COVID-19 Vaccine: Between Myth and Reality

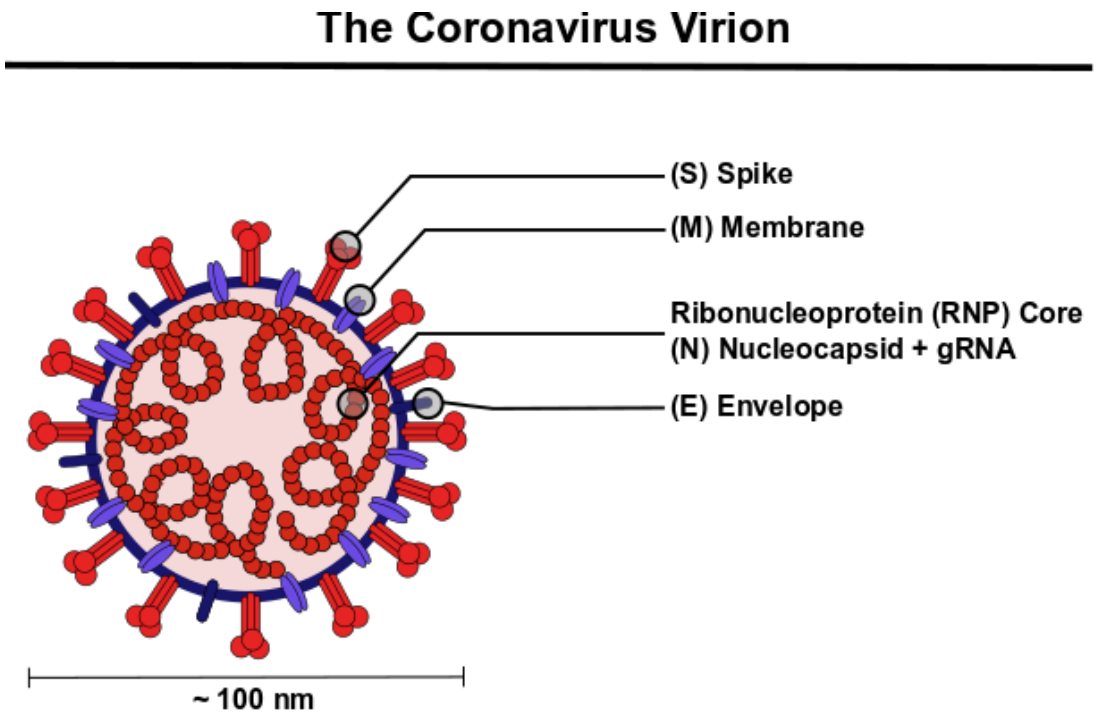
Paul G. Thomas

ASPET virtual seminar

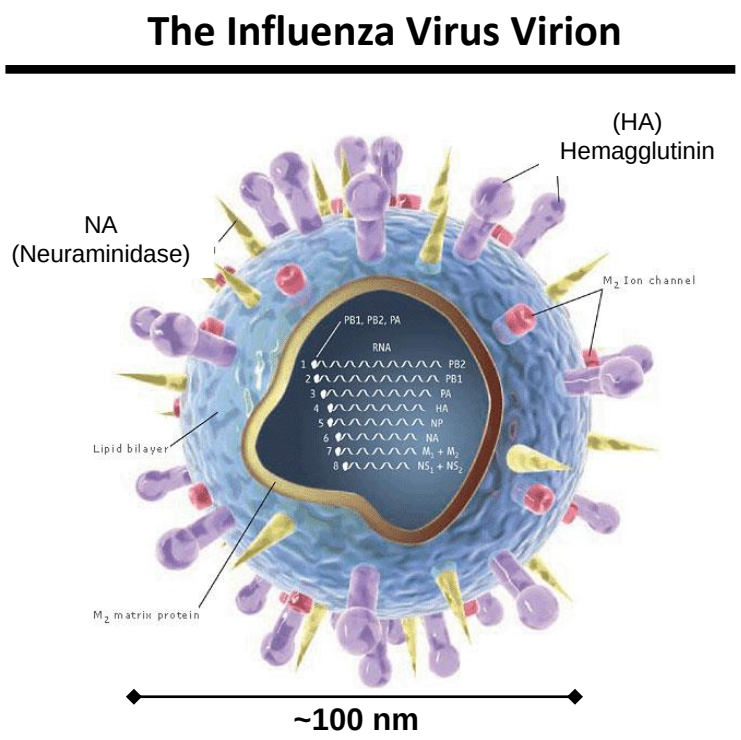
Outline of talk

- 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



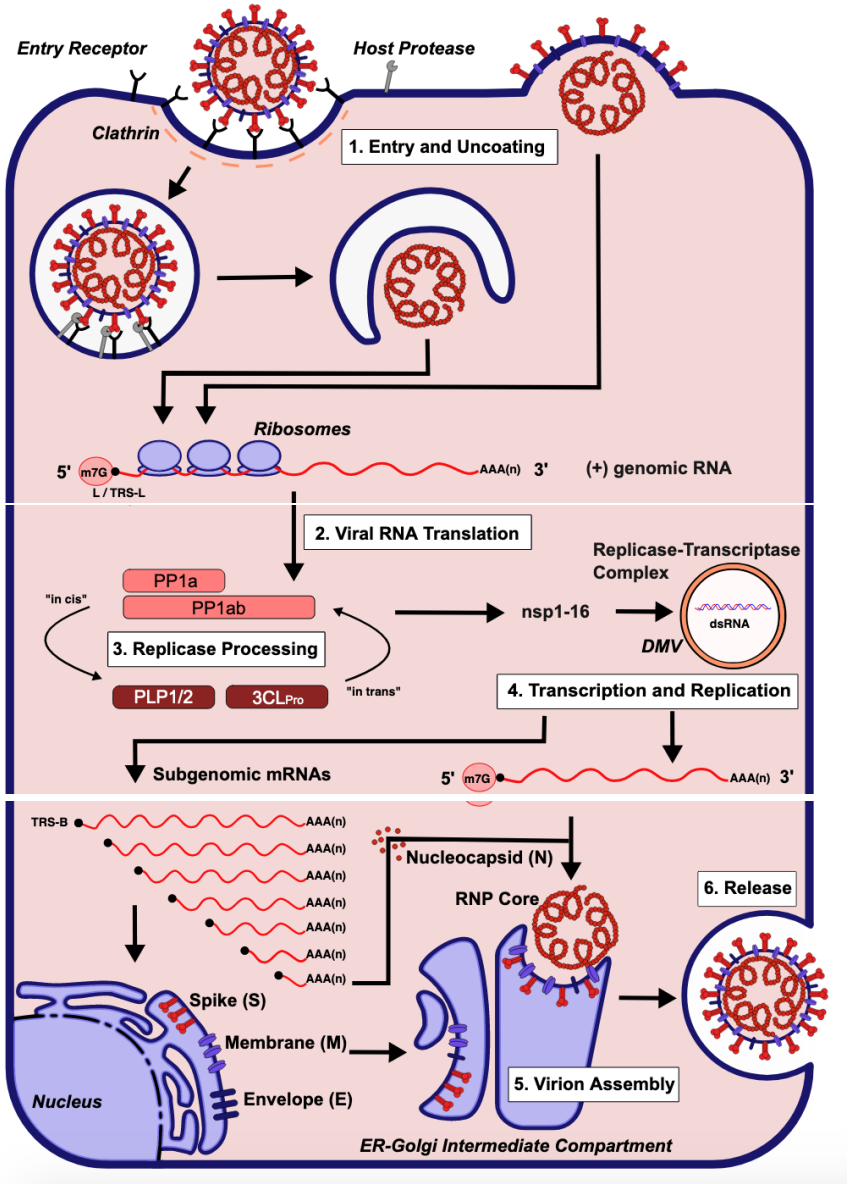
(+) ssRNA genome ~28-32 Kb
29 proteins



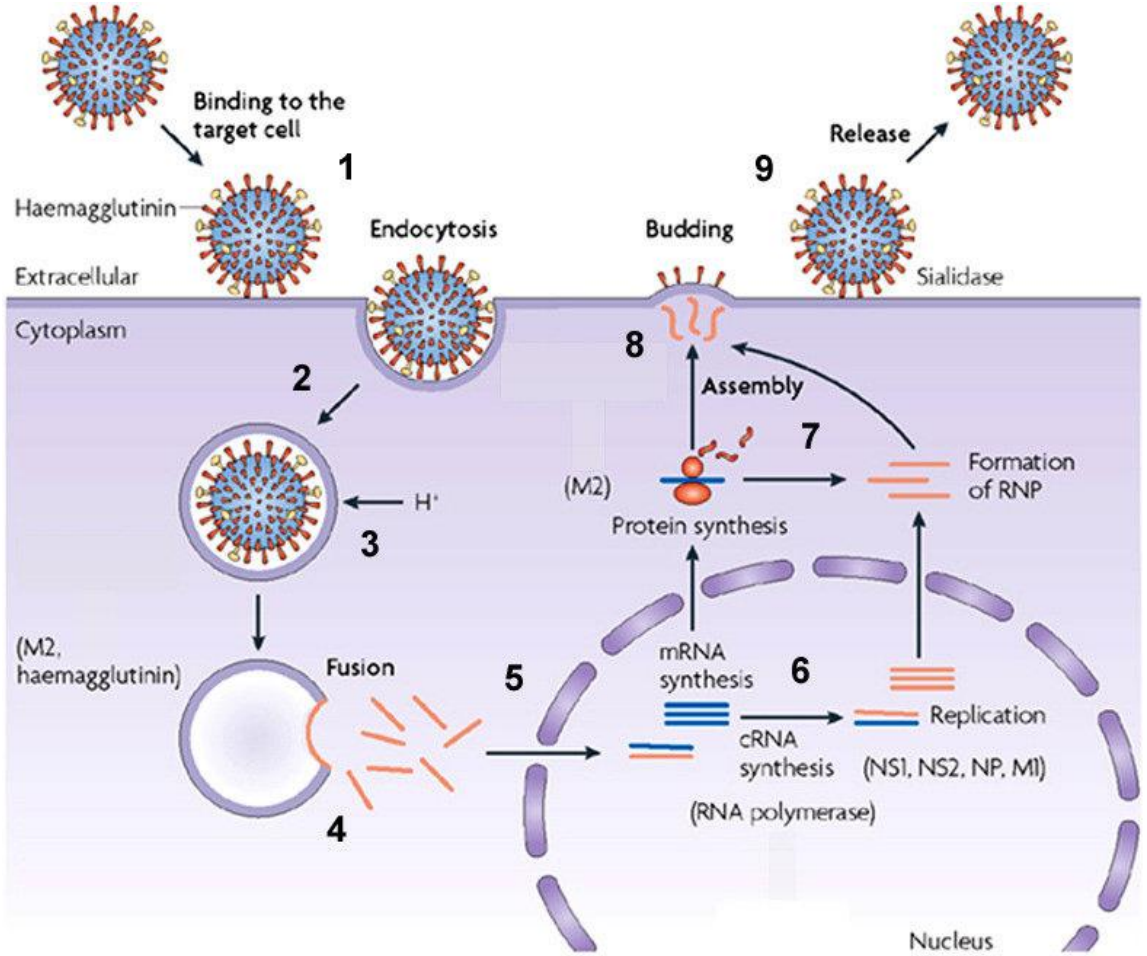
(-) segmented ssRNA genome ~28-32 Kb
~14 Kb, 10-14 proteins

Coronavirus and influenza virus replication cycles

Coronavirus

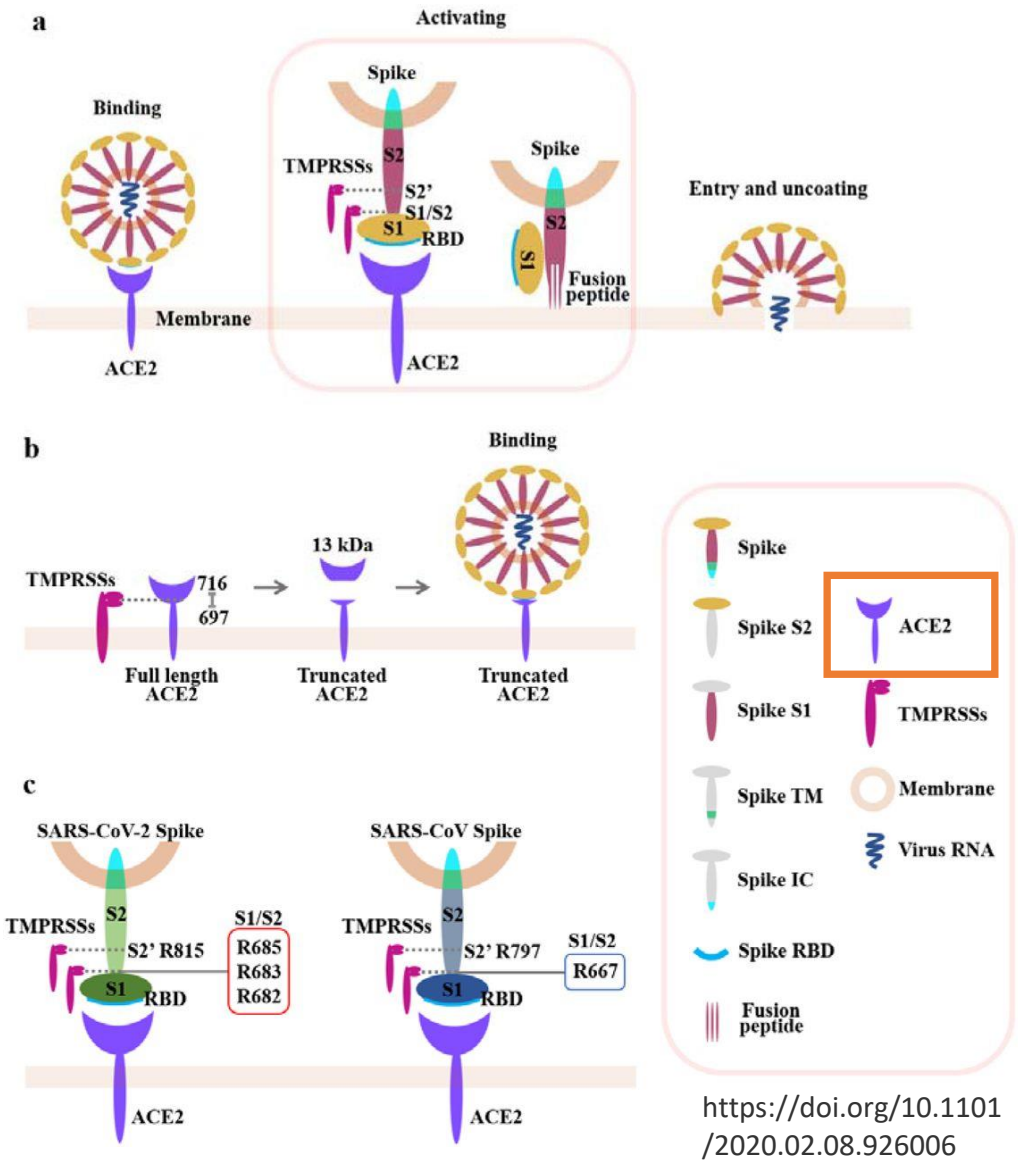


Influenza virus



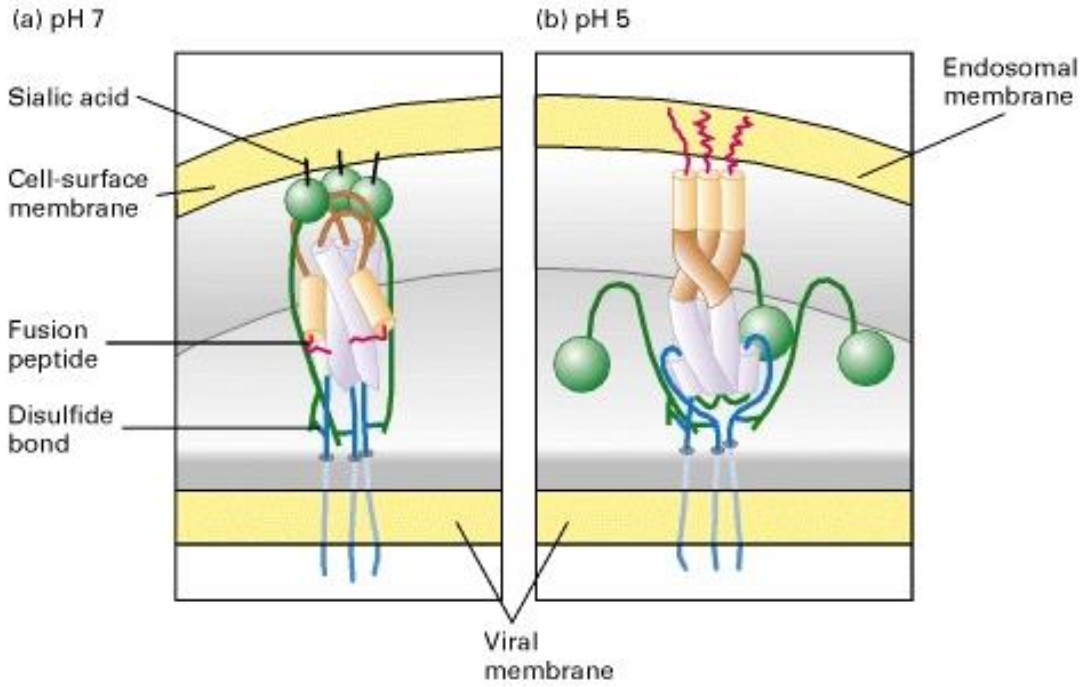
Distinct receptor binding features of SARS vs. influenza viruses

Coronavirus



https://doi.org/10.1101/2020.02.08.926006

Influenza virus

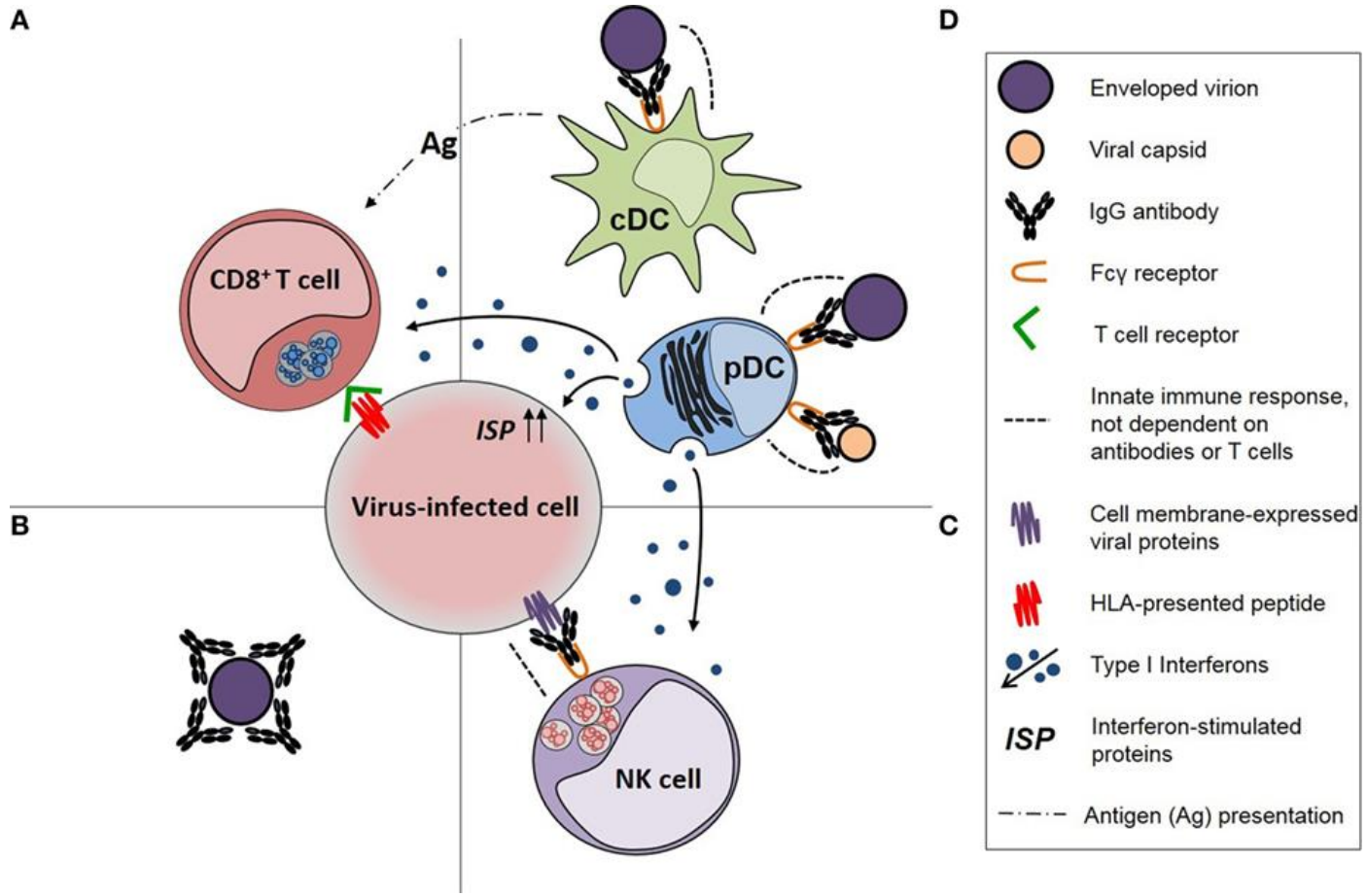


Influenza HA binds to sialic acid residues on diverse surface proteins

How does the immune response protect from or eliminate viruses?

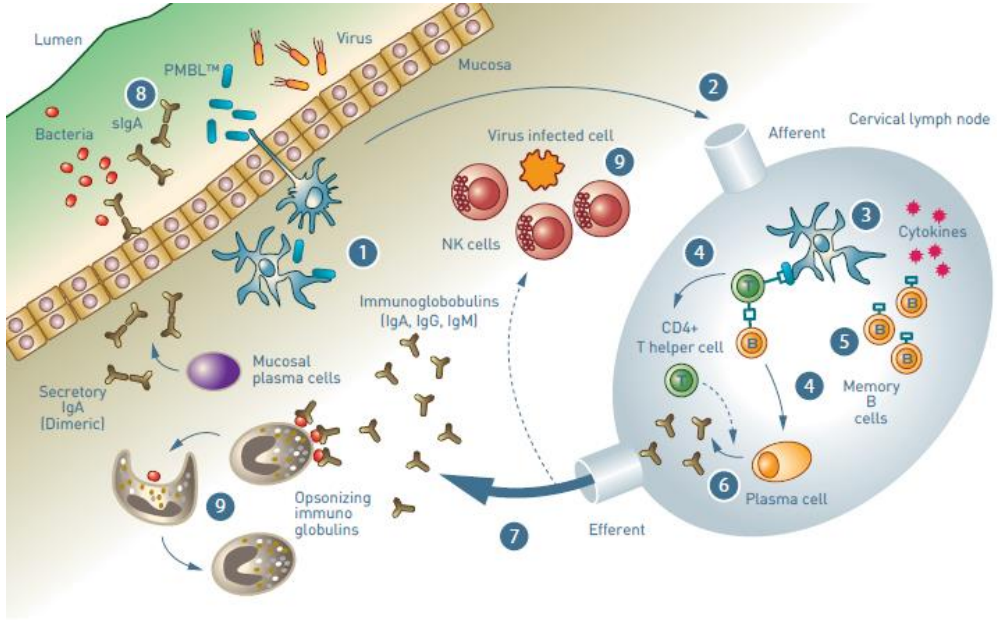
Two main mechanisms of viral clearance

- **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”



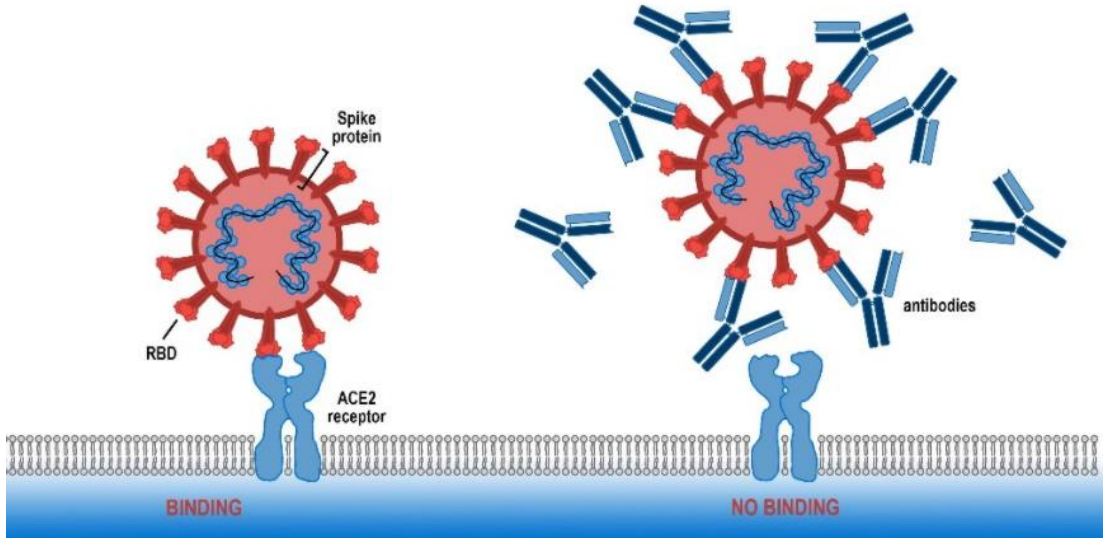
https://www.frontiersin.org/articles/10.3389/fimmu.2017.00780/full

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

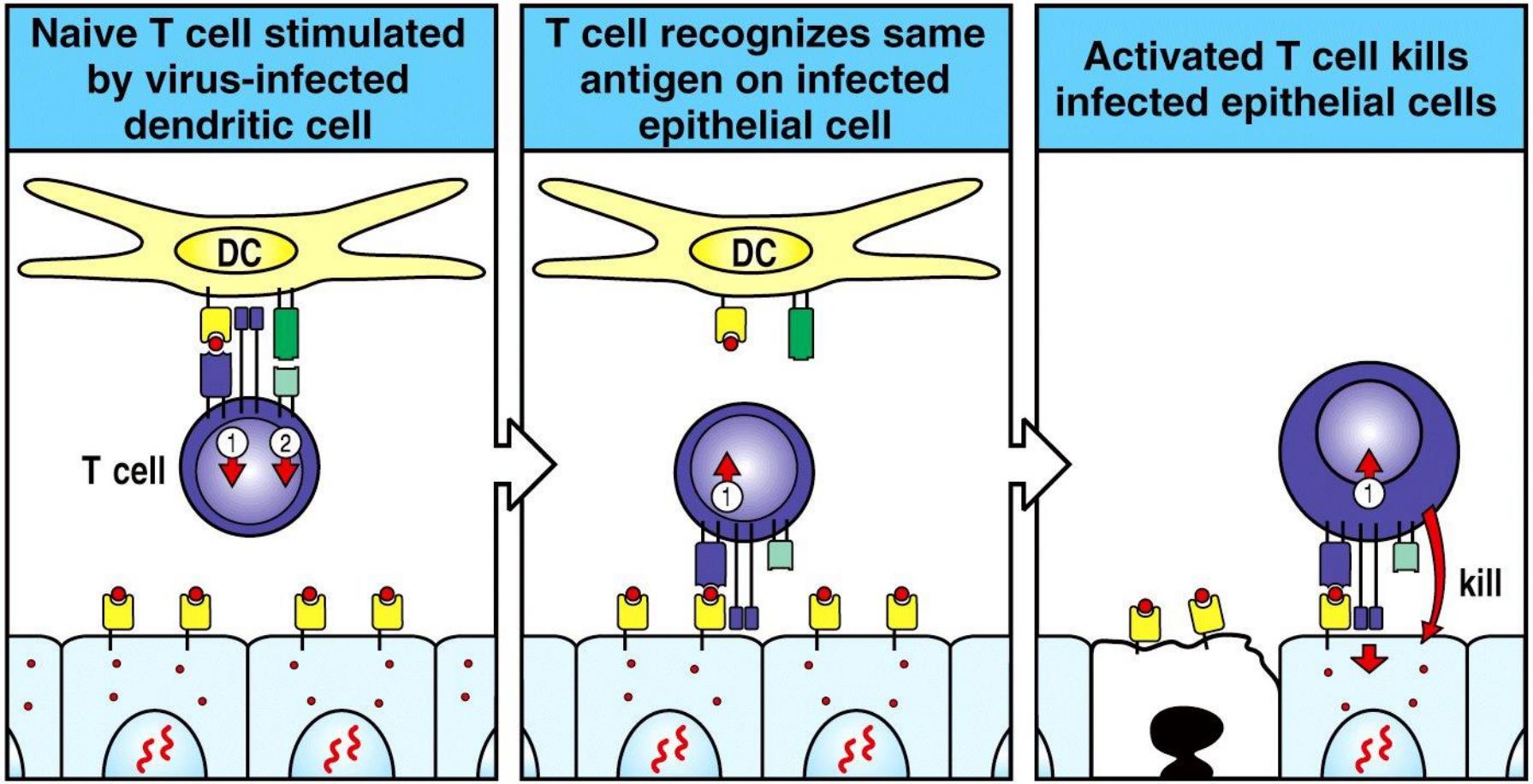


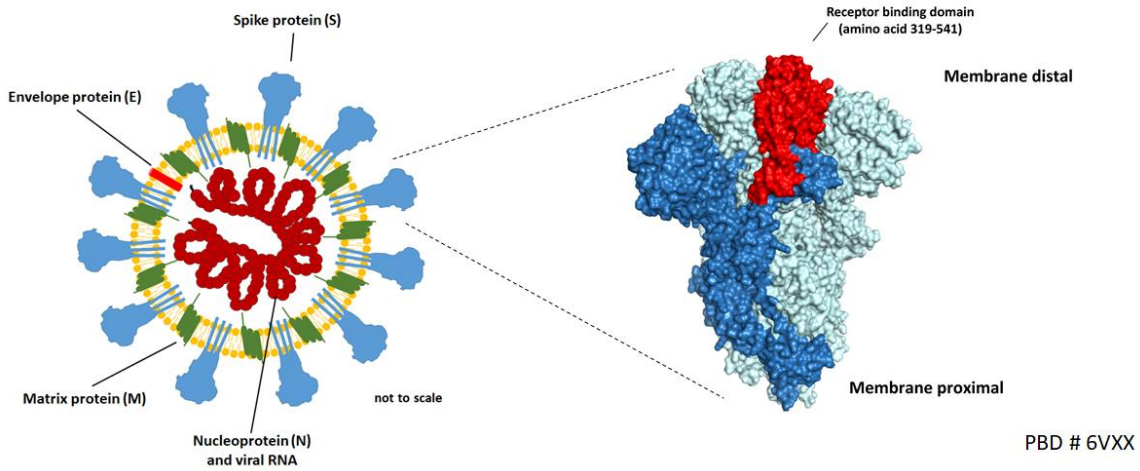
Figure 8-13 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

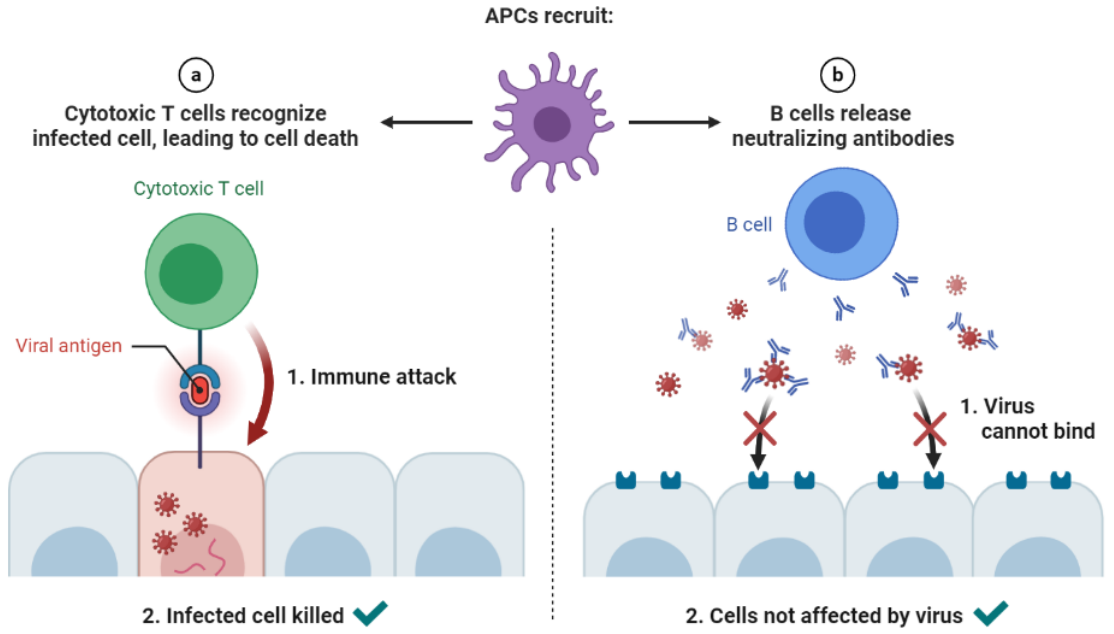
After learning what the virus looks like in the lymph node, CD8 T cells go to the site of infection and kill infected cells

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
  - Relative weak CD8+ response (in many patients)—kills infected cells

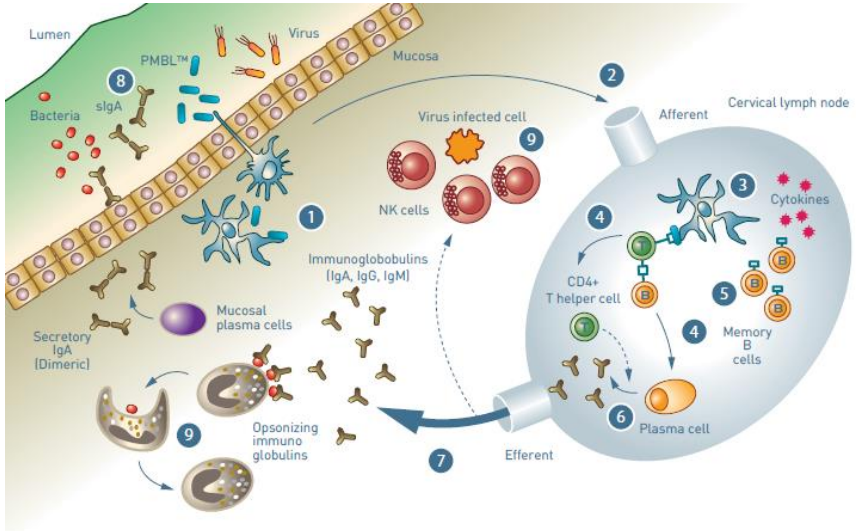




Special thanks to Florian Krammer

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



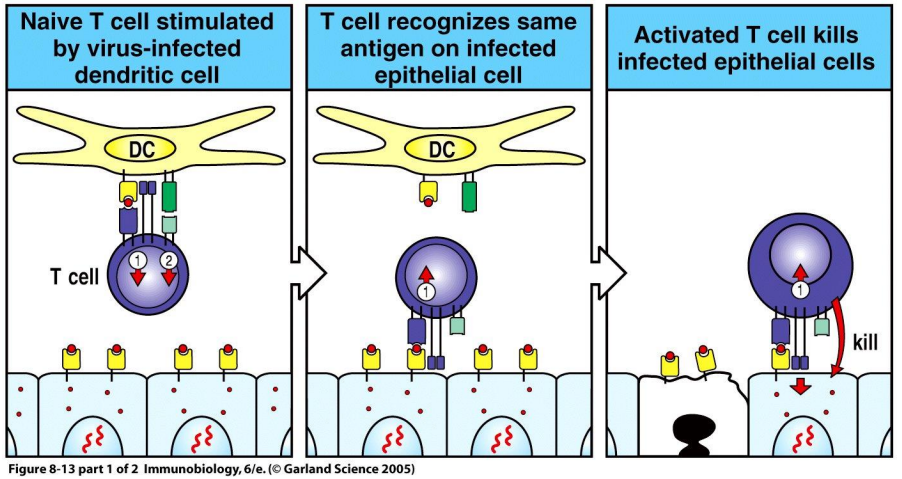


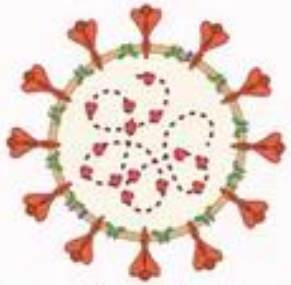
Figure 8-13 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

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



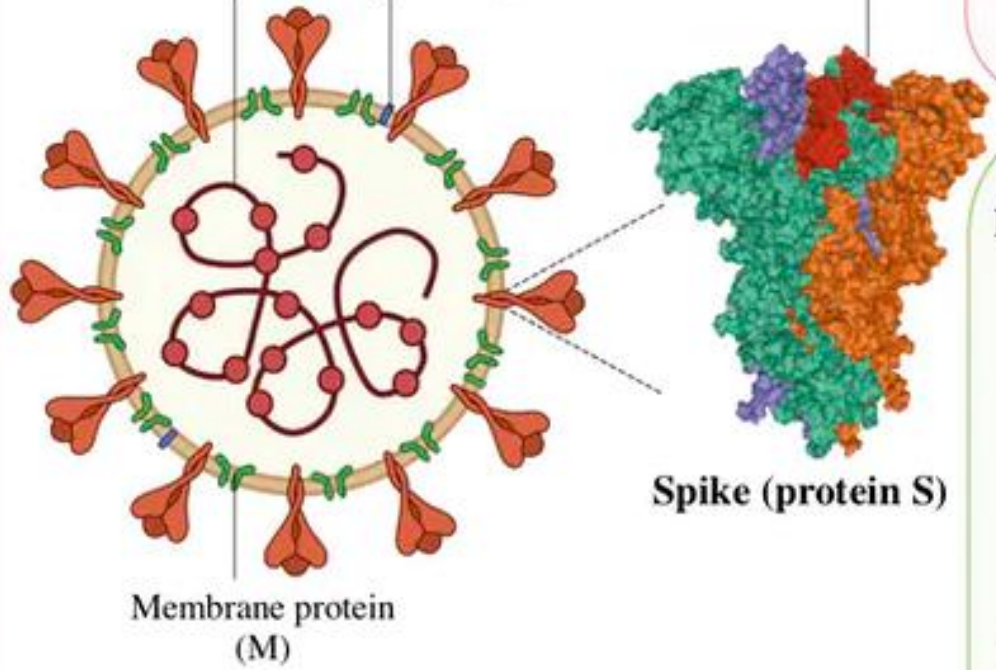
b. Recombinant proteins vaccines

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



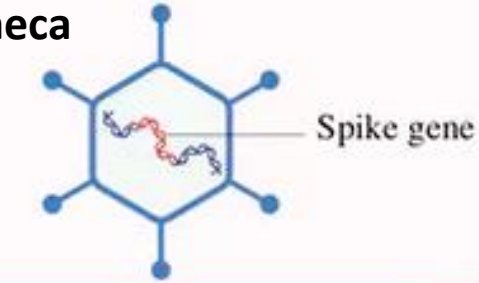
SARS-CoV-2

c. Viral vector vaccines

Viral vector vaccines contain another virus modified to express S protein

JNJ

AstraZeneca

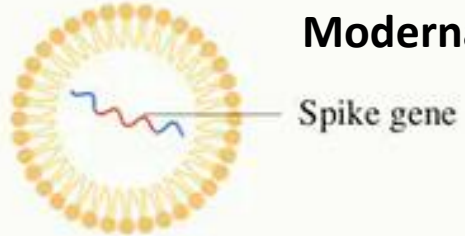


d. RNA vaccines

RNA vaccines consist of RNA packed in lipid nanoparticles

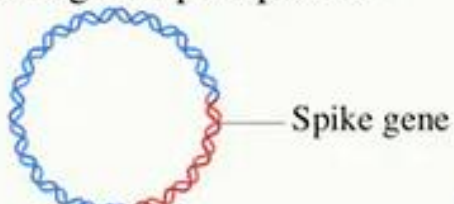
Pfizer/BioNTech

Moderna



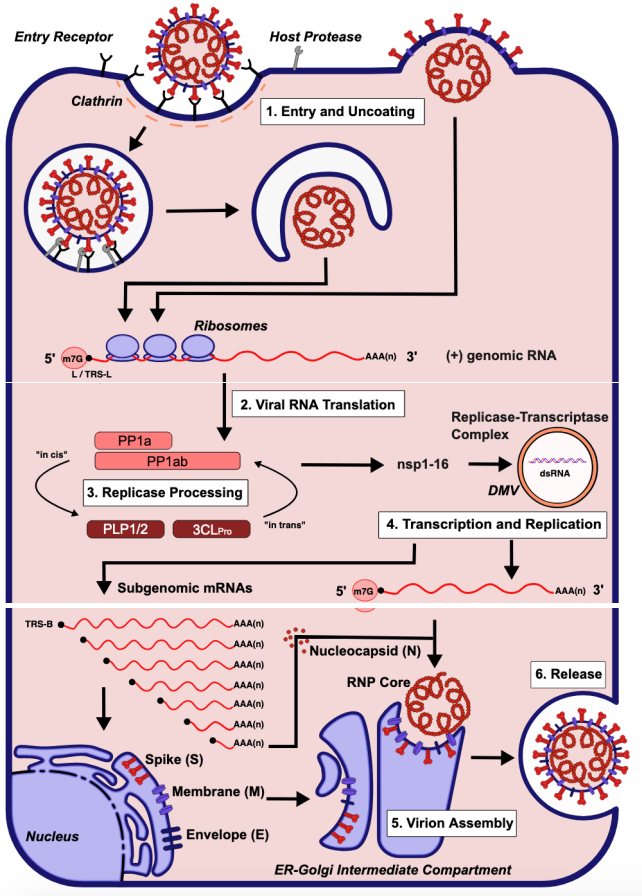
e. DNA vaccines

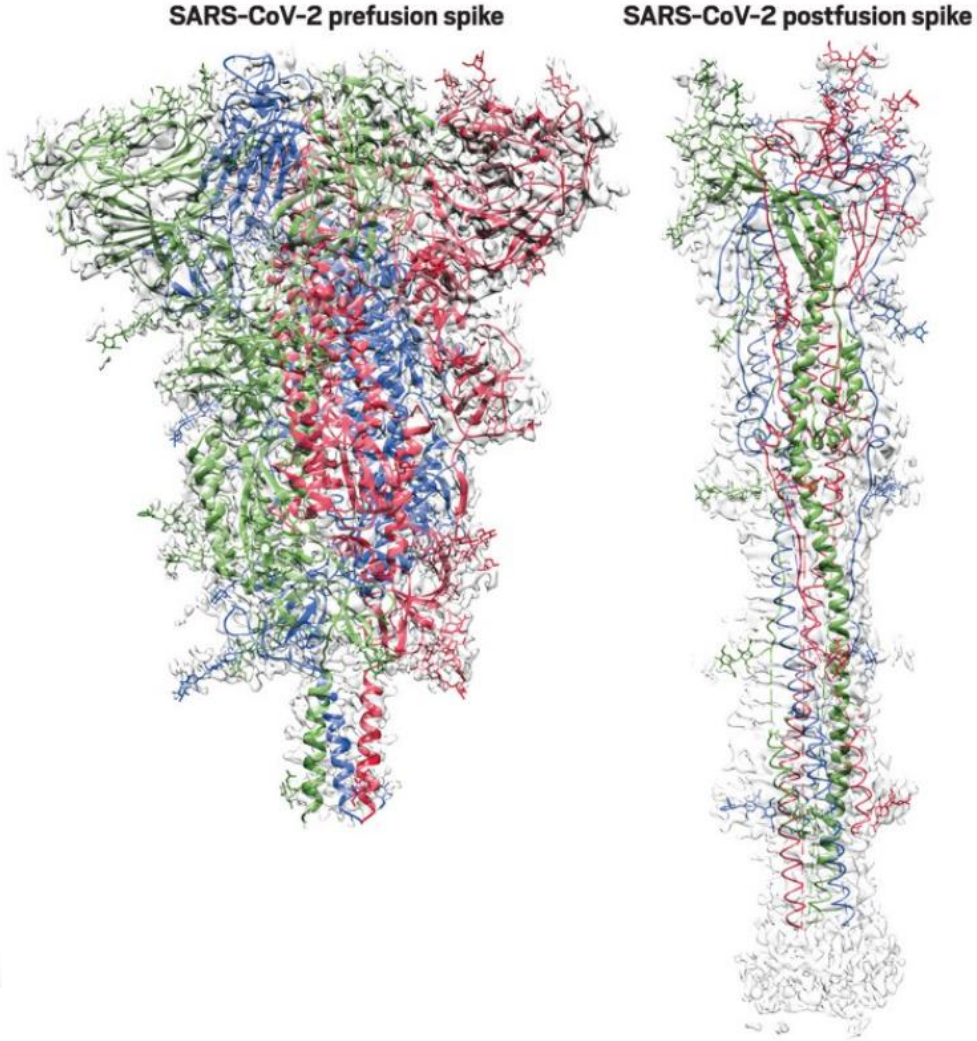
DNA vaccines contain a circular DNA encoding the spike protein



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

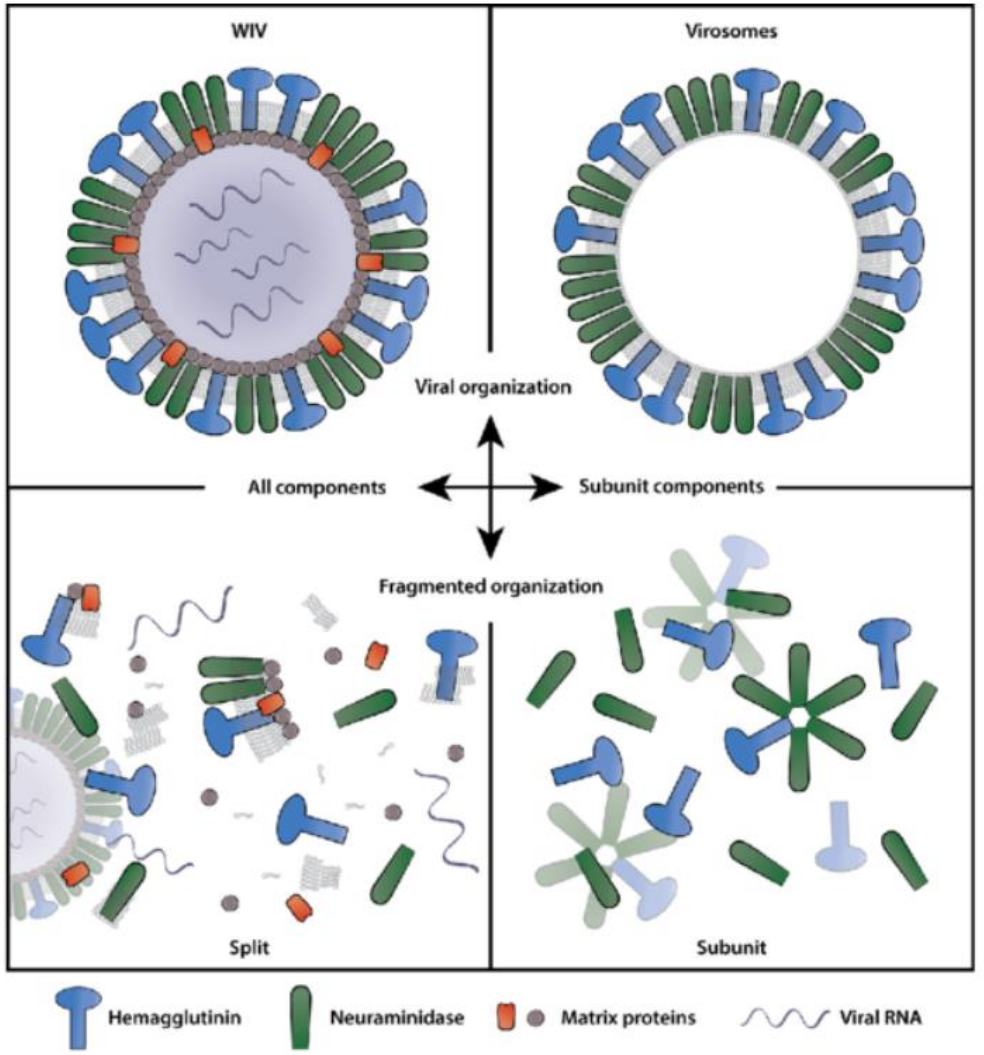
Harvard Medical School virologist Bing Chen determined prefusion and postfusion structures of the SARS-CoV-2 spike protein. The spike sheds a subunit and elongates during fusion with a human cell.

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**

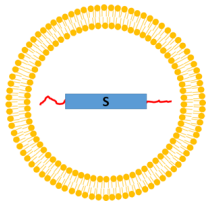


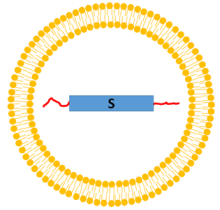
Data from Phase I/II trials

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

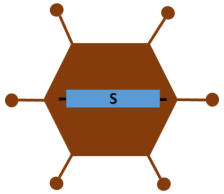
Vaccines in Phase III

- Moderna (94)%



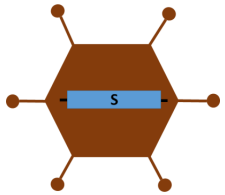


- Pfizer (95%)



- AstraZeneca (62-90%)

IR

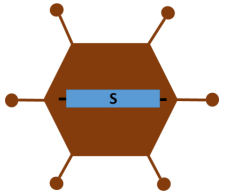


- Janssen (72%)

- Novavax (89-96%)

IR

- Gamaleya (91.6%)

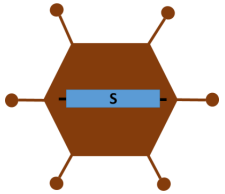


IR

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

IR

- Cansino

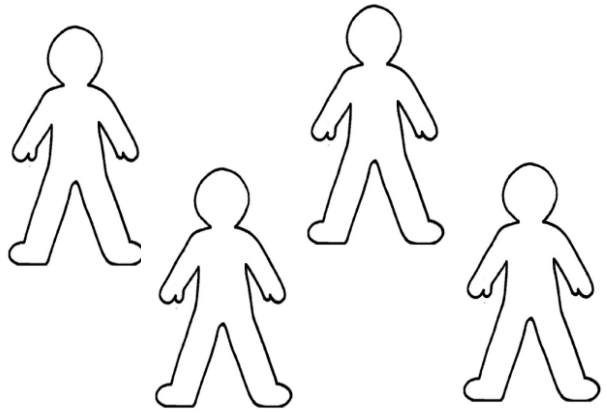


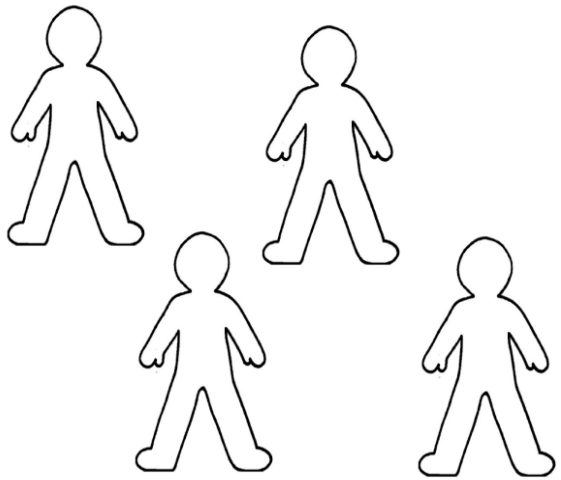
For most of these vaccines two injections are required.

Special thanks to Florian Krammer

How does a Phase III study work?

Vaccine group





Placebo control group

Conducted by independent medical centers (usually geographically distributed)

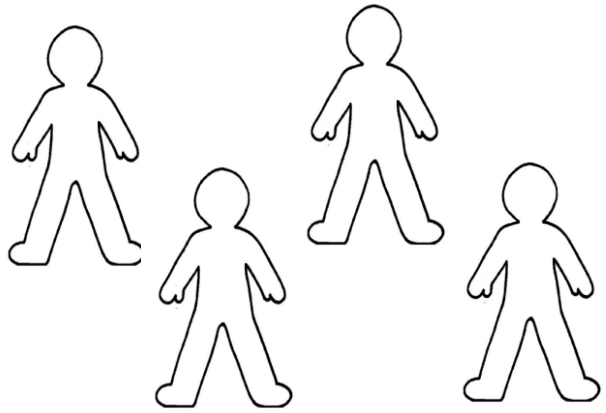
An independent committee watches the data

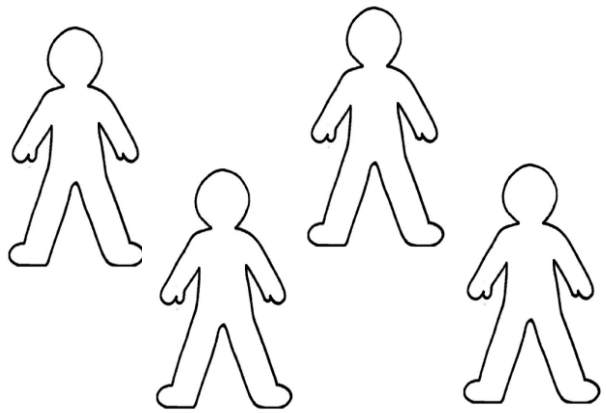
Analysis timepoints and success are pre-defined

Special thanks to Florian Krammer

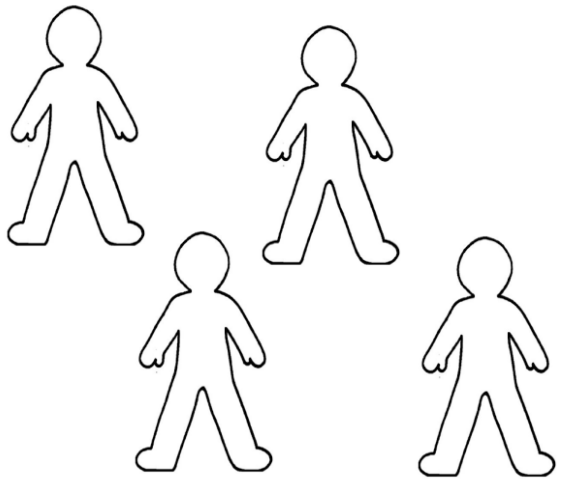
How does a Phase III study work?

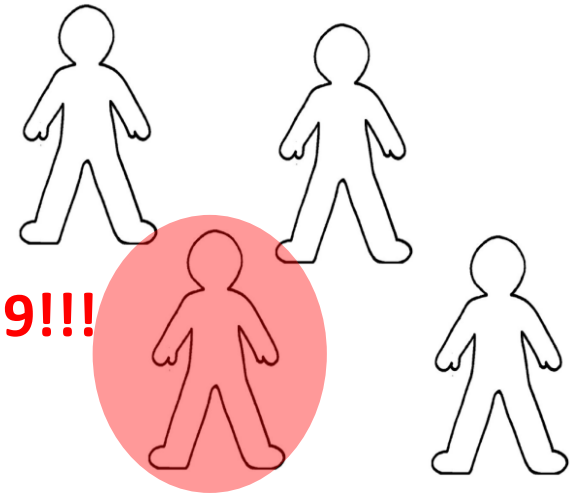
Vaccine group





Time

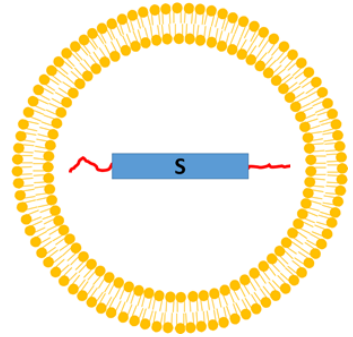




Placebo control group

Special thanks to Florian Krammer

What do the Pfizer results mean?



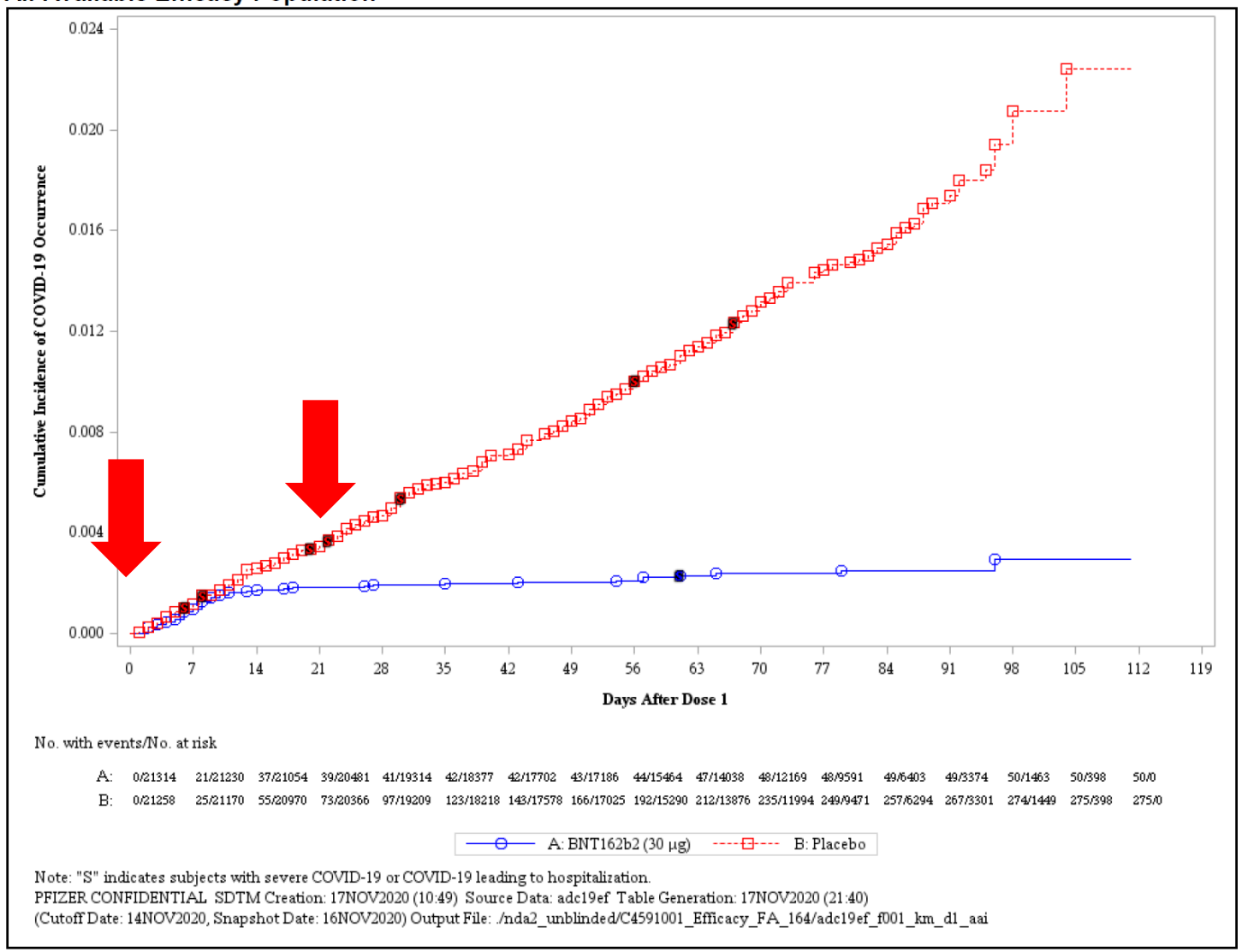
- 43,538 individuals are in the study
- 170 COVID-19 cases were recorded
  - 162 in the placebo group (9 severe)
  - 8 in the vaccine group (1 severe)
- 95% efficacy against symptomatic disease (one symptom plus PCR+, they start measuring this 7 days post dose 2)
- 94% efficacy in the 65-85 year old 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.

<u>Moderna data look almost identical</u>

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



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)

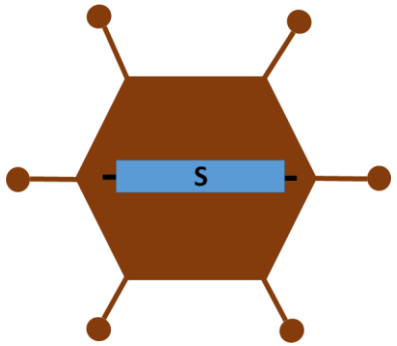
Target	Started in	Individuals enrolled[2]	Company	Status	Phase	Registration number
CMV	2017	181	Moderna	Fully enrolled	Phase 1	NCT03382405
hMPV/PIV3	2019	114	Moderna	Recruiting	Phase 1	NCT04144348
Zika	2019	120	Moderna	Fully enrolled	Phase 1	NCT04064905
Influenza	2017	156	Moderna	Fully enrolled	Phase 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, will likely be licensed in EU in March

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

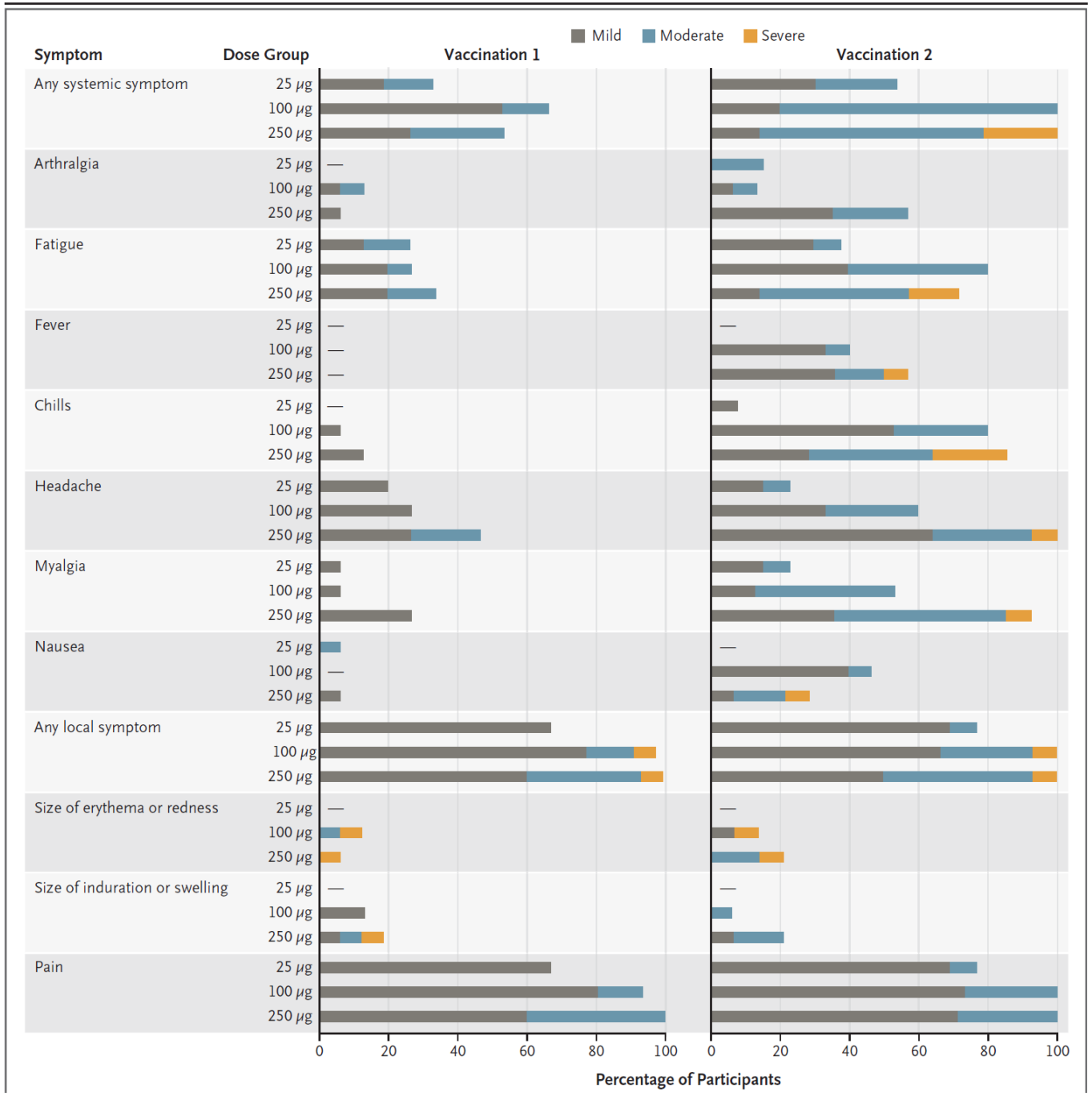
Reactogenicity

- 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?

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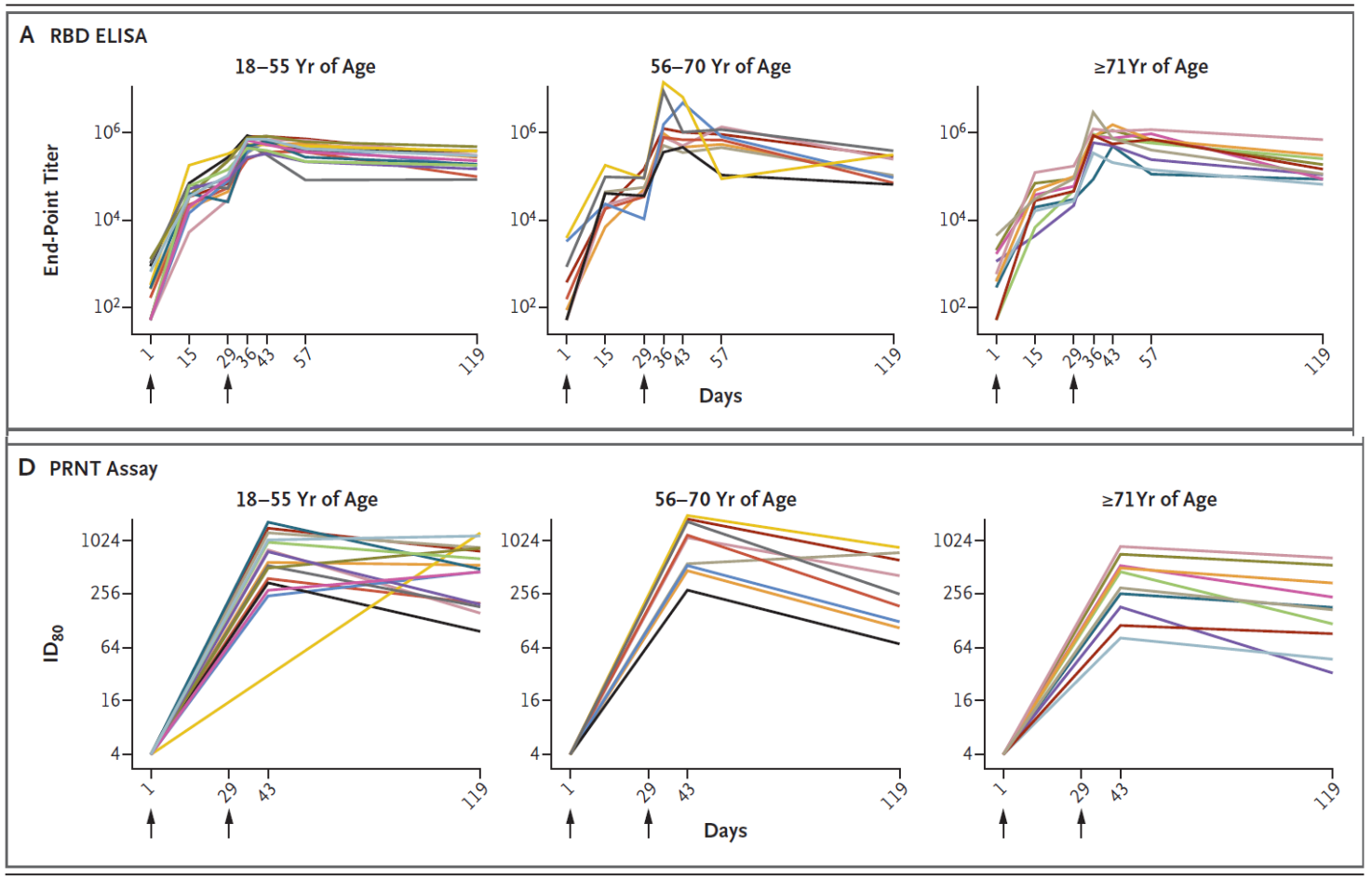
CORRESPONDENCE

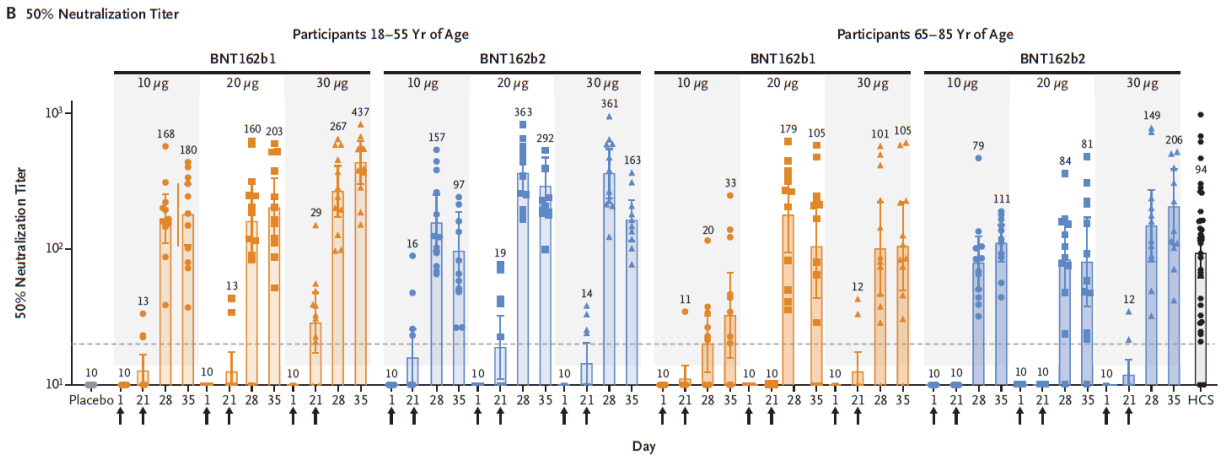
Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination

- 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

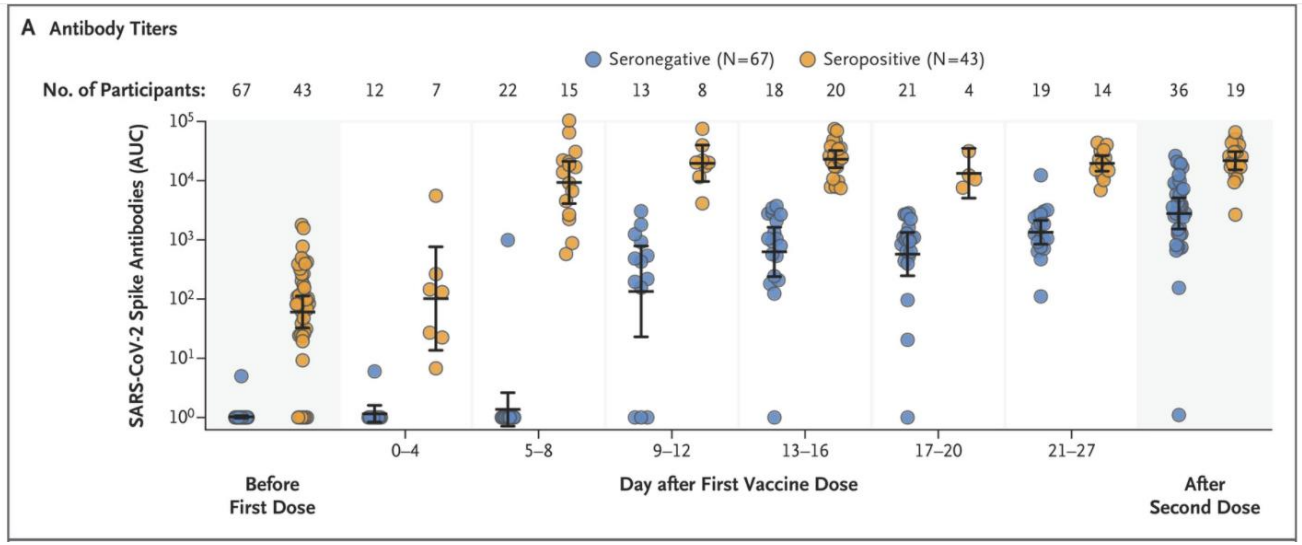


The NEW ENGLAND JOURNAL of MEDICINE

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

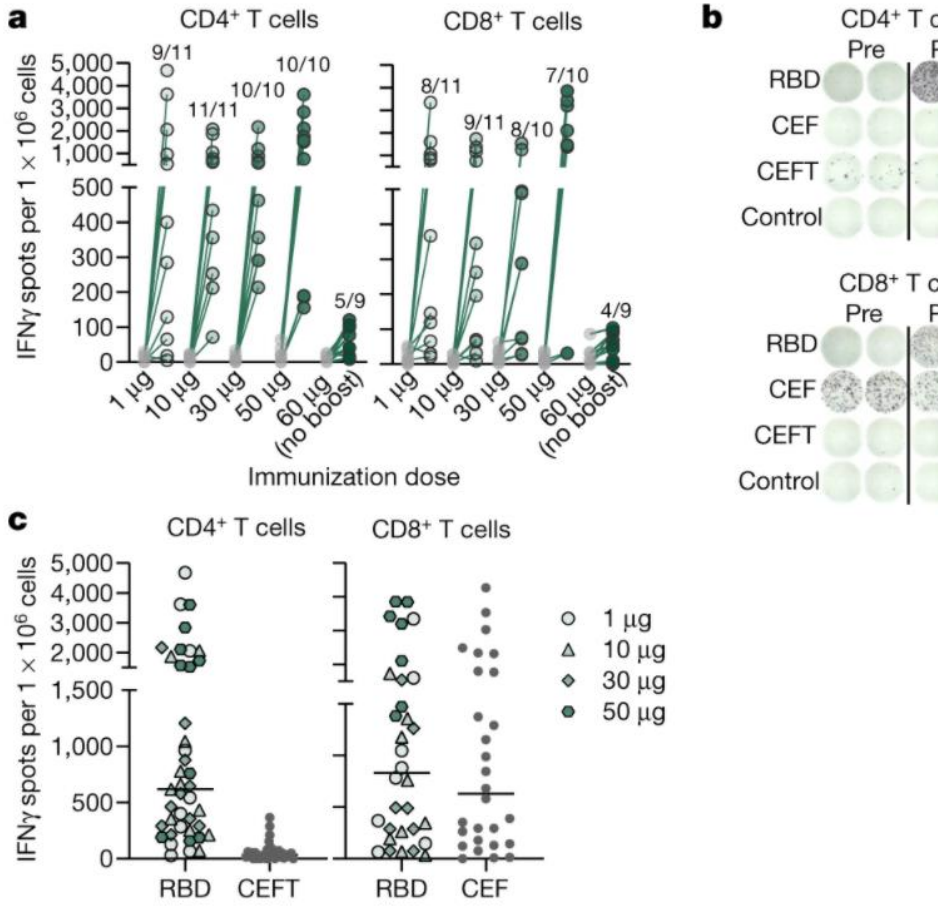
- Post-infection, a single dose of the Pfizer/BioNTech vaccine was equivalent to two doses of the vaccine in naïve individuals
- Still a significant boost!

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

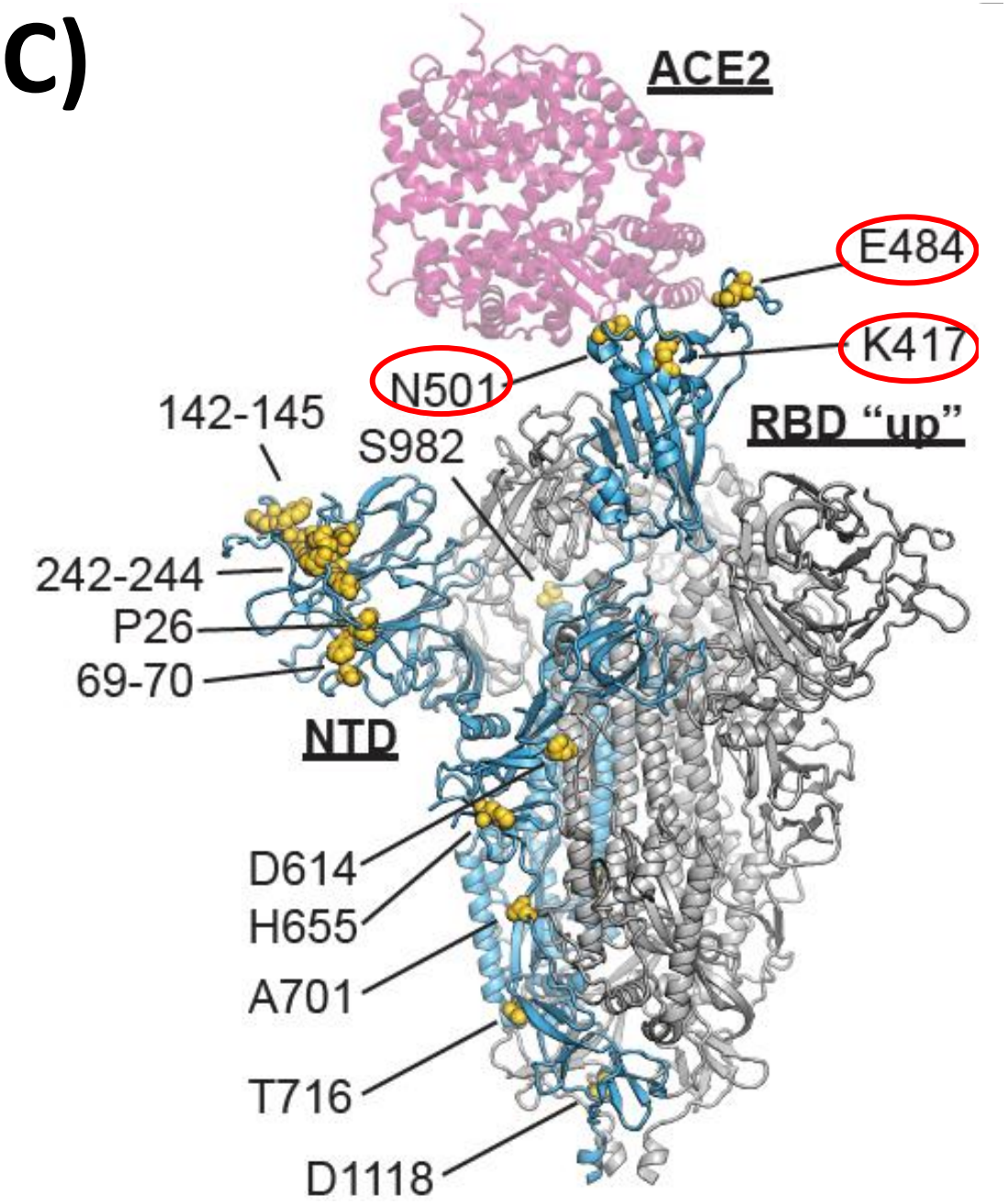
Ugur Sahin ✉, Alexander Muik, [...] Özlem Türeci

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

173k Accesses | **91** Citations | **1022** Altmetric | Metrics

Variants of Concern (VoC)

- **B.1.1.7 – The ‘British-origin’ 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**

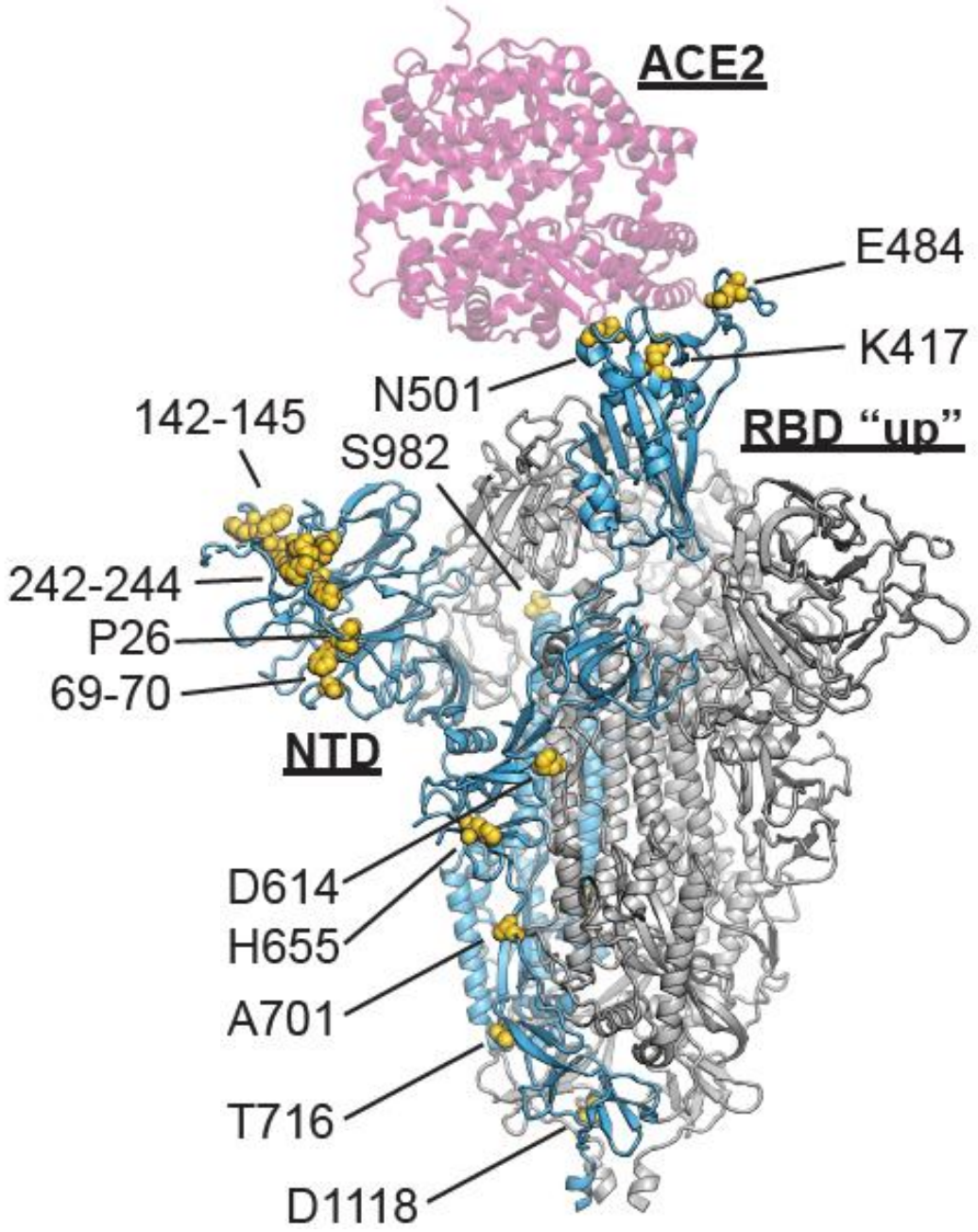


Adapted from Goran Bajic

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

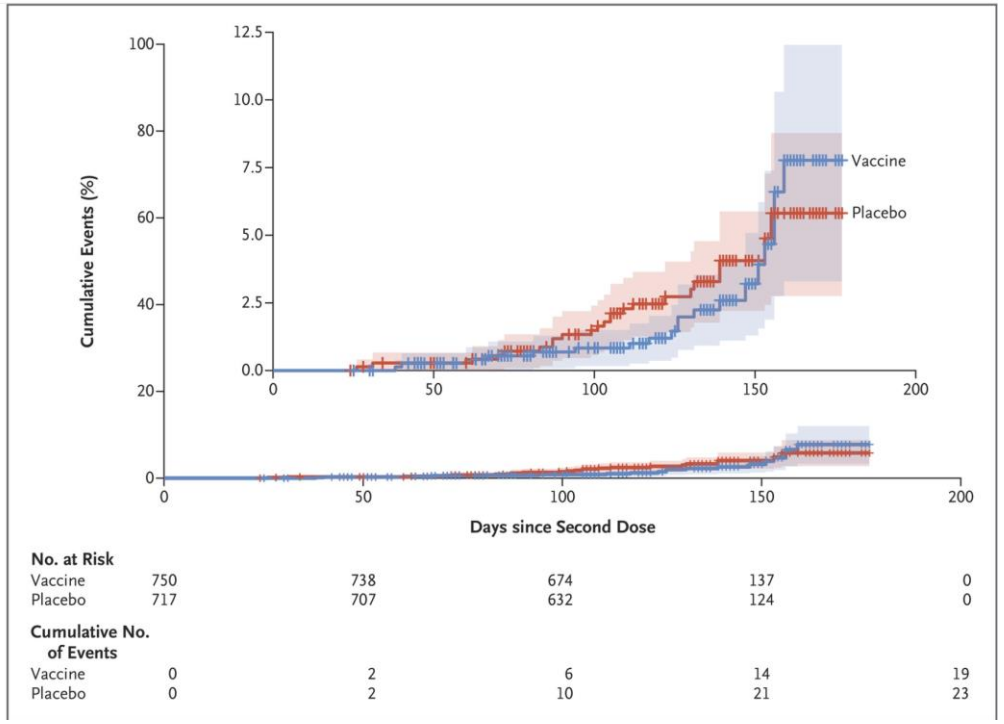
Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant

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*

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



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