INTERNATIONAL SOS WEEKLY SCIENTIFIC UPDATE
Focussing on immunity and vaccine development

Produced by Dr. Doug Quarry
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In this edition:

A. Vaccine Development & Approval

1. COVID Pfizer vaccine approved for use next week in UK

The UK has become the first country in the world to approve the Pfizer/BioNTech coronavirus vaccine for widespread use. British regulator, the MHRA, says the jab, which offers up to 95% protection against

Covid-19 illness, is safe for roll out. Immunisations could start within days for people in high priority groups.

The UK has already ordered 40m doses - enough to vaccinate 20m people, with two shots each. Around 10m doses should be available soon, with the first doses arriving in the UK in the coming days.

2. CDC should warn people of the side-effects of COVID-19 vaccine

"The CDC must be transparent about the side-effects people may experience after getting their first shot of a coronavirus vaccine, doctors urged during a meeting Monday with CDC advisors." CNBC reports.

"Dr. Sandra Fryhofer said that both Pfizer's and Moderna's COVID-19 vaccines require two doses and she worries whether her patients will come back for a second dose because of potentially unpleasant side-effects after the first shot.

"Both companies acknowledged that their vaccines could induce side-effects that are similar to symptoms associated with mild COVID-19, such as muscle pain, chills and headache."

3. Oxford/AstraZeneca vaccine to undergo new global trial

AstraZeneca's Chief Executive Officer, Pascal Soriot, has told Bloomberg News that the company will conduct a new global trial using the lower-dose regimen. Soriot insisted that this move will not disrupt the timeline for regulatory approval and the subsequent rollout of the vaccine in Europe and the UK.

4. UK expert says Russia has presented sufficient evidence about Sputnik V vaccine

A UK expert in virology and epidemiology believes Russia had presented sufficient evidence to prove the efficacy of its Sputnik V vaccine, Canada's CBC has reported.
"'The data is compatible with the vaccine being reasonably effective,' Stephen Evans, Professor of Pharmacoepidemiology at the London School of Hygiene and Tropical Medicine said.
"'These results are consistent with what we see with other vaccines, because the really big message for global health scientists is that COVID-19 is able to be addressed by vaccines,' Professor Evans added."
Russia's vaccine has 91.4% per efficacy from an analysis of more than 18,000 people, said a release on the Sputnik V website. The vaccine's efficacy rose to 95% after 42 days.

5. Implications of an EUA on ongoing Phase 3 trials

Now that both Pfizer and Moderna have applied for an Emergency Use Authorization (EUA) from the US Food and Drug Administration (FDA), the continuation of their Phase 3 trials needs to be considered. An EUA comes with the stipulation that companies have a strategy to ensure that the long-term safety and efficacy of their vaccine, which requires months of data collection. Early vaccine deployment could interfere with the acquisition of this long-term data.

An article in the Annals of Internal Medicine discusses this dilemma. "In countries where the approved vaccine is deployed and the original trial is continuing, investigators should inform study participants about the approved vaccine's status because this information could affect their willingness to continue participating in the trial.

"Re-consent will be necessary and investigators should tell those who are unwilling to re-consent whether they received vaccine or placebo so that those who received placebo can seek vaccine outside the trial.

"If enough study participants decline to re-consent, the trial might have to be terminated early…and investigators may not have enough long-term data to identify late-term safety issues, determine how long vaccine efficacy lasts, etc…."

6. UK MRHA assessing both Pfizer/BioNTech vaccines and Oxford/AstraZeneca

The UK Medicines and Healthcare products regulatory Agency (MRHA) Chief Executive Dr June Raine said in a statement: "Our job will be to rigorously assess the latest data and evidence of the vaccines' safety, quality, and effectiveness."

The British Government has appointed a "Vaccines Minister" to oversee the distribution and administration of COVID-19 vaccines.

The Guardian reports that the UK National Health Service (NHS) could receive first deliveries of Pfizer/BioNTech vaccine as soon as 7 December.

7. Do COVID vaccines prevent viral transmission?

The large Phase 3 trials of the Pfizer, Moderna and AstraZeneca vaccines were not designed to test whether the vaccines stopped person-to-person transmission of the virus.

Transmission would only be stopped if the vaccines cause "sterilizing immunity", where infection is prevented, rather than "non-sterilizing immunity", where infection occurs but with a reduced severity of the illness.

In contrast other vaccines:

- Smallpox vaccine produced sterilizing immunity
- Influenza vaccine produces non-sterilizing immunity; the vaccinated can still become infected but the chance of severe disease and hospitalization is reduced by 94%

Phase 4 post-marketing surveillance studies, or other "boutique" studies, may take several months to definitively determine whether the vaccines reduce or prevent transmission of the virus.

In the meantime, both the vaccinated and unvaccinated should continue to wear masks:

- Those who have been vaccinated could still be transmitting the virus
- Those who have not been vaccinated are probably still susceptible

Note that the concept of "herd immunity" relies on a vaccine preventing all, or almost all, viral transmission.

8. Is two months follow-up enough to identify serious vaccine side-effects?

The US Food and Drug Administration (FDA) requires that vaccine manufacturers not apply for an Emergency Use Authorisation (EUA) until at least half of the vaccine recipients in the Phase 3 trial have had at least two-months follow up. Is this enough time?

Dr. Offit** explained that he feels that two months is enough time, given the urgency of the situation, and said that serious side-effects tend to occur within six weeks of vaccine administration. Examples include:

- Vaccine derived polio (1:1.2M)
- Guillian Barre following flu vaccination (1:1M)
- Viscerotropic disease following yellow fever vaccination
- Narcolepsy following squalene adjuvanted flu vaccine
- Thrombocytopenia following measles containing vaccines

Dr. Grohman*** took a different statistical view on the subject. If a side-effect occurs in one in one million vaccine recipients, then a Phase 3 study with 50,000 volunteers has only a 1:20 chance of finding that side-effect.

It is clear that Phase 4 post-marketing surveillance is required to confirm vaccine safety.

References for 1 & 2
** Dr Paul Offit on VuMedia: Dr Offit is an American pediatrician specializing in infectious diseases, vaccines, immunology, and virology. He is the co-inventor of a rotavirus vaccine.
*** Dr Gary Grohman on HealthEd: Dr Grohman is a vaccine manufacturing expert and former Director of Immunobiology at the WHO.

9. Are RNA vaccines safe?

Prof Shane Crotty** made some very good points on Twitter:

- Cells contain up to 5,000 RNA messages at any one time. These temporary messages are destroyed within minutes or hours
- For COVID-19 vaccines, the RNA codes only for one protein (so the cell cannot make the virus)
- Over 70,000 doses of coronavirus mRNA vaccines have been given and the independent safety boards have not reported serious concerns
- Safety does not equate to "did not hurt at all", or "no fever". In fact, some mild reactions can be a positive sign that "good things are happening".

Prof Florian Krammer*** reminded us on Twitter that Moderna and Pfizer are not the first mRNA vaccines to be developed or administered. Prof Krammer said: "It is true that there is little long-term safety data, but it is not true that there is no long-term safety data."

RNA vaccine trials in humans
(not including a large number of cancer vaccines and therapeutic approaches based on mRNA)

Target	Started in	Individuals enrolled[2]	Company	Status	Phase	Registration numbe
CMV	2017	181	Moderna	Fully enrolled	Phase 1	NCT03382405
hMPV/PIV3	2019	114	Moderna	Recruiting	Phase 1	NCT04144348
Zika	2019	120	Moderna	Fully enrolled	Phase 1	NCT04064905
Influenza	2017	156	Moderna	Fully enrolled	Phase 1	NCT03345043
Rabies	2018	53	Curevac	Fully enrolled	Phase 1	NCT03713086
Rabies	2013	101	Curevac	Completed	Phase 1	NCT02241135
Rabies	2014	72	Curevac	Completed	Phase 1	NCT02238756
CMV	2020	452	Moderna	Recruiting	Phase 2	NCT04232280
Chikungunya[1]	2019	39	Moderna	Fully enrolled	Phase 1	NCT03829384

[1]Passive immunity based on *in vivo* mAb expression
[2]Includes individuals who received placebo, some trials are still recruiting

(A reference was not provided for the table.)

**** Professor Shane Crotty is a virologist and Professor in the Vaccine Discovery Division at La Jolla Institute for Immunology.
***** Professor Florian Krammer is a Professor at the Department of Microbiology, Icahn School of Medicine, Mount Sinai, NYC.

10. Sputnik V vaccine uses a different viral vector for each dose

We reported on 25 November that Professor Gilbert, who designed the Oxford vaccine, gave this possible explanation for the Oxford vaccine having a higher efficacy when half a dose is given first: "It's theoretically possible that a full initial dose generated antibodies to the adenovirus vector itself, which might have limited the immune response to the coronavirus spike protein."

However, the Russian Sputnik V vaccine uses a different adenovirus for the two doses. The first dose uses adenovirus Ad26 and the second dose uses adenovirus Ad5. This should reduce the chance of immunity against the vector virus causing a lower efficacy of the Sputnik V vaccine.

B. Vaccine Purchase & Distribution

1. COVID vaccinations in Germany will take over a year

It will take until 2022 to vaccinate the whole population of Germany against COVID-19 due to capacity limits, according to the head of an expert panel that will help decide in which order people should receive the vaccine.

"'If you can administer shots to 150,000 to 200,000 people a day, on five or six days a week -- assuming vaccines are available and people are willing to be vaccinated -- then you can calculate how long it will take.' Thomas Mertens, Head of STIKO, Germany's expert panel on vaccine use, told Rheinische Post.

"'Then you would need 100 days to vaccinate 15 million people,' he said."

International SOS Comment: We are unable to make Mr Merten's maths work but have reported in good faith.

2. Practical hurdles in UK for Pfizer/BioNTech COVID-19 vaccine

Care home residents and their carers are top of the list to receive the Pfizer/BioNTech COVID-19 vaccine after it cleared all regulatory hurdles and was approved for widespread use across the UK.

The first doses of the messenger RNA (mRNA) vaccine are due to arrive from Belgium imminently. It is anticipated that the vaccine will be transported to 23 locations around the country in temperature-controlled lorries.

However, it has emerged that supplies are unlikely to be sent to care homes initially because the vaccine is distributed in batches of 975 vials that must be stored at minus 70C.

At a news conference, Sir Simon Stevens, Chief Executive of NHS England, suggested it could take weeks before the Medicines and Healthcare products Regulatory Agency (MHRA) approved a way to split the packs for secure cold-chain distribution in smaller quantities.

3. Operation Warp Speed says all Americans can be vaccinated by June

Every American will be able to get a COVID-19 vaccine by the end of June next year if they want one, Operation Warp Speed's Director of Supply, Lt. General Paul A. Ostrowski, told MSNBC on Monday. Lt. General Ostrowski said that the US military will be deeply involved in the logistics and supply chain elements of vaccine distribution, as it is with seasonal influenza vaccine.

4. Spain has announced its COVID-19 vaccination strategy

Spain's Minister of Health announced a COVID-19 vaccination strategy this week. The Government has established three levels of priority. The first to be vaccinated will be care home residents and staff, followed by health workers.

5. Belgium announces a fourth coronavirus vaccine purchase

Belgium (population 11.5 million) has approved a fourth coronavirus vaccine purchase, CureVac. This brings the number of coronavirus doses ordered by Belgium to more than 20 million:

- CureVac: 3 million
- AstraZeneca: 7.74 million
- Johnson & Johnson: 7.74 million
- Pfizer: 5 million

Belgium is due to receive the first doses of COVID-19 vaccine before the end of 2020.

6. Berlin plans six COVID-19 vaccination centres handling 4,000 people a day

Reuters reports that Berlin intends to open six mass-vaccination centres by mid-December. Each centre will be able to vaccinate 4,000 people per day.

"An empty trade fair hall, two airport terminals, a concert arena, a velodrome and an ice rink will be turned into six vaccination centres where it plans to administer up to 900,000 shots against the coronavirus in the first three months. People will be guided through each centre in the same way as shoppers are guided through IKEA stores - in one direction."

C. Outbreaks and Epidemiology

1. COVID-19 disruptions may have fueled hospital superbug outbreak

A case report from a New Jersey hospital published in Morbidity and Mortality Weekly (MMWR) highlights how drug-resistant pathogens can take advantage of COVID-related disruptions to infection control practices.

A total of 34 patients in a 500-bed hospital were found to be infected or colonized with the multidrug-resistant pathogen carbapenem-resistant Acinetobacter baumannii (CRAB), which frequently contaminates healthcare surfaces and is considered an urgent health threat by the CDC.

D. Travel systems

1. Delta Airlines launches the first quarantine-free travel from the US to Europe

Delta Air Lines, the Aeroporti di Roma and Hartsfield-Jackson Atlanta International Airport have joined in a first-of-a-kind trans-Atlantic COVID-19 testing program that will enable quarantine-free entry into Italy.

The airline is piloting the scheme on flights between Rome and Atlanta from December, alongside Italian airline Alitalia. Passengers will have to take two COVID-19 tests before boarding the plane in the US, and another one upon arrival in Italy.

If the Delta flights are 60% full and the tests are combined with other protective measures, the risk of COVID-19 infection "should be nearly one in a million," said Henry Ting, MD, MBA, Chief Value Officer, Mayo Clinic.

E. Other news

1. An outbreak strikes a major PPE supplier

The New York Times reports that "A Malaysian company that makes disposable gloves used around the world for protection against the coronavirus has been hit by a major outbreak among its workers, many of them foreign laborers who live in crowded dormitories.

"The outbreak at 28 factories operated by the company, 'Top Glove Corporation', has infected more than 2,400 workers this month and driven one of Malaysia's biggest spikes in coronavirus cases since the pandemic began.

"Top Glove said it had stopped work at 20 factories in the hope of stemming the outbreak.

"The company makes disposable gloves and face masks and has ramped up production because of the pandemic. The United States and Europe are among its biggest customers.

"Most of Top Glove's workers come from developing countries in Asia — including Bangladesh, Myanmar and Nepal — and live and work in crowded conditions where the virus can easily spread."

2. Vaccination cards will be issued to everyone getting COVID-19 vaccine in the US

CNN reports that: "the Department of Defense has released the first images of a COVID-19 vaccination record card.

"'Vaccination cards will be used as the simplest way to keep track of COVID-19 shots,' said Dr. Kelly Moore, Associate Director of the Immunization Action Coalition, which is supporting frontline workers who will administer COVID-19 vaccinations.

"'Everyone will be issued a written card that they can put in their wallet that will tell them what they had and when their next dose is due,' Moore said. 'Let's do the simple, easy thing first. Everyone's going to get that.'

"Vaccination clinics will also be reporting to their state immunization registries what vaccine was given, so that, for example, an entity could run a query if it didn't know where a patient got a first dose."

COVID-19 Vaccination Record Card, Image: CNN

3. France leads the world in COVID-19 vaccine skepticism

France24 reports that a recent Ipsos study found that 54% of French people say they would get a COVID-19 vaccine if one were available, the lowest rate of any country surveyed.

"'The acceptance of vaccination in general is lower in France than abroad, and even lower for COVID,' Antoine Bristielle, a social sciences professor who has researched attitudes towards vaccines in France, told France24."

4. Public Health England ads a chapter on COVID-19 vaccines to its "Green Book"

"Immunisation against infectious disease," published by Public Health England, and popularly known as the "Green Book", provides the latest information on vaccinations and vaccination procedures for vaccine preventable infectious diseases in the UK.

A new chapter (14a) on COVID-19 vaccination has now been added to the "Green Book."