major Project for Control and Prevention of Infectious Disease in China.)



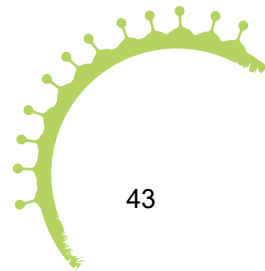
# SARS-CoV-2 - Timeline



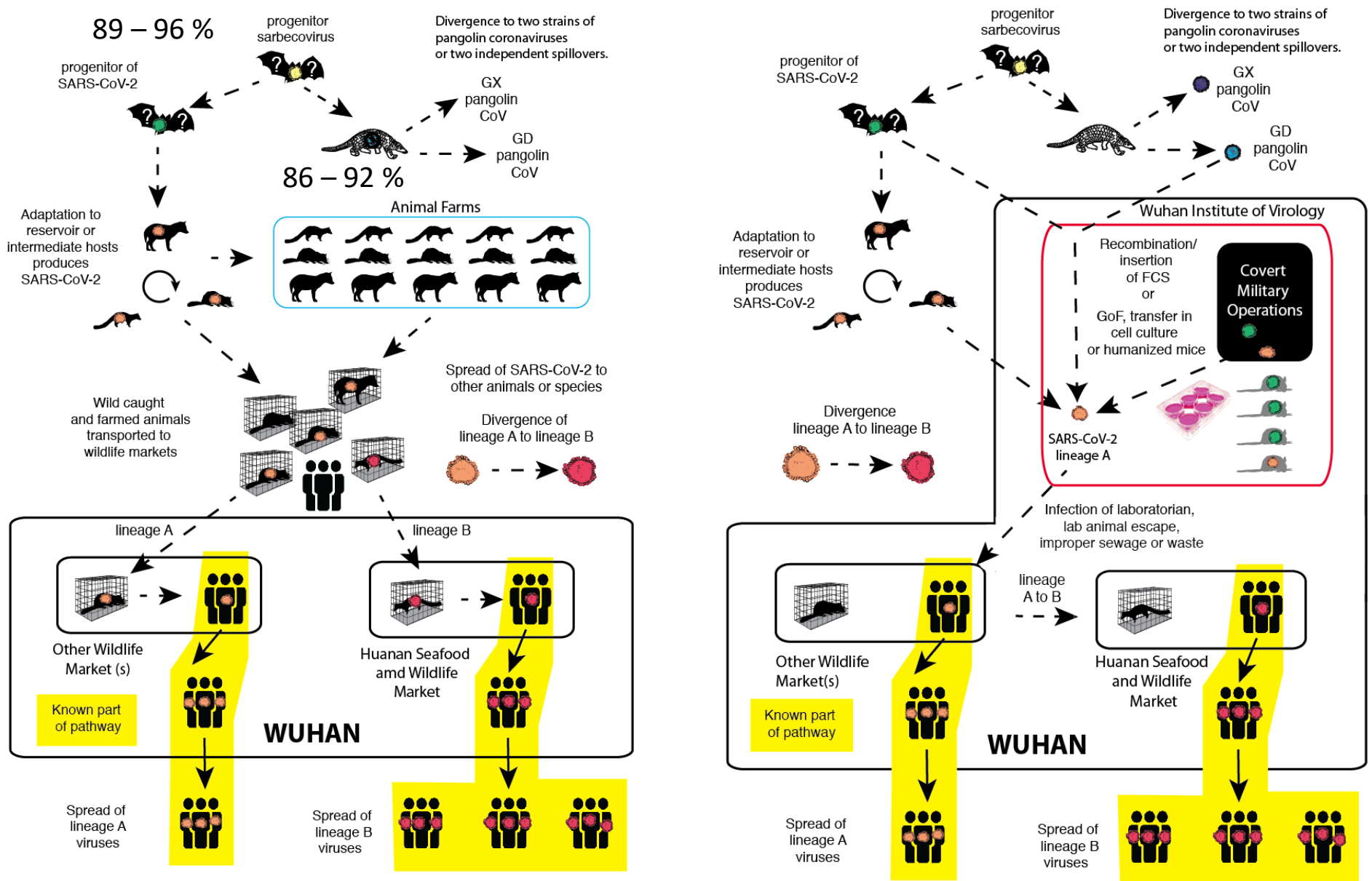


December 2019 (Wuhan)  
Caused COVID-19 Pandemic

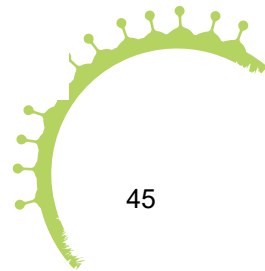
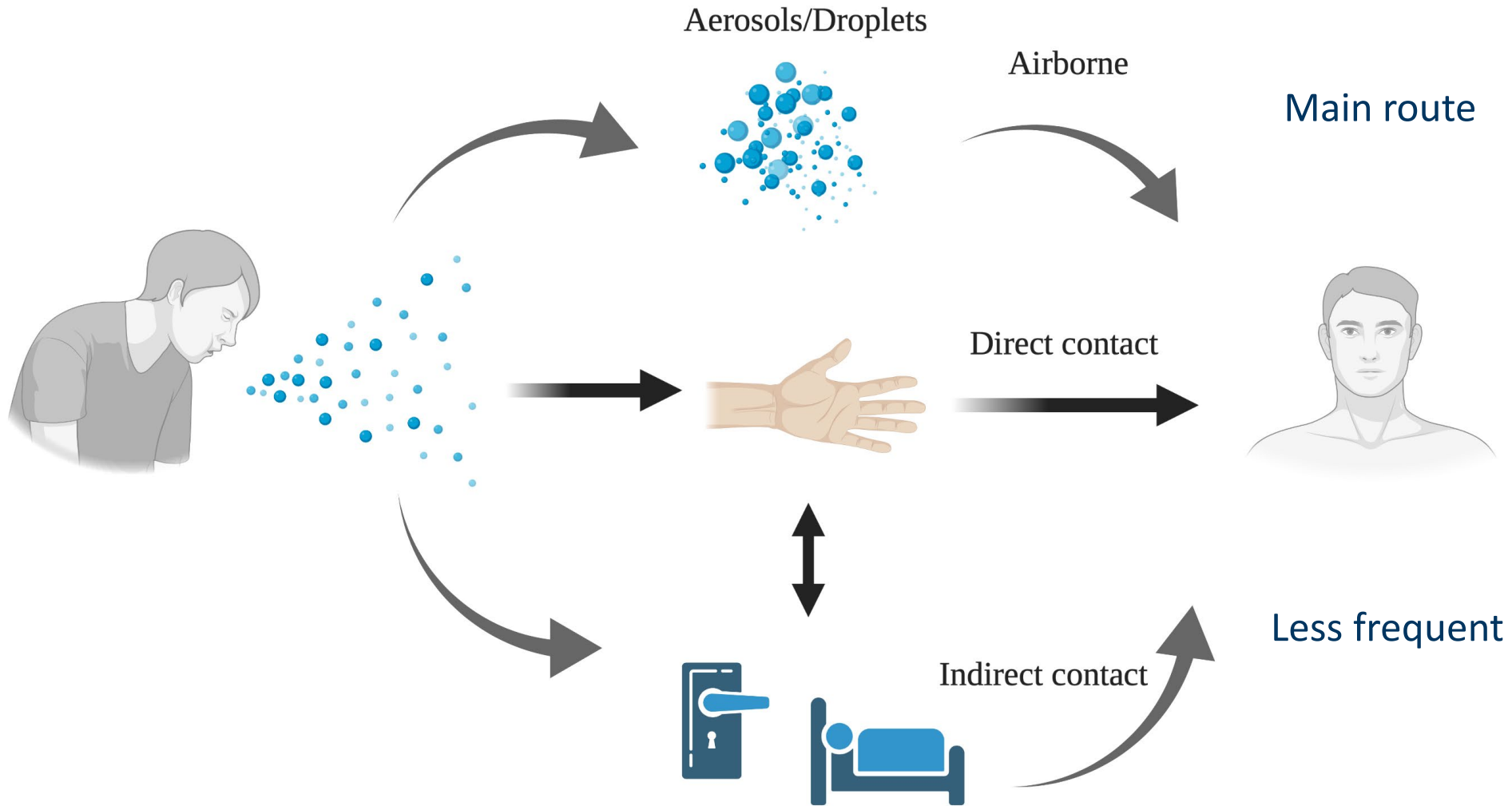
Johns Hopkins University (10/03/2023)



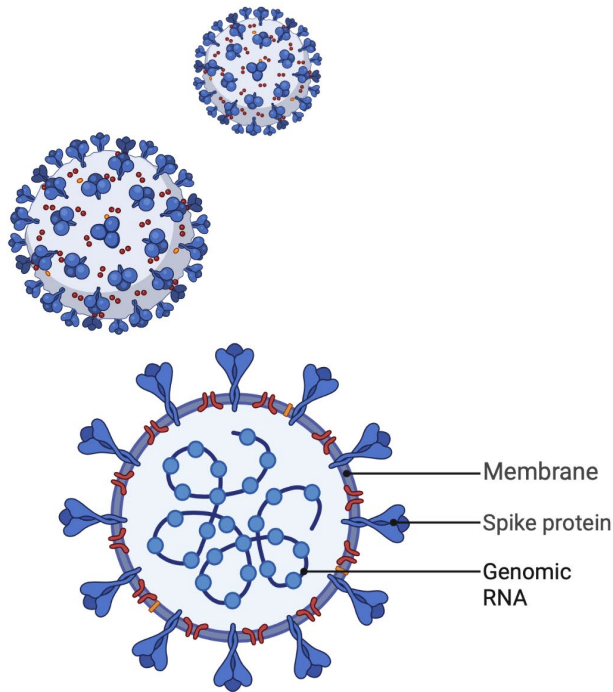
# SARS-CoV-2 – Origin



# SARS-CoV-2 - Transmission



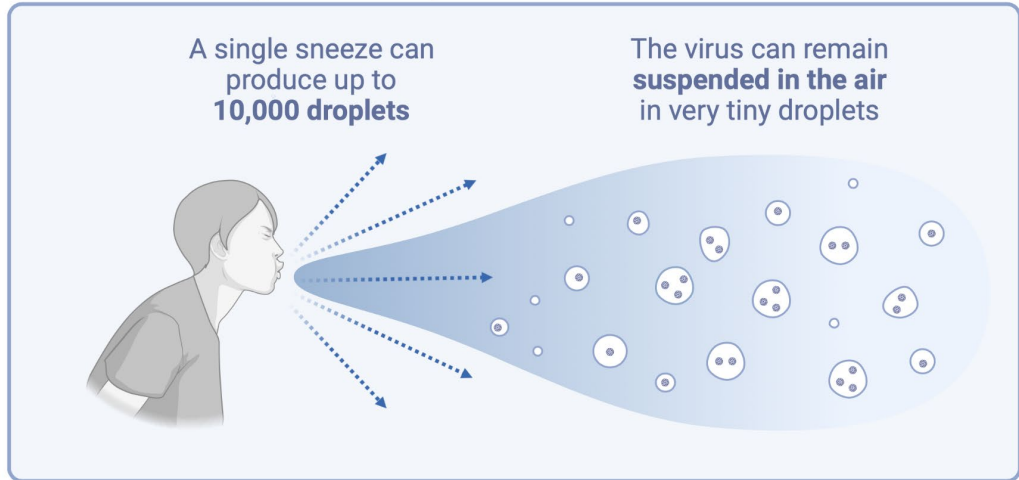
# SARS-CoV-2 - Transmission



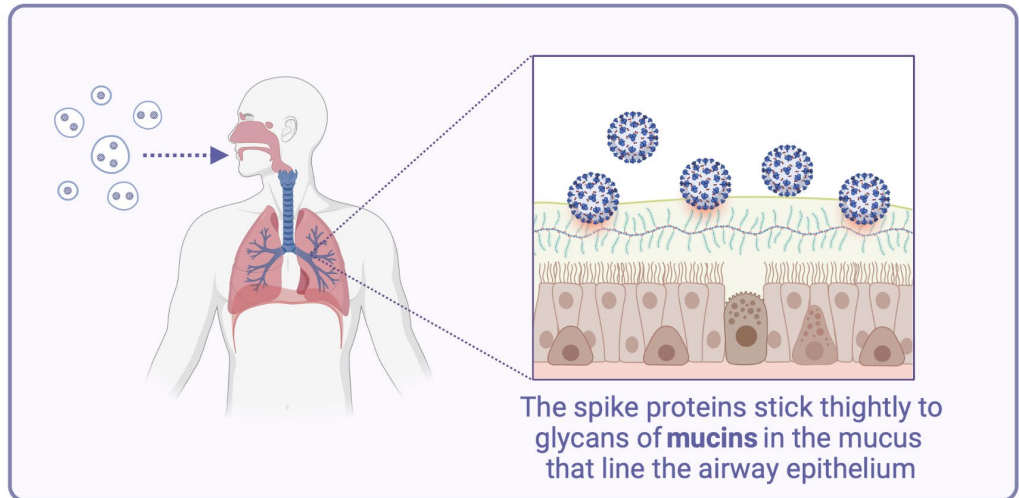
## SARS-CoV-2

How is the virus spread?

### The virus can spread easily

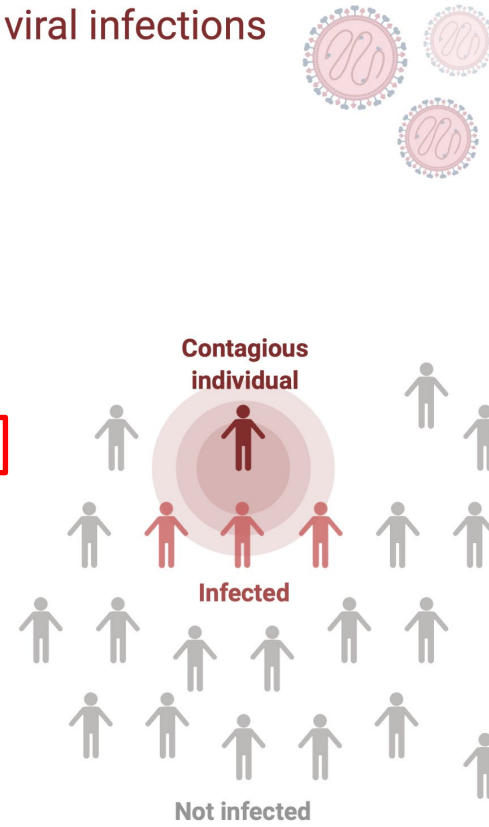
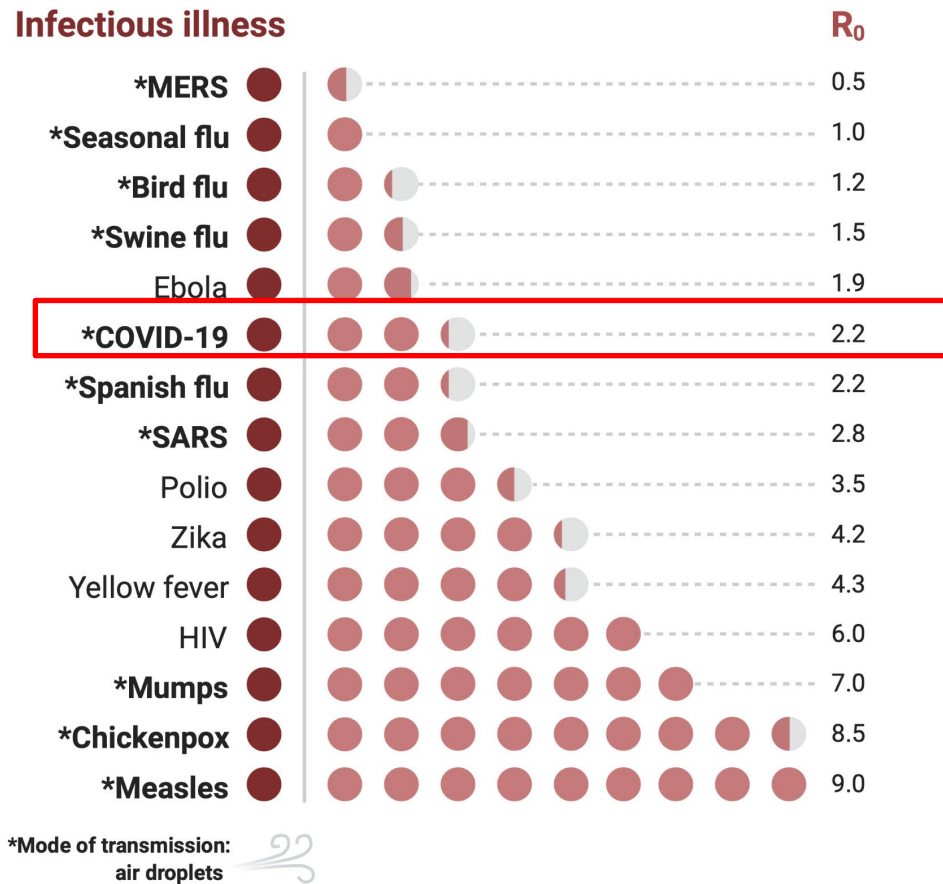


### The virus remains in the airways

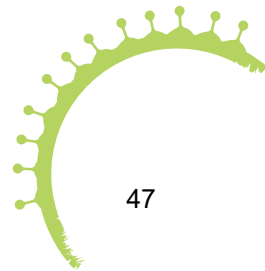


# Reproduction Number

## Average Basic Reproduction Number ( $R_0$ ) of common viral infections



The **average basic reproduction number ( $R_0$ )** is an epidemiologic metric that describes the transmissibility of infectious agents.  $R_0$  measures the expected number of secondary infections produced by a single infectious individual in a susceptible population during the mean infectious period.



# Superspreader – SARS-CoV-2

Transmission

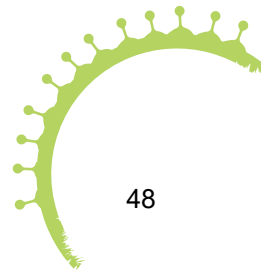
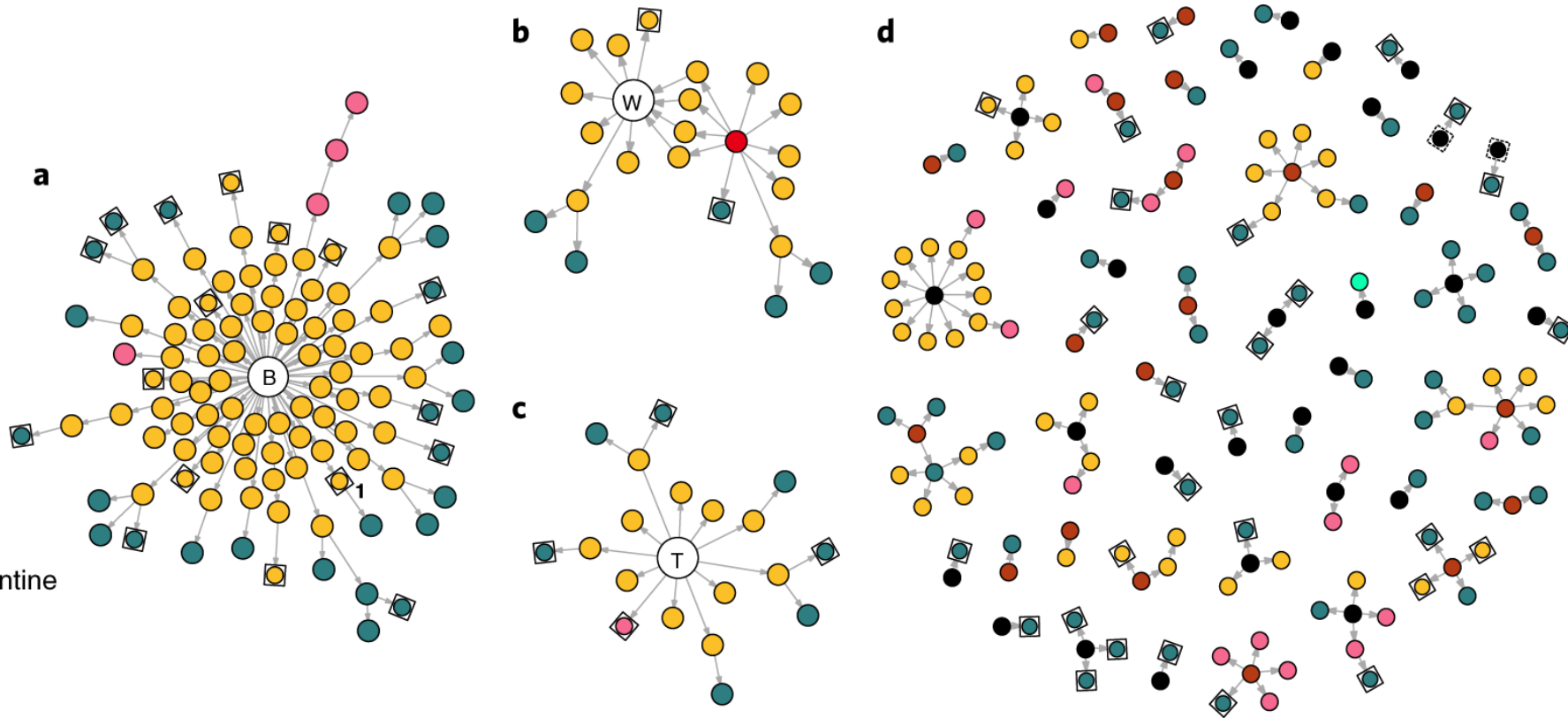
- Social
- Family
- Work
- Local travel
- Ⓜ Wedding
- Ⓣ Temple
- Ⓟ Bar

Source

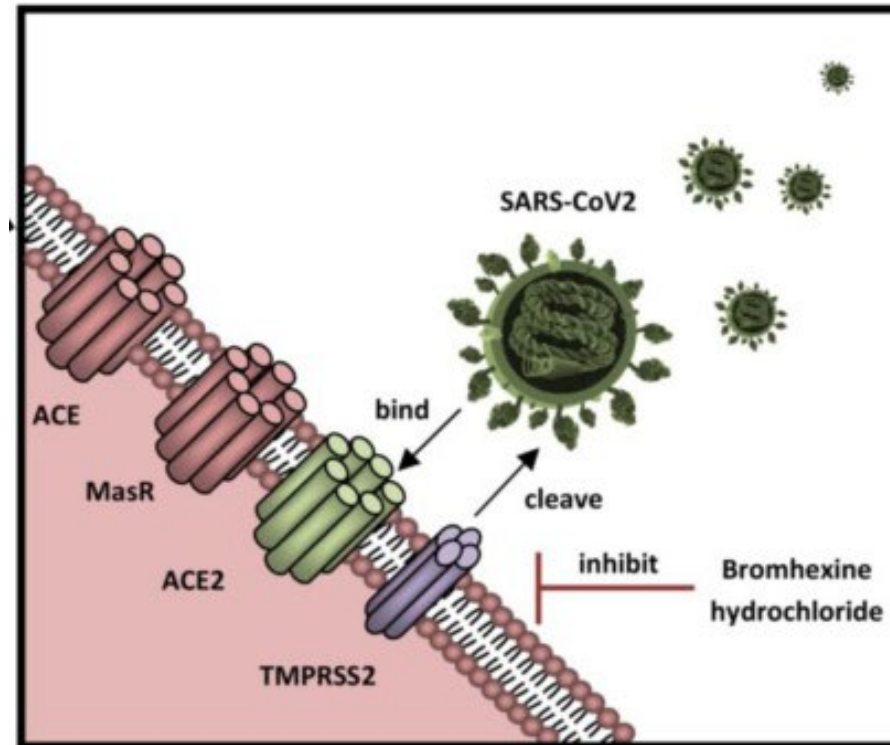
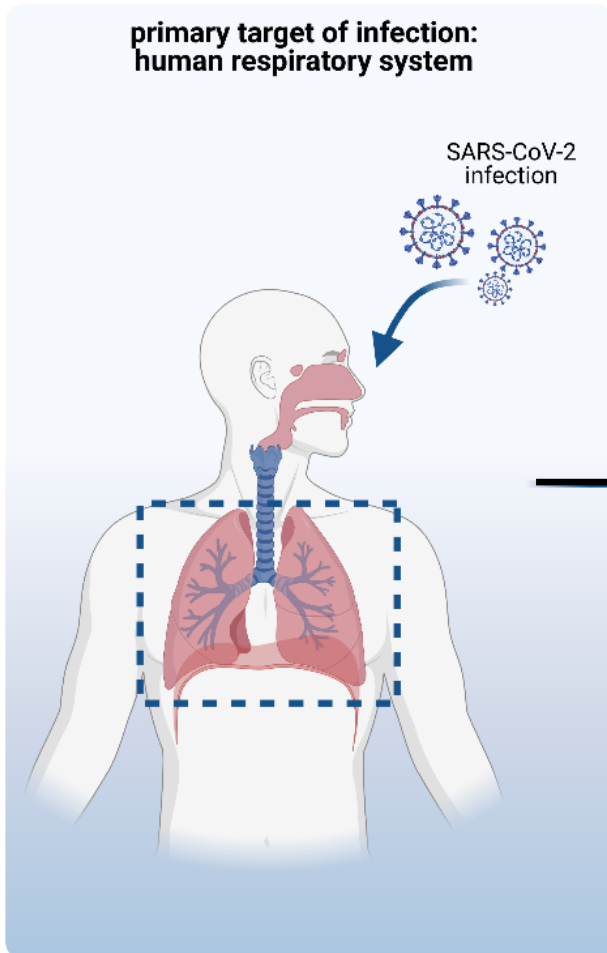
- Imported source
- Local source

Intervention

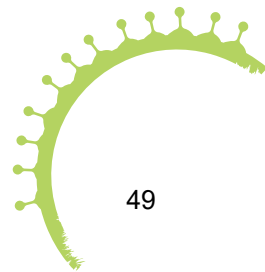
- Government quarantine
- Home quarantine



# SARS-CoV-2 – Tropism

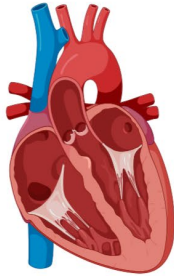


- Entry mediated by ACE2 und TMPRSS2 (Lung)

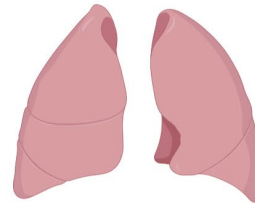


# COVID-19 – Multi Organ Tropism

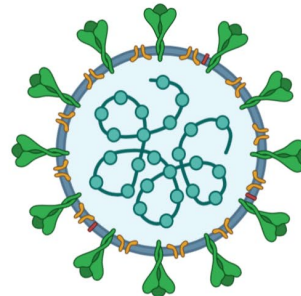
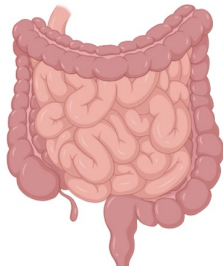
## Heart/Circulation



## Pulmonal Disease

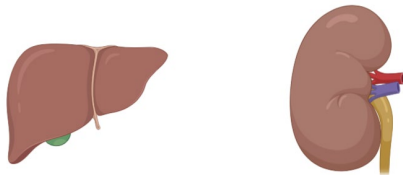
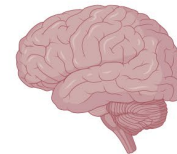


## Gastrointestinal symptoms

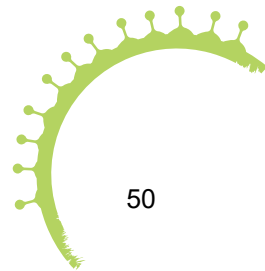
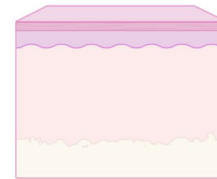


COVID-19

## Neurological Symptoms

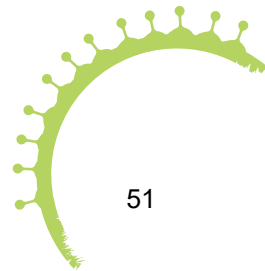
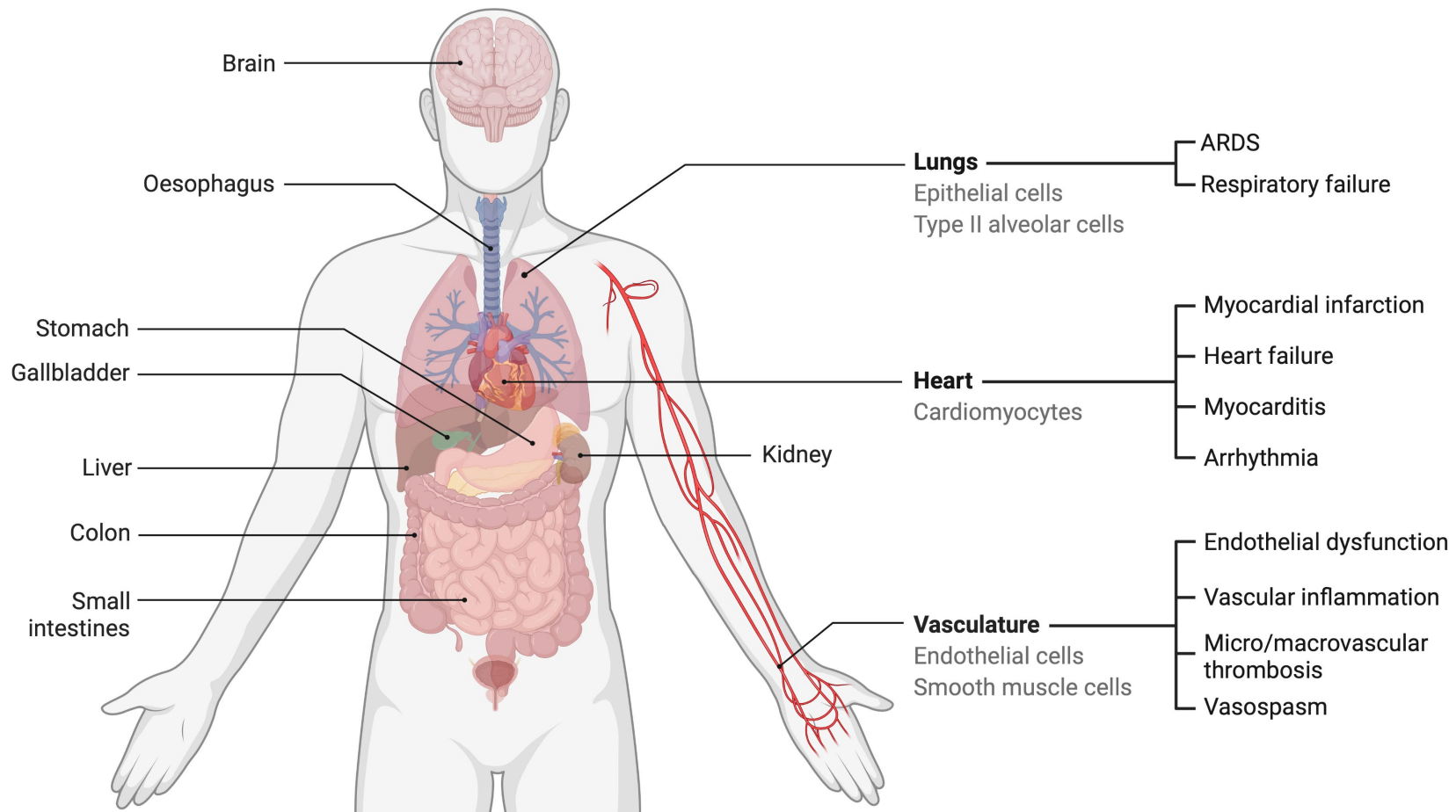


## Dermatological Manifestation

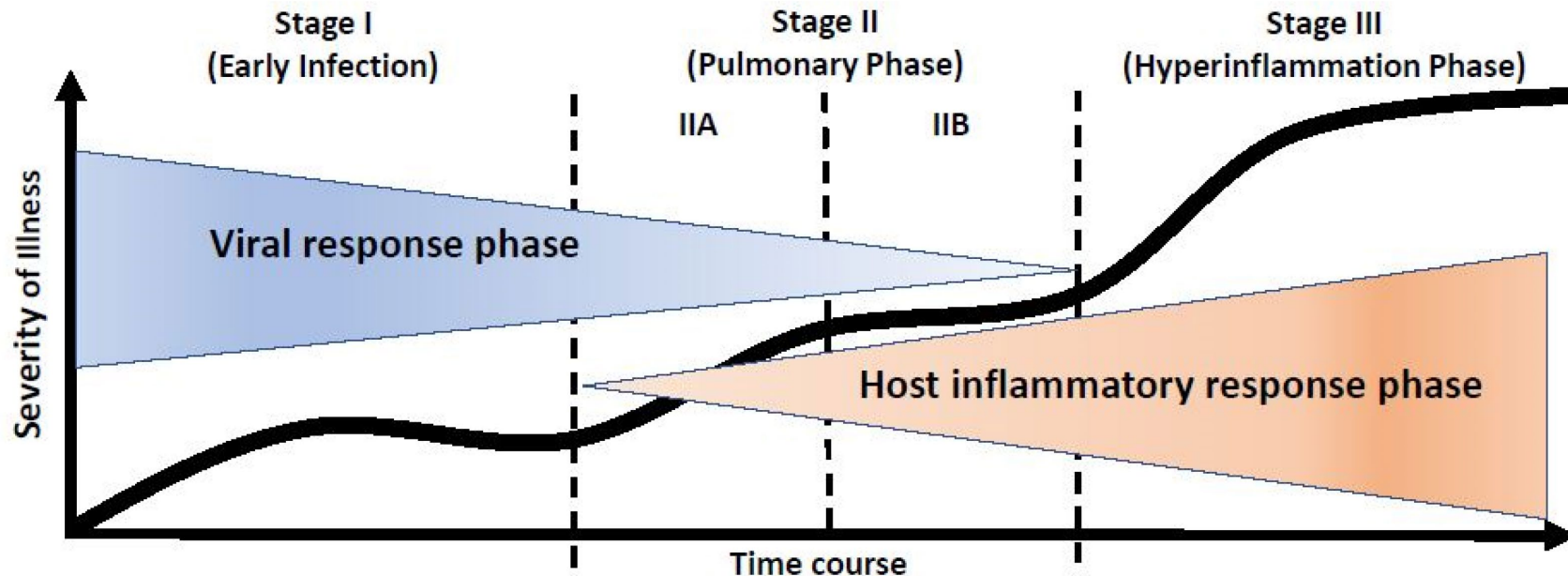


# COVID-19 – Multi Organ Tropism

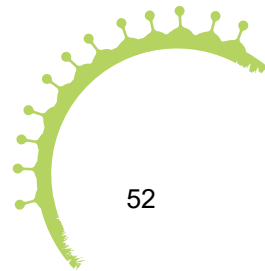
## Host Tissues Known to Express ACE2



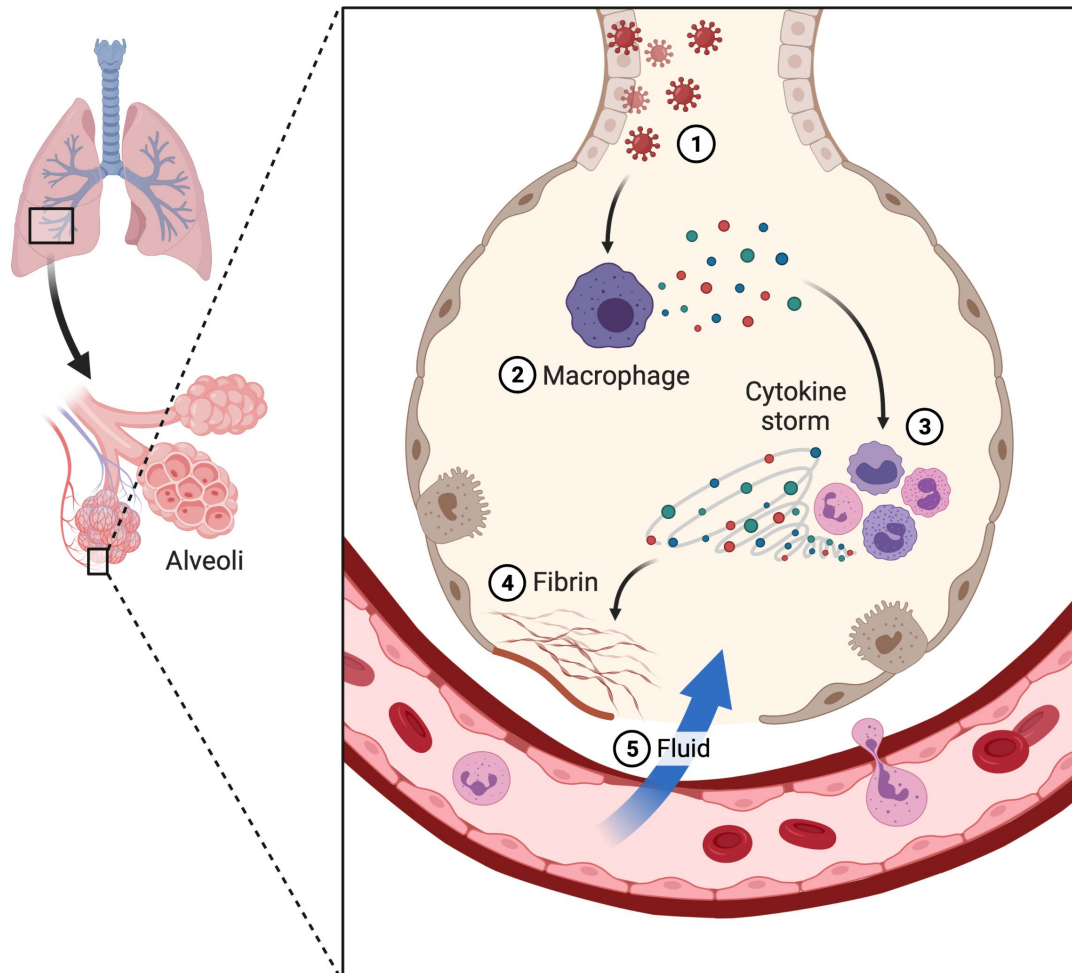
# COVID-19 – Course of disease



	Stage I (Early Infection)	Stage II (Pulmonary Phase)	Stage III (Hyperinflammation Phase)
<b>Clinical Symptoms</b>	Mild constitutional symptoms Fever >99.6°F (37.56°C) Dry Cough, diarrhea, headache	Shortness of Breath Hypoxia (PaO <sub>2</sub> /FiO <sub>2</sub> ≤ 300mmHg)	ARDS SIRS/Shock Cardiac Failure
<b>Clinical Signs</b>	Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)	Abnormal chest imaging Transaminitis Low-normal procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation

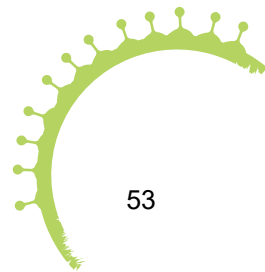


# COVID 19 – Cytokine Storm

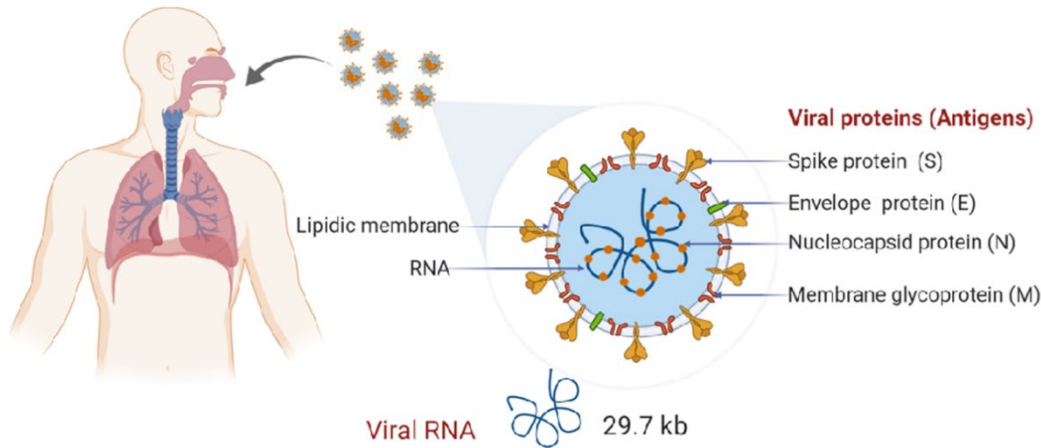


## Cytokine Storm

- ① Coronavirus infects lung cells
- ② Immune cells, including macrophages, identify the virus and produce cytokines
- ③ Cytokines attract more immune cells, such as white blood cells, which in turn produce more cytokines, creating a cycle of inflammation that damages the lung cells
- ④ Damage can occur through the formation of fibrin
- ⑤ Weakened blood vessels allow fluid to seep in and fill the lung cavities, leading to respiratory failure

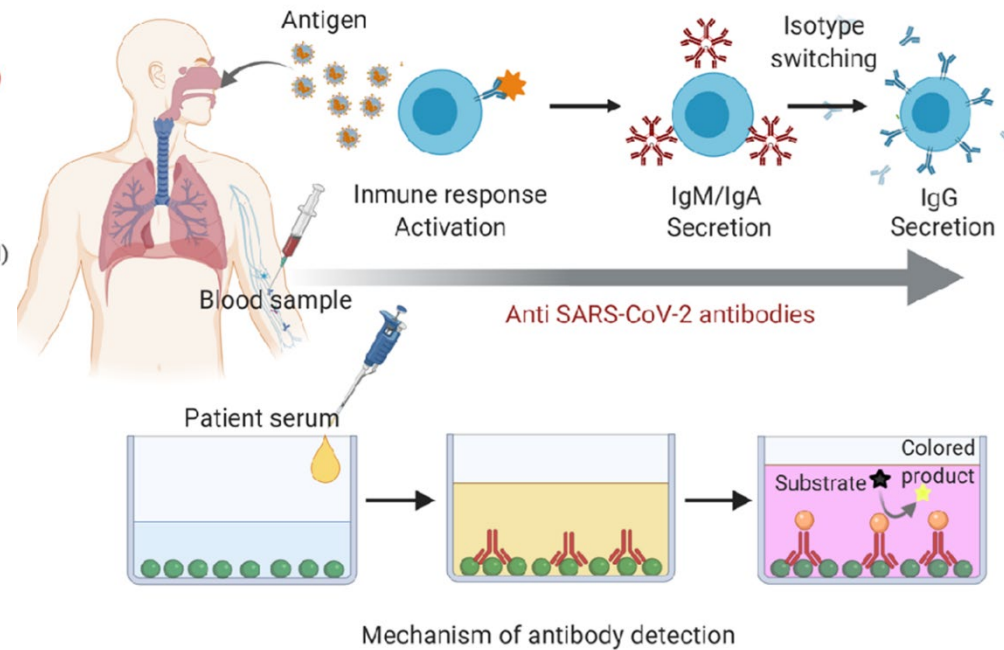


## I) Direct (Virus)

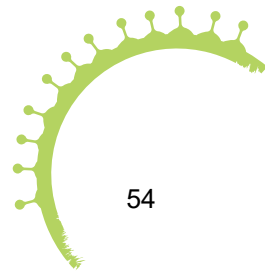


- RT-PCR
- Sequencing
- Antigen-ELISA
- Rapid Antigen Test
- Western Blot
- ...

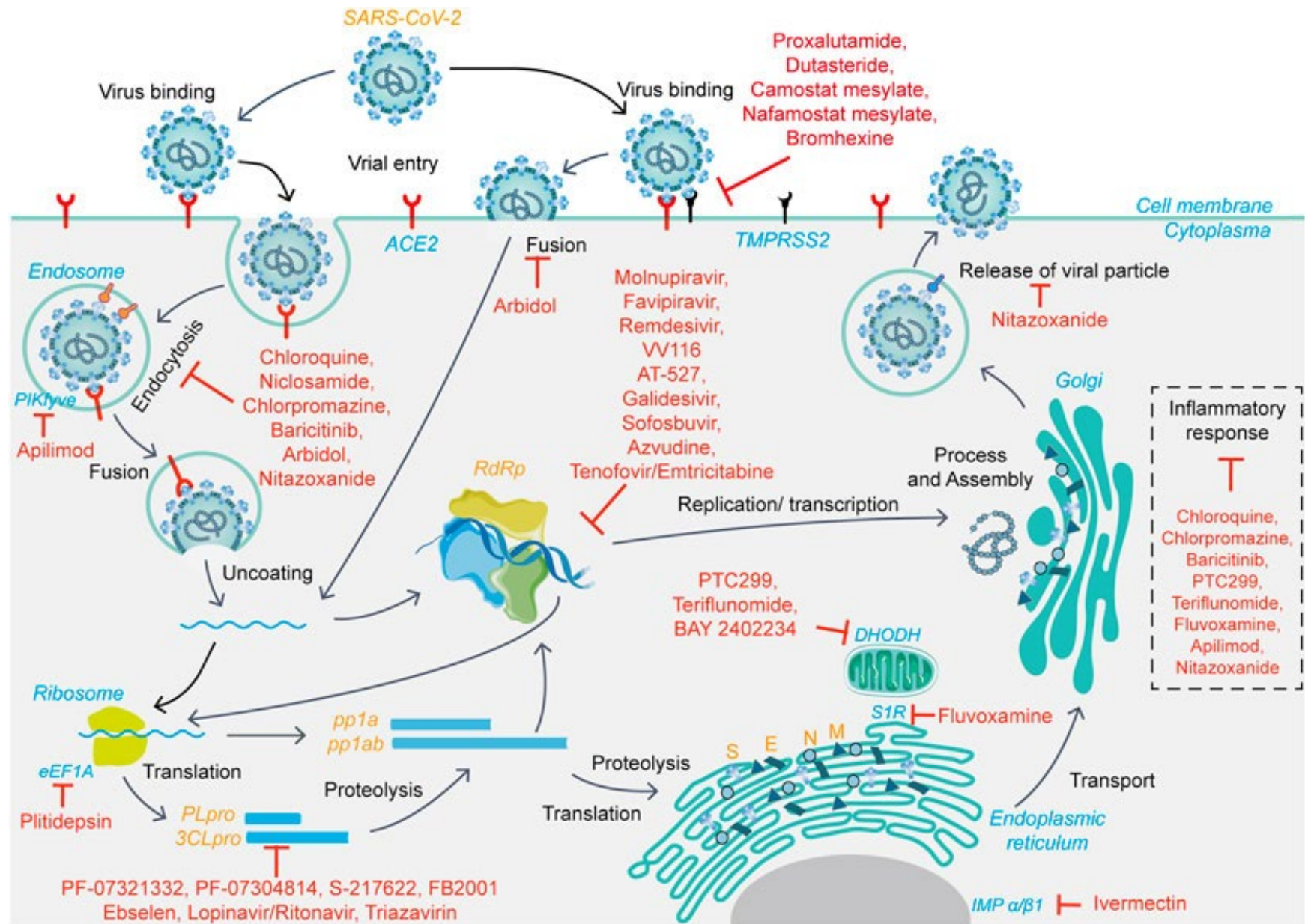
## II) Indirect (Immunreaction)



- Antibody-ELISA
- Neutralization Assay
- T-Cell activity
- ...



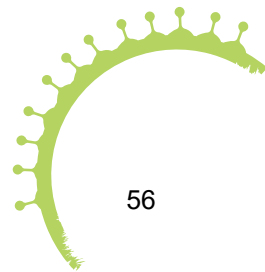
# SARS-CoV-2 - Antivirals



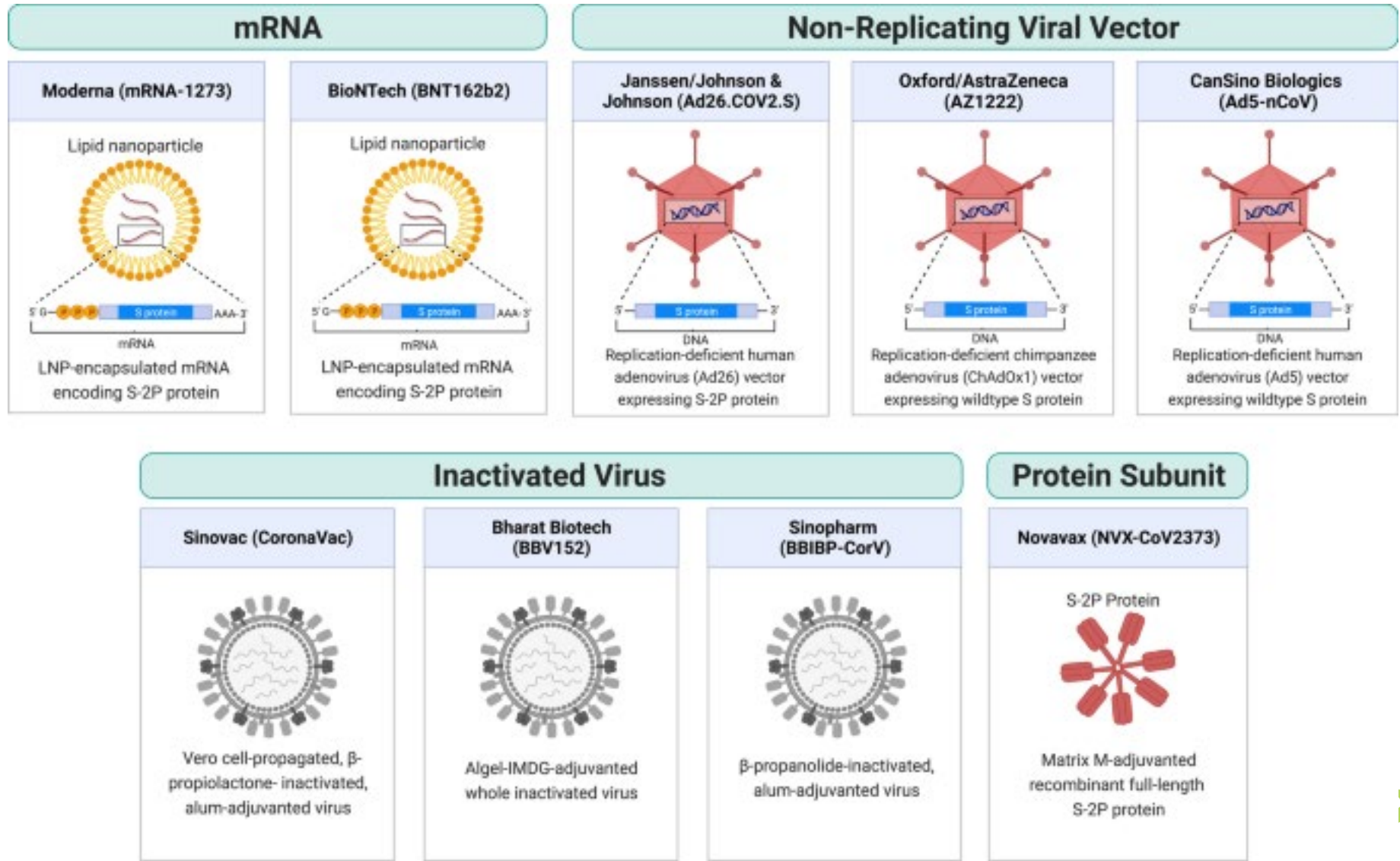
# SARS-CoV-2 - Antivirals

Drug	Class	Target	Application
Remdesivir	Nucleoside-Analog	Replication	I.V
Paxlovid (Nirmatrelvir/ Ritonavir)	Protease inhibitor	M <sup>PRO</sup>	Oral
Molnupiravir	Nucleoside derivate	Copying errors	Oral
Bebtelovimab	mAB	Spike	I.V.

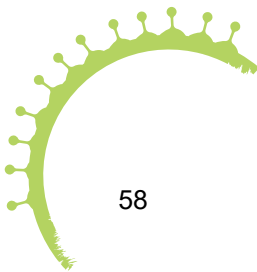
Several more.....



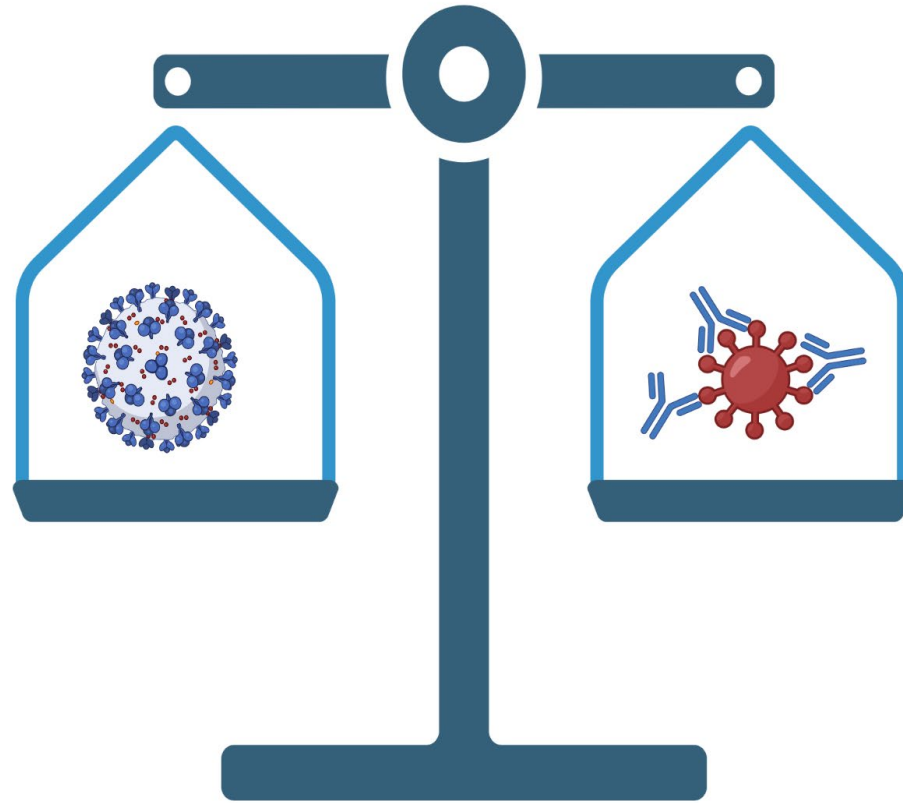
# SARS-CoV-2 - Vaccines



## SARS-CoV-2 Variants

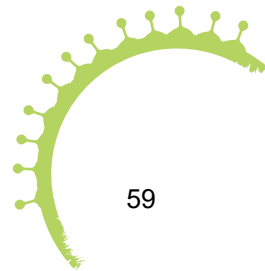


# Coronaviruses – Mutations

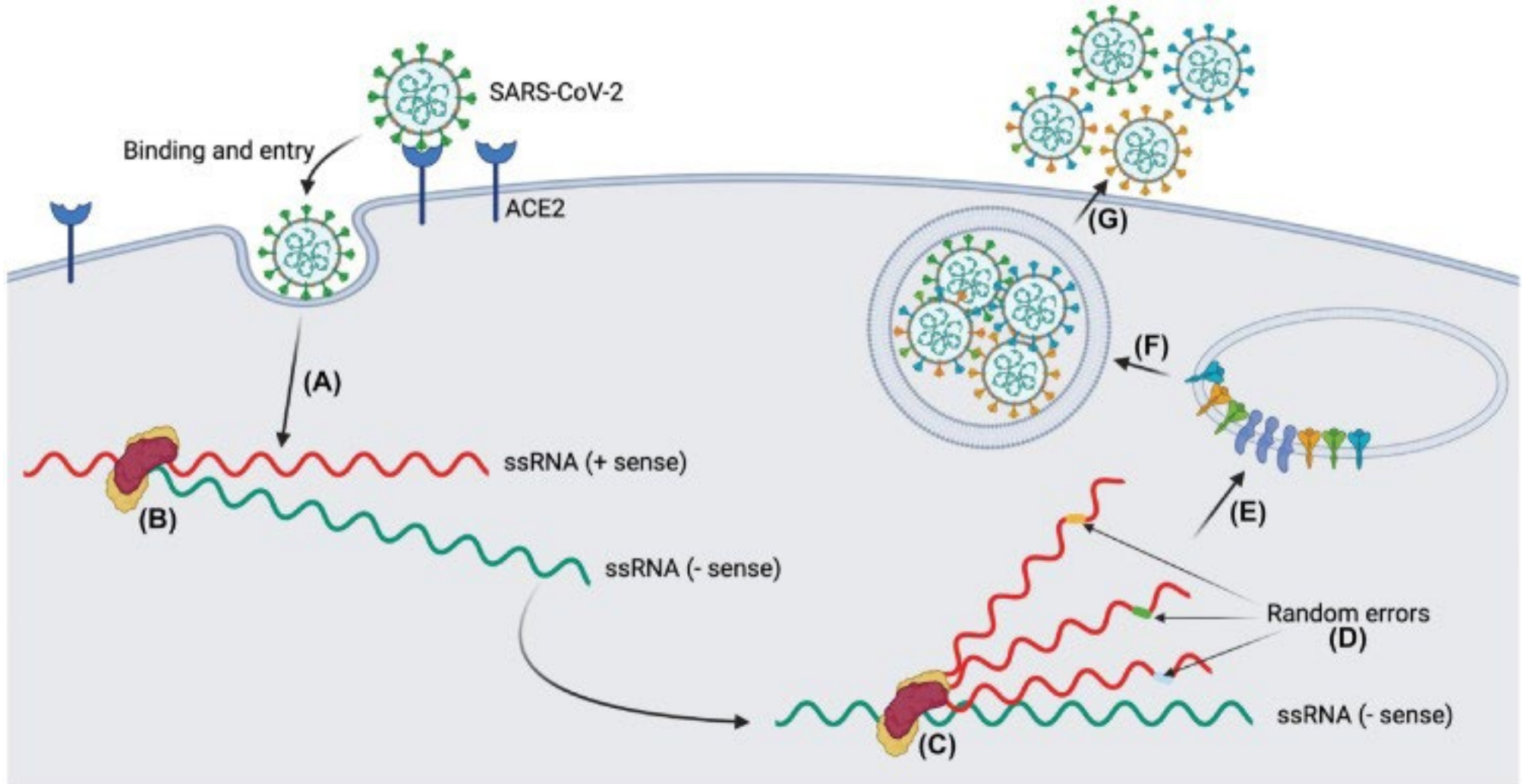


Virus

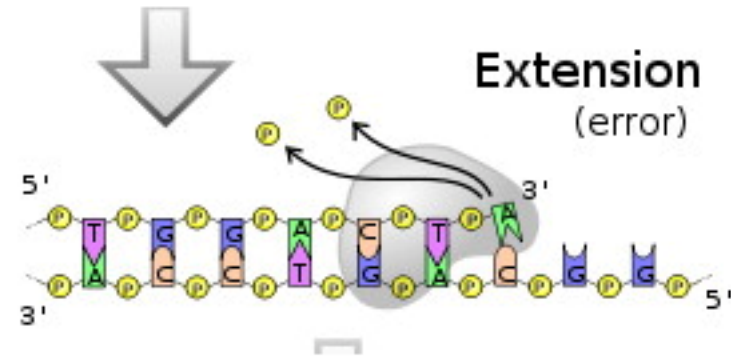
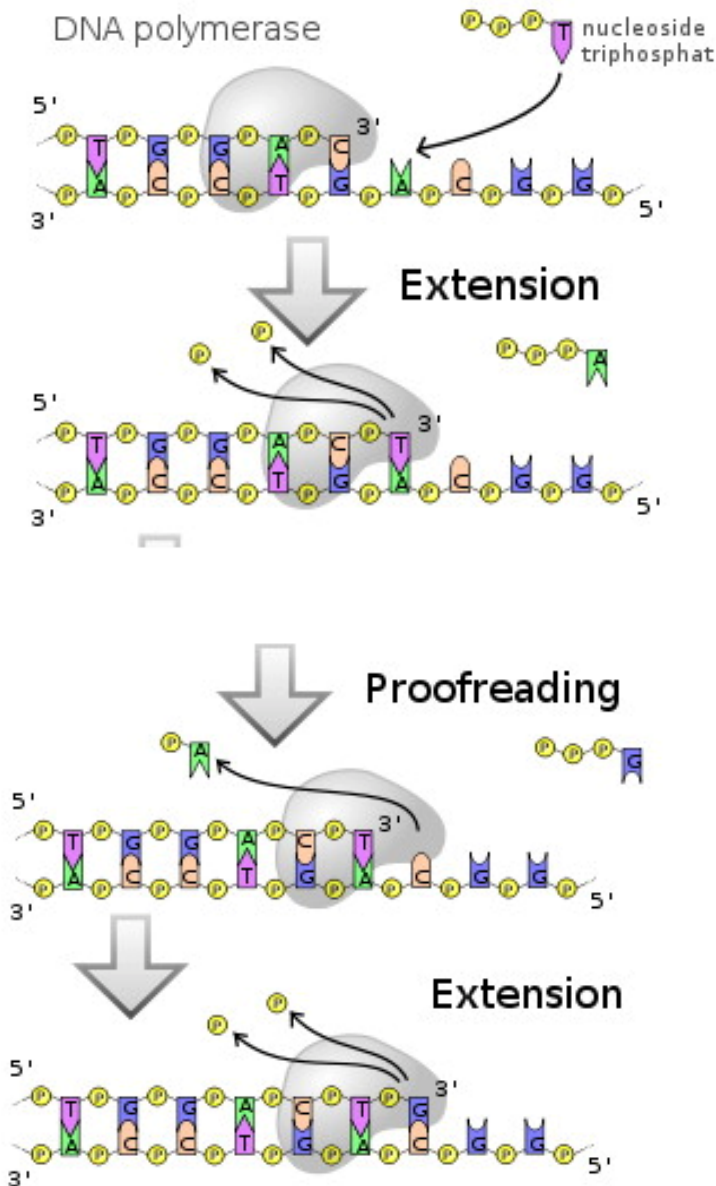
Host



# Coronaviruses – Replication errors



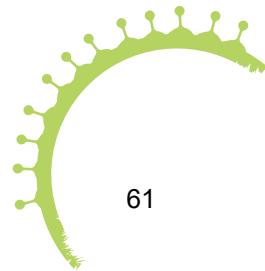
# Coronaviruses – Replication errors



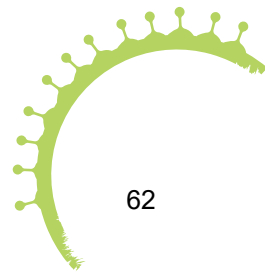
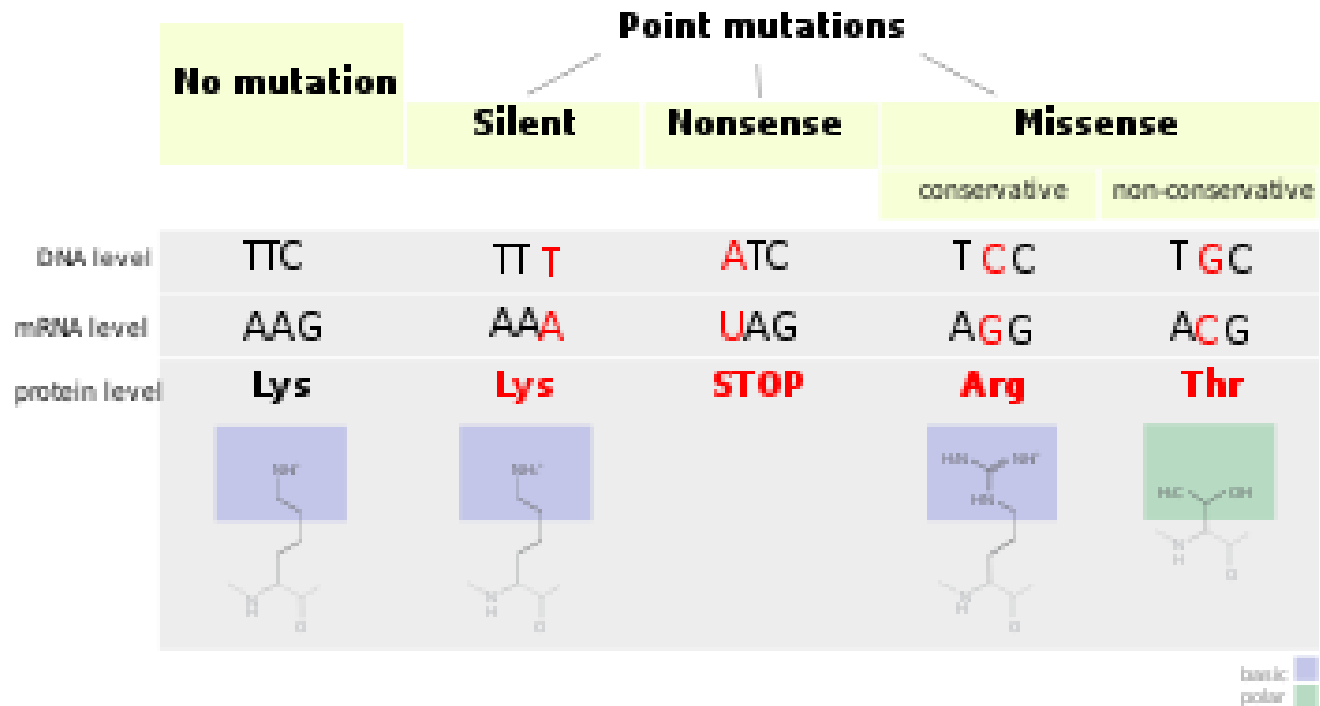
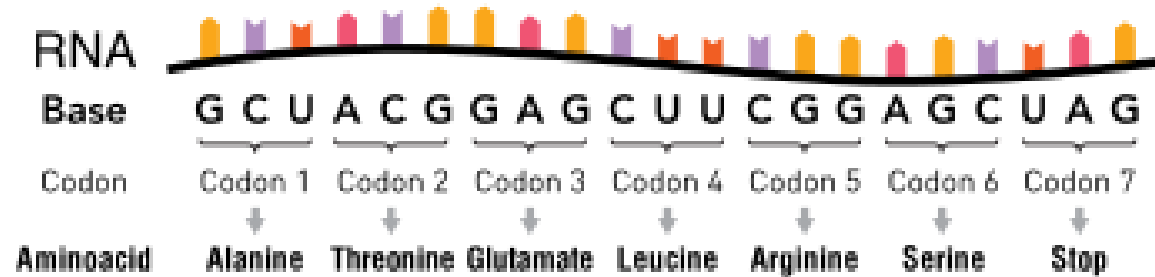
## Errors:

DNA polymerase: 1:  $10^7 - 10^9$  nucleotides  
 RNA polymerase: 1: 1000 – 10.000 nucleotides

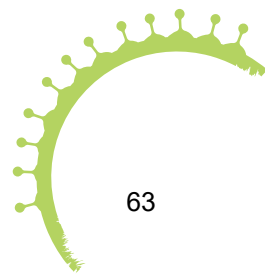
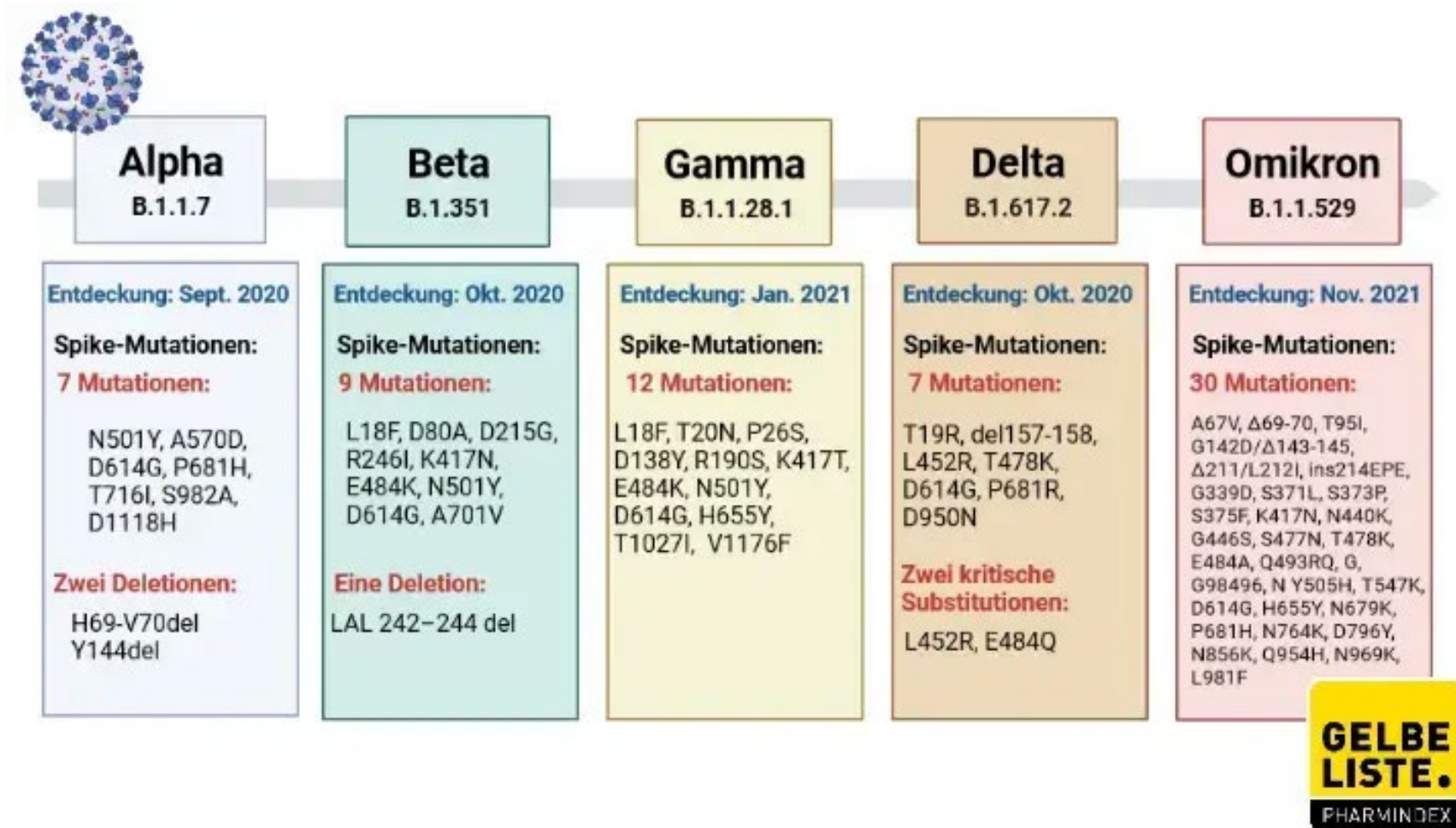
Coronaviruses: Proof-reading function (NSP14)



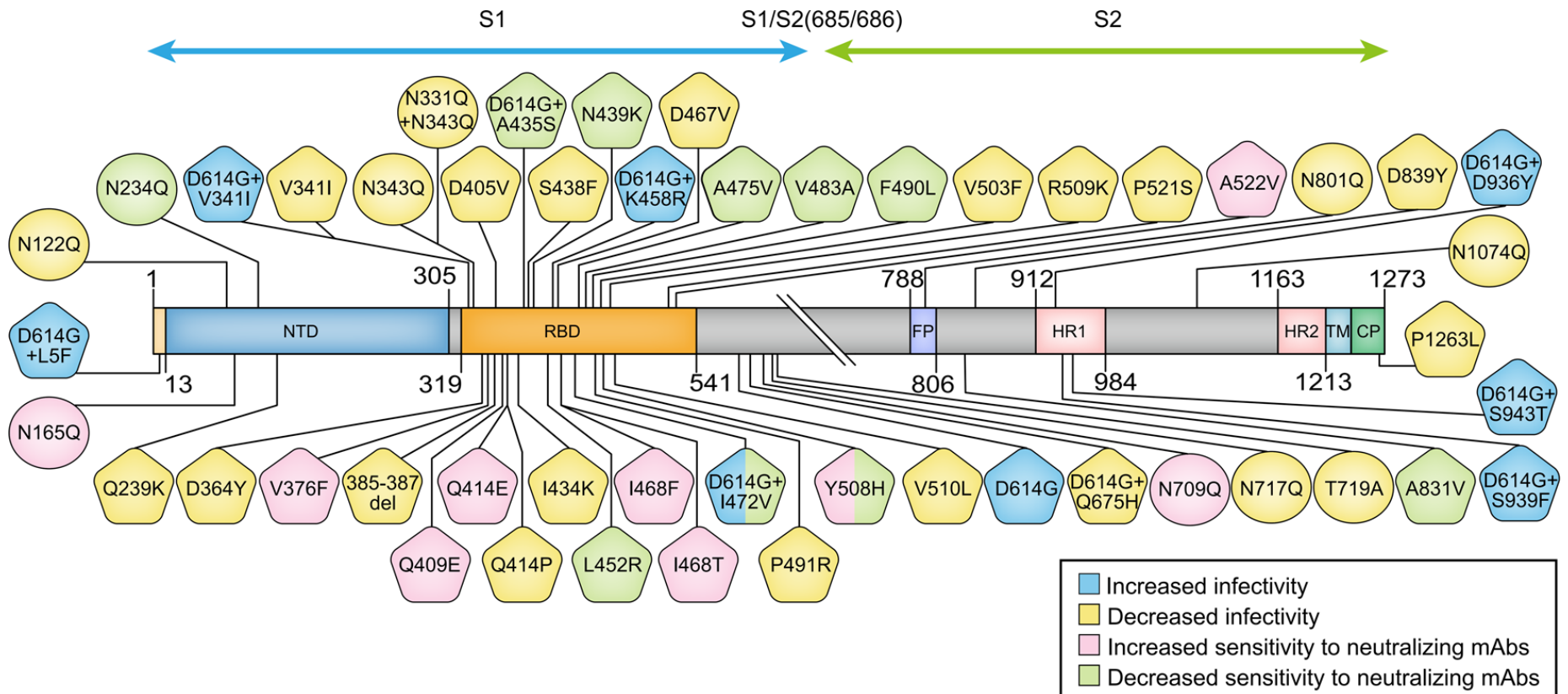
# Coronaviruses – Replication errors



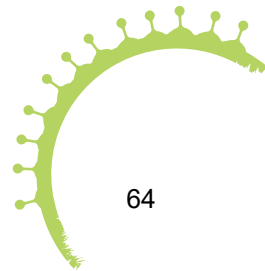
# SARS-CoV-2 - Variants



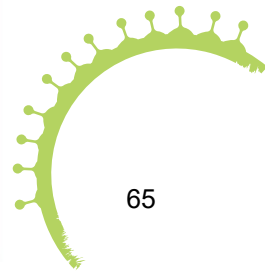
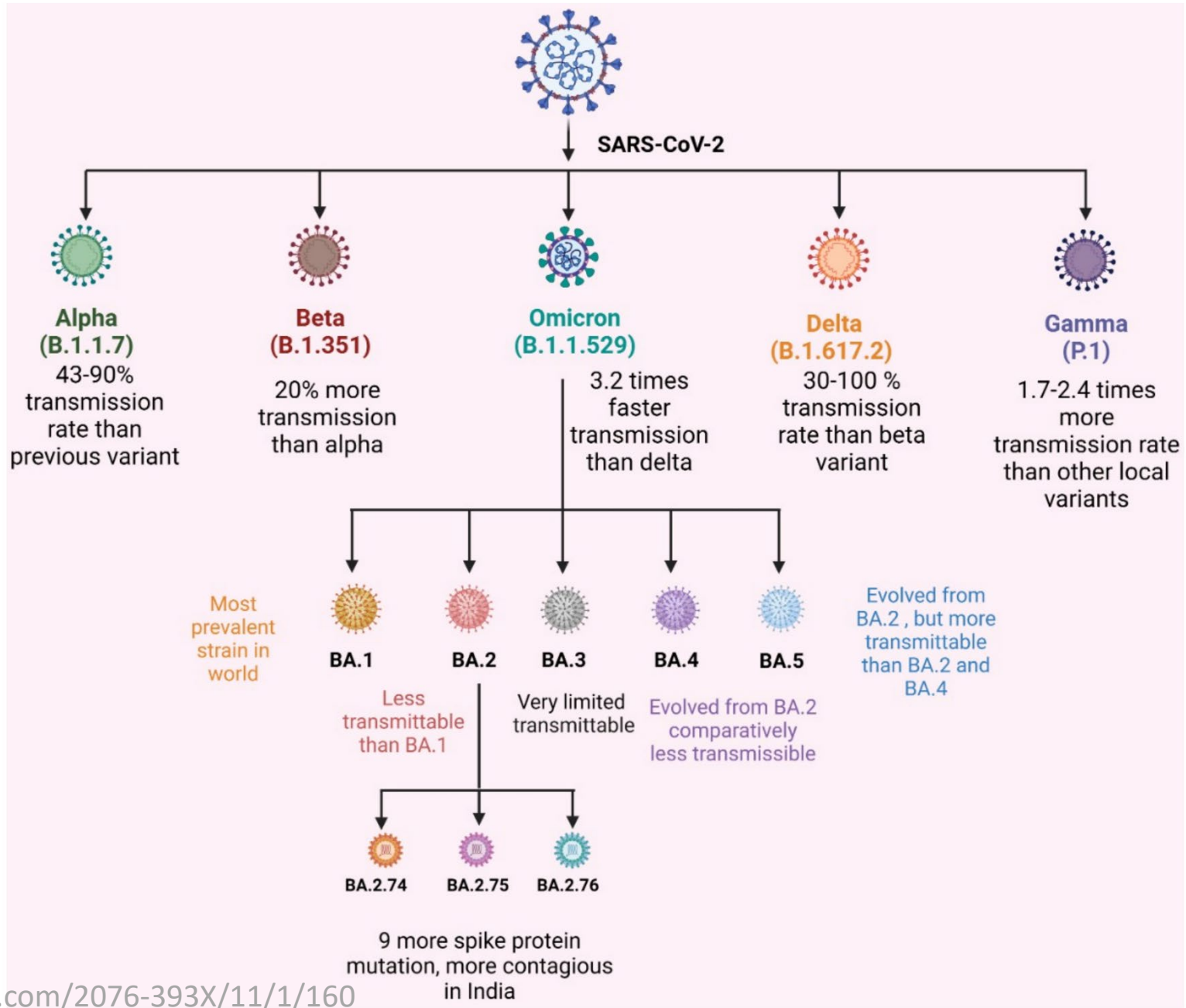
# SARS-CoV-2 - Variants



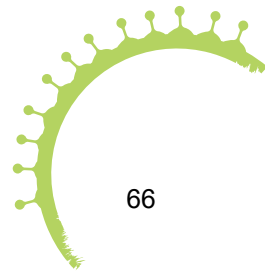
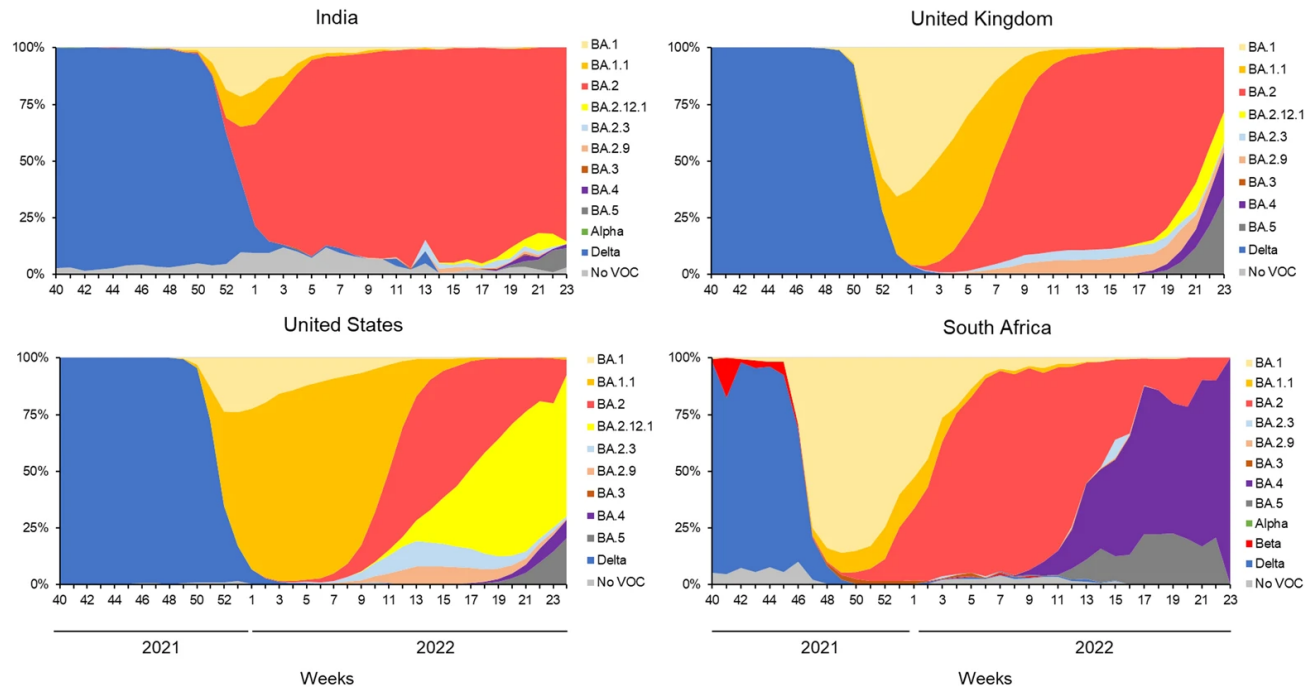
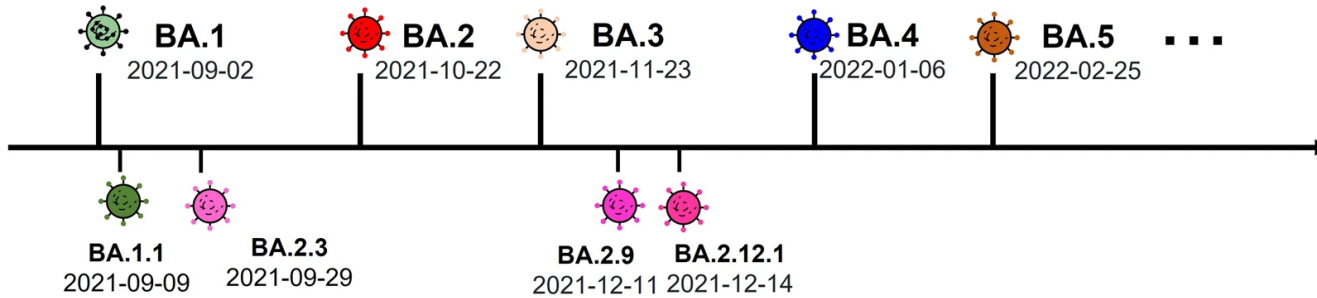
**Spike Mutations: Can affect infectivity and antibody recognition**



# SARS-CoV-2 - Omicron



# SARS-CoV-2 - Omicron spread





# Thank you for your attention

