

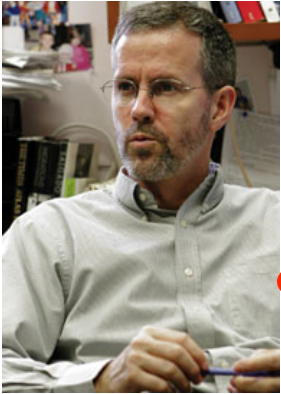


Vaccine Up-Date 2022

**Will the new technologies introduced
during the pandemic change the
vaccine landscape?**

McGill Refresher Course for
Family Physicians
December 6, 2022

Brian J Ward MSc, DTM&H, MDC(M), FRCP(C)
Professor of Infectious Diseases & Microbiology (McGill University)
Medical Officer (Medicago Inc)



Conflict of Interest (Last 5 Years)

Position in Pharma	Medical Officer for Medicago Inc. (Oct 2011 - present)
Consulting	Novartis, Aviex, Carrier, Angany MSSS, US Dept of Justice (Vaccine Compensation Programs)
Contracts	Vaccine trials for virtually many companies
Shared Awards	CIHR-Industry grant (Medicago, Aviex, Carrier) Shared CQDM grant (Medicago, Laval U, SNC Lavalin)
Occasional Speakers Honoraria	None
Investments	None

Vaccine Advances & Set-Backs

2019-2022

Major Set-Backs

- The continued politicization of vaccine science and vaccine policies
- The rise of vaccine hesitancy/Vaccine refusal
- Failure of 2nd major *C. difficile* vaccine

New or Improved Vaccines and Vaccination Strategies

- Expansion of conjugated pneumococcal vaccines
- Growing acceptance of vaccination in pregnancy
- New vaccines for malaria and dengue
- Reduced dose schedules and heterologous schedules for HPV vaccines
- Promising candidates for RSV, *S. aureus*, hemolytic StrepB, others

The explosion of SARS-COV-2 vaccines?

- give credit where credit is due: CEPI's pre-positioning of vaccine technologies
-

The New Arm's Race

What was predicted
to happen did in fact
happen



Mercury- Autism Coverup



Thinktwice on Facebook

photos-b.ak.fbcdn.net/hphotos



my.opera.com



flu fraud.com

Second Major *C. difficile* Vaccine Trial Ends in Failure

THE LANCET
Infectious Diseases

Submit Article Log in F

ARTICLES | VOLUME 21, ISSUE 2, P252-262, FEBRUARY 01, 2021



Purchase

Safety, immunogenicity, and efficacy of a *Clostridioides difficile* toxoid vaccine candidate: a phase 3 multicentre, observer-blind, randomised, controlled trial

Guy de Bruyn, MD • David L Gordon, MD • Theodore Steiner, MD • Paul Tambyah, MD • Catherine Cosgrove, MD • Mark Martens, MD • et al. [Show all authors](#) • [Show footnotes](#)

Published: September 15, 2020 • DOI: [https://doi.org/10.1016/S1473-3099\(20\)30331-5](https://doi.org/10.1016/S1473-3099(20)30331-5) •

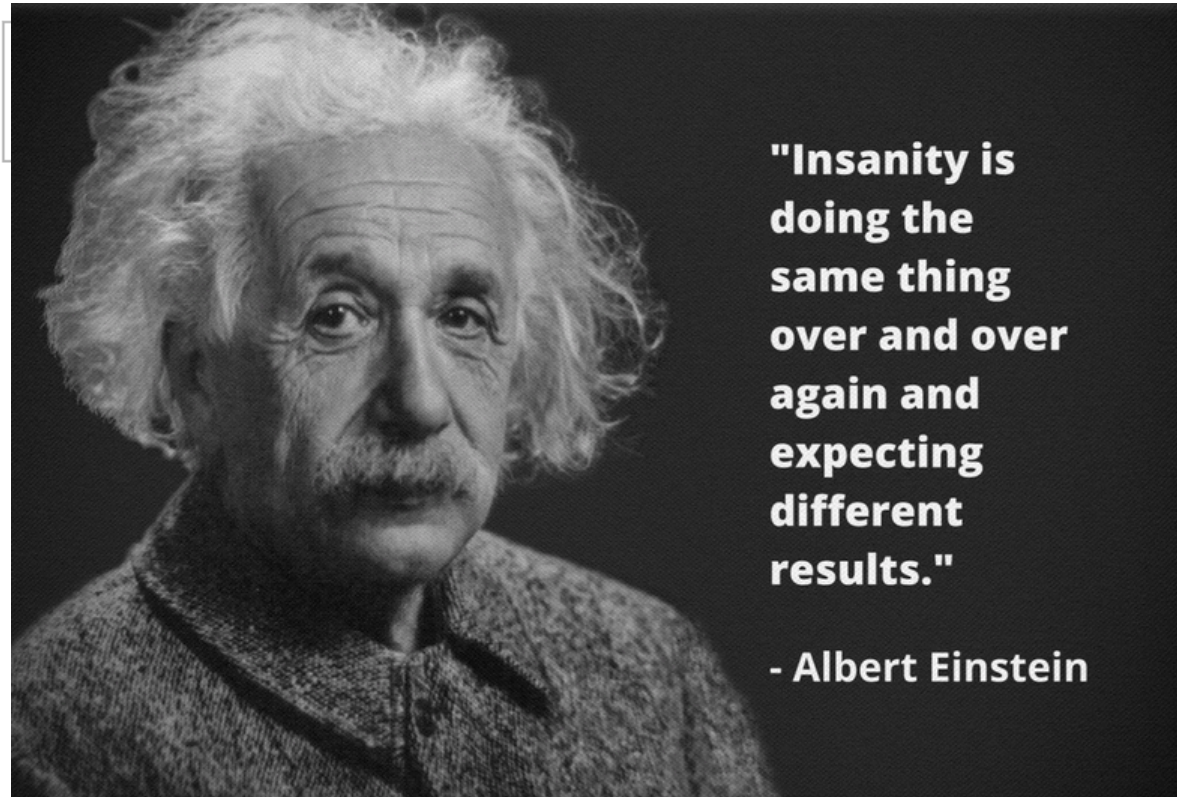


- 3 companies developed multi-dose, adjuvanted IM vaccines for *C. difficile*
- All target the receptor-binding domain of toxins A and B
- Sanofi's candidate terminated in Phase 3 (futility) and Valneva's 'on-hold'
- Pfizer's candidate failed in Phase 3 (only 30% efficacy at best)

Doing the Same Thing Over and Over and Expecting a Different Outcome

Heterologous Vaccination Schedules: HPV

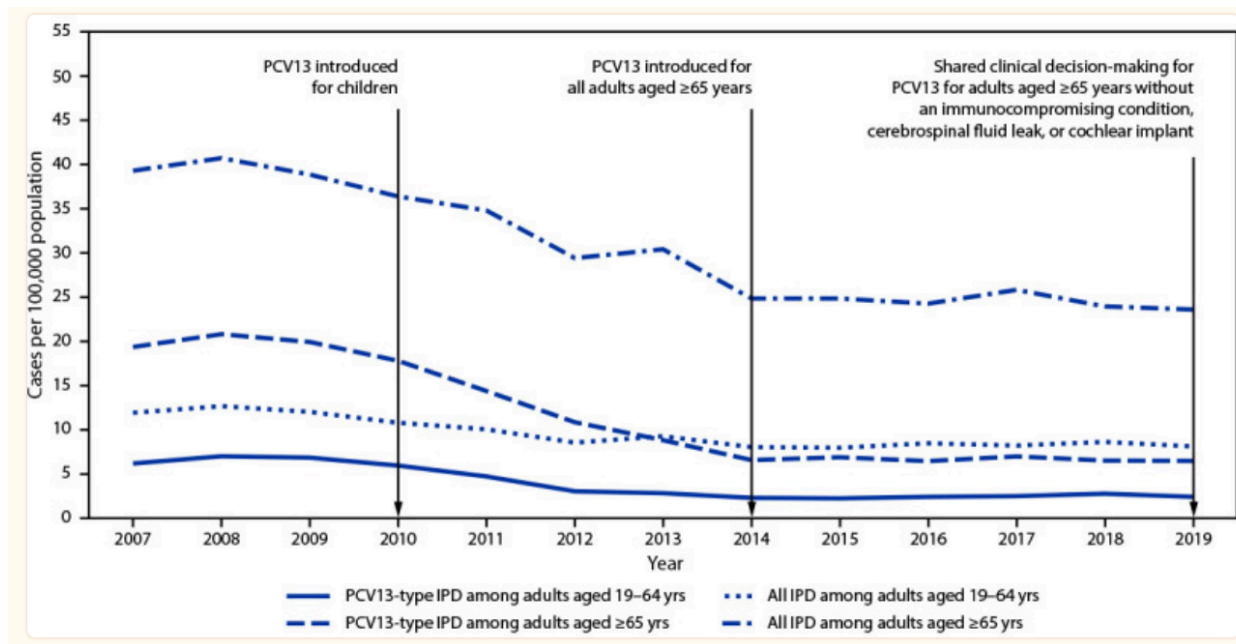
- One dose of nonvalent HPV vaccine followed by bivalent vaccine
- Vaccines have different adjuvants
- Mixed vaccination results better than giving the same vaccine over and over



How Many Serotypes does **YOUR** Vaccine Have?

Streptococcus pneumoniae Vaccines

- There are >90 serotype of *S. pneumoniae* – not all are equally invasive
- Began with 23-valent polysaccharide vaccine for the elderly
- Conjugate 7-valent vaccines introduced for pediatrics
- Then 10-valent, 13-valent, 15-valent and finally (??) 20-valent
- Significant advantages to using the conjugate vaccines in adults





Vaccines in Pregnancy

Tetanus (already widely use

Influenza

dT

dTaP

... others (RSV, GBS, CMV, etc)

... and then came SARS-COV-2



With vaccines, we are building our boat
and sailing it at the same time

David Heymann, World Health Organization

EVERYONE is Making a Vaccine

Major Pharma



Small Companies
that want to grow



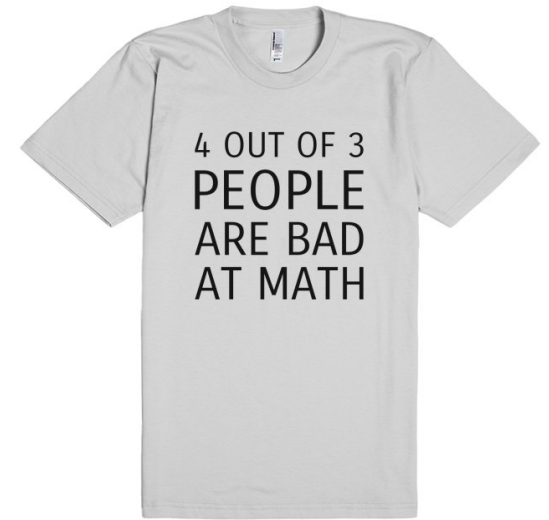
Academic Groups



Your Grandmother



Grossly Underestimated The Need for Doses



One BILLION doses of vaccine sounds like a lot!

Protection against variants requires high titres of neutralizing antibodies so many countries instituting 3rd, 4th and 5th doses

www.sodahead.com

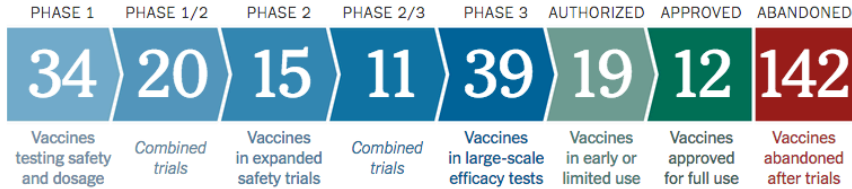
With 7.8 billion people in the world



needed 15.6 billion doses to start

Coronavirus Vaccine Tracker

By [Carl Zimmer](#), [Jonathan Corum](#), [Sui-Lee Wee](#) and [Matthew Kristoffersen](#) Updated April 8, 2022



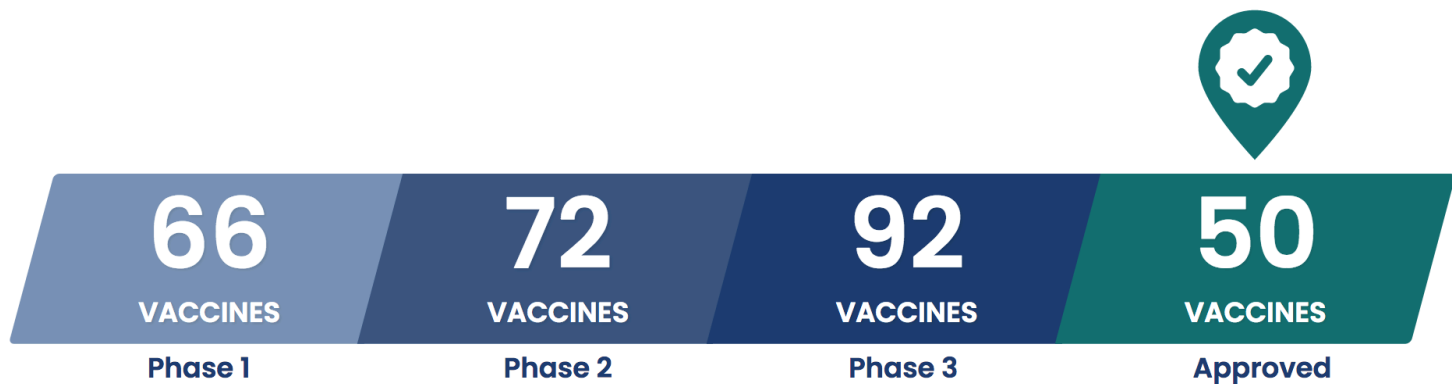
Vaccines typically require years of research and testing before

The Vaccines Themselves

242
Vaccine
Candidates

821
Vaccine
Trials

80
Countries with
Vaccine Trials



12 vaccines no longer progressing

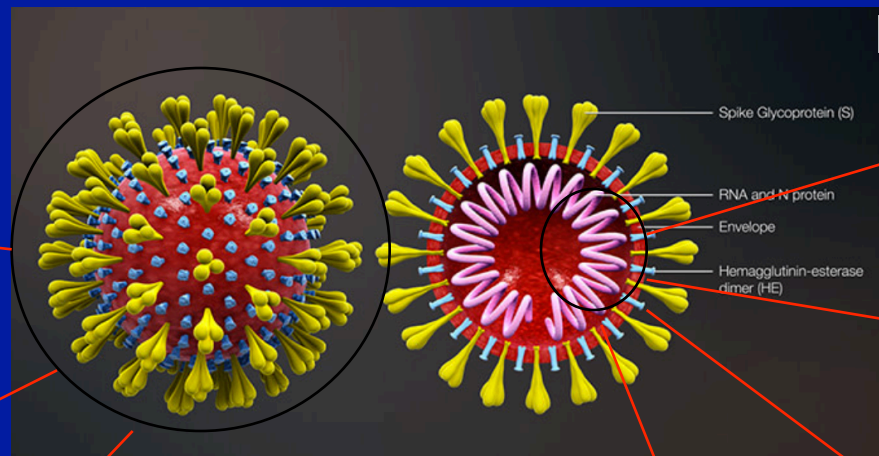
<https://covid19.trackvaccines.org/vaccines/>

**Live-Attenuated
(Hong Kong,
India)**

**While Virion
Inactivated
(SinoVac, CodaGenix)**

**Subunit Vaccines
Mostly Spike Protein
(+ Adjuvants)**

**Medicago (VLP+AS03)
Novavax (rS+MstrixM)
Sanofi (rS+AS03/AF03)
IMV (Peptide+DepoVax)
... many others**

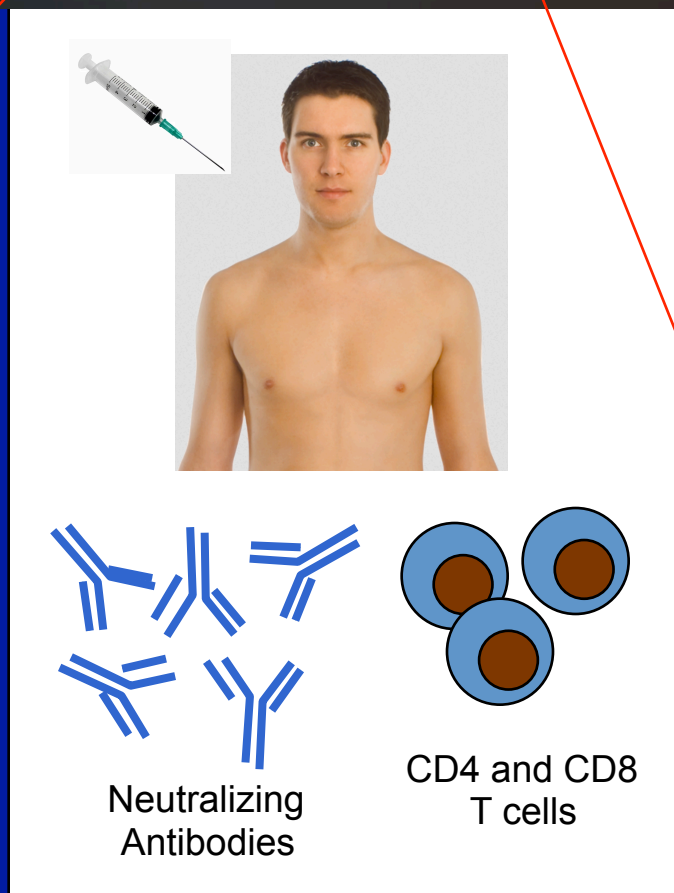


**Lipid-Encapsulated
RNA
(Moderna)**

**'Naked' DNA
Plasmid-Based
(Inovio/NIH)**

**Non-Replicating
Viral Vectors
(Adenovirus)
Oxford (Chimp Ad23)
CanSino (Ad5)
J&J (Ad5)
Gamaleya (Ad5/26)**

**Replicating
Attenuated Vectors
Merck (measles)**



Delivery

Pre-Clinical & Clinical Candidates - I

Intranasal

Aerosol

Oral

Intramuscular

Subcutaneous

Cutaneous

- Electroporation
- Transdermal patch
- Microneedle

Adjuvants

Alum

CpG1018

AS03

MF59

Alum-CpG

GLA

DPX

LNP

SWE

Other CpG

ESSAI O/W 1849101

FAR-Squalene

Mannose-Chitosa

GLA/#M052

... and many others

Replicating and Non-Replicating Chimeric Viruses

Adenovirus 5

Adenovirus 26

Sendai

Modified Vaccinia Ankara

Parainfluenzavirus

Influenza virus (H1N1)

Newcastle Disease virus

Lentiviruses

Vesicular Stomatitis Virus

Avian Paramyxovirus

Rabies virus

Yellow Fever Virus



Pre-Clinical & Clinical Candidates - II

Formats

Inactivated virions	Peptides + Adjuvants
Attenuated SARS-COV-2	Lipid nanoparticles
Other attenuated viruses	Virus-like Particles
Attenuated bacteria	Outer membrane vesicles
mRNA	Polymersomes
DNA/Plasmids	Gold nanoparticles
Proteins + Adjuvants	Autologous cells

Bacterial Vectors

Pertussis
Francisella
B. subtilis

Strategies

Heterologous Primary Series
Heterologous Prime-Boost
Revisiting of inter-dose intervals

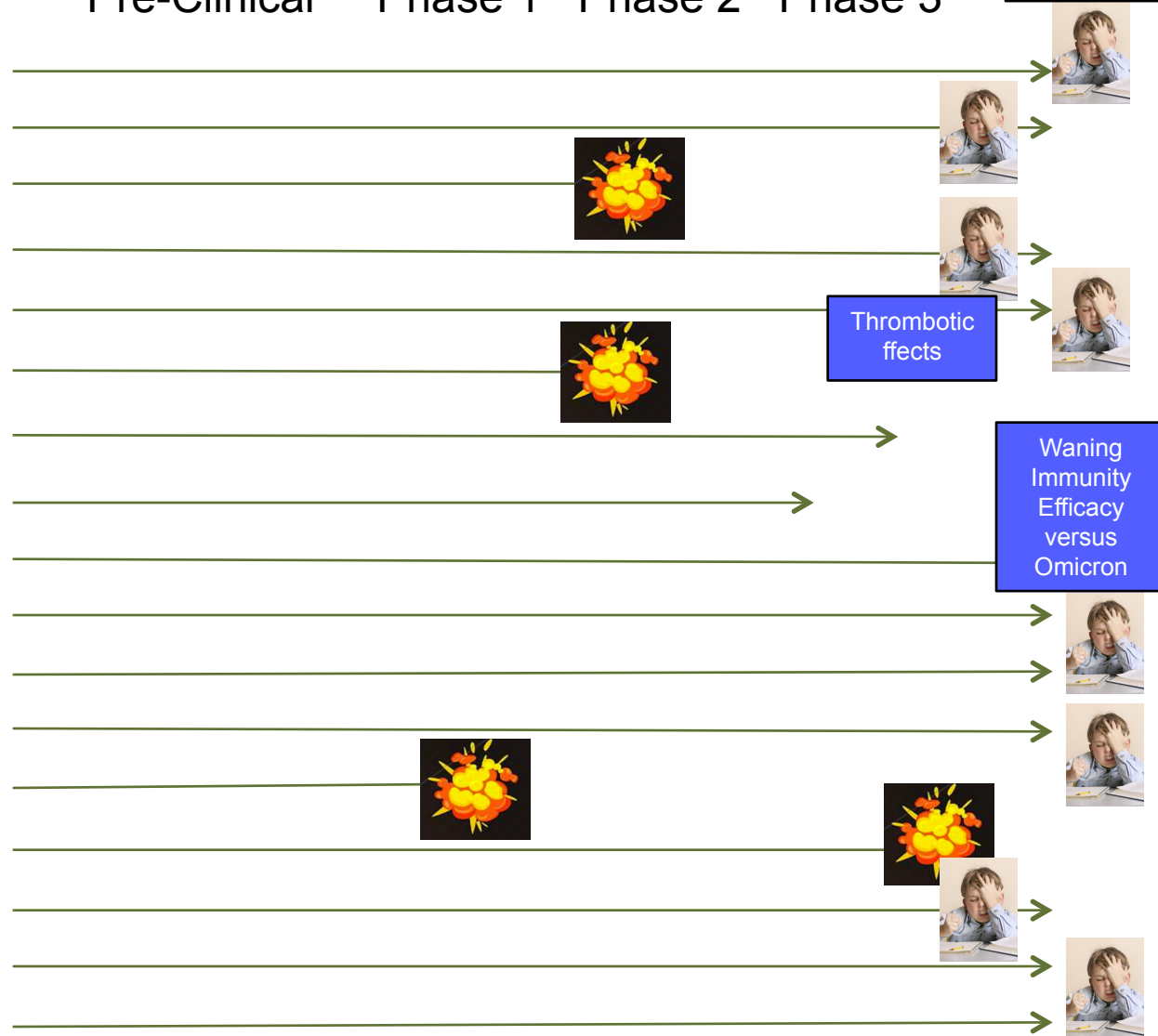
Antigens Targeted

Full-length spike	Envelope
Modified spike	Multiple peptides
Spike RBD	Ancestral strain
Matrix	Variant spike
Nucleocapsid	'Universal' CoV Ags

Companies Still Joining & Dropping Out ...

BNT/Pfizer
Oxford/AstraZeneca
Queesland
Johnson & Johnson
Moderna
Sanofi+Translate
Sanofi+GSK
Inovio
Novavax
SinoPharm
SinoVac
Medicago+GSK
Merck
CureVac
Gamaleya
Bharat Biotech
CanSino

Pre-Clinical Phase 1 Phase 2 Phase 3



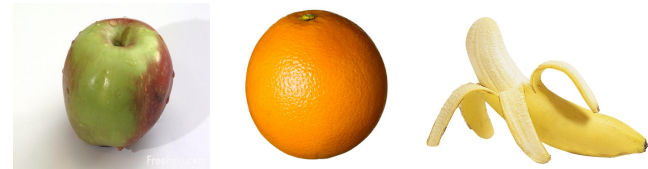
Which Vaccine is 'Best'?

The situation is already complex

It will get much more complex as more products are licensed in different places

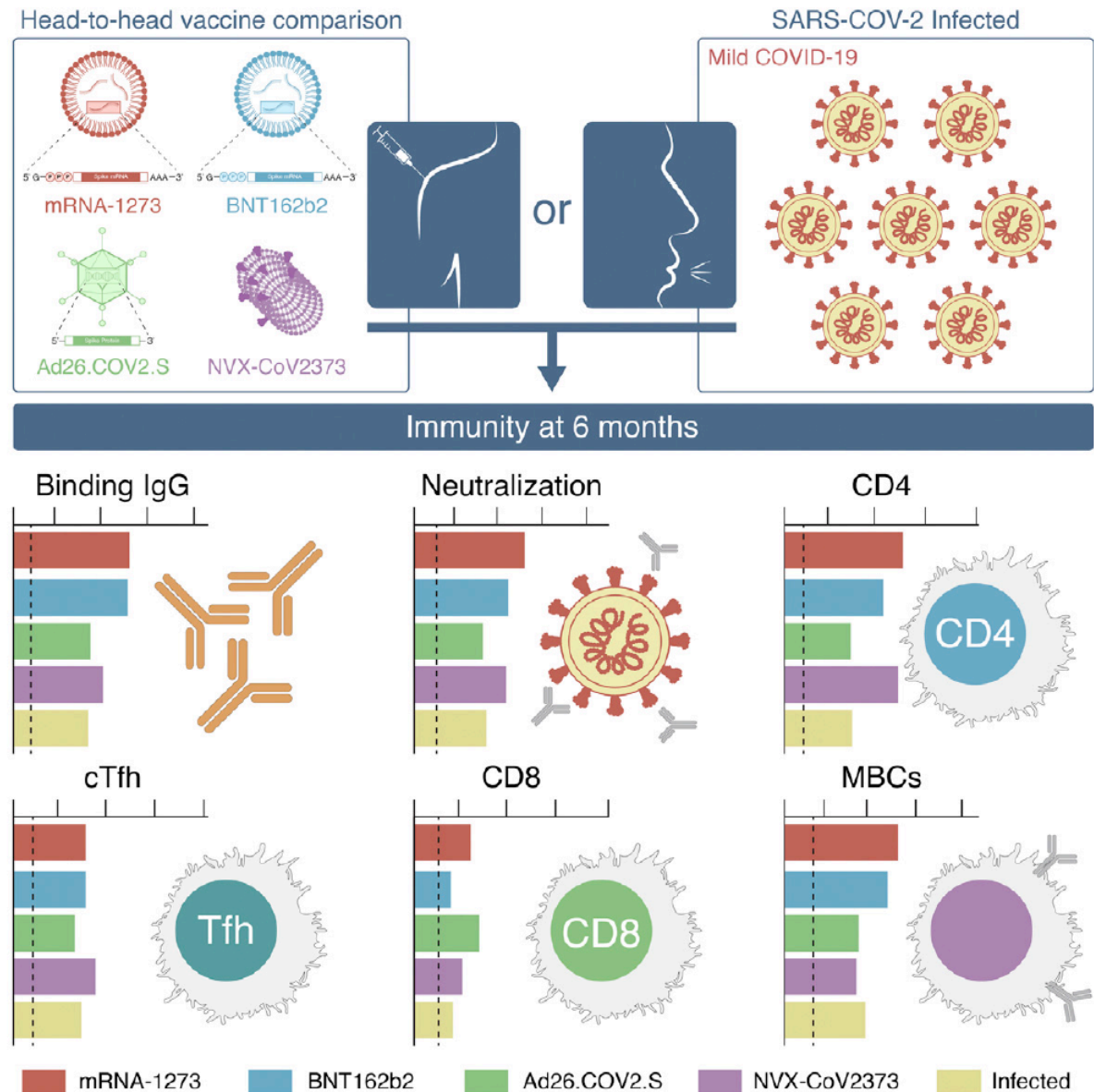
These products are NOT be the same

- ease of use
- side effects
- short-term efficacy
- durability of protection
- cross-protection



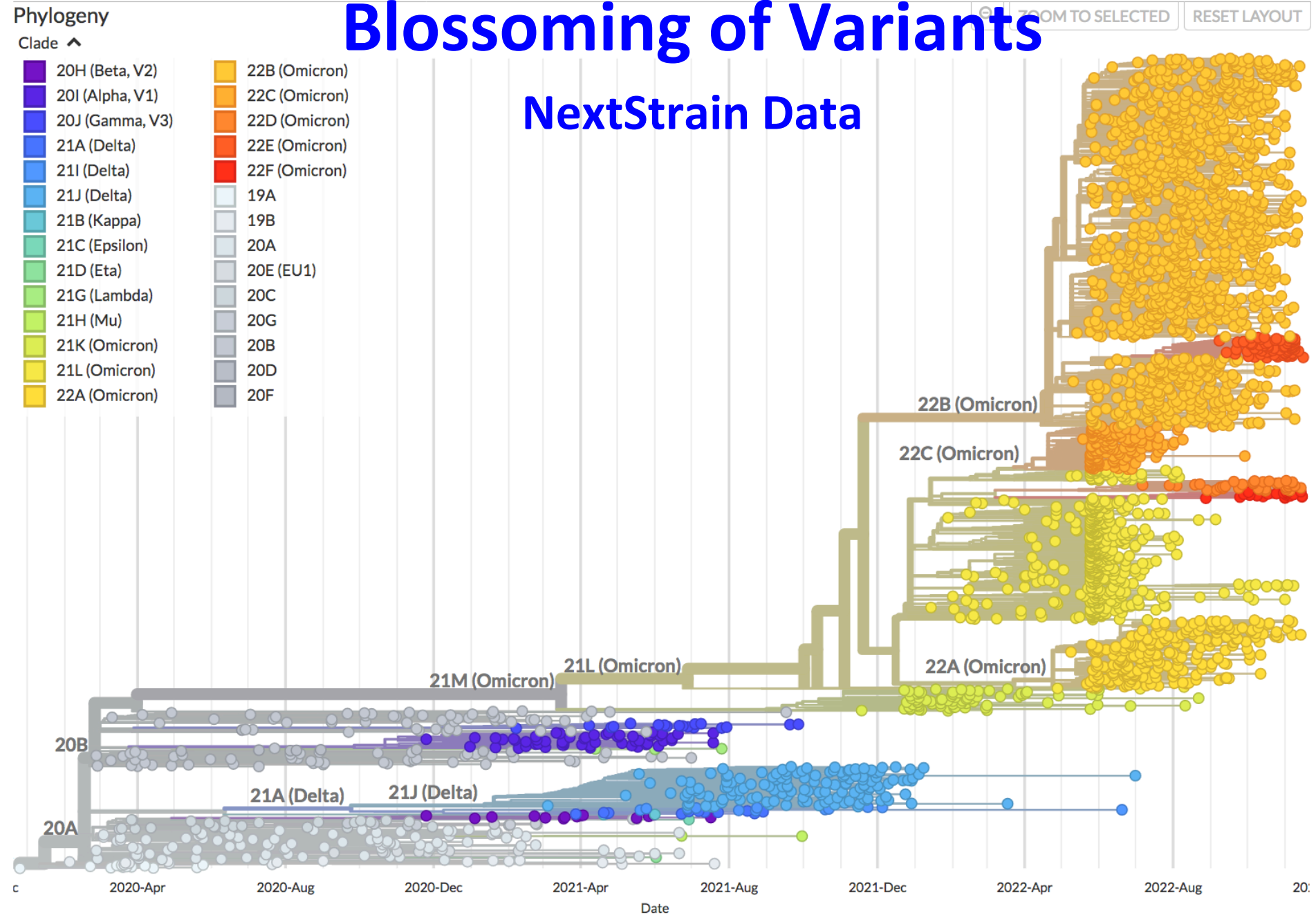
Current vaccines do remarkably well in terms of the breadth of immunity they induce ...

Caveat: these are only anti-S responses



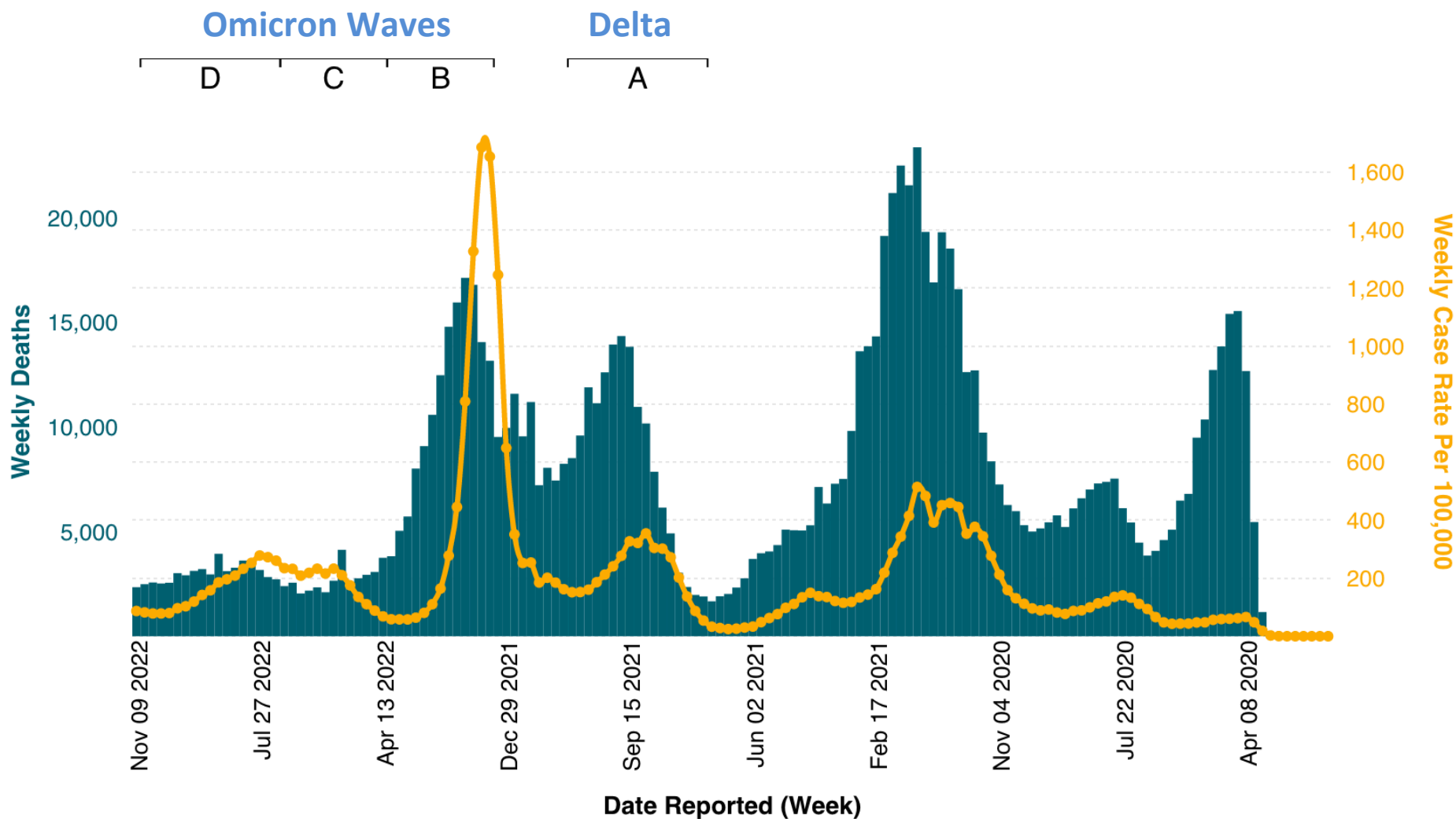
Blossoming of Variants

NextStrain Data



CDC Data for Cases/Deaths

(Nov 9, 2022)

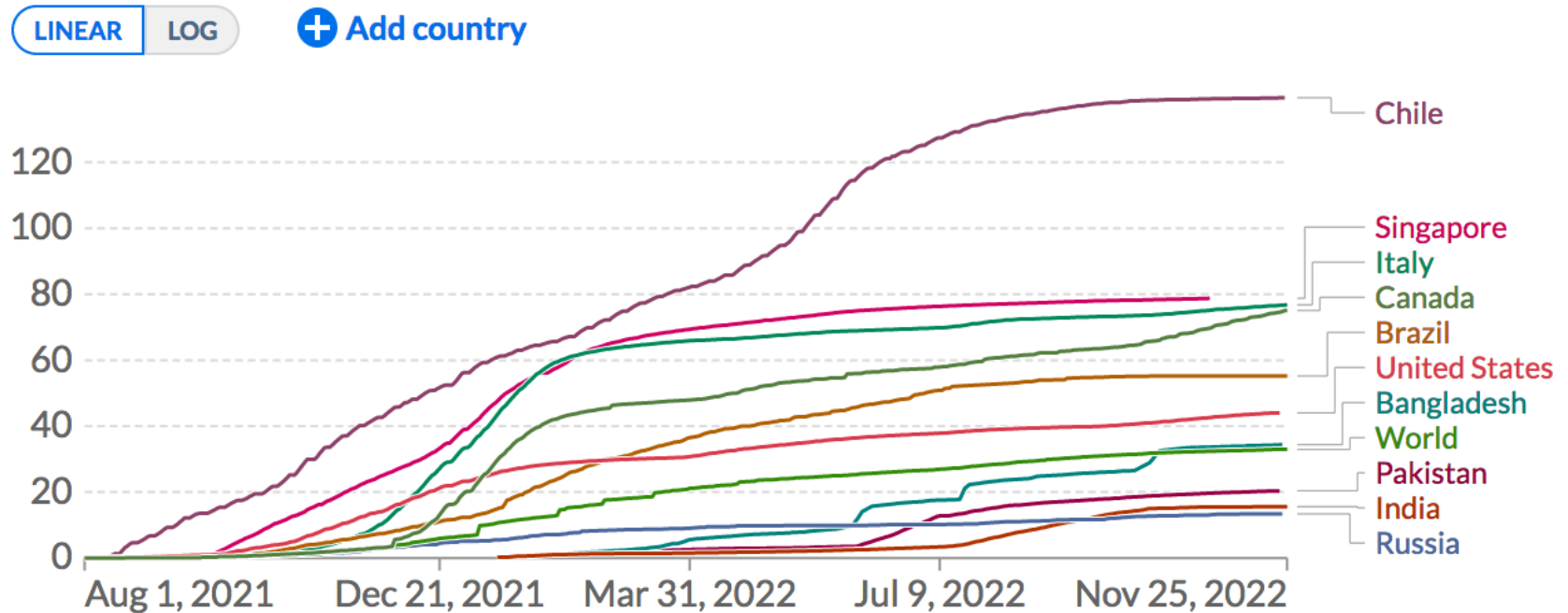


Boosters Administered?

COVID-19 vaccine boosters administered per 100 people

Total number of vaccine booster doses administered, divided by the total population of the country. Booster doses are doses administered beyond those prescribed by the original vaccination protocol.

Our World
in Data



Source: Official data collated by Our World in Data - Last updated 26 November 2022
OurWorldInData.org/coronavirus • CC BY

▶ Dec 29, 2020 ————— Nov 25, 2022

CHART

MAP

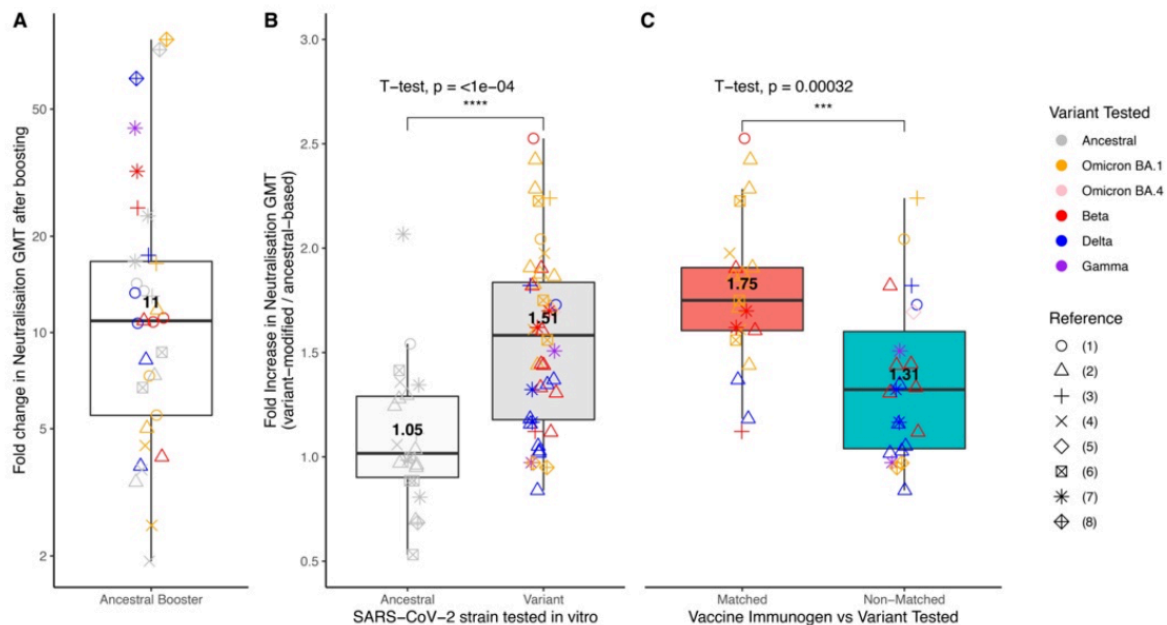
TABLE

SOURCES

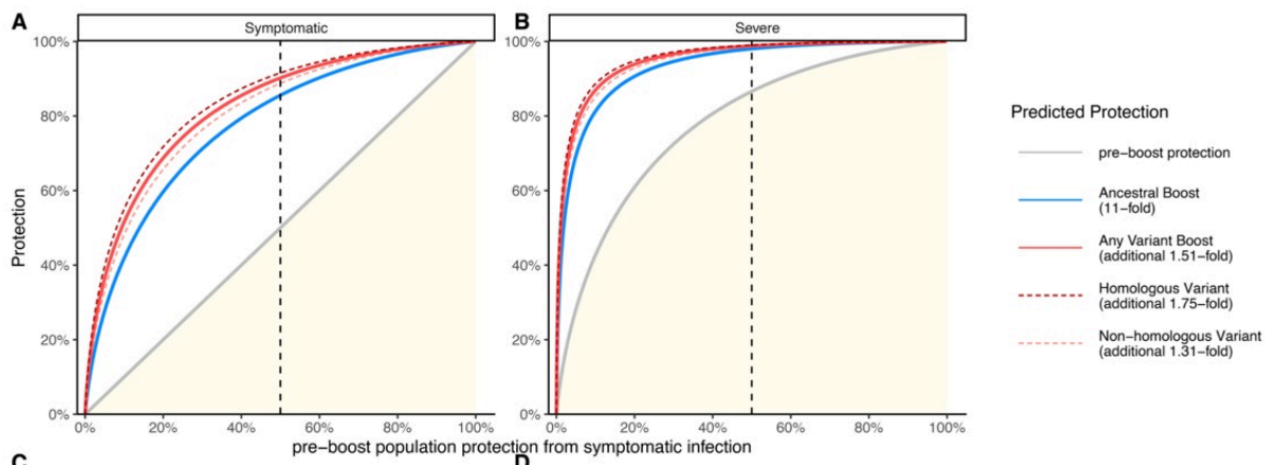
DOWNLOAD



Advantage of a Variant Booster?



- Fold-increase in NAb with an mRNA boost ~10x pre-boost titre
- Fold-increase in NAb (variant/ancestral) with ancestral- versus variant-based vaccine
- Fold-increase: matched vs. not-matched booster

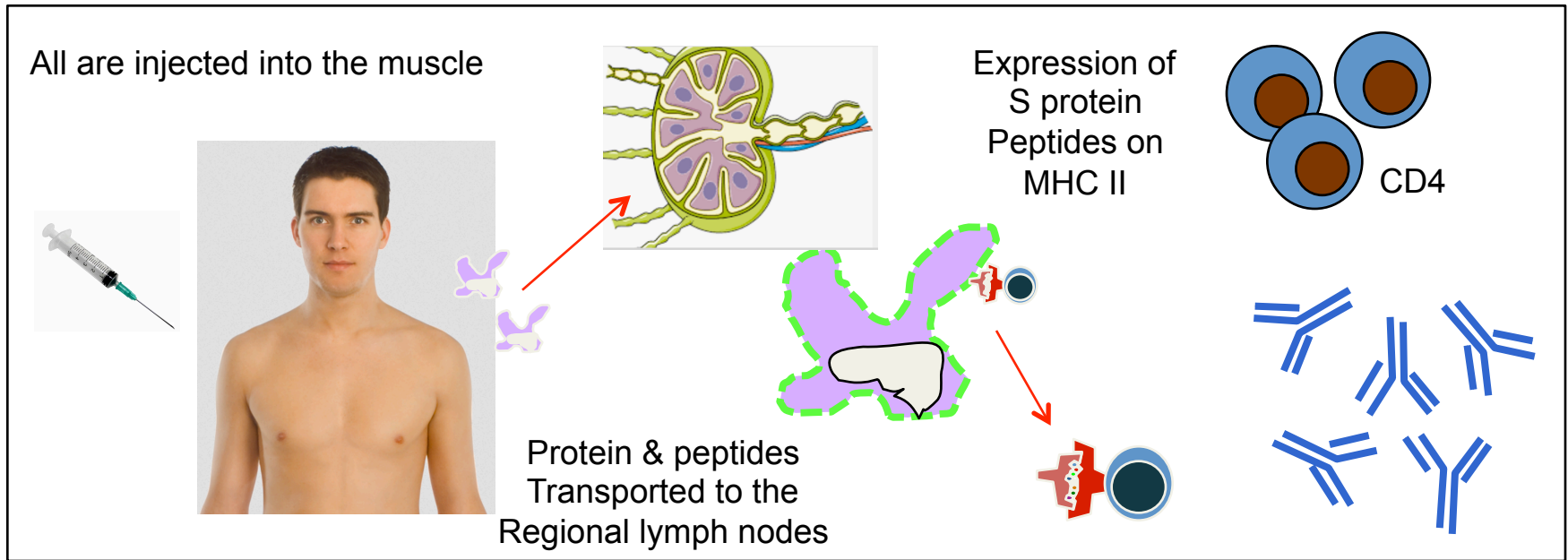


- X-axis: pre-boost level of protection
- Y axis: post-boost level of protection vs. 'any' or severe disease

The Different Platforms

(Various including Sinovac, Novavax others)

Whole Virion, Subunit & Peptide Vaccines



Annual Review of Medicine

Whole Inactivated Virus and Protein-Based COVID-19 Vaccines

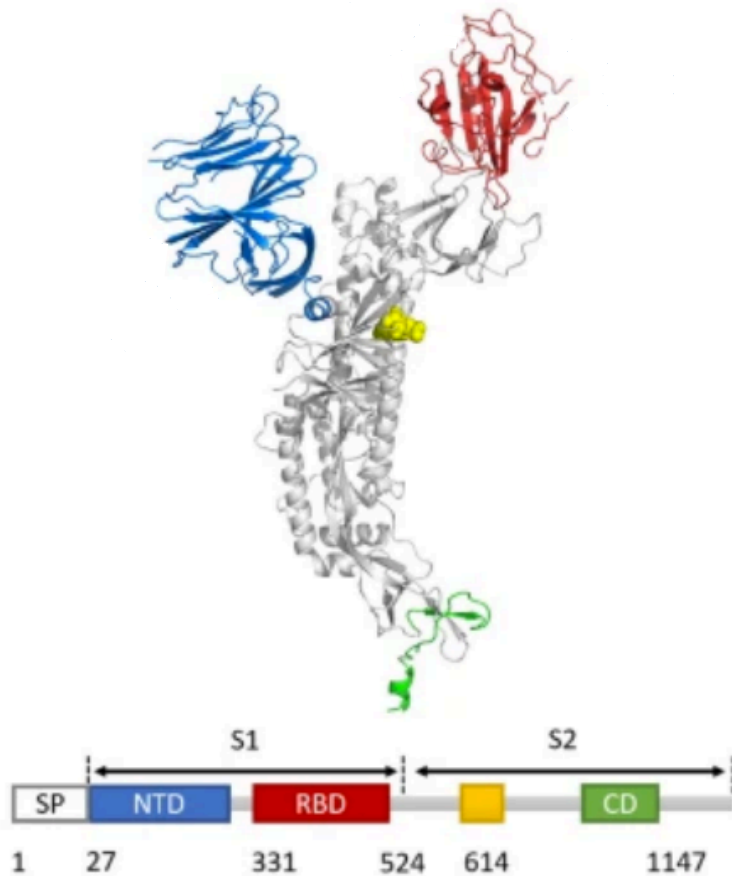
Peter J. Hotez^{1,2,3,4} and Maria Elena Bottazzi^{1,2,3}

**Don't Let the Perfect
be the Enemy of the Good**

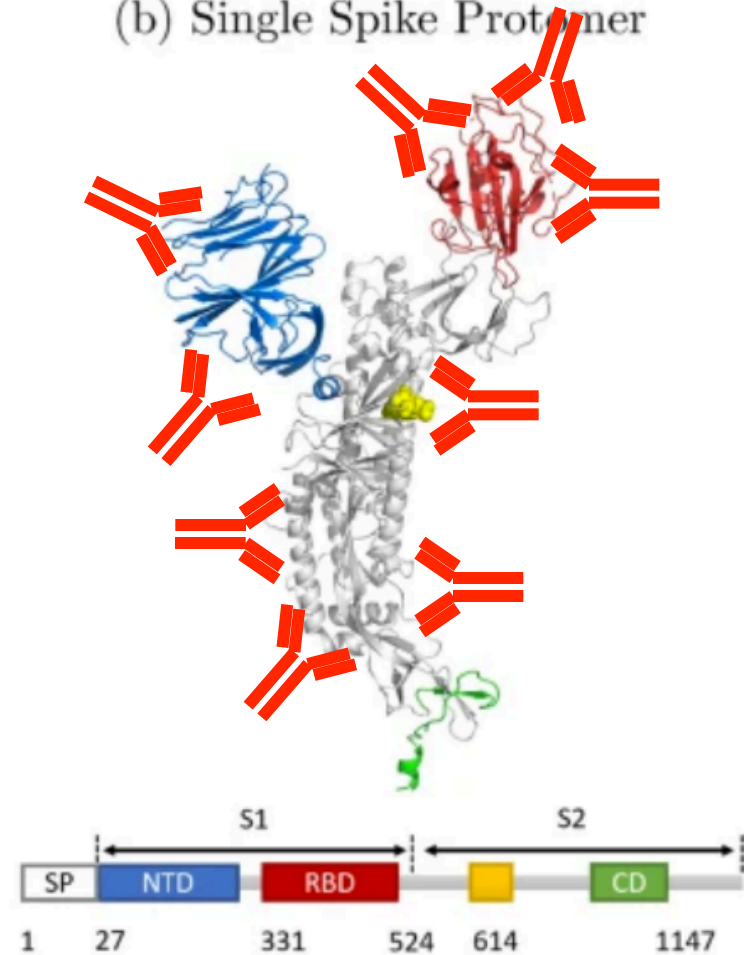
Voltaire

Adjuvants and Epitope Spreading

(b) Single Spike Protomer

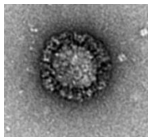


(b) Single Spike Protomer

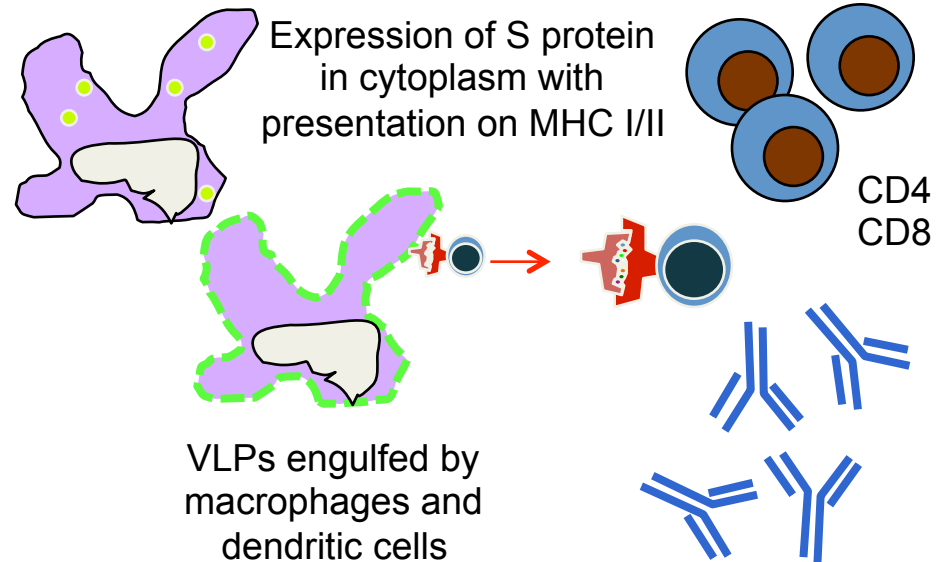
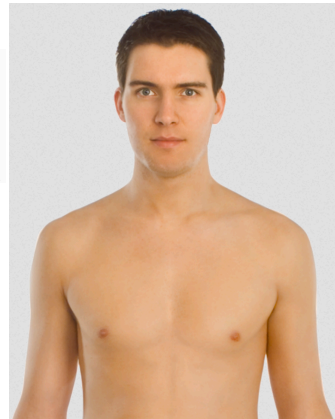


Plant-Derived Virus-Like Particle (VLP) Vaccine

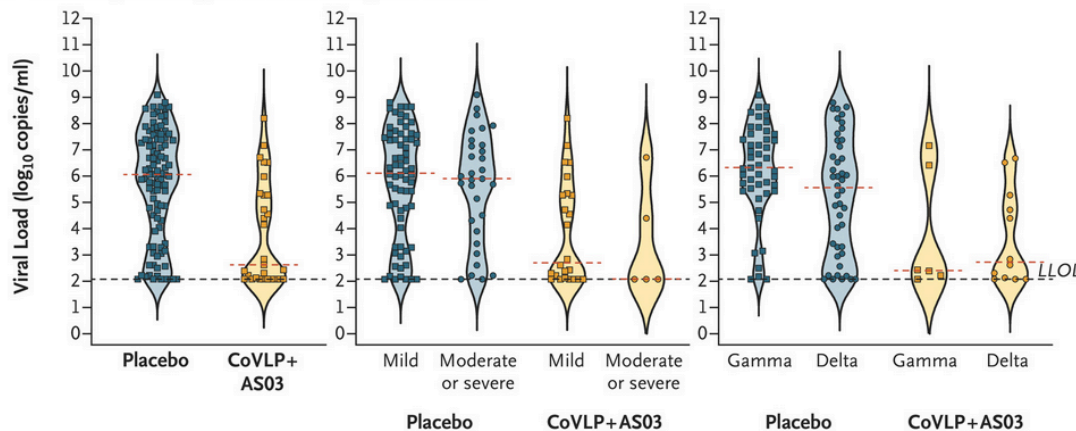
A. tumefaciens-vectored transient transfection of *N. benthamiana* delivering spike protein



VLPs spontaneously form and are purified



A Viral Load, According to Disease Severity and Variant

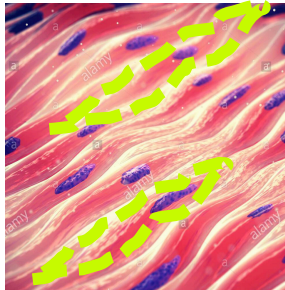


- 70% efficacy against a range of variants
- 100% protection against serious disease & hospitalization
- The only vaccine to date to show large reductions in viral load in breakthrough cases

CanSino Biological Inc. & Beijing Institute of Biotechnology

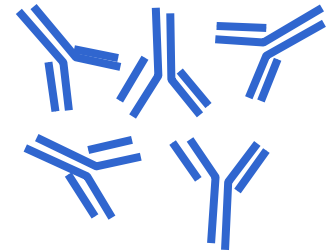
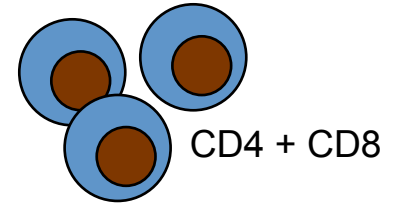
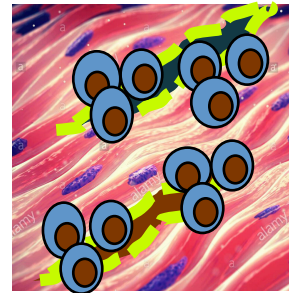
Adenovirus 5-Vectored DNA Vaccine

Injection of replication-defective Ad5 vector into muscle



Transfection of myocytes in deltoid muscle. Cells start to express spike protein

Immune 'attack' of transfected myocytes



COMMENT | February 12, 2021

Adenovirus-vectored Covid-19 vaccines' efficacy during a potential revaccination campaign likely to be stifled by antivector response

Adenovirus-vectored vaccines for Covid-19 are at a disadvantage if vaccination campaigns become periodic to combat new SARS-CoV-2 variants or in the event of low durability, experts said.

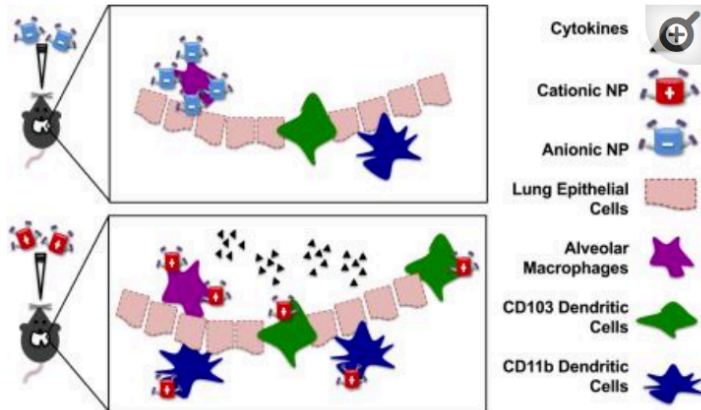
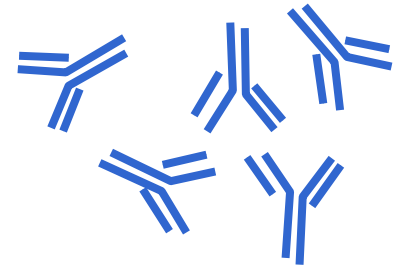
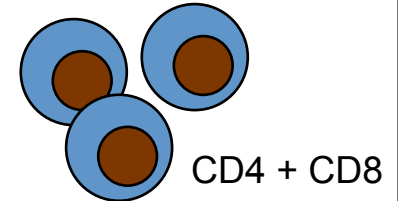
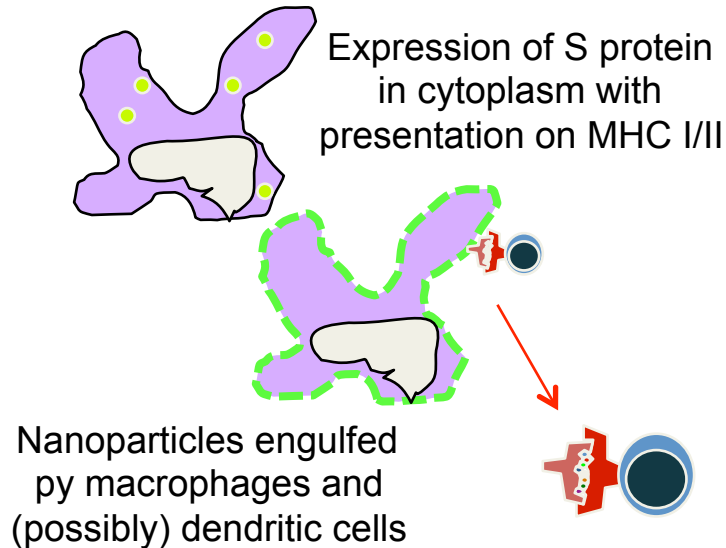
By Reynald Castañeda

- ~30% of world has pre-existing antibodies to Ad 5 (Chimp Adenovirus may have some advantages)

Usefulness for boosters or endemic programs still to be defined

Lipid-Encapsulated mRNA Vaccine

Injection of inert lipid-nanoparticles + mRNA
Into muscle



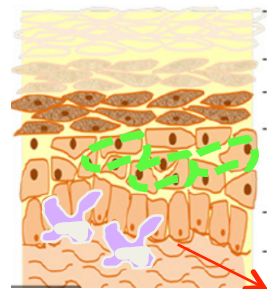
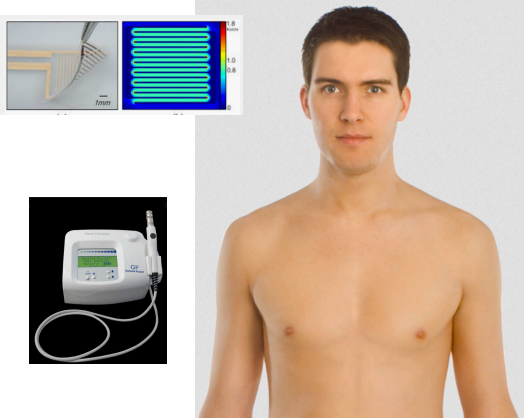
Major Discovery

- Cationic Nanoparticles Better Able to Deliver mRNA to Range of Antigen-Presenting Cells

Various (including Inovio)

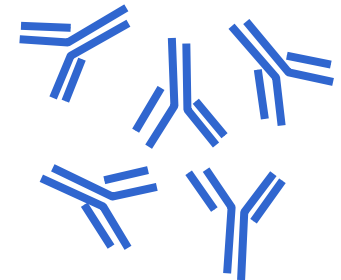
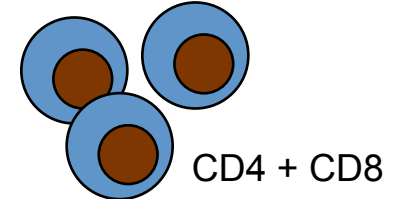
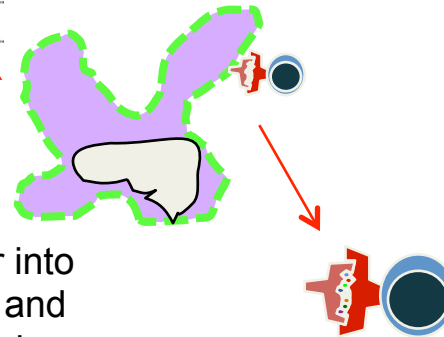
Plasmid-Based DNA Vaccine

Electroporation into the skin using variety of devices



Expression of S protein in cytoplasm with presentation on MHC I/II

Plasmids enter into Keratinocytes and migrating macrophages



Major Issues (so far)

- Reliance on a 'Device' has Slowed Development of these Products

COVID-19 vaccine development and a potential nanomaterial path forward. Shin MD, Shukla S, Chung YH, Beiss V, Chan SK, Ortega-Rivera OA, Wirth DM, Chen A, Sack M, Pokorski JK, Steinmetz NF. Nat Nanotechnol. 2020 Aug;15(8):646-655.

<https://spectrum.ieee.org/inovios-electrical-device-zaps-a-covid19-vaccine-into-the-body>

<https://www.futurity.org/electroporator-vaccines-drug-delivery-microneedles-2648122/>

<https://www.ondrugdelivery.com/imv-development-of-dpx-covid-19-vaccine-its-ongoing-business-and-clinical-operations/>

Codagenix/Serum Institute of India and others

Live Attenuated & Chimeric Virus Vaccines

Many different approaches being taken

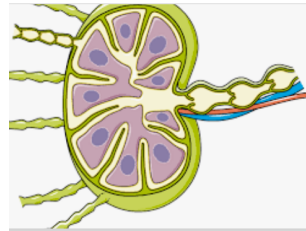
Measles, horsepox, VSV, MVA used as vectors

Almost all target SARS-COV-2 spike protein responses

Administered IM (1-2 doses) – theoretically by aerosol

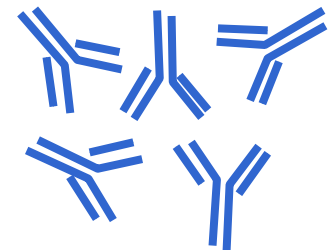
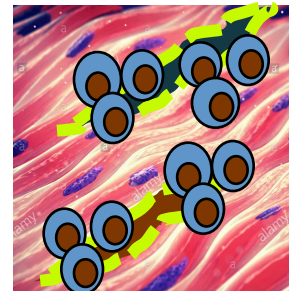
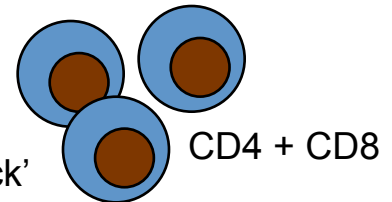
Various dose levels being tested

Injection of live-attenuated
virus or chimeric virus into
muscle



Infection of different
target cells depending on
tropism of viral vector. Active
involvement of proximal
lymph nodes.

Antigen presentation
By professional APCs
(MHC I/II).
Eventual Immune 'attack'
of infected cells





The Crystal Ball

(... but don't hold me to it)

<https://medium.com/@kumariimc/the-crystal-ball-approach-aa61b54a7942>

‘Normal’ viral evolution suggests SARS-COV-2 will mutate towards endemicity which may be happening with Omicron with its high reproduction number $\geq 10-15$

It seems likely that close to 100% of the world's population will be vaccinated \pm exposed to Omicron by the end of 2022

If (a big IF) this occurs and pathogenicity remains high for some groups, we will likely need periodic boosters (just like influenza)

How Has the Pandemic Changed the Vaccine Landscape?

>250 diverse
candidates
Dozens of licensed
products

World first licensed technologies

- Adenovirus vectored vaccines
- mRNA vaccines
- Plant-based vaccine



Vaccination strategies


- heterologous primary series & prime-boost
- combining adjuvants
- re-evaluation of dosing intervals

Infrastructure/organization

- managing ultra-low temperature
- new partnerships
- accelerated timelines
- distributed manufacturing

Social & Political

- hesitancy & resistance
- mandates
- vaccine distribution



We still have a great deal
to learn but we've definitely
made progress

Thank you for your attention
Questions?