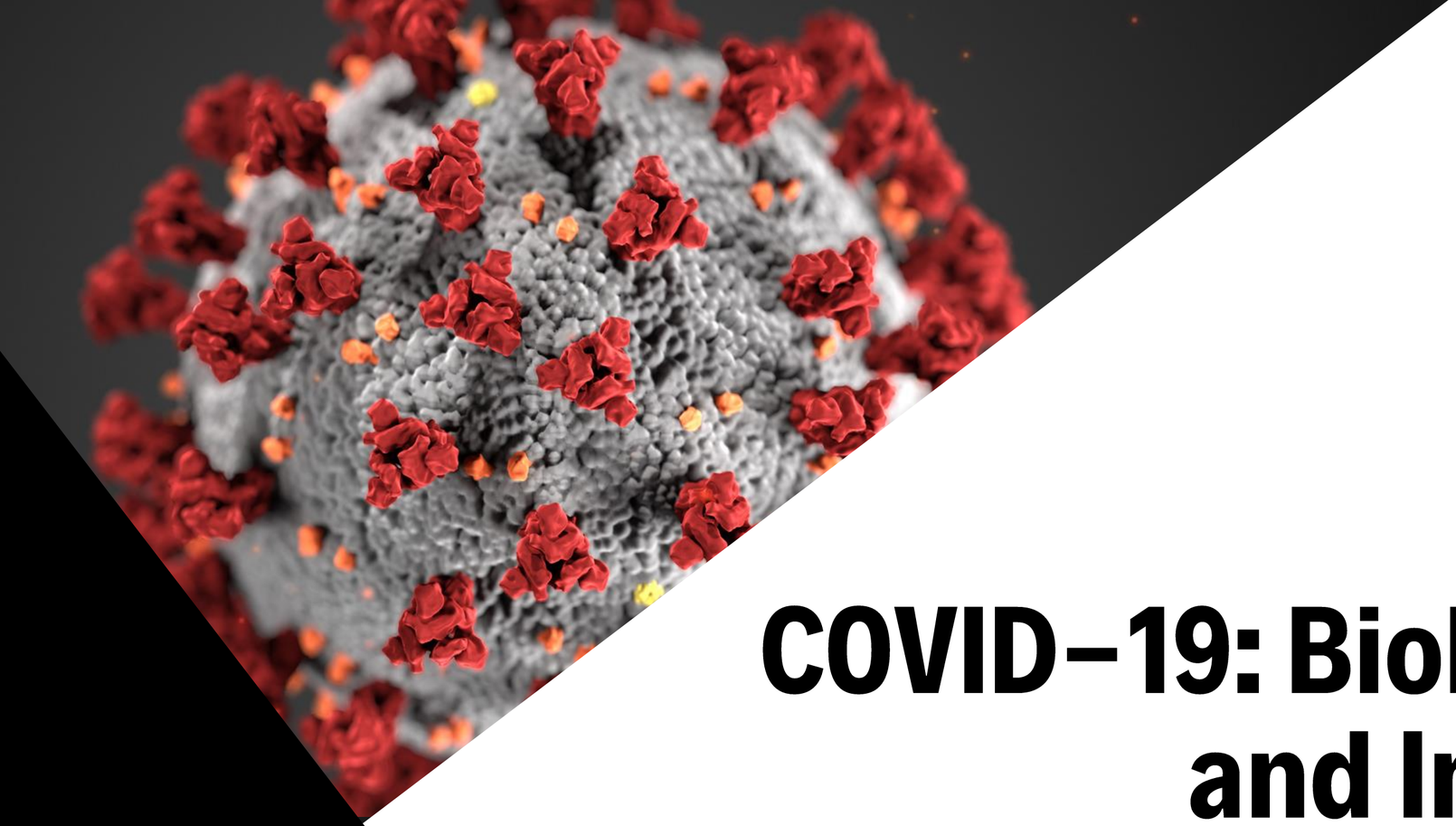


COVID–19: Biology, Symptoms, and Immunoresponse

Shalini Nair, MPH
Analyst, Infectious Disease
Association of State and Territorial Health Officials (ASTHO)

AGENDA

1

BACKGROUND

2

BIOLOGY

3

CLINICAL PRESENTATION

4

ANTIBODY RESPONSE

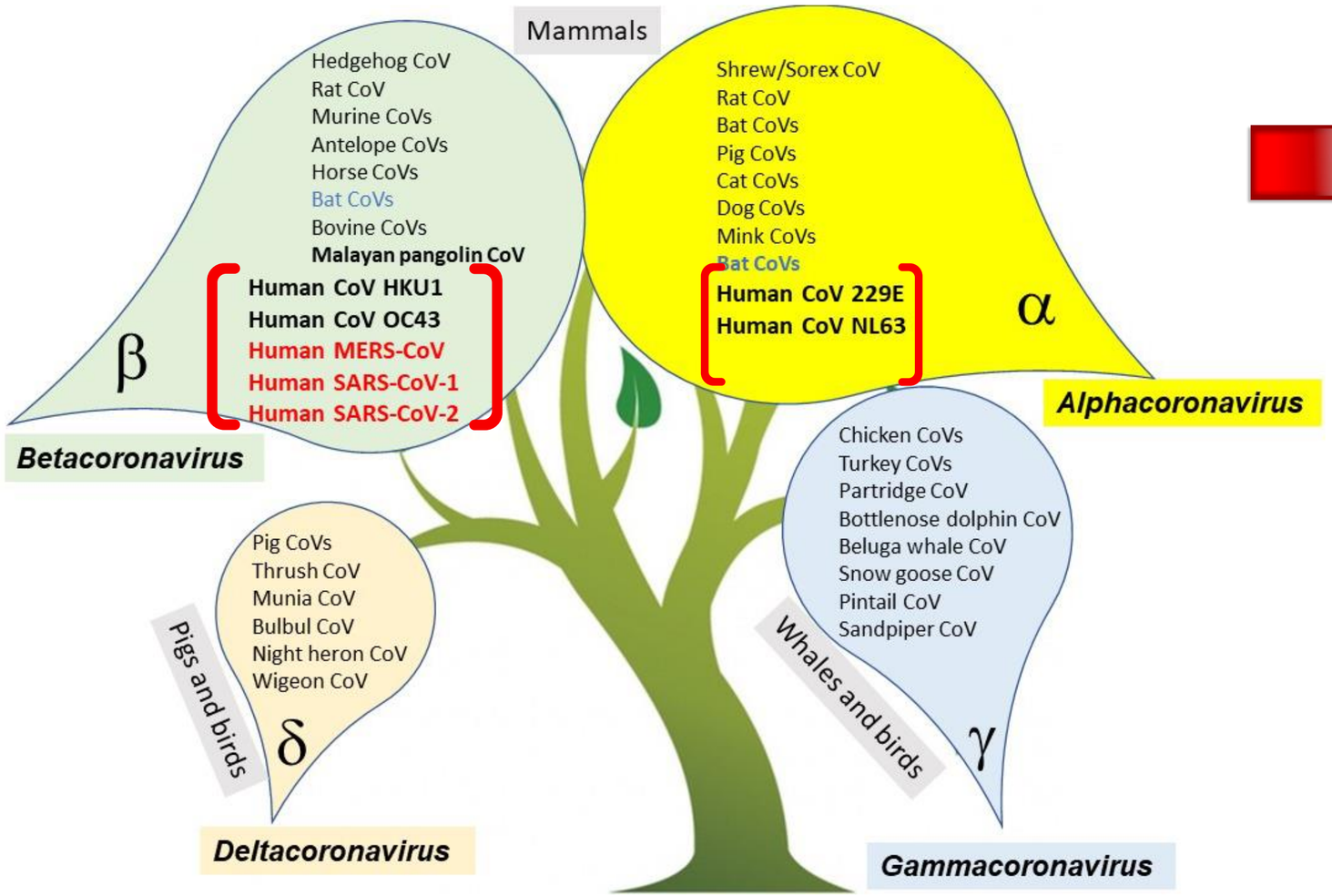
5

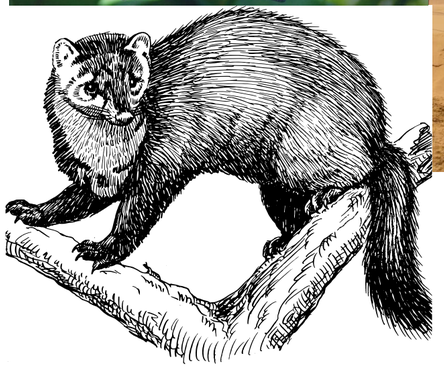
VACCINES

6

VARIANTS AND OUTLOOK

CORONAVIRUSES





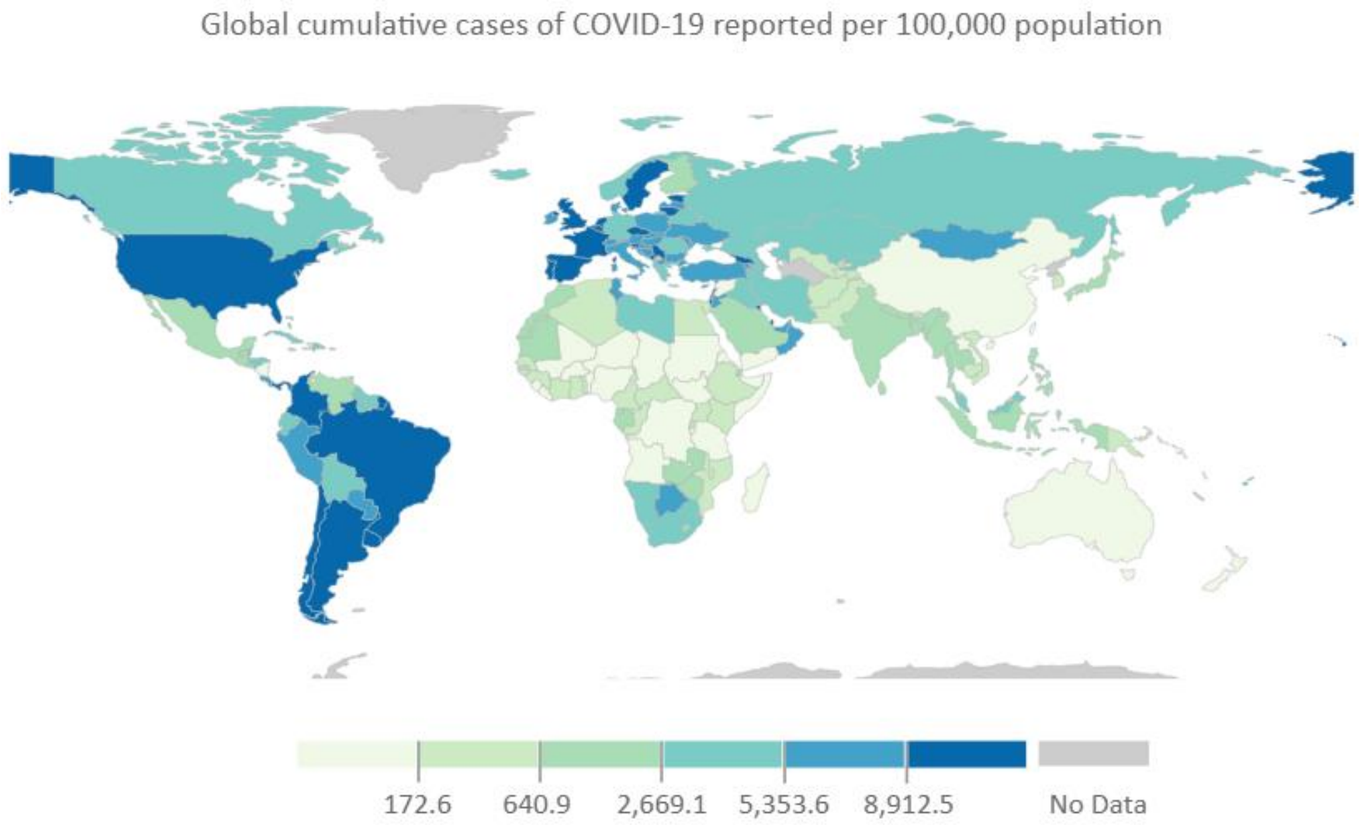
(Shors, 2021)

HIGHLY PATHOGENIC HUMAN CORONAVIRUSES

Betacoronaviruses

Virus	Year of Emergence	Reservoir	Intermediate host	Spread
SARS-CoV	2003			
MERS-CoV	2012			
SARS-CoV-2	2019			

SARS–COV–2: AT A GLANCE

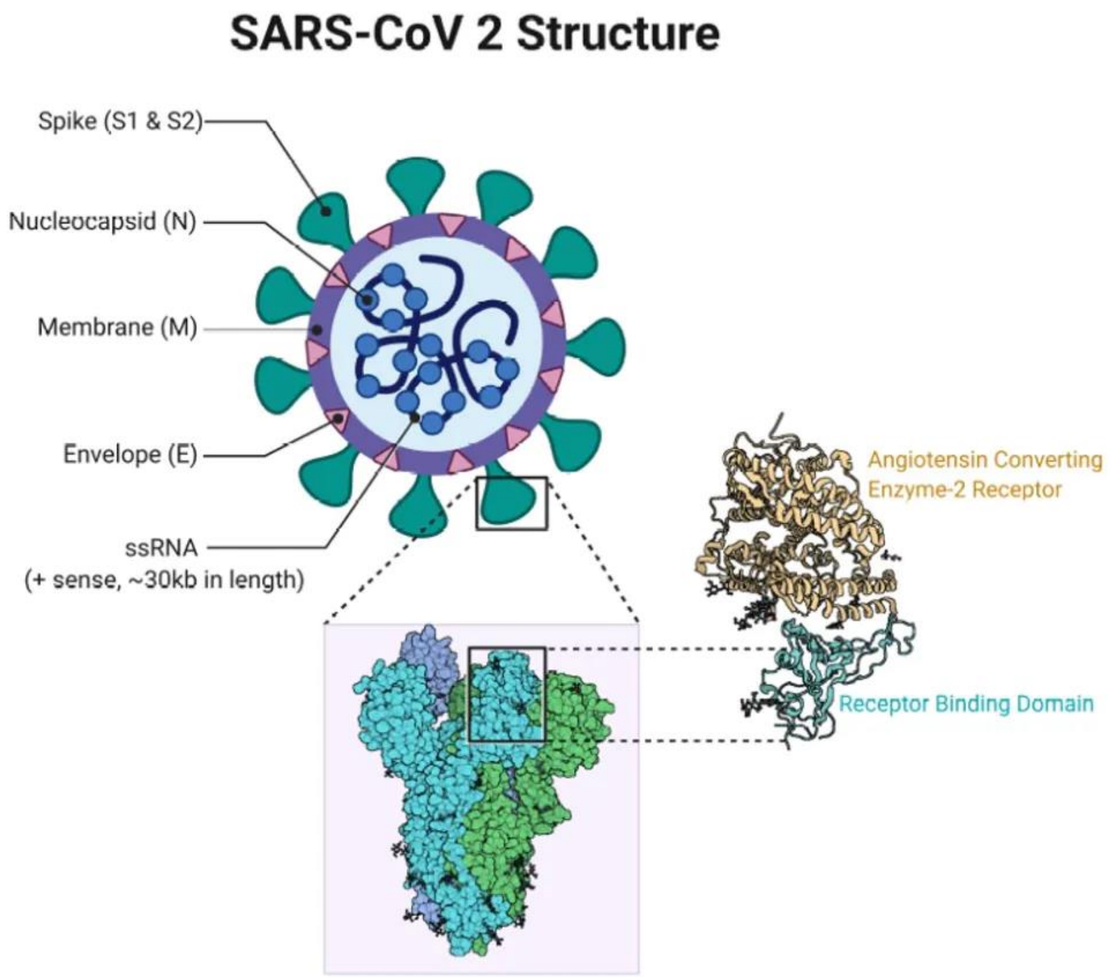


As of 8/20/21

- Genetic similarity to both SARS-CoV (80%) and MERS-CoV (50%)
- High rates of recombination and variability
- Similar risk factors
- Similar routes of human-to-human transmission

(CDC, 2021)

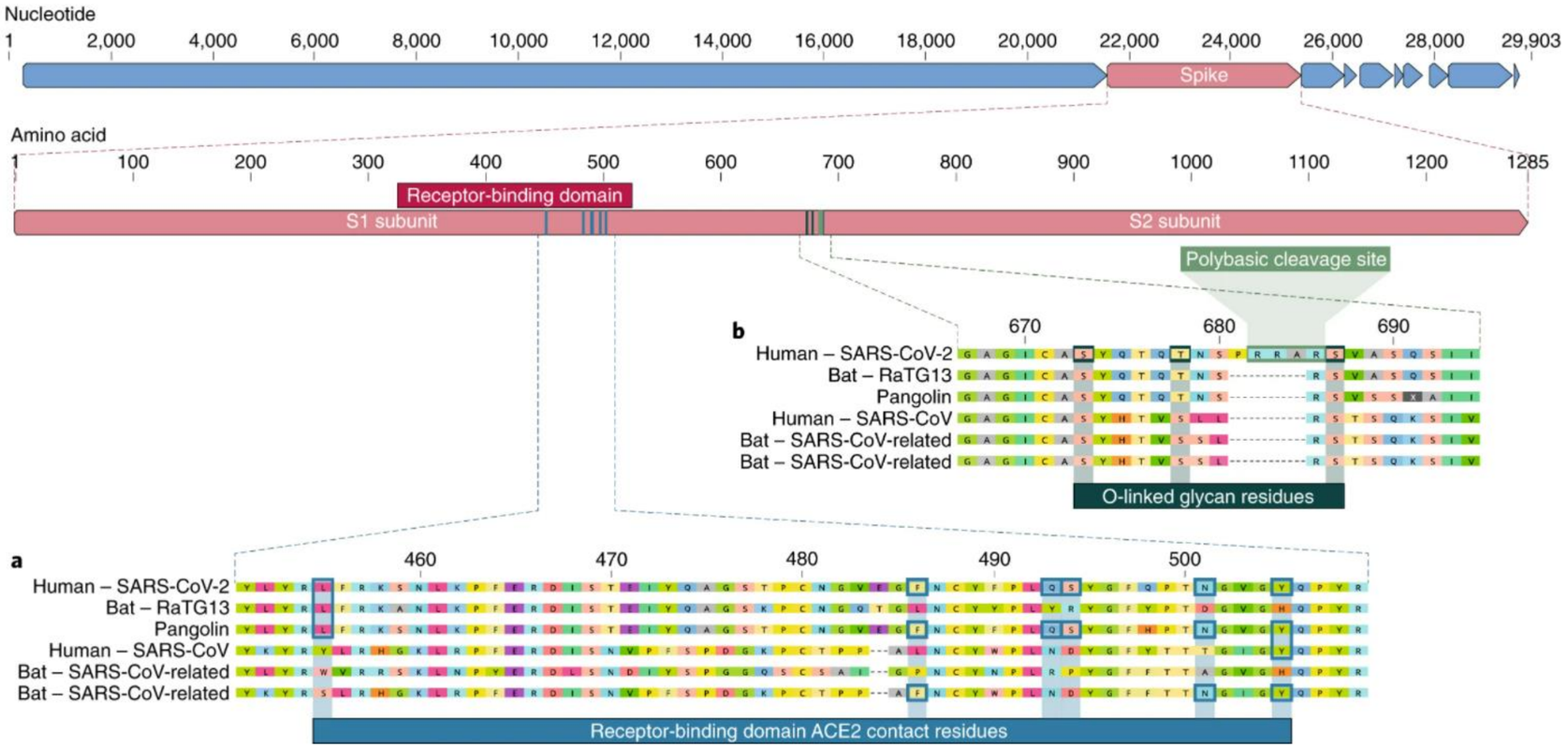
SARS–COV–2: "CORONA" AND STRUCTURE



- Origins of the name
- Enveloped, single-stranded RNA genome
- Spike (S) protein functions:
  - Mediates entry into host cell
  - Main target for immune defense
- E, M, and N transmembrane proteins involved in virus assembly

(Singh, 2021)

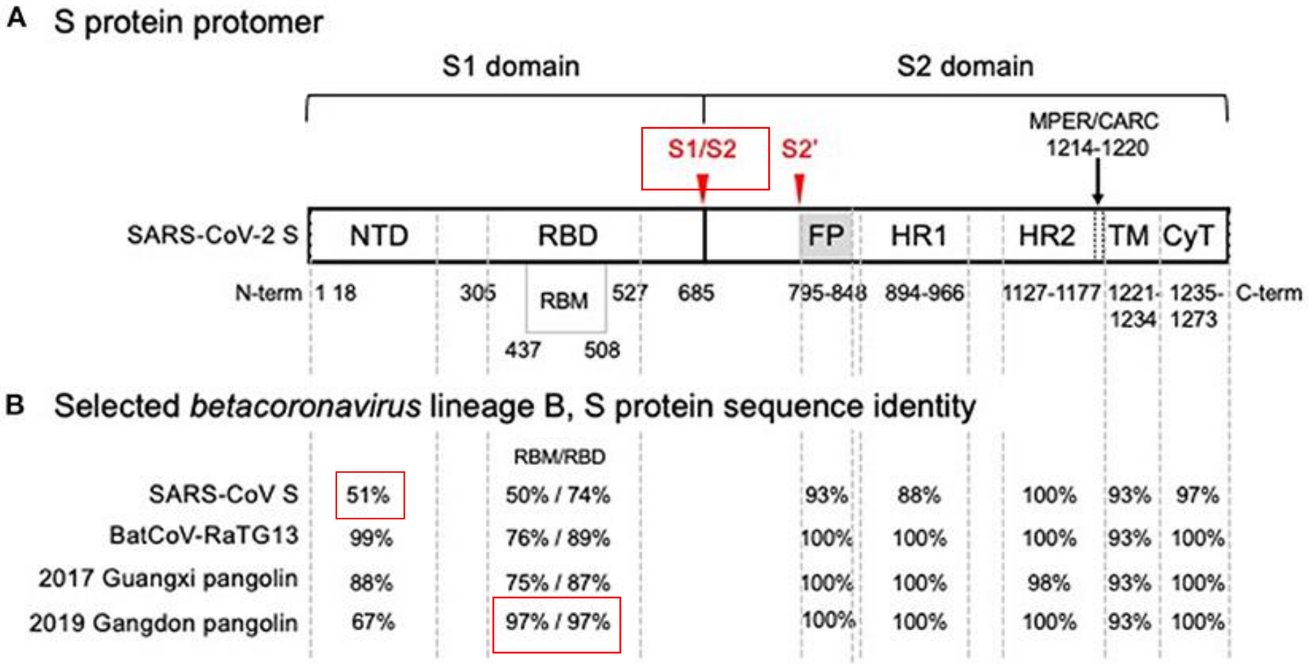
SARS–COV–2: GENETIC CHARACTERISTICS



- Novel acquisitions at the junction of S1 and S2 subunits
- High affinity for angiotensin-converting enzyme 2 (ACE2) receptors
- Increased efficiency of entry into host cells

(Andersen et al., 2020)

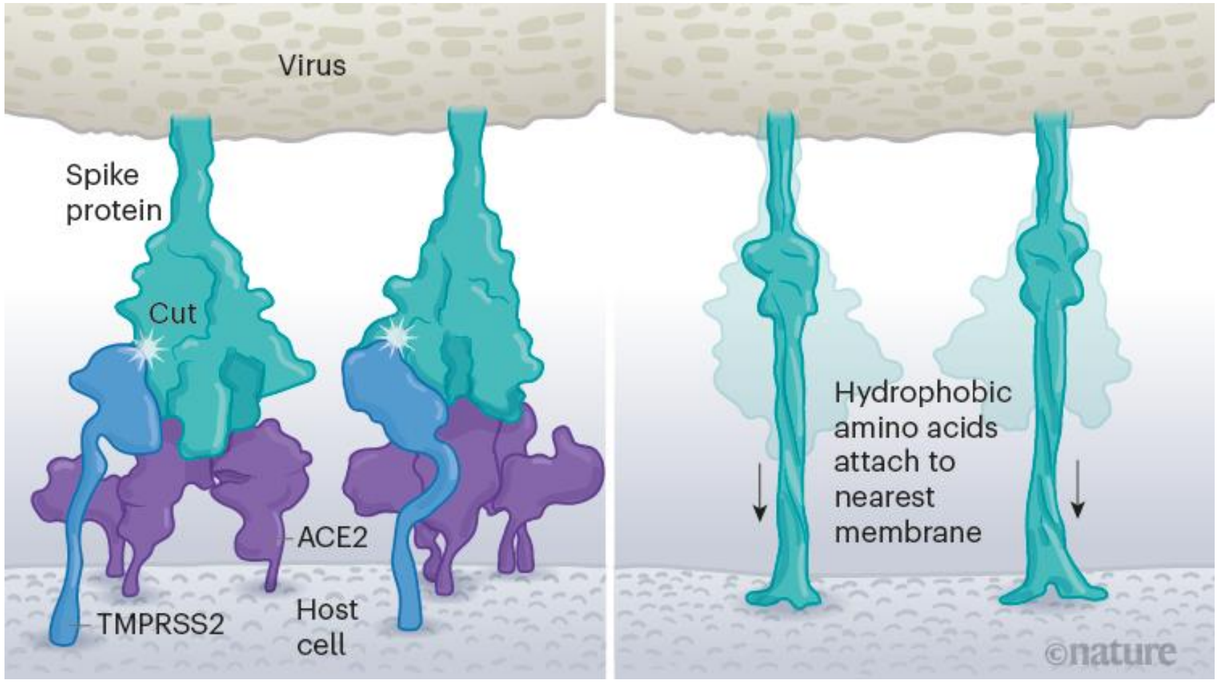
SARS–COV–2: THE S PROTEIN

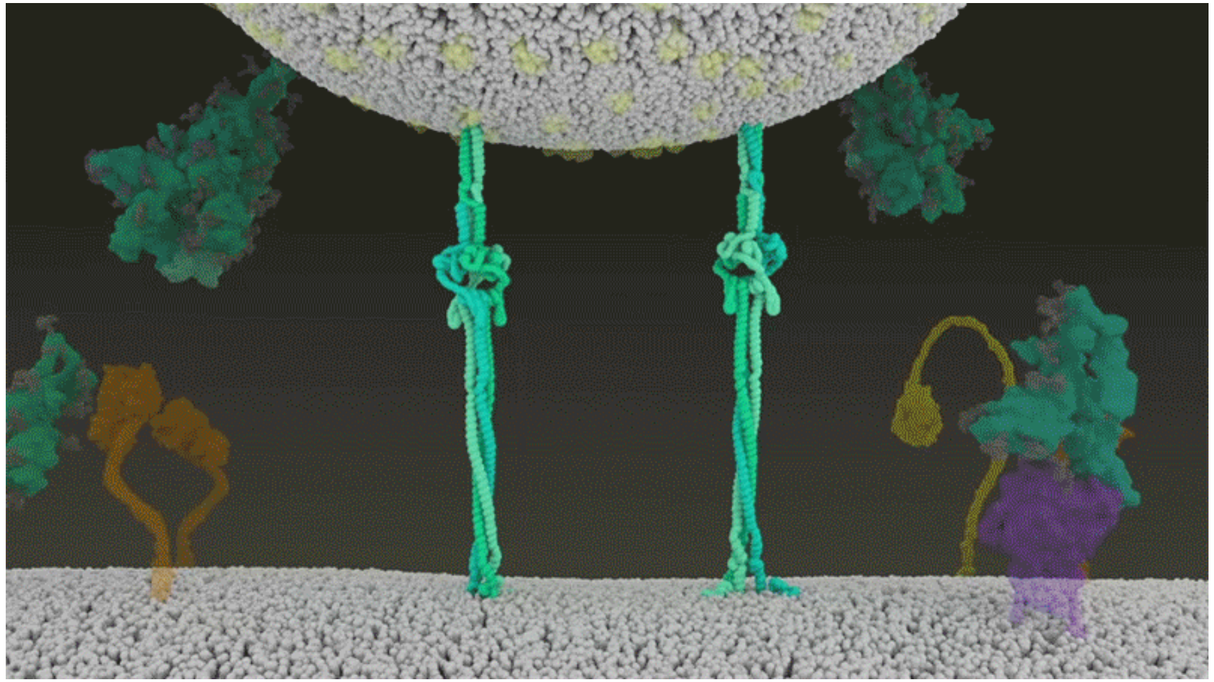


- Composed of S1 and S2 subunits
- S1 houses the receptor binding domain
  - Target of neutralizing antibodies
- S2 facilitates fusion of viral and host membranes
- S2 highly conserved among coronaviruses

(Shah et al., 2021)

SARS–COV–2: VIRAL ENTRY

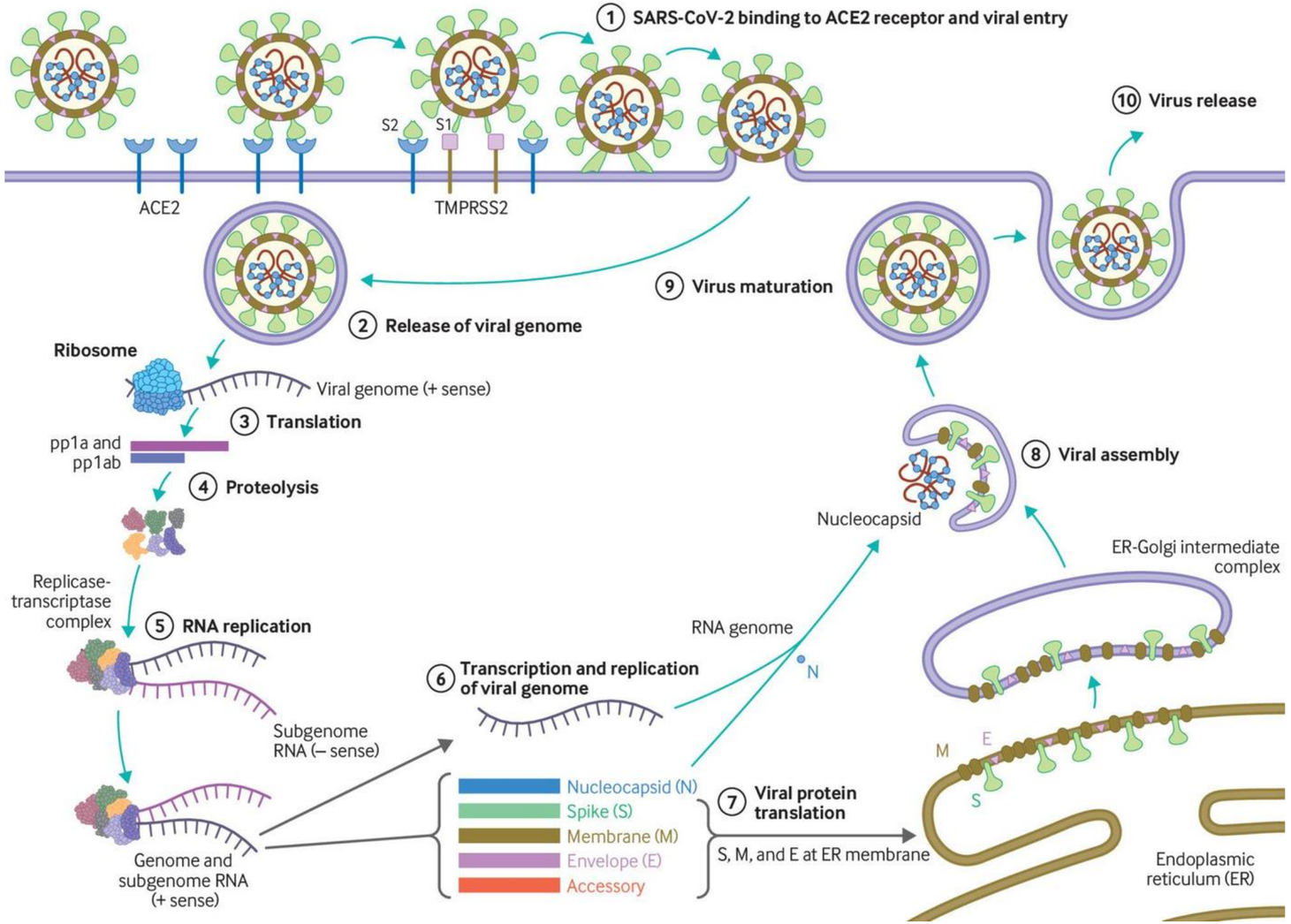




(Spencer/*Nature.*, 2021)

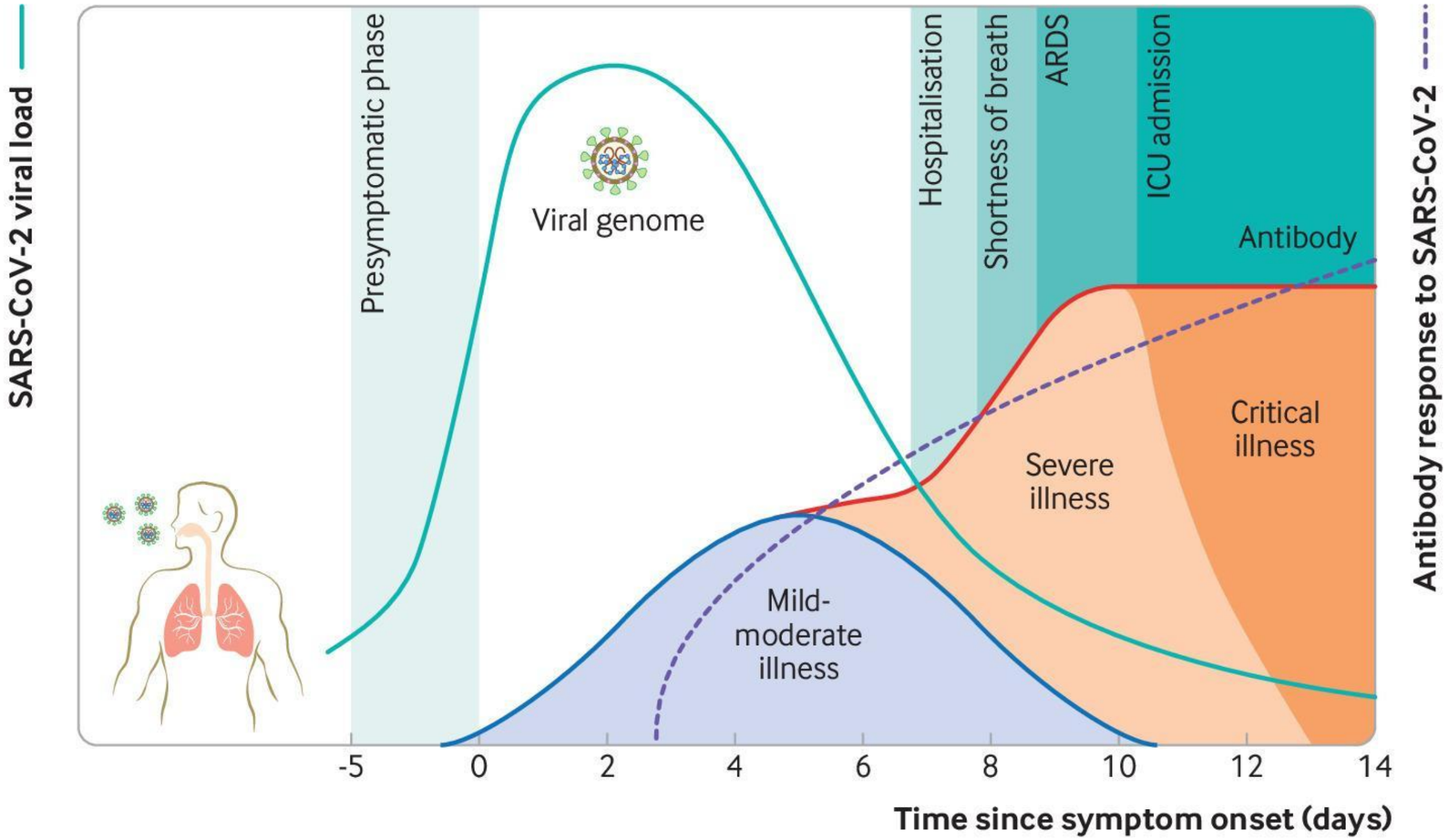
(Iwasa., 2021)

SARS–COV–2: PATHOGENESIS



(Cevik et al., 2020)

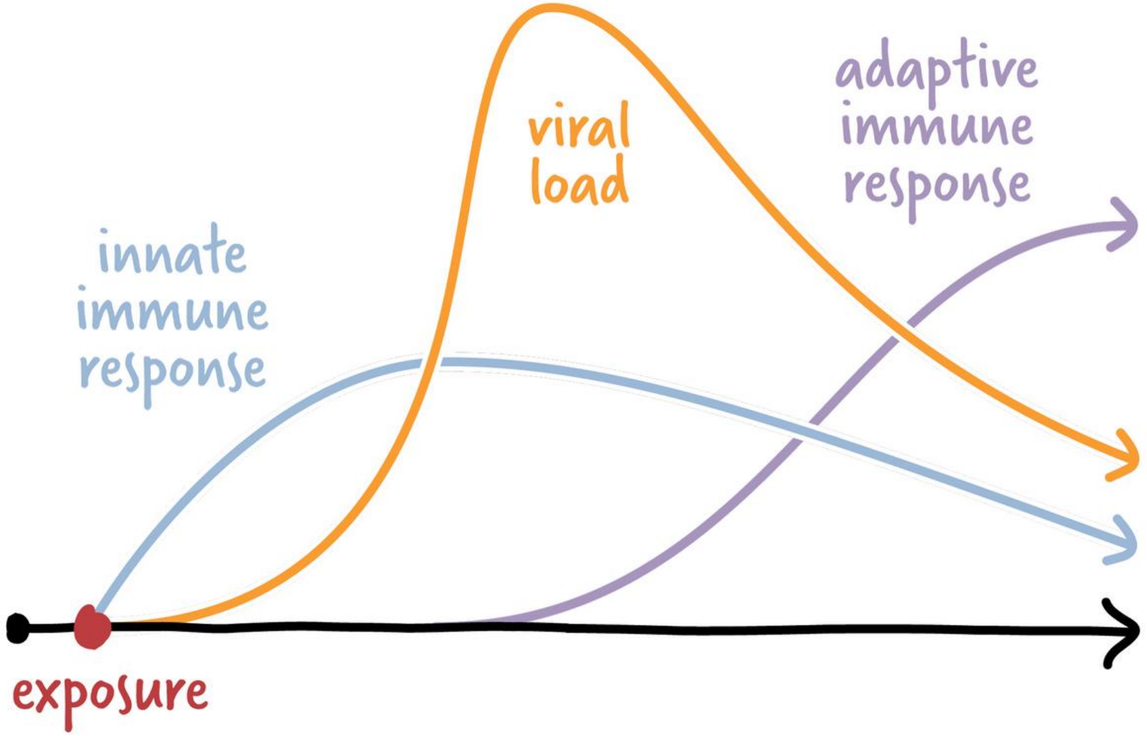
SARS–COV–2: DISEASE PROGRESSION



(Cevik et al., 2020)

SARS-COV-2: THE EARLY RESPONSE

- Following infection:
  - Innate vs adaptive mechanisms
    - Innate sometimes sufficient
  - T-cell recruitment while IgM response develops
  - Memory B-cells and the rise of IgG and IgA titers
    - B-cells recruited upon reinfection
      - Variable effectiveness with variants



SARS-COV-2: SEROCONVERSION

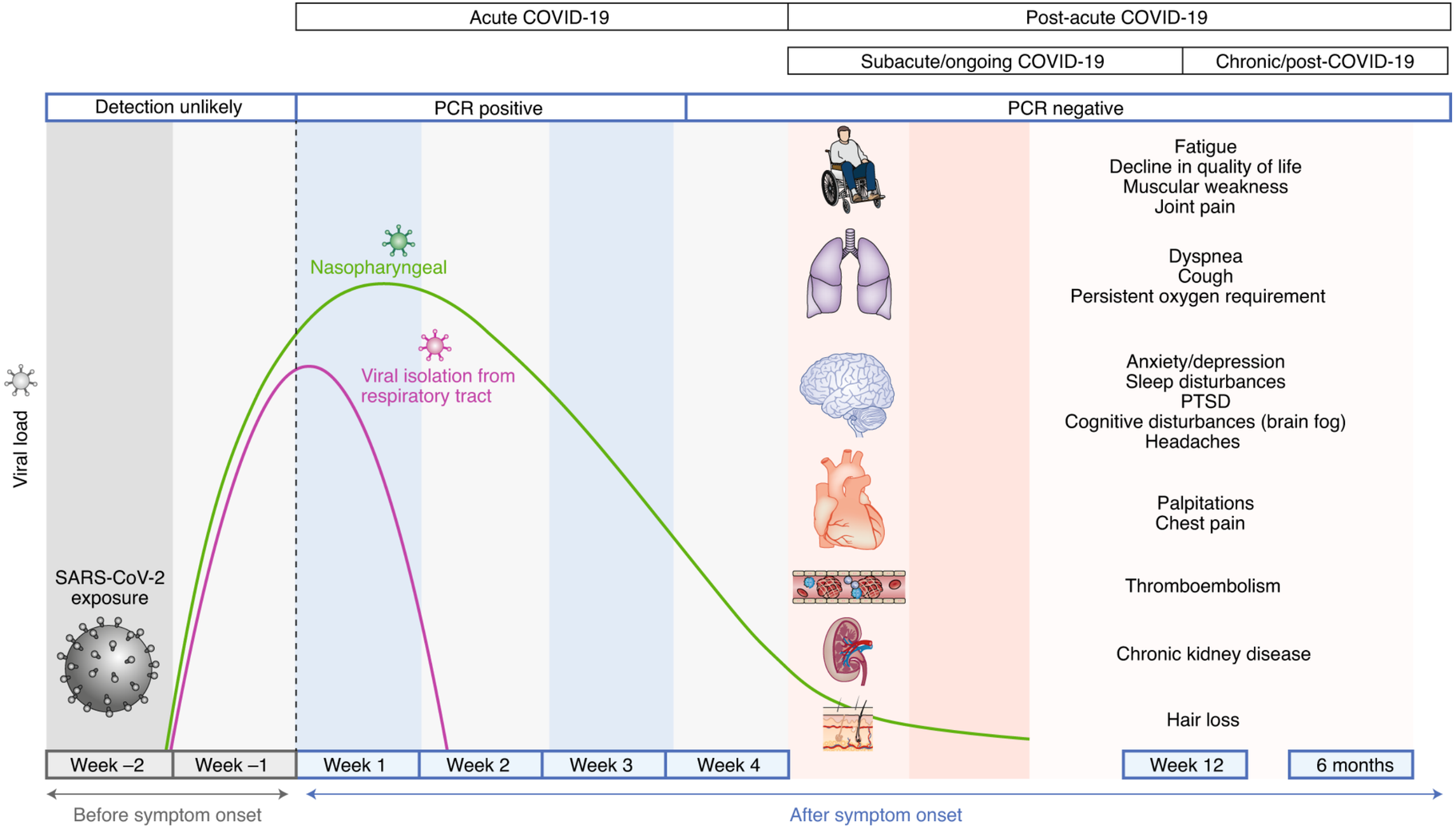
- Antibody responses
  - Immunoglobulin M (IgM): acute indicator
  - Immunoglobulin G (IgG): most abundant, can indicate past OR current infection
  - Immunoglobulin A (IgA): produced in mucosal tissues
- Most patients sero-convert within 10-15 days
- For some, seroconversion ≠ viral clearance
- Ab titers as a surveillance and epidemiological tool

CLINICAL PRESENTATION: SYMPTOMS

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

EMERGENCY SIGNS: trouble breathing, persistent pain or pressure in chest, confusion, inability to wake or stay awake, pale, gray, or blue colored skin, lips, or nail beds

CLINICAL PRESENTATION: LONG COVID



(Nalbandian et al., 2021)

CLINICAL PRESENTATION: RISK FACTORS

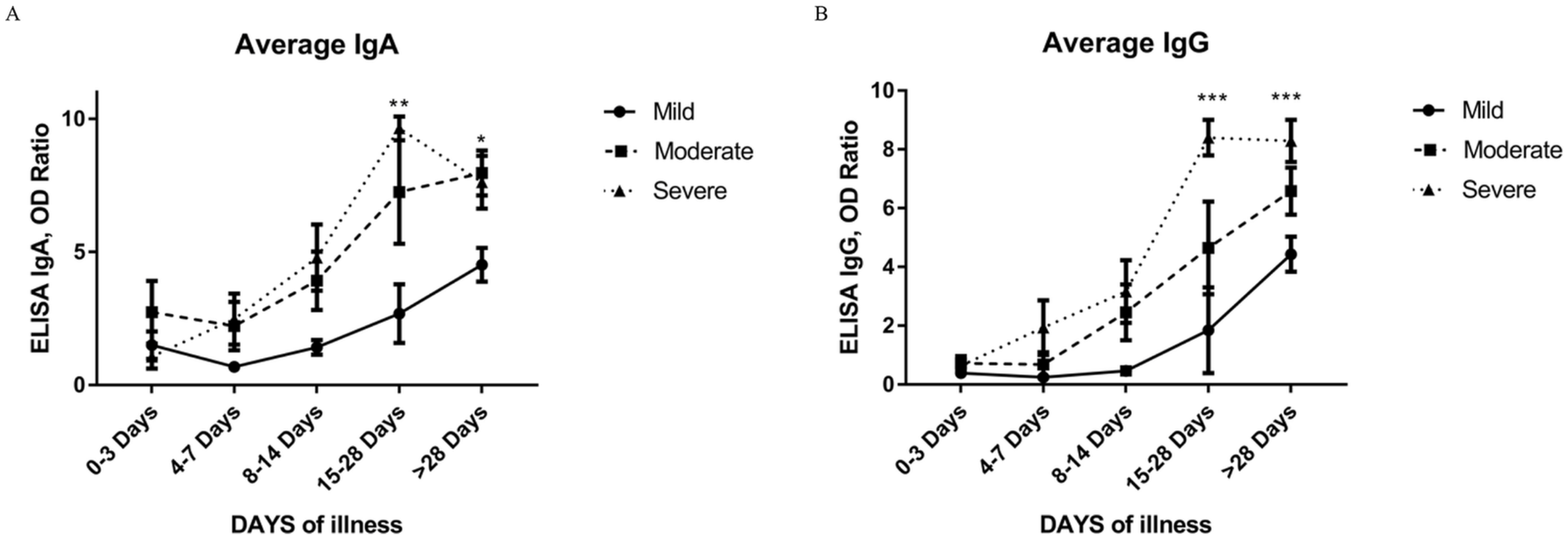
	0-4 years old	5-17 years old	18-29 years old	30-39 years old	40-49 years old	50-64 years old	65-74 years old	75-84 years old	85+ years old
Cases[2]	<1x	1x	Reference group	1x	1x	1x	1x	1x	1x
Hospitalization[3]	<1x	<1x	Reference group	2x	2x	4x	6x	9x	15x
Death[4]	<1x	<1x	Reference group	4x	10x	35x	95x	230x	600x

18-29 was selected as the reference group because it has accounted for the largest cumulative number of COVID-19 cases compared to all other age groups

- Risk factors for severe illness
  - Age
  - Race/ethnicity
  - Gender
  - Some medical conditions
  - Use of certain medications
  - Poverty and crowding
  - Certain occupations
  - Pregnancy

(CDC, 2021)

CLINICAL PRESENTATION: INDICATORS



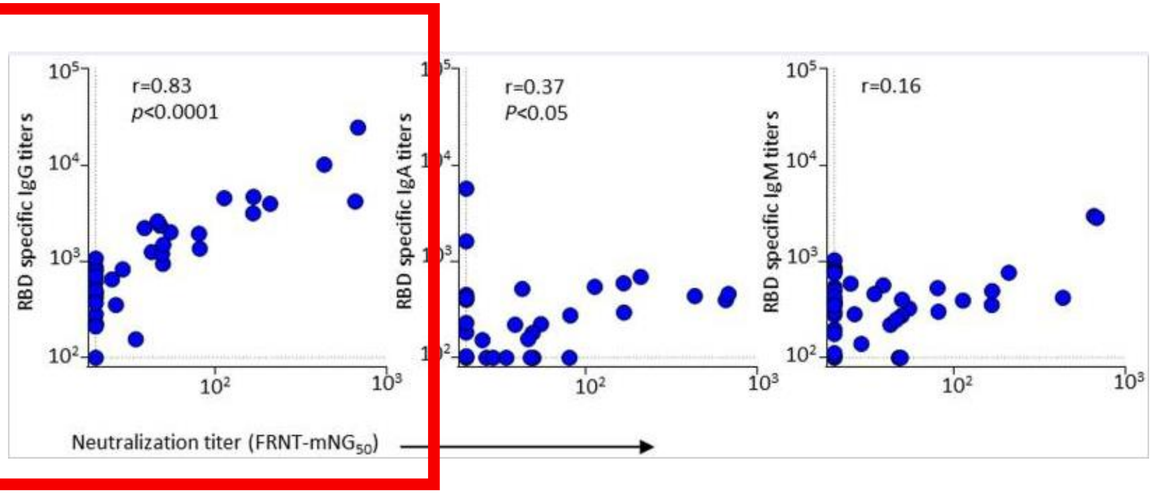
Magnitude of antibody response has been suggested as a possible indicator of clinical severity.

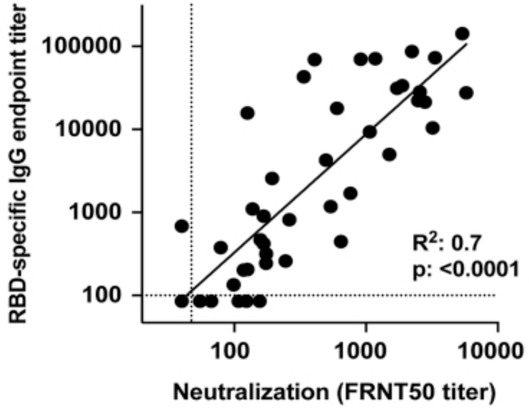
(Kowitdamrong et al., 2021)

CLINICAL PRESENTATION: MECHANISMS

- Higher antibody levels (IgA, IgG, and total Ab) have been found to be associated with:
  - Male sex
  - Older age
  - Hospitalization
- Why?
  - Mechanisms currently unclear
  - Potential role of IgA in mediating the pro-inflammatory response
    - Commonly seen organ impacts
    - Reduced inflammatory response/cytokines in asymptomatic individuals with low Ab levels

ANTIBODY RESPONSE: IMPLICATIONS





- Are IgM, IgG, or IgA levels correlated with a neutralizing response?
  - Positive correlation with IgG
  - Persistence of immunity following natural infection may not be sufficient
    - Asymptomatic vs mild or severe cases
    - Age may also affect length of maintenance

(Nayak et al.., 2021)

(Suthar et al.., 2021)

ANTIBODY RESPONSE

- Current predicted length of immunity: at least 90 days
  - Could be affected by variants
  - Shorter than immunity from SARS-CoV
  - Basis for vaccination even after infection

VACCINES: EFFECTIVENESS

	PFIZER/BIONTECH VACCINE	MODERNA VACCINE	J&J VACCINE
TARGET POPULATION	People ages 16 and older.	People ages 18 and older.	People ages 18 and older.
VACCINE ADMINISTRATION	Two shots are required.	Two shots are required.	One shot is required.
AMOUNT OF TIME BETWEEN DOSES	Delivered 21 days apart.	Delivered 28 days apart.	N/A
VACCINE EFFICACY	95% effective at preventing symptomatic COVID-19 infection.	94.1% effective at preventing symptomatic COVID-19 infection.	66.9% effective at preventing symptomatic COVID-19 infection.

March 15, 2021

www.CDC.gov

(ASTHO, 2021)

VACCINES: EFFECTIVENESS

- Unvaccinated, previously infected patients at higher odds of reinfection

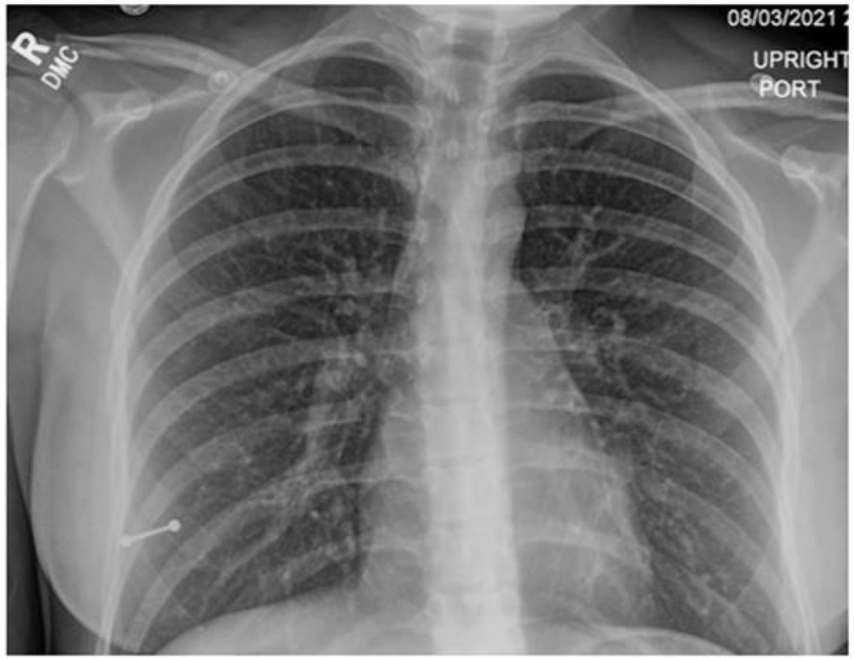
TABLE 2. Association of SARS-CoV-2 reinfection* with COVID-19 vaccination status — Kentucky, May–June 2021

Return

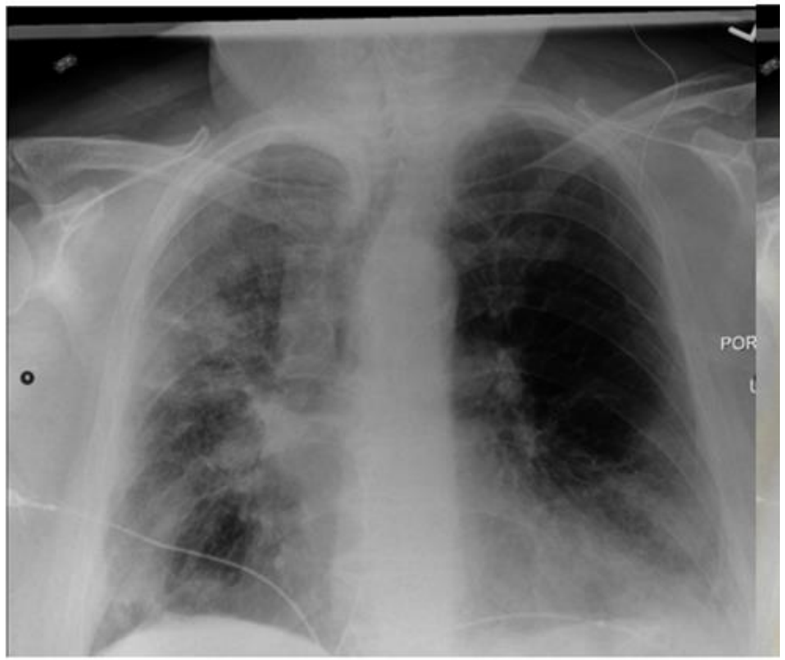
Vaccination status	No. (%)		OR (95% CI)†
	Case-patients	Control participants	
Not vaccinated	179 (72.8)	284 (57.7)	2.34 (1.58–3.47)
Partially vaccinated¶	17 (6.9)	39 (7.9)	1.56 (0.81–3.01)
Fully vaccinated§	50 (20.3)	169 (34.3)	Ref
Total	**246 (100)**	**492 (100)**	—

(Cavanaugh et al., 2021)

VACCINES: EFFECTIVENESS



Vaccinated patient with COVID-19

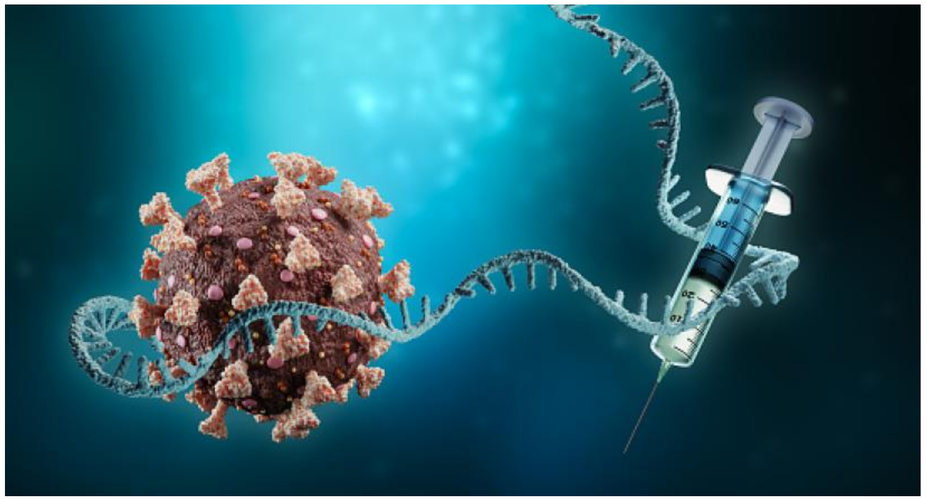


Unvaccinated patient with COVID-19

Picture by UC San Diego

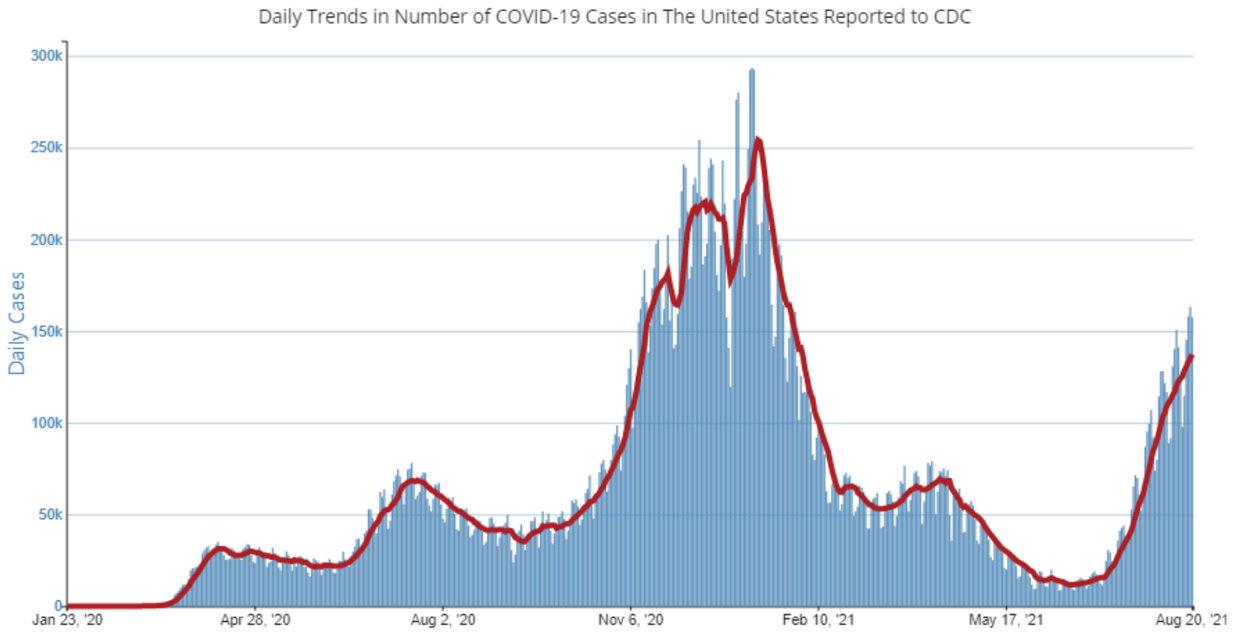
VACCINES: ANTIBODY OUTCOMES

- Antibodies induced by an mRNA COVID-19 vaccine are more targeted to the RBD
- Why?
  - Altered antigen presentation via mRNA delivery
  - Site of exposure (respiratory tract vs arm)
- Encompasses coverage against broader range of mutations
  - Fragile balance as long as virus continues to spread uncontrolled



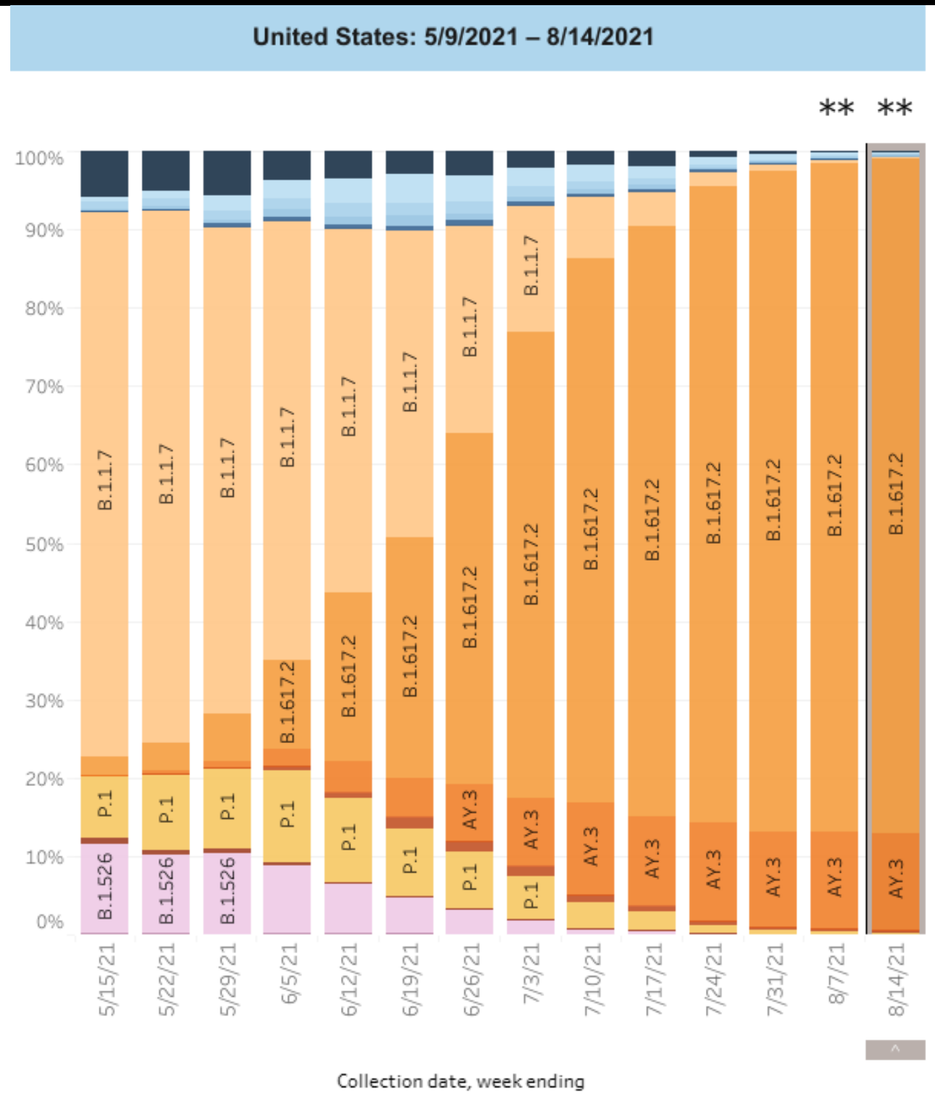
VARIANTS: THE DEAL WITH DELTA

- First identified in India
- Rapidly asserted dominance over other variants - over 2x more contagious
- Potential to cause more severe cases
  - Breakthrough infections
  - Transmission by the vaccinated, although for a shorter period



(CDC, 2021)

VARIANTS: THE LANDSCAPE



United States: 8/8/2021 – 8/14/2021 NOWCAST

USA

WHO label	Lineage #	Type	%Total	95%PI
Alpha	B.1.1.7	VOC	0.3%	0.0-1.0%
Beta	B.1.351	VOC	0.0%	0.0-0.2%
Gamma	P.1	VOC	0.2%	0.0-0.7%
Delta	B.1.617.2	VOC	86.1%	82.6-89.4%
	AY.3	VOC	12.3%	9.1-15.7%
	AY.2	VOC	0.3%	0.0-1.0%
	AY.1	VOC	0.1%	0.0-0.2%
Eta	B.1.525	VOI	0.0%	0.0-0.2%
Iota	B.1.526	VOI	0.0%	0.0-0.2%
N/A	B.1.621		0.4%	0.0-1.0%
	B.1.621.1		0.1%	0.0-0.5%
	B.1.628		0.1%	0.0-0.5%
	A.2.5		0.0%	0.0-0.2%
	B.1.626		0.0%	0.0-0.2%
	B.1.617.1	VOI	0.0%	0.0-0.2%
	B.1.617.3	VOI	0.0%	0.0-0.2%
Other	Other*		0.0%	0.0-0.2%

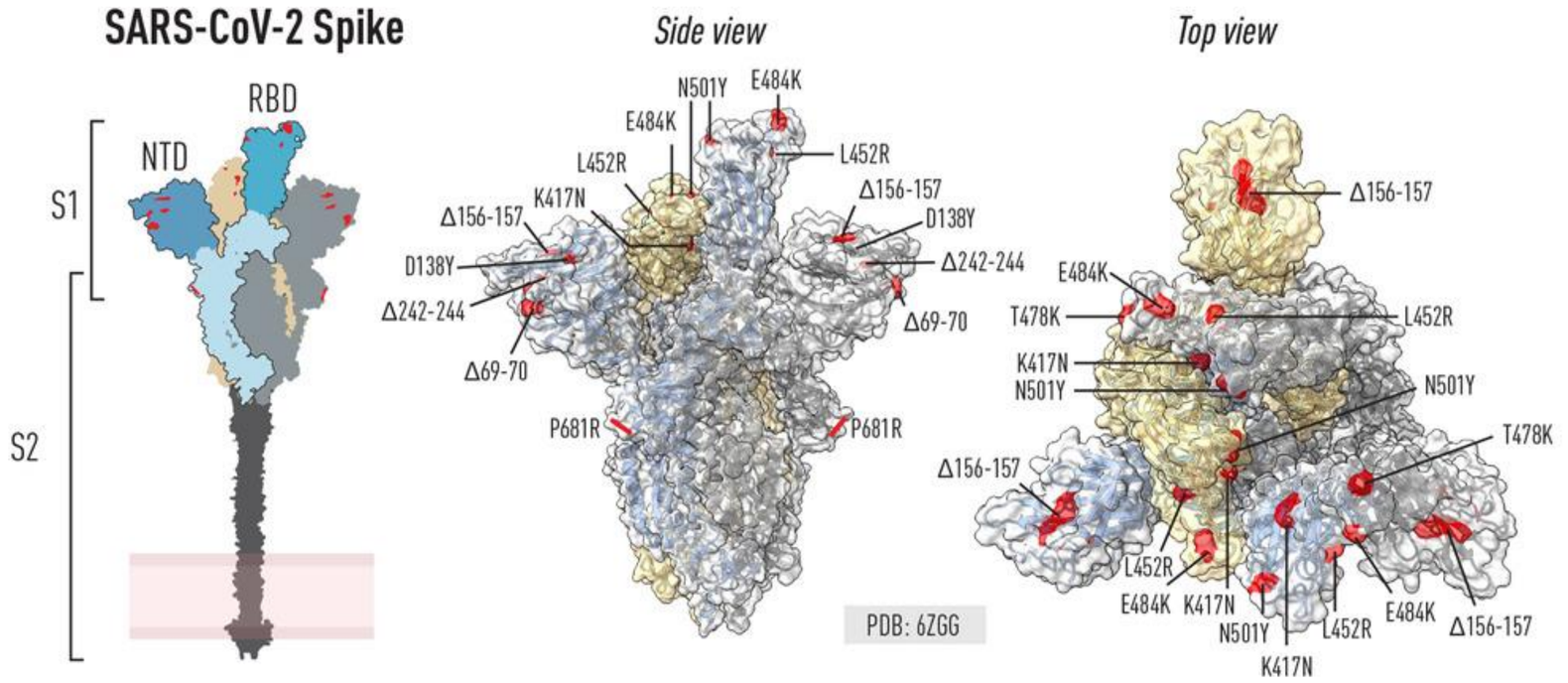
* Enumerated lineages are VOI/VOC or are circulating >1% in at least one HHS region during at least one two week period; remaining lineages are aggregated as "Other".

** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates

Sublineages of P.1 and B.1.351 are aggregated with the parent lineage and included in parent lineage's proportion. AY.3.1 is aggregated with its parent lineage AY.3. AY.4-AY.12 aggregated with B.1.617.2

(CDC, 2021)

VARIANTS: WHAT CHANGED?



Variants of concern

Alpha (B.1.1.7)
N501Y, Δ69-70

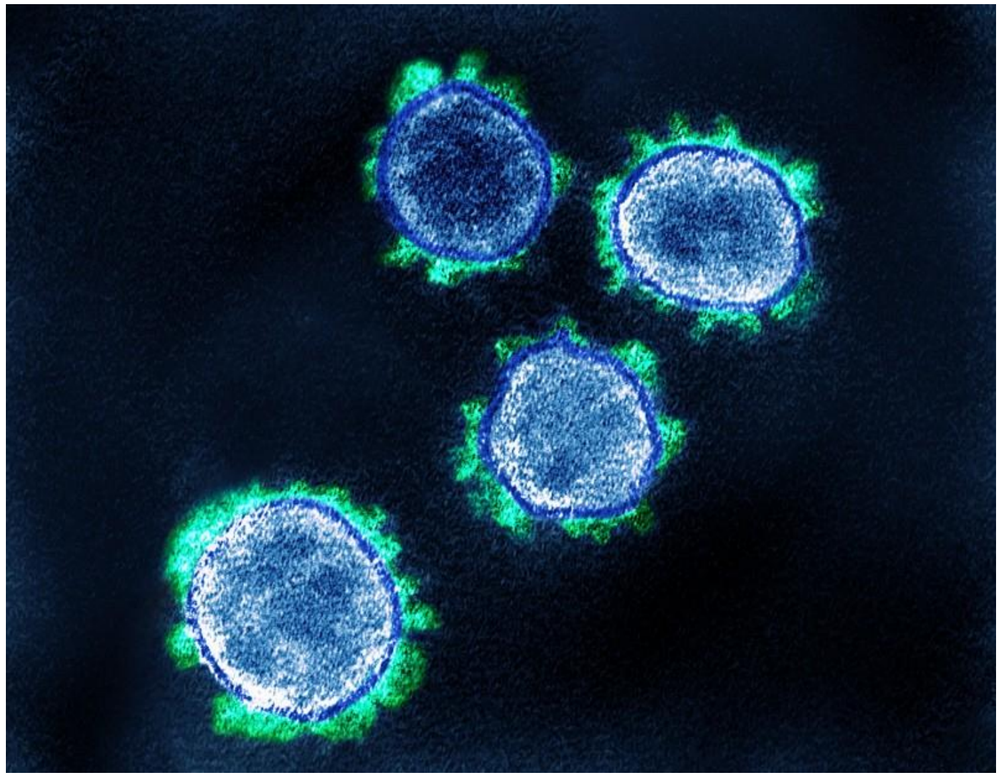
Beta (B.1.351)
Δ242-244, K417N, E484K, N501Y

Gamma (P.1)
D138Y, K417N, E484K, N501Y

Delta (B.1.617.2)
Δ156-157, T478K, L452R, P681R

(Dopico et al.., 2021)

VARIANTS: WHY DELTA?



- Spotlight on mutation to P681R
  - Alters amino acid sequence
    - Increases efficiency of cleaving between S1/S2
- Role of the mutation still unclear
  - Kappa also altered P681R
    - Had much less efficiency

LOOKING FORWARD: CHALLENGES

- Vaccines continue to hold against severe disease, hospitalization, and death
  - Appear to be less effective against symptomatic disease
  - The case for boosters?
    - Global equity concerns
- Outrunning the variant clock

LOOKING FORWARD: OPPORTUNITIES

- Origins and biological response
- Antibody response and prognosis
- Pathogenetic mechanisms of SARS-CoV-2
- The race to vaccinate

THANK YOU

Questions?

Shalini Nair, MPH

Add me on LinkedIn!

REFERENCES

1. Andersen, K. G., Rambaut, A., Lipkin, W. I., Holmes, E. C., & Garry, R. F. (2020). The proximal origin of SARS-CoV-2. *Nature Medicine*, *26*(4), 450–452. https://doi.org/10.1038/s41591-020-0820-9
2. ASTHO. (2021). *ASTHO COVID Vaccine Comparison*. https://astho.org/COVID-19/Vaccine-Comparison/
3. Cavanaugh, A. M. (2021). Reduced Risk of Reinfection with SARS-CoV-2 After COVID-19 Vaccination—Kentucky, May–June 2021. *MMWR. Morbidity and Mortality Weekly Report*, *70*. https://doi.org/10.15585/mmwr.mm7032e1
4. CDC. (2020a, February 11). *Cases, Data, and Surveillance*. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html
5. CDC. (2020b, March 28). *COVID Data Tracker*. Centers for Disease Control and Prevention. https://covid.cdc.gov/covid-data-tracker
6. Cevik, M., Kuppalli, K., Kindrachuk, J., & Peiris, M. (2020). Virology, transmission, and pathogenesis of SARS-CoV-2. *BMJ*, *371*, m3862. https://doi.org/10.1136/bmj.m3862
7. Dopico, X. C., Ols, S., Loré, K., & Hedestam, G. B. K. (n.d.). Immunity to SARS-CoV-2 induced by infection or vaccination. *Journal of Internal Medicine*, *n/a*(n/a). https://doi.org/10.1111/joim.13372
8. *Here's how lung X-rays look between vaccinated and unvaccinated patients*. (2021, August 6). Cbs8.Com. https://www.cbs8.com/article/news/health/ucsd-doctor-compares-lung-x-rays-of-vaccinated-versus-unvaccinated-patients-with-covid-19-coronavirus/509-10421f75-4f41-4eb9-9db8-9a3eb95110c0
9. Iwasa, J. (2021). *SARS-CoV-2 Visualization and Annotation Project*. The Animation Lab. https://animationlab.utah.edu/cova
10. Kowitdamrong, E., Puthanakit, T., Jantarabenjakul, W., Prompetchara, E., Suchartlikitwong, P., Putcharoen, O., & Hirankarn, N. (2021). Antibody responses to SARS-CoV-2 in patients with differing severities of coronavirus disease 2019. *PLOS ONE*, *15*(10), e0240502. https://doi.org/10.1371/journal.pone.0240502
11. Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M. V., McGroder, C., Stevens, J. S., Cook, J. R., Nordvig, A. S., Shalev, D., Sehrawat, T. S., Ahluwalia, N., Bikdeli, B., Dietz, D., Der-Nigoghossian, C., Liyanage-Don, N., Rosner, G. F., Bernstein, E. J., Mohan, S., Beckley, A. A., … Wan, E. Y. (2021). Post-acute COVID-19 syndrome. *Nature Medicine*, *27*(4), 601–615. https://doi.org/10.1038/s41591-021-01283-z
12. Nayak, K., Gottimukkala, K., Kumar, S., Reddy, E. S., Edara, V. V., Kauffman, R., Floyd, K., Mantus, G., Savargaonkar, D., Goel, P. K., Arora, S., Rahi, M., Davis, C. W., Linderman, S., Wrammert, J., Suthar, M. S., Ahmed, R., Sharma, A., Murali-Krishna, K., & Chandele, A. (2021). Characterization of neutralizing versus binding antibodies and memory B cells in COVID-19 recovered individuals from India. *Virology*, *558*, 13–21. https://doi.org/10.1016/j.virol.2021.02.002
13. Scudellari, M. (2021). How the coronavirus infects cells—And why Delta is so dangerous. *Nature*, *595*(7869), 640–644. https://doi.org/10.1038/d41586-021-02039-y
14. Shah, P., Canziani, G. A., Carter, E. P., & Chaiken, I. (2021). The Case for S2: The Potential Benefits of the S2 Subunit of the SARS-CoV-2 Spike Protein as an Immunogen in Fighting the COVID-19 Pandemic. *Frontiers in Immunology*, *12*, 508. https://doi.org/10.3389/fimmu.2021.637651
15. Shors, T. (2021). Coronavirus. *Access Science*. https://doi.org/10.1036/1097-8542.163220
16. Singh, R. (2021, July 30). *[Figure, SARS- CoV 2 Structure.; Made with Biorender.com]* [Text]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK554776/figure/article-52171.image.f3/
17. Suthar, M. S., Zimmerman, M. G., Kauffman, R. C., Mantus, G., Linderman, S. L., Hudson, W. H., Vanderheiden, A., Nyhoff, L., Davis, C. W., Adekunle, O., Affer, M., Sherman, M., Reynolds, S., Verkerke, H. P., Alter, D. N., Guarner, J., Bryksin, J., Horwath, M. C., Arthur, C. M., … Wrammert, J. (2020). Rapid Generation of Neutralizing Antibody Responses in COVID-19 Patients. *Cell Reports Medicine*, *1*(3), 100040. https://doi.org/10.1016/j.xcrm.2020.100040