- This Scientific Update replaces the Executive Summary

INTERNATIONAL SOS WEEKLY SCIENTIFIC UPDATE
Focussing on immunity and vaccine development

Produced by Dr Doug Quarry
25 September 2020

1. MODERNA VACCINE SHOWS PROMISING RESULTS IN ELDERLY PATIENTS IN SMALL TRIAL

MODERNA REPORTED ON PROGRESS OF ITS TRIALS TO ACIP* ON 26 AUGUST 2020

Immunity in older patients

- Older patients developed similar antibody and T-cell responses to younger patients
- All age groups develop similar neutralising antibody levels to convalescent sera from recovered patients

Details

- Trial included ten patients aged 56-70 and ten patients over 71 years
- To get these results, Moderna extended its Phase 1 trial to include elderly patients
- The patients received 2 doses 28 days apart
- This is a report on immunogenicity not efficacy
- Moderna has money to build vaccine production capability prior to Phase 3 results becoming available
- See slides 9, 10, and 11 here
- Short interpretation on TWIV** here

Takeaways from TWIV team
Rich Condit***
"I have not seen any bad news with these vaccines"
Dick Despommier****
"Nice to hear that the vaccine is well tolerated and doing what we would have hoped it would do in this phase of testing"

Comment from DQ:

- These results go some way to reducing our concern that "immuno-senescence" – the concept that the immune system becomes less functional with age – will affect vaccines against coronavirus

***ACIP:** Advisory Committee in Immunization Practices | CDC
****TWIV:** This Week in Virology podcast by Vincent Racaniello, Higgins Professor in the Department of Microbiology and Immunology at Columbia University's College of Physicians and Surgeons. He is a co-author of a textbook on virology, Principles of Virology
***** **Richard Condit,** Professor Emeritus, University of Florida
****** **Dickson Despommier,** Emeritus Professor of Microbiology and Public Health at Columbia University.

2. THE VACCINES ARE COMING, BUT WHEN?

A SHORT REVIEW OF THE SEVEN MAJOR VACCINES IN PHASE 3 TRIALS

It is likely that the first vaccines to be approved in the "west" will be RNA or ADENOVIRUS VECTOR vaccines. Use these tables to compare the vaccines.

TYPE	RNA VACCINES	ADENOVIRUS VECTOR VACCINES
BRANDS	**PFIZER & MODERNA**	**CANSINO / OXFORD-ASTRAZENECA / GAMALEYA**
Country of development	**Pfizer:** Germany **Modera:** USA	**Cansino**: China **Oxford-AstraZeneca**: UK **Gamaleya**: Russia
How do they work	**Pfizer:** codes for the receptor binding domain **Moderna:** codes for the spike protein • RNA is injected • Cells take it up • Cells make the protein and release • Body generates immune response	Use a live attenuated (weakened) adenovirus to deliver the spike protein (all three) **Cansino:** Human adenovirus 5 (used in many vaccines) **Oxford-AstraZeneca:** Use chimpanzee adenovirus **Gamaleya:** Use human adenoviruses 5 & 26
Pros	• **Making RNA is easy and cheap**	• **Possibly one dose only** • Using an adenovirus vector may lead to a more robust immune response • Norma vaccine storage (-4 C)
Cons	• New technology = unknown risks • Risk of autoimmune problems / no data showing high risk • **Storage: -80 C (dry ice)**	**Need complex bio-reactors to produce** **Cansino:** • 37% of people have antibodies to adenovirus 5: may be quickly broken before generating immune response **Oxford-AstraZeneca:** • Trial temporarily stopped due to possible side effect of ? transverse myelitis. Started again. Was that related to the chimpanzee adenovirus? **Gamaleya:** • Concerns about data quality in Phases 1 and 2 published in Lancet
Doses	**Moderna:** • 2 doses, 28 days apart **Pfizer** • Two doses, 21 days apart	**Oxford-AstraZeneca** • One and two doses being trialed **Gamaleya** • Two doses 21 days apart **Oxford-AstraZeneca** • Two doses 28 days apart
Phase 3 progress	**Pfizer** • Have expanded to 44,000 people • Most USA, also Argentina, Brazil • Completion: April 2021	**Cansino** • Unknown **Oxford-AstraZeneca**

	Moderna • Have recruited 15,000 of 30,000 trial in US	• USA: Have recruited 20,000 of 30,000 (saline placebo) • Brazil: 1 dose (control Meningococcal ACYW vax) • Also: UK, South Africa, India • Completion Feb 2020 **Gamaleya** • 3,000 of 40,000 in Phase 3 recruited • 30,000 vaccine, 10,000 placebo
First Phase 3 results due	**Pfizer** • Efficacy: October 2020 • Safety: Later ? when **Moderna** • Efficacy: October 2020 • Safety: Later ? when	**Cansino:** **?** **Oxford-AstraZeneca:** **?** **Gamaleya** ?
Use so far	**NIL**	**Gamaleya:** • Approved before Phase 3 study completed

TYPE	**INACTIVATED VACCINES**
BRANDS	**SINOVAC & SINOPHARM**
Country of development	China
How do they work	• Inject killed virus
Pros	• Typical vaccine methodology • Lots of past experience
Cons	• Hard to scale / expensive • Lack of reported data
Doses	**Sinovac** • Two doses, 14 days apart **Sinopharm** • Two doses, 21 days apart
Phase 3 progress	**Sinovac only** • China: 8,870 healthcare workers / Makes study statistically more "powerful" • No **Sinopharm** • UAE: 15,000 volunteers, 5,000 each in two vaccine groups • Doses either 14 or 21 days apart • No data released
First Phase 3 results due	?
Use so far	**Sinopharm** • Approved for Chinese military and civil servants

NOTE:
In the USA:

- CDC:* has told the states to prepare for vaccine distribution by 1 November
- FDA:** Next meeting: 22 October (first opportunity to approve a vaccine, possibly under EUA)

***CDC: Centres for Disease Control, Atlanta, Georgia, USA**
****FDA: Food and Drug Administration, USA**

Data from:
Medscape, 16 September 2020: The Vaccine Derby, A Guide to the Top Contenders

- **F. Perry Wilson:** Yale School of Medicine, Associate Professor Term; Director, Clinical and Translational Research Accelerator (CTRA); Course Director, Interpretation of the Medical Literature; Co Director, Human Genetics and Clinical Research Core.

VuMedia, 16 September 2020: International Phase 3 COVID-19 Vaccines

- **Daniel R Lucey:** Adjunct Professor of Infectious Diseases at Georgetown University, and a Research Associate in Anthropology at the Smithsonian National Museum of Natural History.

3. FDA RELEASING HIGHER STANDARDS FOR EUA VACCINE APPROVAL

The Washington Post today reported that the FDA (US Food and Drug Administration) will soon release more stringent standard for Emergency Use Authorisation of coronavirus vaccines.

The requirements will include:

- The vaccine needs to be 50% more effective than placebo (prevent 50%of infections)
- The company must follow participants for a median of at least two months from when they receive their second dose of vaccine
- There must be documentation of at least five severe cases of COVID-19 in the placebo group for each trial
- There must be documentation of some cases of the disease in older people

Possible delay to applications

- It will take time for the vaccine companies to prepare their EUA applications to the FDA, whose next meeting to assess applications is not until 22 October.

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What is an EUA (Emergency Use Authorization)

- FDA Commissioner may allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when there are no adequate, approved, and available alternatives.

International SOS Comment

This is a very welcome development which will help to alleviate a growing perception that vaccines may have been approved without sufficient oversight by the FDA.

4. JOHNSON & JOHNSON START PHASE 3 TRIALS OF SINGLE DOSE VACCINE

Advantages of this vaccine
- One shot
- Only needs refrigeration, not deep freeze
- Already being stockpiled

Phase 1 & 2a results
In a public statement on 23 September 2020, Johnson and Johnson said that the Phase 1 and 2a trials demonstrated a safety profile and immunogenicity supportive of further development. The results have been submitted to MedRix and will be published imminently.

The Washington Post reported that the company's Chief Medical Officer, Dr Paul Stoffels, said that the vaccine triggered a promising immune response and that side effects of the vaccine were tolerable, including some fevers that resolved within one to two days.

Phase 3 trials
The Phase 3 trials will enroll 60,000 volunteers in the US, South Africa, Argentina, Brazil, Chile, Colombia, Mexico and Peru. The company released its study protocol as have other companies recently.

"The Company aims to achieve representation of populations that have been disproportionately impacted by the pandemic in the implementation of its COVID-19 Phase 3 trial program. In the U.S., this includes significant representation of Black, Hispanic/Latin, American Indian and Alaskan Native participants."

The Washington Post reported that Dr Stoffels predicted that there may be enough data to have efficacy results by the end of the year. It reported Dr Anthony Fauci saying that once there were 154 cases of COVID-19 in the trial, it would be possible to tell whether the vaccine was effective.
The Phase 3 trials started on Monday, 21 September.

Vaccine details
The vaccine was developed by Janssen, a subsidiary of Johnson and Johnson, and uses the same platform as in their Ebola vaccine and their Zika, RSV and HIV vaccine candidates.

The platform uses Adenovirus 26 as a vector for the coronavirus spike protein. This vector is also used in the coronavirus vaccine from the Russian Gamaleya Institute.

The vaccine will be shipped frozen but can be stored in liquid form at refrigerator temperatures for three months.

Vaccine supply
Johnson and Johnson states that it remains on track to be able to supply one billion doses of vaccine per year with some supply available in 2020.

The New York Times reported that Dr Stoeffels said on 23 September 2020 that the company had begun manufacturing the vaccine on an industrial scale to build up a supply that can be released immediately the vaccine is authorized. He expected to have tens of millions of doses ready by the end of 2020. "We can then ramp up to many more batches", he said.

US Government investment
The New York Times states that the US Government's Operation Warp Speed Program has invested about $1.5 billion in the Johnson and Johnson vaccine development. To date, the program has invested over $10 billion in private companies' coronavirus vaccines.

Other vaccines soon for Phase 3 trials
The Sanofi and Novavax vaccine candidates are likely to start Phase 3 trials soon.

5. THE COVAX PROGRAM

“NO ONE IS SAFE UNTIL EVERYONE IS SAFE” - WHO.

What is the COVAX program?

- It is a WHO-supported program to provide poorer countries with equitable access to COVID-19 vaccines
- It is supporting nine manufacturers to develop and manufacture COVID-19 vaccine
- The 156 nations now committed to COVAX represent about two-thirds of the world’s population

Main principles

- COVAX is a WHO plan in conjunction with CEPI* and GAVI** to support the development and equitable distribution of two billion doses of COVID-19 vaccine before the end of 2021.
- The pooled funding will allow poorer countries to access COVID-19 vaccines they would otherwise have been unlikely to afford.

Supporting vaccine development and manufacture

- CEPI* is leading COVAX research and development and aims to have at least three safe and effective vaccines available for participating countries
- Nine candidates, incorporating a range of technologies and scientific approaches, are currently being supported. These include: Oxford/AstraZeneca, Moderna, University of Queensland/CSL and Clover/GSK. This spreads the risk across vaccine candidates in case some are unsuccessful
- Some of the funding is for vaccine development and some to create a manufacturing capability

Funding

- The program will use funding from 64 higher-income countries to secure vaccine to be shared with 92 lower- and lower-middle-income countries
- Countries were asked to make a binding commitment to participate by 18 September 2020, and to provide funds by early October. These funds will allow COVAX to finalise advance purchase agreements with vaccine manufacturers
- There will be a global coordinated rollout by the WHO from Geneva

Program components: The “Facility” and the “AMC”

COVAX has two major parts: The “Facility” is a purchasing pool for higher-income countries, and the “Advance Market Commitment” (AMC):

- Countries that join the “Facility” get access to any successful vaccines in COVAX’s portfolio
- The AMC is a fund-raising effort for poorer countries that directs development aid to low- and middle-income countries that may not have been able to afford coronavirus vaccine. So far, the AMC has commitments for USD $700 million of the $2 billion required by the end of 2020. The European Union (EU) has committed USD$465 million in guarantees.

Despite high-income countries having made large bilateral deals with vaccine manufacturers, COVAX believes it can secure over two billion doses in 2021.

Who should get the vaccine first?

The idea is to rapidly vaccinate health-care workers, the elderly, and others at high risk in all countries. On average, this comprises about 20% of a country's population.

Opting out and bilateral agreements

- The Russia, US and China are not participating in COVAX
- Some countries and regions (including Australia, Canada, US, Japan, and the EU) have bilateral agreements with vaccine manufacturers and all but the US have joined COVAX. This is seen to give them the greatest number of vaccine options
- France is providing funds but will not take supplies from COVAX. France will obtain vaccine via the European Joint Procurement program which has deals with AstraZeneca, and is in talks with Johnson & Johnson, Sanofi, Moderna, and CureVac

***CEPI:** The Coalition for Epidemic Preparedness Innovations: a foundation that takes donations from public, private, philanthropic, and civil society organisations, to finance independent research projects to develop vaccines against emerging infectious diseases.

****GAVI:** Vaccine Alliance of Governments and Organisations: set up by the Gates Foundation in 1999, with an aim to accelerate access of developing countries to vaccines and support research into health solutions for these countries that are effective, affordable and sustainable.