COVID-19 Vaccines

The way out of the pandemic…?

11 March 2021, Virtual Event Series - Session 1

“Are COVID-19 Vaccines a Way Out of the Pandemic?”

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Virtual Event Series - Session 1

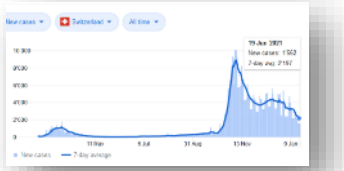
COVID Pandemic Update

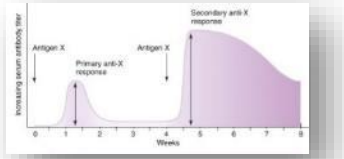
- Numbers, trends
- Variants: General information, UK South Africa, Brazil

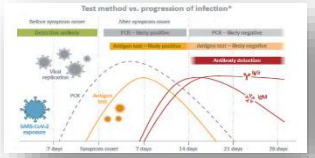
Immunology and vaccines

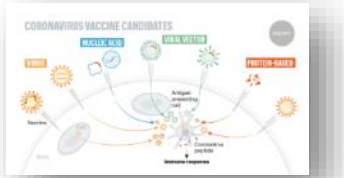
- Ab, nAb, cellular immunity
- Vaccine development - principles
- Currently important approaches
- Vaccine protection – efficacy

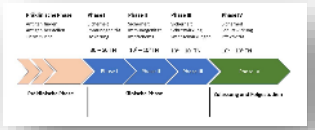
Some common questions









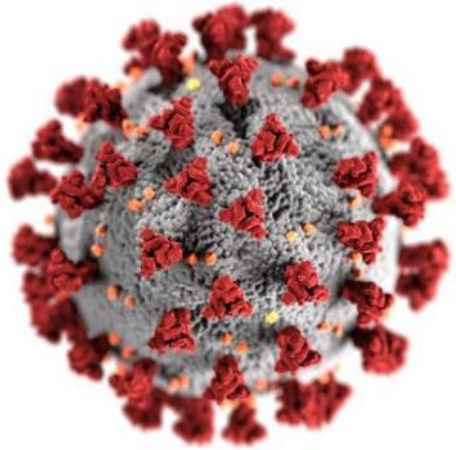


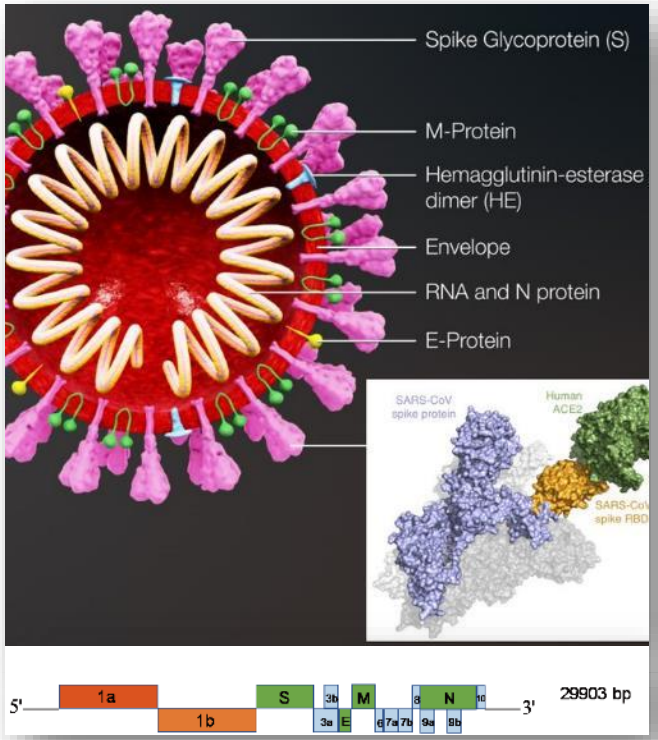
Poll question #1

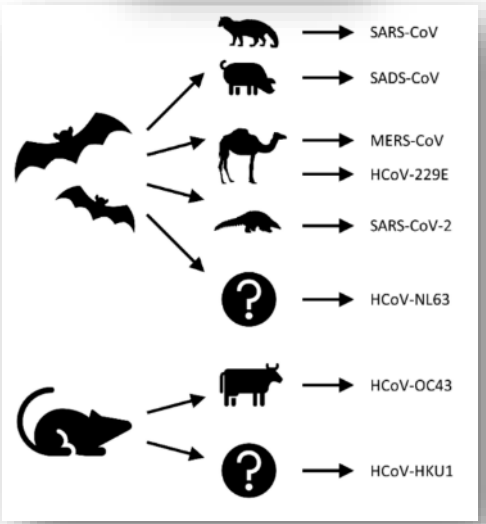
Would you want to be vaccinated with a COVID-19 vaccine today?

1. Yes
2. No
3. Still thinking about it

Coronavirus – SARS-CoV-2







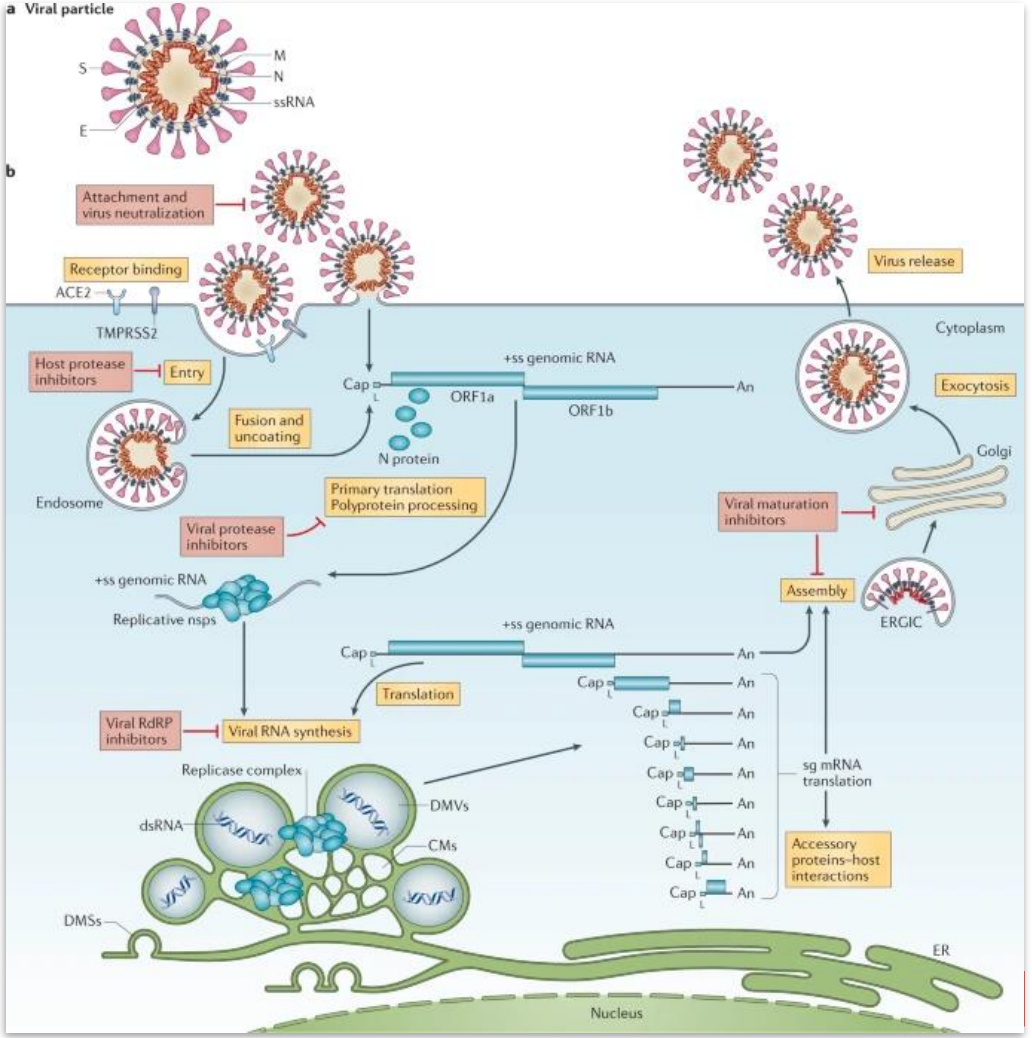
primary – intermediate hosts

SARS-CoV-2 Lifecycle in Host Cells

Endosome

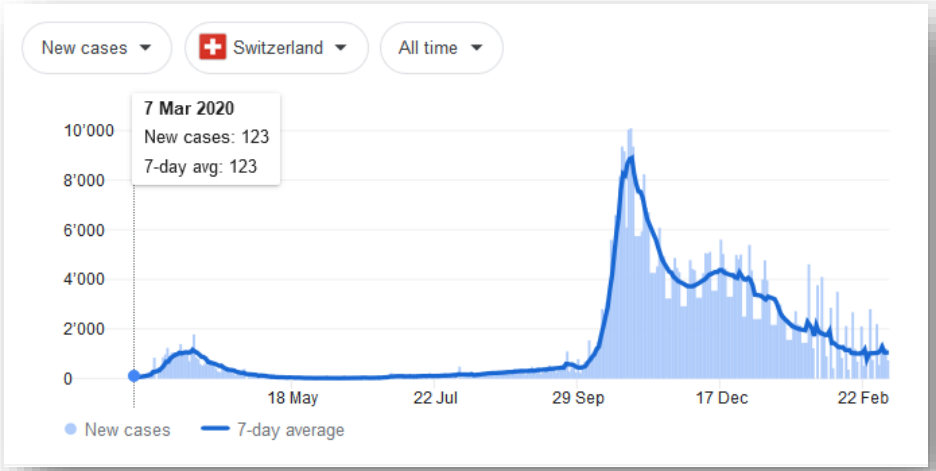
Endoplasmatic Reticulum (ER)

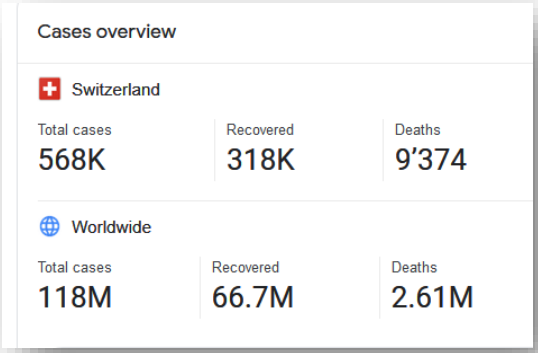
Golgi bodies



V'kovski et al., Nature Rev Microbiology 2020

COVID Pandemic Update





10 Mar 2021

First wave ... Second wave ... and now a third wave ... ?!

Measures (lockdown, shutdown, etc.) - effect, meaning and connection with progress:
"Virus characterisation, health care system, containing the spread, masks, diagnostics, vaccinations, etc."

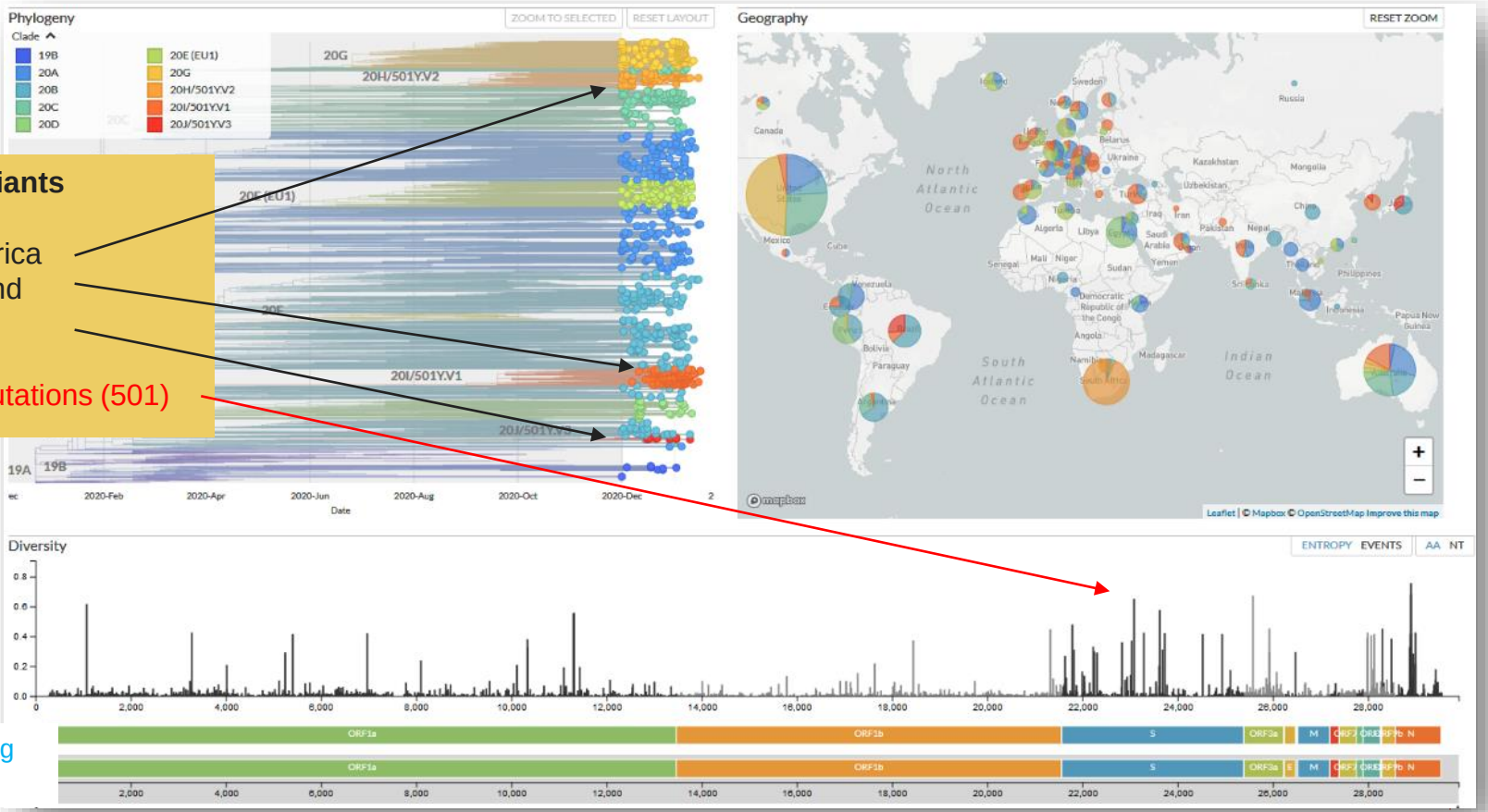
Are vaccines the way out of this pandemic?

COVID Variants Update

New variants

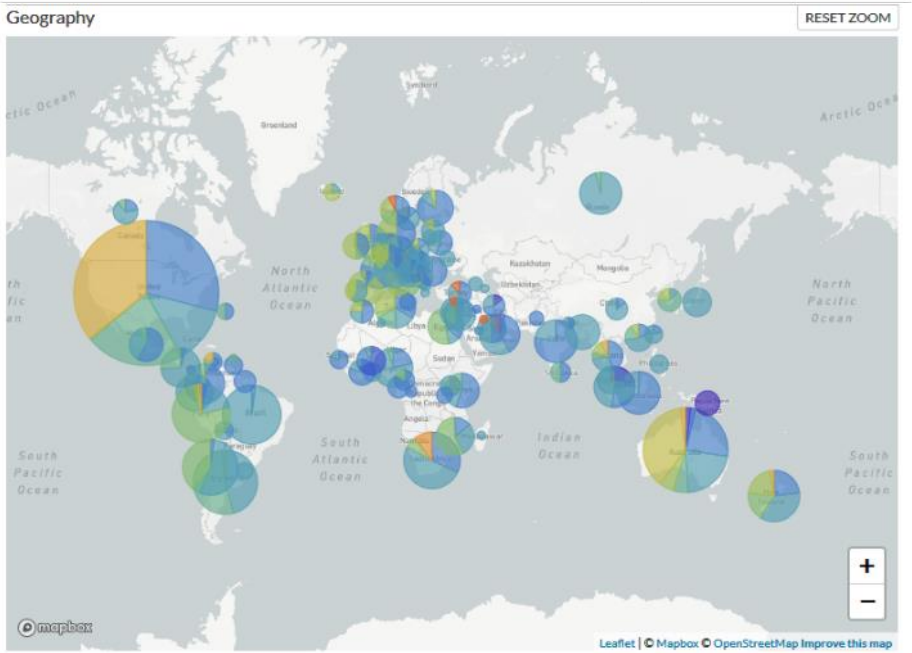
South Africa
UK/Ireland
Brazil

Spike mutations (501)

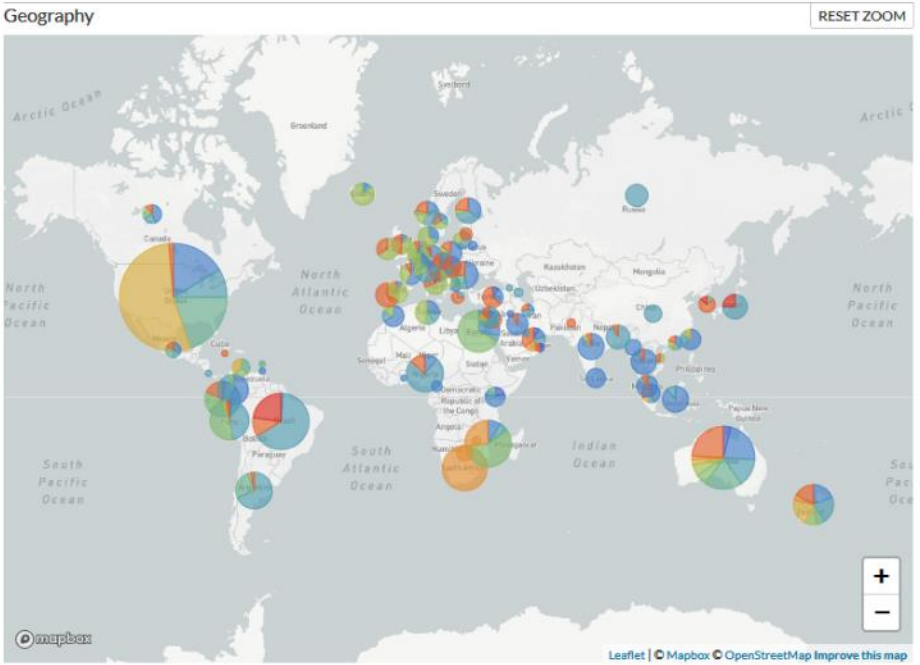


Nextstrain.org
End Jan 2021

COVID Variants Update



October 2020



January 2021

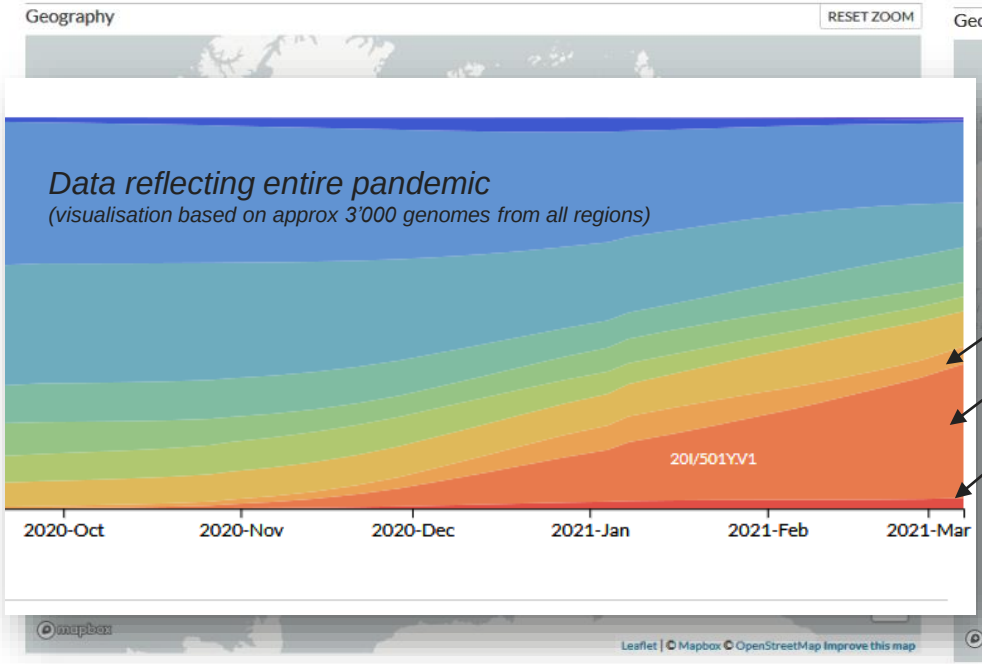
Nextstrain.org
Accessed 2 Feb 2021

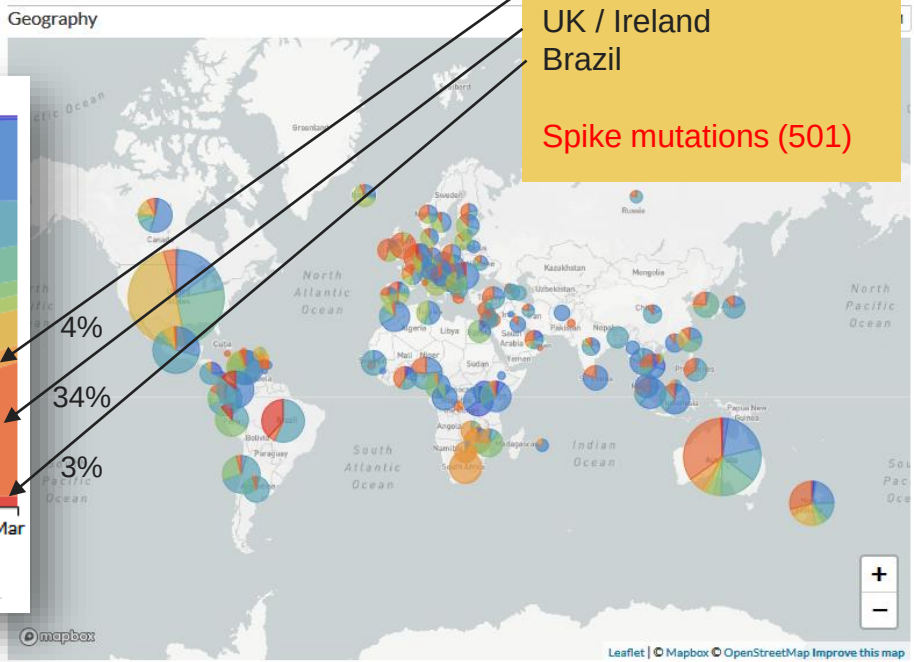
COVID Variants Update

New variants

South Africa
UK / Ireland
Brazil

Spike mutations (501)





31st January 2021

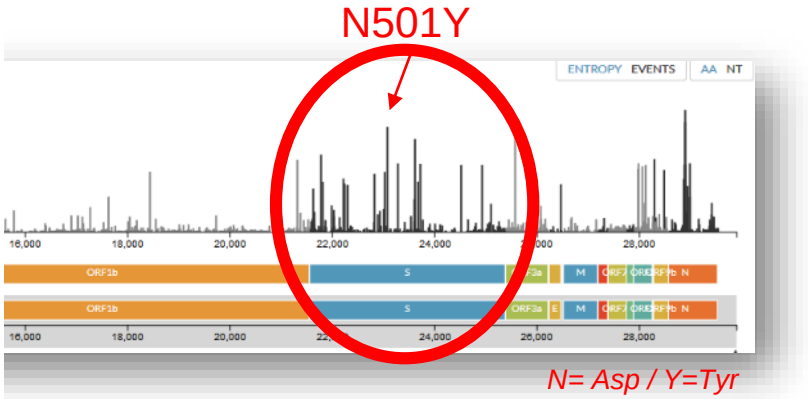
Today - March 2021

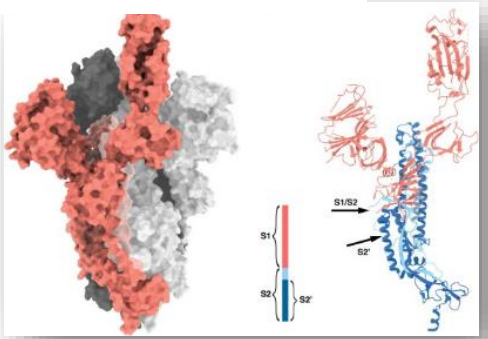
Nextstrain.org
Accessed 11 Mar 2021

CoV-2 Variants – *Evading the immune and vaccine response?*

Variants

- Spontaneous mutations
- Immune selection process
- Implications - diagnosis and vaccines
- Herd immunity
- First step to “vaccine escape”
- Cyclically seasonal patterns - adjustments to a vaccine (similar to influenza)





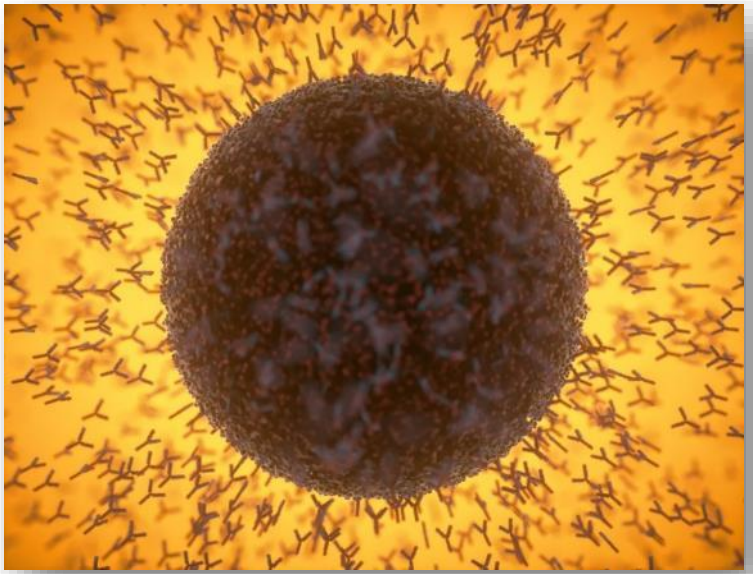
S1= attachment RBD / *S2= fusion*

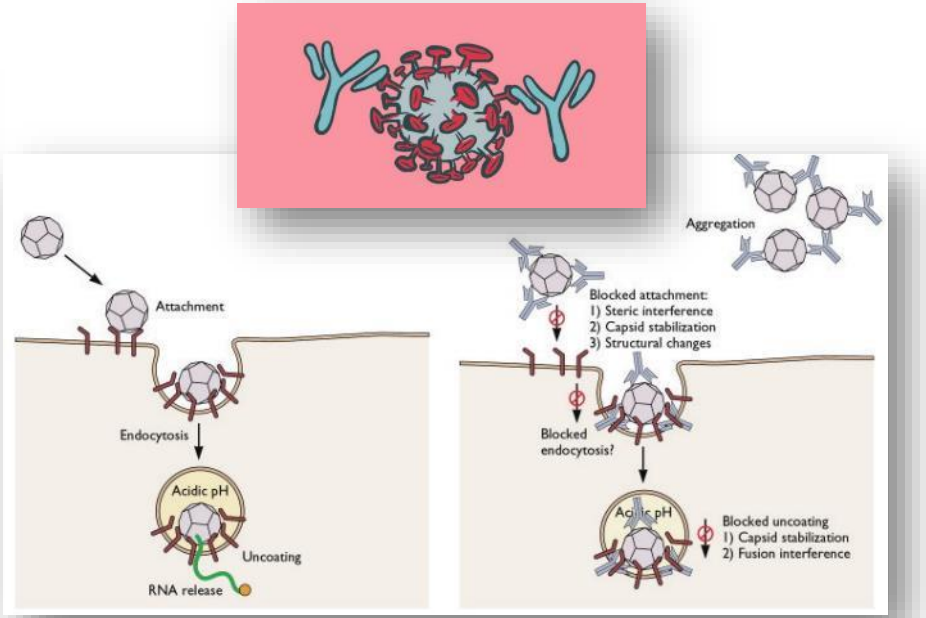
501 mutations

- Mutations in the virus receptor (RBD)
- “Better binding to the ACE2 receptor”
- Additional deletions in S1 provide an evasion of the immune response
- Furin: S1 cleavage simplifies virus entry

Swiss TPH

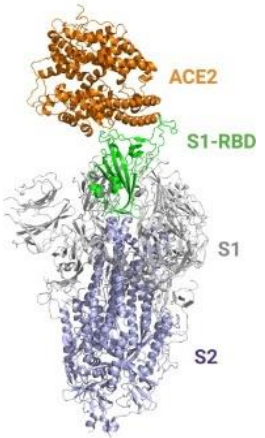
“Neutralising” *versus* “Binding” Antibodies (nAb vs. bAb)



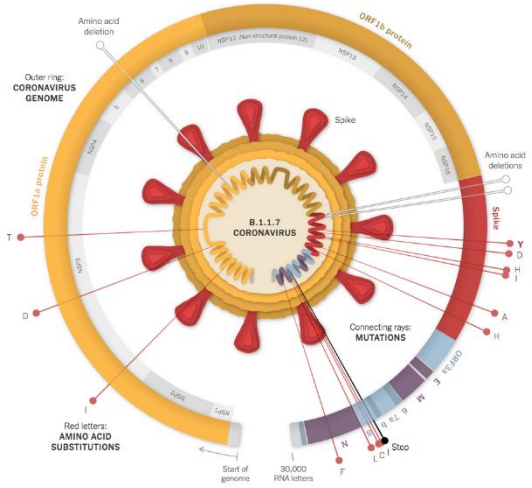


Particle or virus when “neutralised” is no longer infectious or hazardous...

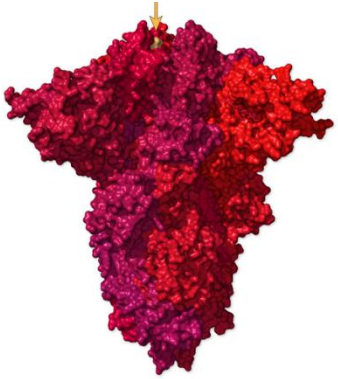
501Y.V1 = B.1.1.7 = '**Kent (UK)**' Variant



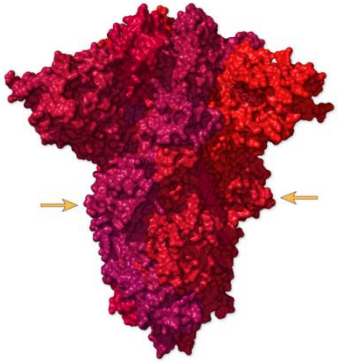
Country first detected	Date first Detected	Classification	AKA	Notable mutations	Transmissibility	Virluence
UK	Oct.20	B.1.1.7	501Y.V1	**N501Y**; 69–70del; P681H	↑	=



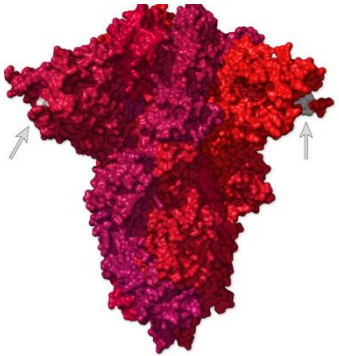
N501Y



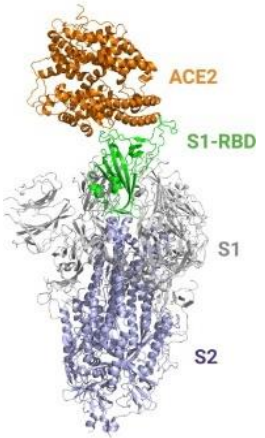
P681H



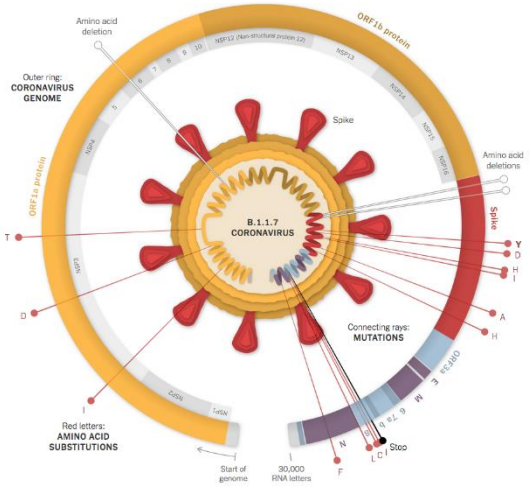
H69-V70del

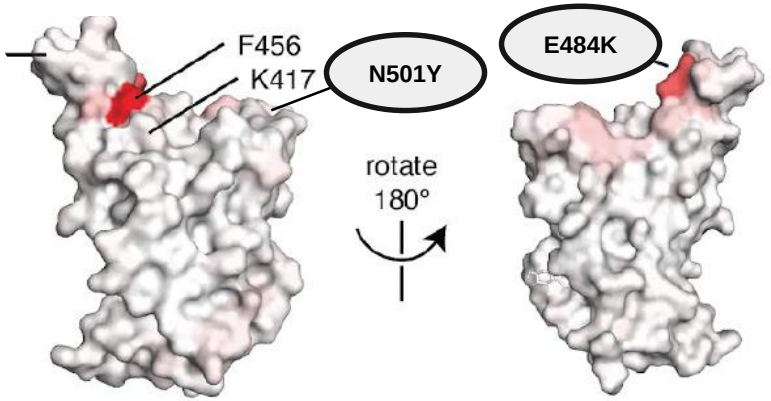


501Y.V2 = B.1.351 = '**South African**' Variant

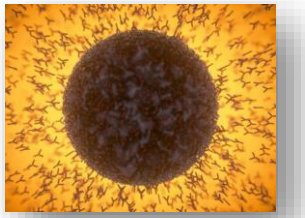


Country first detected	Date first Detected	Classification	AKA	Notable mutations	Transmissibility	Virluence
UK	Oct.20	B.1.1.7	501Y.V1	**N501Y**; 69–70del; P681H	?	=
South Africa	Dec.20	B.1.351	501.V2	**N501Y**; K417N; E484K	?	=

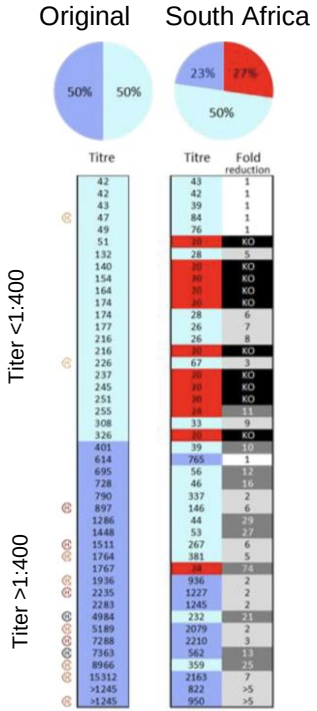


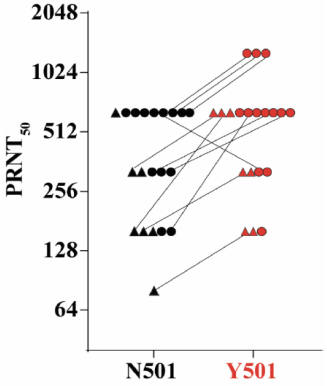


Partial Immune Escape to “South African” Variant



Convalescent Plasma



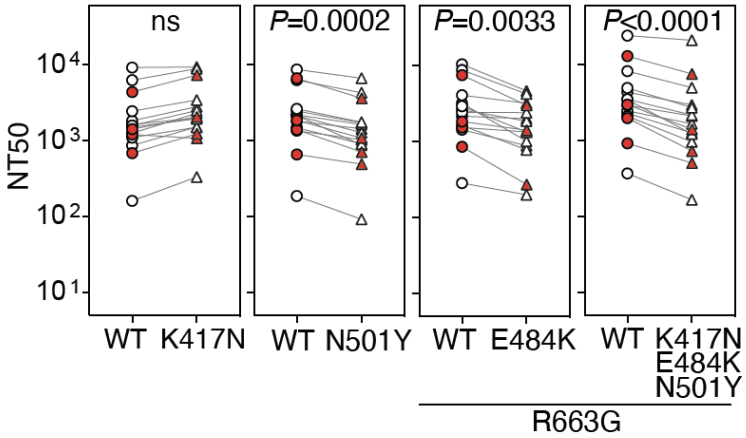


Plaque reduction neutralization test
“higher amount of nAbs needed”

mRNA-BNT162b2 sera (n=20)

Post-vaccination sera

Neutralization 1-3-fold ⇓



Does this mean that vaccines will be 1-3x less effective…?!

NOVAVAX
Creating Tomorrow's Vaccines Today

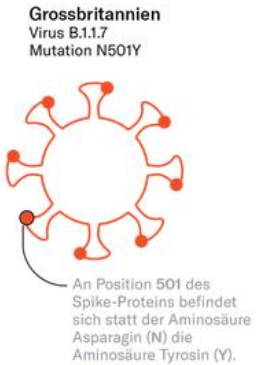
89-96% (WT & UK variant) *versus* **50-60% efficacy in S-Africa**

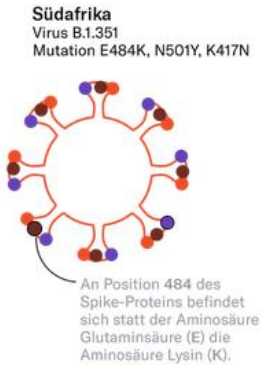
Janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

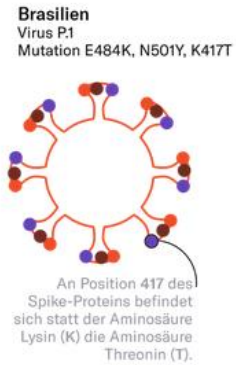
72% (USA) *versus* **57% efficacy in S-Africa** (95% had B.1.351)

Pfizer BIONTECH

2-fold reduced neutralization
(*Brasil variant*)

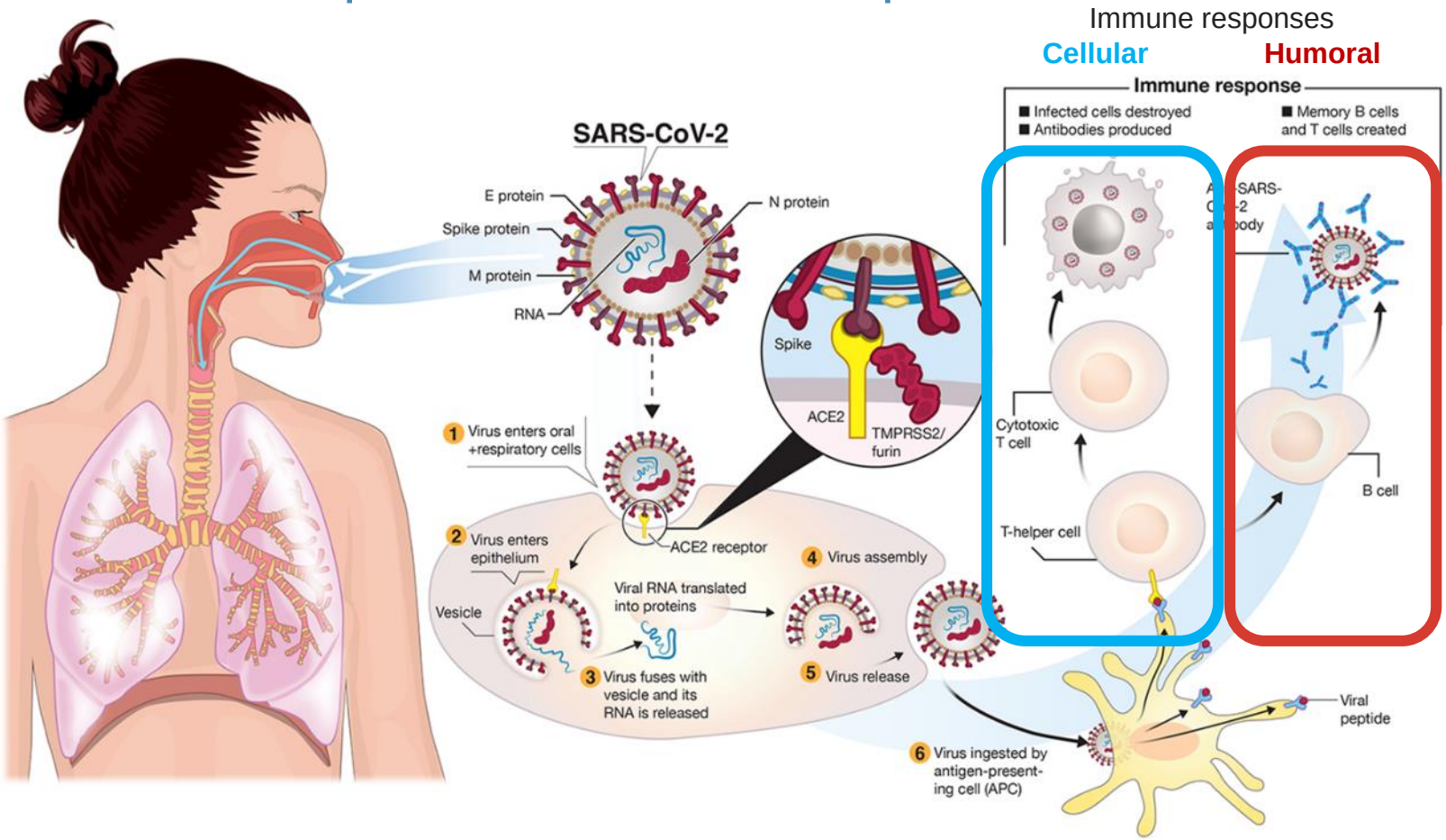






Swiss TPH

Vaccine Development - Immune Response



Poll question #2

The COVID-19 vaccines were developed very rapidly within one year (instead of >10 years). How would you state your trust in them?

1. **Very high** – *no problem at all*
2. **High** – *I trust them, but remain a little skeptical*
3. **Medium** – *They are OK, but there are some issues that concern me*
4. **Low** – *I am worried that they are incompletely evaluated*

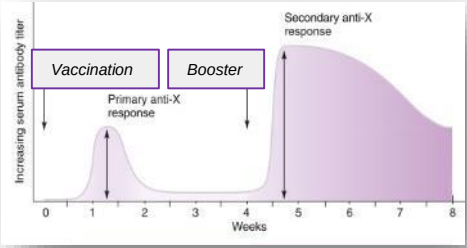
Principle of a Vaccine

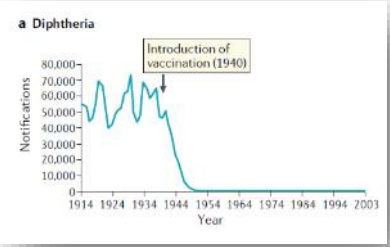
Induce immune response against antigens

Antigen = *antibody generators*

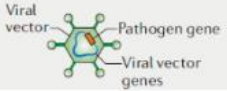
A molecule which triggers an immune response

Such as viral surface protein; polysaccharide (pneumococci capsule), attenuated infectious agent, *etc.*





Inactivated toxin (protein) similar to tetanus

Type of vaccine		Licensed vaccines using this technology	First introduced
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Toxoid		Diphtheria, tetanus	1923 (diphtheria)
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)
Virus-like particle		Human papillomavirus	1986 (hepatitis B)
Outer membrane vesicle		Group B meningococcal	1987 (group B meningococcal)
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid	1987 (*H. influenzae* type b)
Viral vectored		Ebola	2019 (Ebola)
Nucleic acid vaccine		SARS-CoV-2	2020 (SARS-CoV-2)

Swiss TPH

Pollard AJ, Nature Reviews, Jan 2021

Vaccine Development – *"the clinical trial phases"*

FDA, EMA, SwissMedic

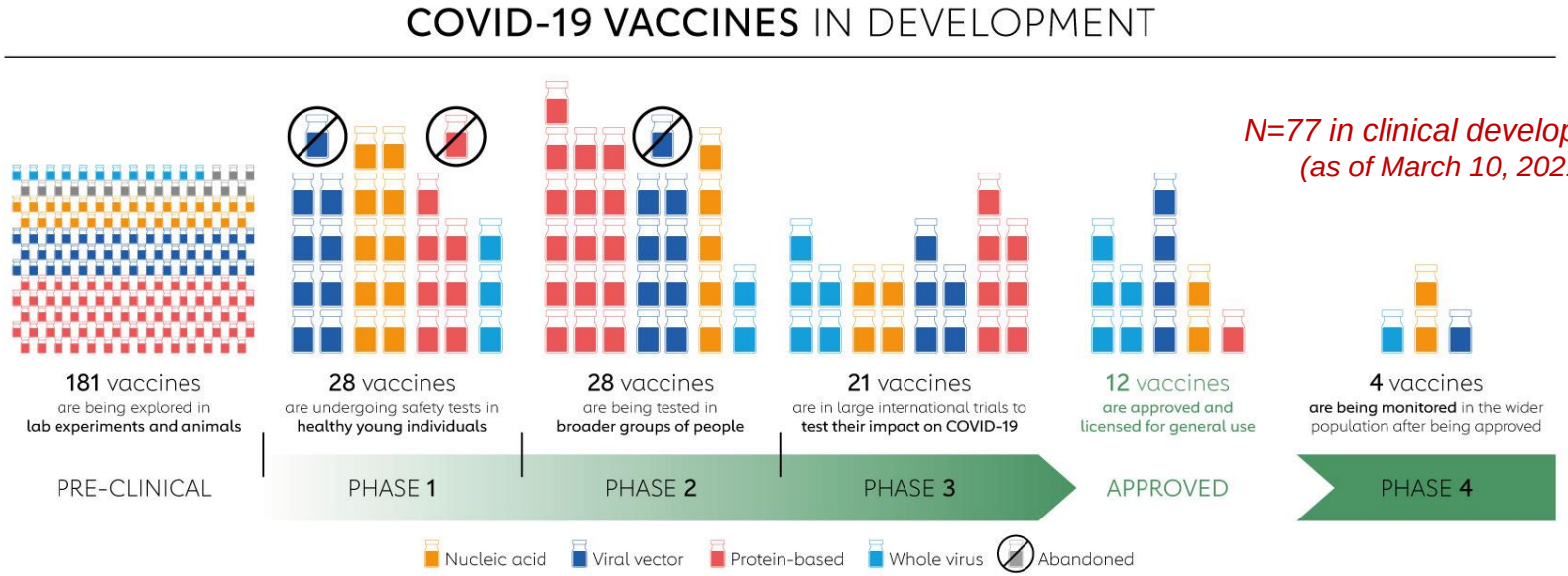
Laboratory development
Investigations in animals
1-2 years

Clinical trials in phases
Phase I: Safety and efficacy, dosage
Phase II: Safety, immune response, dosage - placebo
Phase III: Safety (rare AEs), randomised, double-blind, efficacy

Further investigations
Safety, including logistics use, storage, other effects, etc.

COVID-19 Vaccine Development "*the vaccine race*"

…from new CoV-2 to vaccine in less than one year!



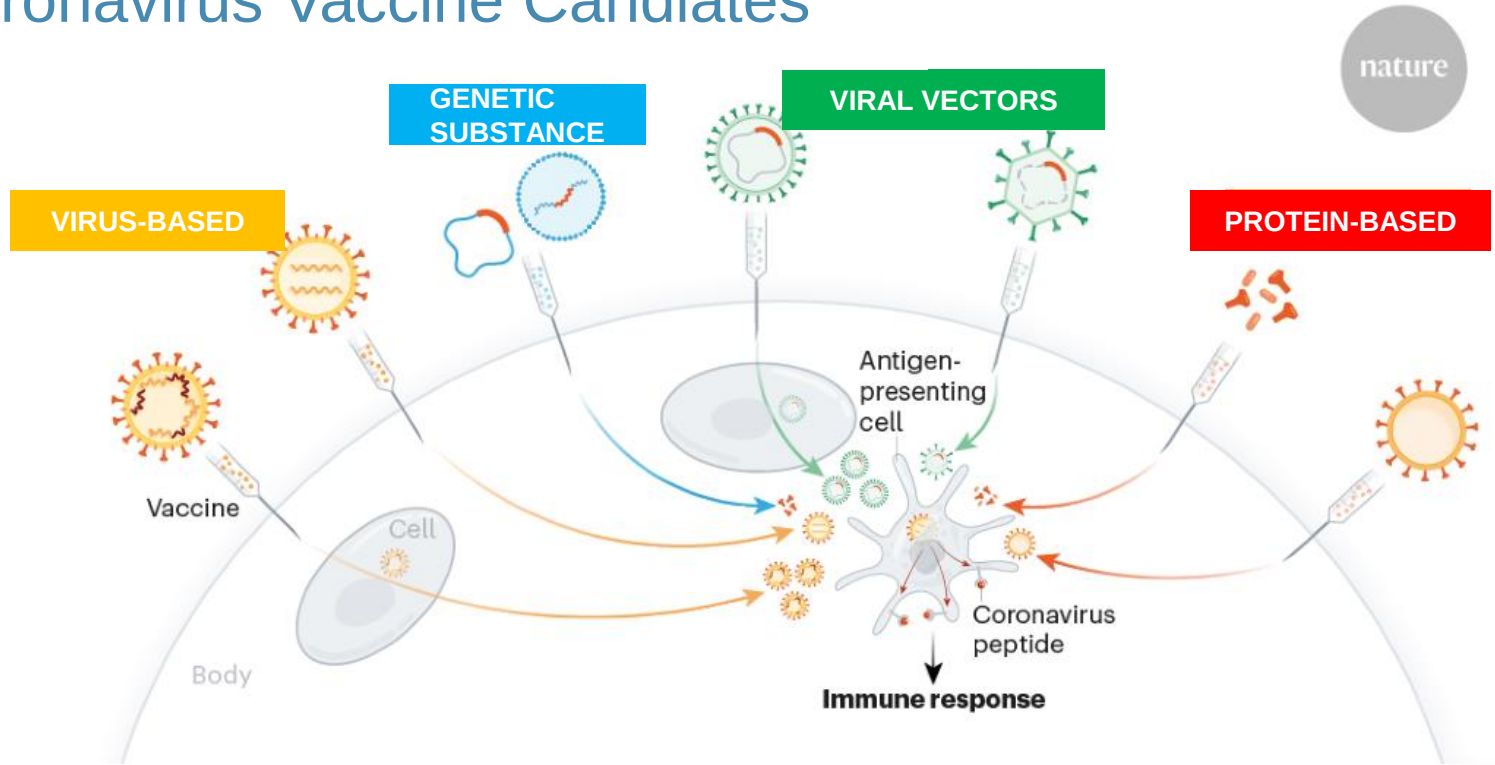
N=77 in clinical development
(as of March 10, 2021)

https://www.gavi.org/vaccineswork/covid-19-vaccine-race

Characteristics of an *ideal* COVID vaccine

- ✓ Low-cost (estimated vaccine dose < $40)
- ✓ Good antibody production (neutralising Ab) and cellular immunity
- ✓ FDA/EMA: min. 50% protection (or 50% protection against severe course)
- ✓ Safety demonstrated in at least 2 studies with >10,000 subjects
- ✓ Sterilising immunity (no viruses in blood, saliva or stool)
- ✓ Protects all age groups (risk: older and immune-suppressed people)
- ✓ Single dose preferred - *if needed*, booster after 4-8 weeks
- ✓ Heat stable and not light-sensitive (store at 2-8 deg. C)

Coronavirus Vaccine Candiates



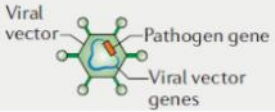
AstraZeneca janssen Pfizer BIONTECH moderna NOVAVAX Sputnik V

COVID-19 Vaccination Strategies

Nucleic acids
mRNA or virus vector

Protein
Particle

Virus
inactivated or attenuated

Type of vaccine		Licensed vaccines using this technology	First introduced
Viral vectored		Ebola	2019 (Ebola)
Nucleic acid vaccine		SARS-CoV-2	2020 (SARS-CoV-2)
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)

Major contenders

Pfizer BIONTECH
moderna
AstraZeneca
Janssen
NOVAVAX

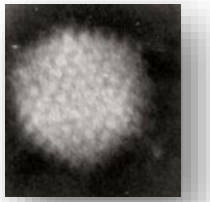
国药集团 SINOPHARM
sinovac
Sputnik V

Swiss TPH

Pollard AJ, Nature Reviews, Jan 2021

Virus Vector Vaccine

Vectors
= non-replicating viruses
- ChAd, Ad26 or Ad5
- such as Ebola vaccine



Human adenovirus
(EM image)

Phase 3 trial results - vaccine efficacy:

Efficacy = Preventing symptomatic disease, COVID-19 (np PCR pos.)

AstraZeneca	70% efficacy	(ChAd, poor results in S-Africa)
Janssen J&J	85% efficacy	(Ad26, 72% USA, 64% SA, 61% Brasil)
Sputnik V	91% efficacy	(Ad26 – Ad5)
Subjects:	24,000 (AZ Ox) 44,000 (Janssen) 22'000 (Sputnik V)	

Storage in refrigerator at 2-8 deg C

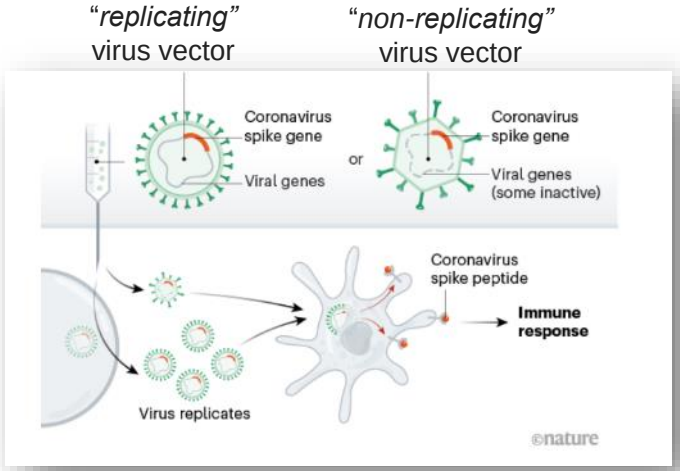
Immune response to the virus vector (!)

Ab and cellular responses

Data for people >70 years

Sputnik to be produced in Italy (Swiss ADIENNE)

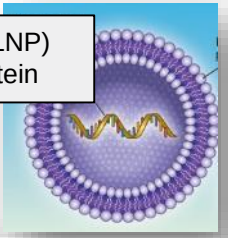
Janssen J&J: single-shot scheme



T. Thanh Le et al. *Nature Rev. Drug. Disc.* http://doi.org/ggrnbr (2020)

mRNA Vaccines

Lipid nanoparticle (LNP)
mRNA - Spike protein



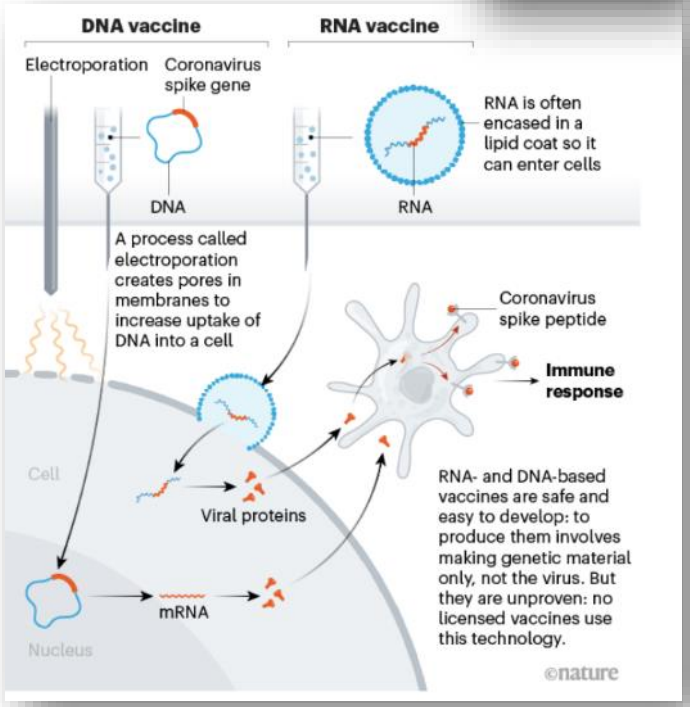
Phase 3 trial results - vaccine efficacy:

Efficacy = Preventing symptomatic disease, COVID-19 (np PCR pos.)

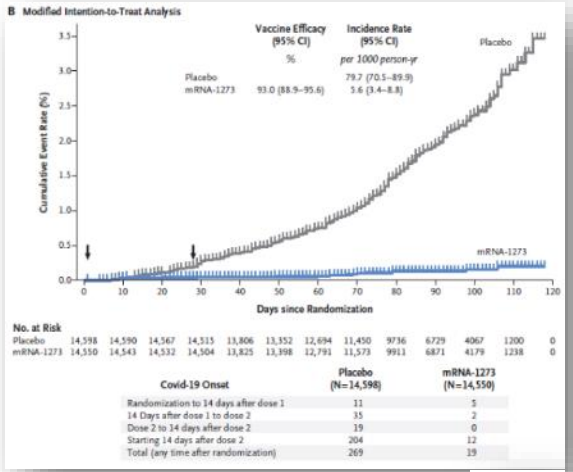
Moderna	94% efficacy
BNT-Pfizer	95% efficacy
Subjects	>30,000 (Moderna)
	>37,000 (BNT-Pfizer)

Storage -20 to -70 deg C
Minimal side effects
nAb - cellular immunity (BNT good, Moderna pending)
Fast to adapt (variants, seasonal cycles, etc.)

Sanofi supports production of the BNT-Pfizer vaccine

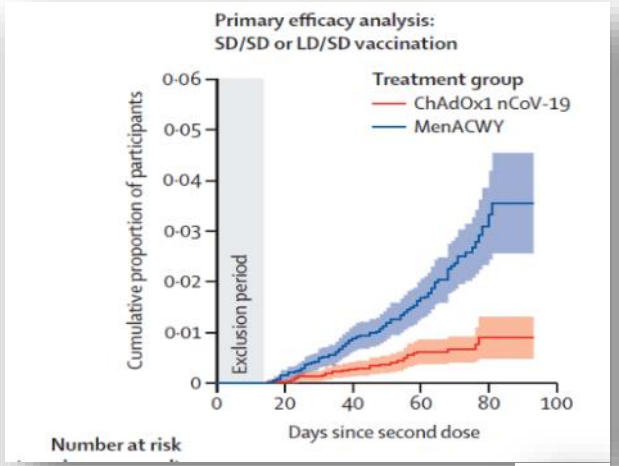


Kaplan Meier Graphs



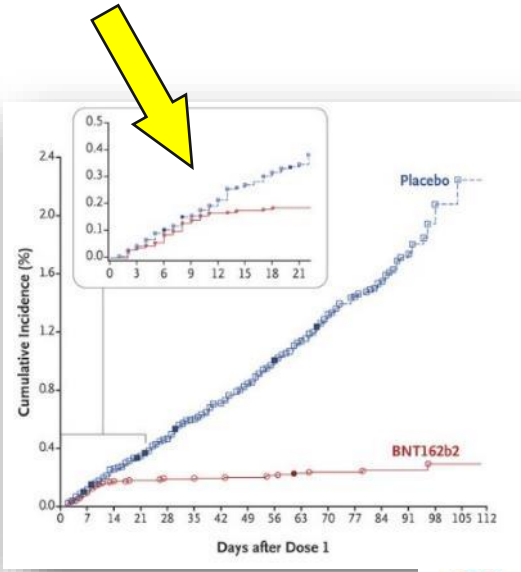
Moderna mRNA1273

Efficacy 80%
after the first dose
after 14 days



AstraZeneca-Oxford ChAdOx1

Efficacy 76%
after the first dose
after 28 days



BioNTech-Pfizer BNT162b2

Protein-Based Vaccines

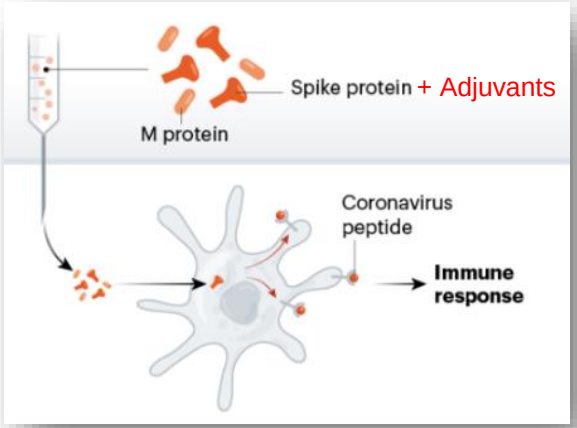
Phase 3 trial results - vaccine efficacy:

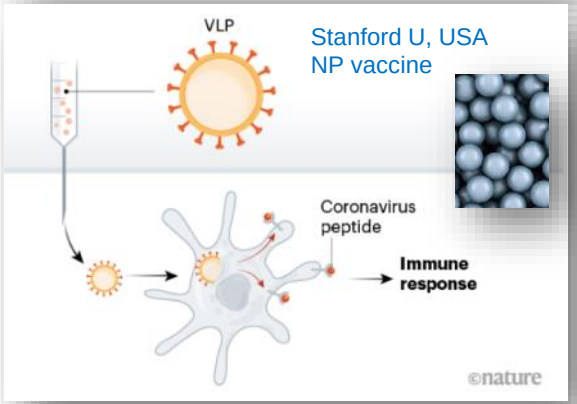
Efficacy = Preventing symptomatic disease, COVID-19 (np PCR pos.)

Novavax	95% efficacy (original CoV-2 strain)	
Subjects:	>15,000 - a further 30,000 planned	
Variants:	UK	86%
	S-Africa	60% (HIV-neg. pop) / 49% (mixed pop.)
	comparison to influenza	*approx. 50-60%*

Vaccination = S1 protein and adjuvants
Proven methods: Influenza, Hep B, HPV
Possible to store at 2-8 deg C
Approval imminent

NOVAVAX





T. Thanh Le et al. *Nature Rev. Drug. Disc.* http://doi.org/ggrnbr (2020)

Attenuated and Inactivated Viruses

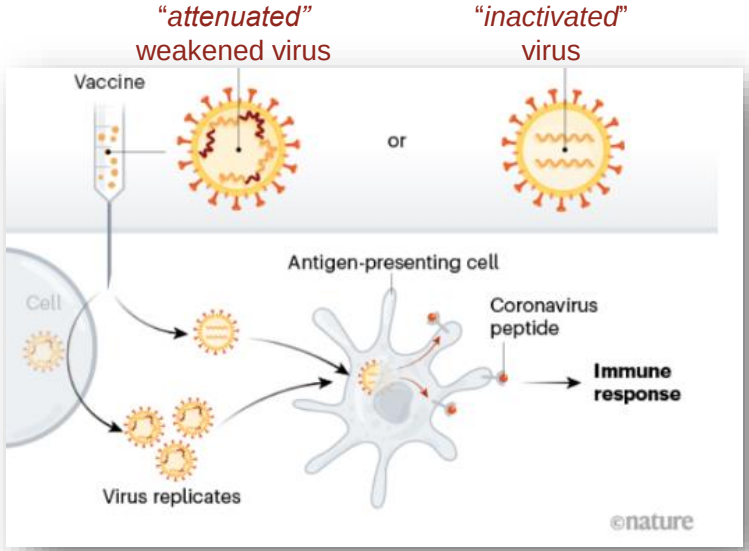
Phase 3 trial results - vaccine efficacy:

Robust immune response and long-lasting cellular immunity (immune memory) against SARS-CoV-2

SINOVAC and SINOPHARM
Traditional vaccines - storage at 2-8 deg C
Dead viruses = all proteins presented to the immune system

Efficacy:
SINOVAC - interim 65% (Indonesia), 78% (Brazil), 91% (Turkey)
SINOPHARM - interim data 79% to 86%

New: COVI-VAC
Intra-nasal spray - no needle - single-dose
Living, attenuated virus (phase 1 studies)



sinovac 国药集团 SINOPHARM CODAGENIX INC.

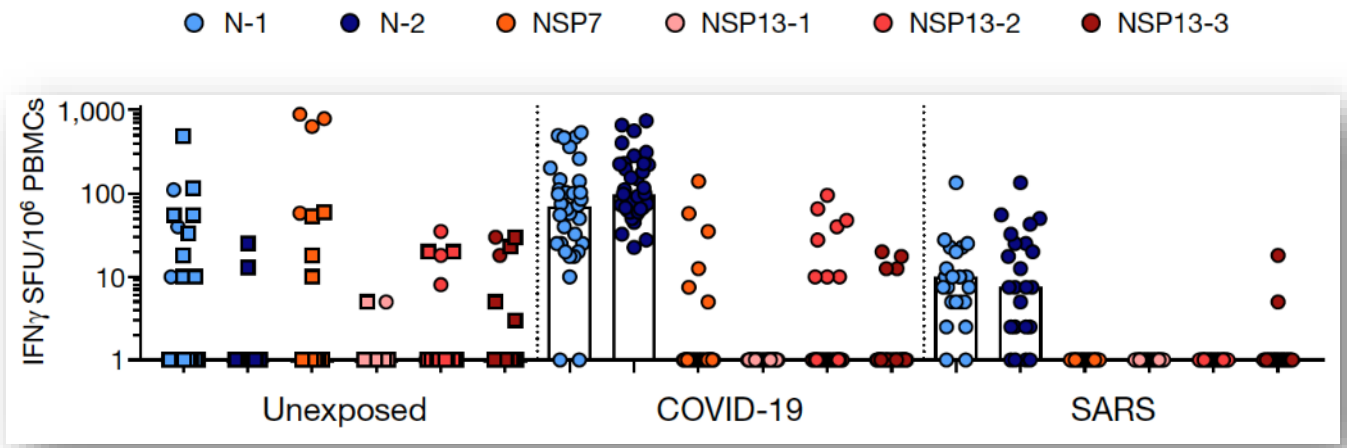
T. Thanh Le et al. *Nature Rev. Drug. Disc.* http://doi.org/ggrnbr (2020)

Poll question #4

If you could choose one vaccine from the following – which one would you prefer?

1. An attenuated virus vaccine (p.ex. SINOVAC)
2. An mRNA-based vaccine (p.ex. MODERNA)
3. A protein-based vaccine (p.ex. NOVAVAX)
4. A viral-vectored vaccine (p.ex. JANSSEN)

Cellular Immune Response ... pre-existing Immunity



N= nucleocapsid

NSP = non-structural proteins

Approx. 10-30% of people have *pre-existing* T cell responses to SARS-CoV2

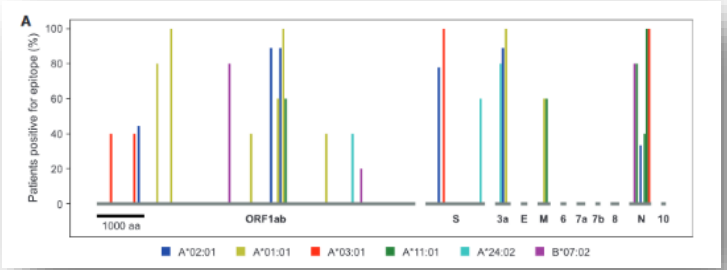
Common cold strains (endemic CoV): OC43, HKU1, NL63 and 229E

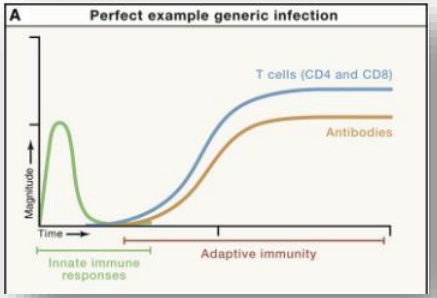
Possibly more rapidly induced antibody responses? Better neutralising antibodies?

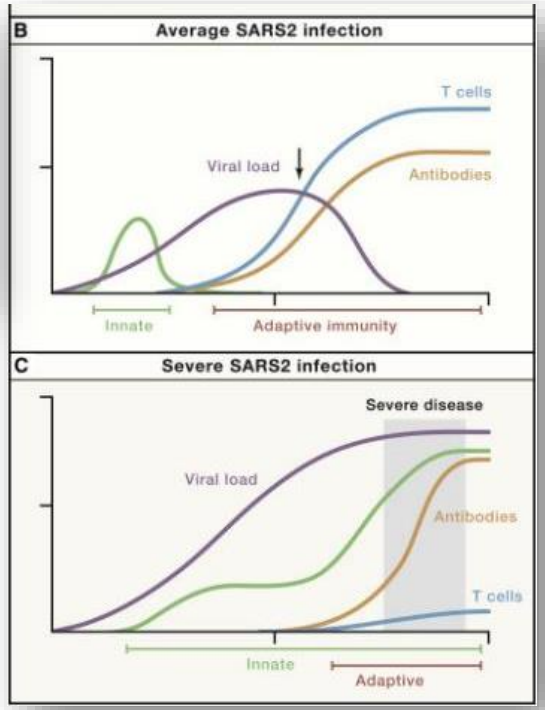
Swiss TPH

LeBert N, Nature July 2020
Sette A & Crotty S, Nature Reviews Immunology July 2020

Cellular Immune Response







T-cell epitopes in the SARS-CoV-2 genome (CD8)
(colour MHC restriction)

Four endemic human coronaviruses: OC43,HKU1, NL63 and 229E

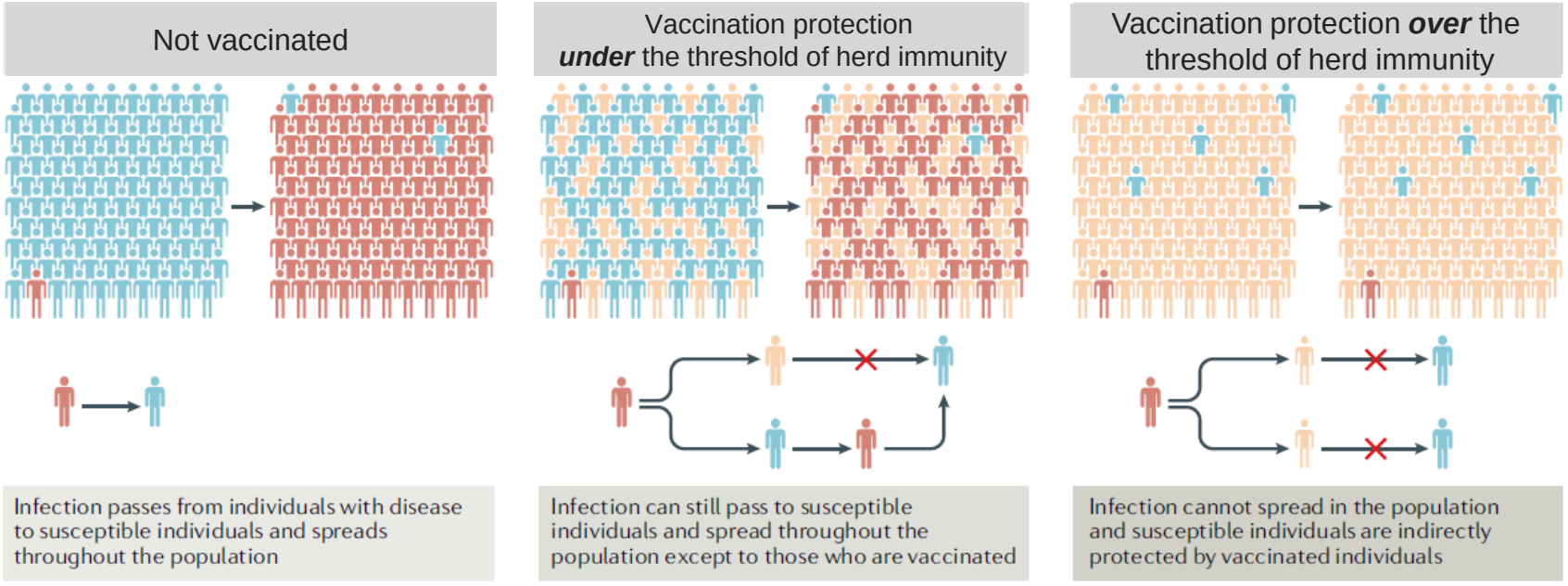
- Almost no reactivity to OC43 and HKU1 (2 of 29 epitopes)
- No reactivity to NL63 and 229E
- No reproducible cross-reactivity to the four endemic corona-viruses

Prior exposure to these viruses is unlikely to provide CD8 T-cell-mediated immune protection from SARS-CoV-2

Swiss TPH

Ferretti et al., Immunity, Nov 2020
Sette A & Crotty S, Cell Reviews Feb 2021

Herd Immunity - Vaccines *and* Natural Infection



Pollard AJ, Nature Reviews, Jan 2021

Herd Immunity - Vaccines *and* Natural Infection

$$R_0 = \beta\tau$$

R_0 = basic reproduction number

β = infection producing contacts per unit time

τ = mean infectious period

	R_0	Infectious duration, D
Swine flu 2009	1.2 to 1.6	3 days
Seasonal flu	1.2	3–6 days
1918 flu	~2 (up to 20)	4 days
SARS	~3	
Measles	>10	
Chickenpox	>7	
Mumps	>10	

Swine 'flu from Fraser et al. [13], seasonal '
Mills et al. [38], SARS from Lipsitch et al.
from Anderson and May [10].
doi:10.1371/journal.pone.0012951.t001

Disease	R0	Threshold (%)
Mumps	4-7	75–86
Polio	5-7	80–86
Smallpox	5-7	80–85
Diphtheria	6-7	85
Rubella	6-7	83–85
Pertussis	12-17	92–94
Measles	12-18	83–94

Values of R_0 of well-known infectious diseases[1]

Disease	Transmission	R_0
Measles	Airborne	12–18
Diphtheria	Saliva	6-7
Smallpox	Airborne droplet	5–7
Polio	Fecal-oral route	5–7
Rubella	Airborne droplet	5–7
	Airborne droplet	4–7
	Sexual contact	2–5
	Airborne droplet	5.5[2]
	Airborne droplet	2–5[3]
	Airborne droplet	2–3[4]
	Bodily fluids	1.5-2.5[5]

Transmission-blocking effect of vaccines...?

Difficult trials!

Confounders: Lockdown effects, behaviour changes, asymptomatic carriers…

Approach: Following close contacts of vaccinated individuals, households etc.

- Moderna: During trial 2/3 drop in asymptomatic carriers in vaccinees (only 2 sampling timepoints 1 month apart)
- AstraZeneca: 49% drop of asymptomatic carriers (vaccinated vs. placebo)
- Pfizer: Ongoing study – swabbing performed every 2 weeks

evidence supporting sterile immunity regarding post-vaccination status is incomplete!

So… we need to wear a mask even if vaccinated !!

Swiss TPH

Nature news, 19th Feb 2021,

Poll question #3

What safety measures would you consider applying even after the pandemic is over?

1. Wearing a mask in public transport
2. Wearing a mask in the office
3. No more hand-shaking in future!
4. Avoiding large event gatherings (p.ex. cultural, music or sports)
5. All of the above!

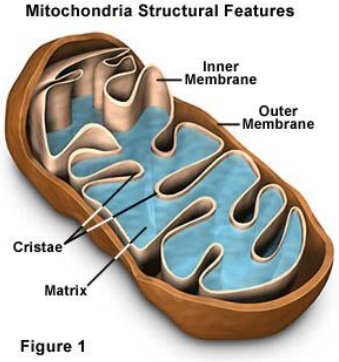
What exactly is “*long COVID*”...?!

Persisting symptoms / sequelae after the normal convalescence

- Fatigue, headaches, shortness of breath, anosmia (loss of smell), muscle weakness, low fever and cognitive dysfunction (brain fog)
- lingering symptoms 13% (>1 month) – 5% (>2 months) – 2.3% (>3 months)
- Occurs in any age group
- Never observed after vaccination

- Risk Factors: age>50y, obesity (BMI), asthma, >5 symptoms in acute phase
- Chronic fatigue syndrome / myalgic encephalitis (ME) – EBV, Parvovirus

- Role of mitochondria, oxidative stress and the response to antioxidants
  - Mitochondria energy metabolism dysfunctional
  - Impaired recycling of ADP to ATP
  - Impaired correction of reactive oxygen species (ROS)



Swiss TPH

Nature Medicine 10th Mar 2021 (yesterday!)

Chron Dis Trans Med Nov 2020 https://doi.org/10.1016/j.cdtm.2020.11.002

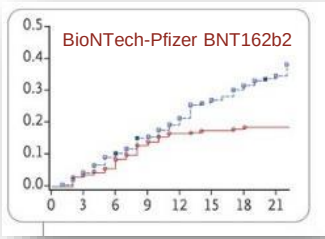
Delivery Problems: *The Delayed Second Dose...?!*

BNT-Pfizer:	Second dose after three weeks	95% efficacy
	12-14 days after the first dose	about 85-90% efficacy
Moderna:	Second dose after four weeks	94% efficacy
	No data for single doses	
Astra-Zeneca:	Two doses four weeks	70% efficacy
	No data for single doses	

Comparisons: Placebo groups / natural infection / data about BNT-Pfizer (single shot)

- suggest positive vaccination effect after about 12-14 days after first vaccination
- suggest that latency is possible up to 12 weeks for the second dose (now 6 weeks)
- All COVID-19 patients have antibodies - IgA (after 12 days) and IgG (after 21 days)

!!! Current data does not provide conclusive assessment...

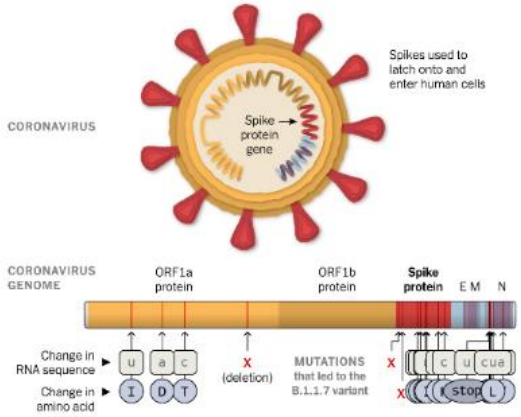


Benefits of a Vaccine-Induced Immune Response...?

Natural immune response against CoV seems to be short-lived... max. three years (SARS, MERS)

Currently limited available data about the role of immune memory

So far, few cases of re-infections with SARS-CoV-2 have been described



<u>Problems</u>:

- <u>Asymptomatic carrier</u> of the virus in the event of re-exposure (throat)
- SARS-CoV-2 seems to <u>modulate our immune response</u>, to “dampen”
- *i.e.* Ab production is lower, as is immune memory...

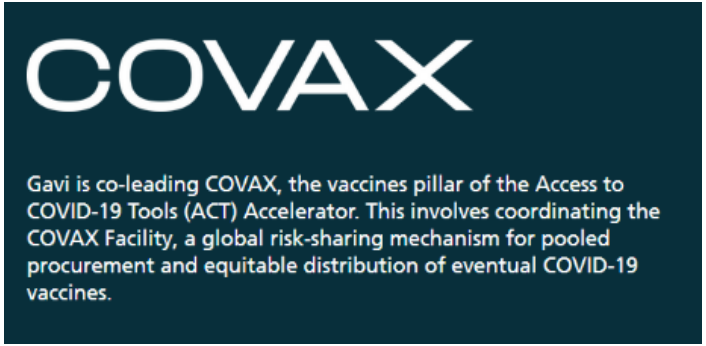
This does not happen, however, with vaccine-induced immune responses

Thus, longer-lasting immune responses against virus proteins and particles are possible

!!! Virus variants and mutations - suboptimal Ab protection from previous infection / vaccination

Vaccine immunity “*selection pressure*” and “*immunity evasive mutations*”

LMICs – Impact in Africa…



Issues:

- Refusal / avoidance of COVID-19
- Way too few tests
- No prospective vaccination strategy
- Massively underestimated numbers (testing!)

Figures from morgues (Zambia): approx. 19% COVID-19 victims

- RF: Tuberculosis, high blood pressure, HIV/AIDS, alcohol consumption and diabetes
- Massive misjudgement possible...

COVAX Global Initiative

https://www.gavi.org/covax-facility

- Access to vaccinations: 190 participating economies
- Donor-financed doses: 1.3 billion vaccinations for 92 economies
- Goal: Population coverage of 20% by the end of 2021

CEPI Gavi The Vaccine Alliance World Health Organization

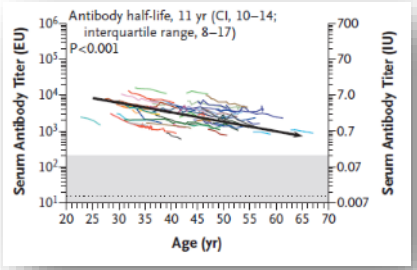
Outlook – *Next Generation Vaccines…*

Nasal spray or inhalation vaccines

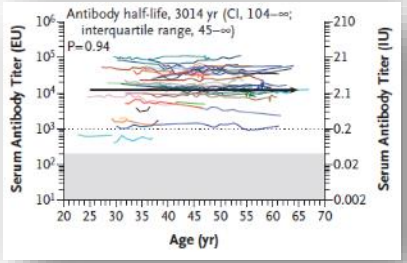
Synthetically attenuated living virus development (SAVE), synthetic biology to recode genes

-> potentially safe and stable vaccines

CODAGENIX INC.



Tetanus (Protein)
$T_{1/2}$ 11 years



Measles (live)
$T_{1/2}$ 3014 years

Attenuated live vaccines = very effective

- offer long-lasting and broad immunity
- only one dose needed in general

Thank you for your attention!

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