INTERNATIONAL SOS WEEKLY SCIENTIFIC UPDATE
Focussing on immunity and vaccine development

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A. Vaccine Development & Approval

1. AstraZeneca and Johnson & Johnson to resume us vaccine trials

AstraZeneca and Johnson & Johnson have been given approval by the FDA (US Food and Drug Administration) to restart their Phase 3 trials in the US.

AstraZeneca, one of the leading vaccine developers, paused its US trial on 6 September after a report of a serious neurological illness, believed to be transverse myelitis, in a participant in the company's UK trial. Trials had resumed in all countries except the US.

Johnson & Johnson paused all of its large, late-stage trial on 12 October after a study participant became ill.

2. FDA COVID-19 vaccine process is “thoughtful and deliberate”

Dr. Mark McClellan, former FDA Commissioner under President George W. Bush, observed Thursday's FDA advisory panel on COVID-19 vaccine research, where independent experts offered advice on the way forward.

McClellan told NPR's Morning Edition that after Thursday's advisory meeting, Americans should feel confident in the FDA's approach toward a vaccine.

"'I think people for the most part - the experts, the others listening - found it very reassuring to know that even though FDA is going fast, it's not cutting corners. And it's trying to be very thoughtful and deliberate about getting the evidence needed before the vaccine becomes available — even the people in the highest risk groups, like health care workers and people living in nursing homes', McLellan said."

3. AstraZeneca's COVID-19 vaccine follows genetic instructions

AstraZeneca's / Oxford COVID-19 vaccine accurately follows the genetic instructions programmed into it by its developers to successfully provoke a strong immune response, according to a detailed analysis carried reported by Oxford University on 22 October 2020.

"The vaccine is doing everything we expected and that is only good news in our fight against the illness," said David Matthews, an expert in virology from Bristol University, who led the research.

4. Pfizer is now including teens in clinical trials for its COVID-19 vaccine

Pfizer is now including teens in clinical trials for its COVID-19 vaccine candidate, expanding the participation age to include high schoolers and middle schoolers, according to USA Today.

Pfizer is the only pharmaceutical company allowing minors to join coronavirus vaccine trials at the moment. The company initially lowered the age to 16, and this week, Cincinnati Children's Hospital Medical Center vaccinated the first 12-year-old.

Vaccine experts and pediatricians have voiced mixed reactions, USA Today reported. Some say drug manufacturers should wait until the vaccines have been approved in adults, but others say it's necessary to proceed with vaccine testing among specific groups, including minors.

5. Novavax delays US trial of COVID-19 vaccine to November

Novavax announced on 28 October 2020 that it has delayed the start of Phase 3 US trials of its coronavirus vaccine until the end of November, blaming delays in scaling up the manufacturing process.

Novavax has a Phase 3 a trial running in the UK which has expanded to 15,000 volunteers. The North American trials, to be conducted with the support of "Operation Warp Speed," is looking to enroll 30,000 volunteers in the US and Mexico.

Novavax is the leader in producing a "subunit vaccine" which contains viral proteins but no RNA or DNA.

6. Info graphic on COVID-19 vaccine development

The Wall Street Journal has released this excellent graphic of COVID-19 vaccine development:

- Row 1 describes the four main types of vaccines
- Rows 2,3 and 4 shows significant dates for the nine leading vaccine candidates

7. What defines an efficacious COVID-19 vaccine?

Some countries have begun deploying COVID-19 vaccines on the strength of immunogenicity, the ability of a vaccine to invoke an immune response.

An article in The Lancet (27 October) notes that "the goal of vaccine development is to gain direct evidence of vaccine efficacy (the ability to prevent or reduce the severity of infections) in protecting humans against SARS-CoV-2."

The article also notes that "**the most important efficacy endpoint, protection against severe disease and death, is difficult to assess in phase 3 clinical trials**.

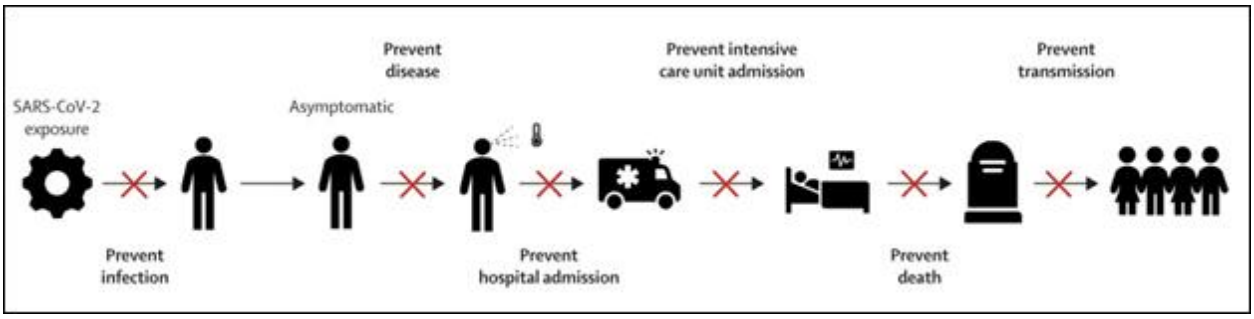
"The effect of an efficacious vaccine on the course of the SARS-CoV-2 pandemic is complex and there are many potential scenarios after deployment (our edits and formatting):

1. "The ability of a vaccine to protect against severe disease and mortality is the most important efficacy endpoint, as hospital and critical-care admissions place the greatest burden on health-care systems.

2. "However, the beneficial effects of such a vaccine on a population can be observed only if the vaccine is efficacious in older adults (eg, approximately >60 years) and widespread distribution of the vaccine exists, including to people who are most susceptible to COVID-19.

3. "High coverage among these groups who are at high risk of severe COVID-19 would have the greatest effect against disease endpoints. Alternatively, vaccines that do not affect the clinical course, but reduce the transmissibility of SARS-CoV-2, could still be valuable interventions on a population level."

The Lancet article includes this diagram that succinctly describes the various potential endpoints of an efficacious COVID-19 vaccine.



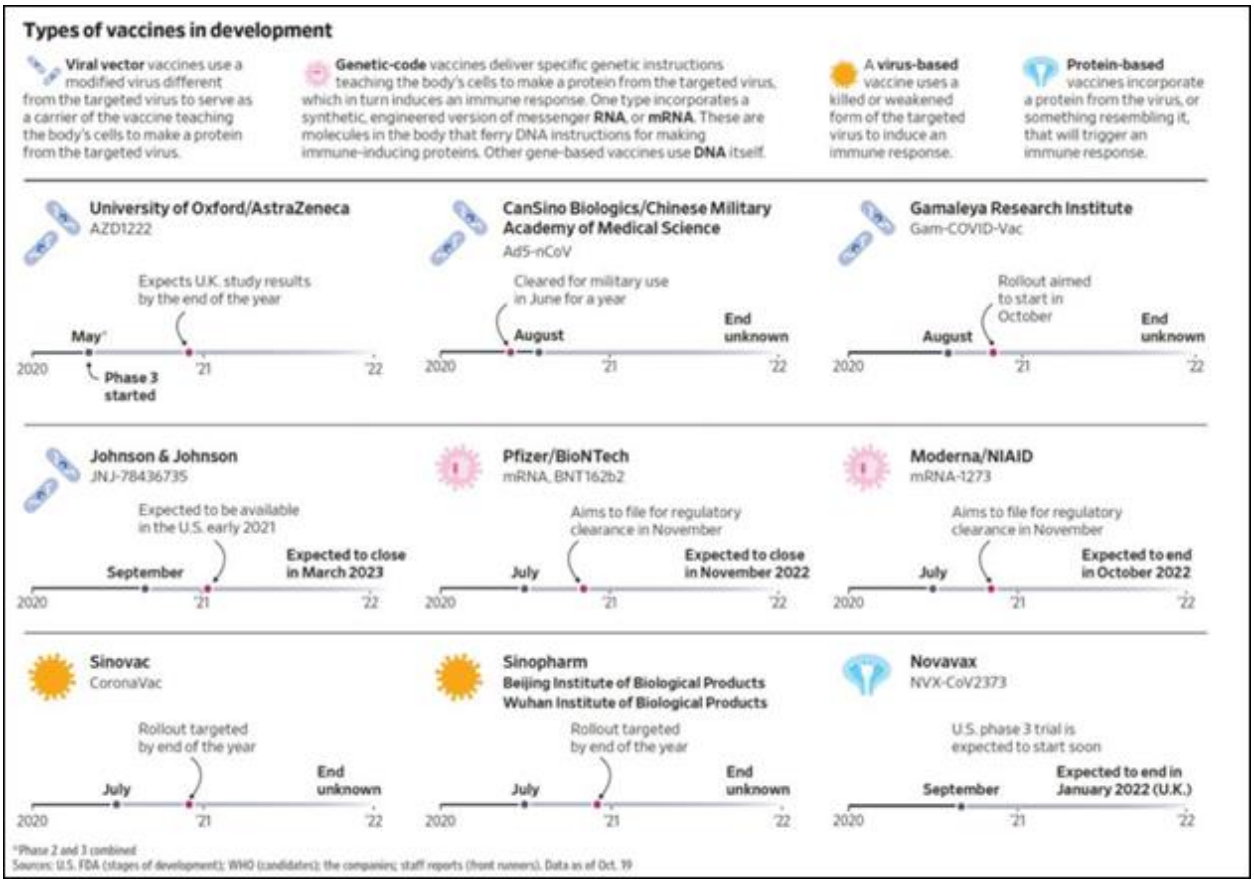
The article contains a detailed discussion of vaccine trial design which we recommend.

Conclusion

"It is probable that there will not be a single vaccine winner; diverse platforms and technologies can offer different strengths and be relevant in distinct epidemiological contexts.

"Additionally, there will probably be insufficient supply, at least initially, of a single vaccine. However, collaboration and standardised approaches for assessing different efficacy endpoints will be important to allow meaningful comparison and ensure that the most effective candidates are deployed.

"Following deployment, well supported pharmacovigilance studies should be established to ensure the ongoing evaluation of vaccine safety."



B.Vaccine Distribution

1. Brazil approves import of China's Sinovac vaccine

Bloomberg reports that Brazil's health regulator has authorized the importation of six million doses of the Chinese Sinvoac vaccine for Phase 3 trials, the Brazilian Health Surveillance Agency, or Anvisa, said in a statement Friday afternoon.

Several other vaccine manufacturers are conducting Phase 3 trials in Brazil including Oxford / AstraZenca, Johnson & Johnson / Janssen and Pfizer.

2. German Health Minister expects a COVID vaccine will be available early 2021

"German Federal Health Minister Jens Spahn expects a vaccine against COVID-19 for the German population 'at the beginning of next year'. It could be January, maybe February or March, or even later. "'Of course, it would be best if a vaccine would prevent new infections. But it would also be a gain if it made the course of the disease milder,' Spahn told Spiegel."

3. Lancet article reviews UK vaccine planning

The UK set up its Vaccine Taskforce under the Department for Business, Energy and Industrial Strategy in May 2020; the chair Kate Bingham**, who authored the Lancet article (27 October).

“The Vaccine Taskforce aims to ensure that the UK population has access to vaccines as soon as possible, while working with partners to support equitable access for populations worldwide, whether rich or poor.”

Ms Bingham notes that we may never have a vaccine, and that if and when we do, the first generation of vaccines may be imperfect and “we should be prepared that they might not prevent infection but rather reduce symptoms, and, even then, might not work for everyone or for long.”

The Taskforce has focused on building a “diverse” portfolio of vaccines across the various technology platforms “recognising that many, and possibly all, of these vaccines could fail.”

“The Vaccine Taskforce has now secured access to six vaccines (from more than 240 vaccines in development) across four different formats: adenoviral vectors, mRNA, adjuvanted proteins, and whole inactivated viral vaccines, which are promising in different ways.”

International SOS Comment

Ms Bingham gives no clinical or technical evidence evidence to support her statement that “the first vaccines may be imperfect”. Rather this is a warning not to be over optimistic.

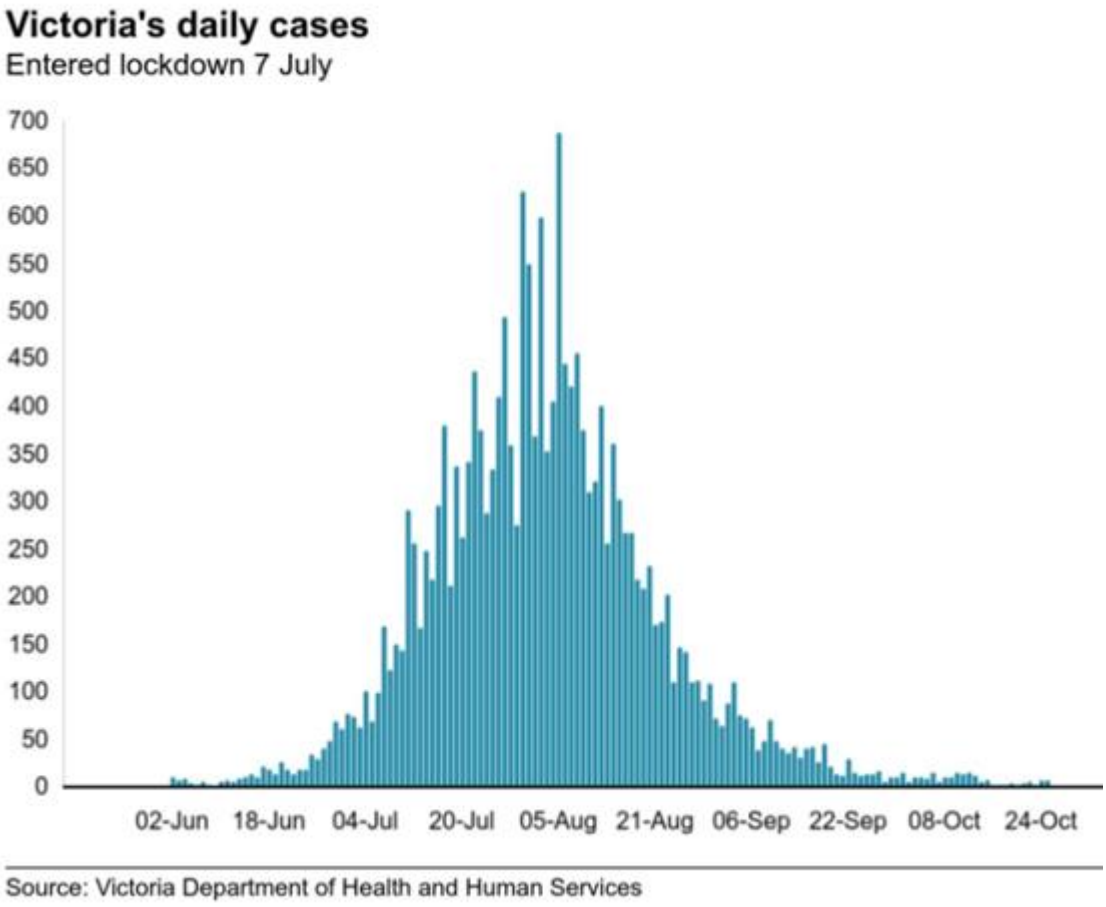
**Kate Bingham is a Managing Partner at SV Health Investors.

C.Outbreaks and Epidemiology

1. Melbourne begins easing lockdown

Melbourne (and the state of Victoria) has recorded no new COVID-19 cases for the first time since Melbourne went into lockdown on 7 July, 111 days ago. This is the longest city lockdown since the pandemic began.

From 11.59pm on Tuesday 27 October, there will be no restriction on Melburnians leaving their houses. Restaurants, hotels, cafes and bars will be able to open with up to 50 patrons outdoors and 20 indoors. The mask policy remains and working from home, where possible, remains in force.



D.Immune Response

1. Oxford vaccine prompts immune response in elderly

AlJazeera reports an AstraZeneca spokesperson saying that the Oxford/AstraZeneca COVID-19 vaccine produces an immune response in both younger and older adults. The vaccine also triggers lower adverse responses among the elderly.

International SOS had reported on 12 September 2020 that the Moderna vaccine produced a strong immune response in older patients.

International SOS Comment

It is encouraging to see that both AstraZeneca and Moderna vaccines produce a good immune response in the elderly, an at risk group. Of course, we await the results of the Phase 3 trials to demonstrate these vaccines' efficacy in preventing illness.

2. Two studies show long-term COVID-19 immune response

Two new studies demonstrate how severity of disease is predictive of longer-lasting antibody production and detail how immunity wanes over time but may exist for up to seven months.

A UK study reported in Nature Microbiology examined 65 people with PCR positive COVID-19 people and 31 seropositive healthcare workers. More than 95% of patients showed SARS-CoV-2 antibodies eight days after symptom onset, but the magnitude of the neutralizing antibody response appears to depend on disease severity, with lower peak antibody levels in individuals exhibiting milder disease.
A Portuguese study reported in the European Journal of Immunology examined antibody levels in more than 500 hospitalized patients, healthcare workers, and volunteers who had recovered from COVID-19. The researchers found that 90% of SARS-CoV-2–positive individuals had detectable antibodies from 40 days up to seven months post-infection, with higher levels in patients with more severe disease.

3. Pre-print showing waning antibodies & Responses from two scientists

A study published by Imperial College on 27 October 2020 has shown that the antibody response to the virus that causes COVID-19 wanes over time.

Analysis of finger-prick tests carried out at home between 20 June and 28 September found that the number of people testing positive dropped by 26.5% across the study period, from almost 6% to 4.4%.

The study abstract includes this statement; “We also show that titers are stable for at least a period approximating three months, and 36 that anti-spike binding titers significantly correlate with neutralization of authentic SARS-CoV-2. 37.

“Our data suggests that more than 90% of seroconverters make detectible neutralizing antibody 38 responses and that these titers are stable for at least the near-term future.”

However, Reuters reports that in a press conference, Dr Wendy Barclay** said; “We can see the antibodies and we can see them declining and we know that antibodies on their own are quite protective. “On the balance of evidence I would say, with what we know for other coronaviruses, **it would look as if immunity declines away at the same rate as antibodies decline away, and that this is an indication of waning immunity at the population level.”**

** **Dr Wendy Barclay** is the Head of the Department of Infectious Disease and Chair in Influenza Virology at Imperial College London. She leads a team of scientists studying the influenza virus and its physiology and morphology to discover novel vaccines.

Response from two scientists

Two renowned scientists, Dr Angela Rasmussen and Dr Florian Krammer have provided short “Tweetorials” discussing immunity and disputing the assumption that decaying antibody levels indicate decaying immunity.

International SOS Comment

Remember that pre-print articles have not been peer reviewed. In addition, this is an example where an eminent scientist (not an author) has drawn a conclusion which has been questioned by other scientists.

Dr Angela Rasmussen

Angela Rasmussen is a Virologist and Associate Research Scientist at the Center of Infection and Immunity at the Columbia University School of Public Health.

“This is misleading. Serum antibody titers normally fall after you recover from an infection...the high titers induced by the infection decrease to baseline. The implications for immunity are unclear.

“Here's a quick summary of some hypothetical scenarios.

1. “Antibodies drop to baseline titers that are undetectable by commonly used serology assays. There are still low levels of antibody as well as memory B cells that can rapidly produce more antibody in the event of re-exposure (anamnestic response).

    - **This is not ‘waning immunity’**

2. “Some of the people identified as part of the 6% were false positives. Serology tests can be notoriously non-specific, so this depends on the tests that were used.

    - **This is also not ‘waning immunity’**

3. “Some people (possibly with mild infection) do not have long-lasting antibodies for whatever reason. They do not have sufficient memory B cells to mount an effective anamnestic response.

    - **This is ‘waning immunity**

“It is also possible that all three scenarios could be true to some degree. Some people have IgG titers below the limit of detection, some were false positives, and some genuinely have fewer antibodies.
“The bottom line is: Implications for long-term immunity are unclear.
“However, this should underscore the fact that "natural herd immunity" is not the way to go. There are too many unknowns to choose this as a safer, easier path to population immunity vs a vaccine that undergoes rigorous evaluation in controlled trials.”

Professor Florean Krammer

Professor Florian Krammer, PhD, currently holds a position as a Professor of Vaccinology at the Department of Microbiology at the Icahn School of Medicine at Mount Sinai. He has published more than 100 papers, is member of the editorial boards of the Journal of Virology, Plos One and Heliyon and is a peer reviewer for more than 30 journals.

“Before we start, a simple primer in B-cell biology:

1. “Plasmablasts make first antibodies

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 decline after some time. But….

2. “Long-living plasma cells migrate to bone marrow and continue to make antibodies

There is a second set of B-cells that secrete antibodies and get activated (complicated process). They migrate mostly to the bone marrow and just sit there and make antibodies, often for a long time. These are the ones that maintain your serum antibody levels for a long time, sometimes lifelong (probably shorter for coronaviruses).

3. “Memory B cells

The third set of B cells is called memory B-cells. They don’t make antibody themselves, but they get quickly reactivated and again become plasmablasts if you get reinfected. This quick plasmablast response might prevent you from getting severe disease or even from getting symptoms after re-infection.
“Summary: So, to recap, initially you get a lot of antibodies from plasmablast, these antibodies decline 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.”

Initial summary of Prof Krammer's tweetorial

- In people who had high titers, their titre decreased. Not a dramatic decrease (less than three-fold) but certainly appreciable
- In people with moderate to low titers however, their titre increased. Mild cases often need time until their antibody titers go up

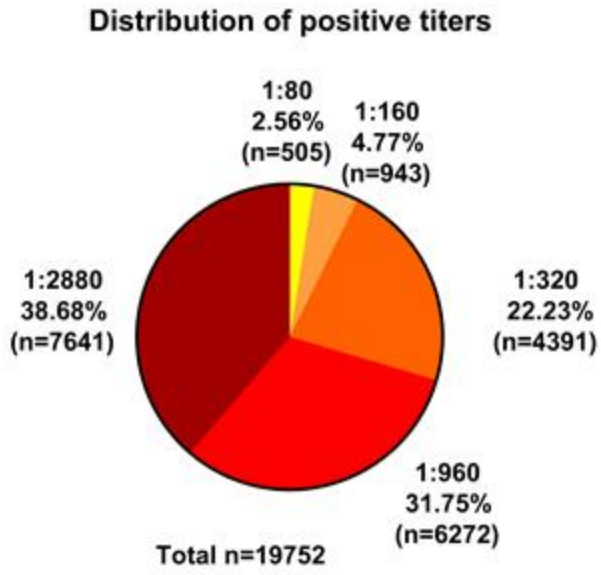
I recommend all read Professor Krammer's entire "Tweetorial", particularly the last paragraph.

Detailed tweetorial by Prof Krammer

"First, Carlos' lab screened >50,000 people using an anti-spike ELISA that my lab designed. In their shop it is FDA emergency use authorized, by the way. These people were screened to look for potential convalescent plasma donors or because they were employees that wanted to know if they had seroconverted. Of the 50,000 people Carlos identified >19,000 people with antibodies to SARS-CoV-2. Those are mostly from mild or even asymptomatic cases.

"Now, what did their antibody responses look like?

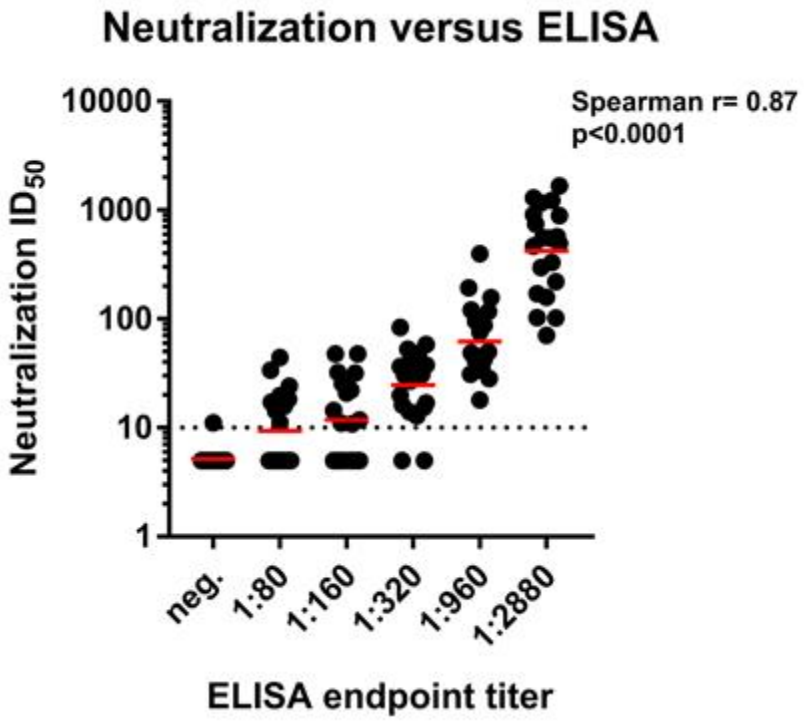
- Very few had what we call low titers (1:80-1:160).
- About 22% had moderate titers (1:320).
- The remaining >70% had high titers (1:960-1:2880)



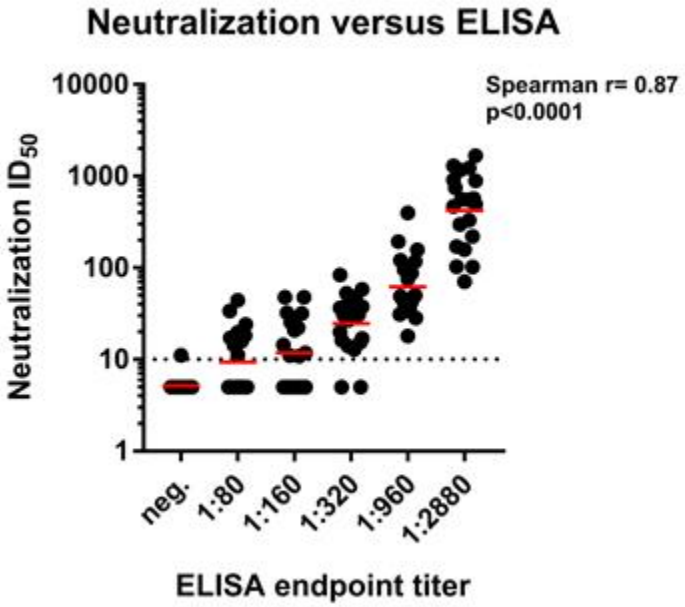
"We know that people with lower titers often have titer increase over time. It seems that people with mild infections often respond slower than severe cases. Keep that in mind, we will get back to that.

"Now, what are these antibodies doing? They bind to the spike and spike antibodies can potentially neutralize the virus. So, we tested a range of titers for neutralization of real SARS-CoV-2 in a

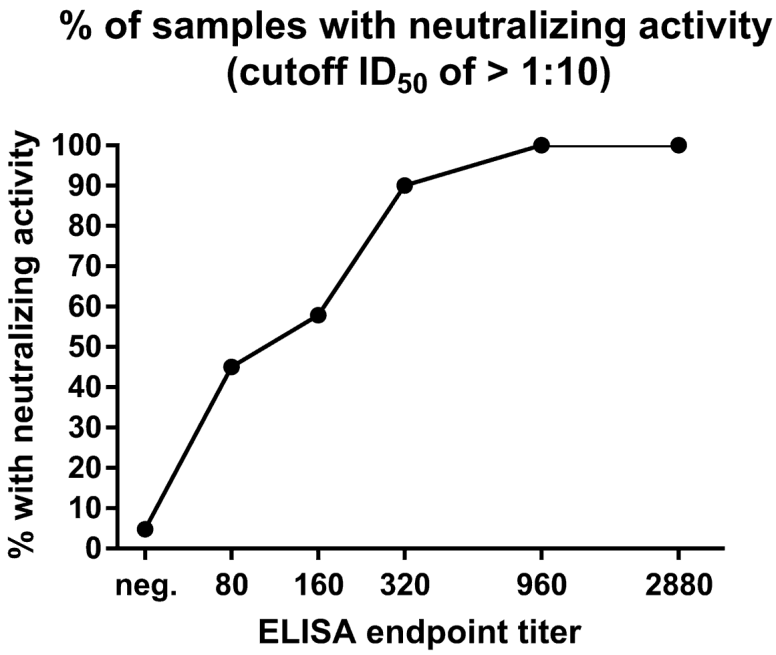
microneutralization assay. First, ELISA titers and neutralization correlate well.



“Of note, the variability in each titer category is high. But that is OK, since different people might target different epitopes, affinity maturation might be different etc.



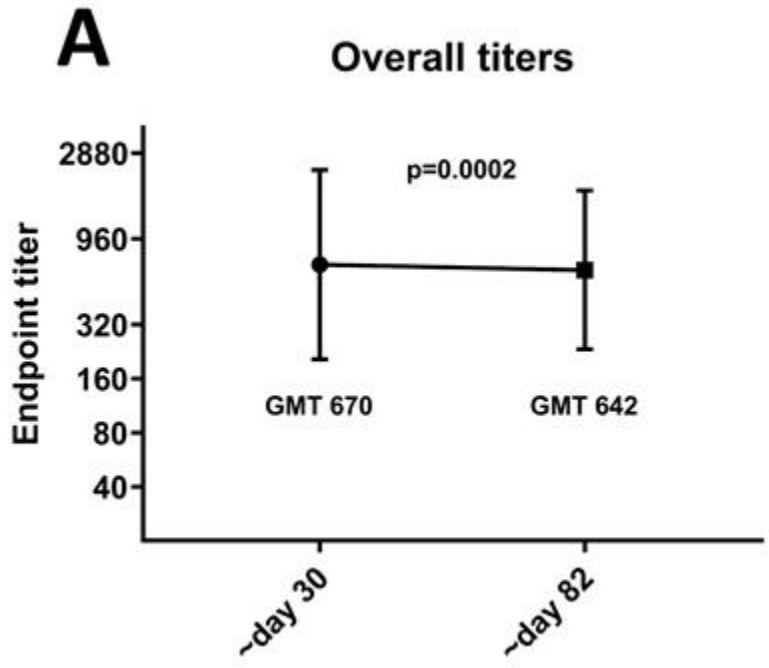
“Now, when looking at the proportion of individuals who have any neutralizing activity, we see that about 50% of the 1:80-1:160 titers have neutralizing activity, 90% of the 1:320 titers have it and 100% of the titers above that have it.



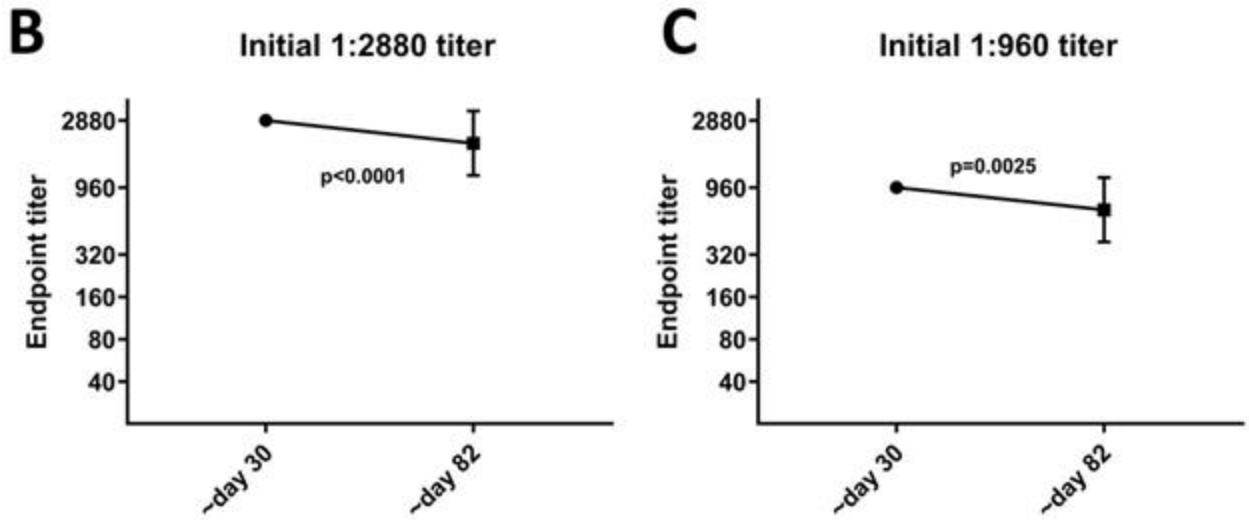
"Of course, this is limited by the lower limit of detection of the neutralization assay (the assay is described in detail here if you are interested, open access of course: …rentprotocols.onlinelibrary.wiley.com/doi/full/10.10…).

"Now, how long do these antibodies live (measured by ELISA against spike)? Dr. Wajnberg selected 121 individuals that were bled around 30 days after their initial symptom onset and brought them back at approximately 82 days after symptom onset.

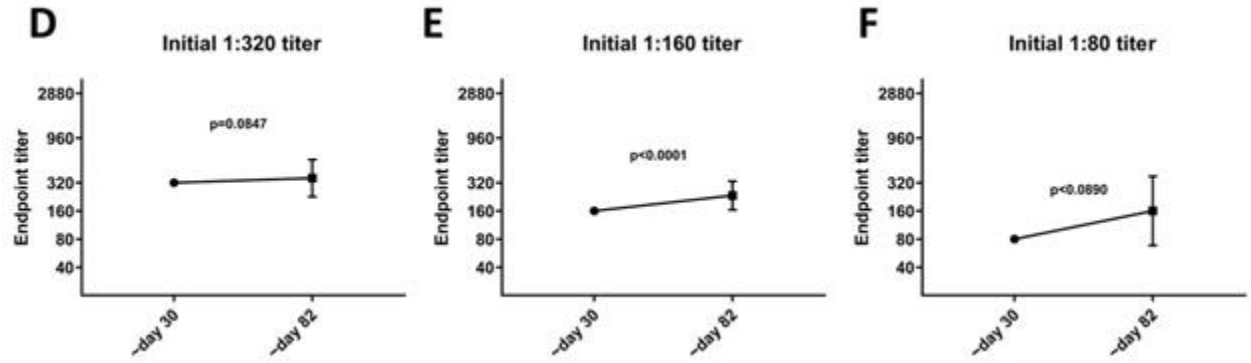
"So, when we looked at the difference between day 30 and day 82 titers, we did see a decline. It was statistically significant but tiny.



“To understand better what was going on, we started to stratify by initial titer. People who had high titers initially had - on average - decrease in titer. Not dramatic decreases (less than three-fold) but certainly appreciable.



“However, in people with moderate to low titers, the titre increases. Again, they were not huge but for sure there was an upwards trend. As mentioned earlier, mild cases often need time until their antibody titers go up.



“So, first, a few caveats: We did not measure the neutralizing titers at the later time point. While we assume the neutralization titers stay the same, we haven't proven that yet. Ratios of neutralizing versus non-neutralizing antibodies might change over time.

“Another caveat is the low number of samples for the neutralization and longitudinal analysis. Also, we had mostly mild cases, disease severity might influence this. Also the highest titer the assay in the clinical lab measures is >1:2880, everything above is also registered as >2880, so we are missing some resolution there.....

“Now, how does this compare to data from other labs? I think the actual data compares pretty well.

“**There are a lot of 'OH MY GOD, THE ANTIBODIES ARE GOING DOWN' headlines, but a lot of data suggests a slow and expected decline over months - which I think is normal.**

“Here are the important questions (which we can't answer yet):

1. What is the long-term baseline titer going to be?
2. How long-lived will that be?

3. How much antibody will you need to be protected from reinfection?
4. How much antibody do you need to be protected from disease?

“These are important questions, and we need to answer them with appropriate studies. Importantly, specific antibody titers that indicate protection (correlates of protection) have been established for influenza, measles, hepatitis A, hepatitis B etc.

“We need to define this titer for SARS-CoV-2 as well. A combination of a protective titer plus detailed knowledge of specific antibody kinetic would allow us to make predictions who is at risk and who is not.

“This is also important for vaccine development and development of vaccination regimens (e.g. to determine when you need a booster dose). The important part to keep in mind is that, even if we define a protective titer, this titer will be associated with a reduction in risk. That does not mean that re-infections are impossible, just not likely. Keep that in mind too. In the end, it all boils down to probabilities.

PS: I did not mention T-cells. But I will get back to that in another Tweetorial.

4. Two thirds of US teens fail to get needed vaccines

IDSociety.org reports that, excluding influenza vaccine, “only 30.6% of US 17-year-olds had received all vaccines” recommended by the CDC.

“The Advisory Committee on Immunization Practices (APIP) recommends that by age 17, adolescents complete three key immunizations: human papillomavirus (HPV); quadrivalent meningococcal conjugate (MenACWY); and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap).”

“State-level variations that ranged from a low of 11.3% in Idaho to a high of 56.4% in Rhode Island”.