SISMID 2021: Immunology of Viruses

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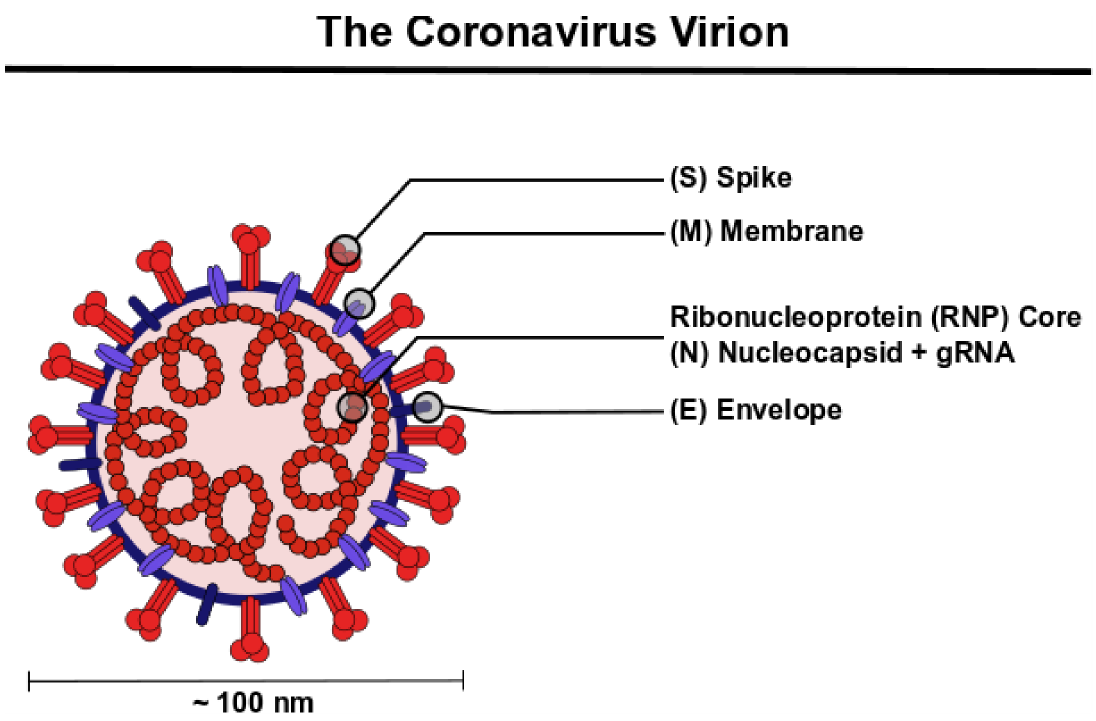
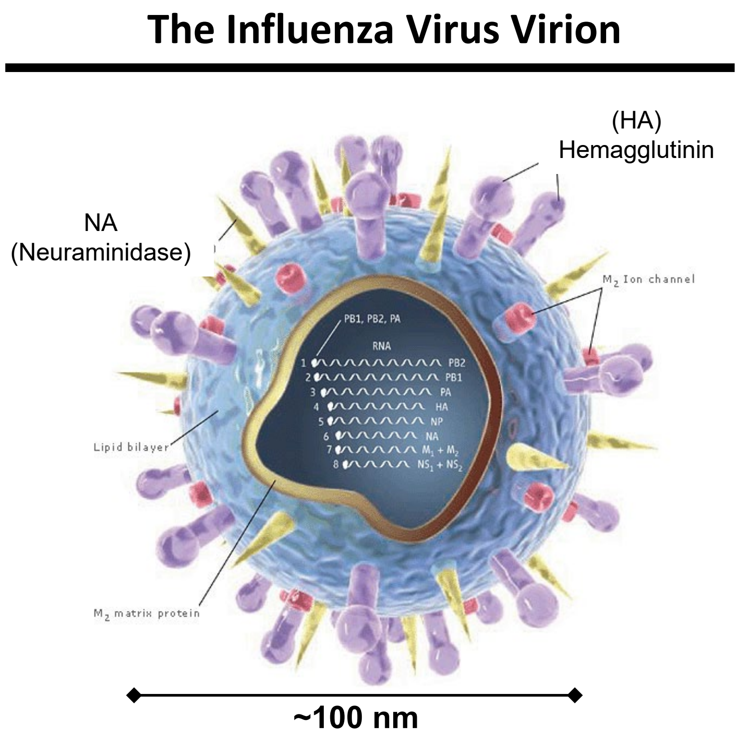
Outline of talk

- Background on SARS-CoV-2/coronaviruses
- Immune mechanisms of viral control
- Vaccine platforms
- Results from vaccination efforts
- Emergence of viral variants

SARS-CoV-2 vs. Influenza virus



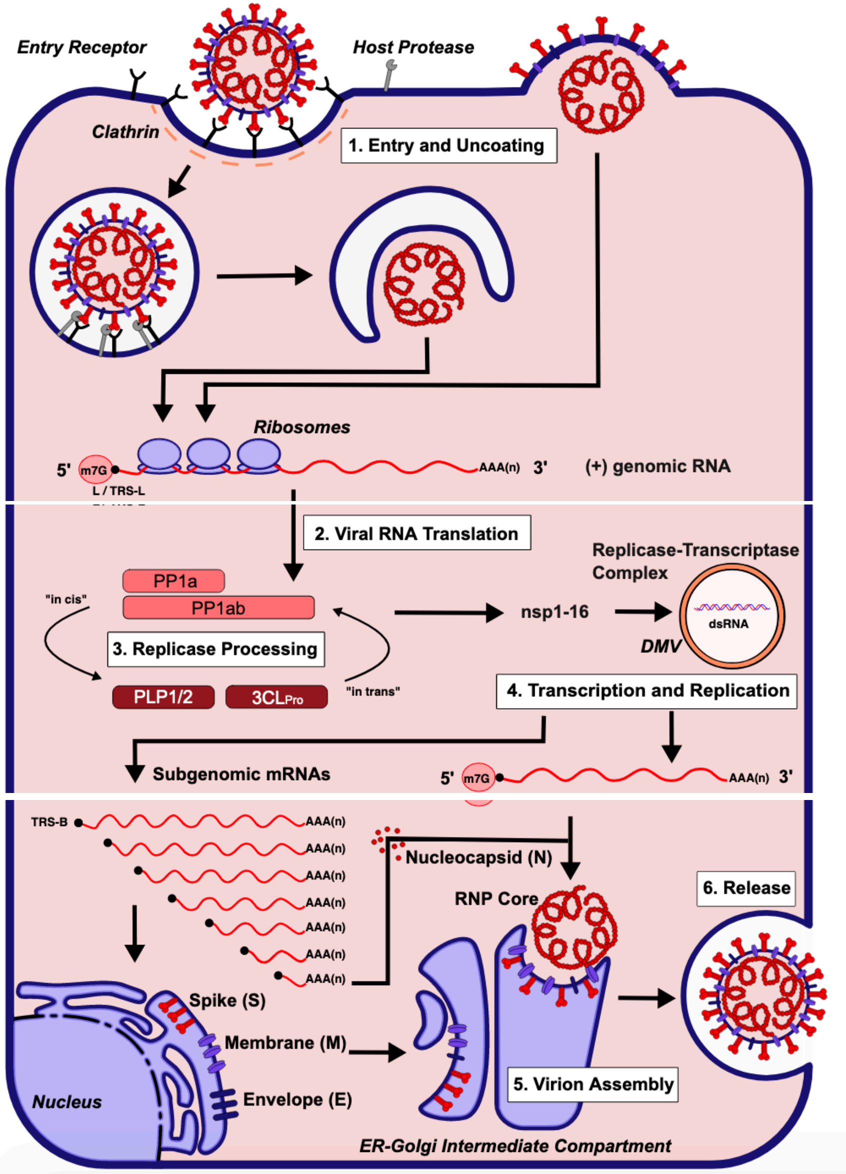


(+) ssRNA genome ~28-32 Kb
29 proteins

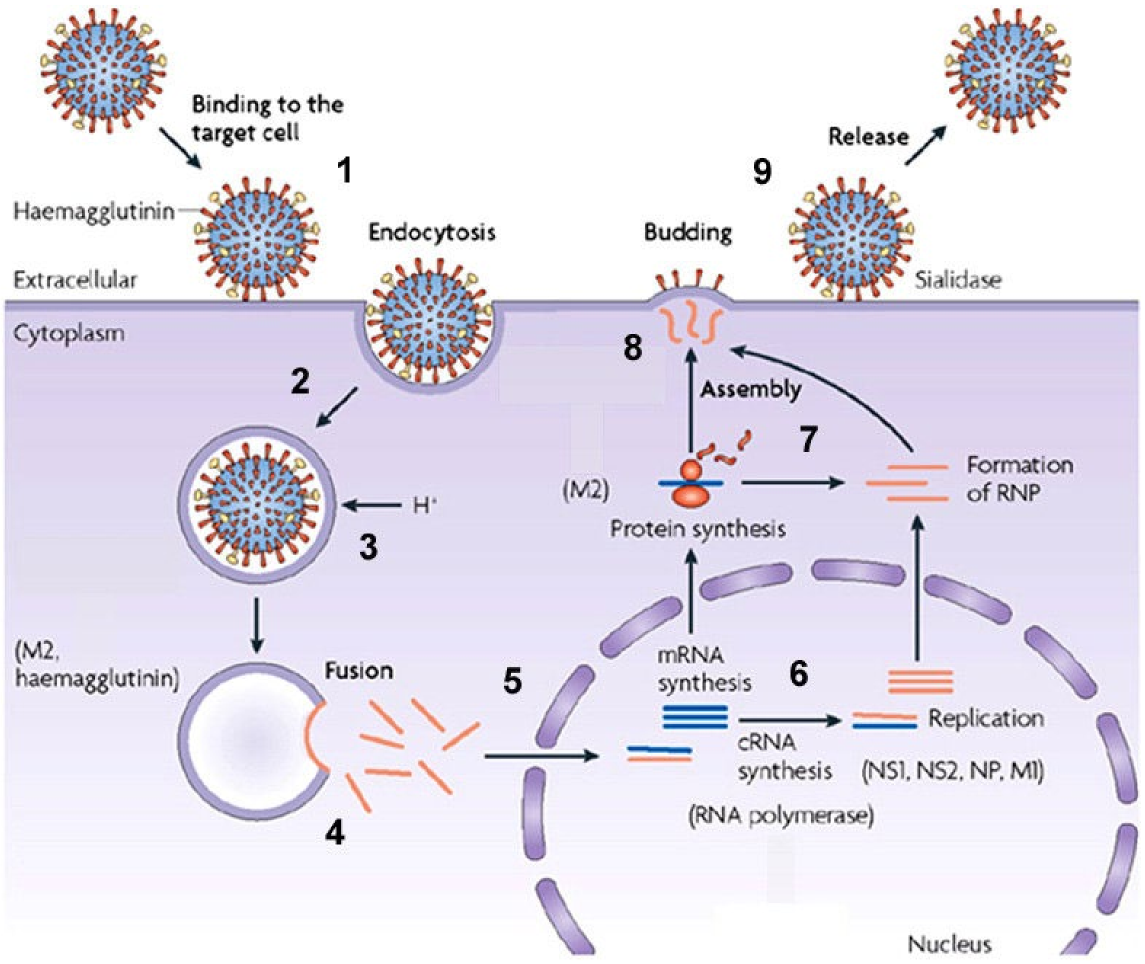
(-) segmented ssRNA genome ~28-32 Kb
~14 Kb, 10-14 proteins

Coronavirus and influenza virus replication cycles

Coronavirus

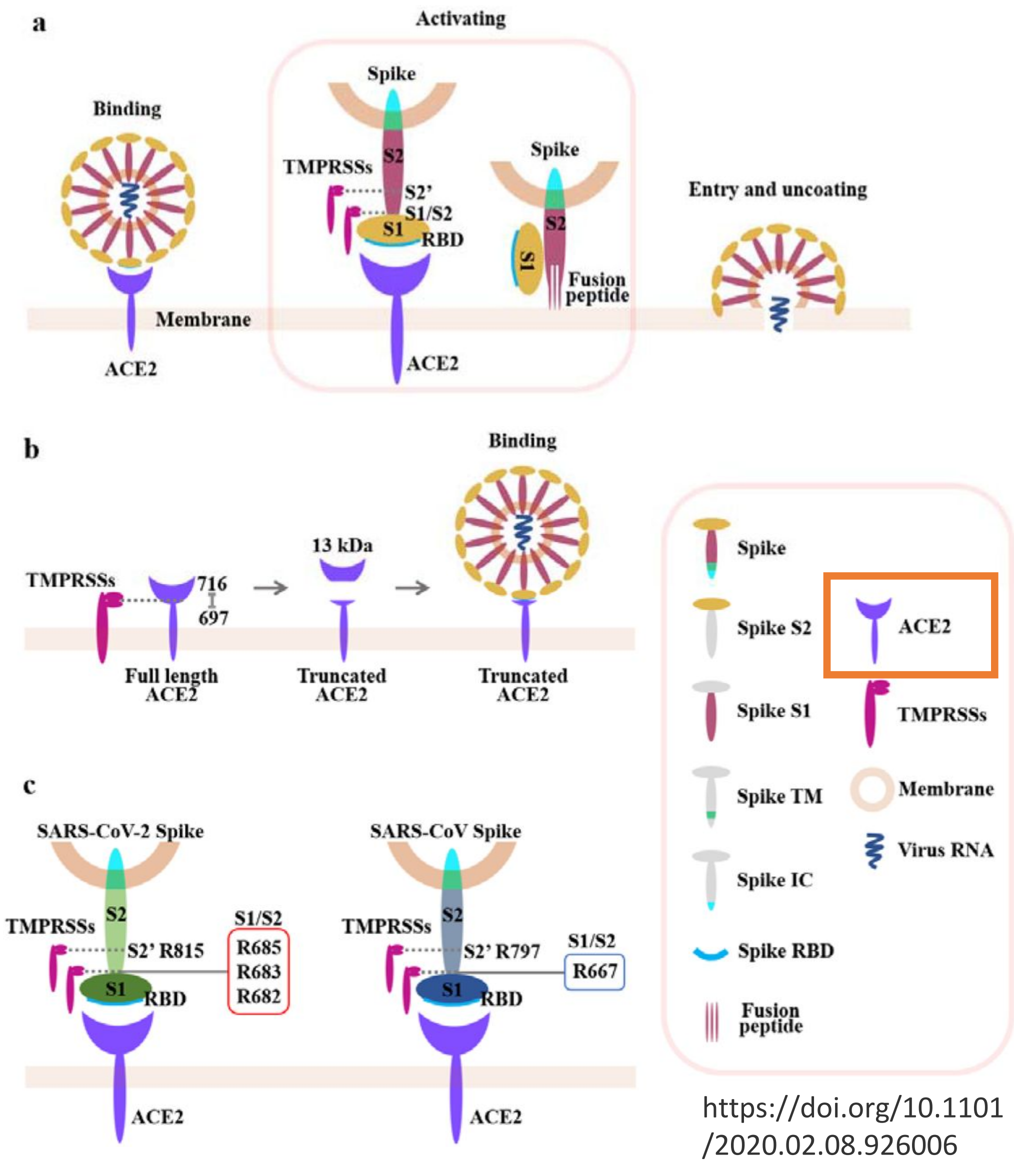


Influenza virus



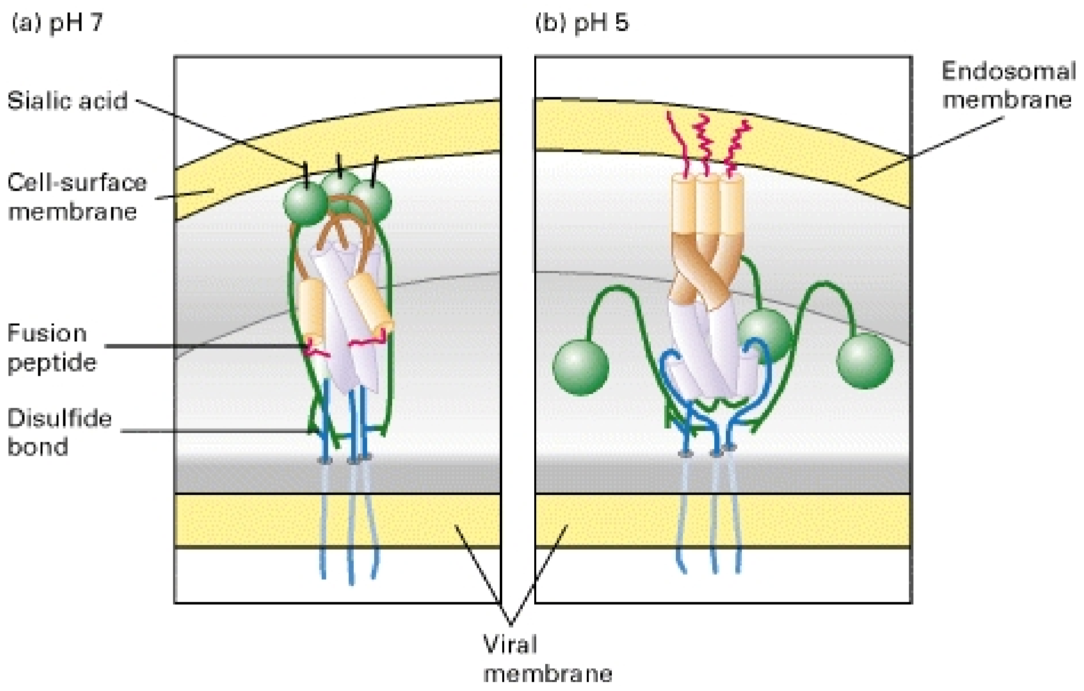
Distinct receptor binding features of SARS vs. influenza viruses

Coronavirus



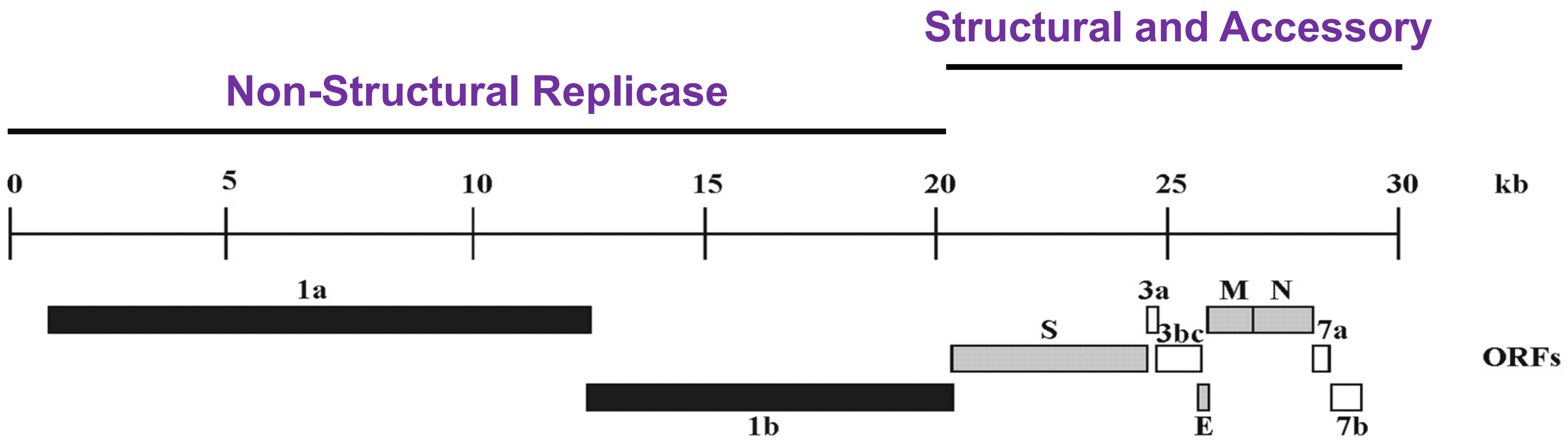
https://doi.org/10.1101/2020.02.08.926006

Influenza virus



Influenza HA binds to sialic acid residues on diverse surface proteins

Coronavirus Genome Encodes Several IFN Antagonists



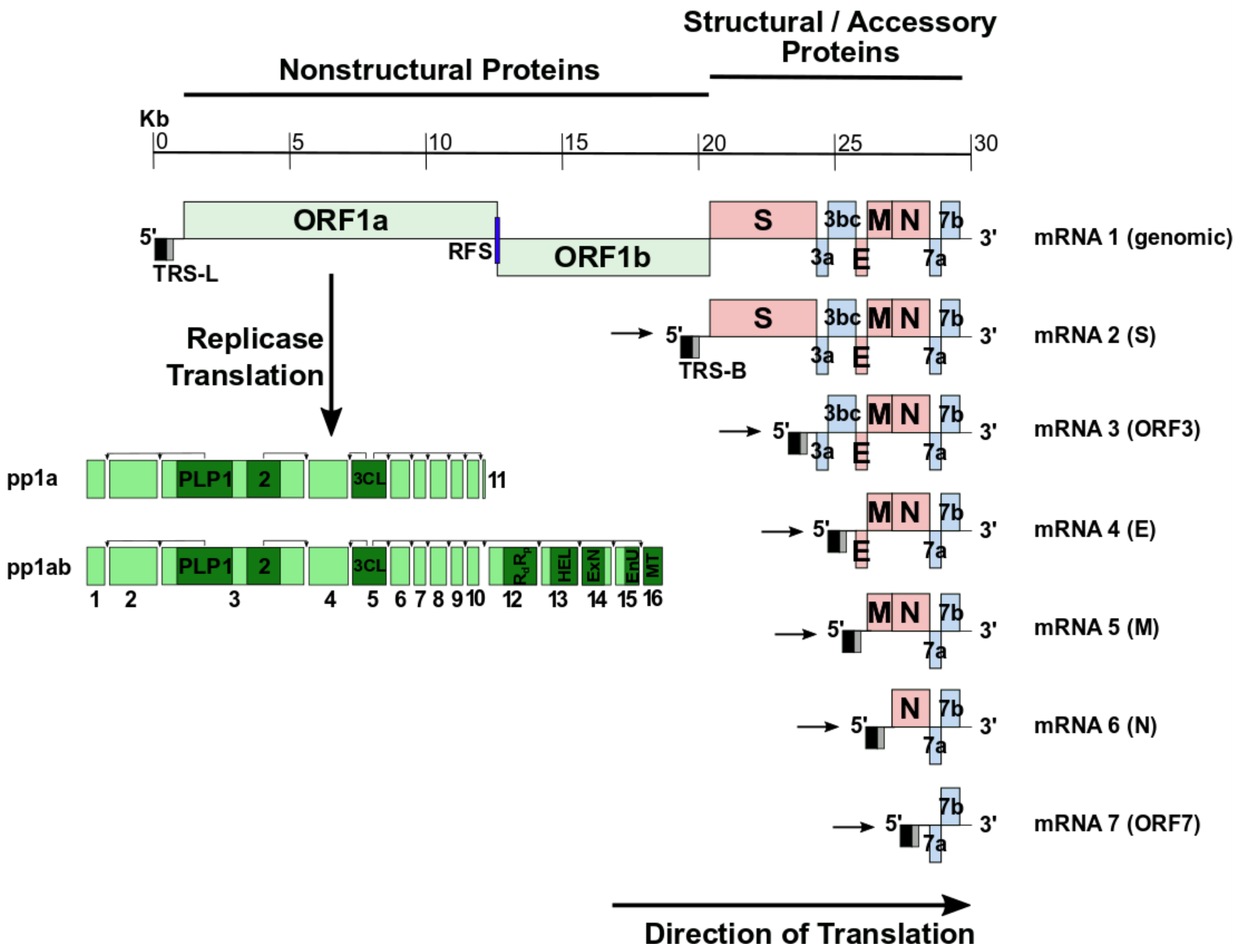
1. Non-Structural Proteins (nsp1-16)

Conserved across CoVs
Various, required functions
IFN antagonists: nsp1, PLP2 (nsp3)

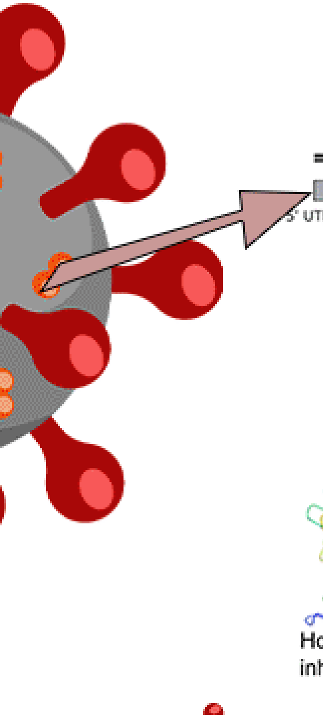
2. Accessory Proteins

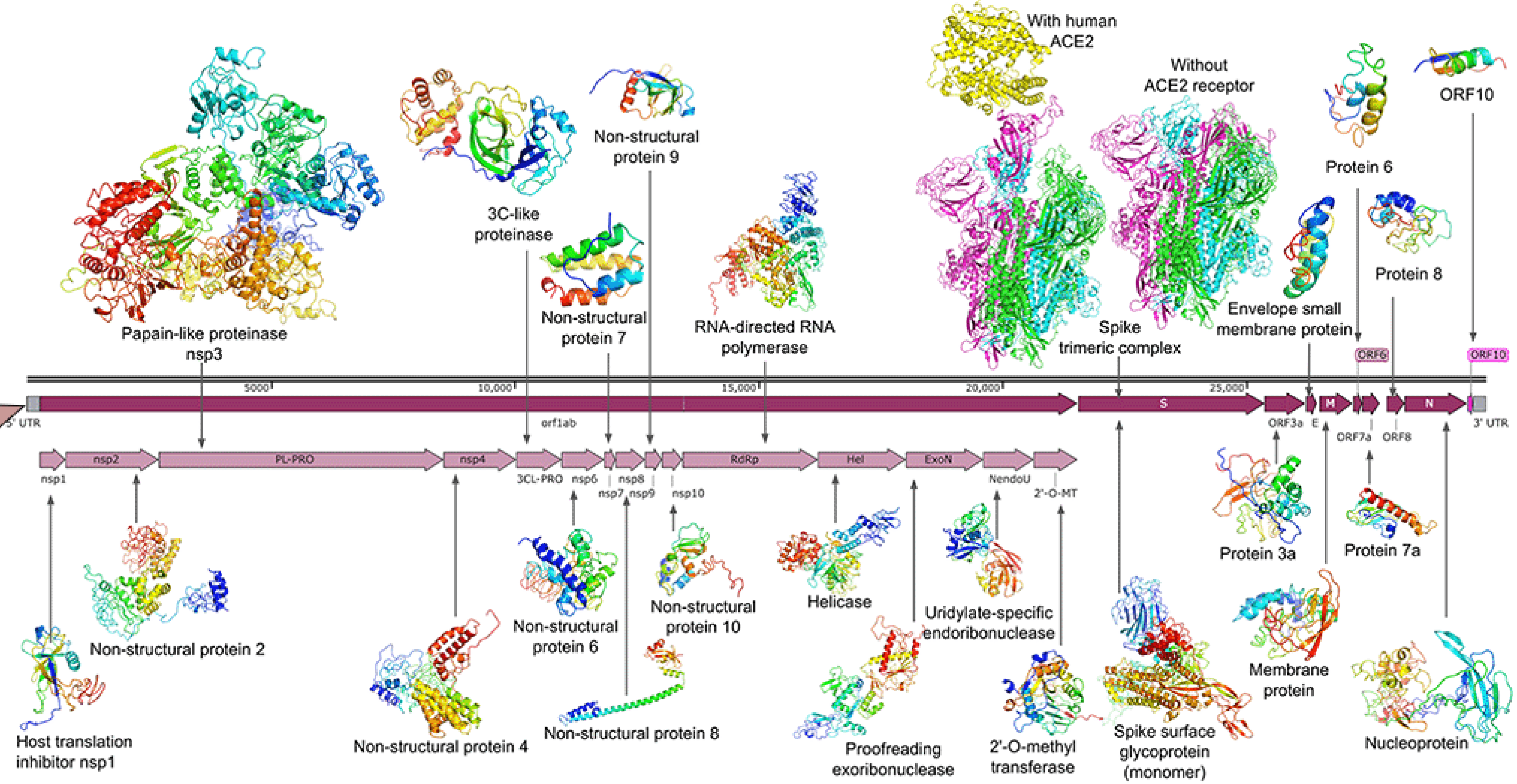
Unique to subfamilies and species
Function dispensable for replication
Encode virulence factors

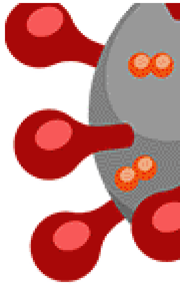
Coronavirus Genome Structure and Duplication



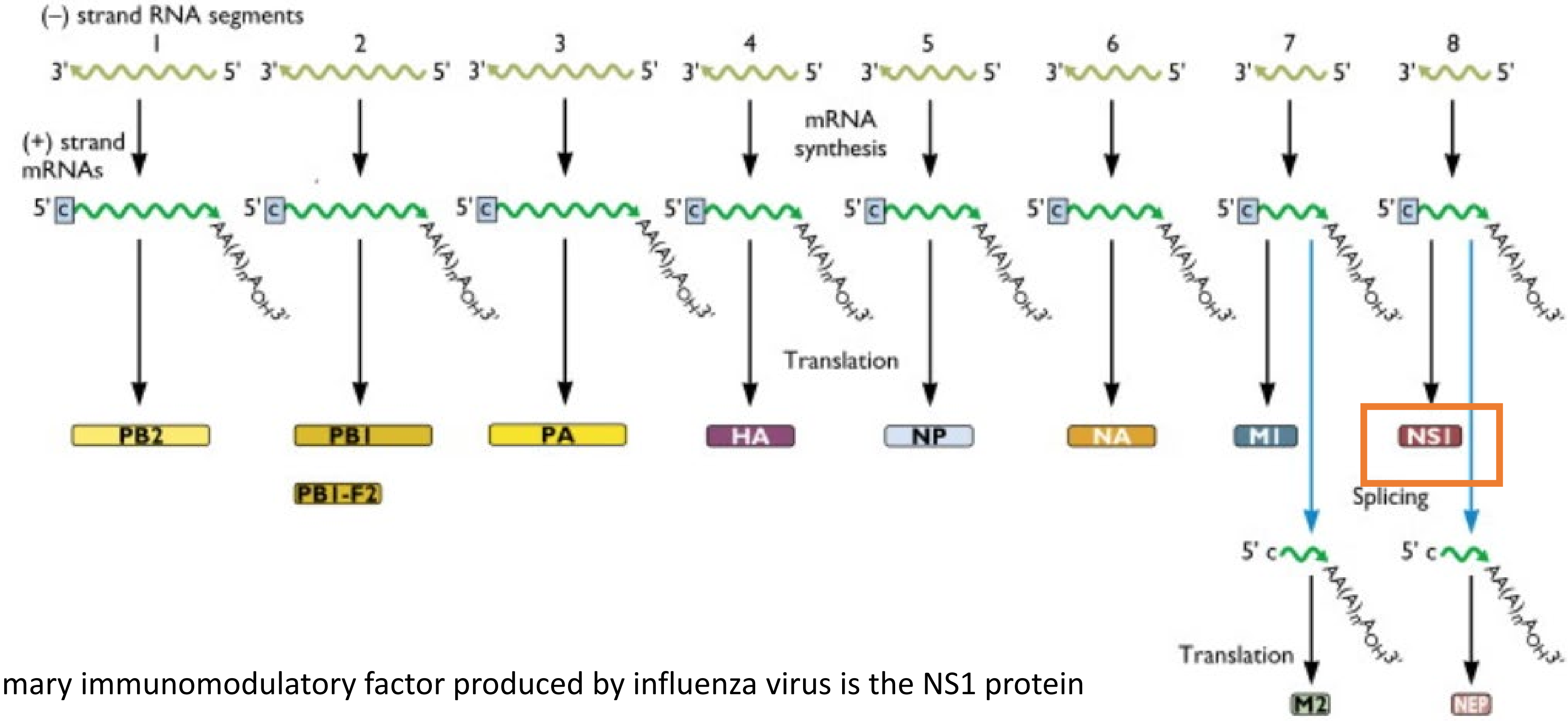
Large SARS-Cov-2 proteome contains many immunomodulatory non-structural proteins







The segmented influenza virus genome



The primary immunomodulatory factor produced by influenza virus is the NS1 protein

NS1 primarily acts by sequestering RNA ligands from host cell recognition

SARS-CoV-2 vs. influenza virus summary

SARS-CoV-2

- RNA virus (+ sense)
- Single segment
- Large genome
- Multiple immune antagonists
- Specific receptor (ACE2)

Influenza virus

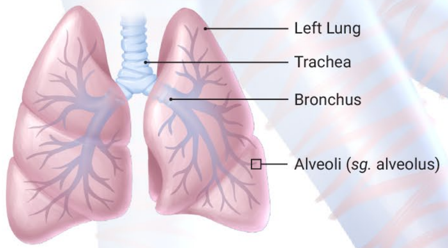
- RNA virus (- sense)
- 8 segments
- Much smaller genome (than CoV)
- Single immune antagonist (ds RNA sequestration)
- Non-specific receptor

COVID-19

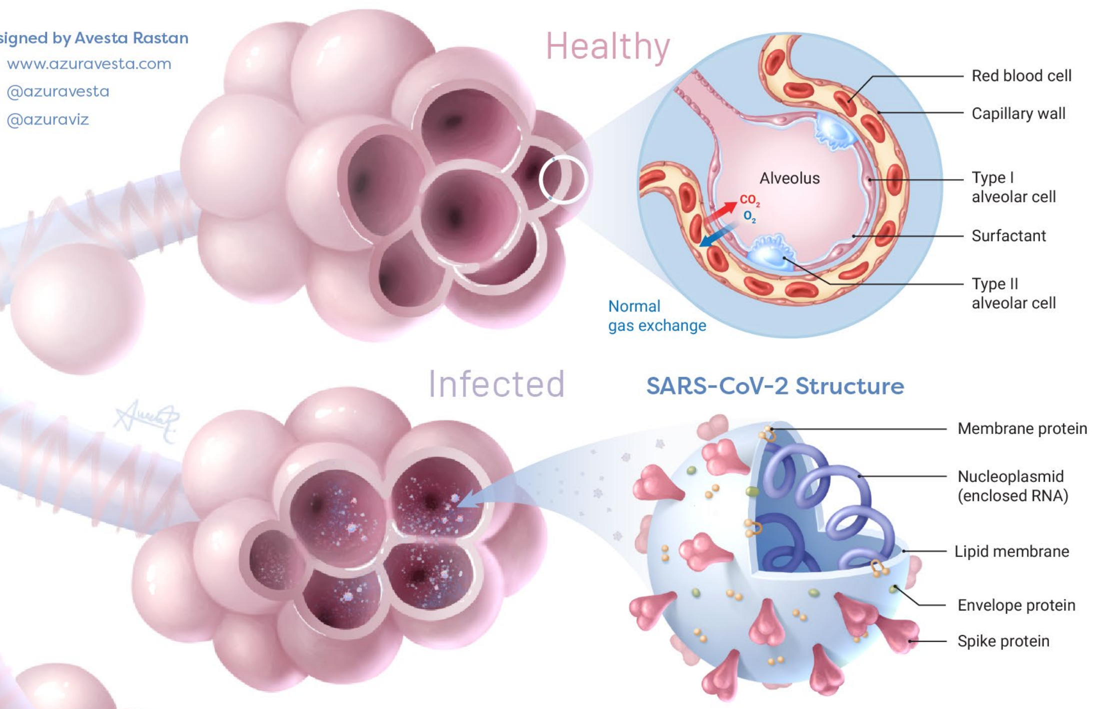
HOW DOES IT AFFECT YOU?

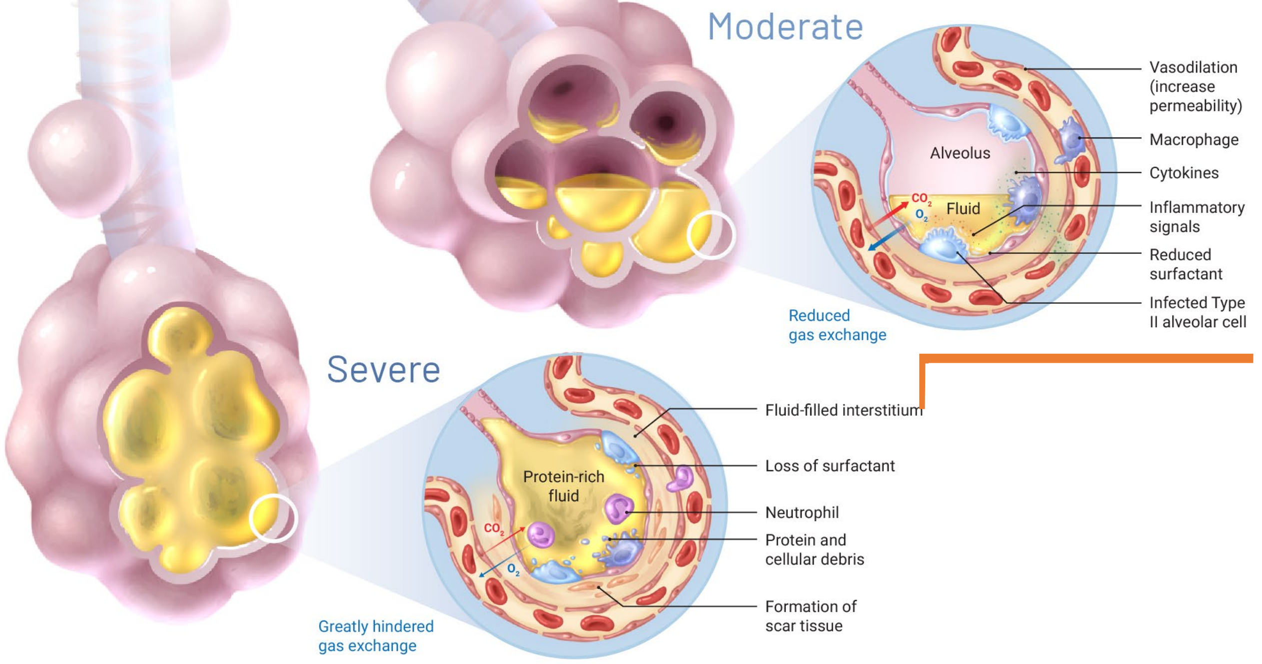
Designed by Avesta Rastan
www.azuravesta.com
@azuravesta
@azuraviz

Coronavirus Disease 2019 (COVID-19) is a pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2, also called SARS-CoV-2. Despite the widespread awareness regarding COVID-19, many are still unaware about how it affects the human body.



SARS-CoV-2 starts its journey in the nose, mouth, or eyes and travels down to the alveoli in the lungs. Alveoli are tiny sacs of air where gas exchange occurs.





COVID-19 is characterized by lung disease

Even asymptomatic patients show signs of lung involvement (ground glass opacities)

Only developed a mildly productive cough for two days

IMAGES IN PULMONARY, CRITICAL CARE, SLEEP MEDICINE AND THE SCIENCES

An Asymptomatic Patient with COVID-19

Jingping Zhang[1], Yonghao Du[1], Lu Bai[1], Jiantao Pu[2,3], Chenwang Jin[1], Jian Yang[1], and Youmin Guo[1]

[1]Department of Radiology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, P.R. China; and [2]Department of Radiology and [3]Department of Bioengineering, University of Pittsburgh, Pittsburgh, Pennsylvania

ORCID IDs: 0000-0002-8105-1576 (J.Z.); 0000-0002-2278-0496 (C.J.).

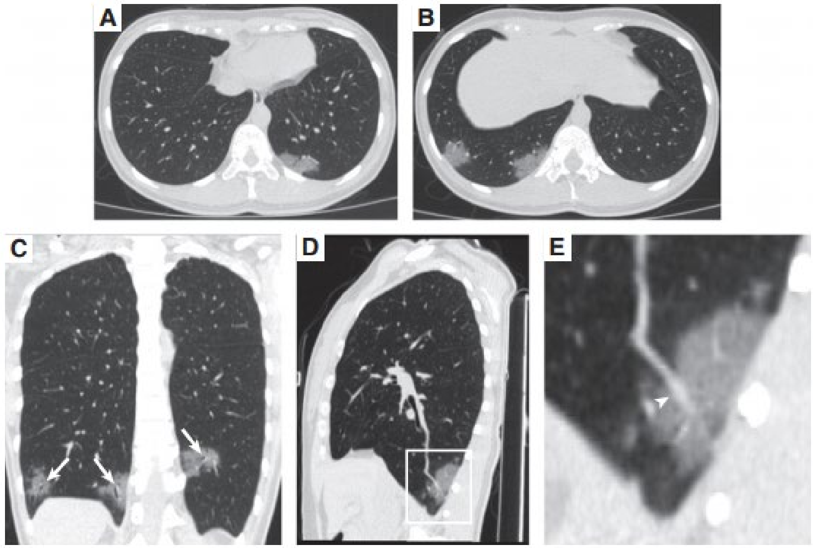
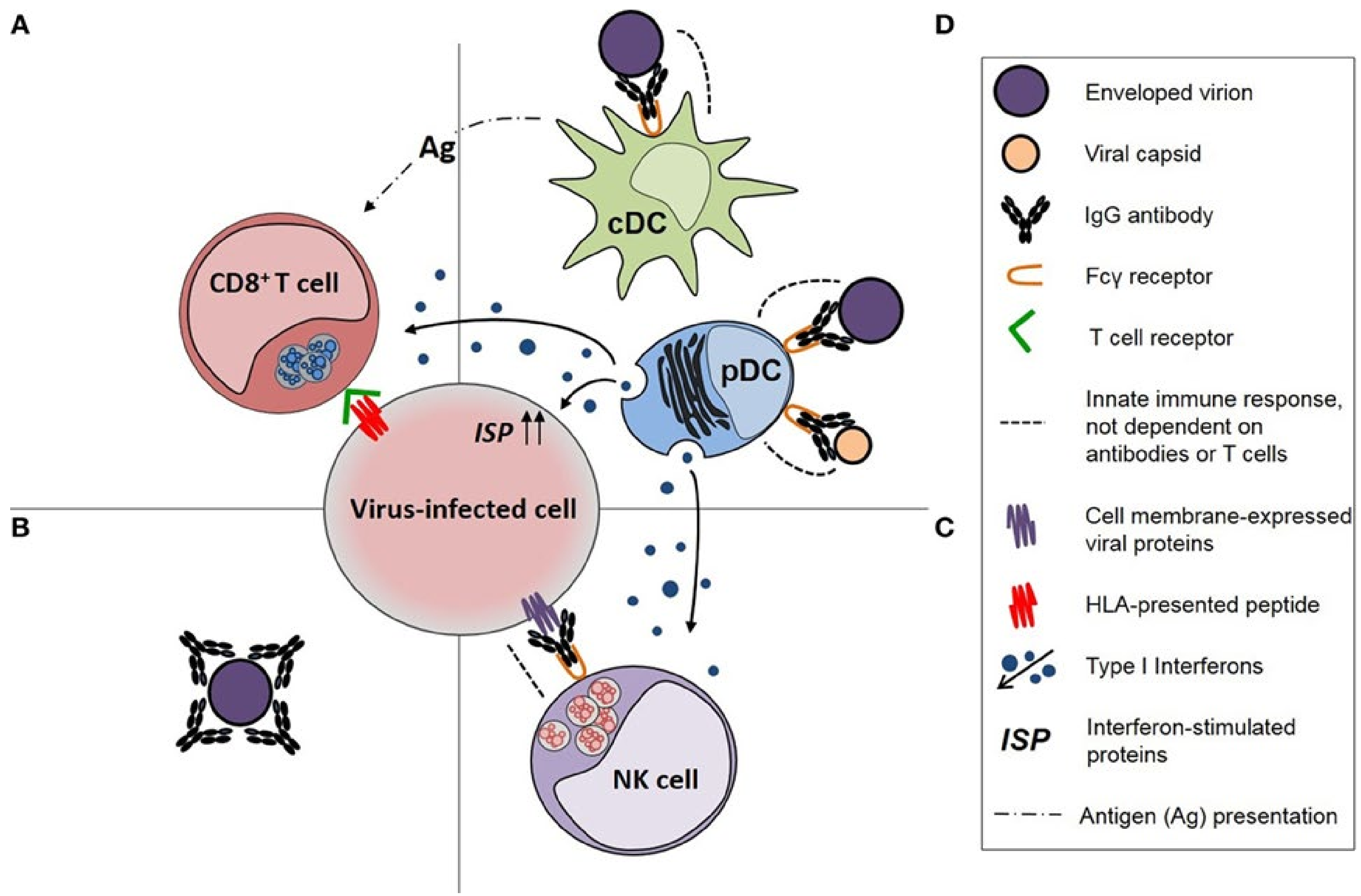


Figure 1. The computed tomography images of an asymptomatic 32-year-old woman with coronavirus disease (COVID-19). (*A* and *B*) The axial views of the chest computed tomography examination showing bilateral subpleural areas of multifocal ground-glass opacities in the basal segment of the lower lung fields. (*C–E*) The coronal (*C*) and sagittal (*D*) views showing air bronchogram (*C*; arrows) and mildly dilated blood vessel (*E*; arrowhead in the partial enlarged view) within the ground-glass opacities.

How does the immune response protect from or eliminate viruses?

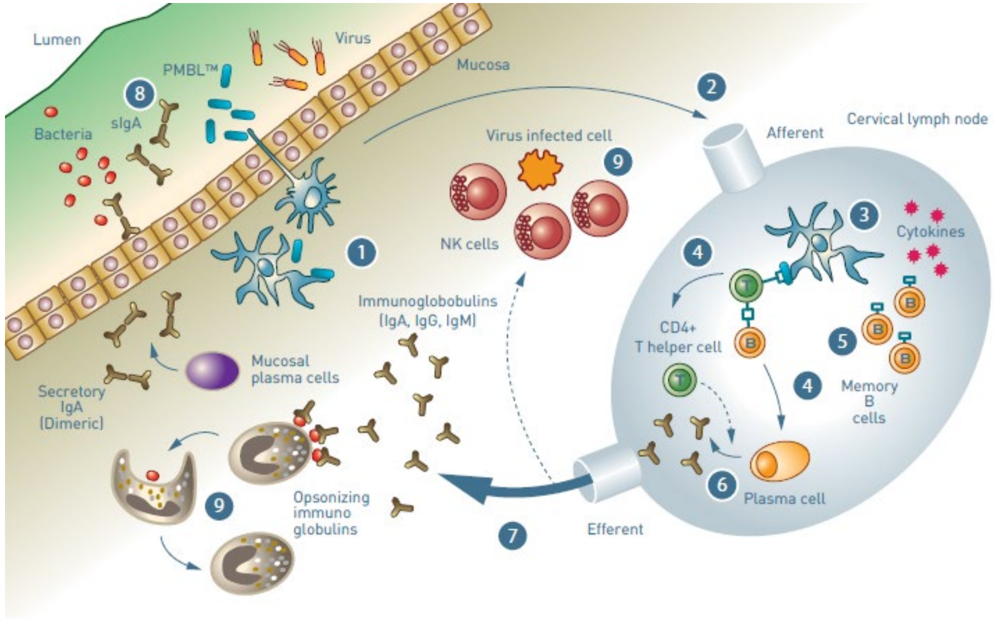
Two main mechanisms of viral clearance

- **Antibodies** can bind to the virus and prevent it from getting in cells to begin with
- **CD8 T cells** can kill a cell once it is infected
- Many other immune components can help limit infection but these do not typically have “memory”



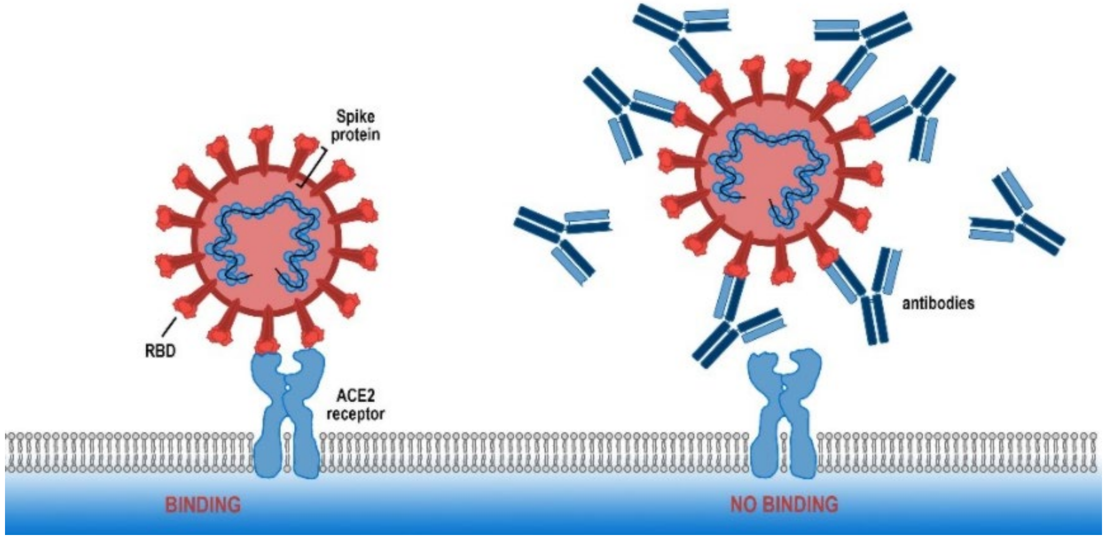
https://www.frontiersin.org/articles/10.3389/fimmu.2017.00780/full

Antibodies are made by B cells in response to specific antigens



Virus-specific B cells “see” antigen in the lymph node, expand, and make antibody that spreads throughout the body

Virus specific B cells need “help” from CD4 T cells



Antibodies are always circulating and can block the virus from entering cells—providing “neutralizing” protection

https://www.lallemandpharma.com/products/pmbl-website/mode-of-action/

https://www.fluidic.com/resources/solution-phase-affinity-profiling-of-a-SARS-CoV-2/

CD8 T cells target small pieces of the virus

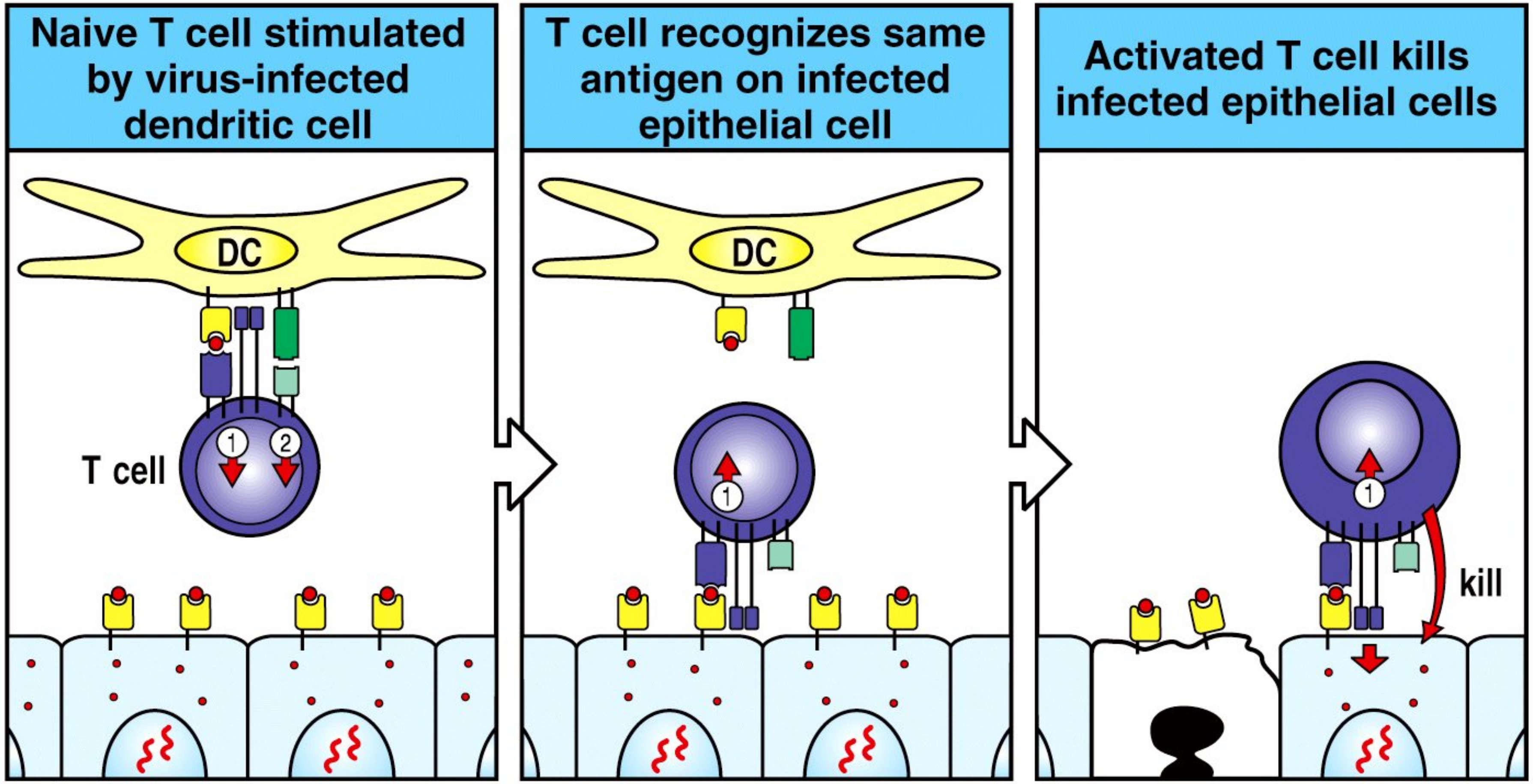


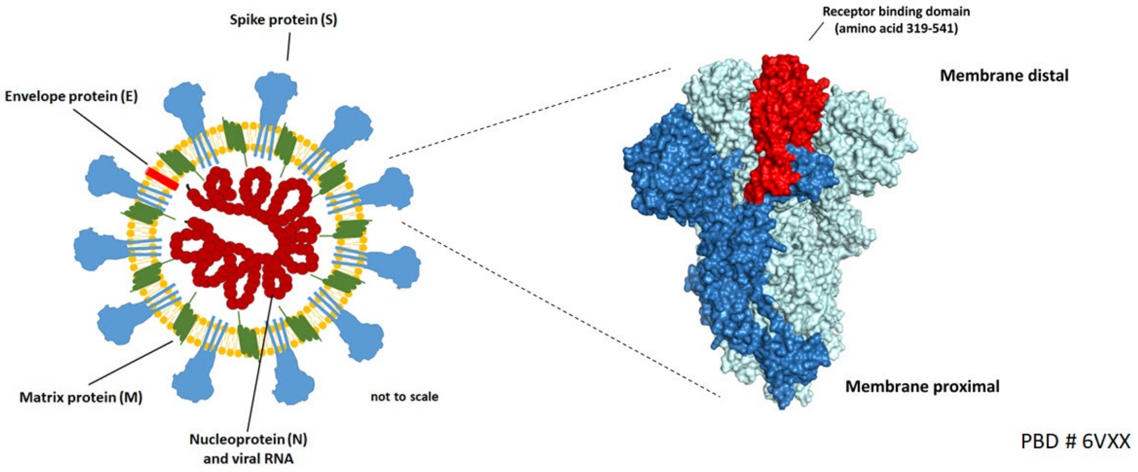
Figure 8-13 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

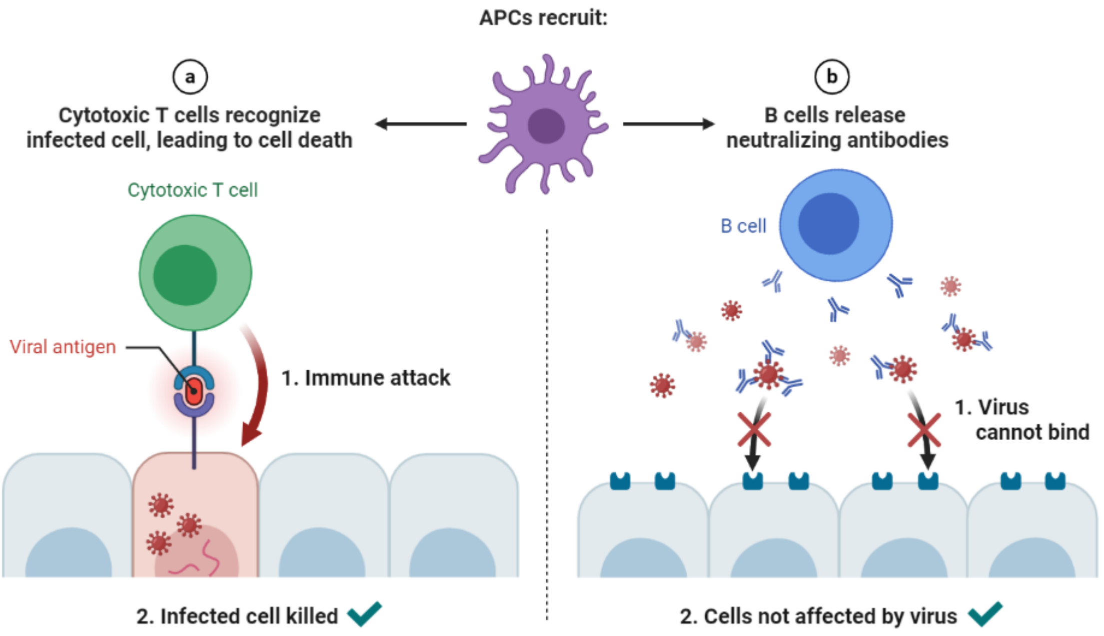
After learning what the virus looks like in the lymph node, CD8 T cells go to the site of infection and kill infected cells

TWO MAJOR FORMS OF PROTECTIVE IMMUNITY

- Antibody responses target the spike protein including the receptor binding domain as well as the nucleoprotein and other targets
  - Anti-spike (and RBD) antibodies are neutralizing and correlate with protection
  - NP antibodies are not neutralizing (we do not know if they are helpful)

- T-cell responses target several proteins, including the spike protein
  - Strong CD4+ response—helps antibodies
  - Relatively weak CD8+ response (in many patients)—kills infected cells

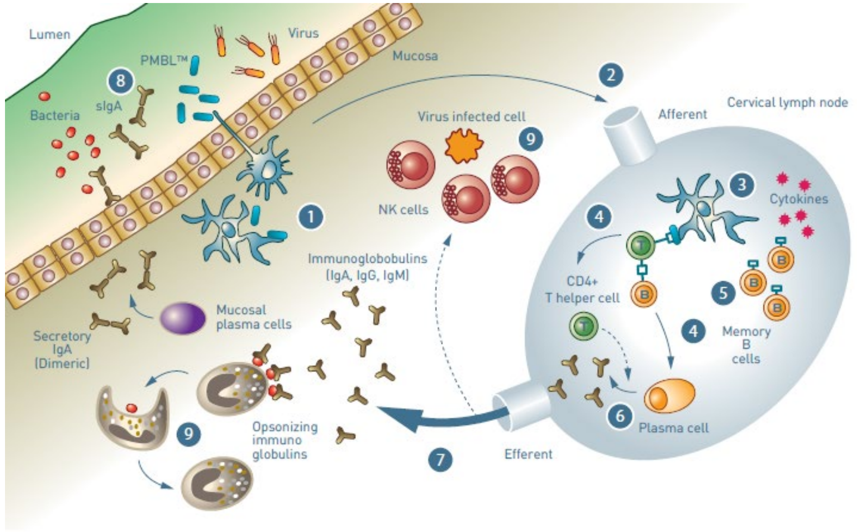




Special thanks to Florian Krammer

One more element—adjuvants are "danger signals"

- Adjuvants prime the innate immune response—little or no memory, but necessary for activating the adaptive (B and T cell) immune response
- Adjuvants mimic danger signals, patterns from pathogens that promote non-specific inflammation
- Patterns can be elements of a virus—like viral RNA or DNA



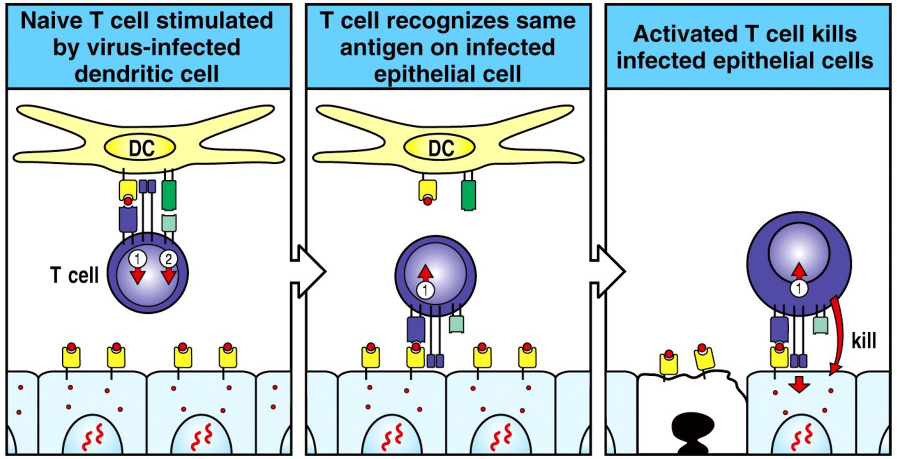
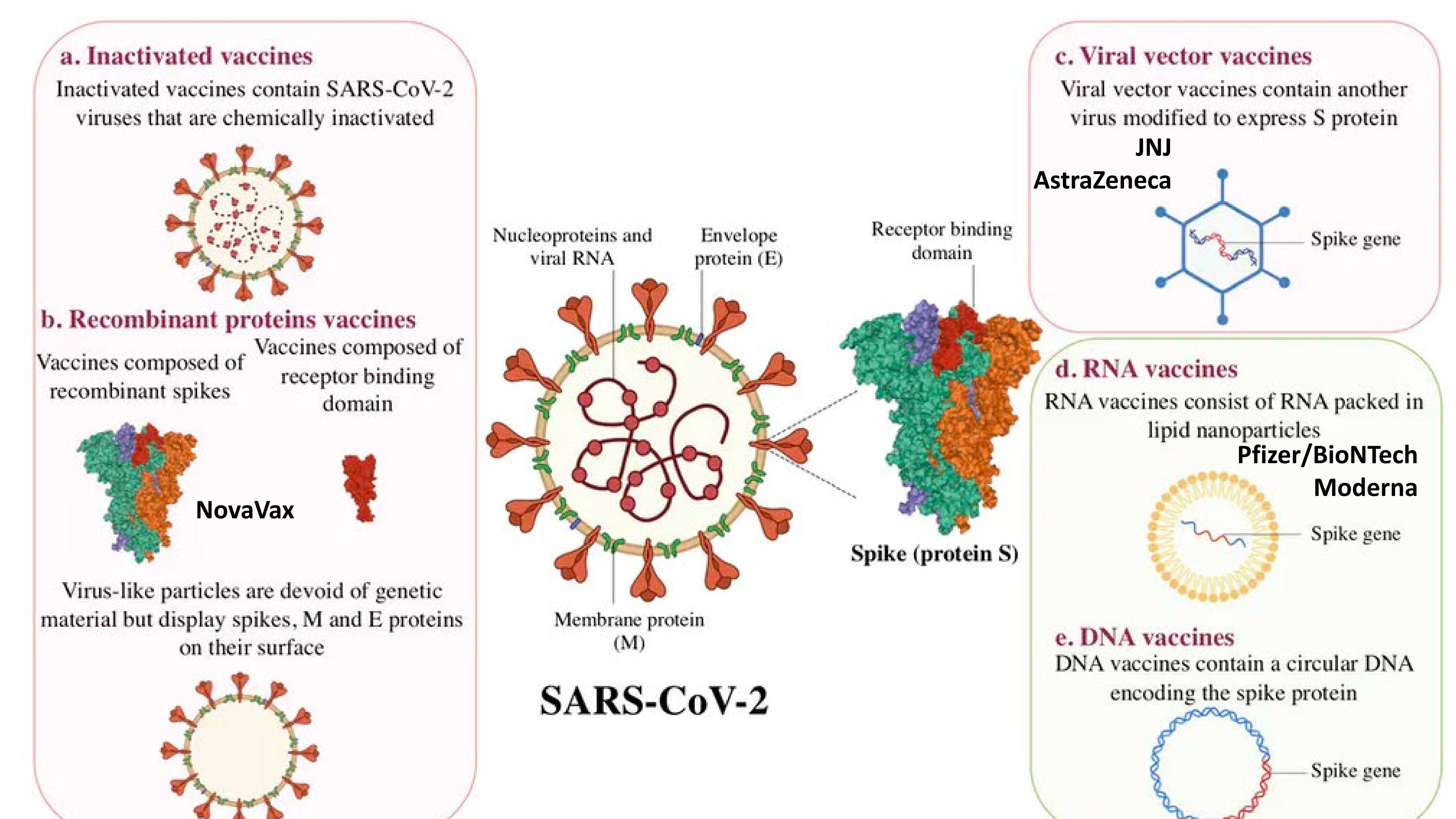


Figure 8-13 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

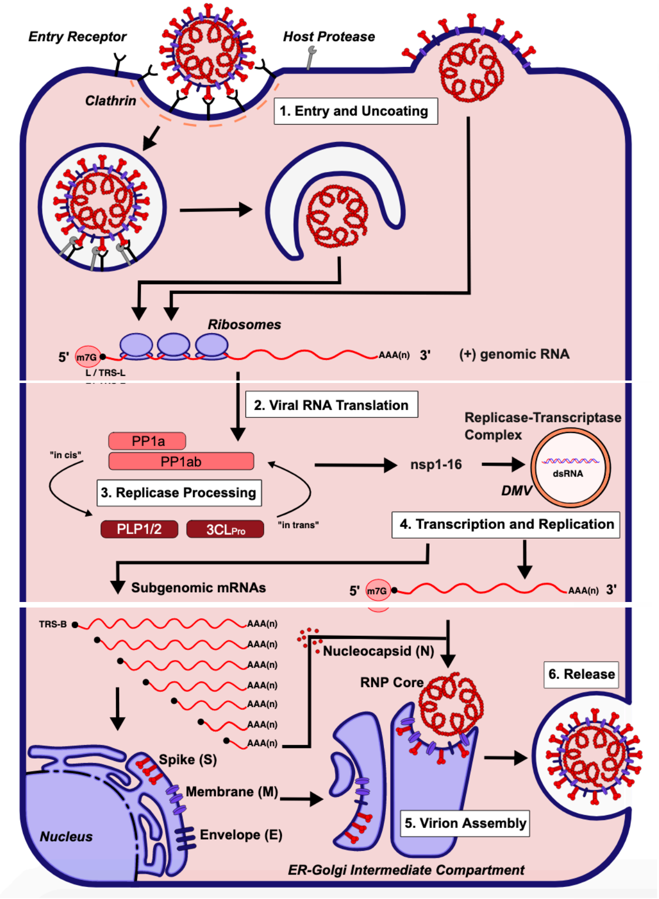
What are the goals of a vaccine?

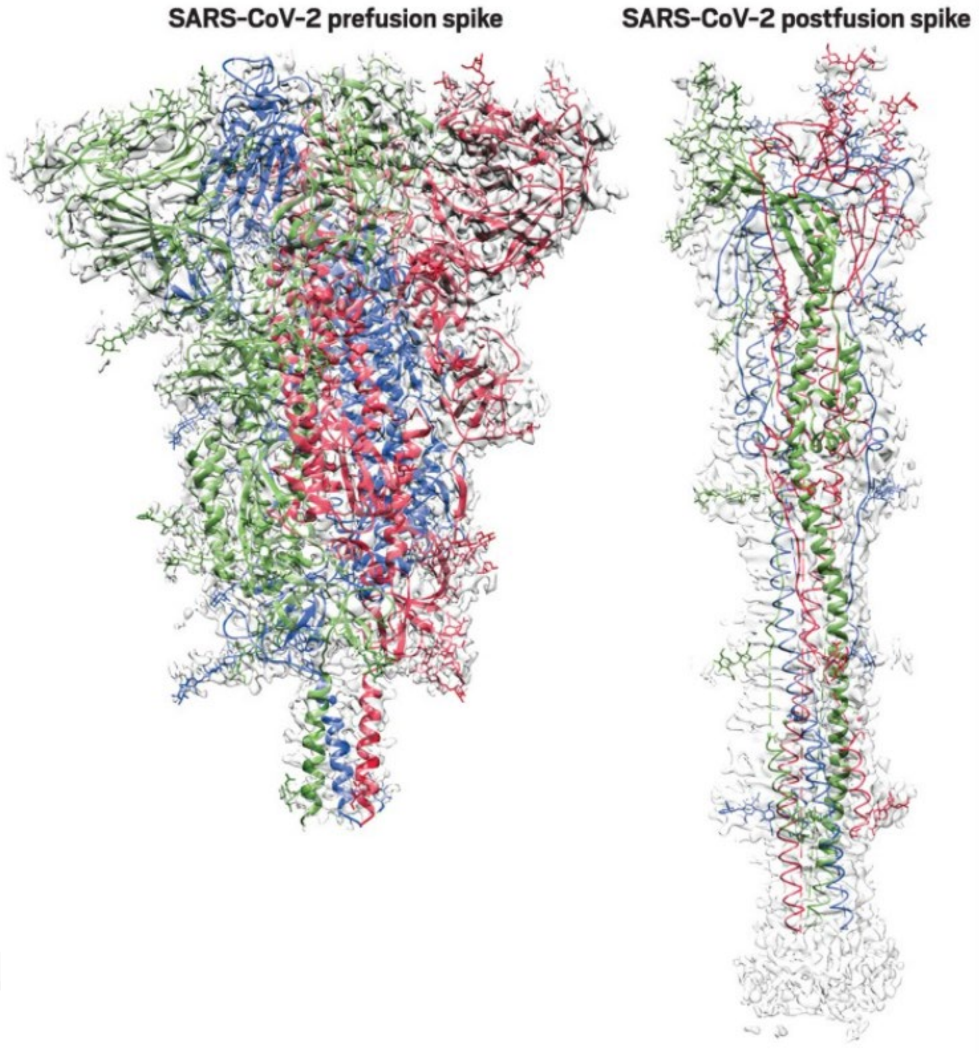
To introduce viral antigens to the immune system, to promote expansion of antigen-specific B cells, CD8 T cells, and CD4 T cells


a. Inactivated vaccines
Inactivated vaccines contain SARS-CoV-2 viruses that are chemically inactivated
b. Recombinant proteins vaccines
Vaccines composed of recombinant spikes
Vaccines composed of receptor binding domain
NovaVax
Virus-like particles are devoid of genetic material but display spikes, M and E proteins on their surface
Nucleoproteins and viral RNA
Envelope protein (E)
Membrane protein (M)
SARS-CoV-2
Receptor binding domain
Spike (protein S)
c. Viral vector vaccines
Viral vector vaccines contain another virus modified to express S protein
JNJ
AstraZeneca
Spike gene
d. RNA vaccines
RNA vaccines consist of RNA packed in lipid nanoparticles
Pfizer/BioNTech
Moderna
Spike gene
e. DNA vaccines
DNA vaccines contain a circular DNA encoding the spike protein
Spike gene

What does the Spike do?

- Spike mediates fusion inside the infected cell, so it has two forms—a binding form and a postfusion form
- Several vaccines have introduced mutations to freeze Spike in the prefusion form—the form the immune system will most likely encounter





Credit: Bing Chen

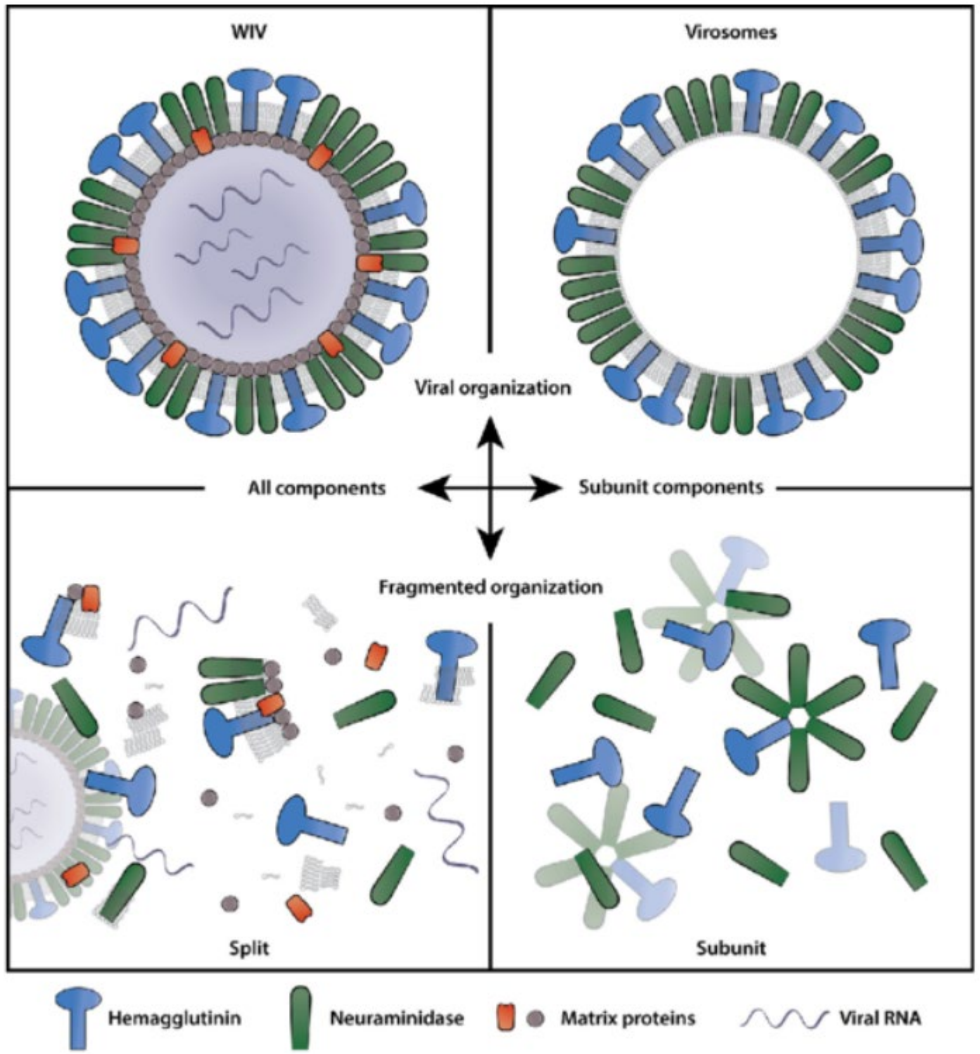
Harvard Medical School virologist Bing Chen determined prefusion and postfusion structures of the SARS-CoV-2 spike protein. The spike sheds a subunit and elongates during fusion with a human cell.

https://cen.acs.org/pharmaceuticals/vaccines/tiny-tweak-behind-COVID-19/98/i38

Comparison: annual "flu shot" QIV

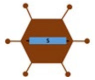
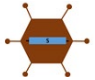
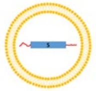
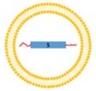
- The annual flu shot is generated by inactivating a whole, attenuated virus, fragmenting it with detergent, and reforming virosomes missing the viral RNA and most viral proteins

- There is **NO ADJUVANT**



Data from Phase I/II trials

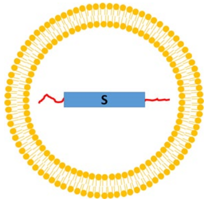


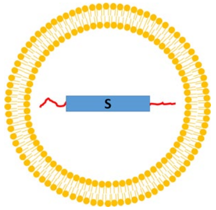

Company (reference)	Vaccine (type)	Dose range (route)	Neut. titre after prime	Neut. titre after boost	T cell response	Trial registration number
Sinovac[35]	CoronaVac (inactivated SARS-CoV-2 + aluminium hydroxide)	3–6 μg (i.m.) 2x	ND	1:30–1:60 range[a]	ND	NCT04352608
Sinopharm	Inactivated whole virus COVID-19 vaccine (inactivated SARS-CoV-2 + aluminium hydroxide)	2.5, 5 or 10 μg (i.m.) 3x (0/28/56 or 0/28) 5ug (i.m.) 2x (0/14 or 0/21)	Not reported in detail	1:316 (2.5 ug, 0/28/58)[c] 1:206 (5 ug, 0/28/58)[c] 1:297 (10 ug, 0/28/58)[c] 1:121 (5ug, 0/14)[c] 1:247 (5 ug, 0/21)[c]	ND	ChiCTR2000031809
CanSino[46]	Ad5 nCoV (non-replicating AdV5 expressing spike protein)	5 x 10^{10}, 10^{11} VP (i.m.)	1:18.3–1:19.5 range[b]	—	Yes	NCT04341389
AstraZeneca[47]	ChAdOx1nCOV-19 (non-replicating chimpanzee AdV expressing spike protein)	5 x 10^{10} VP 1 x or 2´ (i.m.)	Median 1:218[c] Median 1:51[d] Median 1:4–1:16[e]	Median 1:136[d] Median 1:29 [d]	Yes	NCT04324606
Moderna[59]	mRNA-1273 (mRNA)	2x 25, **100**, 250 μg (i.m.)	Low	1:112.3 (25 μg)[f] 1:343.8 (100 μg)[f] 1:332.2 (250 μg)[f] 1:339.7 (25 μg)[g] 1:654.3 (100 μg)[g]	Good $CD4^+$ and low $CD8^+$ response	NCT04283461
Pfizer[60]	BNT162b1 (mRNA)	2x 10, 30, 100 μg (i.m.)	Low	1:180 (10 μg)[h] 1:437 (30 μg)[h]	ND	NCT04368728
Pfizer[84]	BNT162b1 (mRNA) and **BNT162b2** (mRNA)	2x 10, 20, **30** μg	Low	Day 28[h] BNT126b1 (18–55 years): 1:168 (10 μg) 1:267 (30 μg) BNT126b1 (65–85 years): 1:37 (10 μg) 1:179 (20 μg) 1:101 (30 μg) BNT126b2 (18–55 years): 1:157 (10 μg) 1:363 (20 μg) 1:361 (30 μg) BNT126b2 (65–85 years): 1:84 (20 μg) 1:147 (30 μg)	ND	NCT04368728
Novavax[90]	NVX CoV2373 (Matrix-M) Spike protein 'rosettes'	2 x 2.5–25 μg (i.m. ± Matrix-M) 1x 25 μg (i.m. + Matrix-M)	1:128 (25 μg + Matrix-M)[i]	1:3,906 (5 μg + Matrix-M)[i] 1:3,305 (25 μg + Matrix-M)[i] 1:41 (25 μg unadjuvanted)[i]	$CD4^+$	NCT04368988

Vaccines in Phase III

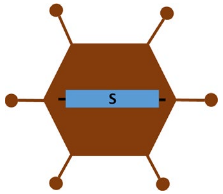
- **Moderna (94)%**



- **Pfizer (95%)**

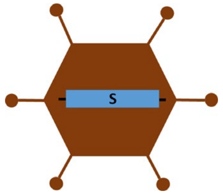


- **AstraZeneca (62-90%)**



IR

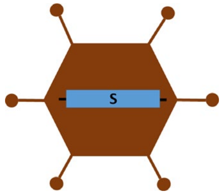
- **Janssen (72%)**



- **Novavax (89-96%)**

IR

- **Gamaleya (91.6%)**



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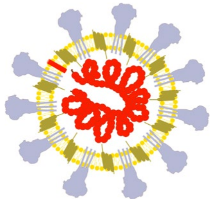
- **Sinovac/Sinopharm (3x) (50-90%)**



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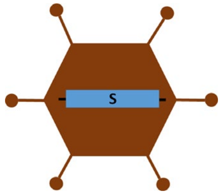
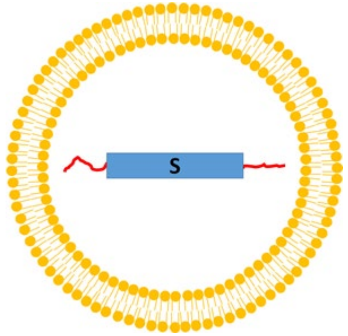
- **Cansino**



For most of these vaccines two injections are required.

Special thanks to Florian Krammer

What do the Pfizer results mean?



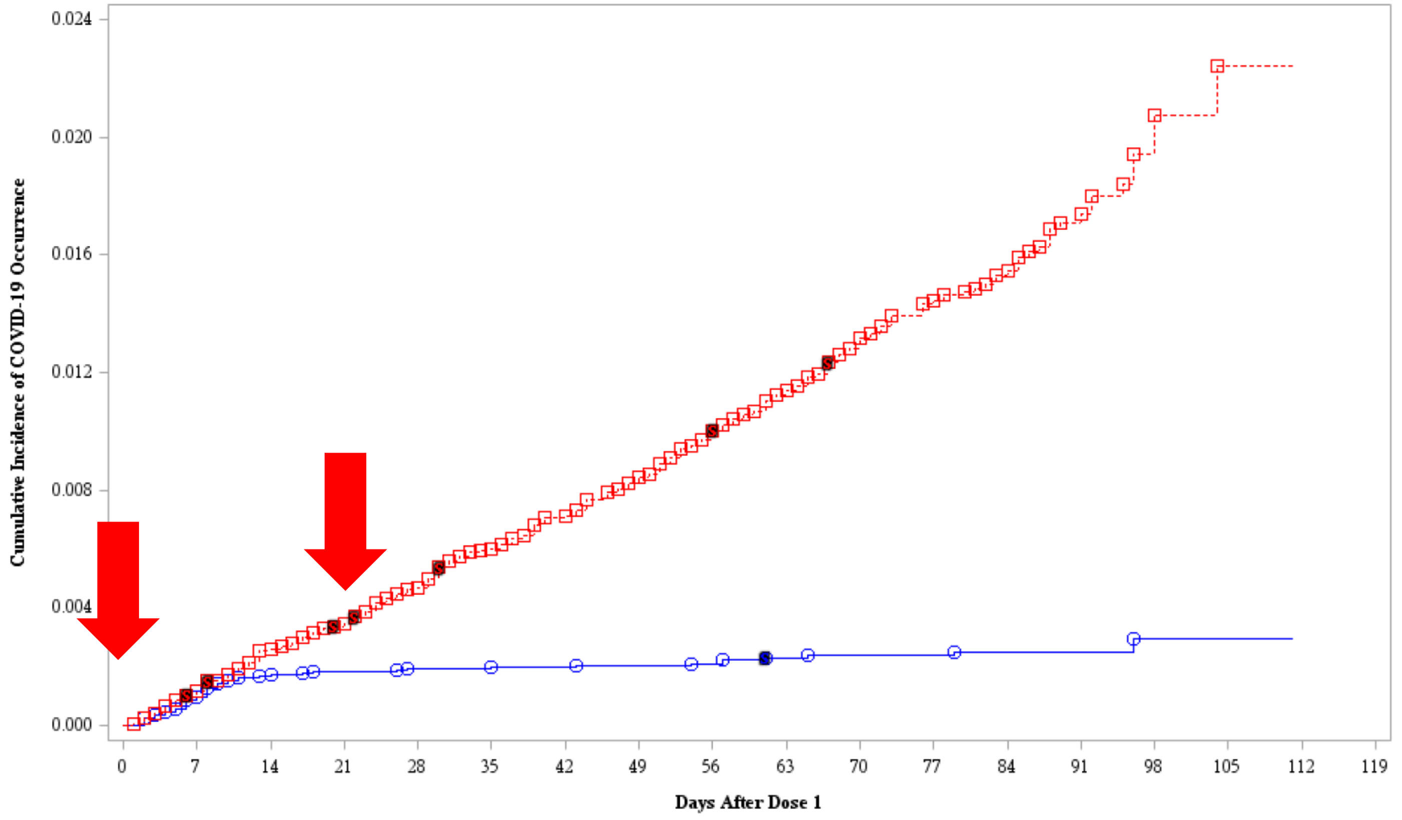
- 43,538 individuals are in the study
- 170 COVID-19 cases were recorded
  - 162 in the placebo group (9 severe)
  - 8 in the vaccine group (1 severe)
- 95% efficacy against symptomatic disease (one symptom plus PCR+, they start measuring this 7 days post dose 2)
- 94% efficacy in the 65-85 year old group
- No significant safety concerns

- The vaccine received different degrees of approval in Bahrain, the UK, Mexico, Canada, Saudi Arabia, the EU, the US etc.

Moderna data look almost identical

Special thanks to Florian Krammer

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Dose 1 All-Available Efficacy Population



No. with events/No. at risk

A:	0/21314	21/21230	37/21054	39/20481	41/19314	42/18377	42/17702	43/17186	44/15464	47/14038	48/12169	48/9591	49/6403	49/3374	50/1463	50/398	50/0
B:	0/21258	25/21170	55/20970	73/20366	97/19209	123/18218	143/17578	166/17025	192/15290	212/13876	235/11994	249/9471	257/6294	267/3301	274/1449	275/398	275/0

A: BNT162b2 (30 μg) B: Placebo

Note: "S" indicates subjects with severe COVID-19 or COVID-19 leading to hospitalization.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adc19ef Table Generation: 17NOV2020 (21:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_f001_km_d1_aai

https://www.fda.gov/media/144245/download accessed 8Dec20

Special thanks to Florian Krammer

RNA vaccines are a relatively new development

RNA vaccine trials in humans
(not including a large number of cancer vaccines and therapeutic approaches based on mRNA)

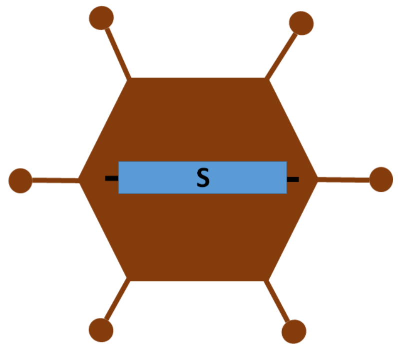
Target	Started in	Individuals enrolled[2]	Company	Status	Phase	Registration number
CMV	2017	181	Moderna	Fully enrolled	Phase 1	NCT03382405
hMPV/PIV3	2019	114	Moderna	Recruiting	Phase 1	NCT04144348
Zika	2019	120	Moderna	Fully enrolled	Phase 1	NCT04064905
Influenza	2017	156	Moderna	Fully enrolled	Phase 1	NCT03345043
Rabies	2018	53	Curevac	Fully enrolled	Phase 1	NCT03713086
Rabies	2013	101	Curevac	Completed	Phase 1	NCT02241135
Rabies	2014	72	Curevac	Completed	Phase 1	NCT02238756
CMV	2020	452	Moderna	Recruiting	Phase 2	NCT04232280
Chikungunya[1]	2019	39	Moderna	Fully enrolled	Phase 1	NCT03829384

[1]Passive immunity based on *in vivo* mAb expression

[2]Includes individuals who received placebo, some trials are still recruiting

Special thanks to Florian Krammer

What do the J&J results mean?



- One dose!
- 43,783 individuals are in the study
- USA, South Africa and Latin America
- US efficacy 72% against moderate to severe COVID-19 (2 symptoms plus PCR+ was counted as moderate)
- 85% efficacy across all studies against severe disease
- 100% protection against hospitalization and death
- No significant safety concerns
- Some indication of reduction of asymptomatic infections

- Now authorized for use in the US

Special thanks to Florian Krammer

Are vectored vaccines a relatively new development?

- Ad26-based Ebola vaccine licensed in the EU
- Ad4 and Ad7 vaccines in use in the US military since 1971

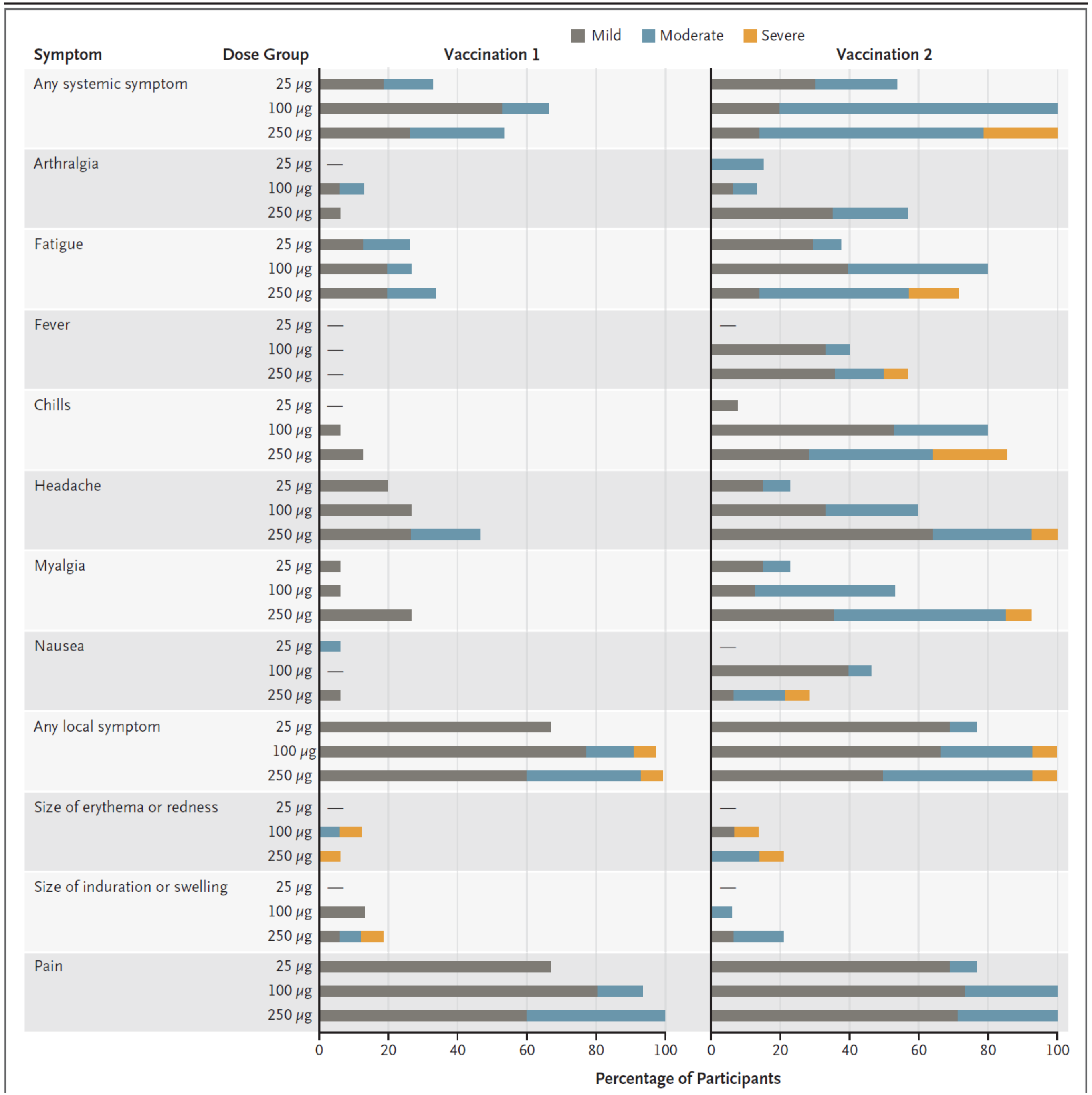
Reactogenicity

- Injection site pain
- Headache
- Fatigue
- Elevated temperature
- Myalgia
- Mild flu-like symptoms

→unpleasant, but not dangerous

AdV=mRNA>recombinant protein>inactivated vaccine

Strength of adjuvant!



Moderna/VRC mRNA 1273 via LNPs

Special thanks to Florian Krammer

What is in each vaccine?

REVIEW ARTICLE

Maintaining Safety with SARS-CoV-2 Vaccines

Mariana C. Castells, M.D., Ph.D., and Elizabeth J. Phillips, M.D.

Table 1. SARS-CoV-2 Vaccines under Emergency Use Authorization (EUA) or in Late-Phase Studies.

Vaccine Platform	Type of Vaccine and Immunogen	Developer (Name of Vaccine)	Dose Schedule and Administration	Phase*	Excipients†
RNA-based vaccine	mRNA encoding spike protein (30 μg)	BioNTech–Pfizer (BNT162b2)	Two doses (day 0, day 21) Intramuscular	Post-EUA	0.43 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(**polyethylene glycol)-2000**]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol, 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% sodium chloride Injection) contributes an additional 2.16 mg sodium chloride per dose
RNA-based vaccine	mRNA encoding spike protein (100 μg)	Moderna (mRNA-1273)	Two doses (day 0, day 28) Intramuscular	Post-EUA	Lipids (SM-102; 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [**PEG 2000**-DMG]; cholesterol; and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose
Adenovirus vector (nonreplicating)	ChAdOx1-Sn Cov-19 Nonreplicating chimpanzee AdV5 expressing spike protein	AstraZeneca and University of Oxford (AZD1222)	One (day 0) or two (day 0, day 28) doses Intramuscular	Phase 3	10 mM histidine, 7.5% (w/v) sucrose, 35 mM sodium chloride, 1 mM magnesium chloride, 0.1% (w/v) **polysorbate 80**, 0.1 mM edetate disodium, 0.5% (w/v) ethanol, at pH 6.6
Adenovirus vector (nonreplicating)	Ad26.COV2.S Adenovirus 26 vectored vaccine using AdVac and PER.C6 technology	Janssen	One (day 0) or two (day 0, day 56) doses Intramuscular	Phase 3	Sodium chloride, citric acid monohydrate, **polysorbate 80**, 2 hydroxypropyl-B-cyclodextrin (HBCD), ethanol (absolute), sodium hydroxide
Protein subunit	Full-length recombinant SARS-CoV-2 glycoprotein nanoparticle with Matrix M adjuvant Spike prefusion protein	Novavax	Two doses (day 0, day 21) Intramuscular	Phase 3	Matrix M1 adjuvant Full-length spike protein formulated in **polysorbate 80** detergent and Matrix M1 adjuvant
Protein subunit	SARS-CoV-2 vaccine formulation with adjuvant (S-protein) (Baculovirus production) Spike protein	Sanofi Pasteur and GSK	Two doses (day 0, day 21) Intramuscular	Phase 1–2	Sodium phosphate monobasic monohydrate, sodium phosphate dibasic, sodium chloride **polysorbate 20**, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride

* Phase information was current as of December 21, 2020. In all cases, the placebo was normal saline.

† Bold entries are excipients potentially related to vaccine reaction that may be cross-reactive to other excipients (e.g., PEG 2000 and polysorbate 80). SM-102, a component of the Moderna vaccine, is a proprietary ionizable lipid.

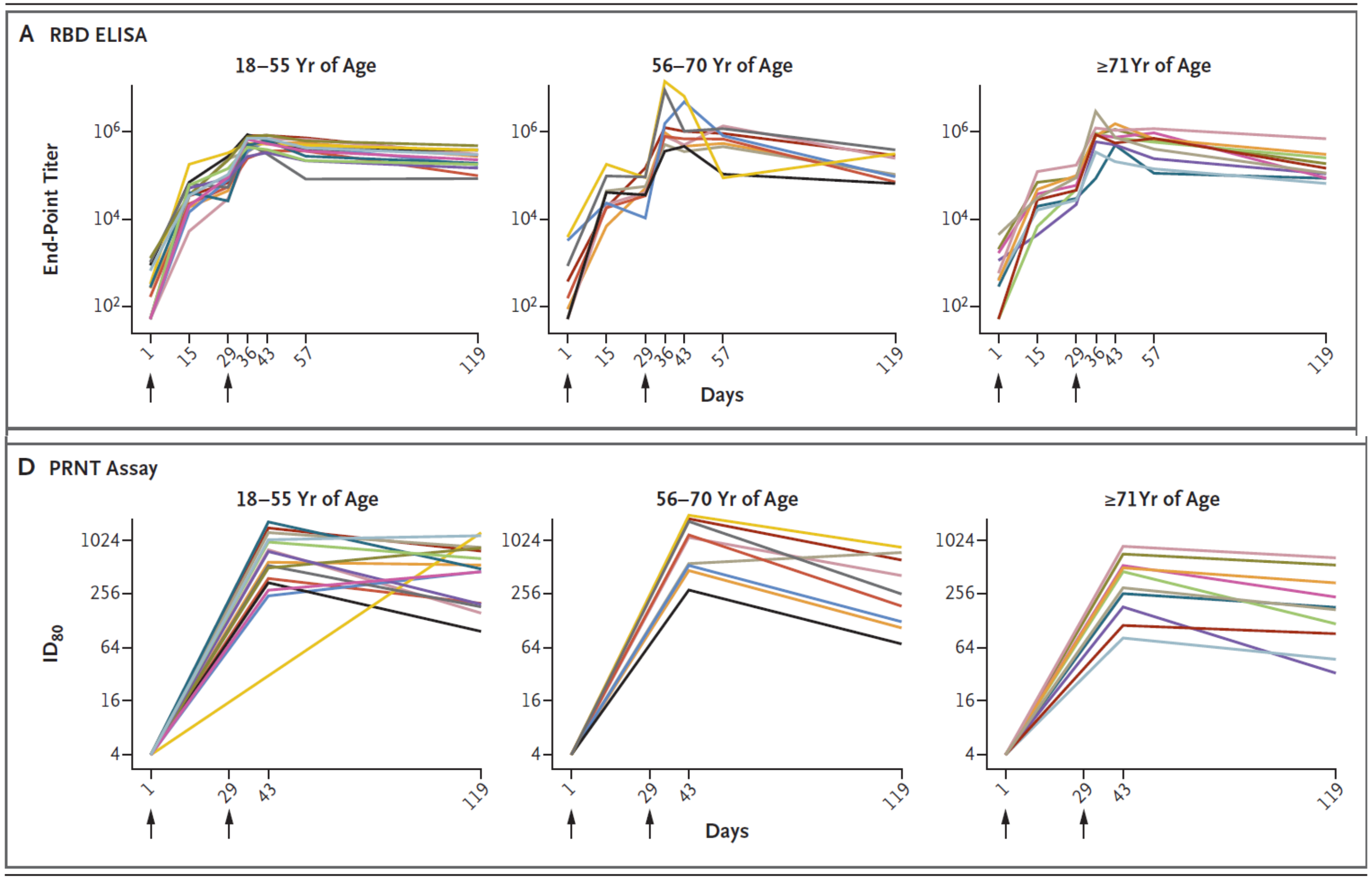
How long does protection last?

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

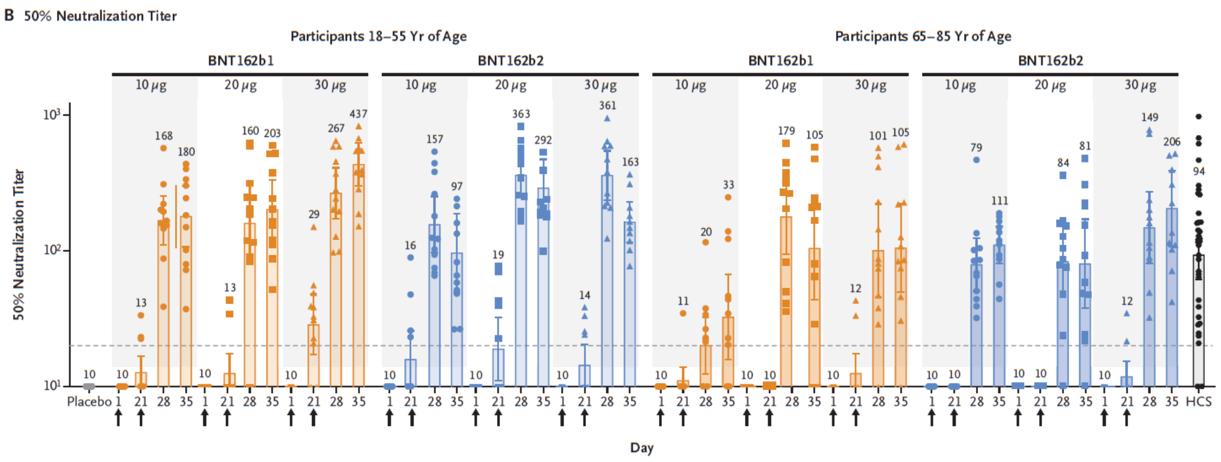
Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination

- Likely for years, based on what we know about immune responses in general and immune responses to SARS-CoV-2
- It might be that booster doses are needed at some point, but that is similar to other vaccines (e.g. tetanus)



Special thanks to Florian Krammer

Vaccines work in older individuals and boost memory in infected individuals

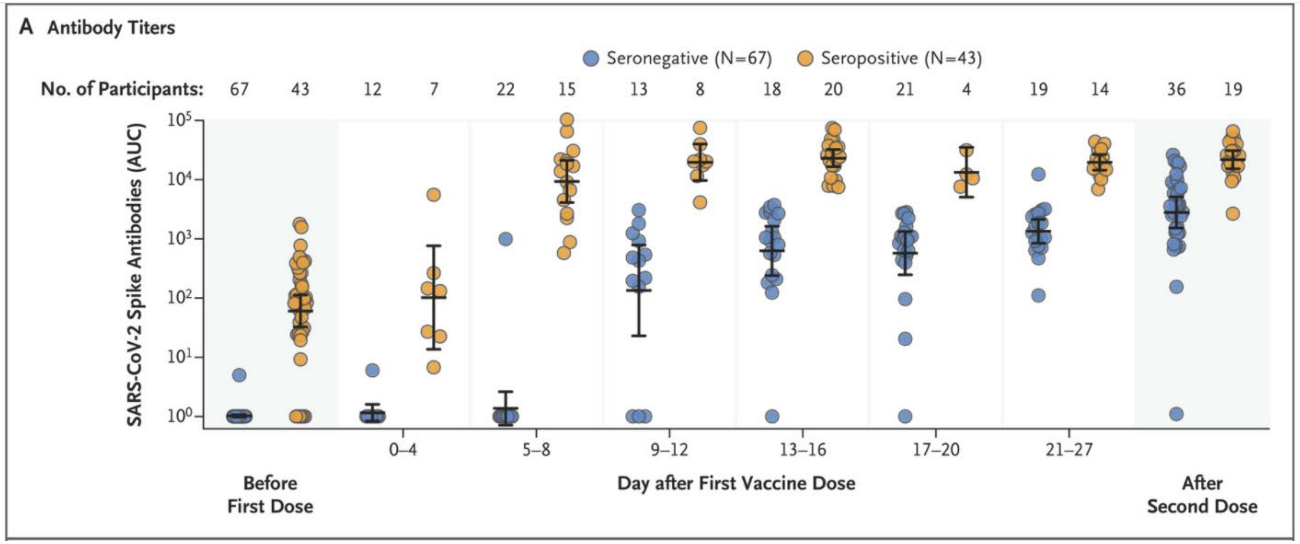


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates

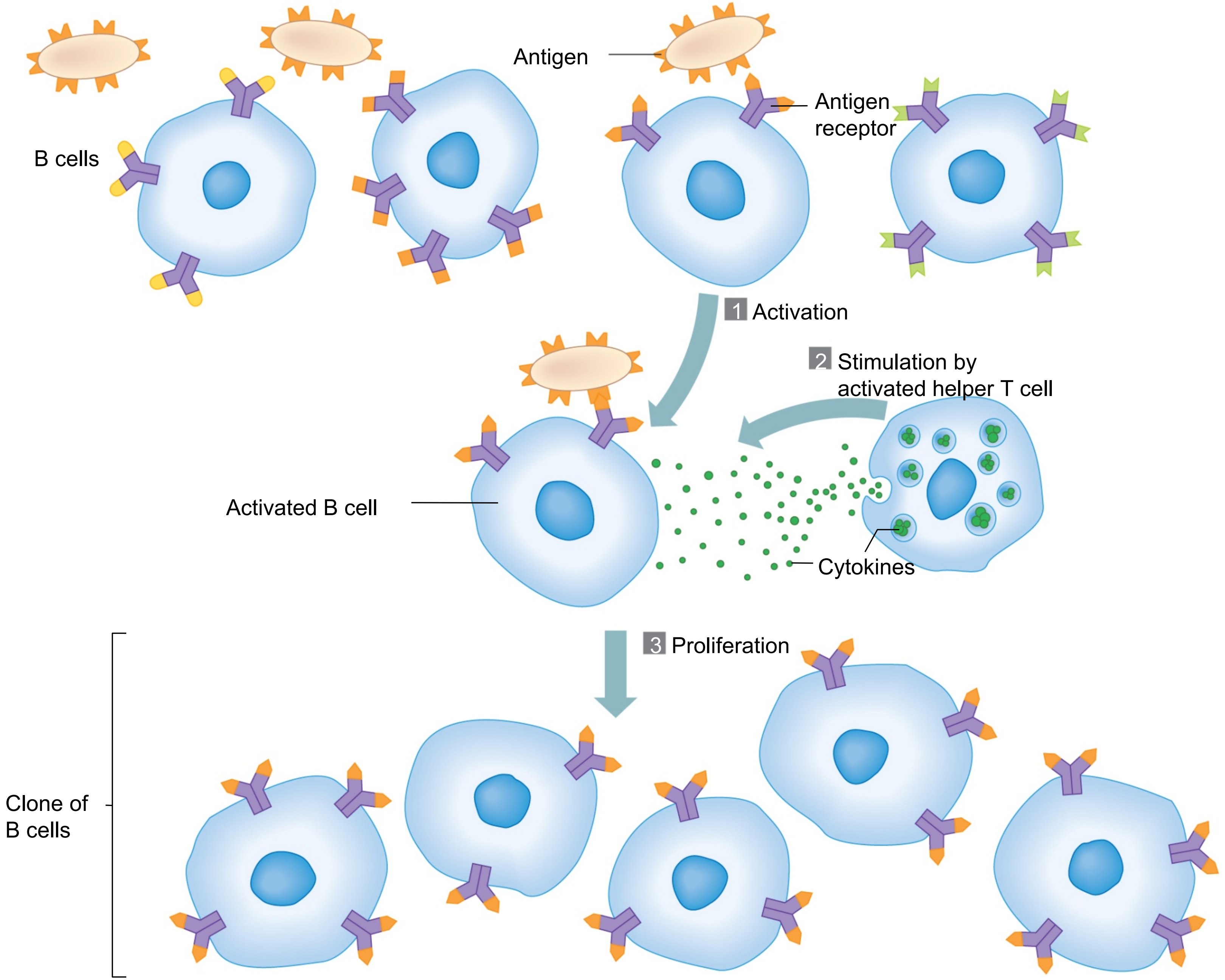
- Vaccines work faster in younger individuals and with lower doses
- With recommended dose, older individuals still generate high levels of protective immunity

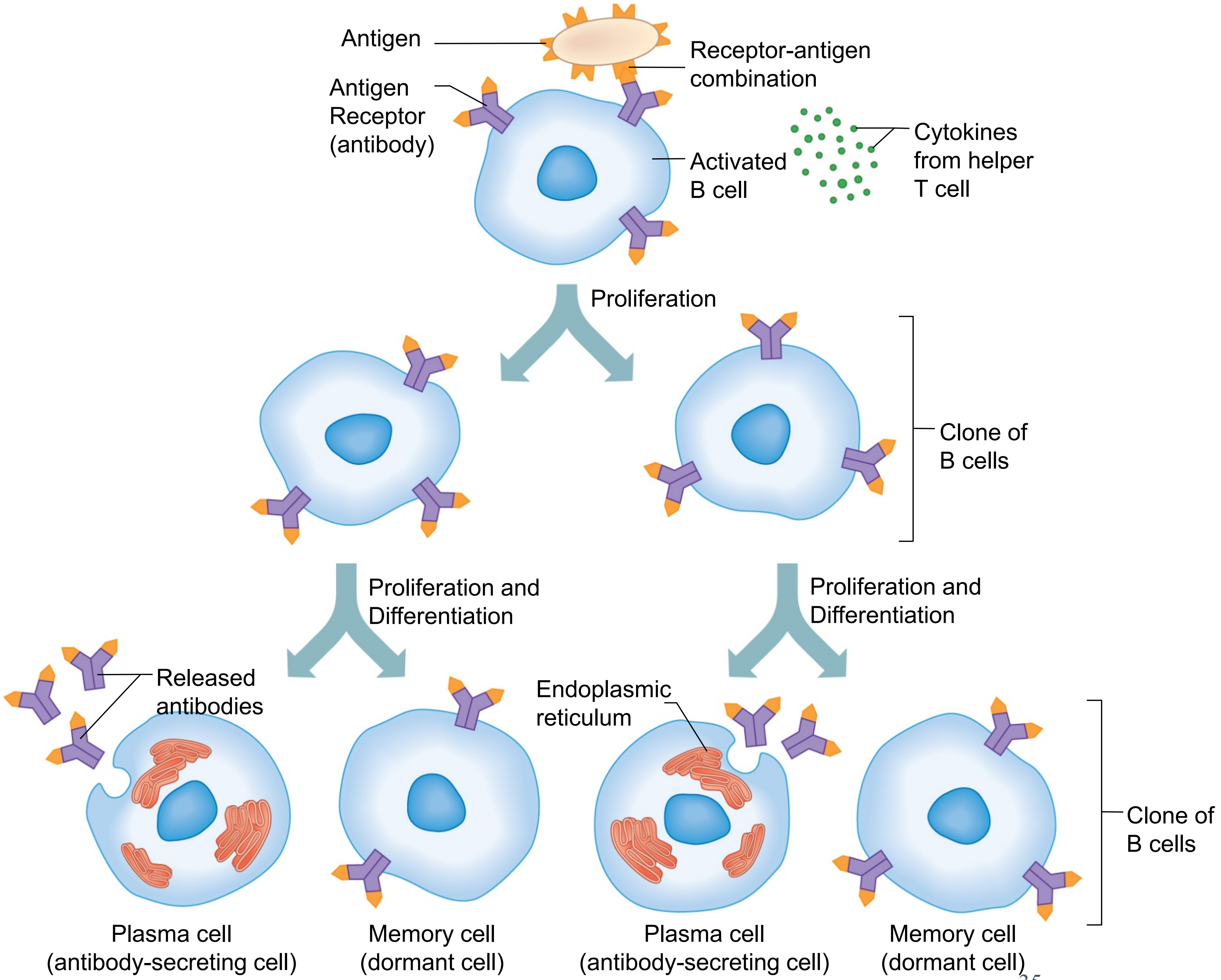


CORRESPONDENCE

Antibody Responses in Seropositive Persons after a Single Dose of SARS-CoV-2 mRNA Vaccine

- Post-infection, a single dose of the Pfizer/BioNTech vaccine was equivalent to two doses of the vaccine in naïve individuals
- Still a significant boost!


Antigen
B cells
Antigen receptor
1 Activation
2 Stimulation by activated helper T cell
Activated B cell
Cytokines
3 Proliferation
Clone of B cells


Antigen
Receptor-antigen combination
Antigen Receptor (antibody)
Activated B cell
Cytokines from helper T cell
Proliferation
Clone of B cells
Proliferation and Differentiation
Proliferation and Differentiation
Released antibodies
Endoplasmic reticulum
Clone of B cells
Plasma cell (antibody-secreting cell)
Memory cell (dormant cell)
Plasma cell (antibody-secreting cell)
Memory cell (dormant cell)

Article | Published: 24 May 2021

SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans

Jackson S. Turner, Wooseob Kim, Elizaveta Kalaidina, Charles W. Goss, Adriana M. Rauseo, Aaron J. Schmitz, Lena Hansen, Alem Haile, Michael K. Klebert, Iskra Pusic, Jane A. O'Halloran, Rachel M. Presti & Ali H. Ellebedy

Nature **595**, 421–425 (2021) | Cite this article

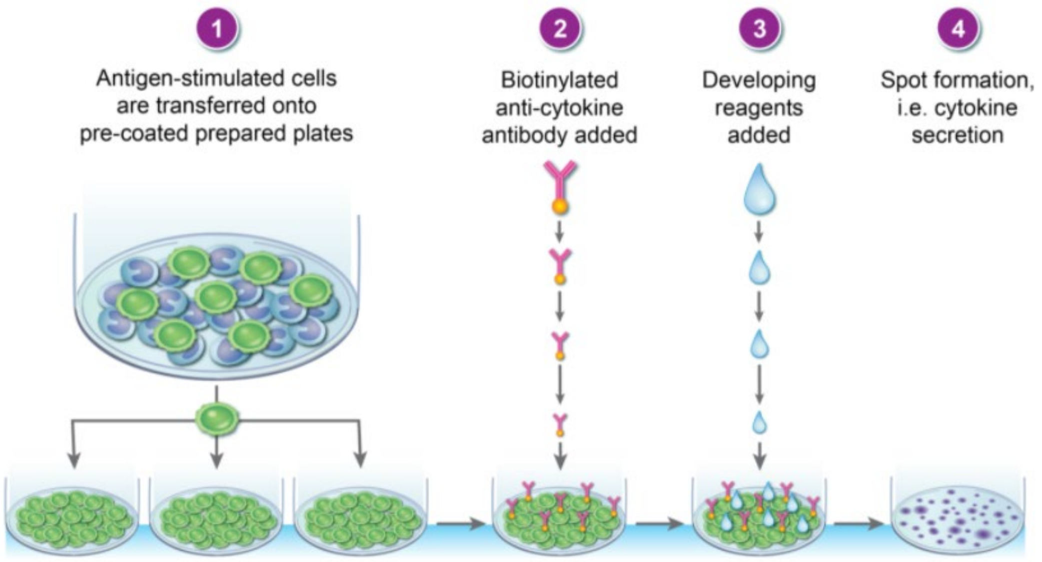
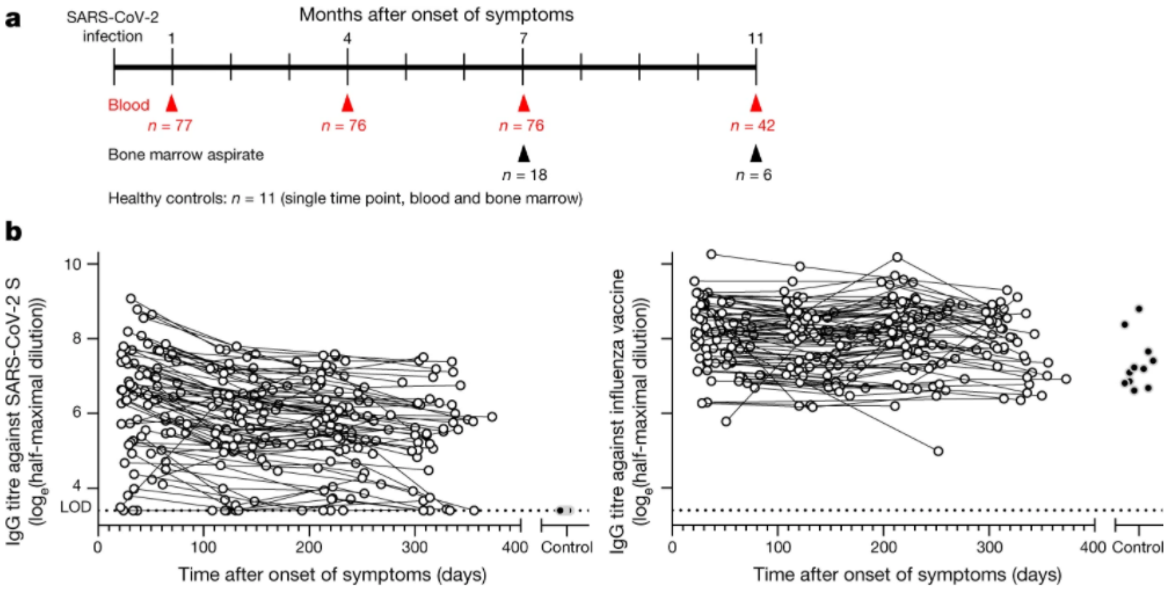


Fig. 1: SARS-CoV-2 infection elicits durable serum anti-S antibody titres.

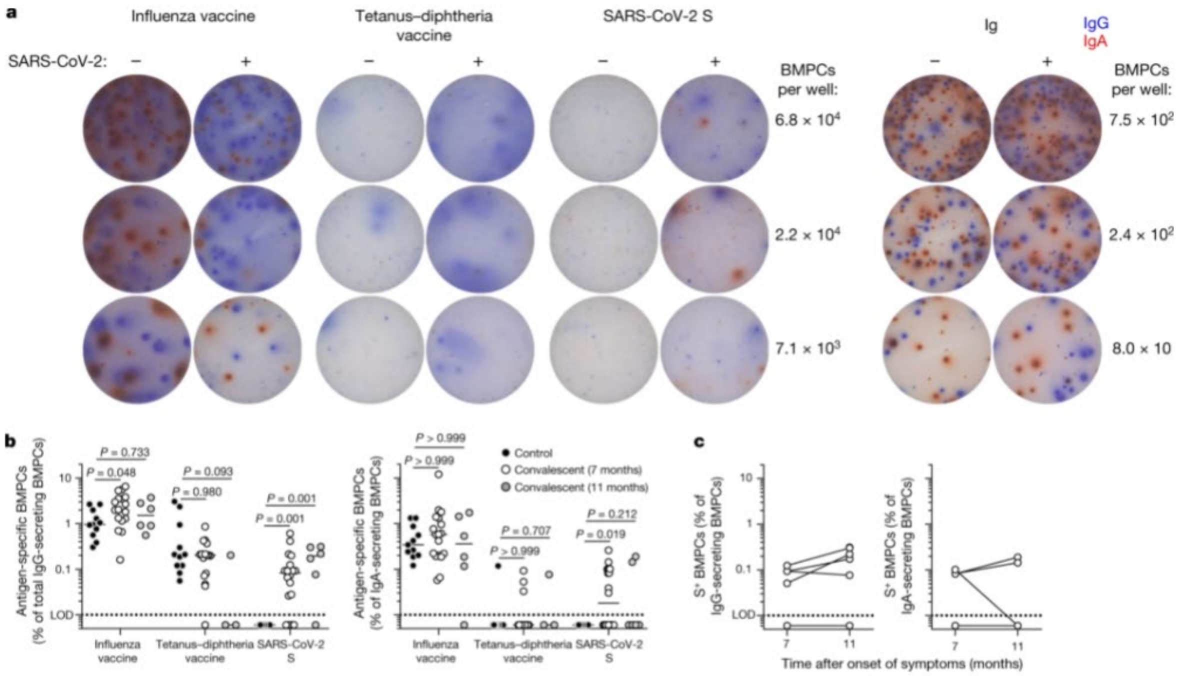
From: SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans



a, Study design. Seventy-seven convalescent individuals who had experienced mild SARS-CoV-2 infections (aged 21–69 years) were enrolled and blood was collected approximately 1 month, 4 months, 7 months and 11 months after the onset of symptoms. Bone marrow aspirates were collected from 18 of the convalescent individuals 7 to 8 months after infection and from 11 healthy volunteers (aged 23–60 years) with no history of SARS-CoV-2 infection. Follow-up bone marrow aspirates were collected from 5 of the 18 convalescent donors and 1 additional convalescent donor approximately 11 months after infection. **b**, Blood IgG titres against SARS-CoV-2 S (left) and influenza virus vaccine (right) measured by enzyme-linked immunosorbent assay (ELISA) in convalescent individuals (white circles) at the indicated time after onset of symptoms, and in control individuals (black circles). The dotted lines indicate the limit of detection (LOD). Mean titres and pairwise differences at each time point were estimated using a linear mixed model analysis.

Fig. 2: SARS-CoV-2 infection elicits S-binding long-lived BMPCs.

From: SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans

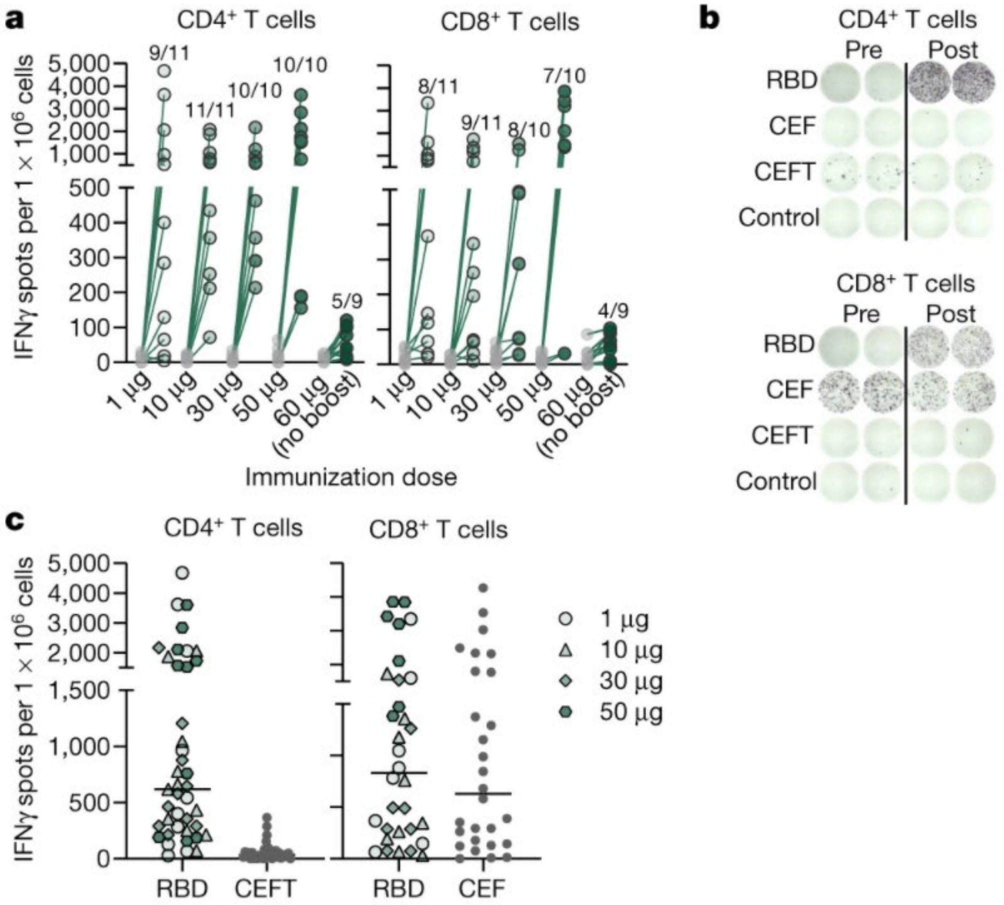


RNA vaccines are inducing robust T cell responses

- Robust primary CD4 and CD8 T cell responses are detectable after RNA vaccines
- Similarly, AdV vaccines (like JNJ) also induced strong T cell responses
- Many T cell antigens are not prone to easy immune escape

Fig. 3: Frequency and magnitude of BNT162b1-induced CD4⁺ and CD8⁺ T cell responses.

From: COVID-19 vaccine BNT162b1 elicits human antibody and T_H1 T cell responses



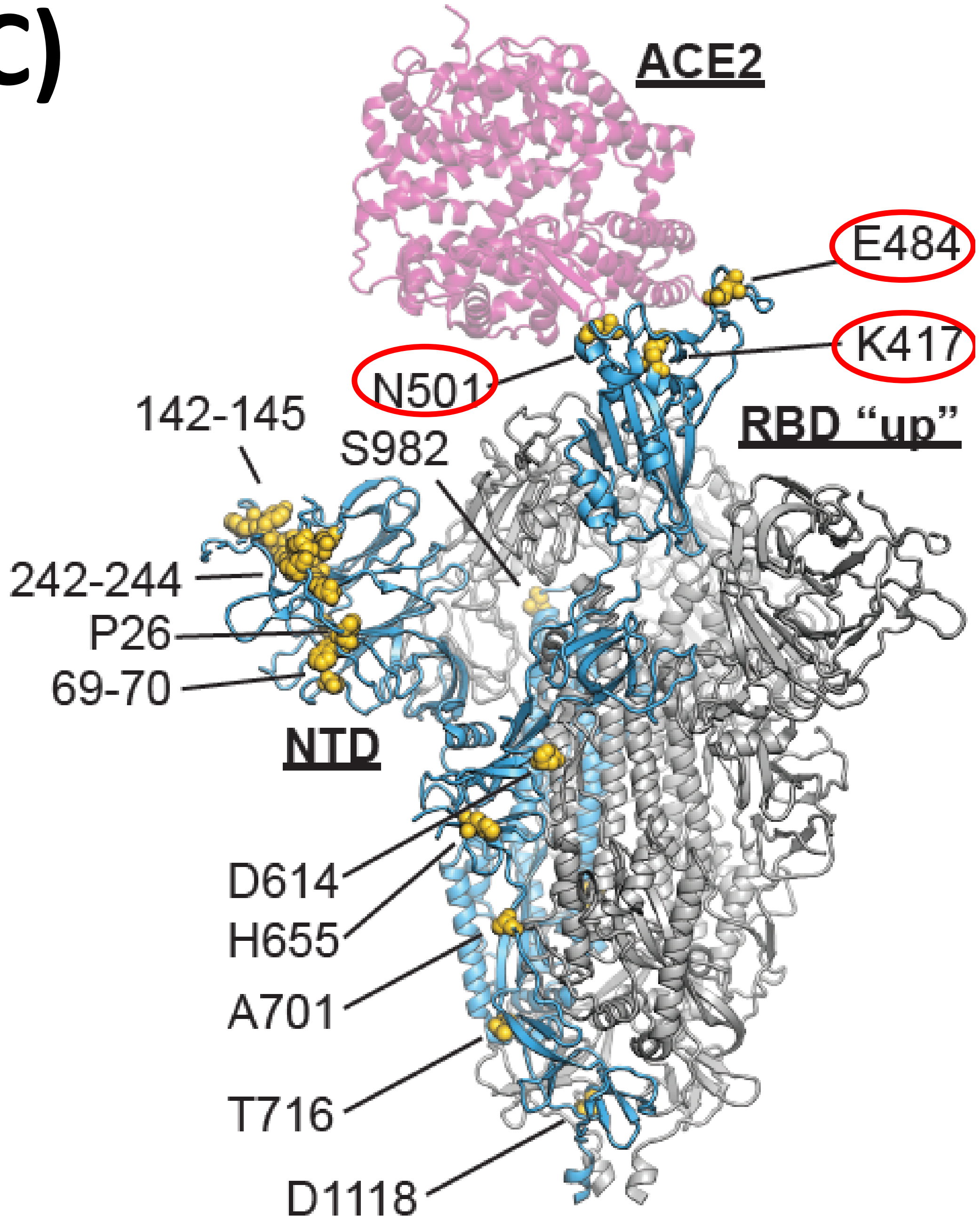
COVID-19 vaccine BNT162b1 elicits human antibody and T_H1 T cell responses

Ugur Sahin, Alexander Muik, […] Özlem Türeci

Nature **586**, 594–599(2020) | Cite this article

Variants of Concern (VoC)

- **B.1.1.7 – The 'British-origin'/Alpha variant**
  - RBD changes: N501Y
  - A little bit more infectious (approximately 35%)
  - No strong evidence that it causes more severe disease
- **B.1.351 – The 'South African-origin' variant**
  - RBD changes: K417N, E484K, N501Y
  - More infectious
  - No strong evidence that it causes more severe disease
- **P.1 – The 'Brazilian-origin' variant**
  - RBD changes: K417T, E484K, N501Y
  - See B.1.351
- **B.1.617.2—The 'India'/Delta variant**

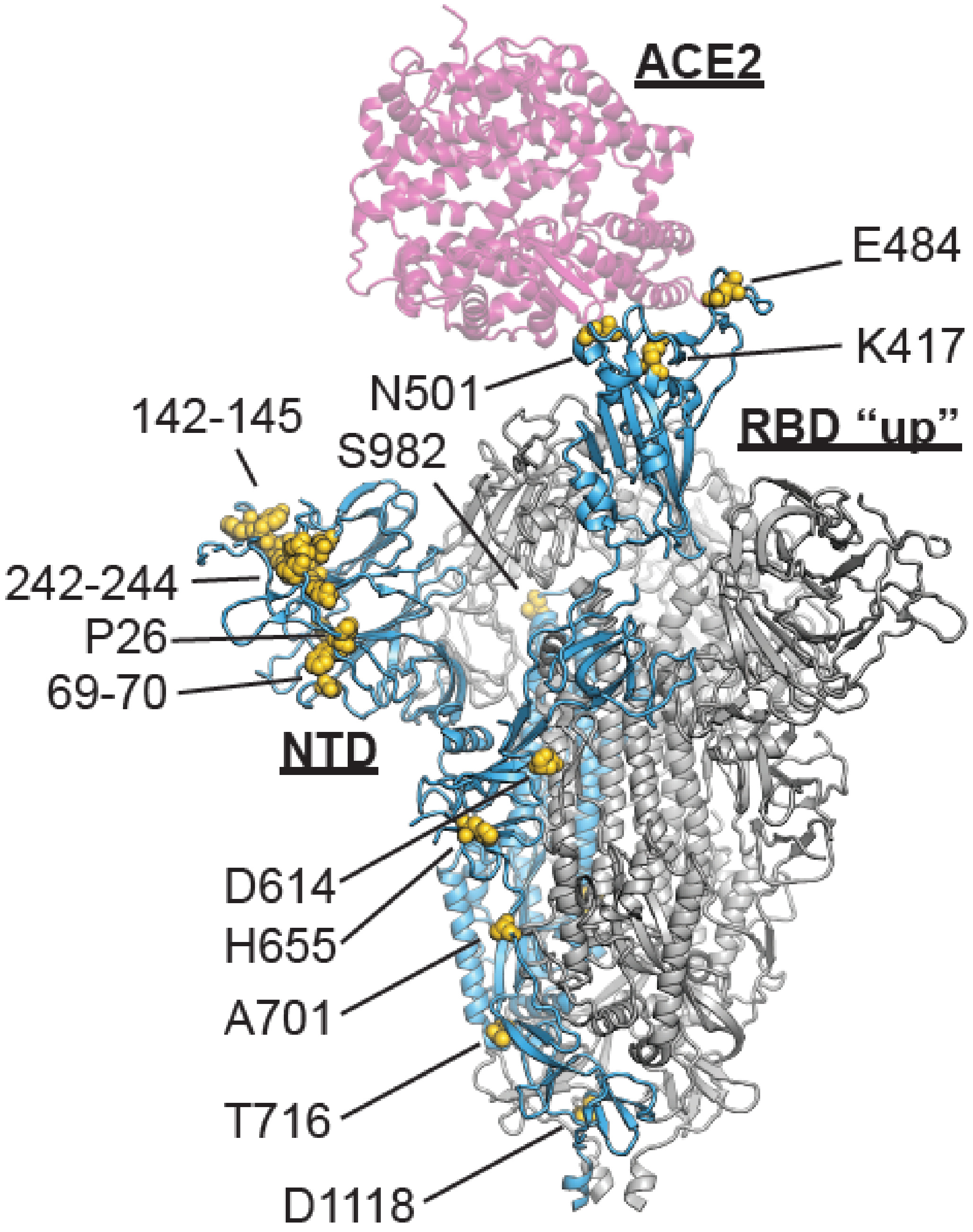


Adapted from Goran Bajic

Special thanks to Florian Krammer

Mutations outside of the RBD are also important, especially deletions in the NTD.

B.1.1.7	B.1.351	P.1
69-70 del	L18F	L18F
Y144 del	D80A	T20N
N501Y	D215G	P26S
A570D	**K417N**	D138Y
P681H	**E484K (ERIK)**	R190S
T716I	**N501Y (NELLY)**	**K417T**
S982A	A701V	**E484K**
D1118H	242-244 del	**N501Y**
		H655Y
		T1027I



Adapted from Goran Bajic

Special thanks to Florian Krammer

Monoclonal antibody therapeutics

Variant	Eli Lilly's therapeutic mAb (LY-CoV555)	Regeneron's therapeutic mAb cocktail (REGN10933 and REGN10987)
B.1.1.7	Still works ✓	Still works ✓
B.1.351	Impaired X	REGN10933 is impaired, REGN10987 still works ✓ X
P.1	Is unlikely to work X	REGN10933 is unlikely to work, if REGN10987 still works is unclear X ?

Many mAbs are not impaired by the mutations and development of several of these mAbs as therapeutics is in progress.

Special thanks to Florian Krammer

Efficacy in vaccine trials

ORIGINAL ARTICLE

Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant

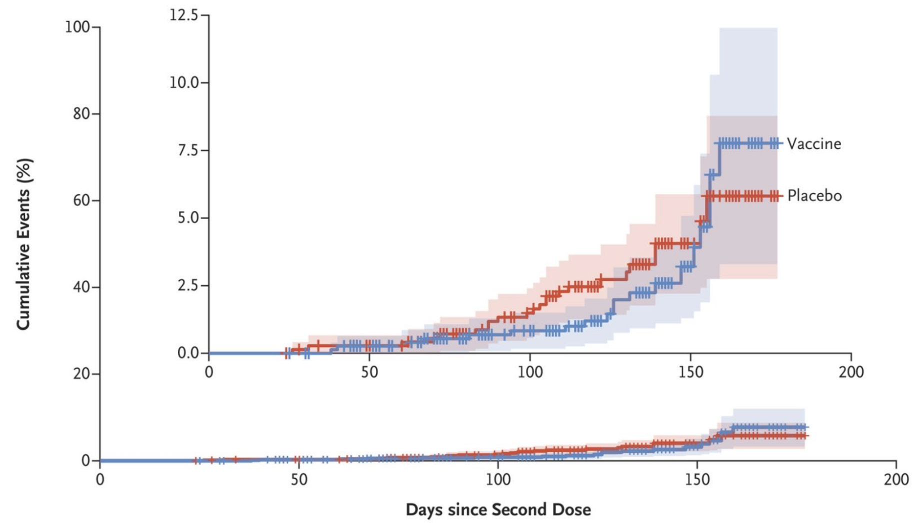
Shabir A. Madhi, Ph.D., Vicky Baillie, Ph.D., Clare L. Cutland, Ph.D., Merryn Voysey, D.Phil., Anthonet L. Koen, M.B., B.Ch., Lee Fairlie, F.C.Paeds., Sherman D. Padayachee, M.B., Ch.B., Keertan Dheda, Ph.D., Shaun L. Barnabas, Ph.D., Qasim E. Bhorat, M.Sc., Carmen Briner, M.B., B.Ch., Gaurav Kwatra, Ph.D., et al., for the NGS-SA Group Wits–VIDA COVID Group*

Article Figures/Media Metrics

March 16, 2021
DOI: 10.1056/NEJMoa2102214

AZ vaccine showed no evidence of efficacy against the SA (B.1.351) variant

Likely similar against Brazil strains and some other emerging strains in the US



	0	50	100	150	200
No. at Risk					
Vaccine	750	738	674	137	0
Placebo	717	707	632	124	0
Cumulative No. of Events					
Vaccine	0	2	6	14	19
Placebo	0	2	10	21	23

Efficacy in vaccine trials

Variant	J&J (Ad26 vector)	Novavax (recombinant spike)	AstraZeneca	Pfizer/BioNTech	Moderna
Wild type (garden variety) SARS-CoV-2	72%	95.6%	84% (60-90%)	95%	94%
B.1.1.7	ND	85.6%	74.6%	*In vitro* data only, but likely no impact on efficacy	*In vitro* data only, but likely no impact on efficacy
B.1.351	57% (95% B.1.351 lineage in South African part of trial) (100% against hospitalization)	60% (in HIV- individuals, >90% B.1.351 lineage in South African part of trial)	10%?	*In vitro* data only, but likely only moderate impact on efficacy	*In vitro* data only, but likely only moderate impact on efficacy
P.1	ND	ND	ND	ND	ND

Important point:
Even if vaccine efficacy against symptomatic disease is reduced, efficacy against severe disease is likely to remain high

Special thanks to Florian Krammer

Conclusions

- Multiple, highly effective vaccines with low levels of side effects available against SARS-CoV-2
- Difficult to estimate the extent to which asymptomatic infection is reduced—more studies are needed, but some effect is likely
- More vaccines are likely to be approved in US soon (Novavax? AZ?)
- Variants can reduce vaccine efficacy—variant emergence will be limited by rapid vaccine uptake