RUHR-UNIVERSITÄT BOCHUM

RUB

Coronaviruses and SARS-CoV-2

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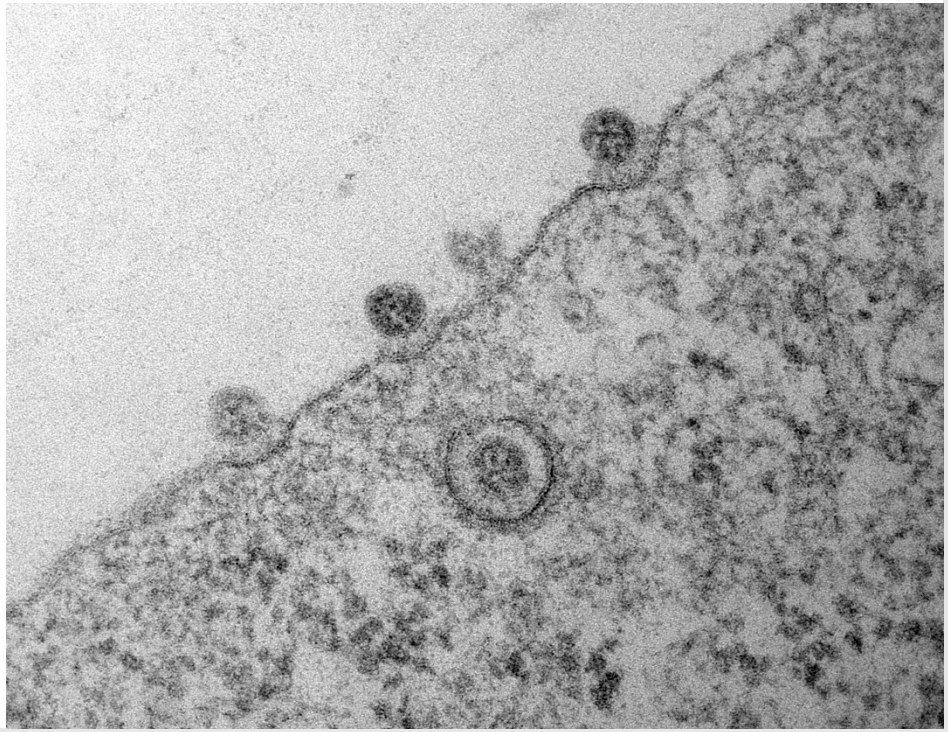
Department for Molecular and Medical Virology

04.06.2025



Molecular & Medical Virology

Goals for today's lecture

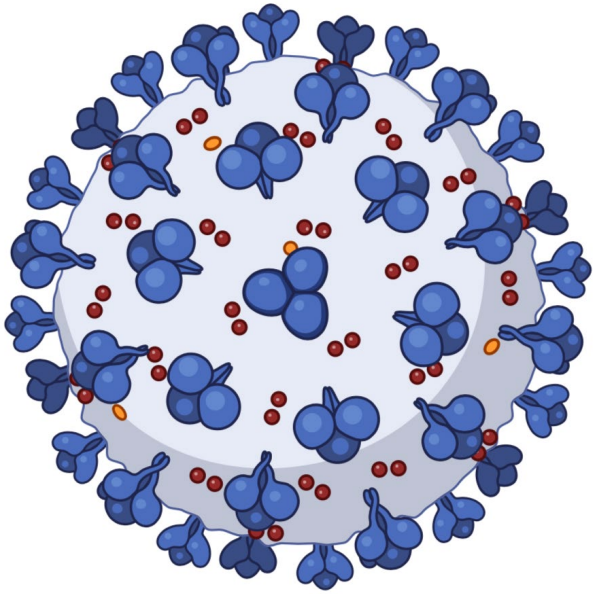
- Understanding about the coronavirus replication cycle
- Overview about highly pathogenic coronaviruses
- Update: SARS-CoV-2 and COVID-19

Molecular & Medical Virology

Coronaviruses

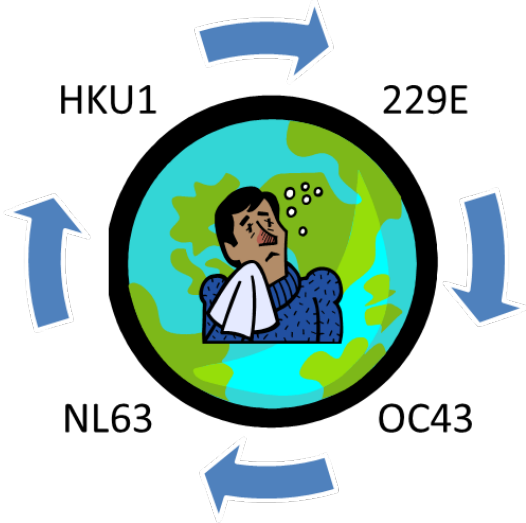
Coronaviruses

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

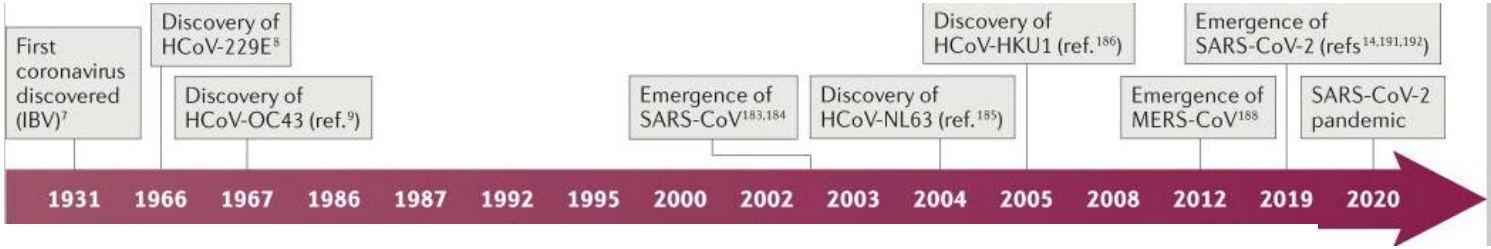


Coronaviruses – Epidemiology

- Human Coronavirueses are endemic worldwide
- Cause approx. 15% of the yearly common colds

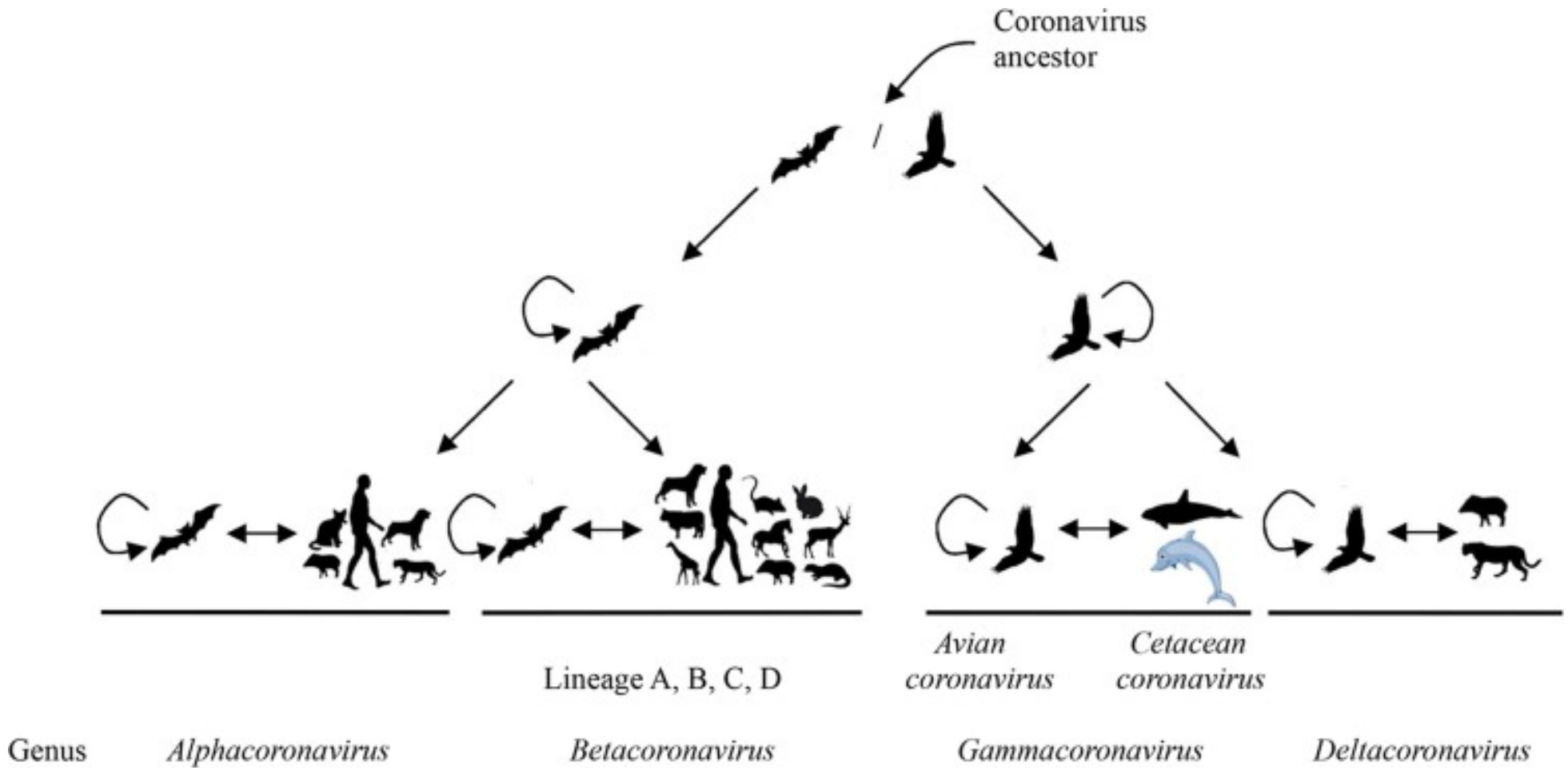


- Three pathogenic human Coronaviruses
  - SARS-CoV
  - MERS-CoV
  - SARS-CoV-2



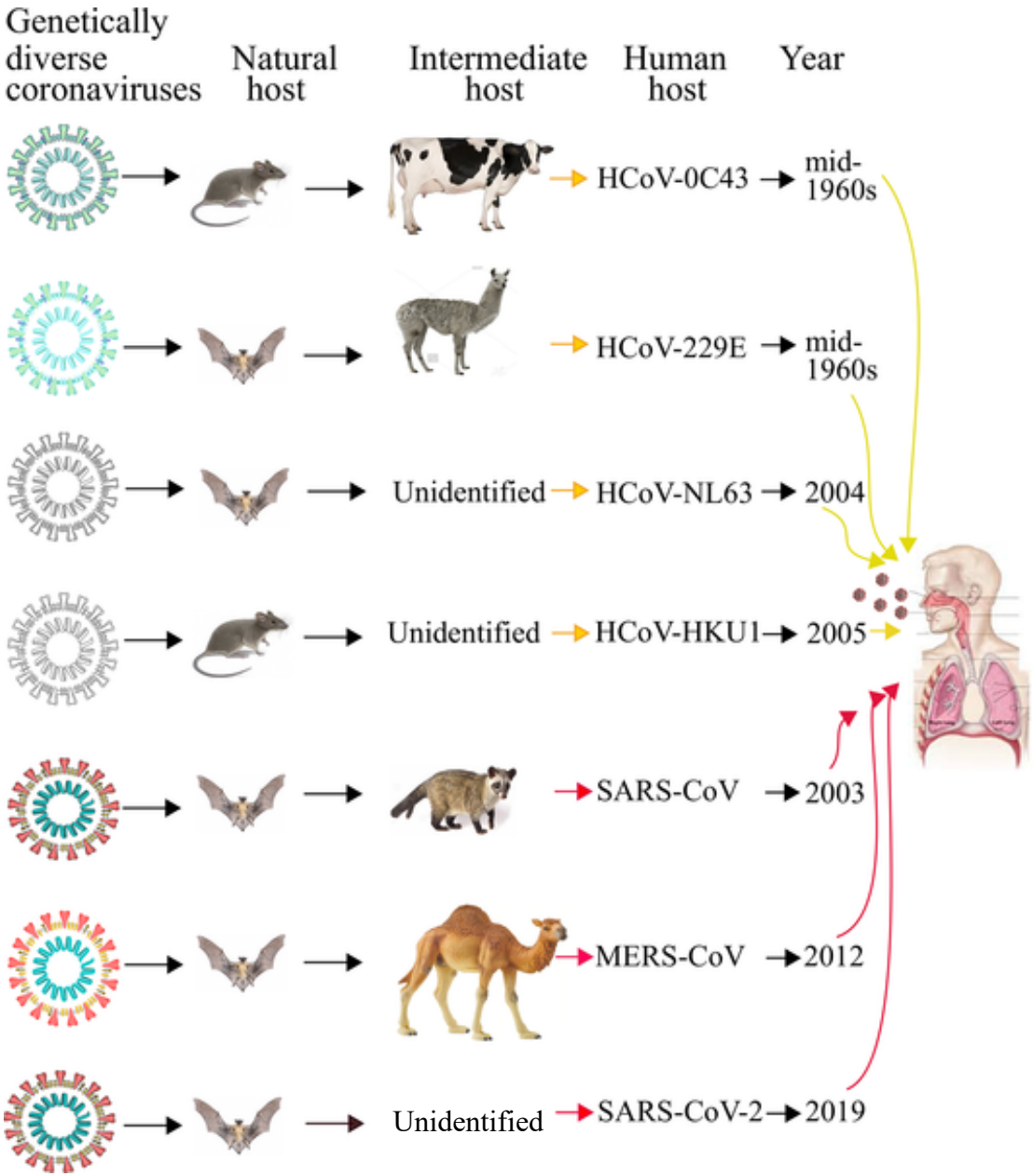
V Kovski Nat Rev Microbiology 2020 https://doi.org/10.1038/ s41579-020-00468-6

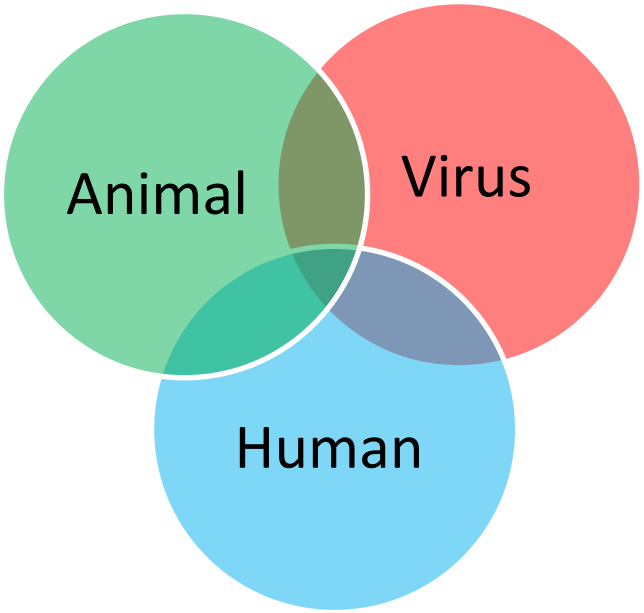
Coronaviruses - Genera



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

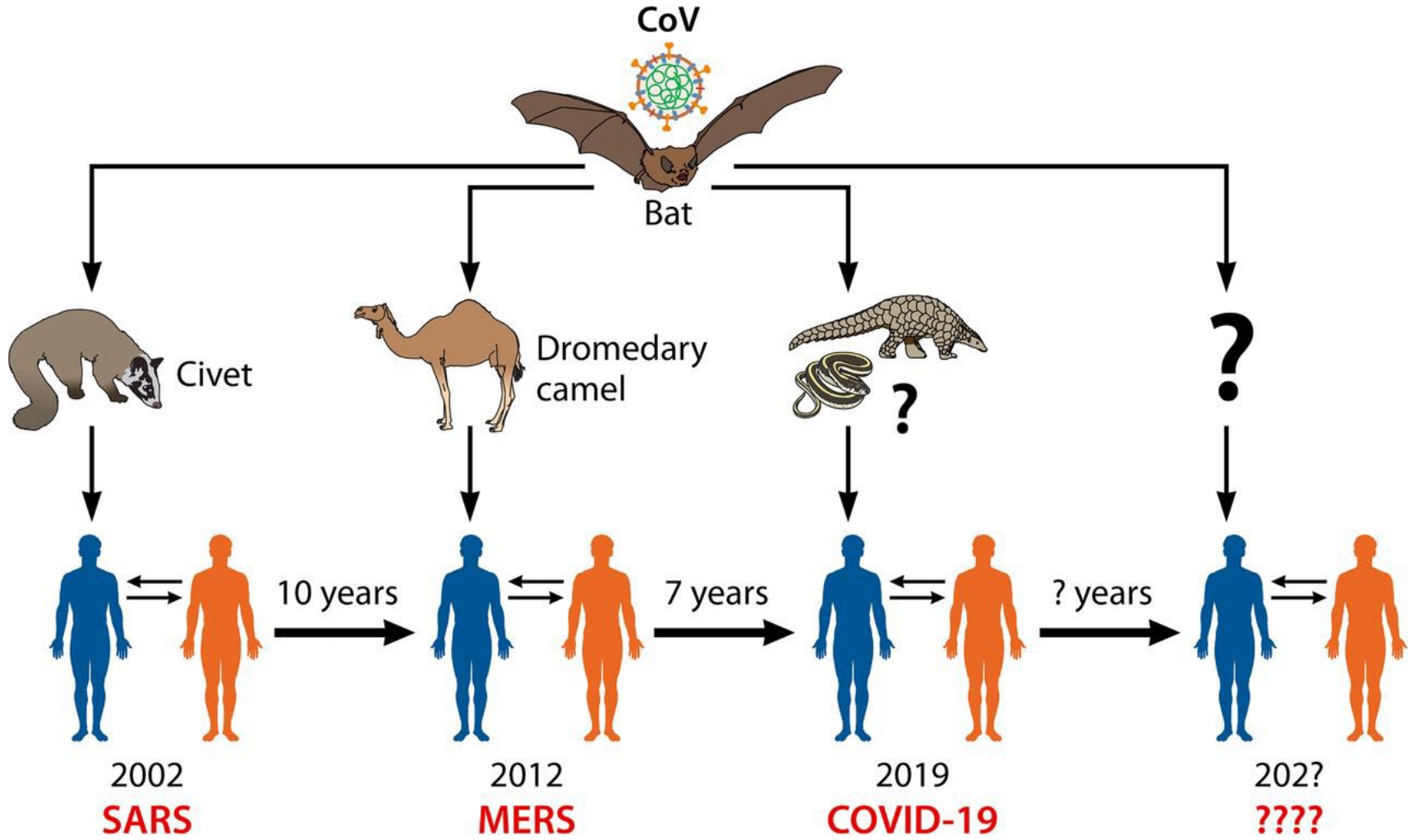
Coronaviruses - Zoonosis





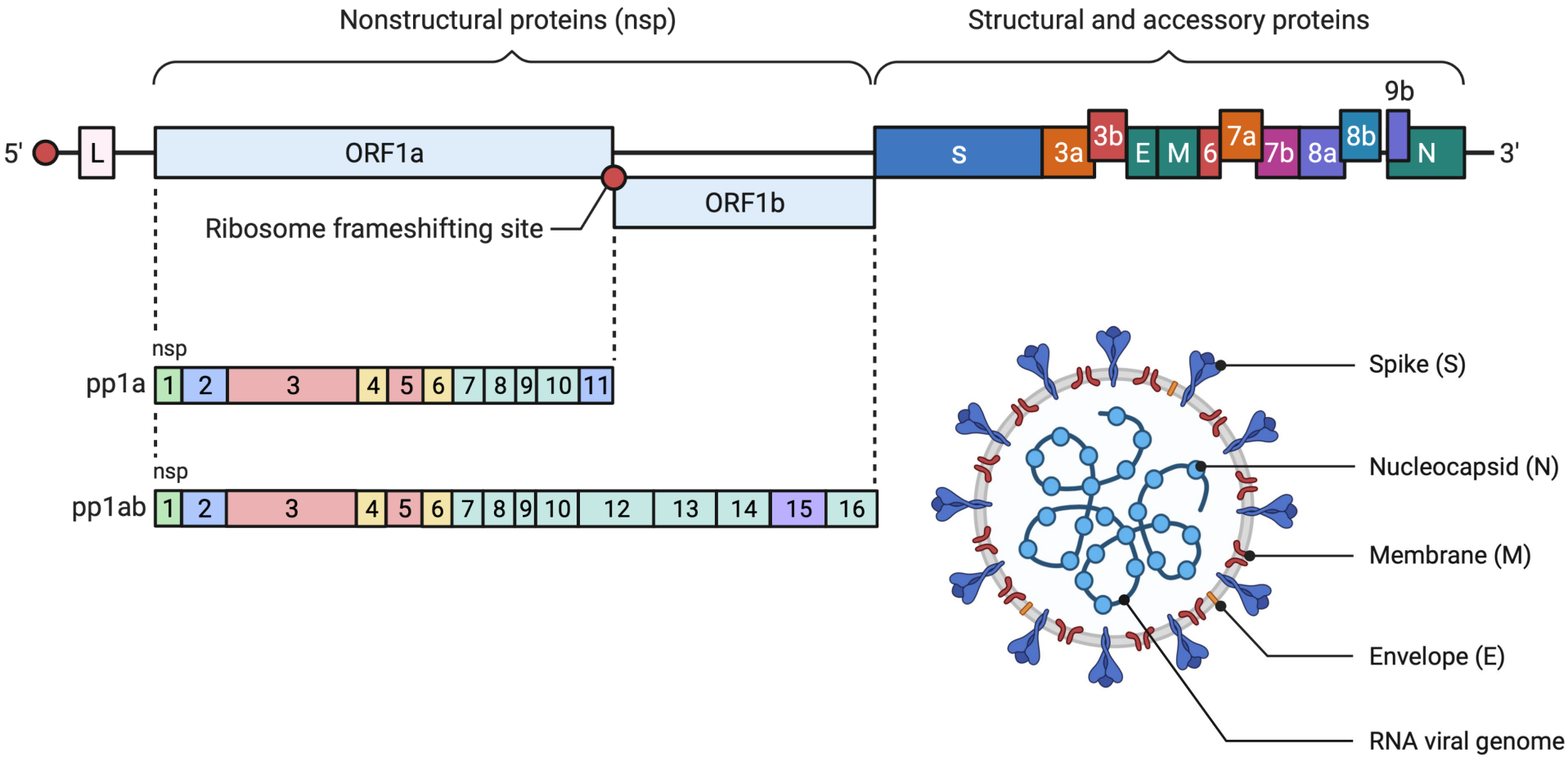
PLoS Pathog 16(8): e1008762.

Past – Present – Future?



Genomic Organization and Replication Cycle

Coronaviruses –Genomic organisation



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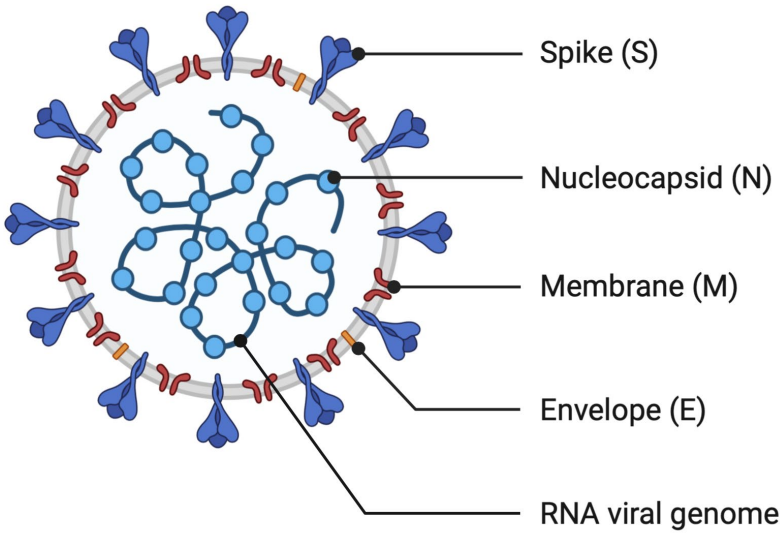
Coronaviruses – Structural proteins



- 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

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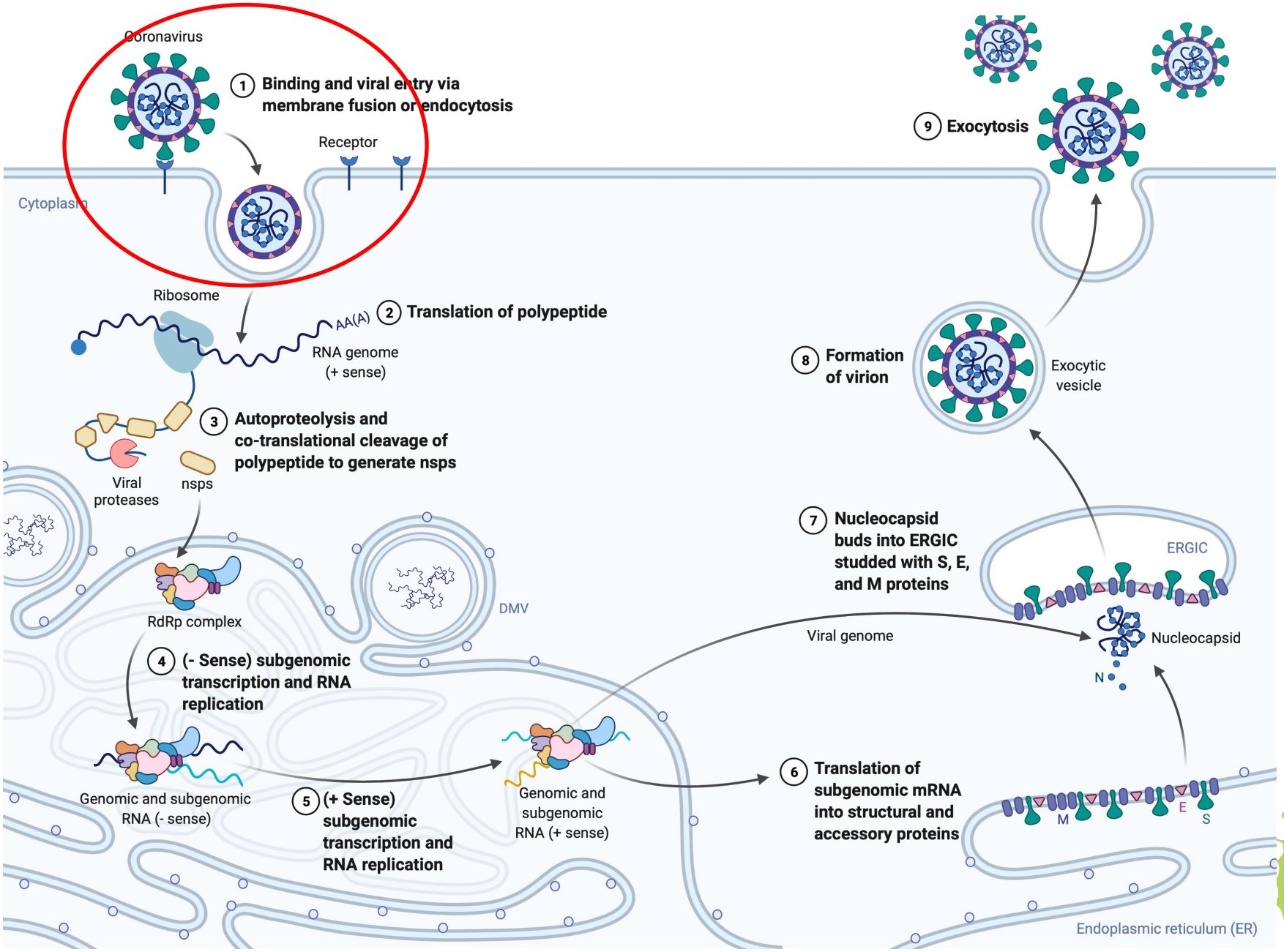
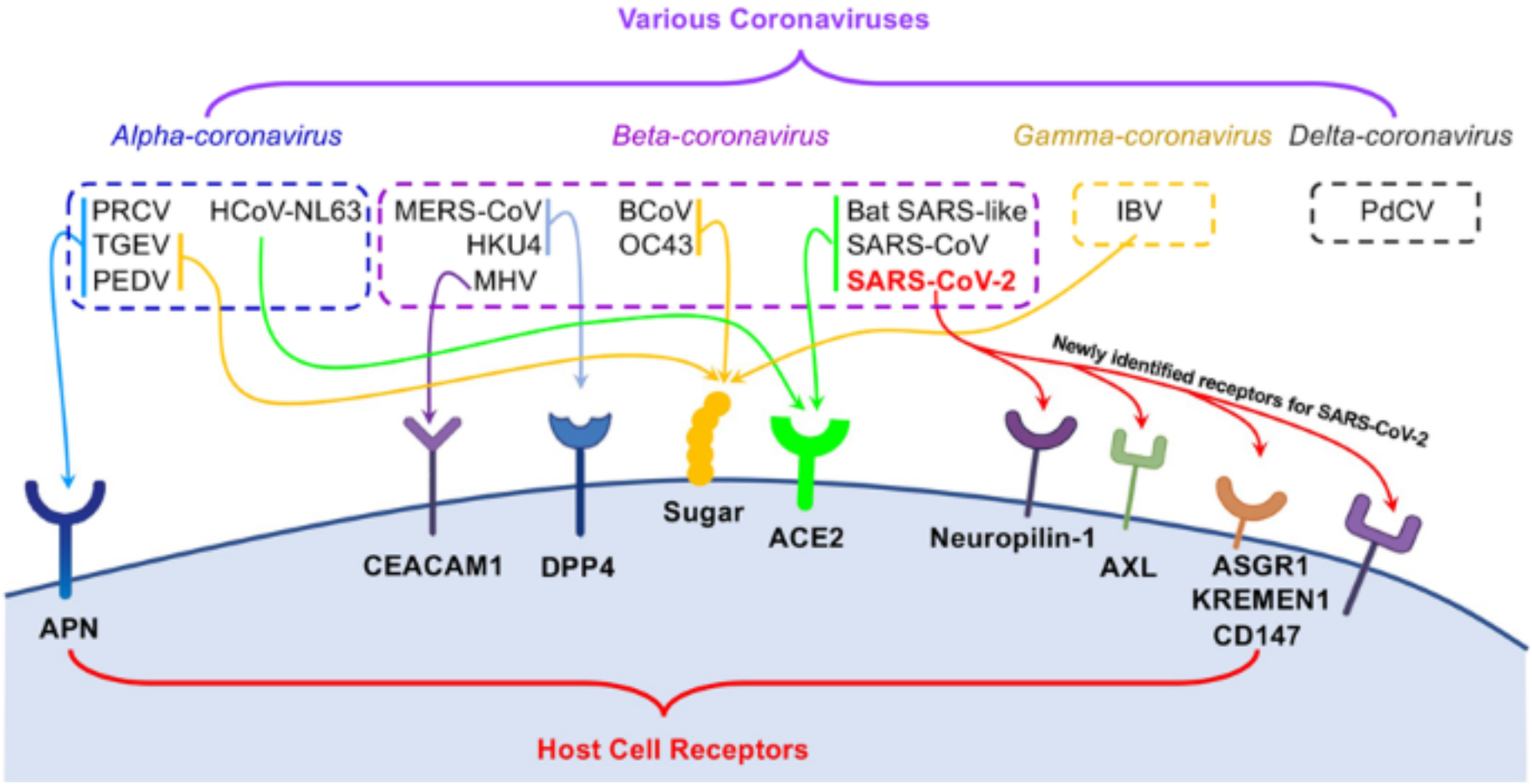
Coronaviruses – Replication cycle

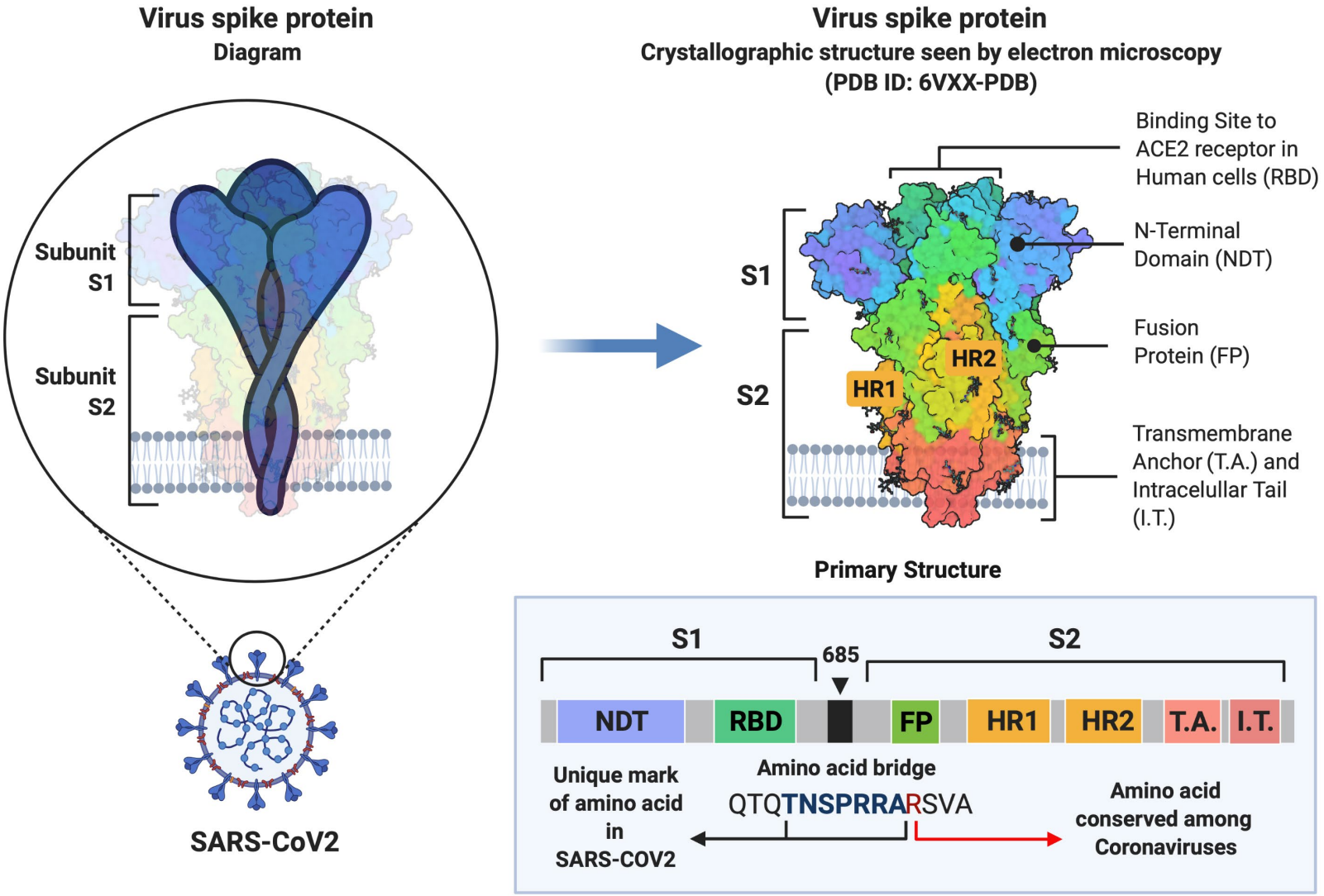


Coronaviruses - Receptor



Sig Transduct Target Ther 6, 233 (2021).

Coronavirus - entry



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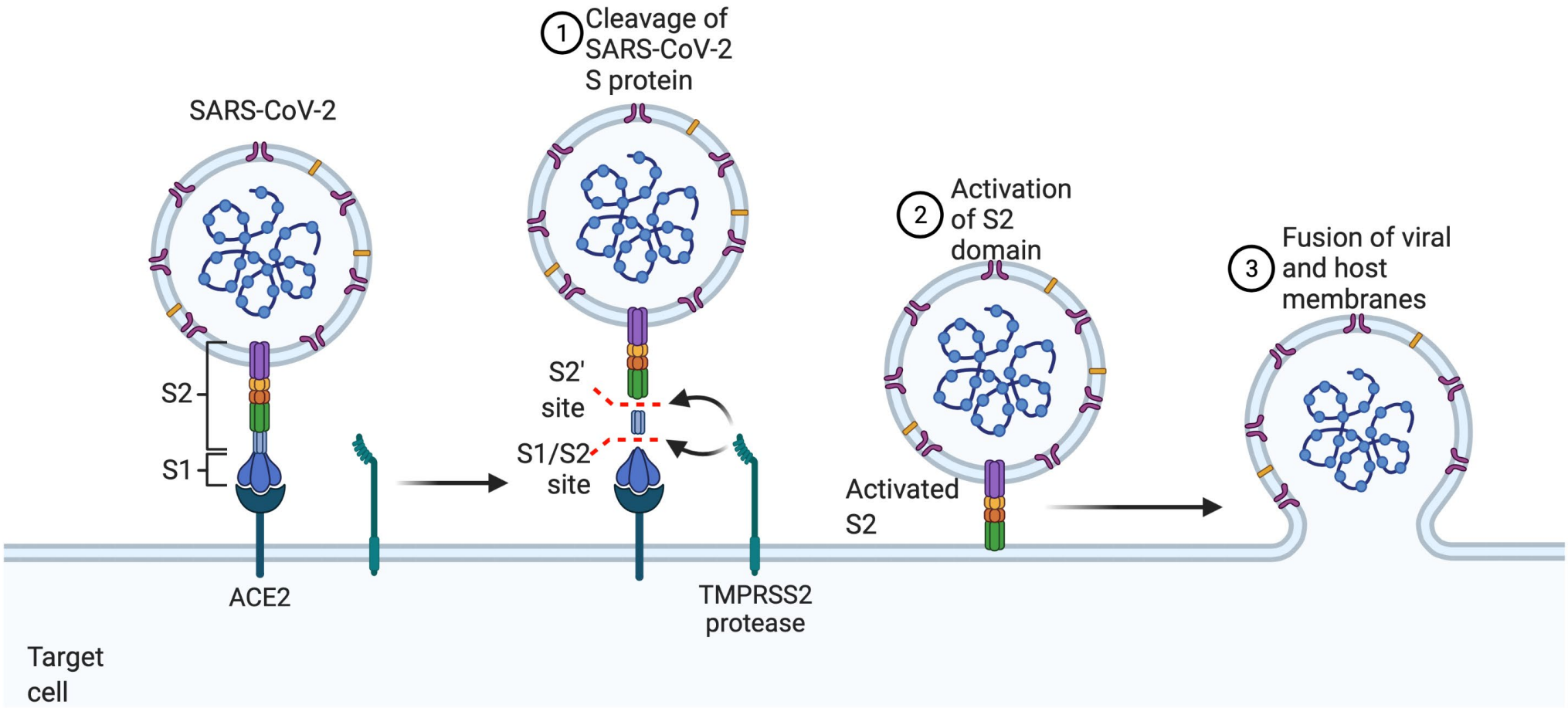
Coronavirus - entry



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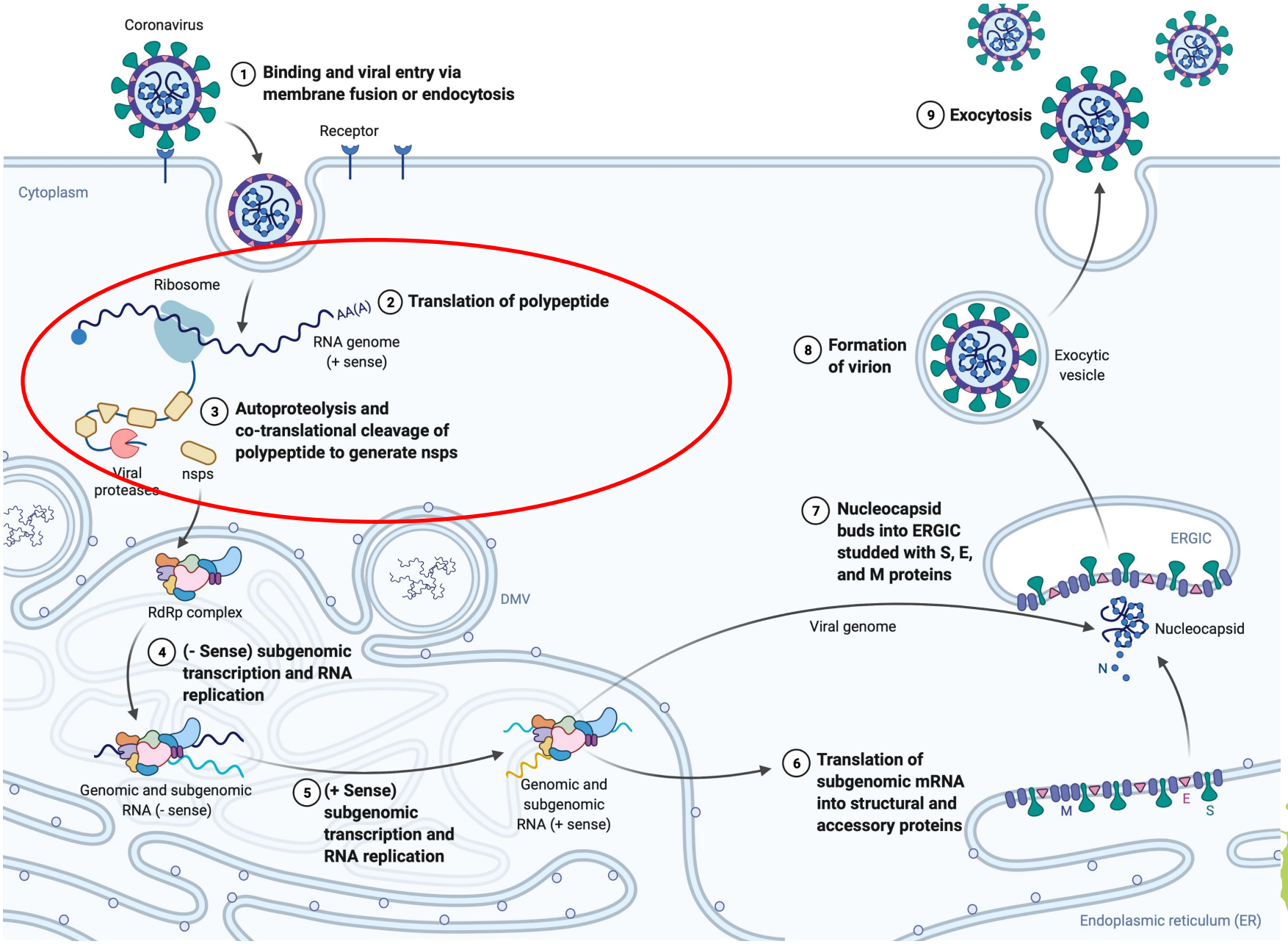
Coronaviruses – Replication cycle



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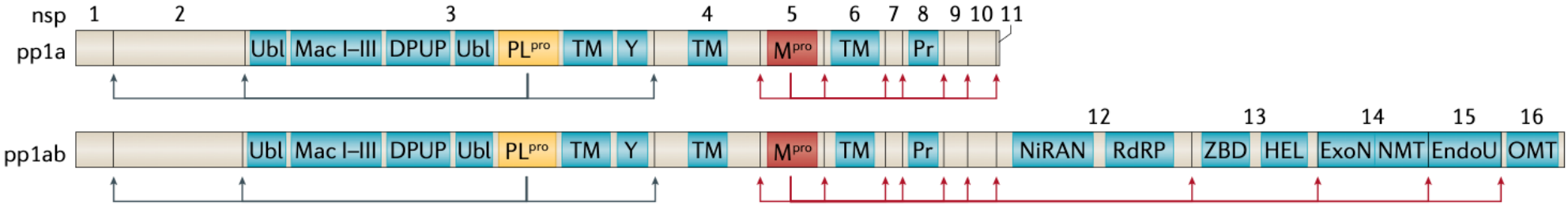
Coronaviruses - Polyprotein



nsp1 Host mRNA degradation, translation inhibition

nsp2 Unknown

nsp3 Ubl Mac I–III DPUP Ubl PLpro TM Y — Polyprotein processing, de-ADP-ribosylation, deubiquitination, interferon antagonist, DMV formation

nsp4 TM — DMV formation

nsp5 Mpro — 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

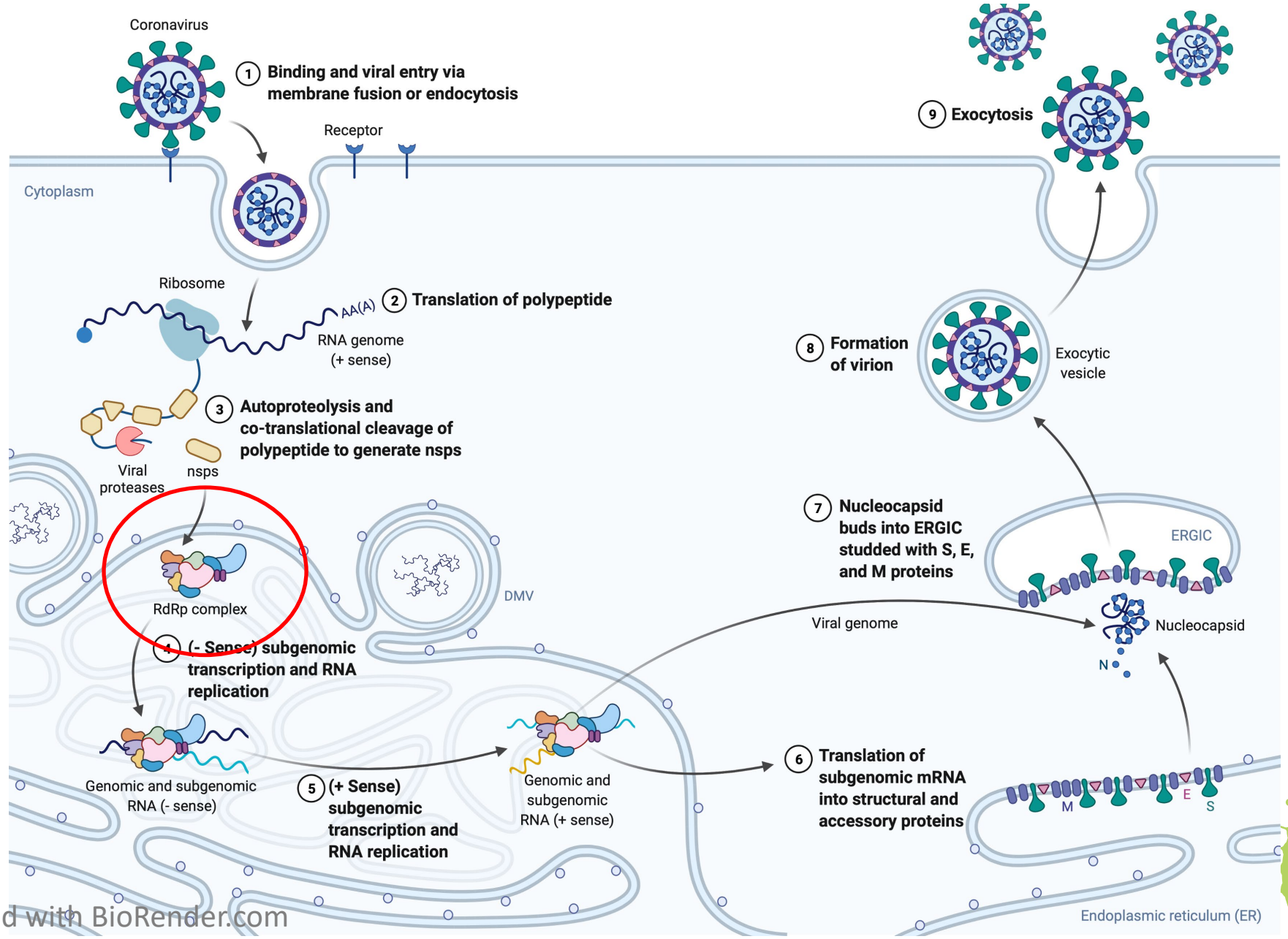
nsp14 ExoN NMT — 3′ to 5′ exoribonuclease, proofreading, RNA cap formation, guanosine *N*7-methyltransferase

nsp15 EndoU — Endoribonuclease, evasion of immune response

nsp16 OMT — RNA cap formation, ribose 2′-*O*-methyltransferase

V Kovski Nat Rev Microbiology 2020 https://doi.org/10.1038/ s41579-020-00468-6

Coronaviruses – Replication cycle



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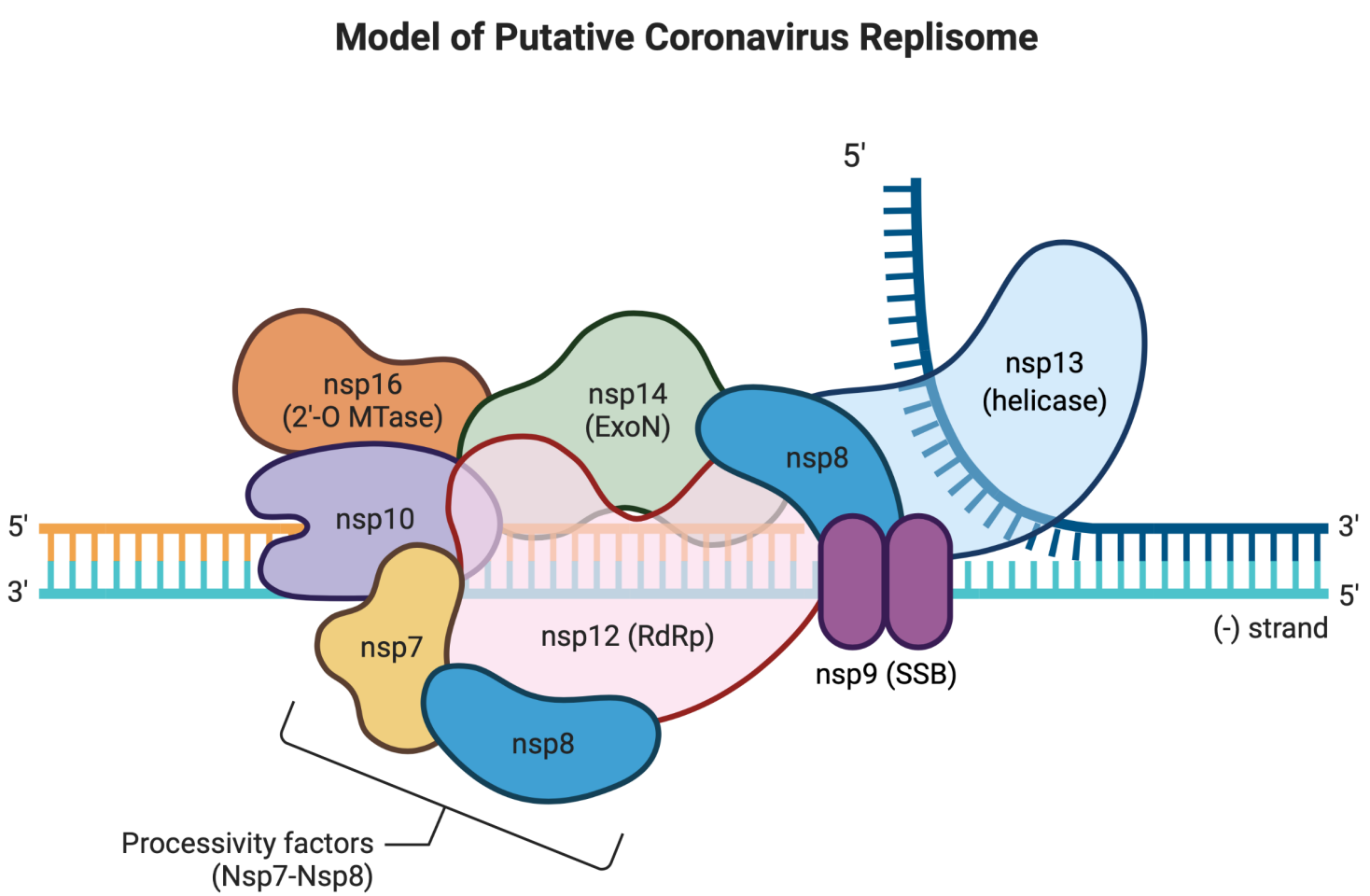
Coronaviruses – Replication complex



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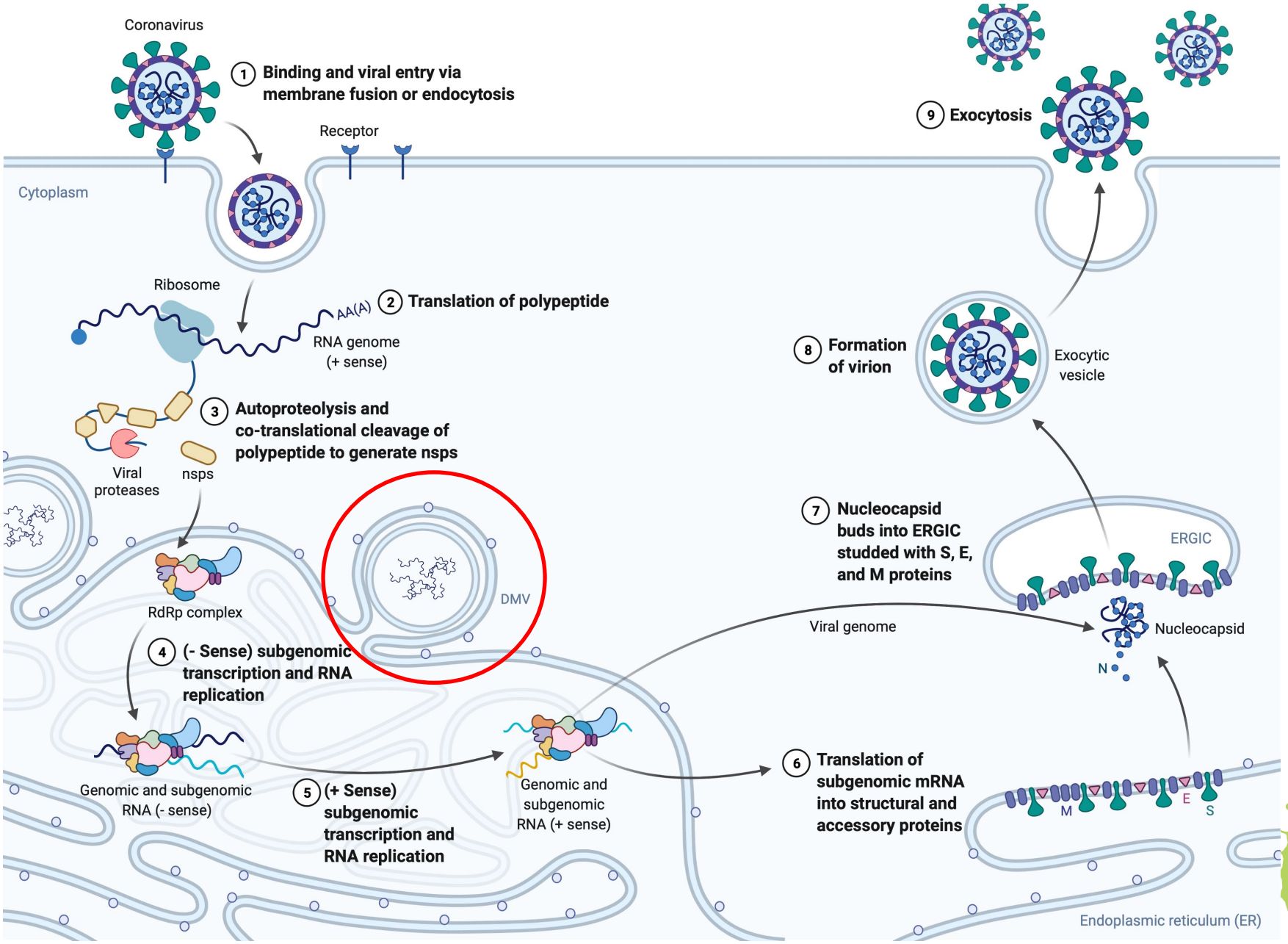
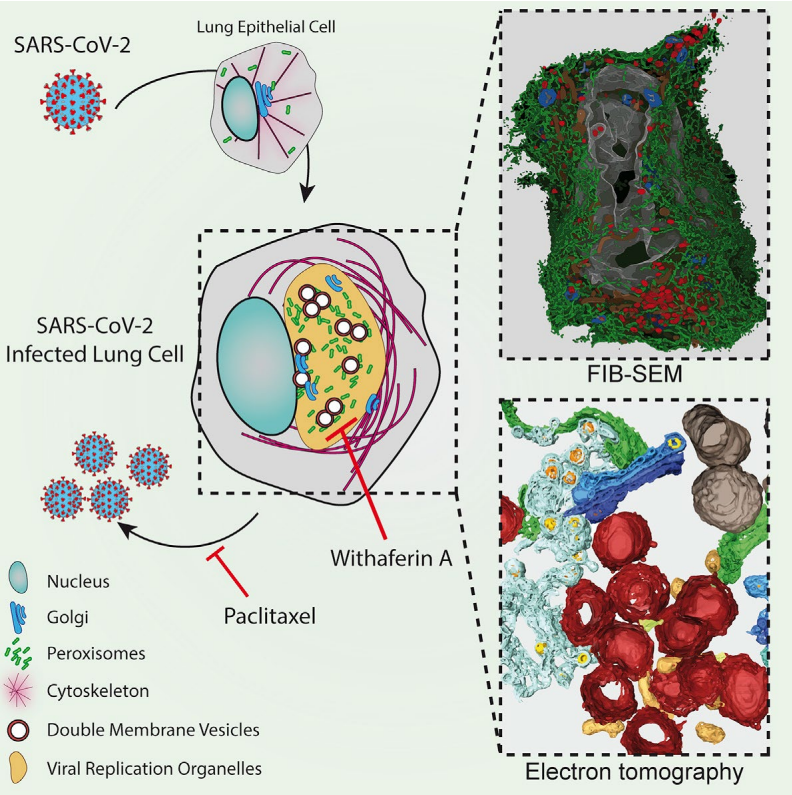
Coronaviruses – Replication cycle



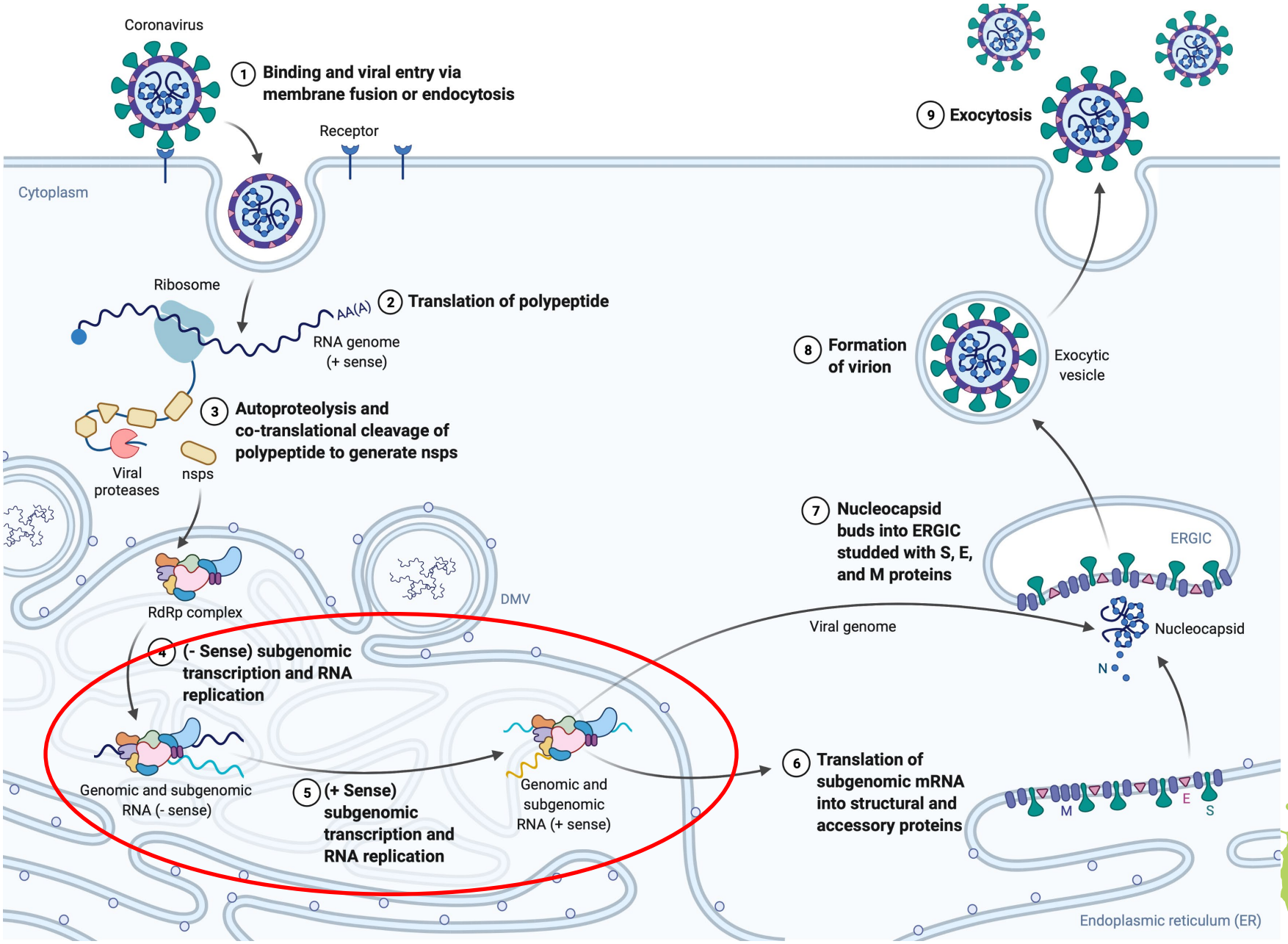
Coronaviruses – Double Membrane Vesicle



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

Cortese et al., 2020. Cell Host & Microbe 28, 853-866

Coronaviruses – Replication cycle



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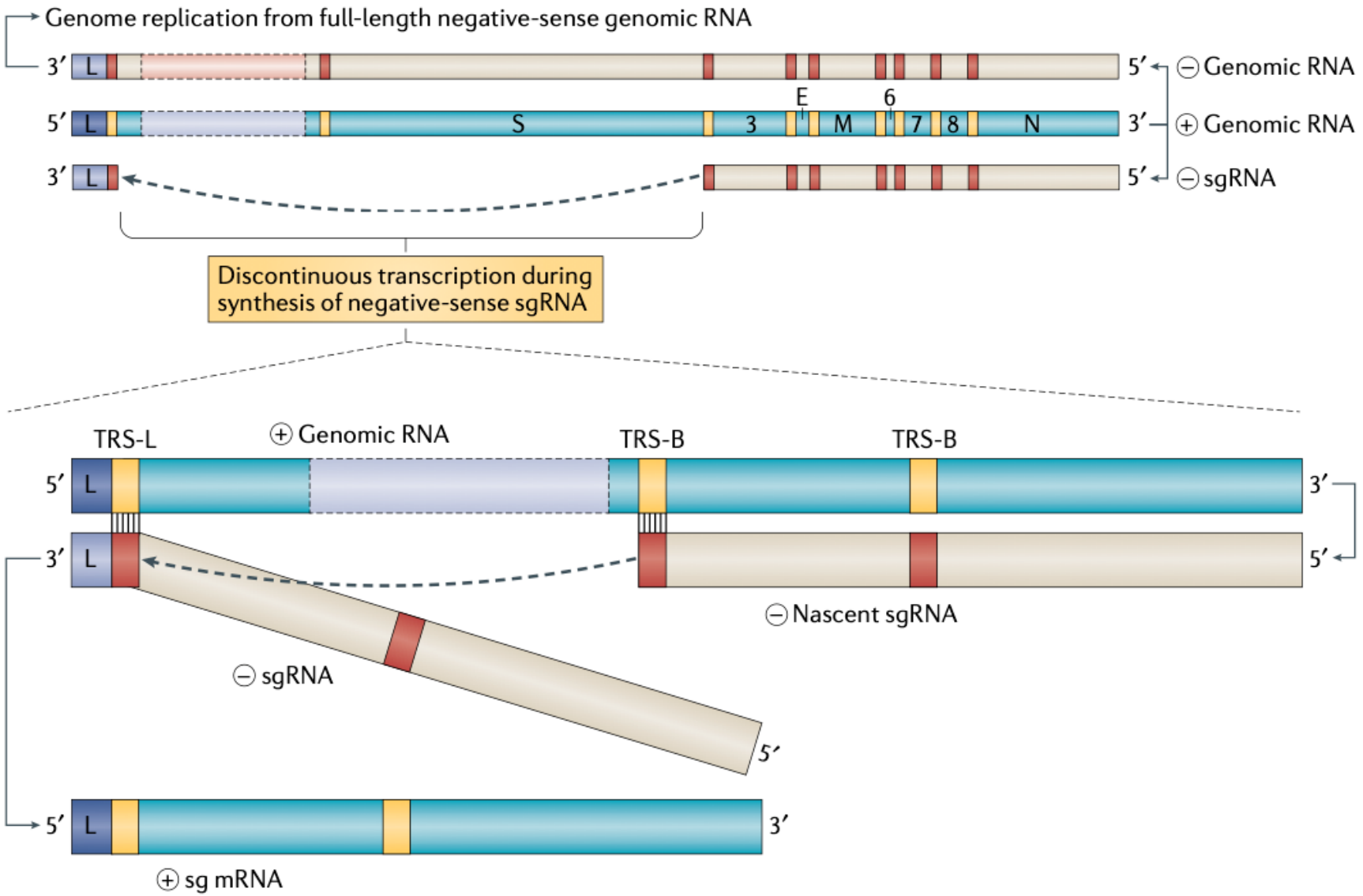
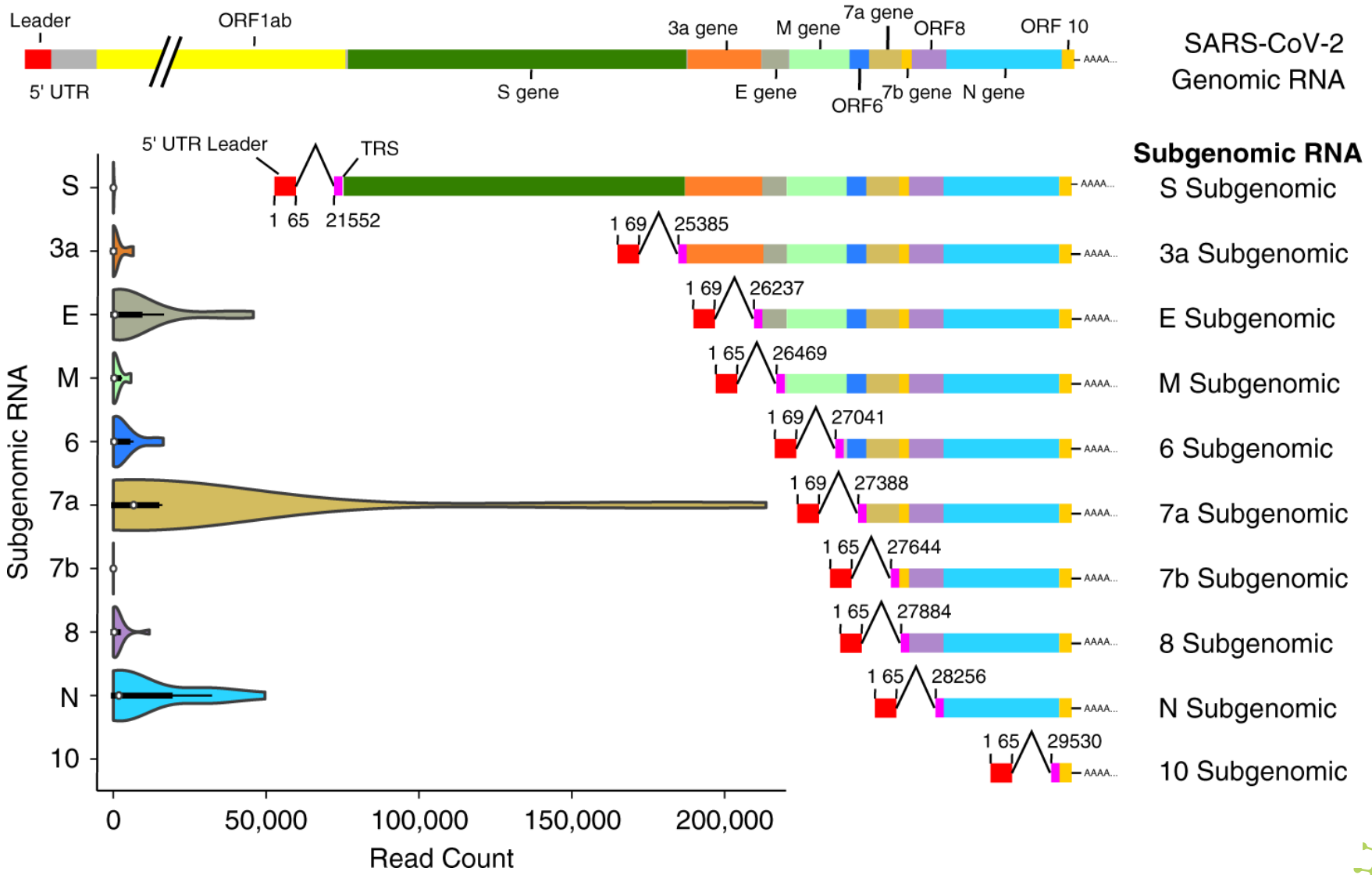
Coronaviruses - Replication



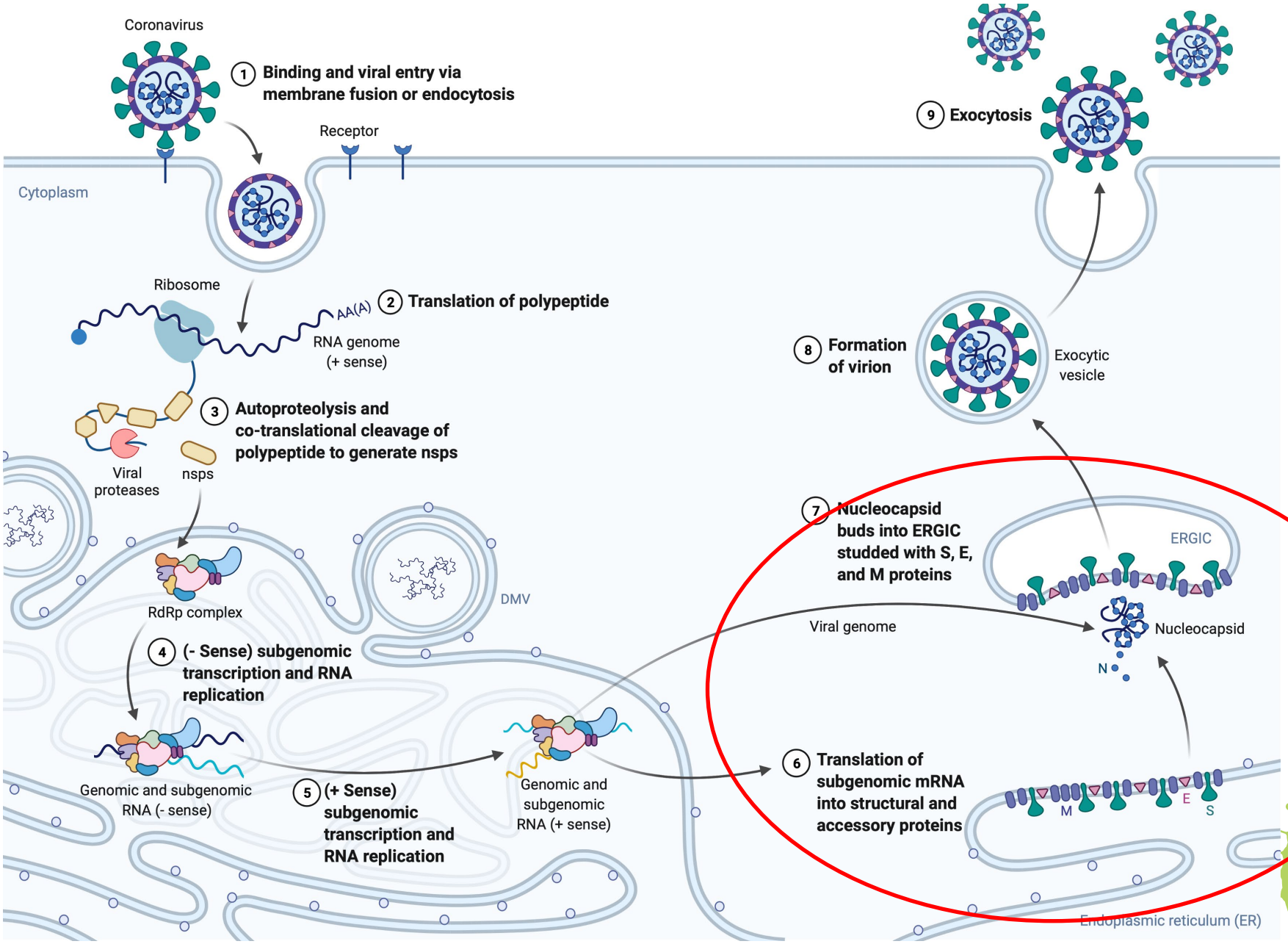
V Kovski Nat Rev Microbiology 2020 https://doi.org/10.1038/ s41579-020-00468-6

Coronaviruses - Replication



Nat Commun 11, 6059 (2020).

Coronaviruses – Translation/Assembly



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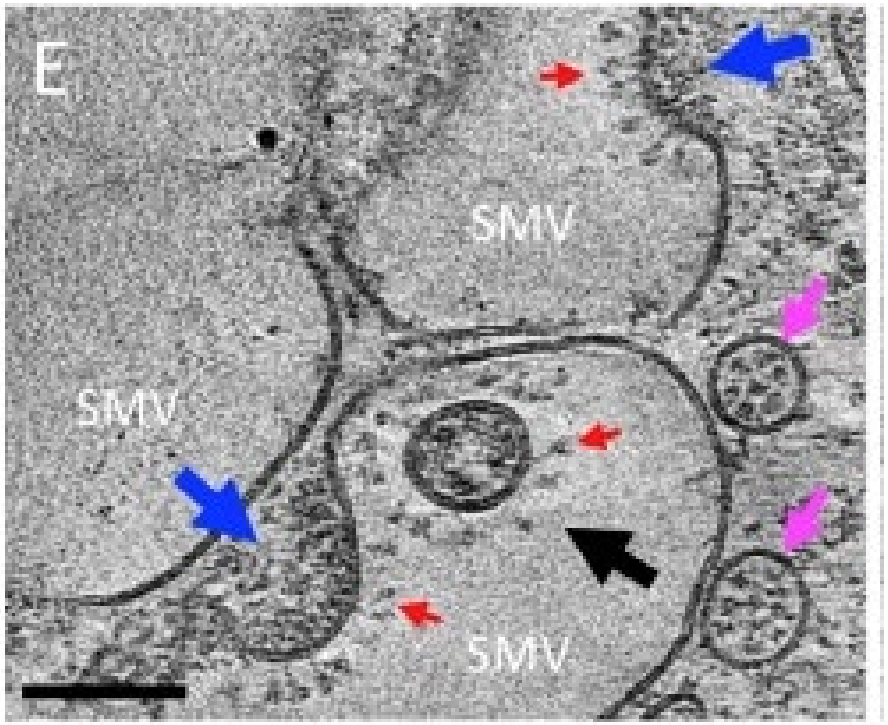
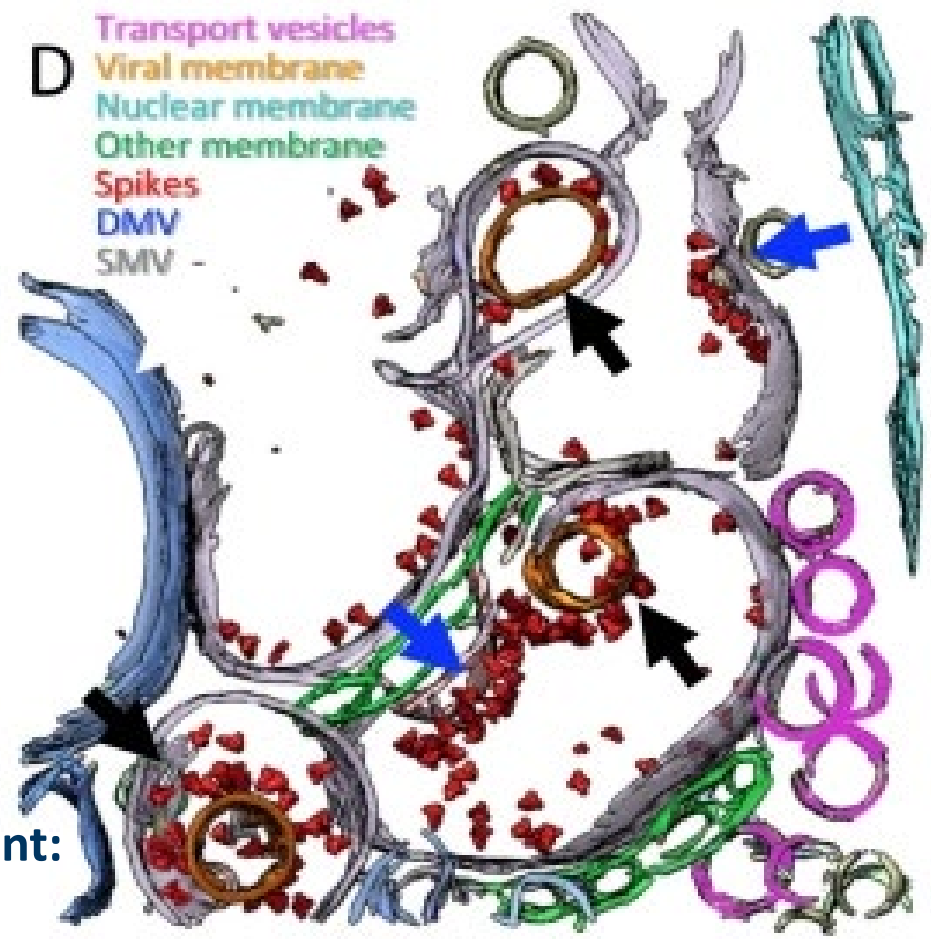
Coronaviruses – Translation/Assembly





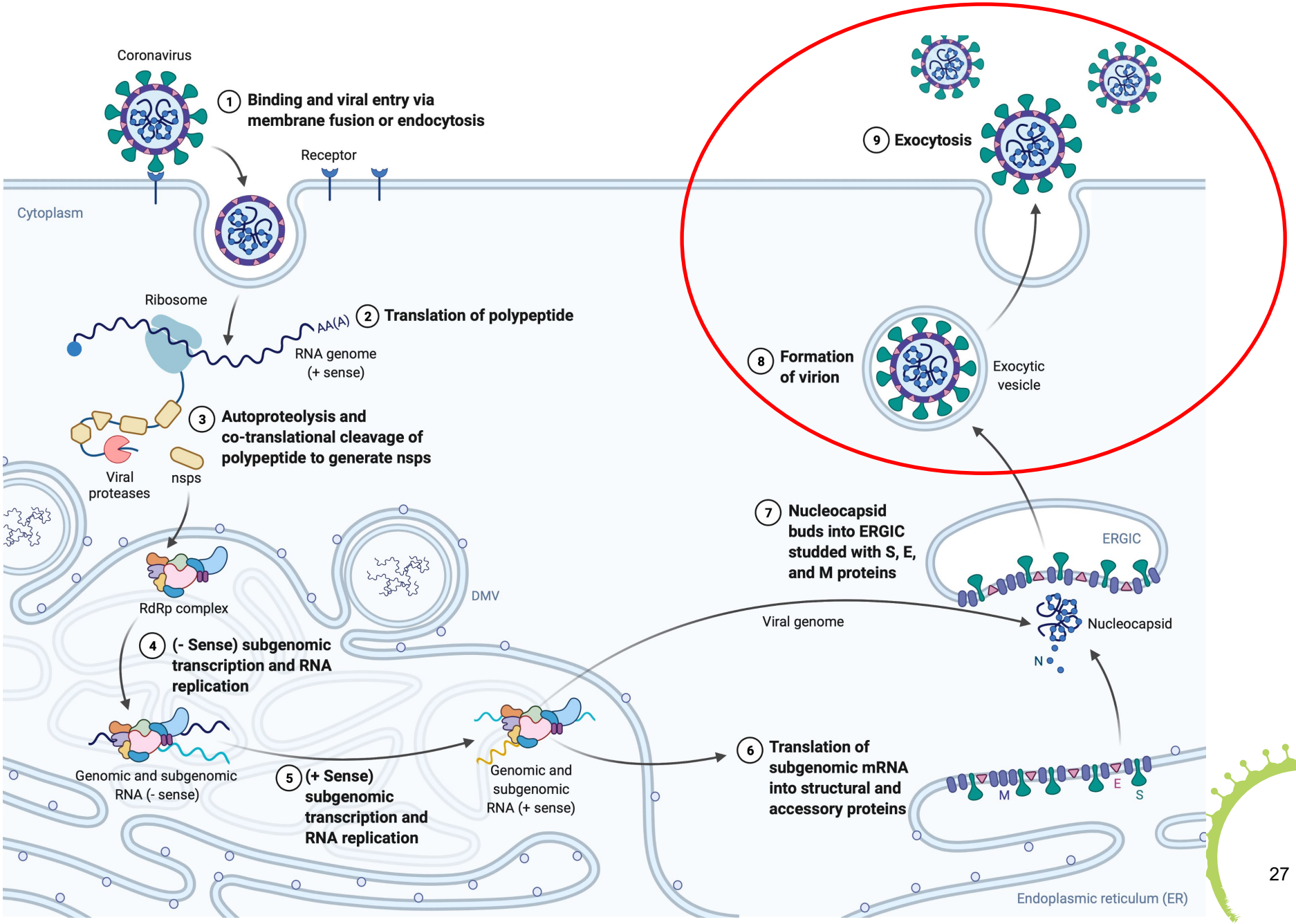
ER and ER-GOLGI Intermediate compartment: (ERGIC) Assembly and budding site

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*

https://www.nature.com/articles/s41467-021-24887-y
Created with BioRender.com

Coronaviruses – Egress



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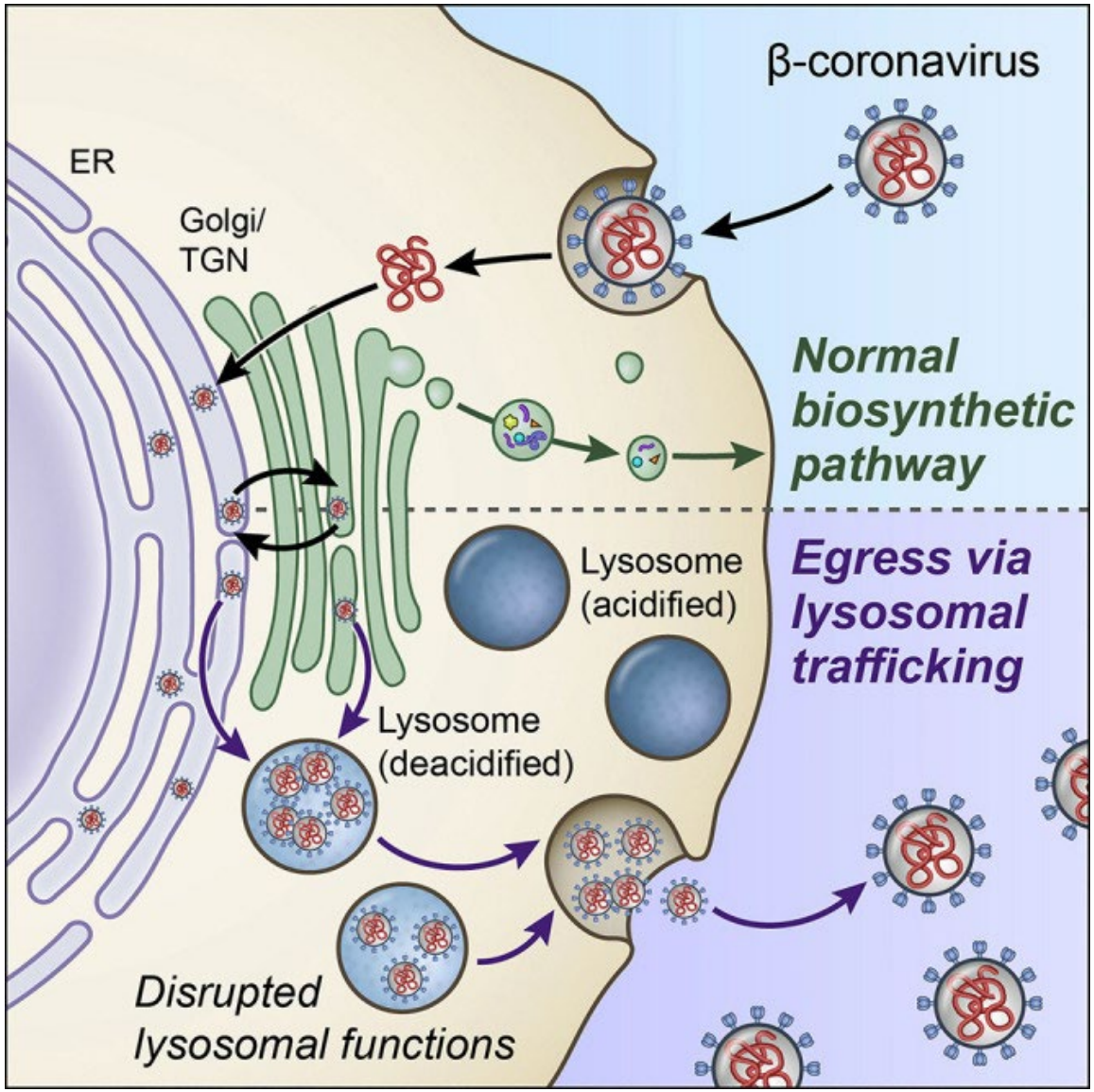
Coronaviruses – Egress

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



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7590812/

Highly pathogenic coronaviruses

SARS-CoV

MERS-CoV

SARS-CoV-2

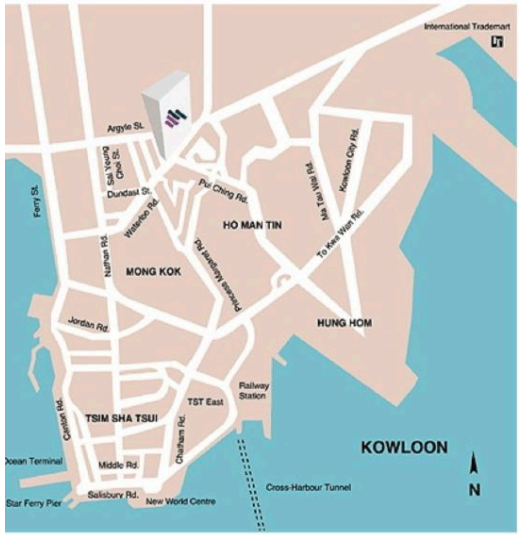
SARS-CoV

Severe acute respiratory Coronavirus

SARS-CoV - Transmission

Friday,
Feb 21 2003

Metropole Hotel
Professor Liu
checks into the
9th floor



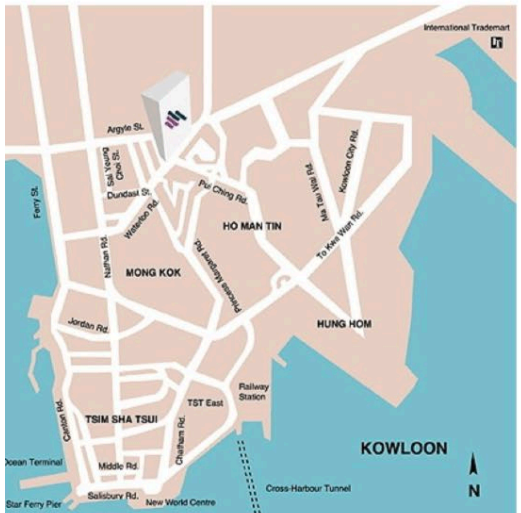
- Prof. Liu enters the hotel
- In the elevator he meets
  - Businessmen from the US
  - Lady from Toronto
- In the hallway:
  - Stewardesses from Singapur
- A couple of days later….

…. he dies!

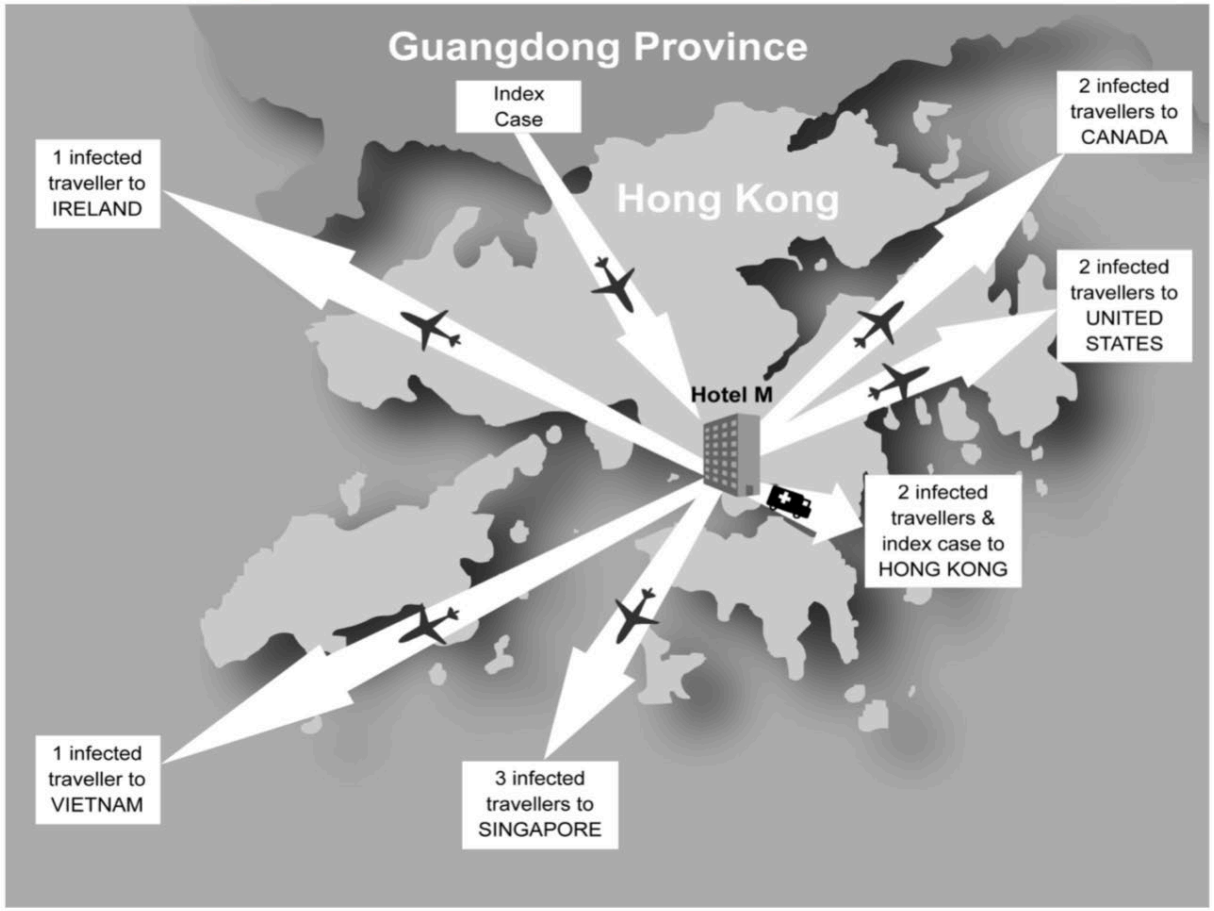
SARS-CoV - Transmission

Friday,
Feb 21 2003

Metropole Hotel
Professor Liu
checks into the
9th floor



Next days ...



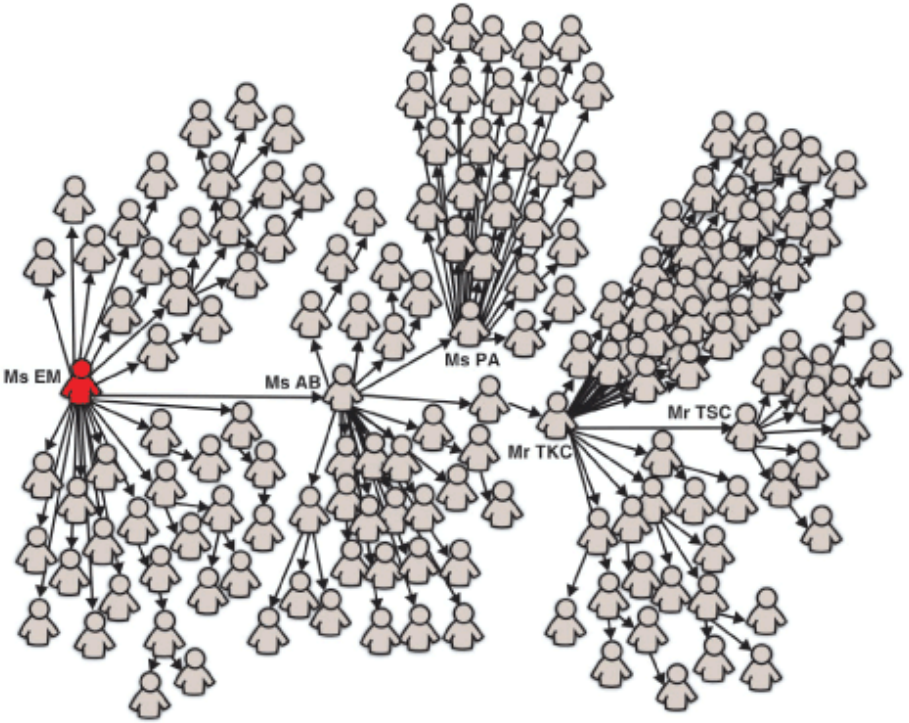
Finally ... 8‘098 infected, ... 774 (9.6%) died

60

SARS-CoV - Conclusion

2002/2003 SARS

- Severe atypical pneumonia in Guandong 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



Science 15 Mar 2013: Vol. 339, Issue 6125, pp. 1272-1273

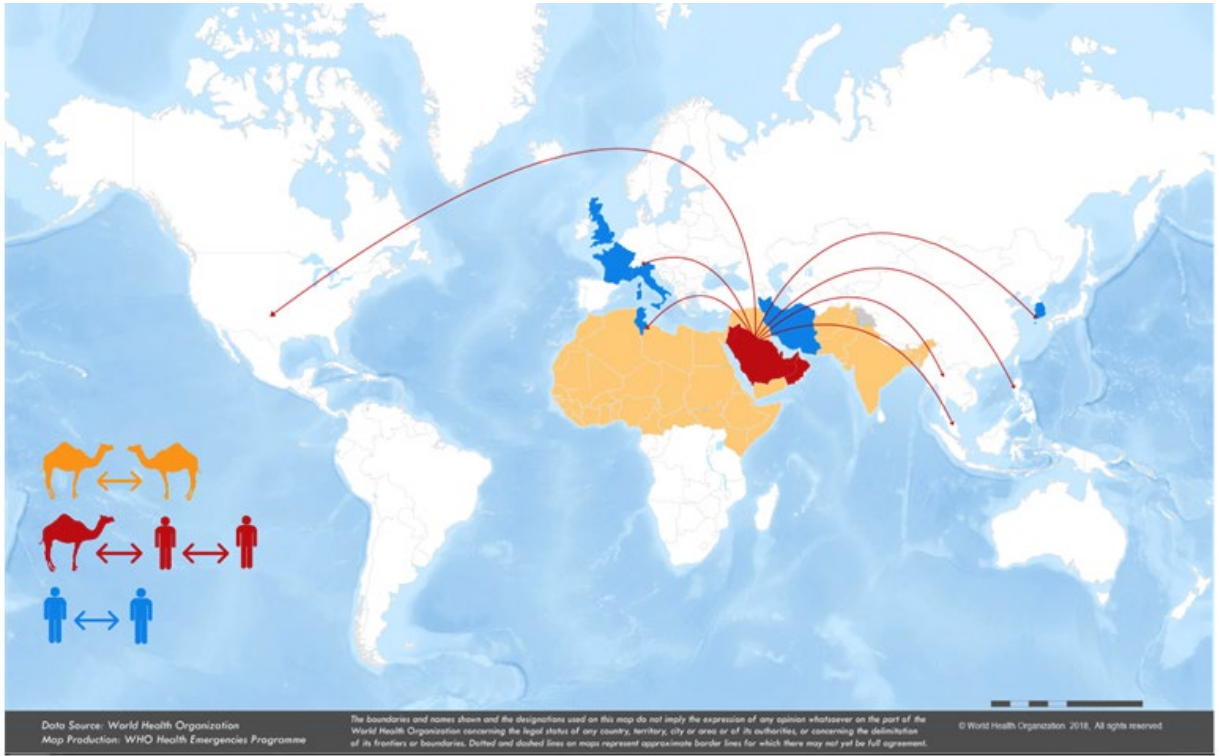
MERS-CoV

Middle East Respiratory Sydrome Coronavirus

MERS-CoV

2012 MERS

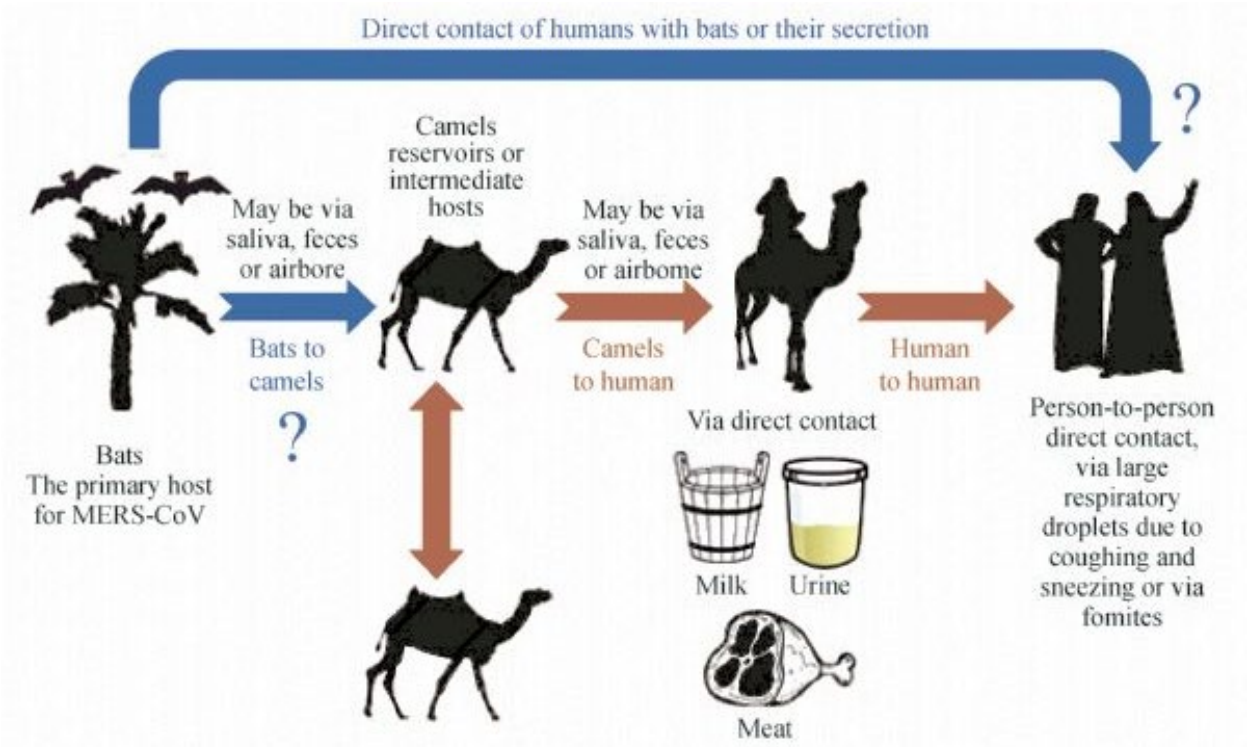
- Identified in Saudi Arabia
- So far 2.589 laboratory confirmed cases in 27 countries (940 deaths)
- Acute respiratory syndrome, Pneumonia
  - Ca. 34.3% CFR



MERS-CoV - Transmission

- Zoonotic transmisson
  - Close contact to infected animal
  - Camels are zoonotic reservoir

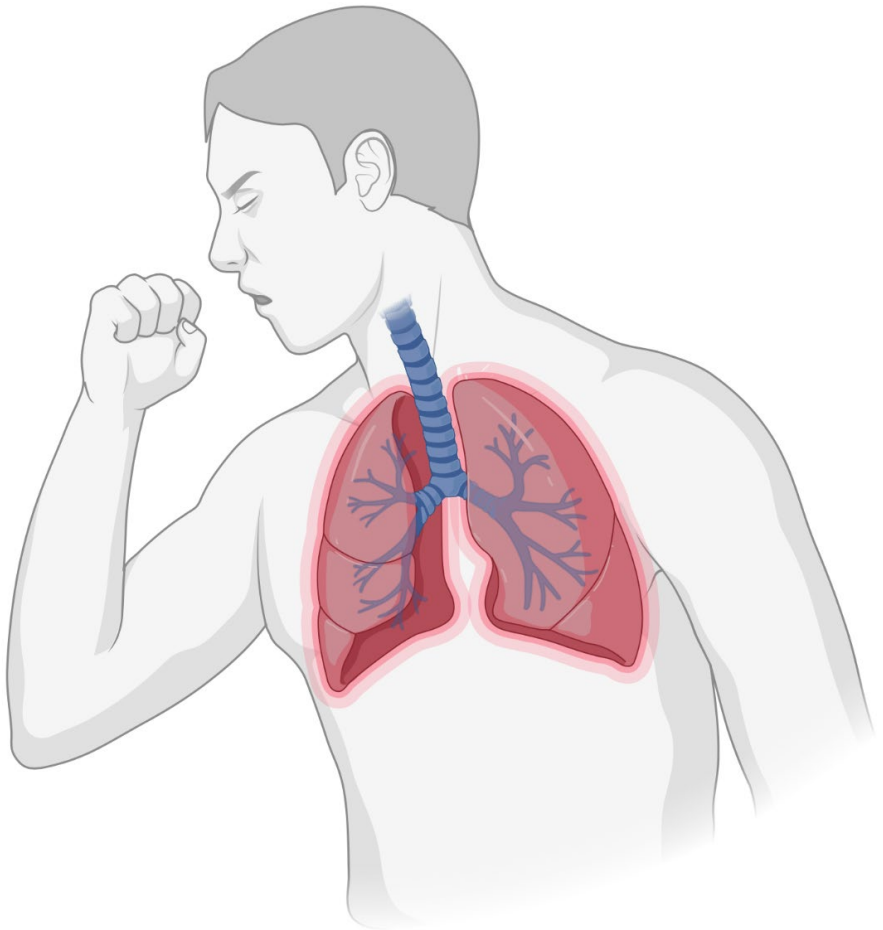
- Human-to-human transmission (not very efficient)
- Aerosol/Droplet



SARS-CoV-2

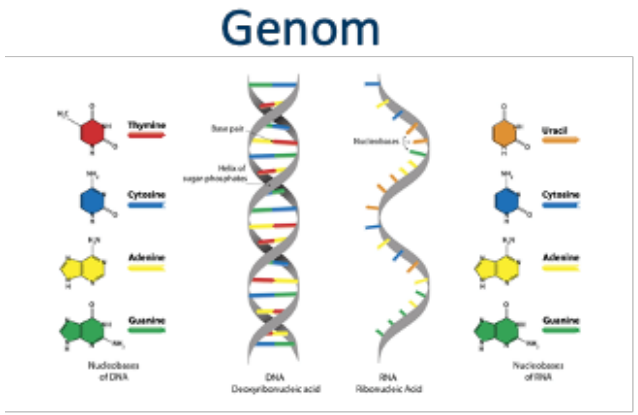
Severe Acute Respiratory Syndrome Coronavirus - 2

A novel Disease breaks out

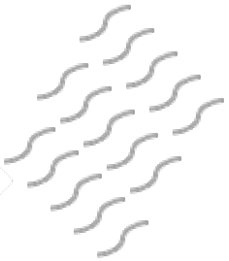


SARS-CoV-2 – Identify Pathogen

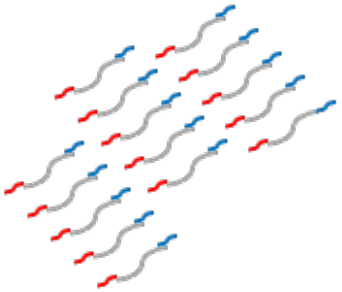
Next Generation Sequencing:



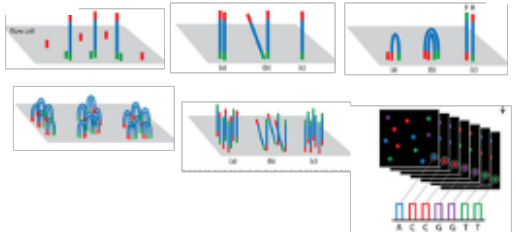
Fragmentation



Adapter Ligation



Cluster Amplification



Assembly

Annotation

Identification

SARS-CoV-2 – Identify Pathogen

The NEW ENGLAND JOURNAL of MEDICINE

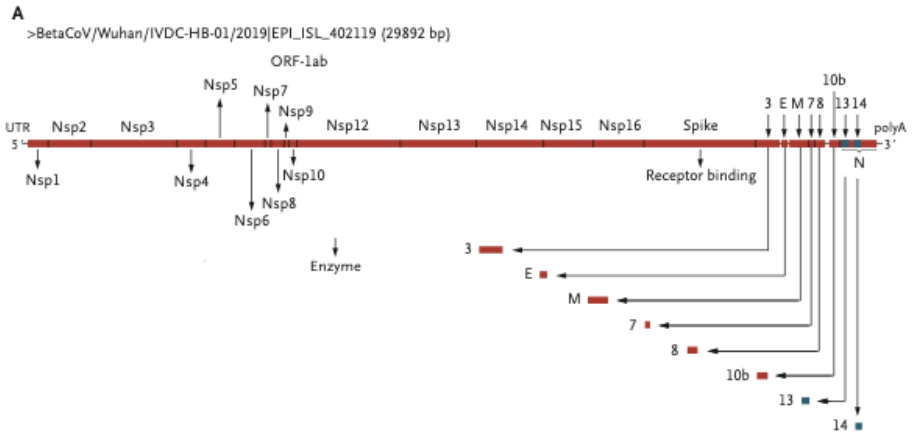
BRIEF REPORT

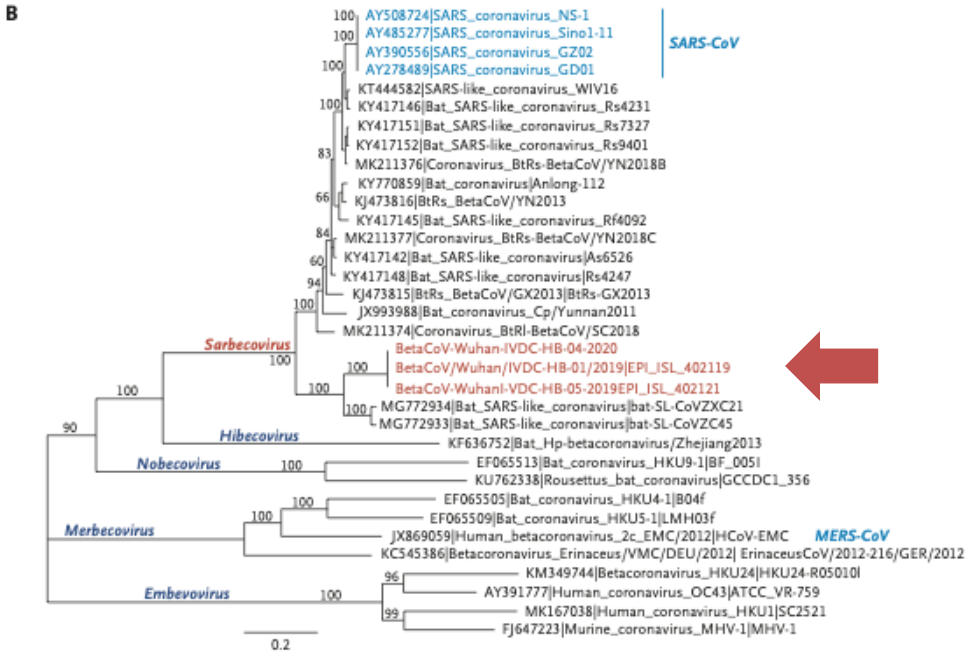
A Novel Coronavirus from Patients with Pneumonia in China, 2019

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

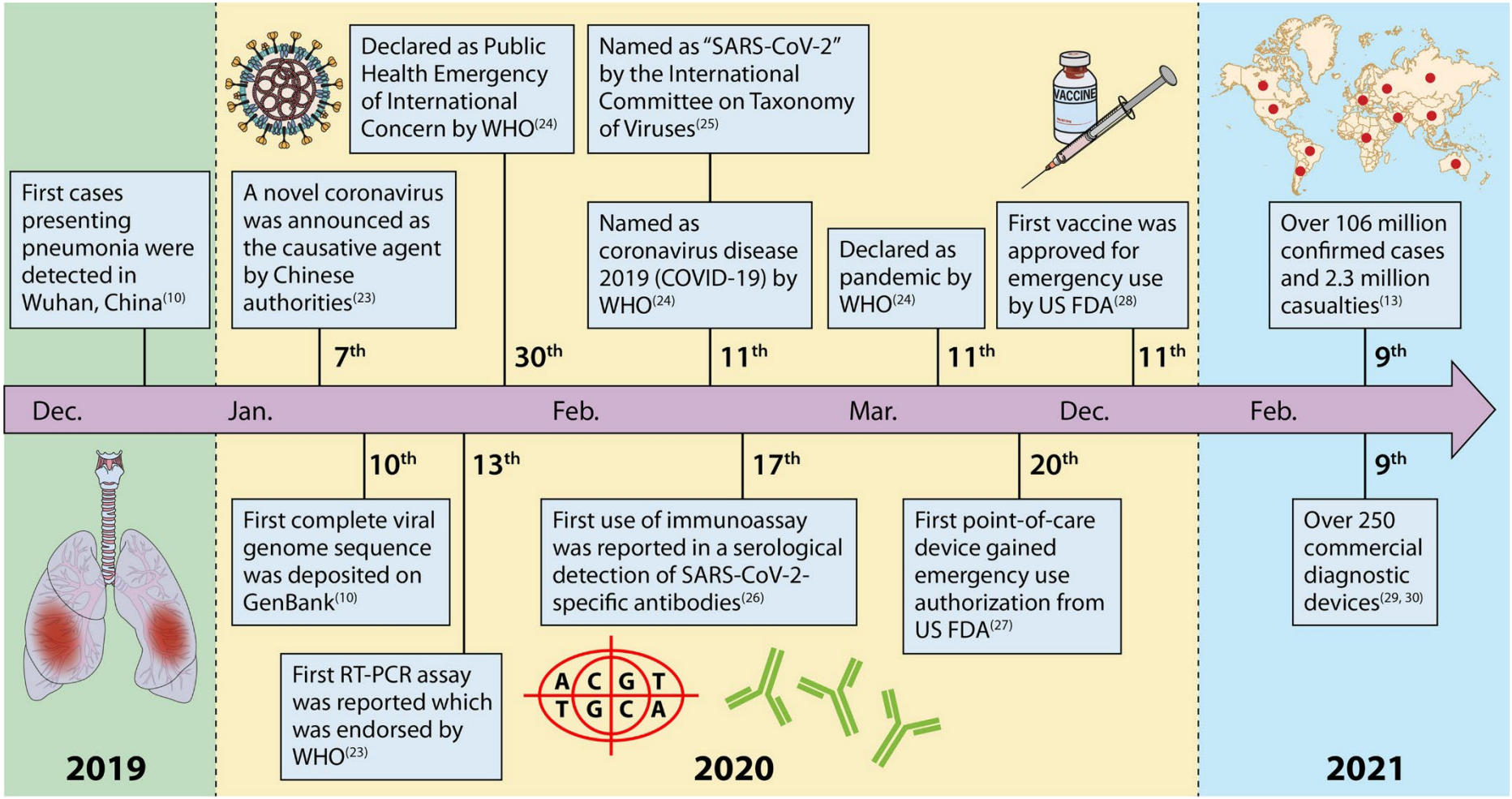
SUMMARY

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.)



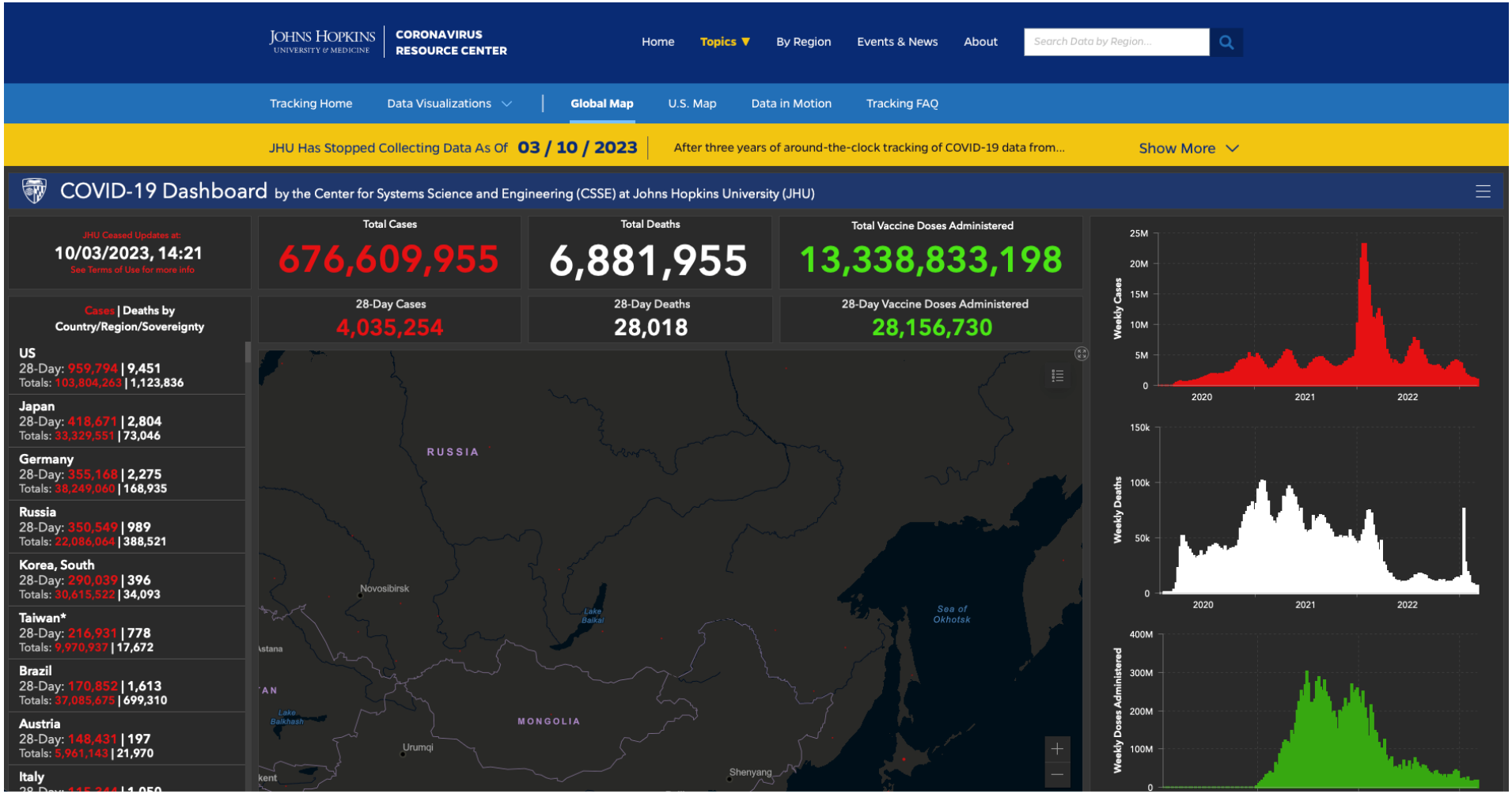


SARS-CoV-2 - Timeline



https://doi.org/10.1128/CMR.00228-20

SARS-CoV-2 - Pandemic

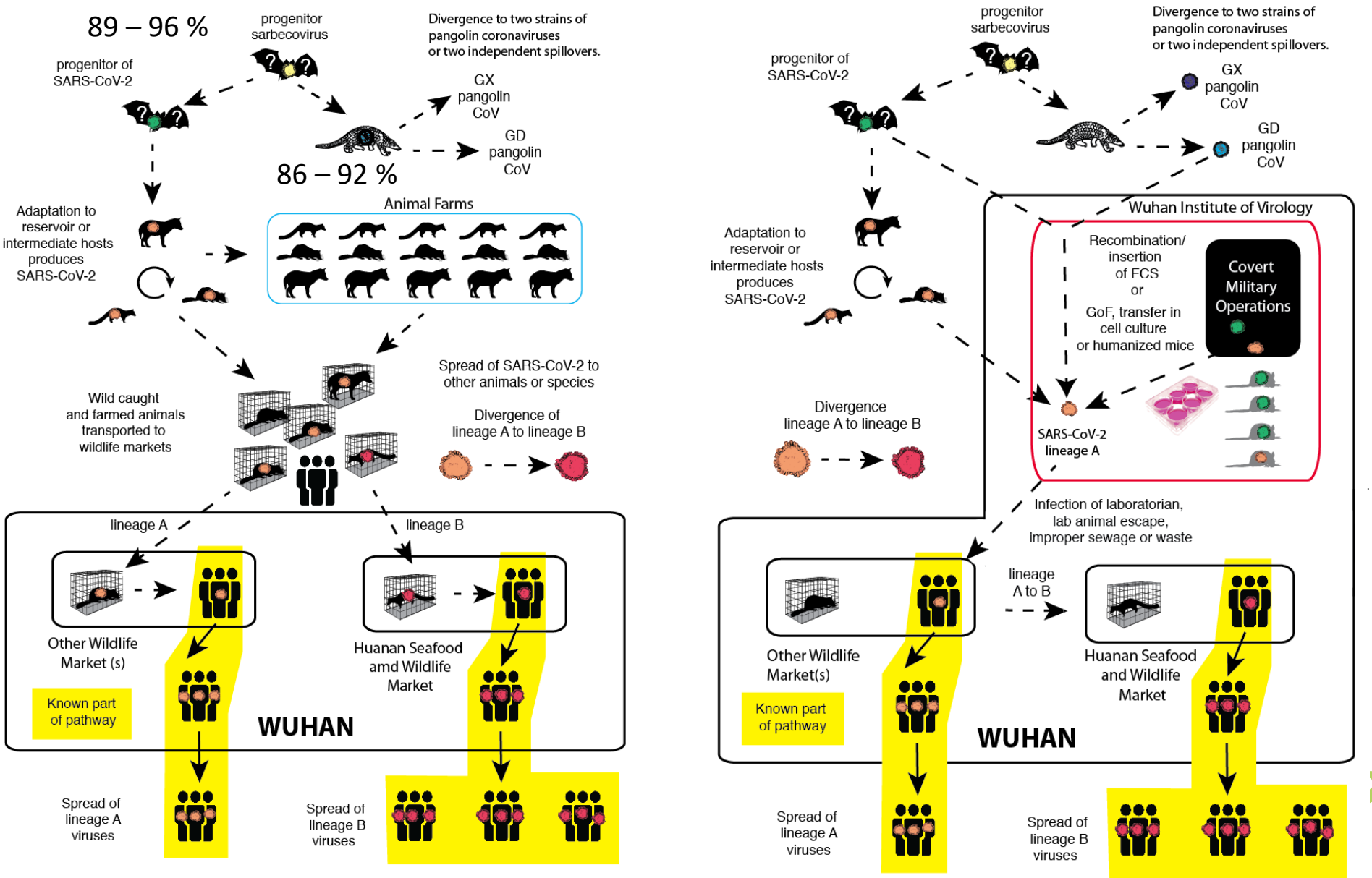


December 2019 (Wuhan)

Caused COVID-19 Pandemic

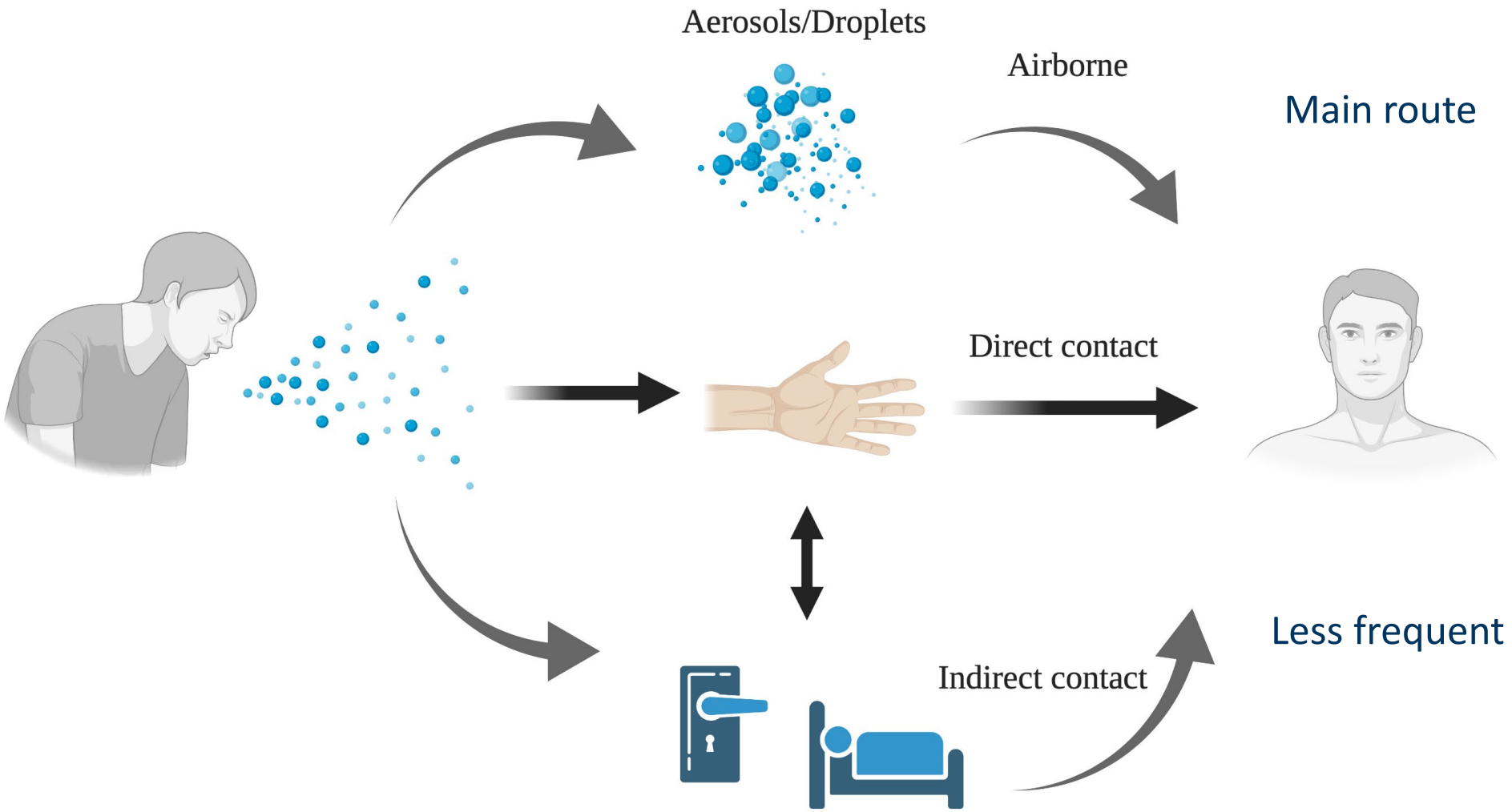
Johns Hopkins University (10/03/2023)

SARS-CoV-2 – Origin



https://virological.org/t/early-appearance-of-two-distinct-genomic-lineages-of-sars-cov-2-in-different-wuhan-wildlife-markets-suggests-sars-cov-2-has-a-natural-origin/691

SARS-CoV-2 - Transmission



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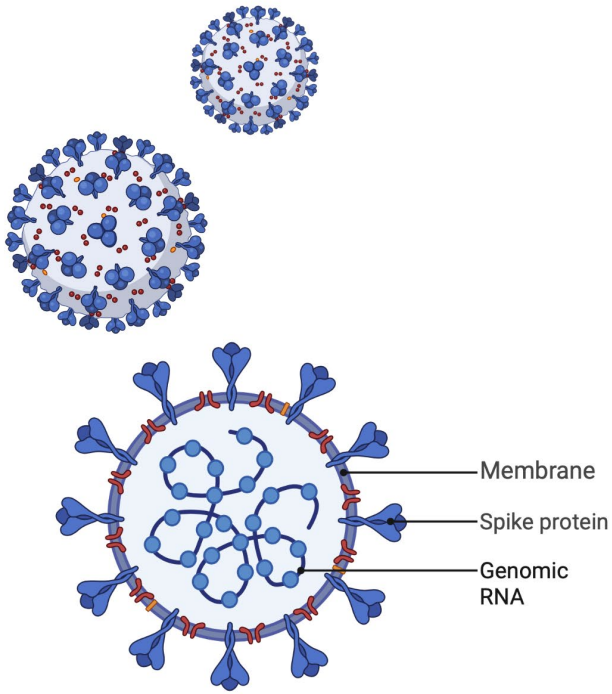
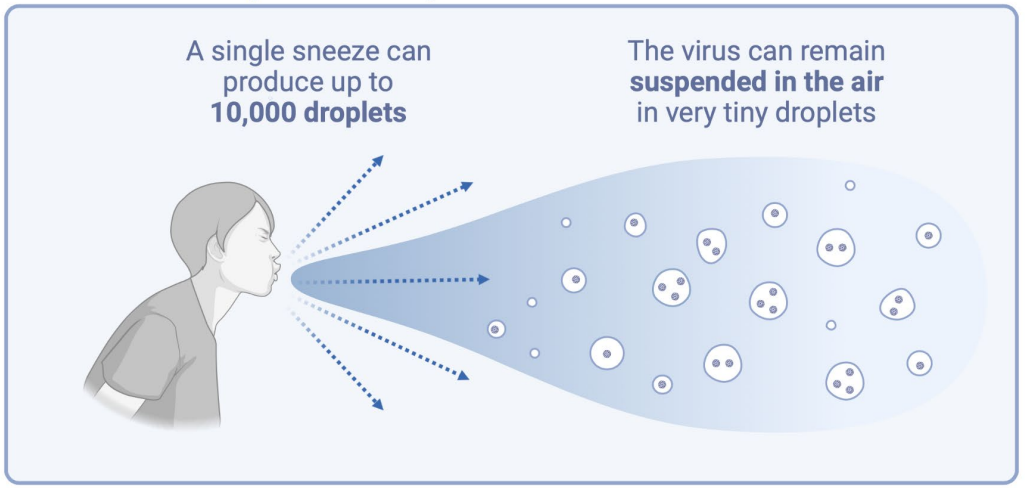
SARS-CoV-2 - Transmission



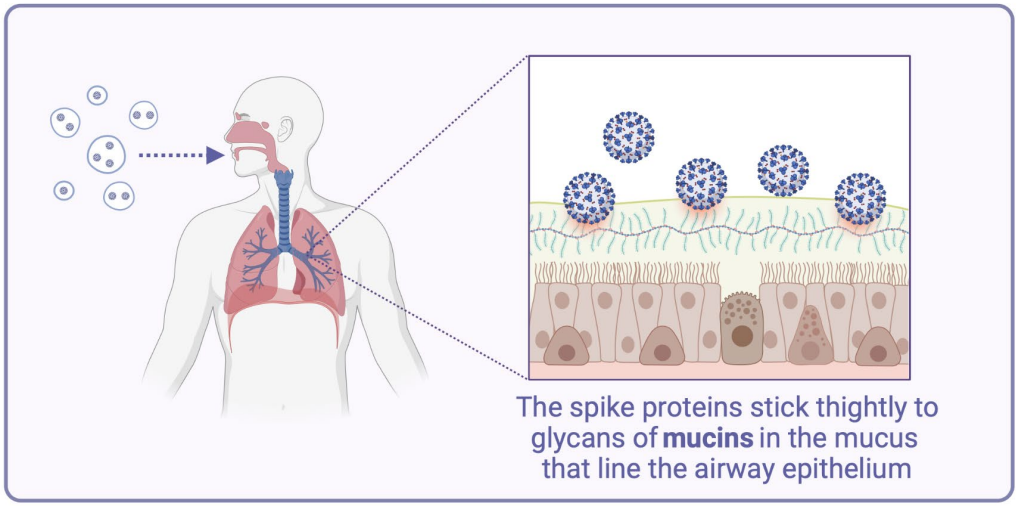
SARS-CoV-2

How is the virus spread?

The virus can spread easily



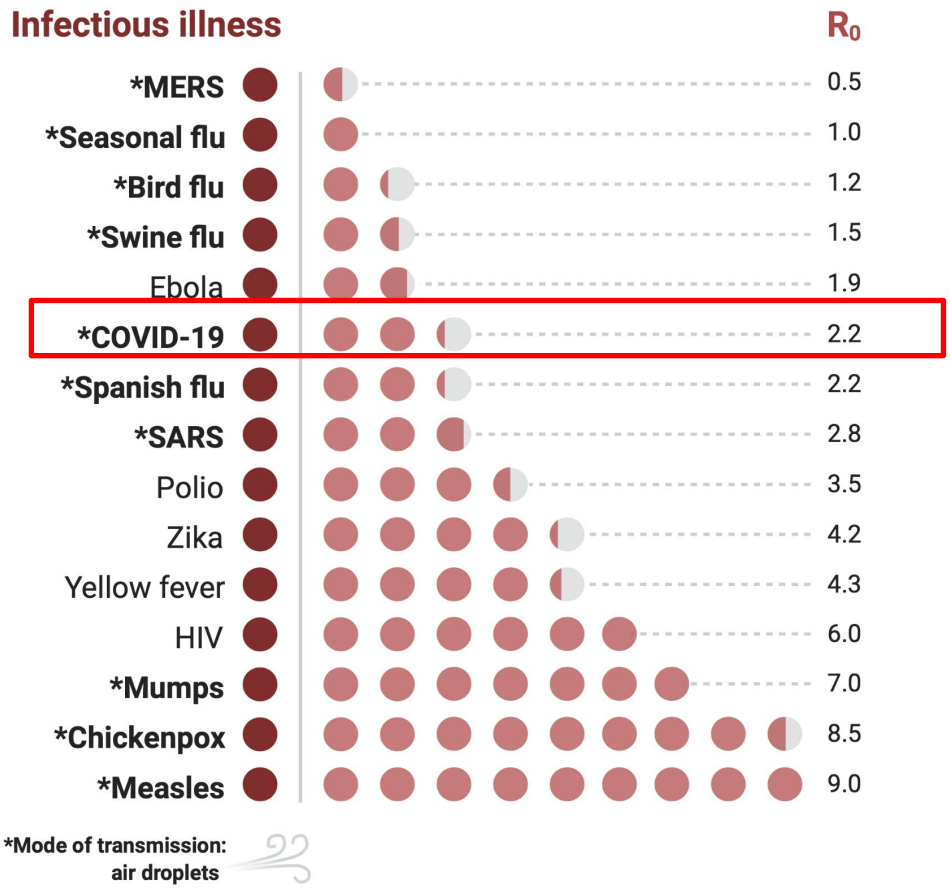
The virus remains in the airways

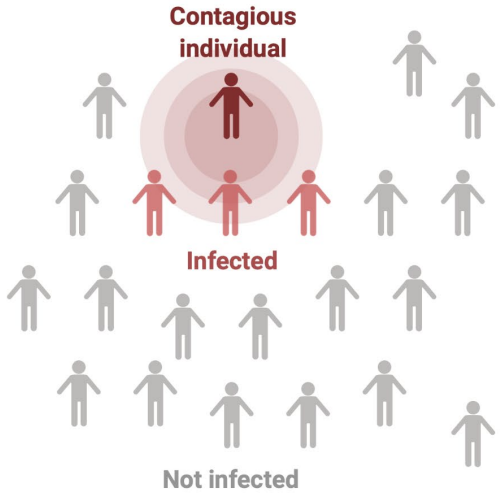


Created with BioRender.com

Reproduction Number

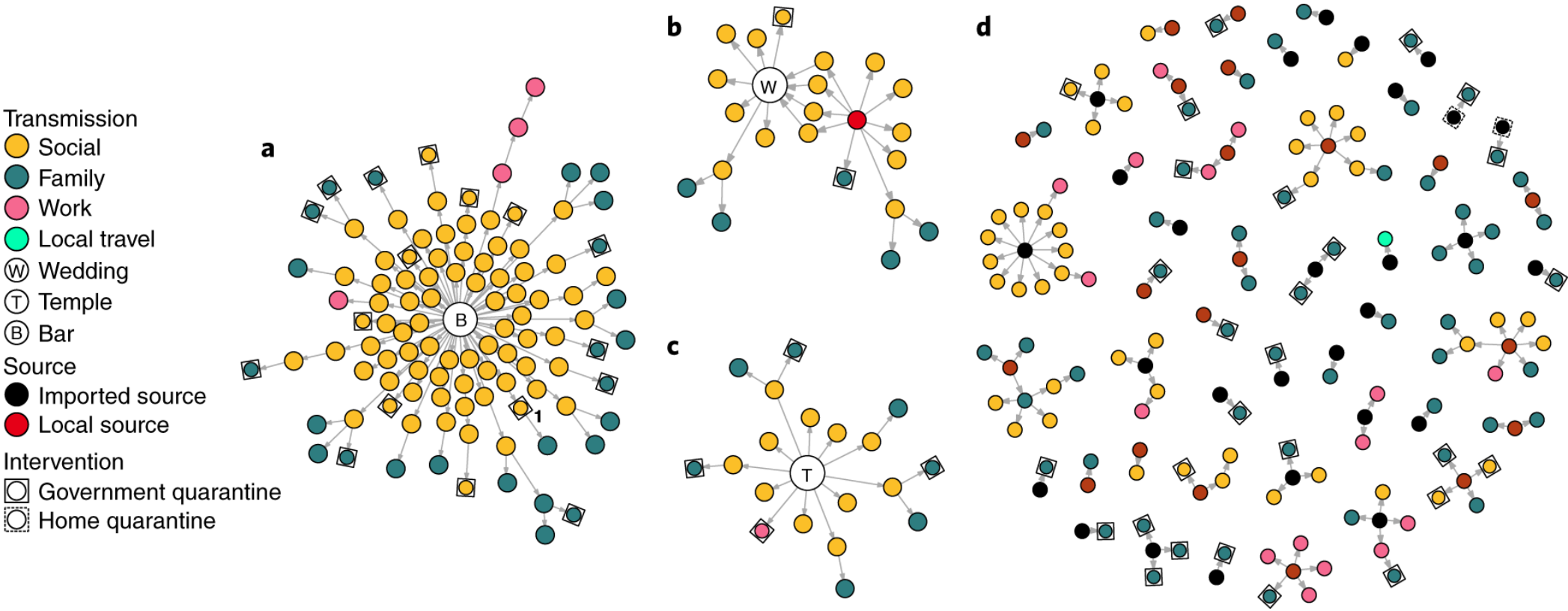
Average Basic Reproduction Number (R_0) of common viral infections





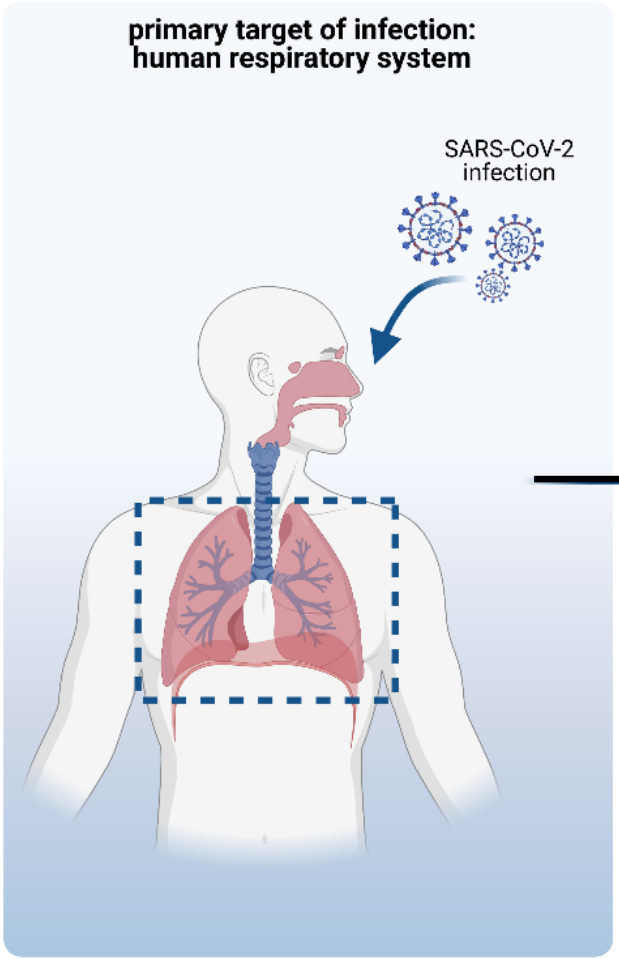
The **average basic reproduction number (R_0)** is an epidemiologic metric that describes the transmissibility of infectious agents. R_0 measures the expected number of secondary infections produced by a single infectious individual in a susceptible population during the mean infectious period.

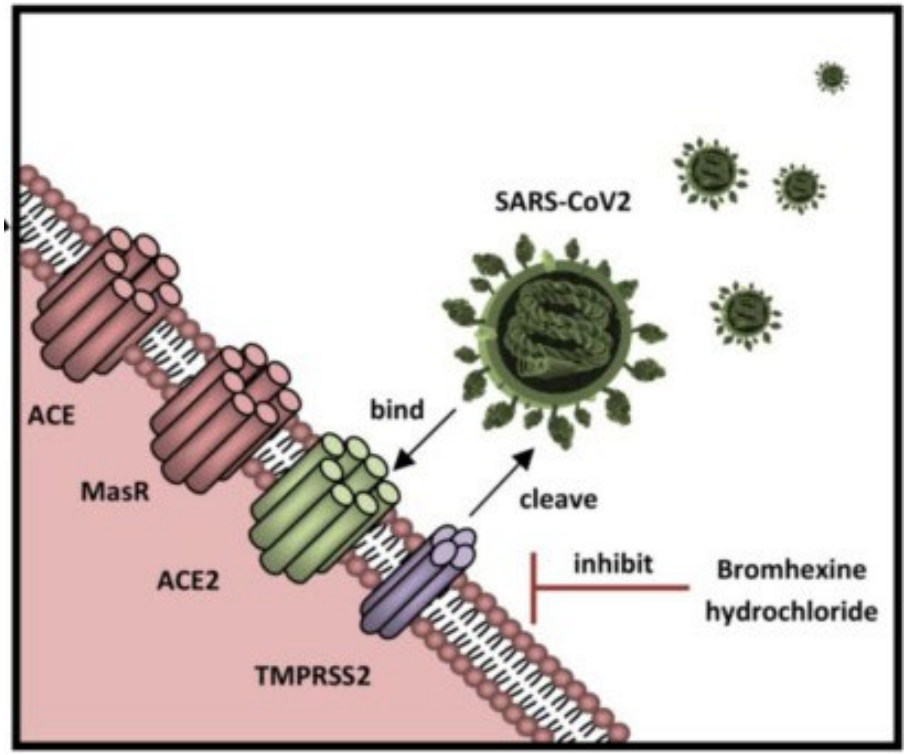
Superspreader – SARS-CoV-2



Nat Med **26,** 1714–1719 (2020).

SARS-CoV-2 – Tropism





- Entry mediated by ACE2 und TMPRSS2 (Lunge)

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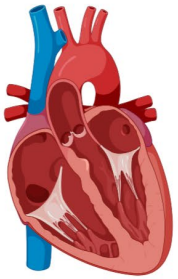
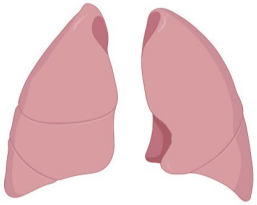
COVID-19 – Multi Organ Tropism

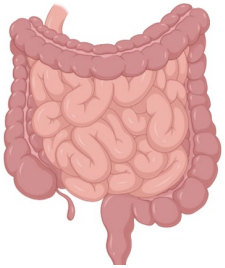
Heart/Circulation

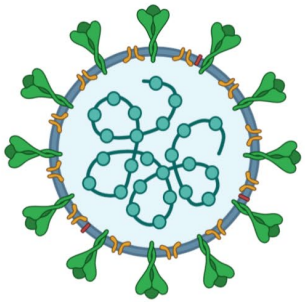


Pulmonal Disease



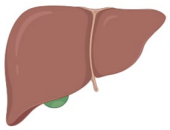
Gastrointestinal symptoms

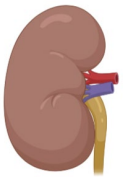




COVID-19

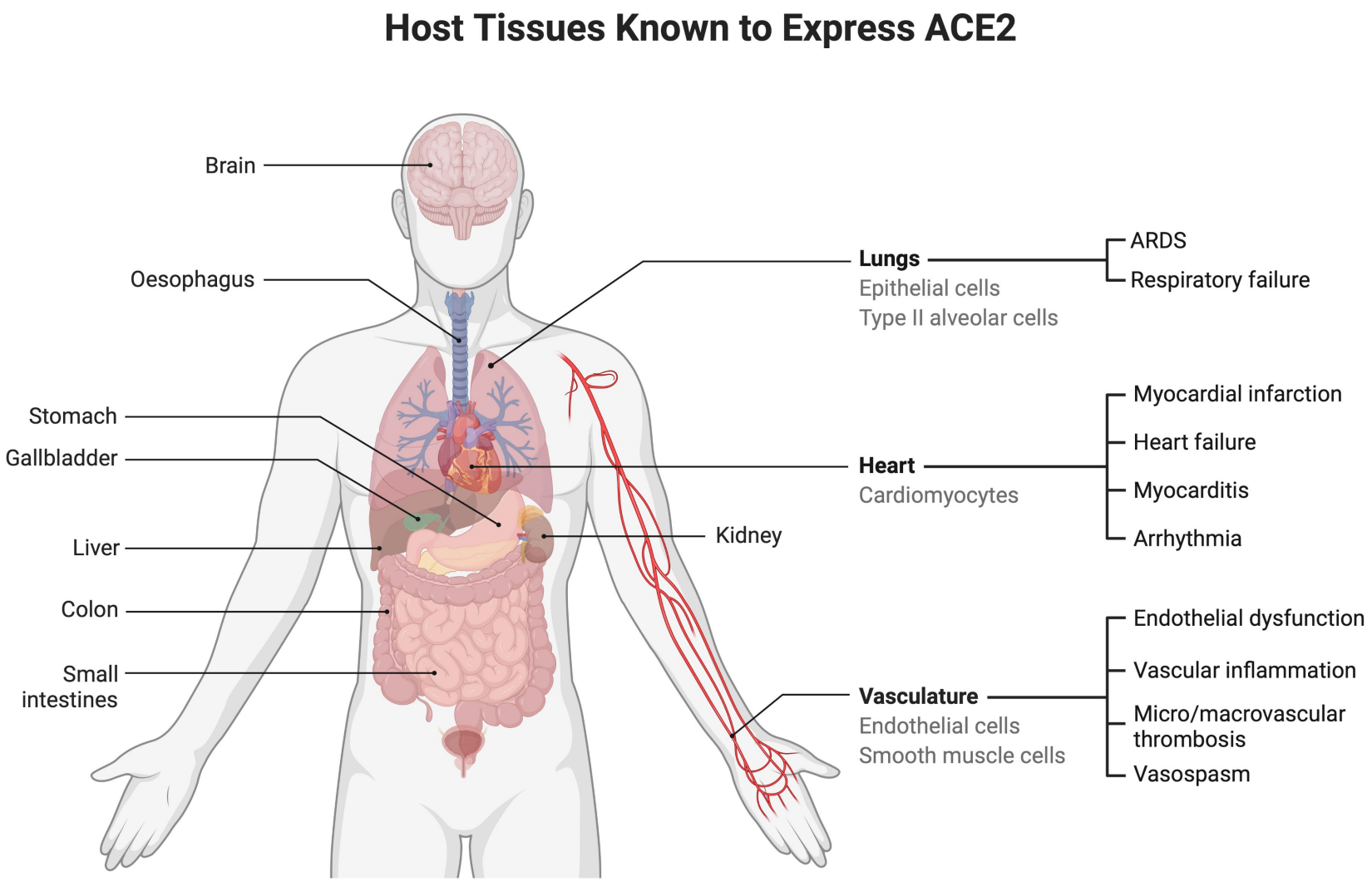
Neurological Symptoms





Dermatological Manifestation

COVID-19 – Multi Organ Tropism



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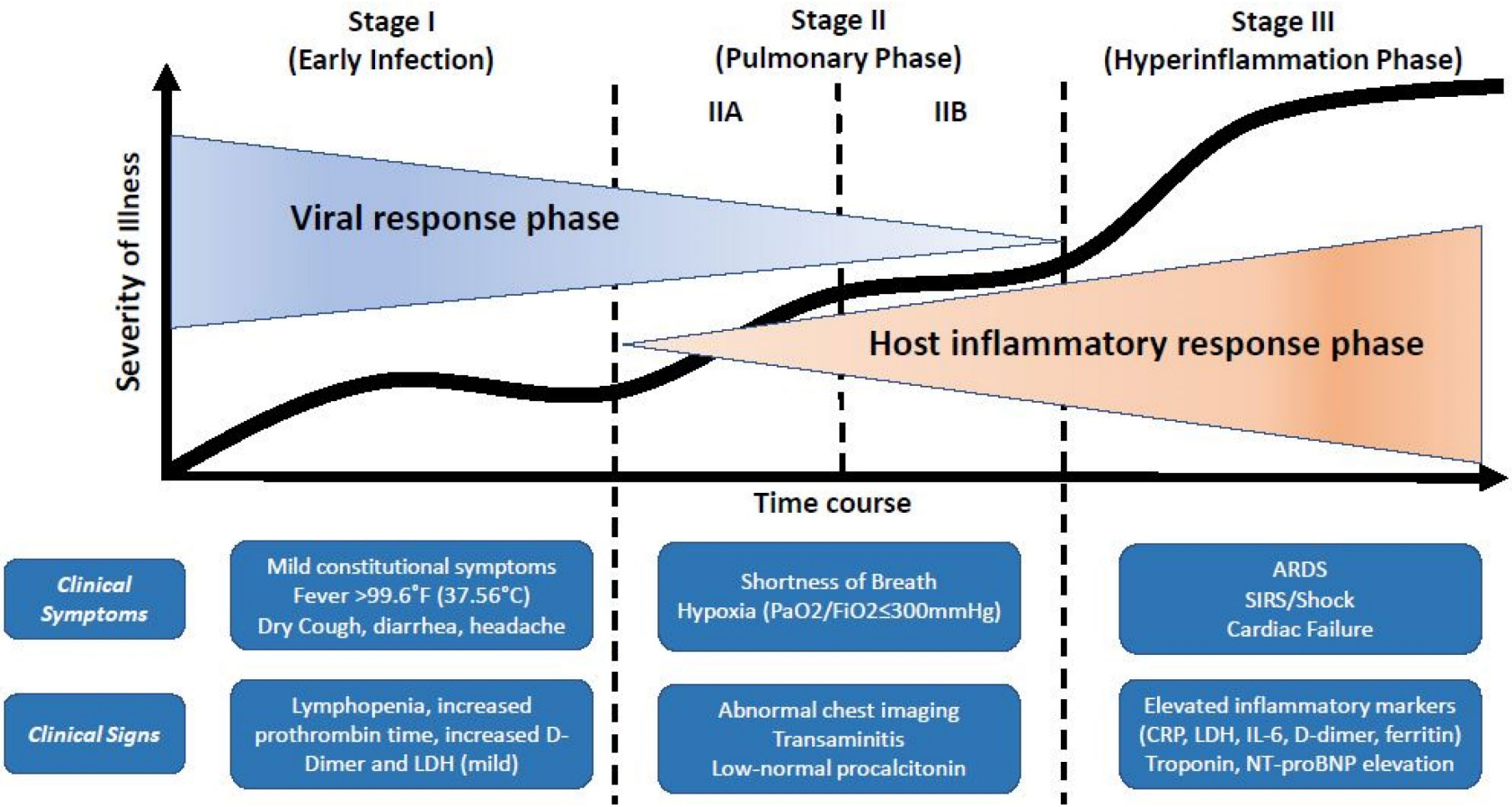
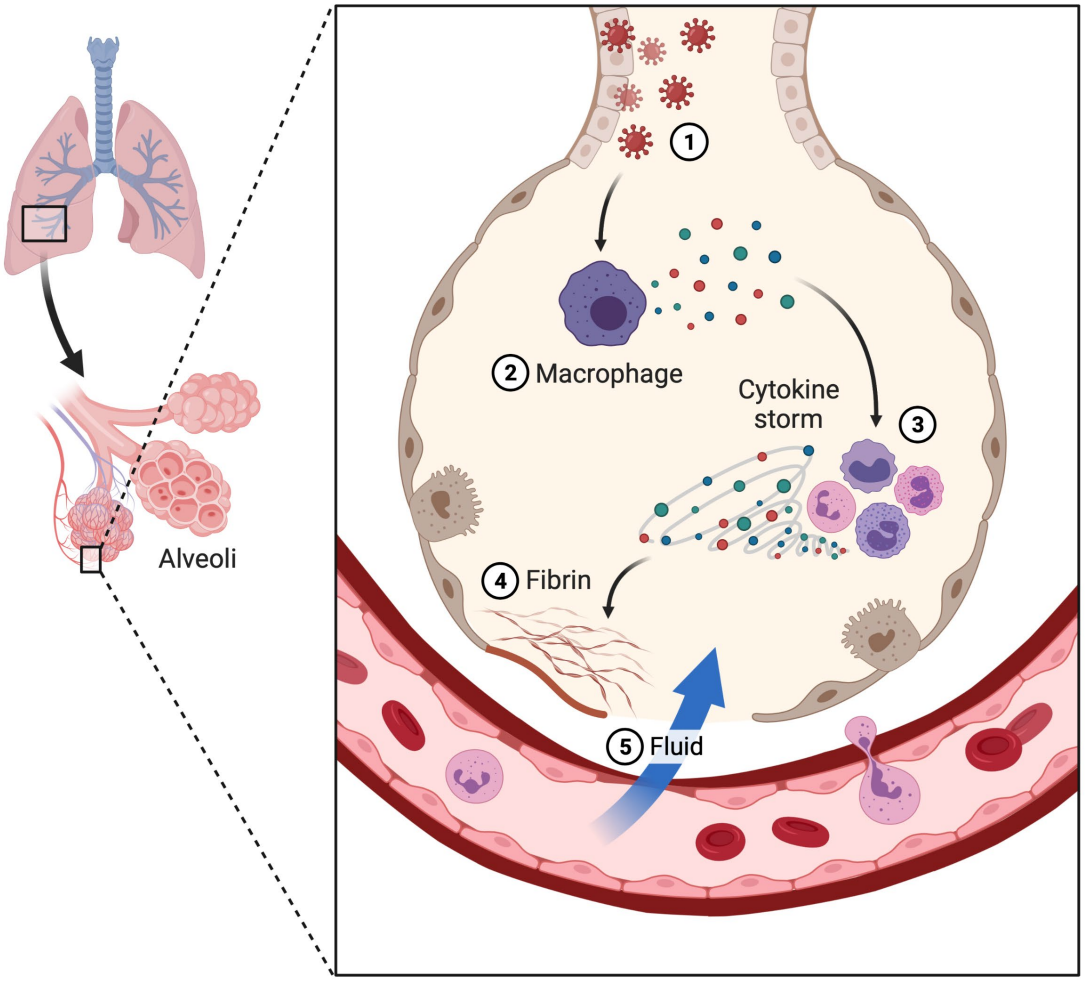
COVID-19 – Course of disease



https://doi.org/10.3390/transplantology1010001

COVID 19 – Cytokine Storm

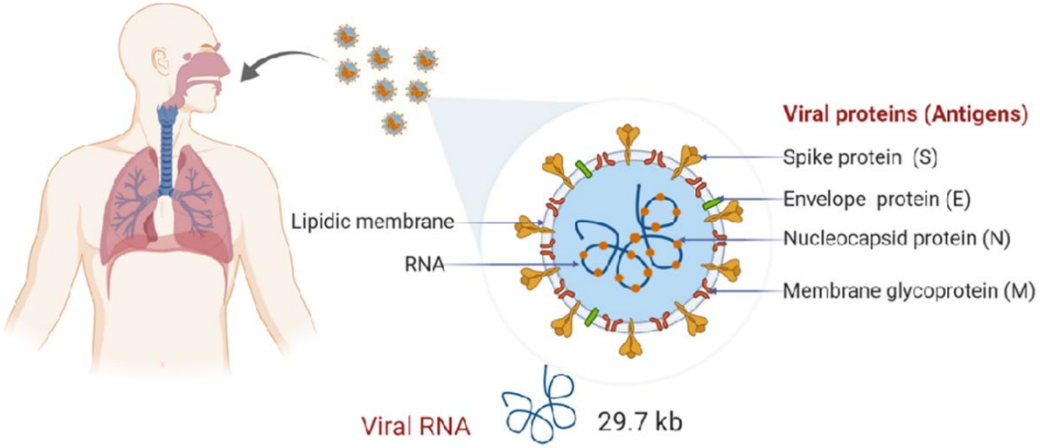


Cytokine Storm

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

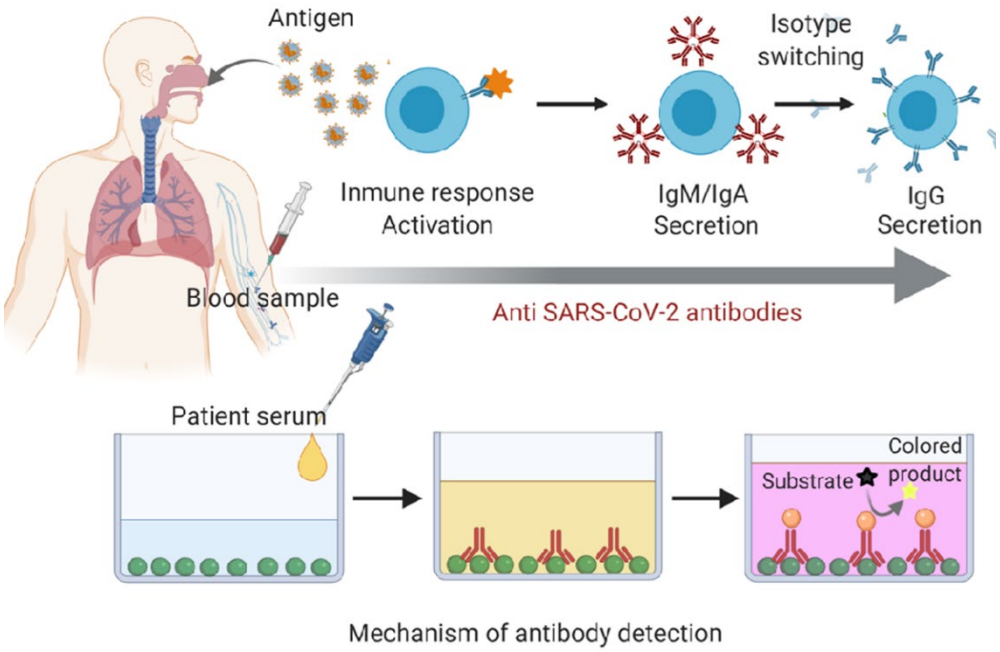
SARS-CoV-2 - Diagnostic

I) Direct (Virus)



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

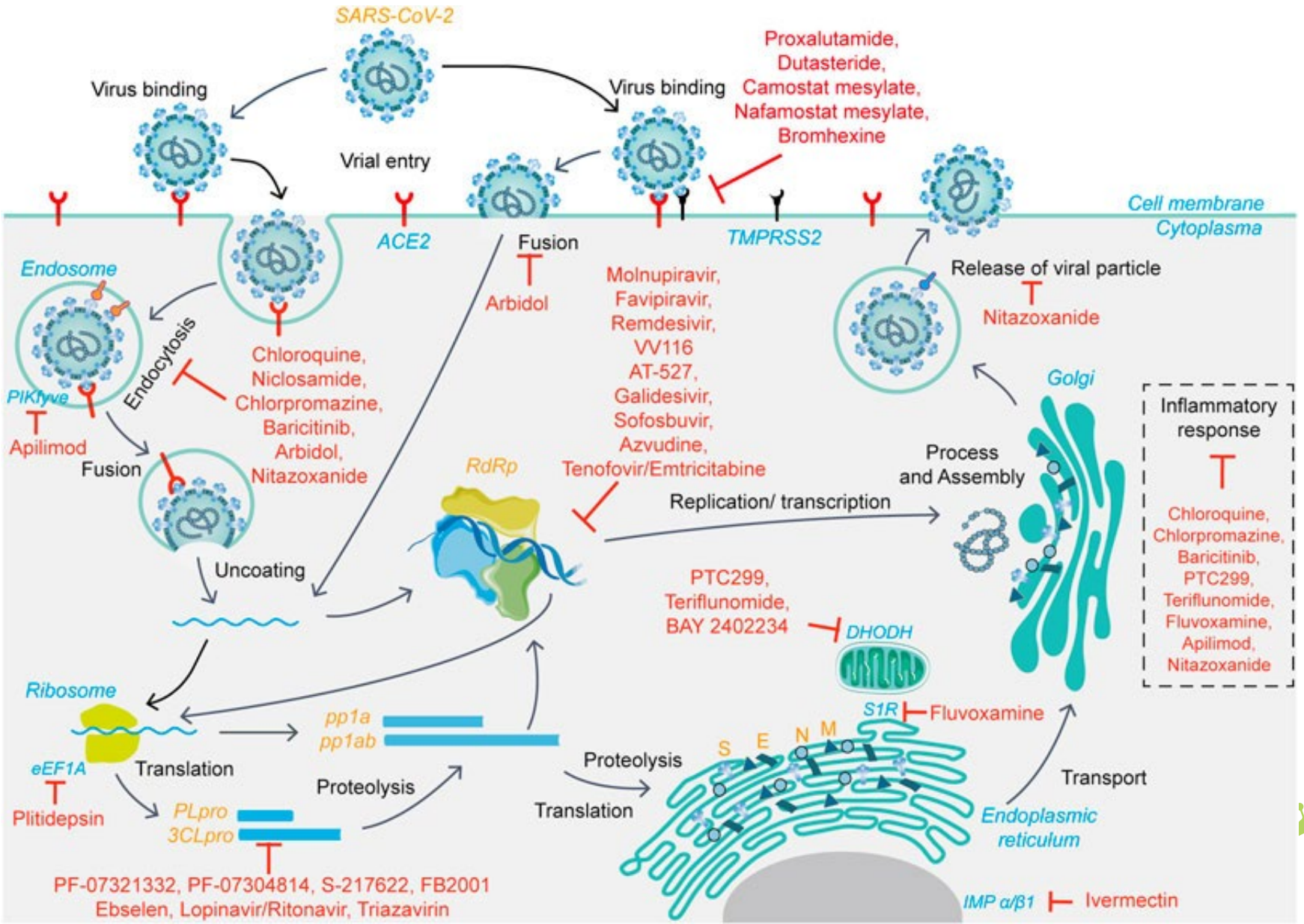
II) Indirect (Immunreaction)



Mechanism of antibody detection

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

SARS-CoV-2 - Antivirals



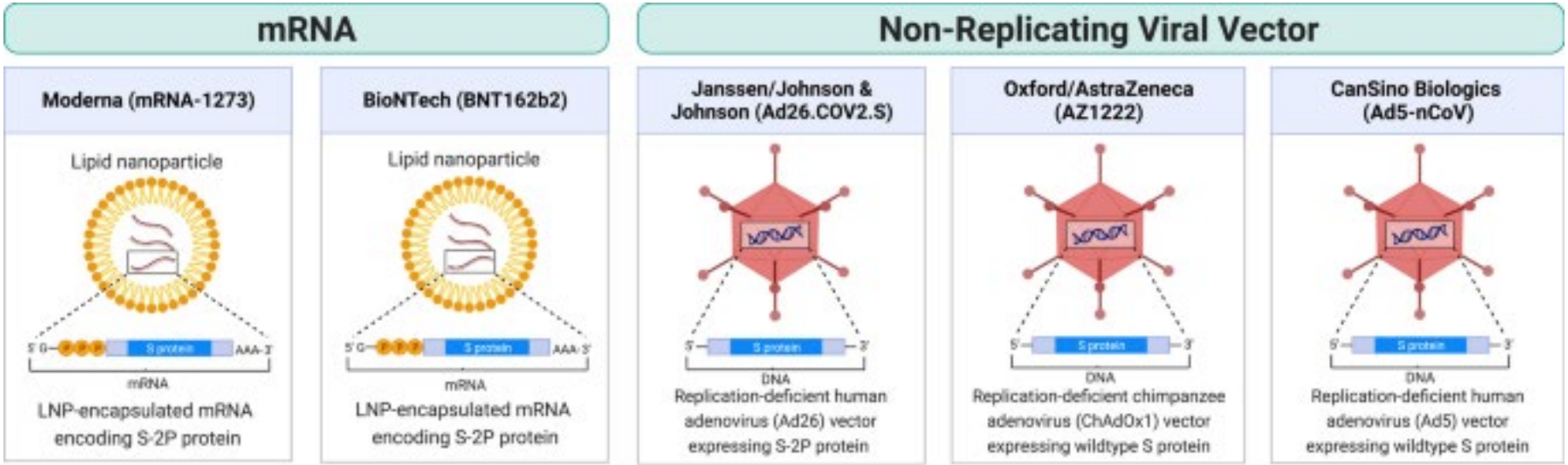
https://www.frontiersin.org/articles/10.3389/fphar.2022.840639/full

SARS-CoV-2 - Antivirals

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

Several more…..

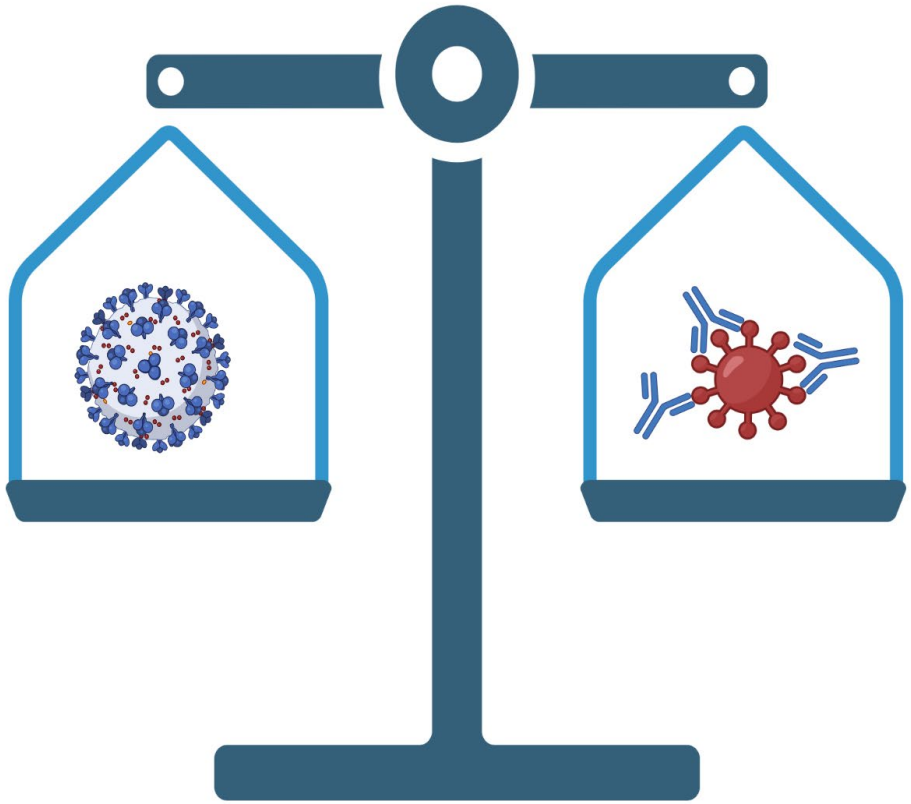
SARS-CoV-2 - Vaccines



https://jbiomedsci.biomedcentral.com/articles/10.1186/s12929-022-00853-8

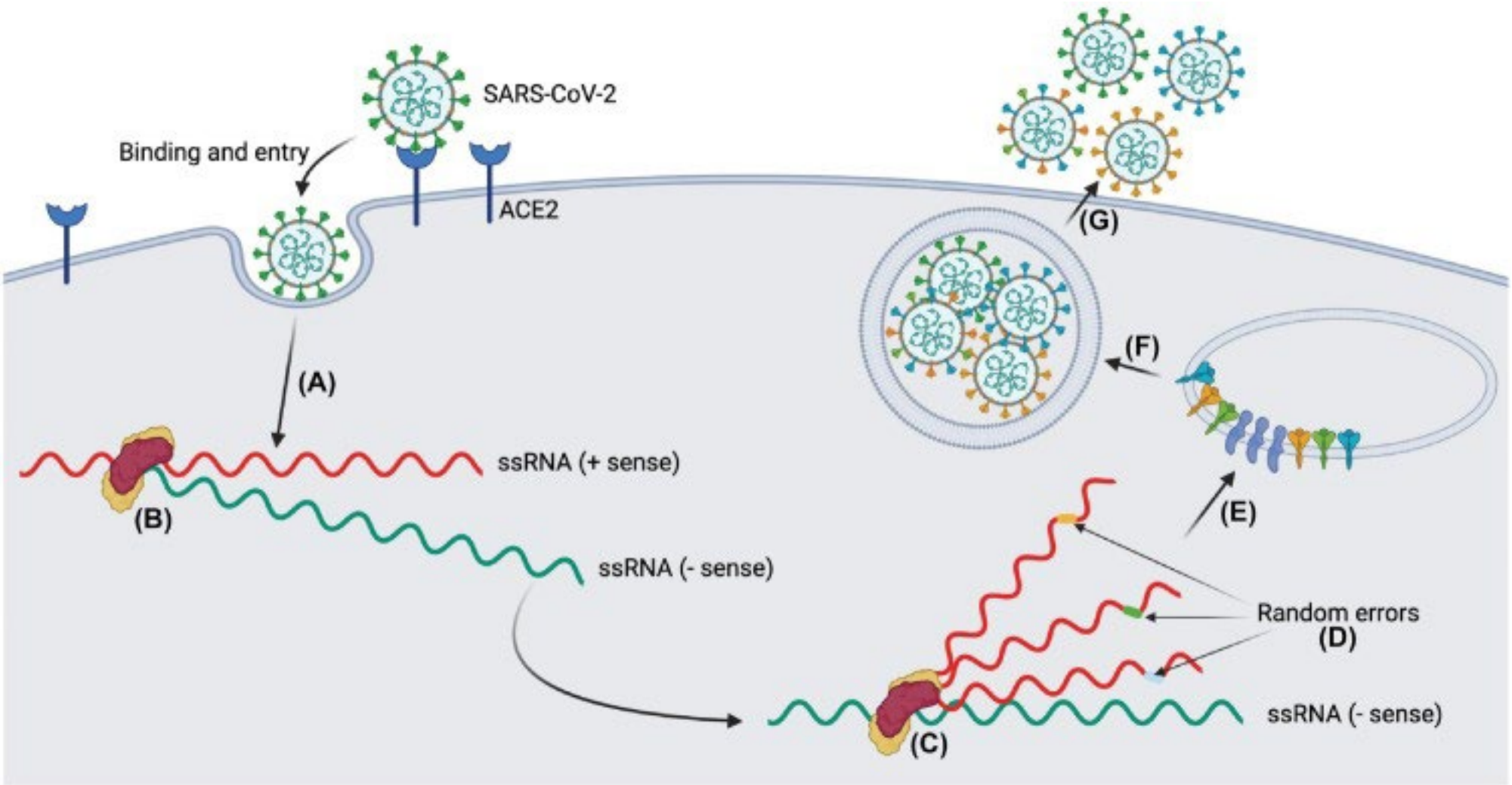
SARS-CoV-2 Variants

Coronaviruses – Mutations



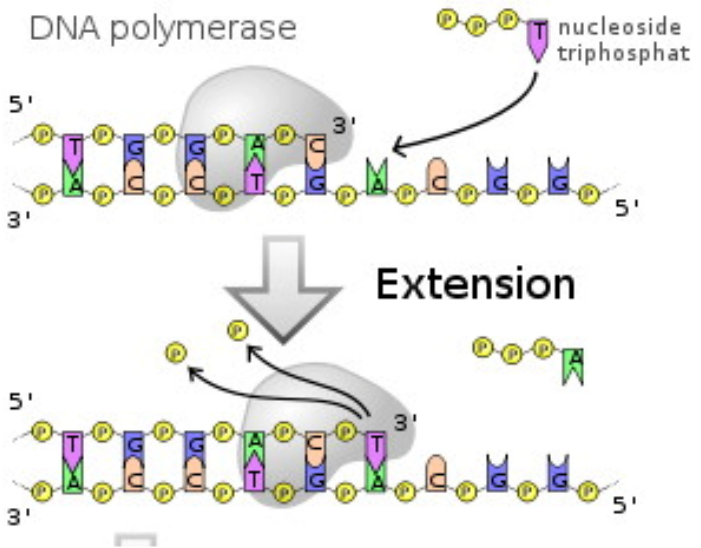
Virus Host

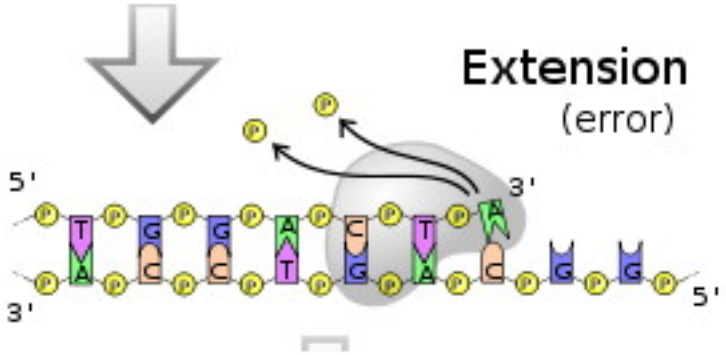
Coronaviruses – Replication errors

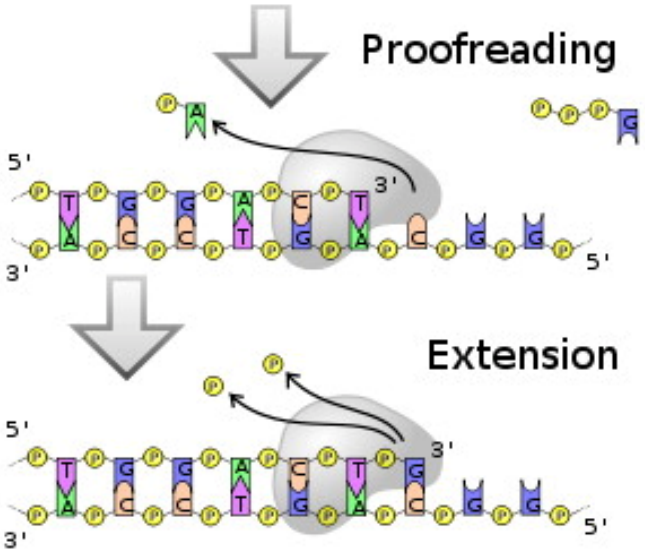


Trends in Microbiology

Coronaviruses – Replication errors







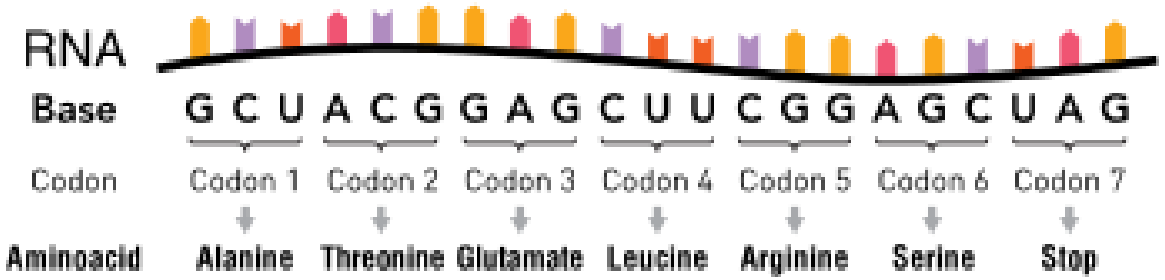
Errors:

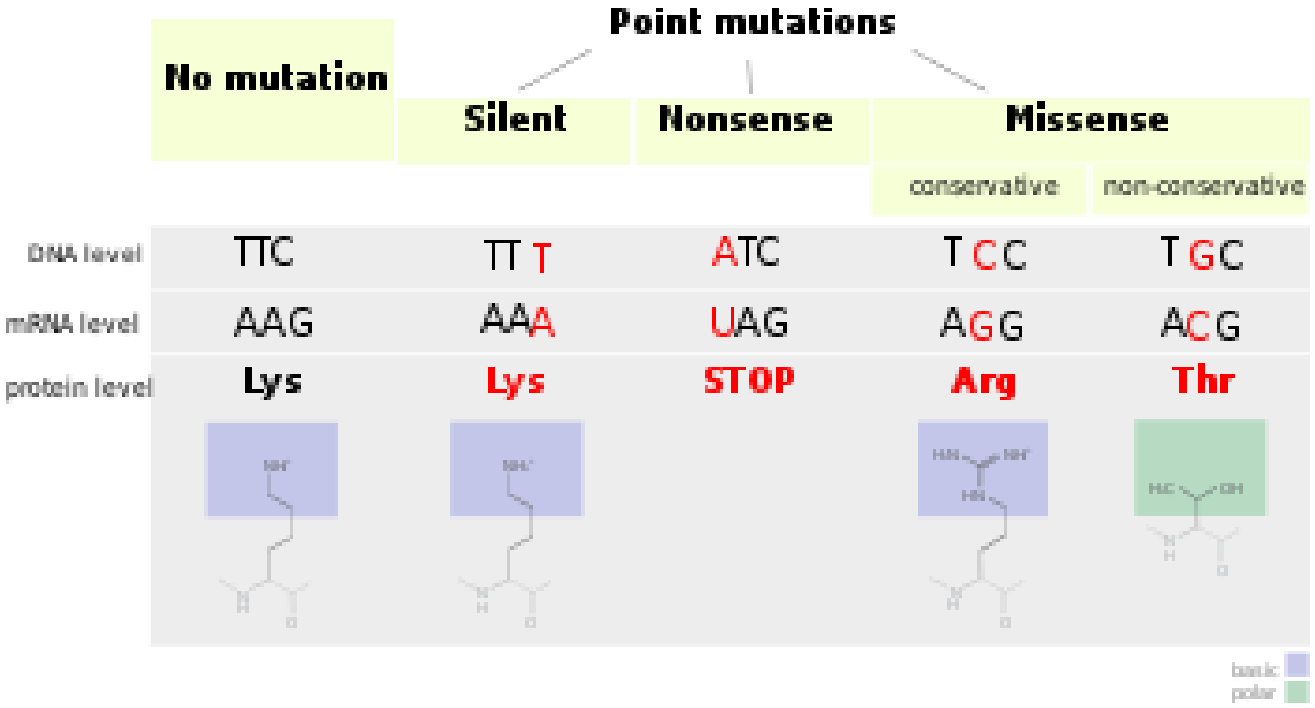
DNA polymerase: 1: 10^7 – 10^9 nucleotides

RNA polymerase: 1: 1000 – 10.000 nucleotides

Coronaviruses: Proof-reading function (NSP14)

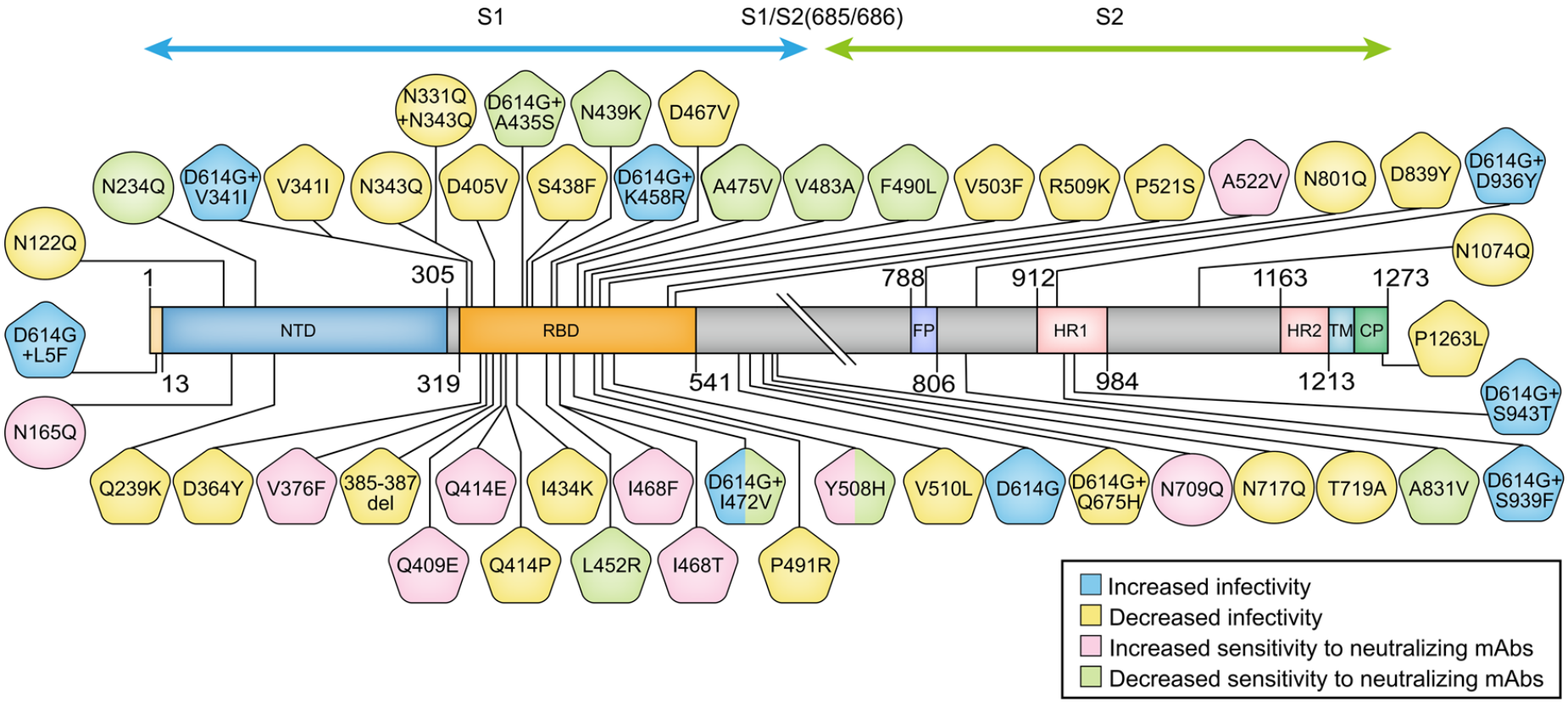
Coronaviruses – Replication errors





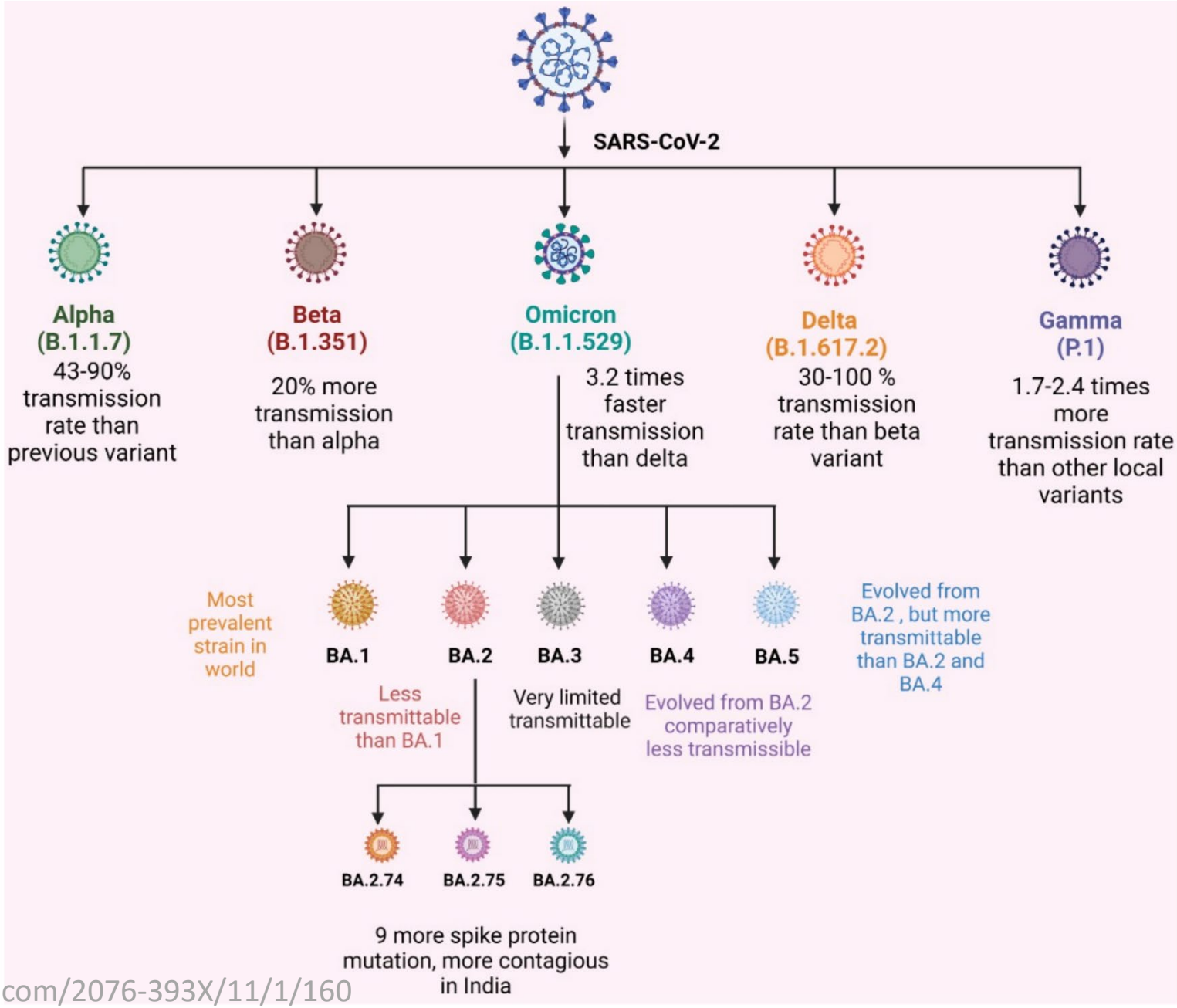
SARS-CoV-2 - Variants

SARS-CoV-2 - Variants



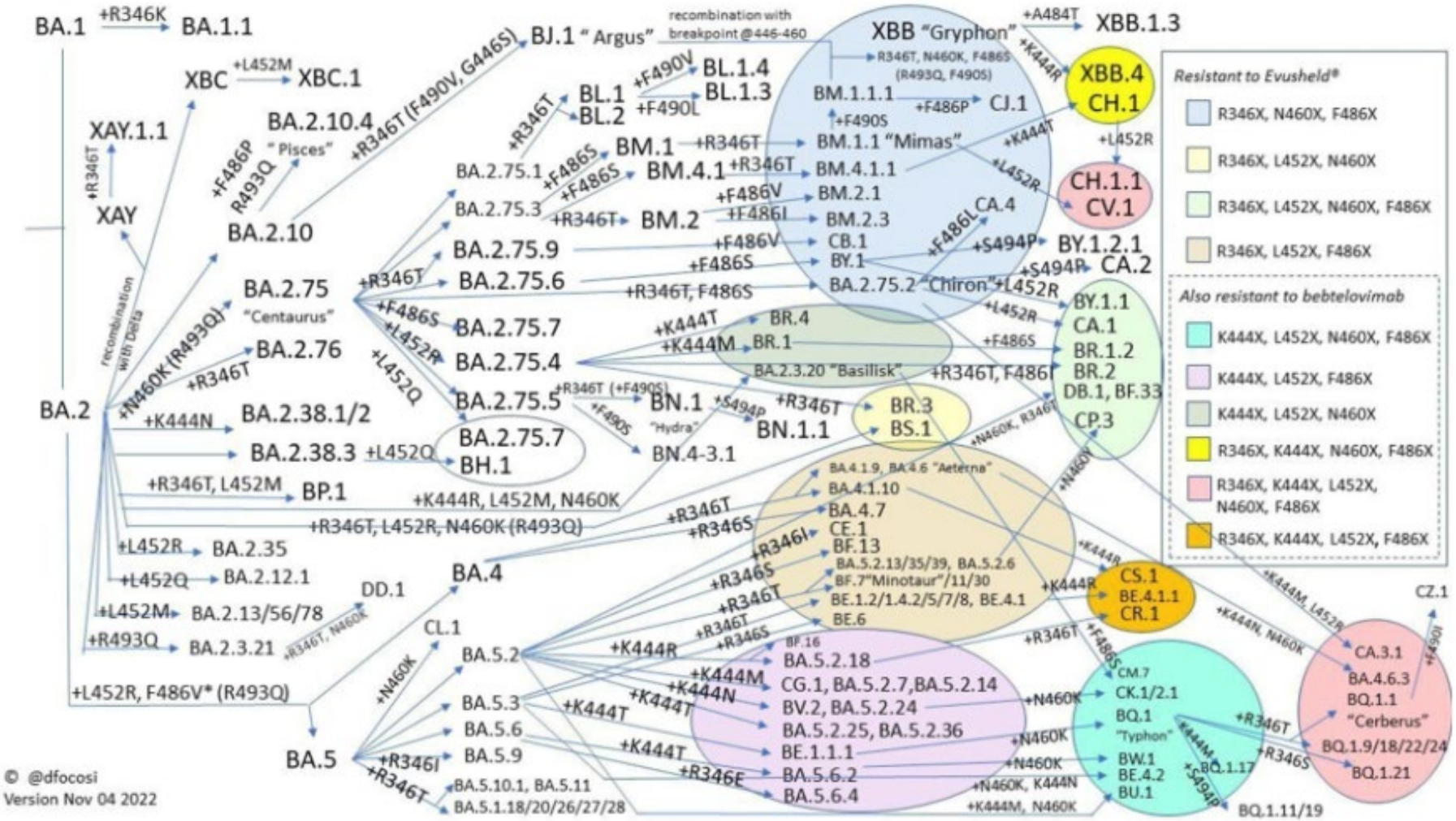
Spike Mutations: Can affect infectivity and antibody recognition

SARS-CoV-2 - Omicron



https://www.mdpi.com/2076-393X/11/1/160

SARS-CoV-2 - Omicron



Credit: Daniele Focosi

Quelle https://publichealth.jhu.edu/2022/omicrons-many-subvariants

Thank you for your attention