

Authors

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Professor Oxford is on vacation

The Executive Summary is produced weekly and contains in-depth analysis.

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THE COVID-19 VACCINE RACE

More than 150 possible COVID-19 vaccines are being developed and tested around the world. There are 23 candidate vaccines in human clinical trials.

- WHO has an excellent tabular summary [here](#).
- Global Vaccine Alliance (GAVI) has an excellent map-based summary [here](#).

Trial phases

Promising vaccines are evaluated in clinical trials with human volunteers. Researchers ask:

- Phase I trials: Is the vaccine safe, and what dose should be used?
- Phase II trials: Can the vaccine generate an immune response?
- Phase III trials: Can the vaccine protect from infection or disease?

The front runners

- In Phase II testing, the SinoVac, the Oxford/AstraZenica and the Moderna/NIAIA vaccines have produced strong humoral and cellular immunity in test subjects
- All are starting Phase III trials

What is needed next?

- All vaccines need Phase III trials to prove that they can **prevent infection**
- We need to be sure that COVID vaccine do not cause "[Immune Enhancement](#)" (when a vaccine worsens an infection rather than preventing it)

When do we get a vaccine?

- Some of the vaccine developers, including Oxford and Moderna, say if studies are successful, a vaccine could become available for emergency use by the end of this year
- Some public-health officials say it is likely that several vaccines would be needed to control the pandemic

Experts say much more work is needed

Speaking at a [media conference on Monday 20 July](#), Dr Michael Ryan, Executive Director of the World Health Organisation's Health Emergencies Programme, noted that the findings were from trials in their early stages and the data is very new.

"We now need to move into larger-scale, real-world trials," he said. "But it is good to see more data, and more products moving into this very important phase of vaccine discovery, and we congratulate our colleagues for the progress they have made."

TABLE 1: SUMMARY COVID VACCINE LEADERS

DEVELOPER	VACCINE TYPE	PHASE OF TRIALS	COMMENTS
Oxford/AstraZeneca	Chimpanzee adenovirus vaccine expressing the SARS-CoV-2 spike protein	3 (started)	Phase II results in The Lancet (20 July)
Sinovac	Inactivated virus + alum	3	Phase II results in Report in Chinese (6 June)
Moderna/NIAID	LNP encapsulated mRNA	3	Phase II reported in NEJM (14 July)
CanSino	Human adenovirus vaccine expressing the spike glycoprotein of a SARS-CoV-2 strain.	2	Phase II results in The Lancet (20 July)
Anhui Zhifei Longcom	Adjuvanted recombinant protein	2/1	Starting Phase II Reuters (9 July)

STUDY SUGGESTS LONG-LASTING T CELL IMMUNITY TO CORONAVIRUSES

[Nature](#) (15 July)

The T cells, along with antibodies, are an integral part of the human immune response against viral infections due to their ability to directly target and kill infected cells.

A Singapore study has uncovered the presence of virus-specific T cell immunity in people who recovered from COVID-19 and SARS, as well as some healthy study subjects who had never been infected by either virus.

The findings suggest infection and exposure to coronaviruses induces long-lasting memory T cells, which could help in the management of the current pandemic and in vaccine development against COVID-19.

The team tested subjects who recovered from COVID-19 and found the presence of SARS-CoV-2-specific T cells in all of them, which suggests that T cells play an important role in this infection. Importantly, the team showed that patients who recovered from SARS 17 years ago after the 2003 outbreak, still possess virus-specific memory T cells and displayed cross-immunity to SARS-CoV-2.

International SOS Comment:

This long-lasting virus-specific T-cells from coronavirus infection may reassure those who are concerned that some patients who have recovered from COVID-19 show rapidly waning levels of natural antibodies.

A waning antibody response might mean that the immune system does not "remember" an infection, which could mean that the body may also not "remember" a vaccination.

T-cells may be particularly important for fighting COVID-19 - they may generate long-lasting immunity.

OXFORD / ASTRAZENICA PHASE II TRIAL RESULTS

Technology

Recombinant **chimpanzee adenovirus**-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein

[Note: chimpanzee adenovirus selected as humans are less likely to have pre-existing immunity to it]

Phase II Trial results ([The Lancet 20 July](#))

- Trial began in April
- Five trial sites in the UK
- Involved 1,077 health adult volunteers.
 - Half the participants were given the new vaccine, while
 - Half were a control group given a meningitis vaccine.

The results:

- The vaccine was well tolerated and safe
- It generated both antibodies and “an excellent” T-cell response.
- Antibody response peaked by day 28 and remained high for the duration of the study (56 days)

Side effects

- No serious side effects
- Fatigue: 70%
- Headache 68%
- Others: muscle ache, malaise and feeling feverish

Limitations of the Phase II trial

- Participants were capped at age 55
- Short-term follow-up after vaccination

Phase III trials

- A 10,000-patient trial in Britain has almost finished recruiting
- Recruitment rising quickly for a trial in Brazil
- Trials in South Africa have just started
- Another trial will begin in America in the coming weeks

Approval?

- Researchers may know by the end of August whether the vaccine prevents COVID-19
- If results positive, possible emergency approval in October prior to further trials are conducted

Mass production?

- Vaccine may be ready for mass production in September
- Vaccine production in India
 - The [Serum Institute of India](#) will produce millions of doses once the Phase II/III trials are complete

Government purchase

- The U.S. is providing funding for several vaccines, including Oxford's.
- In May it agreed to pay AstraZeneca \$1.2 billion to secure at least 300 million doses.
- The company, which also has supply deals with other countries, is committed to making 2 billion doses, with up to 400 M available this year.

SINOVAC PHASE I & II TRIAL RESULTS

Technology

Inactivated (killed) whole virus plus adjuvant

Phase I & II Trial results ([Report in Chinese](#))

- Trial of 743 healthy subjects
- Day 0 and 14 or 0 and 28 schedule

The results:

- The data shows that the vaccine has good safety and immunogenicity
- Neutralising antibody >90% 14 days after second vaccination

Side effects

No serious adverse reactions reported.

Mainly:

- Mild pain at the injection site
- Fatigue and
- Low fever in individual subjects

Phase III Trials

- Sinovac has announced a partnership to start in July with Instituto Butantan to conduct its Phase III trial in Brazil
- Will include nearly 9,000 health care workers across 12 sites

MODERNA / NIAID PHASE I TRIAL RESULTS

Technology

mRNA vaccine (encodes the SARS-CoV-2 spike protein / designed to cause the body to produce neutralizing antibodies against the novel coronavirus's spike protein)

Phase I Trial results ([NEJM 14 July](#))

- Dose escalation trial
- 45 health adults aged 18 to 55 years
- Two vaccinations 28 days apart
- Doses of either 25ug, 100ug, or 250ug (15 in each group)
- Seattle and Emory University in Atlanta
- Vaccinations from 16 March to 14 April

The results:

- The vaccine induced anti-SARS-CoV-2 immune responses in all participants, and no trial-limiting safety concerns were identified
- mRNA-1273 also induced Th1-biased CD4 T-cell responses
 - Additional testing in animals and ongoing T-cell analysis of clinical specimens will continue to define the safety profile of mRNA-1273.
- The trial was broadened in April to include participants older than 55 years and now has 120 enrollees

Side effects

- Adverse events that occurred in more than half the participants included fatigue, chills, headache, myalgia, and pain at the injection site.
- Systemic adverse events were more common after the second vaccination, particularly with the highest dose, and three participants (21%) in the 250-µg dose group reported one or more severe adverse events.

Limitations of the Phase I trial

- The researchers noted that they were not able to evaluate long-term immune response to the vaccine
- However, participants will be monitored through regular blood collections for one year after the second dose
- Immune responses that decline with age – this population relatively young

Phase II & III trials

- Recruitment for a Phase II mRNA-1273 clinical trial sponsored by Moderna began in late May
- The study authors said that they plan to enroll 600 adults in the phase 2 trial to assess the effects of 50- and 100-µg vaccine doses.

Phase III trials

- Moderna will begin a Phase III efficacy trial of the 100-µg dose in late July
- Trials will be run in US “hotspots”
- Results are expected towards the end of 2020

CanSino BIOLOGICS PHASE II TRIAL RESULTS

Technology

Recombinant **human adenovirus** type-5 (Ad5) vectored COVID-19 vaccine expressing the spike glycoprotein of a SARS-CoV-2 strain.

Phase II Trial ([The Lancet 20 July](#))

- More than 500 volunteers in Wuhan
- Dose escalation trial / no control
- Three groups:
 - 5×10^{10} viral particles
 - 1×10^{11} viral particles
 - 1.5×10^{11} viral particles

The results:

- Vaccine was safe
- Rapid onset of immune responses within 14 days
- Significant humoral and cellular immune responses within 28 days in the majority of the recipients

Side effects

- No serious side effects
- Mild or moderate reactions only
- Some experienced fever, fatigue and injection site pain, most of which were mild or moderate,
- Most common fatigue, fever and headache.
- 74% of the 129 who received the lower dose and 72 per cent of those who received the medium dose reported at least one negative reaction but none had serious adverse reactions

Limitations of the Phase II trial

- Entire participant population from Wuhan.

Possible problems with the vaccine

- Some participants in the study had pre-existing immunity to the adenovirus, which seemed to mute the immune responses against the coronavirus. Researchers said it might be necessary to provide an additional dose to people with pre-existing immunity to the adenovirus.

Phase III trials

- Plan to start a Phase III study as soon as possible.
- Will use the lower dose of vaccine

PFIZER/BioNTECH

Technology

mRNA vaccine (**lipid nanoparticle** formulated, **nucleoside-modified messenger RNA** designed to stimulate the body to make neutralized antibodies against a SARS-CoV-2 receptor binding domain (RBD) antigen)

Phase II Trial – Part 2 ([medrxiv 20 July 2020](#))
(currently undergoing peer review)

Dose escalation study

- Total 60 participants in study
- Mean age of 41 years (range 18 - 55 years)
- 51.1% were male and 48.9% were female
- Most participants were white (82.2%) and non-Hispanic/non-Latino (93.3%)
- Randomized to receive 2 doses, separated by 21 days
 - 12 received 1 µg – repeated at day 22
 - 12 received 10 µg – repeated at day 22
 - 12 received 30 µg – repeated at day 22
 - 12 received 50 µg – repeated at day 22
 - 12 received 60 µg ONLY

Vaccine-induce antibody response

- Antibodies
 - Immunised participants showed a strong, dose-dependent vaccine-induced antibody response
- Cellular immune response:
 - CD4: 94% mounted a specific CD4 T cell response
 - CD8: 80% mounted a strong CD8 T cell response
 - CD8 response correlated with CD4 response but NOT with antibody titres
- Cytokines
 - Robust release of immune-modulatory cytokines such as IFN γ , which is a key cytokine for several antiviral responses.

Side effects

Local reactions and systemic events:

- Were dose-dependent
 - Generally mild to moderate, and
 - Transient.
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“TWEETORIAL” ON DECAY OF ANTIBODY LEVELS

Florian Krammer

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There has been discussion / controversy over what appears to the decay of antibodies following COVID-19 and subsequent inference that immunity may be short-lived. This section is a primer to remind us all how humoral immunity works.

Simple B-cell biology

- B-cells make antibodies. Not all, all the time, but let me explain in a simple way. When you get infected, initial subsets of B-cells called plasmablasts get activated and make tons of antibody a few days after infection. They are responsible for your initial antibodies. They die after about two weeks, but their antibodies stay for some time since IgG antibodies have a half-life of approximately 21 days. Of course, the antibody levels from these initial plasmablasts will start to go down after some time.
- But there is also a second set of B-cells that secrete antibodies and gets activated (complicated process). They migrate mostly to the bone marrow and just sit there and make antibodies, often for a long time (that's why they are called long-lived plasma cells). They are the ones that maintain your serum antibody levels for a long time, sometimes life-long (probably shorter for coronaviruses).
- And then, there is a third set of B-cells. They are called memory B-cells. They don't make antibody. But they get quickly reactivated and become plasmablasts if you get re-infected. This quick plasmablast response might prevent you from getting severe disease or even from getting symptoms after re-infection.
- So, to recap initially you get a lot of antibodies from plasmablast, these antibodies go down after weeks to months and then usually hit a stable titer which is maintained by the bone-marrow residing plasma cells. So, you expect a peak, a decline and a stabilization phase.
- PS: I did not mention T-cells. But I will get back to that in another Tweetorial.

INHALED INTERFERON BETA - NEW TREATMENT LOOKS PROMISING

[Synairgen](#), a small British biotechnology company, said it will soon present findings that its inhaled form of interferon beta is effective.

- When given to COVID patients in a small trial involving 100 patients, it significantly reduced the numbers who required intensive care.
- The odds of requiring ventilation were reduced by 79% and patients were two to three times more likely to recover.

Caution

- Synairgen has not yet released information about how it conducted its trial
- Their findings have not been peer-reviewed

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