Vaccine Development for COVID-19

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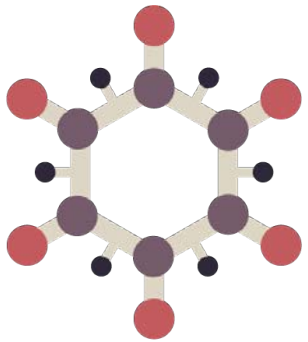
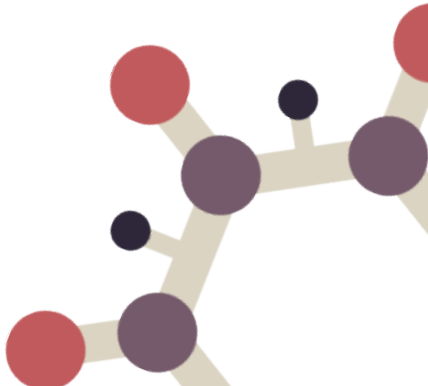


IMMUNISATION

COALITION

COI/Disclosures

- Employed by Nucleus Network as the Principal Investigator on numerous vaccine clinical trials including the following SARS-CoV-2 vaccines;
  - UQ
  - Novavax
  - Serum Institute of India
  - Symvivo
- Member of Novotech IBC
- Immunisation coalition Director and Scientific Advisory Board Member



Outline

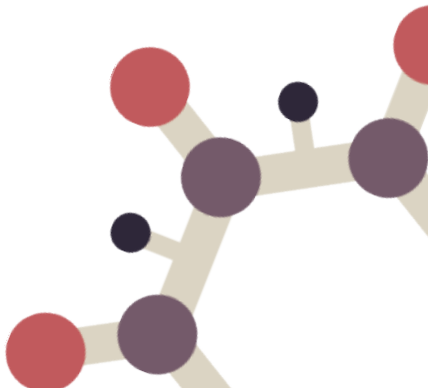
- History of Coronavirus Vaccines
- Clinical Trials
- Clinical Trials for COVID-19 Vaccines
- COVID-19 Vaccine Tracker
- Viral Vectored Vaccines
- Protein Based Vaccines
- Adjuvants
- COVID-19 Vaccines in Australia
- My Prediction
- Ongoing questions
- Conclusion
- References

History of Coronavirus vaccines

- No licenced human coronavirus vaccine previously
- Many currently in use for animals including;
  - IBV (Infectious bronchitis virus) vaccine for chickens (live attenuated and inactivated)
  - Bovine coronavirus (live attenuated)
- Many candidates for SARS
  - A number of different platforms, recombinant and inactivated
  - Many animal models (small animals and NHP) suggested high levels of immunogenicity
  - Complicated by
    - Immunopathology
      - T_H2 based
    - Enhanced disease (ADE)
  - Ultimately eradicated with infection control measures
    - More severe disease
    - Total cases 8422 with case fatality rate 11%

Clinical trials

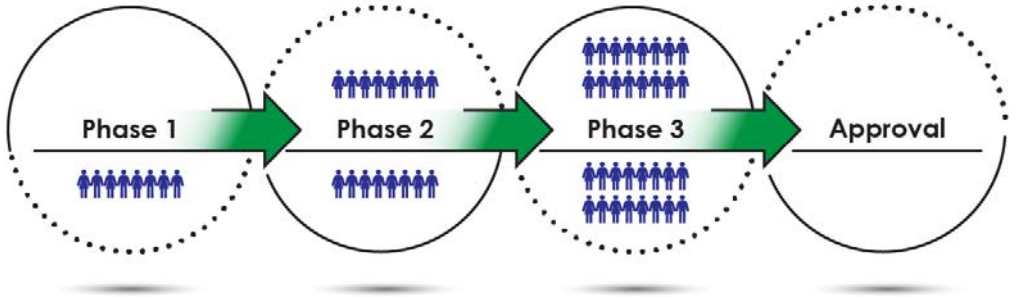
- Preclinical
  - Laboratory and animal data to support progressing to trials in humans
  - Extent required depends on vaccine construct/platform and supportive data available from related products
  - Minimum is GLP toxicology and some basic immunology in animals
  - Animal challenge/protection not required to commence first in human studies (for COVID-19)
- Phase 1
  - Small, usually up to 100 healthy volunteers
    - Small age range and relatively strict inclusion/exclusion criteria
  - Primary focus is to confirm safety
  - Often multiple doses/adjuvant combinations explored
  - Surrogates of immunogenicity collected but typically a secondary objective



- ICMRA Global regulatory workshop on COVID-19 vaccine development
- https://www.scimex.org/newsfeed/explainer-vaccine-clinical-trial-phases

Clinical trials

- Phase 2
  - Slightly larger size, often 100's up to ~1000
  - Focus still on safety but also on immunogenicity
    - Both through surrogates of immunogenicity and first look at efficac
      - But not powered to confirm protection
  - Inclusion/exclusion criteria more liberal
    - Often include greater age range and more comorbidities
      - but still stable/relatively healthy
  - May still include multiple doses/preparations
- Phase 3
  - Large; 10 000 to 30 000
  - Generally many countries
  - Safety and immunogenicity remain key objectives
    - Efficacy/protection become the focus
  - Inclusion/exclusion criteria more liberal again
- Phase 4
  - Post marketing surveillance
    - Information on vaccines continues to be collected once in more widespread use

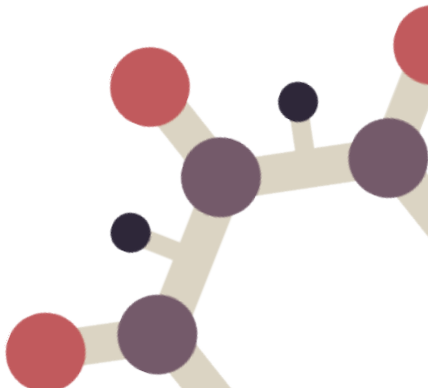


https://www.scimex.org/newsfeed/explainer-vaccine-clinical-trial-phases

Poll question

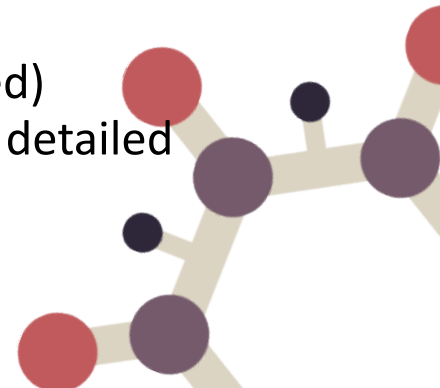
- What are the typical primary objectives of the phase III SARS-CoV-2 vaccine studies

a) Need for mechanical ventilation
b) Safety
c) Laboratory correlates of protection (e.g. Antibody levels)
d) Tolerability
e) Reactogenicity
f) Prevention of COVID-19
g) C and D
h) B, D, E and F



Clinical trials for COVID-19 vaccines

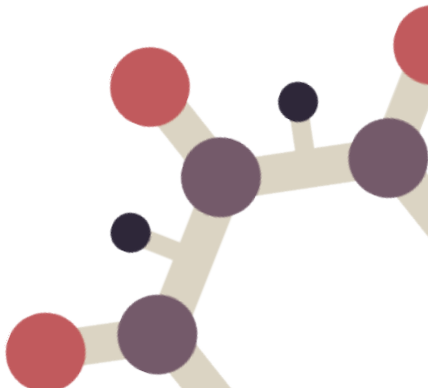
- Objectives
  - Phase 3
    - Primary:
      - Prevention of COVID-19 (often symptomatic PCR proven disease)
      - Safety, tolerability and reactogenicity
    - Secondary:
      - Many laboratory correlates of protection: neutralising antibodies, antibody titre, cellular responses
      - More detailed clinical responses including: asymptomatic infection, severe disease, emergency visits, admissions, mortality (all cause and COVID-19 related)
  - Phase 2
    - Primary: Focus on laboratory correlates whilst still closely monitoring safety
    - Secondary: Includes prevention but not sufficiently powered for this to be primary outcome
  - Phase 1
    - Primary: Safety, tolerability and reactogenicity (laboratory correlates also measured)
    - Secondary: Extensive additional safety parameters in addition to those in primary, detailed immunological assessments, infections still monitored



Clinical trials for COVID-19 vaccines

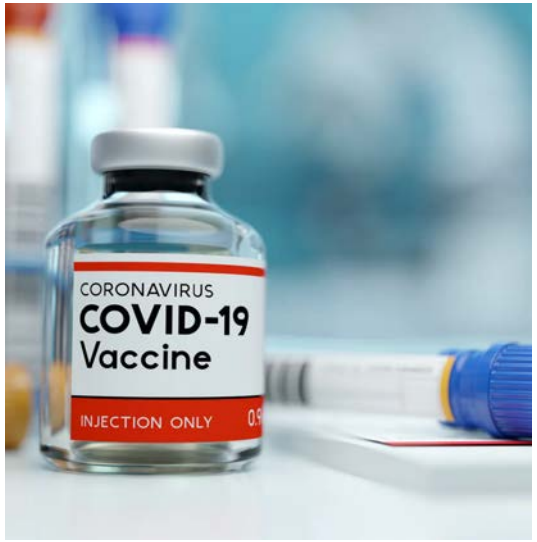
- How is everything happening so fast
  - Not skipping any of those steps
- Funding
  - Lead candidates have access to ample funding
    - Not iterative funding based on results of clinical trials
  - CEPI: coalition for epidemic preparedness innovations
    - Funding 9 of the lead candidates
      - Clover $69.5 million
      - Curevac $15.3 million
      - Inovio $22.5 million
      - Institut pasteur $5 million
      - Moderna $1 million
      - Novavax $388 million
      - Oxford and AstraZeneca $384 million
      - Hong Kong University $620 000
      - UQ and CSL $4.5 million (first announced in 2018)
  - Also generous government funding and advanced purchasing deals
    - Concerns of nationalism

CEPI | New vaccines for a safer world

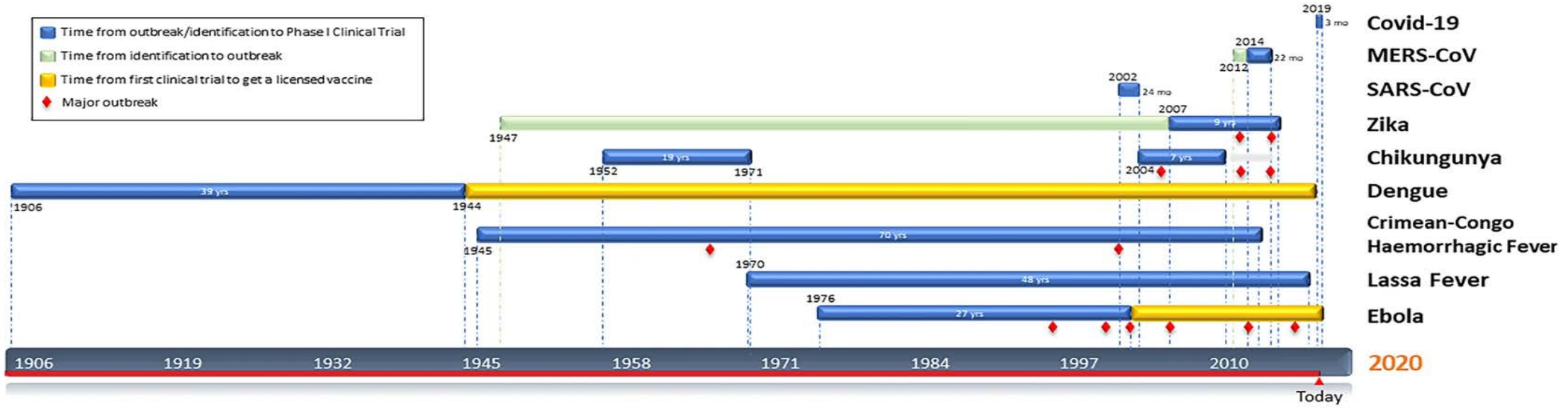


Clinical trials for COVID-19 vaccines

- Hastened regulatory processes
  - Essentially real time approvals
- Scaling of manufacturing
  - Given access to funding
    - Scaling of manufacturing occurring often in parallel with early phase trials
- Study design
  - Most commence with phase 1/2 studies
    - As soon as phase 1 data supports from safety perspective, phase 2 commenced
      - Many with expanding groups e.g. elderly cohorts
- Preclinical data
  - Same tox data required
    - Often submissions commence prior to report being ready
      - Provided available prior to dosing
  - Some leniency in efficacy data
    - Animal challenge studies occurring in parallel to clinical trials



Clinical trials for COVID-19 vaccines



Examples of how fast regulatory approvals obtained

Vaccine study	1	2	3
HREC submission date	9th April	3rd June	9th July
HREC review date	9th April	5th June	14th July
Independent expert review date	12th April	5th June	19th July
Approval date	23rd April	*12th Jun* – 7th Jul	*4th Aug* – 19th Aug
First participant first dose date	26th May	13th July	1st Sep
Days	47	40	54

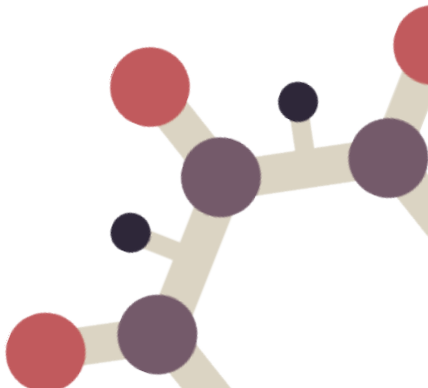
Clinical trials for COVID-19 vaccines

Challenges

- Clinical trial participation generally thought to have declined with COVID-19
  - For COVID-19 studies have seen unprecedented responses to calls for volunteers
    - Often 4000 to 5000 expressions of interest
  - Lower than normal conversion rates
    - Fear relating to misinformation
      - Contracting COVID-19 from trial participation
      - Vaccine safety
- Keeping staff and volunteers safe
  - Pre screening
  - Strict infection control protocols
    - Temp scanning
    - Masks
    - Ready access to testing

Clinical trials for COVID-19 vaccines

- Challenges
  - Serology
    - Baseline for most studies
    - New test, often performed at nonclinical labs so difficult to understand test performance
    - Infection control implications of positive results, highly variable
    - Mostly seem to be false positives
      - Likely cross reactivity with other coronaviruses thus far
  - Management of AE's
    - Need to ensure COVID-19 excluded first for a large number of reported AE's
      - Offsite to ensure safety of staff and volunteers
        - Unable to in GMO trials
      - Delayed assessment until results available
  - Enhanced disease and immunopathology



Clinical trials for COVID-19 vaccines

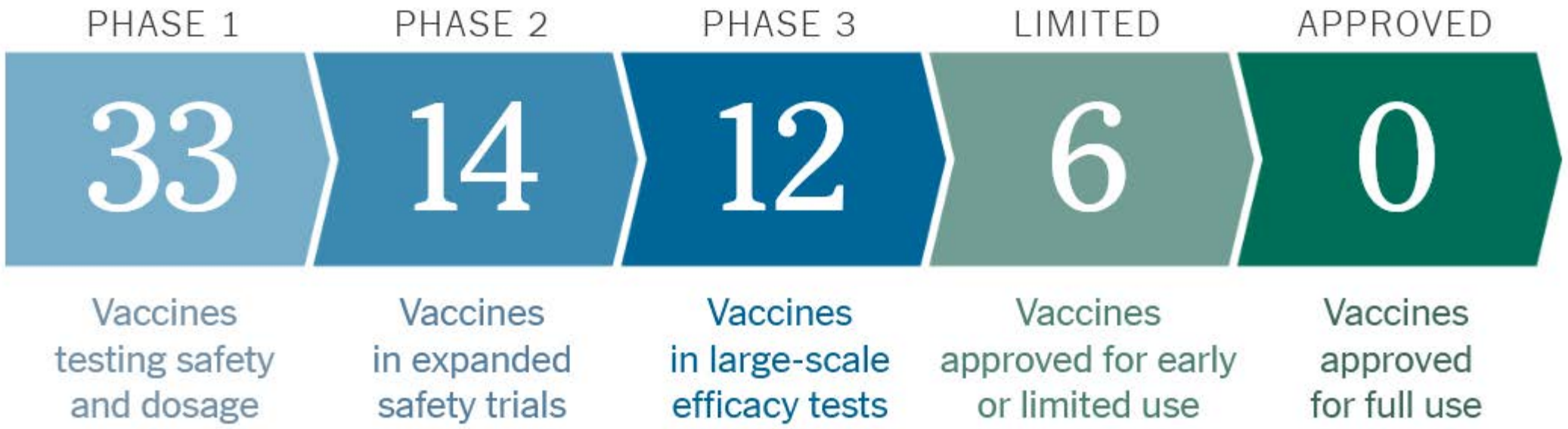
- Challenge Trials
  - Extensively used to hasten the development of interventions for other infectious diseases
    - Most commonly used for Malaria and Influenza
    - Many others including Zika, Group A strep, Norovirus, Dengue, Shigella, Pertussis
    - Can combine with phase 1 in an adaptive protocol to very significantly hasten the clinical trial process
  - Not yet established for COVID-19 but strong push to establish
    - https://1daysooner.org/
  - Benefits
    - Allows infection dynamics to be studied more closely than native infection, particularly early
    - Much more controlled than phase III in community
    - Not dependent on transmission in community
    - Therefore quicker, cleaner and more information generated
  - Negatives
    - Complex ethics
    - Infection control issues
    - Selected population, limited generalisability
    - No “rescue” yet available
    - Long term issues

Coronavirus Vaccine Tracker

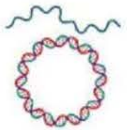
The New York Times

Coronavirus Vaccine Tracker

By Jonathan Corum, Sui-Lee Wee and Carl Zimmer Updated October 24, 2020



SARS-CoV-2

PLATFORMS		CANDIDATE VACCINES	COMMENTS
NUCLEIC ACID VACCINES 	DNA DNA plasmid vaccine with electroporation	**INO-4800/** USA, South Korea/ Inovio Pharmaceuticals, CEPI, Korean Institute of Health, International Vaccine Institute Planned *Phase II-III* trials *Phase I* completed (two doses/ a dose every four weeks	Multiple doses Fast speed Not licensed technology Scale: low to medium The skewed response of T helper (TH_2) cells Safe
	RNA LNP encapsulated mRNA 3 LNP-mRNAs	**mRNA-1273** /USA/Moderna/NIAID *Phase 2* NCT04405076 (IND submission) *Phase 1* NCT04283461 Immune response, Safety; 3 arms (doses 25, 100, 250 mcg)/ Recruiting BNT162 (a1, b1, b2, c2)/ BioNTech/ USA/Fosun Pharma/Pfizer *Phase 1/2* 2020-001038-36 NCT04368728	
VIRAL VECTOR VACCINES 	Non- Replicating Adenovirus Type 5 Vector	**Ad5-nCoV/China/**CanSino Biological Inc./Beijing Institute of Biotechnology *Phase 2* ChiCTR2000031781/ Immune response, Safety; n=500; Randomized double-blind placebo controlled/ Recruiting *Phase 1* ChiCTR2000030906/, Safety; n=108, completed **ChAdOx1 nCoV-19/UK/**University of Oxford *Phase 3* ISRCTN89951424 , Phase2b/3 2020-001228-32 Phase 1/2 PACTR202006922165132 2020-001072-15 Immune response, safety, n=510; Single-blinded randomized placebo controlled multicenter, completed	Single dose Medium speed Licensed technology Scale: high requires booster shots for long-term immunity Safe
VIRUS VACCINES 	Attenuated Codon deoptimized live attenuated vaccines Inactivated Inactivated SARS-CoV + Alum (Inactivated)	Pre-clinical stage Codagenix/Serum Institute of India Indian Immunologicals Ltd/Griffith University **PiCoVacc** (Sinovac Biotech) *Phase 3* NCT04456595 *Phase 1/2* NCT04383574 NCT04352608 Immune response, safety, n=144, Randomized double-blind single-center placebo-controlled, completed	Single-dose, Slow speed Licensed technology Scale: high, Inexpensive Single-dose, Fast speed Not licensed technology Scale: medium to high Needs adjuvants for immune response
PROTEIN-BASED VACCINES 	Subunit Full-length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Clover Biopharmaceuticals Inc/GSK; Vaxil Bio, AJ Vaccines Genrex/EpiVax/University of Georgia; Sanofi Pasteur; Novavax Heat Biologics/University of Miami University of Queensland/GSK/ Baylor College of Medicine; iBio/CC-Pharming	Multiple doses Licensed technology Medium to fast speed Scale: high Safe

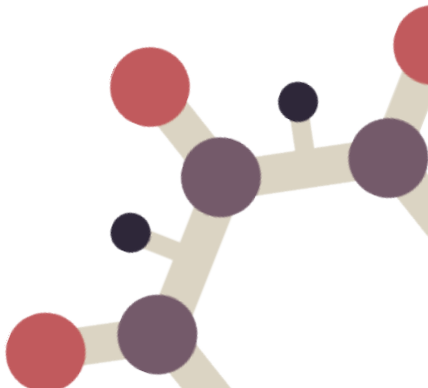
Vaccines platforms and current status of potential candidate COVID-19 vaccines

Calina et al, 2020

Viral Vectored Vaccines

- Background
  - An unrelated harmless virus delivers gene of target antigen to human cells
    - For example adenoviruses (human or simian commonly)
  - Can be replicating or non-replicating
  - Pro's: typically produce high cellular and humoral (antibody) response
  - Con's: pre-existing or newly generated immunity against vector may impact efficacy, potential limitations in scaling-up

- Examples of licenced vaccines
  - Merck Ebola Vaccine: recombinant, replication competent vesicular stomatitis virus vaccine expressing glycoprotein from the Zaire ebolavirus
- COVID-19 Vaccine examples
  - CanSino, Sputnik V, Oxford, J & J



1. NCIRS Vaccine Platforms: http://ncirs.org.au/vaccine-platforms

Viral Vectored Vaccines

- **CanSino**
  - Chinese
  - Adenoviral vectored (Ad5)
  - Approved by Chinese military on 25th June
  - Phase 3 still ongoing
  - Rolling out reported recently
- **Sputnik V**
  - Russian
  - Adenoviral vectored (Ad5 and Ad26)
  - Phase 1/2 results recently published, Lancet Sep 4th
    - 76 participants in total
  - Approved “conditional registration certificate”

Viral Vectored Vaccines

- **University of Oxford**
  - Collaboration with AstraZeneca
  - Adenoviral vectored ChAdOx1
    - Chimpanzee adenovirus
  - Phase 1/2 published in Lancet
  - Phase 2/3 in England and India
  - Phase 3 in Brazil, South Africa and US
  - Pre purchase
    - EU purchased 400 million doses
    - Australia: enough for entire population
  - Emergency use expected very soon
  - Total manufacturing capacity said to be 2 billion doses
  - Study on hold 8th September
    - Now resumed

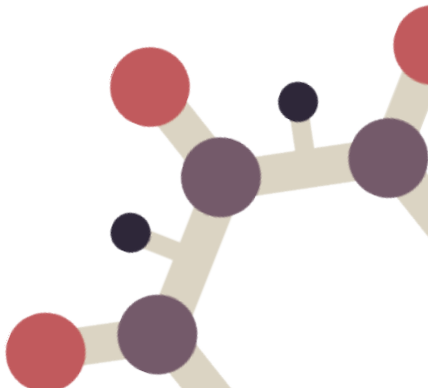
Viral Vectored Vaccines

- Johnson & Johnson
  - USA
  - Adenoviral vectored (Ad26)
  - Promising animal studies in macaques and hamsters
  - Ad26 neutralising antibodies uncommon in Europe and USA (10-20%)
    - More common elsewhere, e.g. Africa 80-90
  - Phase 3 underway
    - Paused due to an unexplained illness (not regulatory hold)

Protein Based Vaccines

- Background
  - Components of target antigen produced in laboratory
    - Now often associated with additional technologies
      - Nanoparticles/Virus Like Particles/Molecular Clamp etc
  - Pro's: Easy to manufacture (from sequence), no live virus, well established platform, specifically targeting essential antigens can reduce reactogenicity
  - Con's: can have high production costs, often require adjuvant and or multiple doses

- Examples of licenced vaccines
  - HPV, Hepatitis B, HiB
- COVID-19 Vaccine examples
  - UQ, Novavax, Clover/GSK, Serum Institute of India, Sanofi/GSK



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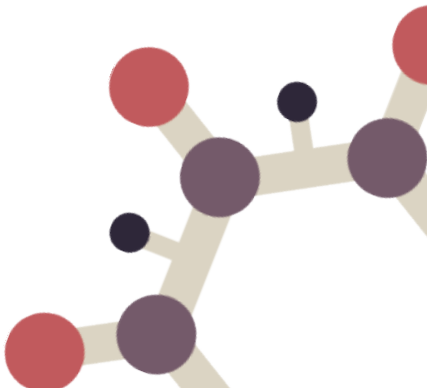
Protein Based Vaccines

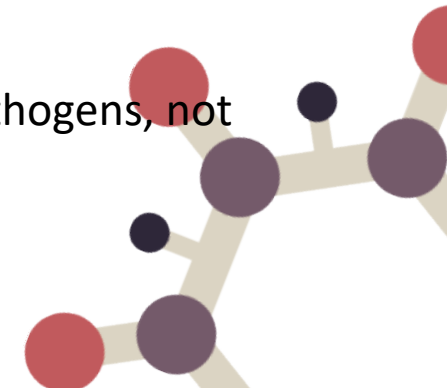
- Sanofi/GSK
  - Recombinant protein based technology Sanofi use in their seasonal influenza vaccines
  - GSK's established pandemic adjuvant technology
  - Phase 1/2 study commenced in Paris and London September 3rd (400 subjects planned)

- UQ/Novavax/Clover/Serum Institute of India all being trialled in Australia
  - See below



Adjuvants

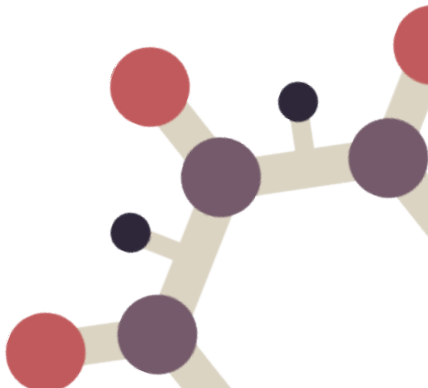
- Background
  - Adjuvant: ingredient used in some vaccines to stimulate a more potent immune response
  - Even more important for COVID-19;
    - Given the target population is basically the entire world, an effective adjuvant could reduce the dose of antigen required and therefore facilitate availability of more doses/scalability
    - Issues with previous human Coronavirus vaccines, ADE / immunopathology, are likely dependent on the type of T helper response generated and this is in some ways adjuvant dependent
      - ADE: Antibody dependent enhancement, likely driven by a TH2 type response
        - TH1: IFNγ driven, mostly cellular response with cytotoxic T lymphocytes
        - TH2: cytokine driven, IL-4, B cells make antibodies, good for extracellular pathogens, not good for coronaviruses



1. Bolles, Meagan, et al. "A double-inactivated severe acute respiratory syndrome coronavirus vaccine provides incomplete protection in mice and induces increased eosinophilic proinflammatory pulmonary response upon challenge." *Journal of virology* 85.23 (2011): 12201-12215.
2. Wang, Qidi, et al. "Immunodominant SARS coronavirus epitopes in humans elicited both enhancing and neutralizing effects on infection in non-human primates." *ACS infectious diseases* 2.5 (2016): 361-376.

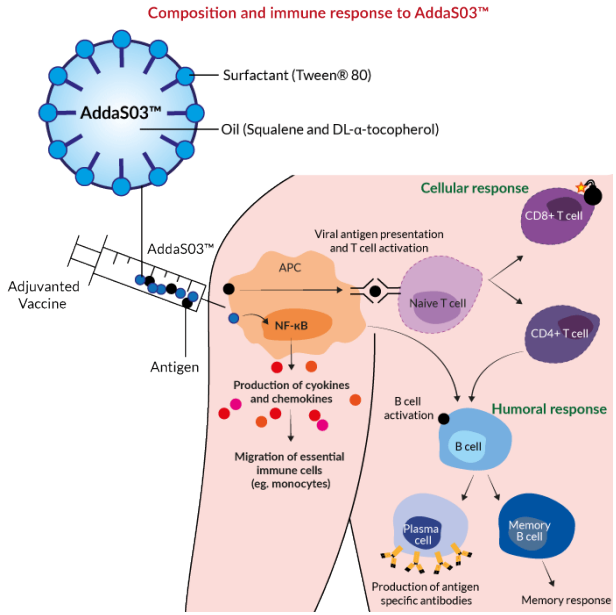
Adjuvants

- Mechanisms:
  - Trapping antigen at injection site,
    - Slowing release to continue stimulation of immune system (e.g. Alum and MF59)
      - Increase recruitment and activation of antigen presenting cells
  - Aggregate formation
    - Particulate adjuvants can bind antigens to form multi-molecular aggregates to increase uptake by APC's (e.g. Alum)
  - Directing presentation
    - Some adjuvants can direct antigen presentation by MHC
  - Ligands for PRR (pattern recognition receptors)
    - Induce innate immunity, target APC's and influence adaptive response



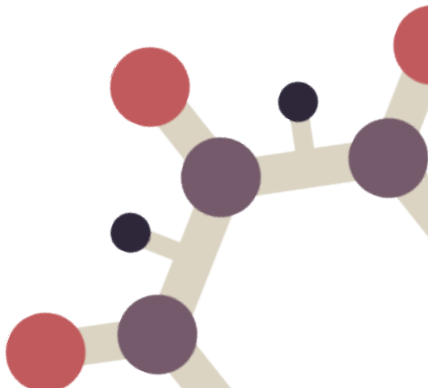
Adjuvants

- Some examples in SARS-CoV-2 vaccines
  - Aluminium based (aluminium hydroxide/phosphate etc)
    - Most commonly used adjuvant
    - Used in DTP, HPV and Hepatitis vaccine
    - Tends to induce TH2 response
    - Serum institute of India, Sinovac
  - MF59
    - oil-in-water emulsion of squalene oil,
    - Aggregate formation and also triggers dept generation and induction of MHC response
    - Potent stimulator of TH1 and TH2
    - UQ
  - CpG
    - Synthetic oligodeoxynucleotides
    - Boost antibody responses 500 fold
    - TH1 response and induce APC response
    - Serum Institute of India
  - Matrix M
    - Proprietary, purified saponin with cholesterol and phospholipid
    - Balanced TH1 and TH2
    - Novavax



Adjuvants

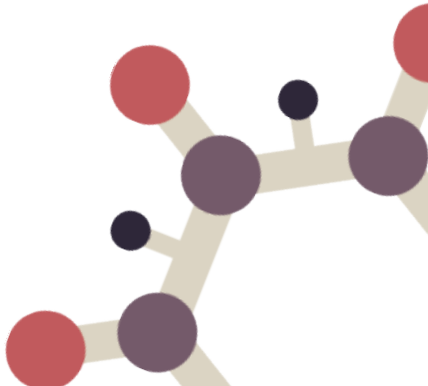
- Particularly required for protein or subunit vaccines (as well as inactivated vaccines)
  - Relatively weekly immunogenic
- For mRNA based vaccines, the mRNA serves as an adjuvant (Moderna)
- For viral vectored vaccines, including ChAdOx1, the viral vector serves as adjuvant
  - Past exposure to vector/related viruses may be relevant



Poll question

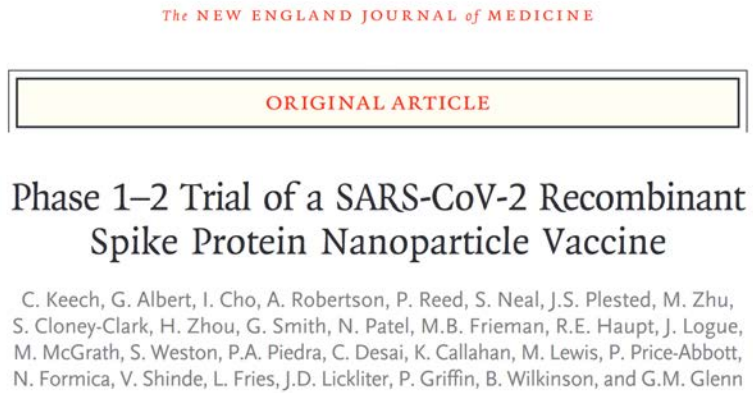
- How many COVID-19 vaccines have been or currently are being trialled in Australia

a) 3
b) 9
c) 5
d) 4
e) 7



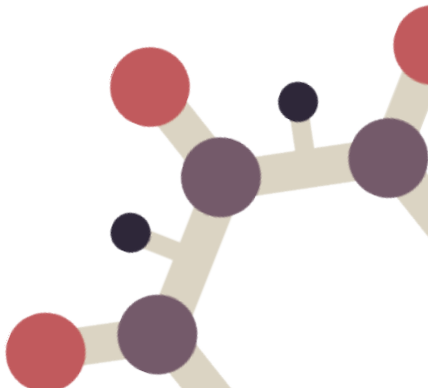
COVID-19 Vaccines in Australia

- 5 Vaccines in clinical trials in Australia
  1. Novavax NVX-CoV2373 (PI)
     - First vaccine to commence human trials in southern hemisphere, 26th May
     - Recombinant Spike protein nanoparticle with matrix M
     - Results of phase 1 published in NEJM
     - Now expanded age inclusion criteria
     - Many phase 2 sites in Australia and elsewhere
  2. University of Queensland Sclamp (PI)
     - Recombinant spike protein with molecular clamp
     - First dosed 13th July
     - Rapid response project commenced around 2 years ago
     - CEPI funded predominantly
     - Phase 1 underway
     - Excellent preclinical data



COVID-19 Vaccines in Australia

3. Clover (with GSK)
   - S-trimer vaccine (recombinant)
   - Chinese based clinical stage biotech
   - Phase 1
   - Linear in Perth
4. Vaxine/Flinders University
   - Nicolai Petrovsky
   - Reported to have completed phase 1 with 30 actives that supported progressing
   - No results published as yet
   - Spike protein using plant sugar with insect cell expression system



COVID-19 Vaccines in Australia

5. Serum Institute of India (PI)
   - RBD VLP (Receptor Binding Domain Virus Like Particle) attached to Hep B sAg (spycatcher/spytag)
   - Multiple adjuvants
   - Phase 1 commenced last month

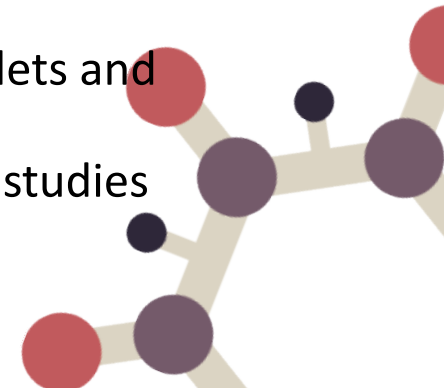
- Oral about to commence (PI)
  - Symvivo bacTRL-Spike
  - Oral room temperature stable DNA vaccine

My Prediction

- A number of candidates will be successful enough in phase 3 studies to be recommended for use
  - Likely “moderately” successful in terms of efficacy
  - Will need boosting, hopefully less than annually
  - Likely in the first half of 2021
- Prioritised utilisation initially
  - HCW/aged care/first responders/military
  - Vulnerable patients will depend on vaccine and likely efficacy in this population
- Uptake will remain a challenge
  - Once prioritised roll out complete, few of the general population will volunteer, initially
- Will need some ongoing public health/infection control measures while vaccine rolling out
  - Broader restrictions should be able to begin to ease relatively quickly, but then gradually
- The vaccine in itself is the key intervention, but not the whole story
  - Need better testing, therapies, technological solutions to aid contact tracing etc
- We will see iterative improvements in the vaccine that will ultimately lead to eradication
  - Timeframe??

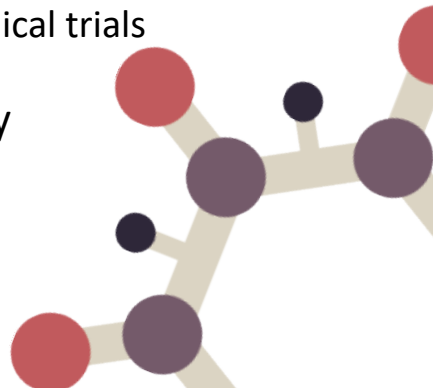
Some FAQ answers

- Is it true the vaccine trials won't tell us about prevention of mild disease or more severe disease etc
  - No
    - Most phase III trials have been designed to look at a complete spectrum of disease
      - Including using surrogates to look at all disease severities including ED presentations, all cause and COVID-19 related mortality, hospital admission, ICU admission, ventilation etc
      - Also include regular virological assessment, even in asymptomatic participants
- Is it true that current vaccines won't reduce transmission
  - No
    - Reducing case numbers will clearly reduce number of infectious cases in community and therefore spread overall
    - Reducing symptoms in those infected reduces ability to shed viral containing droplets and therefore ability to transmit
    - Many vaccines studied have shown reductions in viral shedding, at least in animal studies



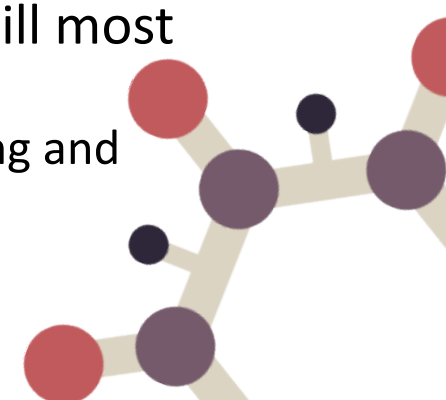
Outstanding questions

- If we have multiple generations of vaccines how will we know which are compatible, which combinations are potentially beneficial vs otherwise
  - Impossible to know
    - Don’t know which first generation vaccines are going to have sufficient data for more widespread use,
    - How effective they will be,
    - How long immunity will persist for etc.
  - This is work that will follow in time
    - May be that certain combinations give the best protection e.g. prime with mRNA or viral vectored and boost with protein/subunit (a guess)
- Vulnerable populations
  - High demand for effective vaccines in immunocompromised, elderly etc.
    - Most phase I/II studies have expanded age cohorts, often up to around 85
      - Always a delicate balance between need for this data and challenges of including this cohort in clinical trials
      - Some have no upper age limit so we will have some data
    - Studies in immunocompromised patient groups are planned but I’m yet to see any underway
      - Again delicate balance between need for data and potential to undermine clinical trial progress



Outstanding questions

- Longevity and requirement for boosting
  - Unable to answer yet
  - Most do currently utilise 2 doses
  - Something to be addressed by second (or later) generation vaccines
  - The more boosters required and the shorter the interval, the lower our probability of achieving sufficient coverage
- Will vaccination be mandatory/required for travel/other activities
  - Impossible to answer
  - Ideally voluntary uptake sufficient so this won't be required
  - I strongly suspect will be linked to travel in some way but ability to travel still most likely dictated by epidemiology at the time
    - And will require additional mitigation strategies including mask wearing and testing and perhaps still even a short quarantine period



Conclusion

- Vaccine development/clinical trials progressing faster than ever before
  - Without omitting any critical steps
- All vaccine platforms have been applied to COVID-19
  - Many promising viral vectored and protein based vaccines
    - Some already approved for early/limited use
    - Some may have sufficient phase III data for more widespread use in the coming weeks/months
- Once data supports their use, the scaling of manufacturing that has already occurred will facilitate relatively rapid roll out
  - However it will still likely be lengthy process with complex logistics
    - Therefore ongoing mitigation strategies will be required
- While progress has been phenomenal, many unanswered questions remain

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