Burnet Institute
Medical Research. Practical Action.

Vaccine development for COVID-19

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Disease Elimination

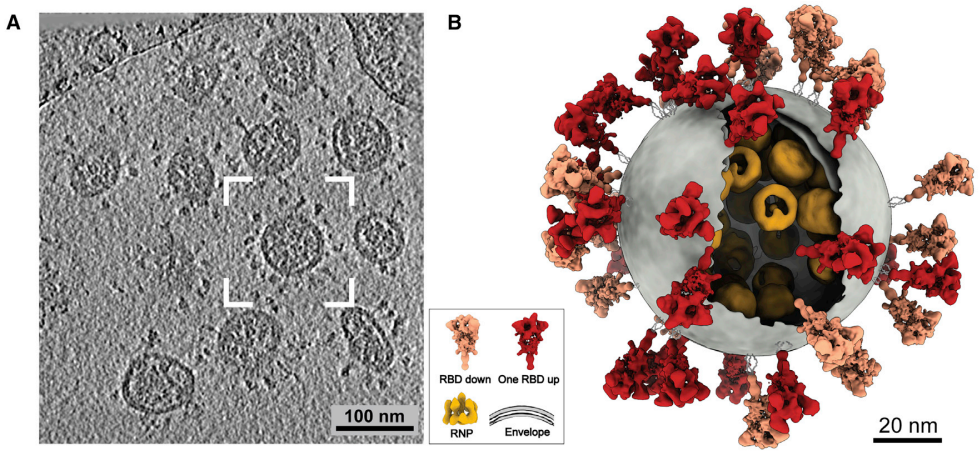
Proudly supporting the global
COVID-19 health response.

Virus structure

Please cite this article in press as: Yao et al., Molecular Architecture of the SARS-CoV-2 Virus, Cell (2020), https://doi.org/10.1016/j.cell.2020.09.018

Cell
Article

CellPress



- Four main structural proteins
- Matrix (M)-most abundant protein, gives virus its shape
- Nucleocapsid (N)-sole component of the capsid and has two RNA binding domains. Also binds M and the replicase nsp3 and tethers capsid to replication complex
- Spike (S)-trimeric responsible for attaching to ACE2 and membrane fusion and entry. Divided into S1 and S2 domains.
- Envelope (E)-small protein present in low abundance with ion channel activity

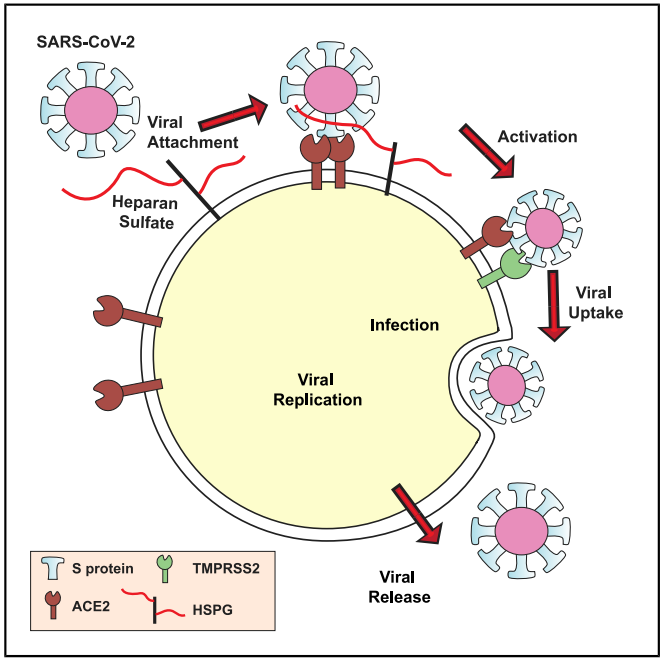
Virus entry and replication

Cell

Article

SARS-CoV-2 Infection Depends on Cellular Heparan Sulfate and ACE2

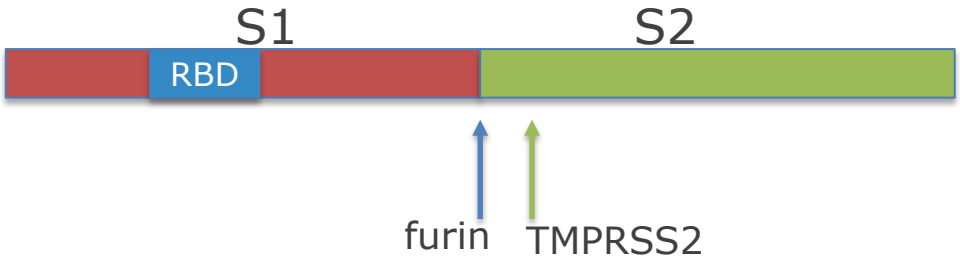
Graphical Abstract



Clausen et al., 2020, Cell 183, 1–15
November 12, 2020 © 2020 Elsevier Inc.
https://doi.org/10.1016/j.cell.2020.09.033

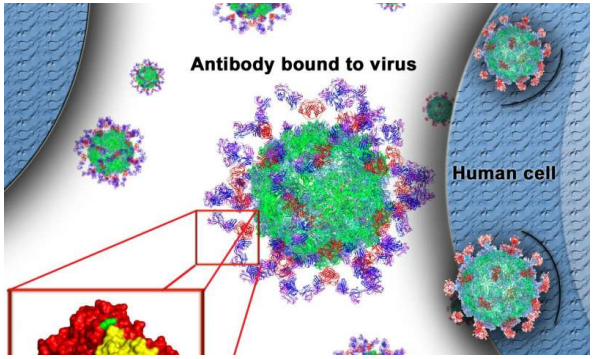
CellPress

- Initial binding event to heparan sulfate on cell surface primes spike for binding ACE2
- Spike binds ACE2 via RBD at low nM affinity
- TMPRSS2 cleaves within S2 to activate ability of S2 to mediate fusion
- Virus creates hole in cell membrane to deliver nucleocapsid and begins replicating



What are vaccines and how do they work?

- All human vaccines work by generating neutralizing antibodies that stop or restrict infection by viruses or other pathogens
- Neutralizing antibodies are produced by immune cells that circulate in our bodies and can be detected in our blood and on mucosal surfaces
- Vaccines can also generate a cellular immune response that destroys any cells that may have become infected with an infectious agent



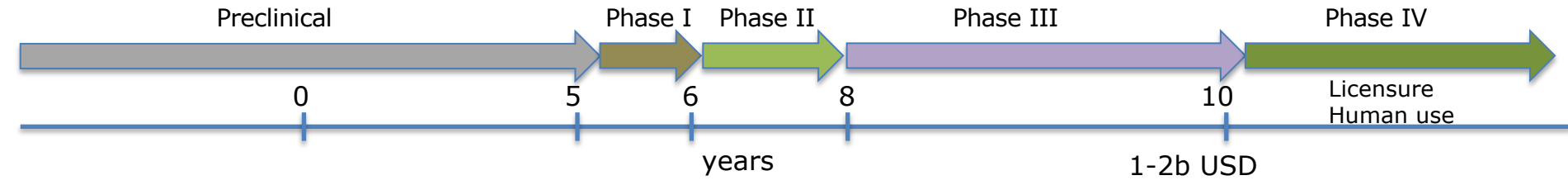
Credit:https://phys.org/news/2016-11-human-astrovirus-antiviral-therapies-vaccines.html

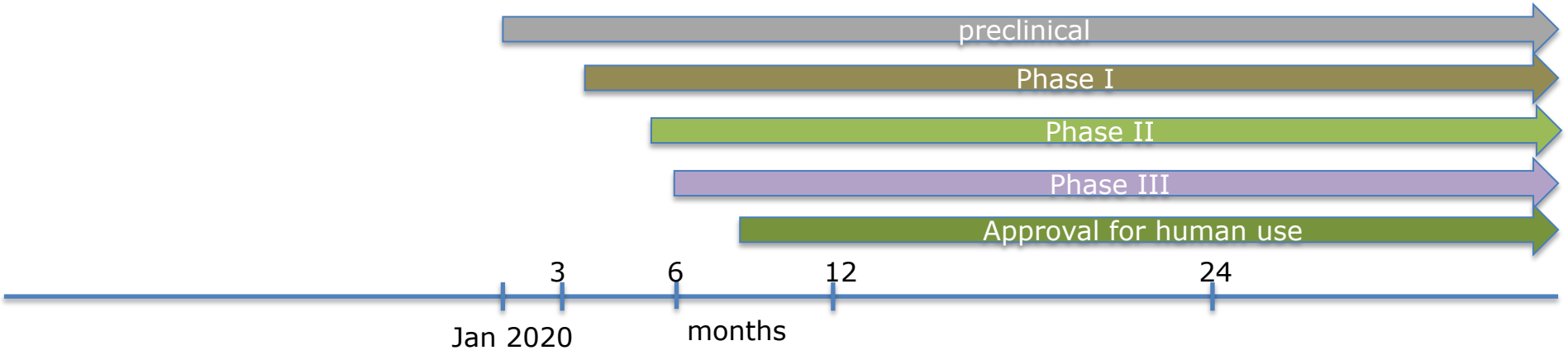
Stages of vaccine development

	Preclinical	Phase I	Phase II	Phase III	Phase IV
Safety	■	■	■	■	■
Immunogenicity	■	■	■	■	■
Efficacy	▒	▒	■	■	■
Durable immunity				■	■

- 150+ vaccines are in development for COVID-19 globally and 42 have entered human clinical trials

Usual vaccine timelines v COVID vaccine timelines





What do we want from a COVID-19 vaccine?

1. Safe-no harmful side effects, no disease enhancement
2. Primary outcome is lab confirmed symptoms >14 days after vaccination complete
3. Prevention of severe disease and reduction in deaths.
4. Prevention of infection and reduction in transmission.
5. Minimum of 50% efficacy-WHO guidelines (see below)
6. Long lasting immunity.

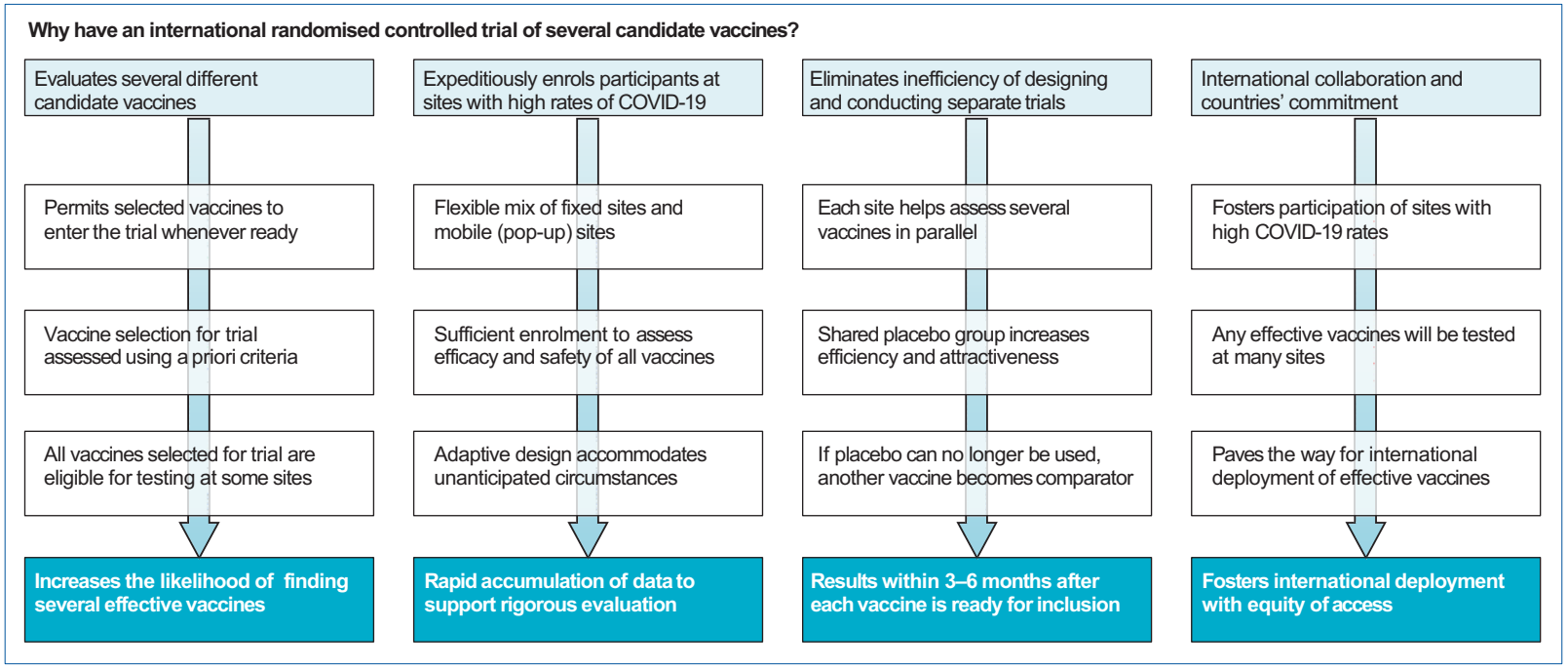


Figure: **Selected design features of the WHO Solidarity Vaccines Trial**
The primary outcome is laboratoryconfirmed symptoms >14 days after vaccination is completed. Analyses of each vaccine after about 40, 70, and 100 primary outcomes occur in the placebo group will report success if they show ≤10 versus 40, ≤30 versus 70, or ≤50 versus 100 outcomes. The third analysis is reported regardless of its findings. In all cases placebocontrolled followup continues until at least month 12 (or local deployment of an effective vaccine) to assess safety, disease severity, and duration of protection.

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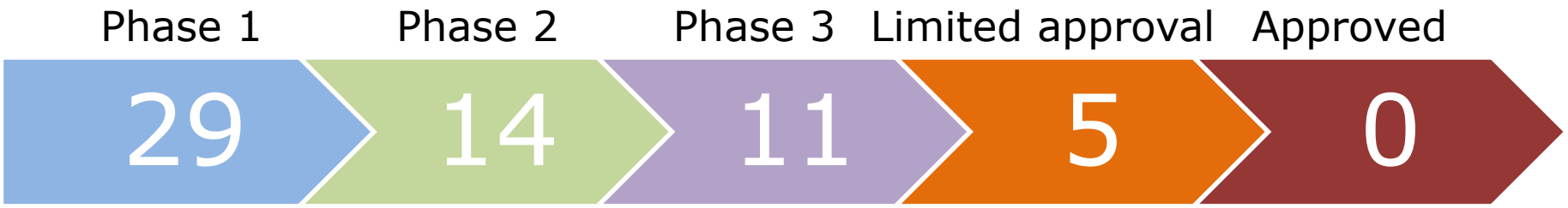
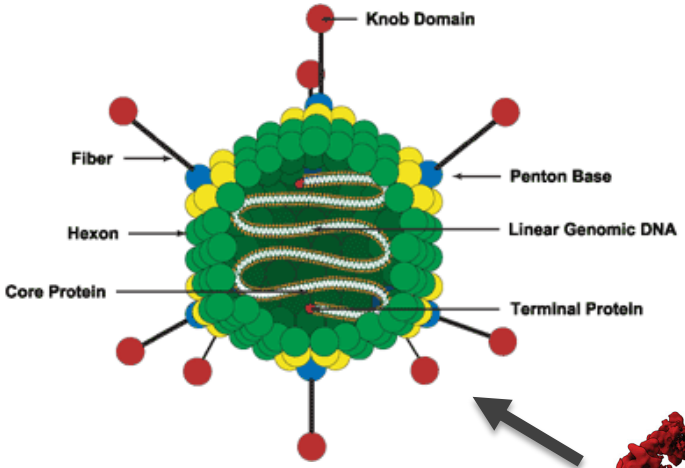
Vaccine progress.



Source New York Times

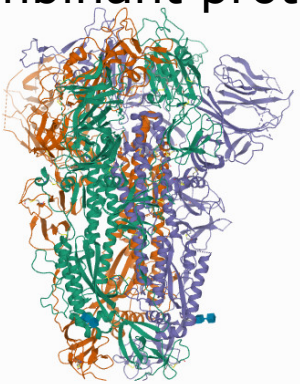
COVID vaccine strategies

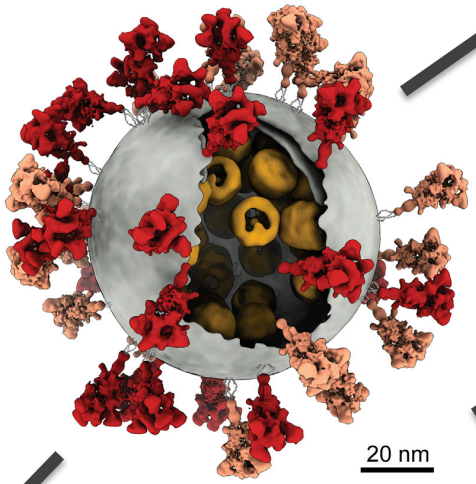
Viral vectored



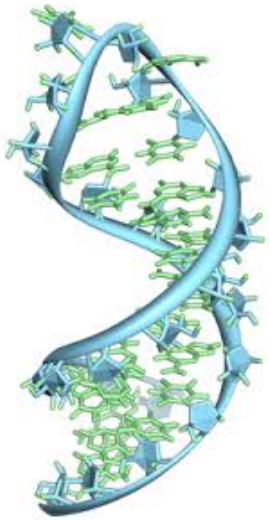
DNA

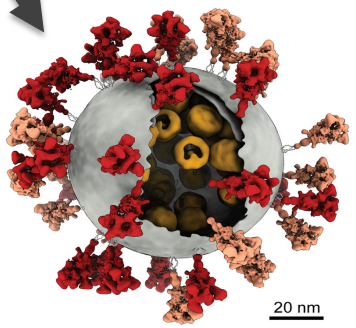
Recombinant protein





RNA



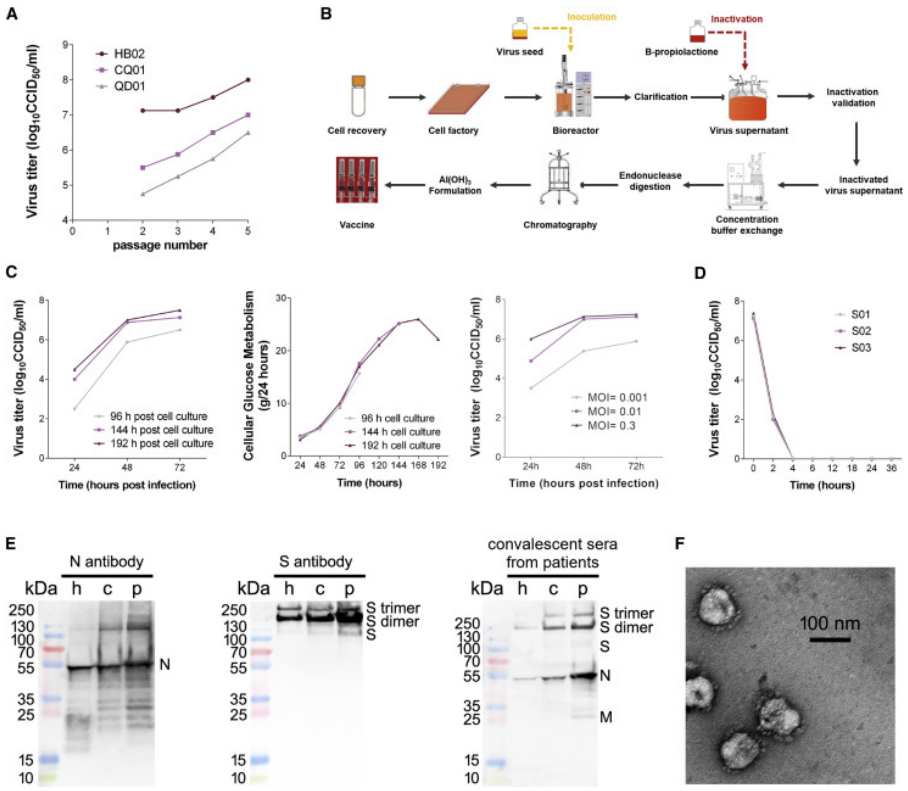


Inactivated or live attenuated

Leading vaccine candidates: Inactivated vaccines

Sinovac, Sinopharm

- Classic approach to vaccine manufacture
- Virus grown in cells in bioreactors and inactivated in situ.
- No replication in host
- Delivers all the structural proteins of the virus, S, N, M, E
- Potent inducers of humoral immunity and cellular responses and protection from severe disease in macaques
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7275151/
- Induces neutralizing antibodies in humans in Phase 1/2 interim study reports
- https://pubmed.ncbi.nlm.nih.gov/32789505/
- No SAE, 2 doses sufficient



Benefits:

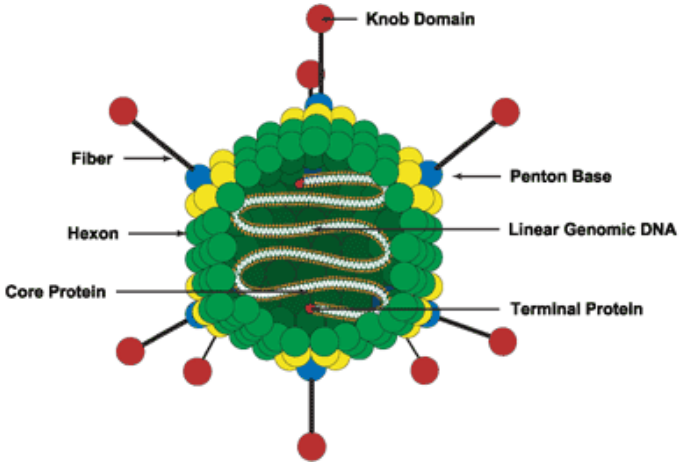
- Easy to make using standard virus growth procedures, cheap, safe,

Limitations:

- Biosafety issues
- Cannot monitor background infection in vaccinated populations

Viral vector platforms

1. ChAdOx1nCoV-19 or AZD1222.



- Gene for spike protein encoded in an attenuated, replication defective adenovirus genome
- Chimpanzee adenovirus so no pre-existing immunity to adenovirus in humans ATM
- Expression of spike is within the infected cell
- Generates cellular immunity (CD4+, CD8+) and antibody responses
- Phase 1/2 study published. No SAE. https://pubmed.ncbi.nlm.nih.gov/32702298/
- One or two doses given i.m. 4 weeks later examined immune responses
- 2 doses better than 1. After 2 doses, all subjects had neutralizing antibody responses
- Strong cellular responses
- Preclinical study showed protection from severe disease in macaques; no pneumonia and significant reduction in viral titre https://pubmed.ncbi.nlm.nih.gov/32731258/

AstraZeneca

- Benefits: Easy to make, cheap, safe, technology is being transferred to CSL for production in Broadmeadows
- Can monitor background infection in vaccinated populations

- Risks: Homologous boosting not effective

Viral vectored platforms cont.

2. Adenovirus 5, 26. CanSino, Gamaleya Research Institute (sputnik V), Janssen

- Human adenovirus serotypes
- Gene for spike protein encoded in an attenuated, replication defective adenovirus genome.
- Pre-existing immunity to human adenoviruses
- Phase 1/2 Sputnik V results published. No SAE https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31866-3/fulltext
- 1 or 2 doses examined in a heterologous prime/boost
- 100% seroconversion rate, 2 doses boosted responses
- NAbs developed in all participants
- Strong cellular responses
- Approved for limited use in Russia

Benefits:

- Easy to make, cheap, safe, technology,
- can monitor background infection in vaccinated populations

Risks/limitations:

- Background immunity to Ad5 may compromise efficacy, particular in sub-Saharan Africa and South East Asia. Ad26 better.
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3138857/

RNA vaccines

Moderna, Pfizer, BioNTech, CureVac

- Novel technology
- Uses mRNA to deliver the spike gene
- Major benefit is there is no chance of recombination into human genome, can be made at large scale relatively easily, any gene can be incorporated and expressed within the cell
- Generates both antibody and cellular responses
- RNA can be engineered to increase stability, and enhance protein expression
- Formulated with a lipo-nanoparticle (LNP) carriers to deliver gene into cell
- Phase 1/2 results published from Moderna trial
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7377258/
- Safe, no SAE
- 100% seroconversion, All had neutralizing antibody responses, CD4 and CD8 T cell responses.

Benefits:

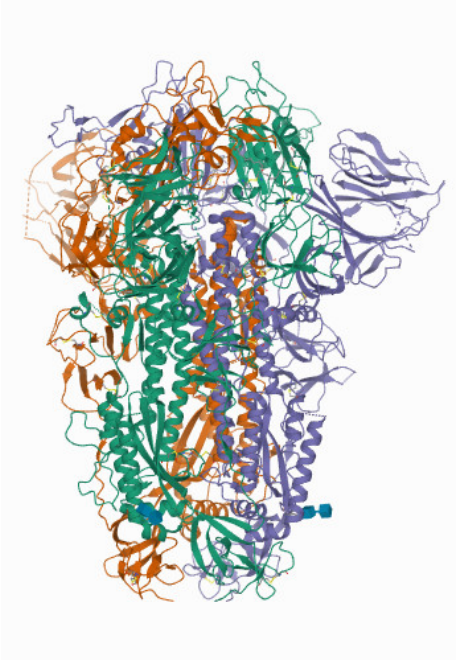
- Easy to make, cheap, safe, technology,
- can monitor background infection in vaccinated populations

Risks/limitations:

- Has never been an approved product from this technology
- Manufacturing technology

Recombinant protein based vaccines

UQ/CSL, UoM, NovaVax,



- Recombinant spike proteins formulated with adjuvants to enhance immune response
- No genetic material

UQ/CSL technology

- Engineered spike protein that have the spike trimer linked to a "clamp" that stabilizes the trimer and increases protein expression. Made in mammalian cell lines in bioreactors. Production will occur in Melbourne. Have agreement to make 51 million doses per year.

Novavax technology NVX-CoV2373

- Spike protein formulated with MatrixM forms nanoparticle.
- Agreement with Serum Institute of India to make 2B doses annually

Benefits:

- Safe, no genetic material
- Can monitor background infection in vaccinated populations

Risks/limitations:

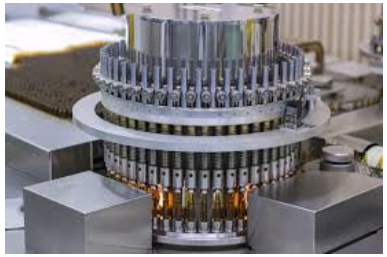
- More expensive to make
- Requires manufacturing skill/technology
- Requires more powerful adjuvants to stimulate immune response
- Stability-requires 2-8°C
- Major response will be antibody and limited cellular response-CD4

Future prospects

- Earliest possible arrival of a vaccine is sometime in 2021
- Need a global strategy to deliver the vaccine-COVAX https://www.gavi.org/vaccineswork/covax-explained
- Part of the Access to COVID Tools (ACT) global accelerator convened by GAVI, WHO and CEPI
  - Aims to deliver 2 Billion doses of vaccine for the most vulnerable in the world by end of 2021
  - Australia is a signatory to COVAX
  - Agreements in place with AstraZeneca and CSL to manufacture vaccines in Australia
  - Other agreements likely to be made to ensure we have earliest possible access

Future limitations to vaccines

Manufacture



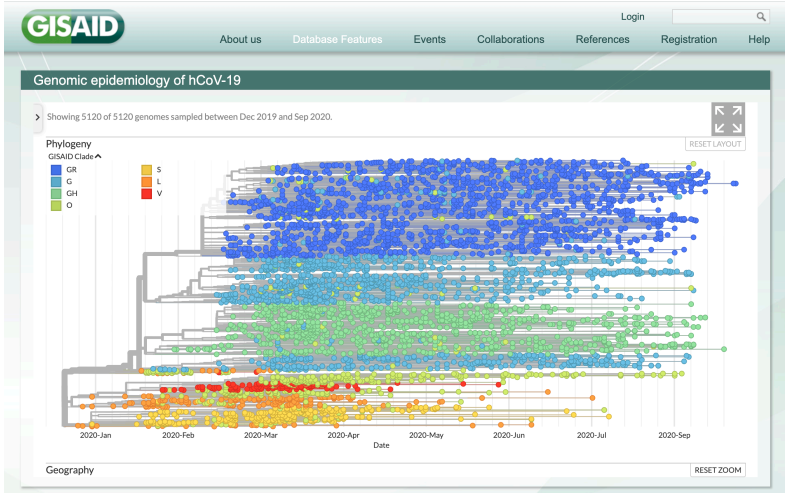
Implementation

Efficacy with pre-existing immunity

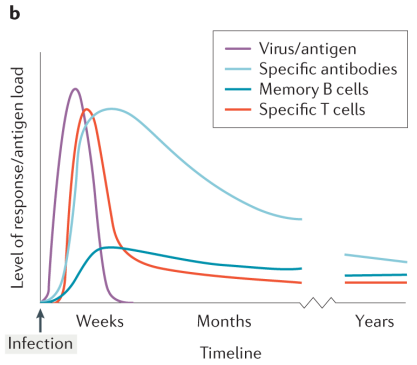
Efficacy in aged?

? Vaccine skepticism

Evolution of the virus



Durability of the immune response



https://www.nature.com/articles/s41577-020-00436-4/figures/1