



### [3] Anti-virals, vaccines, convalescent plasma and monoclonal antibodies: an update

Contents:

- Vaccine update – featuring what we know on the Pfizer/BioNTech vaccine (p. 1)
- What if COVID is also a vascular disease and not just a pulmonary one? The potential benefits of anticoagulants, statins and ACE inhibitors for infected patients (p. 6)
- Anti-viral, immuno-modulator and corticosteroid update (p. 7)
- Convalescent plasma and monoclonal antibodies (p. 9)
- Additional information on anti-virals, vaccines and flu vaccine timetables (p. 11)

#### Vaccine update

The table below explains the general approaches that different vaccine companies are taking to provoke a lasting neutralizing antibody response<sup>1</sup>. **Important detail:** a lot of are companies are working on vaccine types #4 and #5, which are completely new approaches that have rarely been approved for use in developed countries. J&J’s Ebola vaccine received approval in July 2020 in Europe, the first approval of a vector vaccine.

Type	Method of provoking antibody response to SARS-CoV-2	Drug companies	Existing licensed vaccines
1	A live but weakened coronavirus that will infect cells and cause them to make viral proteins	Codagenix	Measles, yellow fever, mumps, smallpox, polio
2	Coronavirus proteins themselves, produced industrially in outside cell cultures, which will be recognized as foreign matter by the immune system	GlaxoSmithKline/Sanofi, Novavax*	Tetanus, pertussis, flu, shingles
3	A "killed" coronavirus that will get recognized as foreign matter by the immune system	Sinovac/Dynavax, SinoPharm	Polio (dev countries)
4	A different virus (human or ape adenovirus, measles, etc) that is engineered to include genetic components coding for the SARS-CoV-2 spike proteins, which causes the body to then produce them	CanSino, Oxford, J&J**, Merck/Themis	Ebola
5***	DNA or RNA that will be taken up by cells and will cause them to make coronavirus proteins	Moderna, Inovio, BioNTech/Pfizer	

\* Protein vaccines are not new, but the Novavax vaccine is combined with a proprietary adjuvant which has not been approved for use before

\*\* J&J’s adenoviral vector vaccine for Ebola was approved for use in Europe in July 2020, the first approval of a vector vaccine

\*\*\* There are no approved DNA or RNA vaccines yet, and neither have ever been tested before COVID in a large scale clinical trial

Source: J.P. Morgan Asset Management. September 2020.

<sup>1</sup> **Neutralizing antibodies** defend cells by binding to surface proteins of invading viruses, rendering them incapable of being infectious, or by attaching to receptor molecules on the cells themselves. The presence of neutralizing antibodies can be determined by cell culture tests, some of which measure the degree of plaque damage to healthy cultured cells caused by the virus (i.e., less plaque damage = more neutralization). Only a small subset of antibodies that bind to a virus are capable of neutralization, which is why these measurements are vital to Phase I studies to establish an epidemiological justification for proceeding to Phase II/III trials.

**What we know about the Pfizer/BioNTech vaccine:**

Pfizer/BioNTech developed four mRNA vaccine candidates, and selected one of them for Phase II/III trials in a large, diverse sample of 43,538 participants:

- Initial Phase III trial results showed the vaccine demonstrated greater than 90% efficacy compared to the control group in preventing COVID among vaccine participants 7 days after receiving a second dose of the vaccine
- Protection provided by the vaccine is expected to last about a year. More information is to come on whether the vaccine prevents severe cases and whether the vaccine prevents people from being infected with asymptomatic COVID-19
- Pfizer/BioNTech plans to request Emergency Use Authorization from the FDA by late November, once half of the patients in the study have been observed for any safety issues for at least two months following their second dose
- The FDA is estimated to take 2-4 weeks to approve an EUA filing, with vaccination to begin in high-risk groups by late December or early January 2021
- The main hurdle with Pfizer's vaccine is distribution given the vaccine must be stored at -94°F/-70°C and requires a booster shot 21 days after the first vaccination
- Distribution concerns aside, Pfizer announced they will produce 50 million doses globally by the end of the year, with 1.3 billion doses produced in 2021
- While Pfizer received no federal funding for its vaccine research and development, the company received \$1.95 billion from the U.S. government's Operation Warp Speed initiative to fund the large-scale manufacturing and distribution of 100 million doses of the vaccine in the U.S. The federal government will own the 100 million doses of the vaccine, which Pfizer will deliver upon receiving FDA EUA approval
- The positive efficacy results bode well for other vaccines in later stages of testing, for example those developed by Moderna, Oxford/Astrazeneca and J&J. More data on these trials are still to come



### **Select vaccine candidates, using pre-existing vaccine types 1, 2 and 3**

**Sanofi/GlaxoSmithKline** accelerated development of a vaccine based on delivery of SARS-CoV-2 spike proteins into humans, a process designed to engender an antibody response. Their existing Flu-Blok process (approved in 2013) would work as follows: take the genetic sequence of the SARS-CoV-2 virus, splice it into an insect virus and wait for cells from insects (moths, actually) to generate SARS-CoV-2 spike proteins, which are then injected into humans. GSK's "adjuvant" of organic chemicals is added to provoke an even stronger immune response (small amounts of aluminum have been used in vaccines since the 1930's for this reason). Sanofi/GSK initiated Phase I/II trials in September in 440 participants, with first results expected in December and initiation of Phase III trials before the end of the year. They expect to file for regulatory approval by June 2021.

- GSK is also using their adjuvant to develop a vaccine with Canada-based Medicago (partially owned by Philip Morris). Medicago's plant-based production platform uses plant leaves as bioreactors to produce spike proteins, an approach I wrote about in the Eye on the Market in March 2010. Tobacco plants have plenty of leaf biomass, quick growth patterns and an easily modifiable genetic blueprint

A **Novavax** press release summarized Phase I/II results of their vaccine candidate, which like GSK, involves the production of SARS-CoV-2 spike proteins which are injected to elicit an antibody response. The vaccine produced neutralizing antibodies in all non-placebo participants after a single dose, although antibody responses were 4x higher after two doses, and also stronger with the use of an adjuvant. The vaccine was generally well-tolerated and had a "reassuring safety profile" (no serious adverse side effects reported). A New England Journal of Medicine article included data showing Novavax vaccine antibody responses that were equal to or higher than those seen in convalescent plasma. The vaccine can be stored at 2-8 degrees Celsius, making it easier to store/distribute using existing infrastructure compared to mRNA vaccines.

**Sinovac/Dynavax** are partnering on development of an inactivated virus vaccine with an adjuvant. Over 90% of participants in Phase I/II trials showed neutralizing antibodies, with no data yet on antibody levels ("titers"); no severe side effects were reported; Phase III trials are underway in Brazil and Indonesia. The Chinese government has authorized its use in high-risk groups of government employees.

**SinoPharm (China)** is working on a vaccine candidate based on an inactivated virus. Phase I trials demonstrated only mild adverse reactions, and the company has now moved on to Phase II. SinoPharm moved forward with a dosage protocol based on the highest safety data and lowest antibody response of all the protocols examined in Phase I. As with most vaccine candidates, the dosage protocol requires a second booster shot.

## Select vaccine candidates, using new vaccine types 4 and 5

**Oxford University and AstraZeneca** are developing an adenovirus “vector” vaccine. Vector vaccines use a “Trojan Horse” approach to deliver genetic instructions to the body’s cells: the process involves the use a virus *different* from SARS-CoV-2 to “infect” cells with genetic coding instructions for SARS-CoV-2 spike proteins. The body produces these spike proteins, which provoke an antibody response. Oxford’s vector vaccine relies on a chimpanzee virus that is altered to be harmless to humans, and for which humans have no antibodies. Four million doses are expected to be distributed by year-end if clinical trials are successful. Some recent news:

- Phase I results were positive: over 1,000 patients enrolled. Of 35 participants whose antibody responses were fully analyzed in a paper released on July 20<sup>2</sup>, 90% produced neutralizing antibodies after a single shot (compared to other vaccines which require second booster shots). The presence of neutralizing antibodies rose to 100% after a second shot. T-cell responses were confirmed, and side effects were not alarming (some fever and headache). Enough grounds for cautious optimism as large Phase II/III trials began in September in the US, the UK, South Africa, and Brazil with 23,000 participants globally. Final results from the trials are expected by the end of the year with distribution to begin soon after (pending regulatory approval).
- Update: In September, AstraZeneca and Oxford paused trials in the US and UK due to spinal cord inflammation in a vaccine trial participant. Trials resumed in the UK in September and resumed in the US in October, after the FDA found the vaccine was not responsible for the illness.

**J&J** announced an ambitious timetable for a COVID-19 vaccine that uses the same technology platform as their experimental Ebola vaccine (which has just been approved for use in Europe). This platform is also used by J&J for its Zika, RSV, and HIV vaccine candidates currently in Phase II/III trials. J&J’s plans for emergency use production as early as spring 2021 with production of a billion doses per year. They have identified a lead vaccine candidate using the same vector approach as Oxford, but with a human adenovirus as the carrier instead of a chimpanzee virus. Initial Phase I/II data show that a single dose of the vaccine generated a strong antibody response, with 98% of participants testing positive for neutralizing antibodies 29 days after vaccination. The vaccine also elicited a strong t-cell response. Side effects were mild to moderate (fever, fatigue, headache, pain at injection site) and generally resolved themselves 1 or 2 days after vaccination. So far, J&J is one of the only companies moving forward with a vaccine that does not require a booster shot.

- Update: In early October, J&J paused its Phase III trials due to a stroke in a vaccine participant. A couple weeks later, J&J resumed the trial after finding no evidence that the vaccine triggered the stroke.

Like Oxford and J&J, **CanSino** is also developing a vector vaccine (AD5-nCov) which uses an altered live adenovirus to deliver the SARS-CoV-2 spike proteins into the body. Unlike Oxford and J&J, CanSino is using a virus that humans have already been exposed to. Vector vaccines have been used in human trials for HIV, influenza, Ebola, tuberculosis and malaria, but none have been approved yet.

- Past adenovirus efforts have run into challenges since if people have antibodies to the adenovirus being used as a delivery mechanism, such antibodies could interrupt the process of delivering the SARS-CoV-2 spike proteins as well. This appears to have happened in CanSino trials as well: immunity to CanSino’s vector is 50% in China, 30% in the US and 80% in India
- In CanSino early trials, most recipients reported flu-like symptoms (fever, muscle pain) but nothing more serious. Immune responses were complicated; all patients showed a neutralizing antibody response to SARS-CoV-2, but older patient antibody responses were weaker

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<sup>2</sup> “Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial”, Folegatti et al, University of Oxford, July 20, 2020.



**Moderna RNA vaccine.** This vaccine aims to engineer RNA to enter human cells which would then generate virus proteins. After completion of its Phase I study (which is primarily designed to assess tolerability rather than whether sufficient levels of antibodies will provide immunity), Moderna began Phase II trials with 600 participants and Phase III trials with 30,000 participants, and announced a partnership with Lonza to scale up production to 500 million to 1 billion per year.

- Phase I studies are primarily designed to establish safety rather than efficacy. The Phase I Moderna study showed that adverse events (fever, chills, pain at the injection site) were common after the second injection, which is not unusual, and there were no severe adverse safety events
  - Moderna also measured antibody responses in its 45 Phase I subjects. The response was modest after the first injection, but was several times higher after a second booster shot. Antibody responses after the booster shot were the same or higher than antibody levels in recovered patient convalescent plasma. After the booster shot, antibody responses in older adults (56-70 and 71+ age groups) were comparable to those seen in younger age groups, and 3-4x higher than those seen in patient convalescent plasma
- Antibody levels peaked at 6 weeks post-vaccine, and fell thereafter. However, the level of antibodies required to prevent COVID re-infection are not known, so the mere existence of an antibody decline over time does not negate Moderna's findings
- Antibodies are not the only part of the body's artillery against reinfection; T-cells play an important role as well (see section 5). T-cell responses reported in Moderna's Phase I study were lower than some observers were hoping for, but again, T-cell levels required for durable immunity have not been established yet
- If the purpose of the Phase I trial was to establish the basis for proceeding to Phase II/Phase III, Moderna achieved its goal. But the Phase I antibody responses are not a proxy for what will be measured in Phase II/III trials: the level and duration of immunity across a large population

**Merck** announced that they are buying Themis, a Vienna-based company working on a weakened form of the human measles virus as a vector for SARS-CoV-2 vaccine delivery. In September, a coronavirus vaccine candidate using this technology entered Phase I/II trials in Belgium with 260 participants. However, the study is not projected to be completed before 2022.

**China** has offered employees intending to travel overseas the opportunity to be inoculated with one of two COVID vaccines being developed by China National Biotec. However, there is not a lot of other information available at this time.

**Other vector vaccine candidates in very early stages of development:** Reithera (Italy), Altimune (US), Vaxart (US), CureVac (Germany), Imperial College (UK), Genexine (S Korea), Amms/Abogen/Walvax (China)



**Vaccine distribution and production objectives and challenges**

Since most vaccine companies received funding from Operation Warp Speed, **the US government will own and distribute initial supplies**. Given limited supplies upfront, initial vaccine distribution will likely be determined based on the CDC’s Advisory Committee on Immunization Practices (ACIP) prioritization (obviously, there is some overlap in these categories):

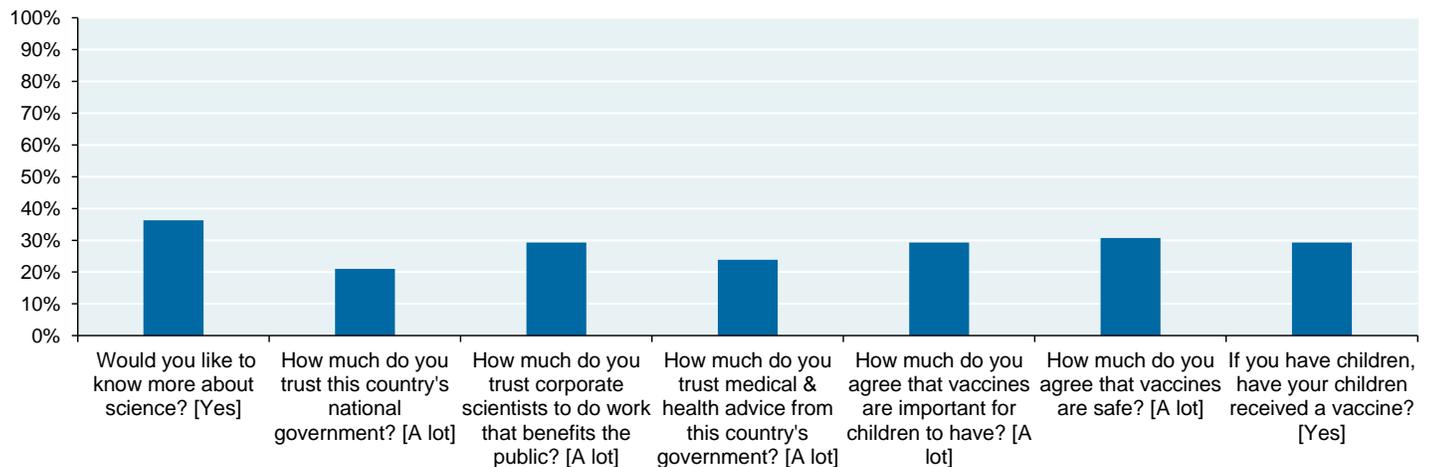
- 20 million healthcare workers
- 60 million essential service workers (food and & agriculture, transportation, education, energy, water/wastewater and law enforcement)
- 100 million individuals with “high risks” other than age (obesity, diabetes, chronic obstructive pulmonary disease (COPD), heart conditions, chronic kidney disease)
- 50 million people over age 65
- Then, the remaining general population

One major challenge to widespread vaccine adoption is the reluctance of many Americans to get vaccinated. A few key data points:

- 51% of US adults would get vaccinated with a COVID vaccine, according to a Pew Research poll. In a separate Suffolk University/USA Today survey, only 27% of US adults say they will get a COVID vaccine as soon as it becomes available
- This compares to 20% of Swiss respondents, 18% of French respondents, and 16% of British respondents who would refuse a vaccine, according to the Vaccine Confidence Project and a YouGov survey
- Despite the US leading the world in medical and biotech patents, and despite 22 of the top 40 universities for clinical research being located in the US (as per *US News & World Report*), Americans rank below most of the world on interest and trust in science, on trust in science advice from government agencies and on belief in the importance, safety and utilization of vaccines. See chart below for more details:

**How Americans rank globally on trust in science, medicine and vaccines**

Percentile rank, 144 countries



Source: Wellcome Trust/Gallup Global Science and Health Monitor. 2018.



### ***Some caveats and challenges for Chinese and Russian vaccine developers***

Chinese vaccine companies may have a tougher road if their goal is to develop and distribute a vaccine in the West:

- “Trials usually require tens of thousands of participants, and with the outbreak in China largely under control, companies are having to test their vaccines elsewhere...”
- Chinese vaccine-makers face other challenges, too. Their vaccines will probably face extra scrutiny, given the country’s opaque regulatory system and previous vaccine scandals, say scientists. In 2018, hundreds of thousands of children reportedly received defective diphtheria, tetanus and whooping cough vaccines...
- Some observers also question whether Chinese companies will be able to work at the promised speed, and with the precision that such trials require. And the fact that China was willing to approve CanSino’s vaccine for use in the military before Phase III trials were complete raised eyebrows. “The decision is political, and not scientific in nature. It doesn’t demonstrate anything on the potential efficacy of this vaccine,” says Marie-Paule Kieny, a vaccine researcher at INSERM, the French national health-research institute, in Paris”.

*“China’s coronavirus vaccines are leaping ahead but face challenges as virus wanes”*, Nature Magazine, July 31, 2020

As for the **Russian vaccine**, it comes from the Gamaleya Research Institute. Members of my science advisory group see the announcement as nothing more than a publicity stunt given that it was only in human trials for less than two months and has already received regulatory approval in Russia. There do not appear to be any data on clinical trial results; the only information we have is that the Russian Minister of Health claimed in a press release that the vaccine showed “high efficacy and safety” with no serious side effects. The vaccine candidate is a mixture of two adenovirus vectors (see page 4 for more details). The idea behind the vaccine doesn’t seem to out of the ordinary; it’s the development timelines that raise all the necessary questions.



## What if COVID is also a vascular disease and not just a pulmonary one?

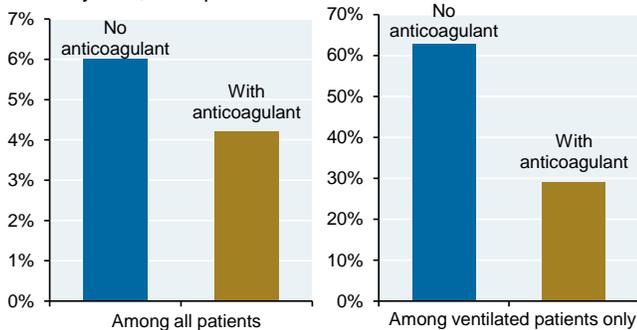
### The potential benefits of anticoagulants, statins and ACE inhibitors for infected patients

Before getting into anti-virals, it's important to mention that the understanding of COVID's impact on the body is still evolving. Healthcare professionals have noticed a range of unconnected vascular phenomena that aren't seen with SARS-CoV-1 or H1N1. Medical directors at Brigham and Women's Hospital Heart and Vascular Center in Boston believe that COVID is a "vasculotropic" disease, and that SARS-CoV-2 can infect endothelial cells that line the inside of blood vessels (these cells protect the cardiovascular system and release proteins that influence everything from blood clotting to the immune response)<sup>3</sup>:

- Damage to endothelial cells causes inflammation in blood vessels, which can cause accumulated plaque to rupture, causing a heart attack. Blood vessel damage could also explain why people with pre-existing conditions like high blood pressure, high cholesterol, diabetes, and heart disease are at a higher risk for severe complications from a virus that's supposed to just infect the lungs. All of those diseases cause endothelial cell damage, and additional damage in blood vessels caused by the infection could result in more severe complications and death
- This theory could also explain why ventilation often isn't enough to help patients breathe better. Moving air into the lungs via ventilation can help, but the exchange of oxygen and carbon dioxide in the blood is just as important to provide the rest of the body with oxygen; that requires healthy blood vessels in and around the lungs
- **If COVID is in fact a vascular disease, there are existing drugs that might help protect against endothelial cell damage.** Potential solutions could include ACE inhibitors and statins. In a New England Journal of Medicine study of 9,000 people with COVID, the use of statins and ACE inhibitors were linked to higher rates of survival<sup>4</sup>
- Similarly, a May report in the Journal of the American College of Cardiology analyzed medical records of 2,773 COVID-19 patients in NYC hospitals. The study was initiated after doctors realized that COVID can result in life-threatening blood clots. Notable findings: survival rates for 395 intubated patients treated with anticoagulants were 62% compared to 29% for those who were not<sup>5</sup>

#### Anticoagulant impact on COVID mortality rates

Mortality rate, % of patients



Source: New England Journal of Medicine, American College of Cardiology. '20.

<sup>3</sup> "Endothelial cell infection and endotheliitis in COVID-19", Z. Varga et al. Department of Pathology and Molecular Pathology, University Hospital Zurich. April 20, 2020

<sup>4</sup> "Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19", M. Mehra et al. Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, New England Journal of Medicine. May 8, 2020

<sup>5</sup> "Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19", I. Paranjpe et al. Journal of the American College of Cardiology. May 2020



## Update on the latest anti-viral, immunomodulator and corticosteroid trials underway

The “Solidarity” trial has been launched by the WHO to determine the effectiveness of Remdesivir, Chloroquine, Lopinavir-Ritonavir and Lopinavir-Ritonavir-Interferon Beta-1a. While such trials can take years to design and conduct, the Solidarity trial may reduce the timeline by 80% by conducting a single global clinical trial. Similar efforts include the “Recovery” trial in the UK and the “Remap-Cap” trial conducted by the University of Pittsburgh. In addition, the US NIH announced the “Accelerating COVID-19 Therapeutic Interventions and Vaccines” partnership (ACTIV), a collaborative effort with 16 pharmaceutical companies to prioritize vaccine and drug candidates and streamline clinical trials.

*Dexamethasone (corticosteroid).* Dexamethasone is a steroid which reduces inflammation (typically used to treat asthma and arthritis), and has now been shown to minimize effects of cytokine storms of severely infected patients. Compared to monoclonal antibodies and immune-modulators, they are **generally much cheaper and also readily available**. Results from the UK “Recovery” trial:

- Randomized, controlled trial of 2,104 patients in treatment group vs 4,321 in control group
- Reduced deaths from 40% to 28% in ventilated patients, and reduced the risk of death from 25% to 20% in patients receiving oxygen only; no benefit for patients not requiring respiratory support

*Remdesivir (anti-viral).* Modest benefits but only for patients in the earlier stages of disease.

- The New England Journal of Medicine recently published the final results of a 1000-patient randomized, double-blind controlled trial conducted by the NIH.<sup>6</sup> The study showed Remdesivir reduced time to recovery from 13-18 days in the control group to 9-11 days in the group receiving Remdesivir, and reduced mortality from 15.2% to 11.4%. The benefit of Remdesivir was more pronounced when given to patients earlier in the illness, for example to those receiving oxygen but not yet on a ventilator. While not a “miracle drug”, the NEJM study showed that Remdesivir may provide modest benefits for higher-risk patients when administered in early stages
- However, interim results from the WHO’s “Solidarity” trial concluded that Remdesivir has no benefit in reducing mortality, recovery time or ventilation based on a study of 2,700 hospitalized patients receiving it. In the WHO trials, both treatment and control groups had mortality rates of around 11%. Our sources point out that the NIH/NEJM study had fewer patients on oxygen and ventilation in its treatment group than the WHO study, suggesting the NIH results could be more similar to the WHO study if both treatment groups had the same characteristics (i.e., the NIH/NEJM study concentrated on less sick patients).
- Remdesivir is given intravenously rather than orally, so it would only be used in hospital settings, which implies a narrower healthcare impact than drugs that can be delivered on an outpatient basis. Gilead is currently working on an inhalable Remdesivir treatment and subcutaneous injections as well, which would broaden the scope of potential uses

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<sup>6</sup> “Remdesivir for the Treatment of COVID-19 – Final Report”, Beigel et al. National Institutes of Health, New England Journal of Medicine. October 8, 2020



*Interferon beta (anti-viral)*. In double-blind placebo controlled trials with 50 patients, nebulized interferon reduced ventilation by 80%. Patients were 2-3x more likely to resume everyday activities, and average time in hospitals was reduced by a third.

*Favipiravir (anti-viral)*. Fuji has begun Phase III trials in Japan, after reported clinical trials in China were successful. This drug is an existing flu treatment first approved in Japan in 2014. There are some obscure news reports coming out of Russia indicating successful outcomes in early trials, but hard data is scarce.

*Tocilizumab (immunomodulator)*. This FDA-approved drug treats rheumatoid arthritis and cytokine release syndrome. A French study showed that Tocilizumab reduced deaths and the need for ventilators, and in China, Tocilizumab is included in COVID treatment guidelines. In June 2020, a U. Michigan Tocilizumab trial found a 45% lower likelihood of death compared to control group, a higher % of discharged patients and hospitalized patients not requiring ventilation; and appears to dampen “cytokine storm” severity<sup>7</sup>. The study also noted that Tocilizumab suppresses the immune system, which increases risk of infection. The treatment group was twice as likely to develop a further lung infection (generally bacterial pneumonia).

In contrast, a study from Italy showed that Tocilizumab failed to help patients in early stages of the virus. Roche/Genentech (developer of Tocilizumab/Actemra) announced that it had no effect on clinical status or mortality. In a 452-person trial, 19.7% of patients died in the treatment group vs 19.4% in the control group; the primary endpoint (difference in clinical status) was not met; and hospital discharge was shorter in treatment group (20 days) vs control group (28 days). Furthermore, the safety data monitoring committee from the French trial resigned over disagreements about how the trial was characterized.

*Ruxolitinib (immunomodulator)*. Designed to treat individuals suffering from a cytokine storm. Currently available in the US under the emergency access program, and now entering Phase III trials outside the US.

*Ravulizumab-cwbz (immunomodulator)*. Phase III trials to be conducted in May 2020 in COVID patients with severe pneumonia or acute respiratory distress syndrome. Preclinical data demonstrated reduced lung inflammation in animals with pneumonia.

*Apilimod (immunomodulator)*. We’re keeping an eye on this drug since it showed promise inhibiting COVID in vitro as per a recent *Nature* paper that analyzed 12,000 possible compounds. AI Therapeutics and Yale University announced a randomized, double-blind placebo-controlled Phase II trial with 142 patients. Like other immunomodulators, Apilimod may impair immune functions even as it protects against the virus, so that will be an important outcome to monitor from future trials.

*Other anti-virals in Phase II/III trials: Merck/Ridgeback Therapeutics (MK-4482)*

*Chloroquine/hydroxychloroquine (anti-viral)*: on April 19, an NIH panel recommended against the use of HCQ and azithromycin to treat COVID patients. In June, the US Food and Drug Administration revoked its emergency use authorization for hydroxychloroquine and chloroquine for treatment of Covid-19. A **case study** in bad science, bad medicine, bad reporting and according to some accounts, bad behavior as well<sup>8</sup>.

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<sup>7</sup> Some COVID-19 fatalities experienced **sudden multiple organ failure**. Doctors don’t know yet if that’s because of the viral infection itself, or because of immune system damage caused by a “cytokine storm”, which is a large, rapid release of cytokines into the blood as a result of viral infections or immunotherapy. From oncology doctors at Washington University in St. Louis: “we believe that there is increasing evidence that cytokine storm syndrome is occurring co-incident with the progressive pneumonia and in severe cases may be driving the pathology and increasing the risk of death above and beyond what would be expected by the viral infection by itself”.

<sup>8</sup> <https://blogs.sciencemag.org/pipeline/archives/2020/03/29/more-on-chloroquine-azithromycin-and-on-dr-raoult>



## **Convalescent plasma and monoclonal antibody therapy**

Convalescent plasma refers to virus-neutralizing antibodies harvested from recovered patients to treat infected patients and vulnerable populations. It was used during the Victorian era before antibiotics to treat meningitis & pneumonia by injecting bacteria into horses and harvesting horse serum. Convalescent plasma is currently used to treat immuno-deficient individuals against measles and mumps, and was successfully used to treat patients during both SARS in 2002 and the 2009-2010 H1N1 influenza pandemic. **Like antivirals and vaccines, convalescent plasma applied to COVID-19 will require clinical trials to demonstrate both safety and efficacy.**

Trump announced Emergency Use Authorization (EUA) for convalescent plasma to expand access despite the lack of rigorous scientific evaluation. In contrast, the EUA for Remdesivir took place only after randomized controlled trial results were available.

**The details:** the Mayo Clinic study reported that mortality rates were lower for patients given convalescent plasma within 3 days of COVID diagnosis compared to patients receiving it after 3 days (7-day mortality rates 8.7% vs 11.9%, 30-day mortality rates 21.6% vs 26.7%). But in the absence of a randomized controlled trial, it's hard to draw firm conclusions since we don't know anything about patient characteristics, dosages, treatment settings, etc. Such "observational studies" were the basis for media speculation a few months ago on hydroxychloroquine (HCQ). There's probably more benefit to convalescent plasma, since it has been used for over 100 years to treat infectious disease. But randomized controlled trials are the only way to conclusively prove efficacy, check for adverse outcomes and determine the optimal dosage regime. It's disappointing that over 70,000 patients have been treated with convalescent plasma in the US with no scientifically rigorous control data produced yet.

Fauci and the director of the NIH discouraged the FDA from issuing an EUA for convalescent plasma (citing concerns over weak data), but the FDA issued it anyway. Yesterday there was a **completely embarrassing fiasco** in which the FDA Commissioner admitted misrepresenting the study results (after being chided by a prior FDA commissioner), and main authors who worked on the study said they had **no idea** where the 35% mortality improvement statistic cited by the White House came from. From Derek Lowe at Translational Medicine:

"A big effect of this plasma announcement, as far as I can tell, was to sow doubt about what the administration considers a breakthrough and what its intentions are about authorizing a vaccine before the November election... the President himself, in his Sunday morning Twitter duties, accused the so-called "deep state" at the FDA of literally dragging their feet in trying to not get a vaccine before the election. Which was a suggestion I found false, infuriating, and as harmful as such a short statement could be to the chances of rolling out a vaccine in an orderly and medically justified way."

Rockefeller University released a study on the dynamics of convalescent plasma antibodies. They found that most donors do not have high levels of antibodies, and that for one third of donors, neutralizing antibodies were undetectable, rendering their plasma contributions worthless. Furthermore, only 1% of donors showed "elite" high-level neutralizing antibodies. **However, elite donor antibodies are sufficiently powerful** so that even when diluted 1000-fold, the plasma can still neutralize the virus and last for several months. As a result, Rockefeller scientists are trying to clone these elite antibodies

This approach would not confer long-term immunity, and would at best provide temporary benefits. However, that might be enough when dealing with infection over a short period. Convalescent plasma might be difficult to scale and runs the risk of transmission of other undiscovered viruses as well



Like convalescent plasma, **monoclonal antibody therapy** (mAb) involves infusion of antibodies with the goal of preventing infected people becoming ill, and preventing the ill from dying. How do mAb work? They are engineered with the goal of being more precise than convalescent plasma: neutralize the infectivity of SARS-CoV-2 by binding specifically to the spike protein that enables it to enter human cells. A likely treatment regimen could contain 2 or 3 different mAbs. While convalescent plasma relies on antibodies harvested from recovered individuals, mAb can be harvested from recovered humans, from mice genetically modified to have the immune system of a human being, via genetic engineering or from advanced cell cultures. While mAb are used to treat cancer and autoimmune diseases, few have been developed for infectious diseases. However, mAb worked against Ebola, several companies are entering human clinical mAb trials:

- **Regeneron** (REGN-COV2). In July, Regeneron initiated Phase III trials in 2,000 people to evaluate mAb ability to prevent infection among uninfected people who have had close exposure to a COVID-19 patient (preventative). Regeneron is also testing mAb in Phase II/III trials for treatment of hospitalized and non-hospitalized COVID patients (treatment). Initial results from the Phase II/III trial of 800 non-hospitalized participants found that the treatment reduced the viral load by 10-fold in the treatment group compared to the placebo, and reduced COVID-related medical visits by 57% through day 29. In participants with at least one risk factor (e.g. age, higher viral load or pre-existing conditions) the treatment reduced medical visits by 72% compared to the placebo group. Results were similar in both the lower and higher dosage level, so Regeneron is asking the FDA for Emergency Use Authorization for the lower dose. In August, Regeneron announced collaboration with Roche to develop, manufacture and distribute its mAb
  - Update: In November, Regeneron paused its trial in hospitalized patients receiving high-flow oxygen or ventilation due to a potential safety concern and what the company called an “unfavorable risk/benefit profile”. However, Regeneron is continuing trials of its monoclonal antibody in less severe hospitalized patients, as well as its study on non-hospitalized patients.
- **Regeneron/Sanofi** (Kevzara). US trial was stopped, but a separate Sanofi-led trial is ongoing outside of the US in hospitalized patients with severe and critical COVID. Companies expect to report results of ex-US trial in Q3 2020
- **Eli Lilly/AbCellera** (LY-COV55). Completed Phase I study of hospitalized patients (40 participants), began a Phase II study in people recently diagnosed with COVID-19 (450 participants) and began a Phase III study for prevention of COVID in residents and staff at long-term care facilities (2,400 participants). Two additional trials led by the NIH were also initiated in August: a Phase II trial studying people recently diagnosed with COVID-19 (220 participants) and a Phase III trial on hospitalized patients (300 participants). Based on Phase I results, Eli Lilly reports that its mAb are well tolerated at all doses tested and that no drug-related severe adverse events were observed. Recent data from the Phase II/III trials in 450 recently diagnosed individuals showed that mAb treatment reduced hospitalization rates to 1.7% compared to 6% in the placebo group. However, the study found that only the middle dosage level led to a decline in the viral load, while the other doses showed no benefit compared to the placebo group. Regardless, Eli Lilly is asking for Emergency Use Authorization for the smallest dose of its treatment. Our sources tell us that these results are disappointing to say the least.
  - Update: In October, the NIH-led Phase III trial of Eli Lilly’s monoclonal antibody treatment in hospitalized patients was halted because the study did not find any clinical benefit in patients receiving treatment. However, the company is continuing trials in recently diagnosed COVID patients and in at-risk populations (as a preventative treatment), with the hope that the treatment may provide a benefit for people when administered in early stages.

**The advantages of mAb:** probably available more quickly than a vaccine, and can be used both as acute therapy for COVID patients and as a prophylactic for front-line health care workers. The disadvantages: higher cost than vaccines; harder to produce at scale since a large dose of recombinant proteins might be needed since your body isn’t making them for you; and temporary. While a vaccine is preferable given its ability to immediately halt the spread of the disease, mAb may be an important treatment regimen for sick patients and front line workers until a vaccine can be realized.



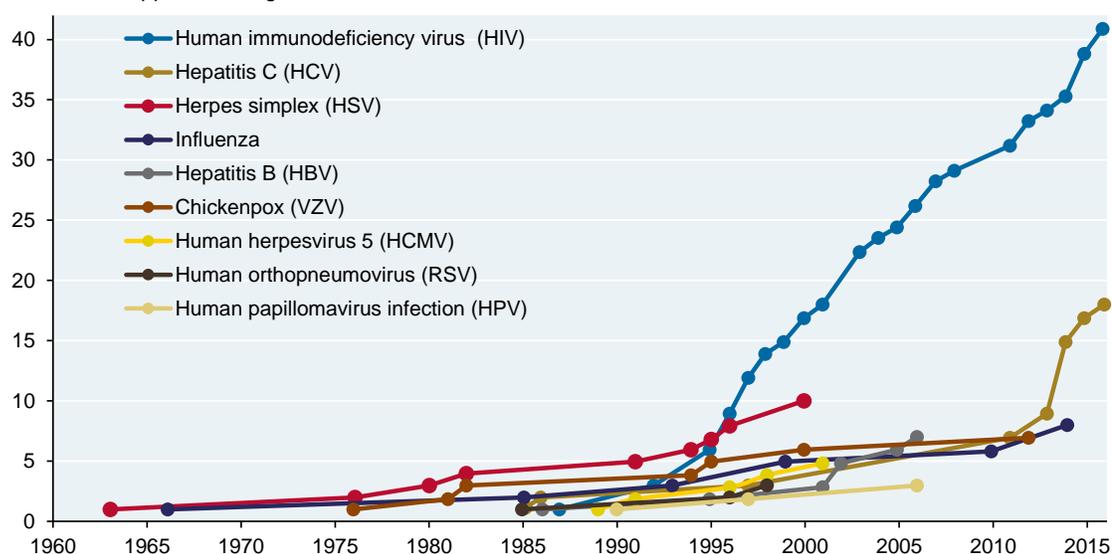
## Additional information on anti-virals, vaccines and flu vaccine timelines

Some challenges to keep in mind on anti-virals:

- Viruses reproduce by hijacking the host's own biological machinery. Having very few of their own enzymes and proteins, they typically present few opportunities for specific drugs to target
- That might explain why **only 90 anti-virals were ever approved for final use** from 1963 to 2016 out of the thousands proposed in scientific literature (see chart below). And even this number overstates reality since some single agents are counted more than once for each virus they cover, several have been withdrawn due to lack of efficacy and others are rarely prescribed at all
- This might also explain the lack of anti-viral success against **Ebola**, for which numerous therapies were tested (chloroquine, favipiravir, brincidofovir, monoclonal antibodies, remdesivir and convalescent plasma). Ultimately, none were effective despite some showing success in non-human primates

### History of antiviral drug development

Number of approved drugs



Source: De Clercq and Li, "Approved anti-viral drugs over the past 50 years", Clinical Microbiology Reviews. June 2016.

While the genetic sequence of SARS-CoV-2 and its various mutations were identified in record time, a **COVID-19 vaccine is not a foregone conclusion**. The world is still searching for an HIV vaccine; in 2020, another large-scale HIV vaccine study failed to show efficacy, and no vaccine has ever been developed for any human coronavirus.

Scientists have to figure out which part of the SARS-CoV-2 virus to target for the vaccine. Its "spike protein" is being used by many candidates, but could result in *worse* outcomes due to a phenomenon known as "antibody dependent enhancement" (**ADE**). In ADE, virus clearance pathways typically used by the body's immune system are hijacked by the virus and end up *enhancing* viral infection instead. That's why human Phase II/III clinical trials are vital to the vaccine approval process. The **good news** is that two front-running vaccine candidates (Oxford and Sinovac) see no sign of ADE in animal studies .

In recent decades, it has generally taken several years for vaccines to be tested and approved. However, this timeline has been improving. It took 20 months for a SARS vaccine to reach human testing (it was never completed since the virus was eradicated first through non-pharmaceutical intervention), it took only six months to move to testing for Zika virus, and Moderna entered coronavirus testing in humans for its mRNA-1273 vaccine in just two months (animal testing was skipped).



**Phase II trials** typically focus on efficacy in different populations (age, gender, pre-existing health conditions and range of medications being taken), all with different dosing schedules, and are designed to set the stage for larger Phase III runs. Some steps can be accelerated by running a lot of simultaneous trials instead of sequential ones, but not all of them.

**Scaling up vaccine production can be challenging.** Even for influenza vaccines, for which many production facilities exist, demand in the case of a pandemic could exceed production capacity. Live-attenuated virus, inactivated virus, recombinant protein, and nucleic acid vaccines all entail completely different production and distribution methods; a commitment by the Gates Foundation to fund 7 vaccine factories at once could help accelerate the timetable.

**Comparisons to flu vaccine timelines.** Most flu strains are based on combinations of H and N proteins. For example, 1918 was H1N1, 1968 was H3N2, and 1976 and 2009 were both H1N1 again. Flu vaccine companies have decades of experience in determining which combinations will be in effect each season, and in preparing large quantities of vaccines without having to do a lot of Phase I studies to test for safety. There's a seasonal aspect to it: dominant flu strains in the Southern Hemisphere are used to provide vaccines for the Northern Hemisphere. Every once in a while, flu vaccine companies miss the target, as in 2014-2015 ([www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm](http://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm)).

In contrast, scientists don't have decades of experience with this coronavirus. Its proteins have probably been identified but that still has to be proven with a vaccine, and no one knows how protective immunity will be even if a vaccine is developed. Even more importantly, a lot of leading vaccine candidates are using new technology whose vaccines have never been approved for use before in any developed country. As a result, COVID vaccines will require extensive testing that typical flu vaccines do not require, even when the flu strains mutate. Bottom line: 4-6 month flu vaccine timelines do not appear very relevant for COVID.



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