



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

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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 new approaches that have now been approved for use for the very first time. 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 Attenuated	A live but weakened coronavirus that will infect cells and cause them to make viral proteins	Codagenix	Measles, yellow fever, mumps, smallpox, polio
2 Recombinant	Recombinant coronavirus proteins, produced industrially in outside cell cultures, which are recognized as foreign matter by the immune system	GlaxoSmithKline/Sanofi, Novavax*	Tetanus, pertussis, flu, shingles
3 Attenuated	A "killed" coronavirus that will get recognized as foreign matter by the immune system	Sinovac/Dynavax, SinoPharm	Polio (dev countries)
4 Genetic (vector vaccines)	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 Genetic	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

Source: J.P. Morgan Asset Management. 2021.

<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 plaque damage to healthy cultured cells caused by the virus (i.e., less plaque damage = more neutralization).

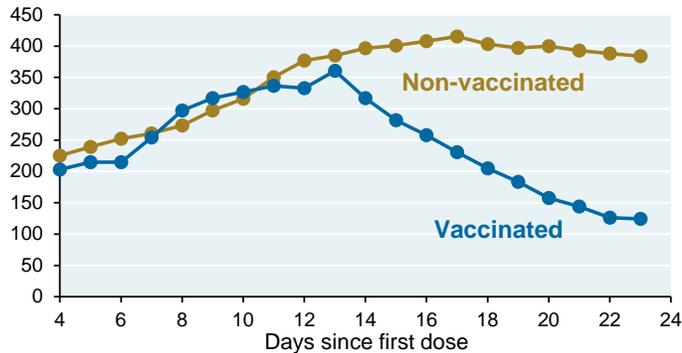


**Breaking news: preliminary Pfizer vaccine efficacy measured in Israel**

Israel has vaccinated ~30% of its population, and there’s positive preliminary data on vaccine efficacy in one of the most important cohorts: people over age 60. A group of 480,000 people insured by Maccabi Healthcare aged 60+ were analyzed as vaccinations were provided to 50,000 of them. Infection rates continued to rise in the unvaccinated group but fell by 2/3 in the vaccinated group, and that’s before most received their booster shot. Even more importantly, new COVID hospitalization admissions fell sharply in the vaccinated group once vaccine antibodies kicked in, which is typically around day #14.

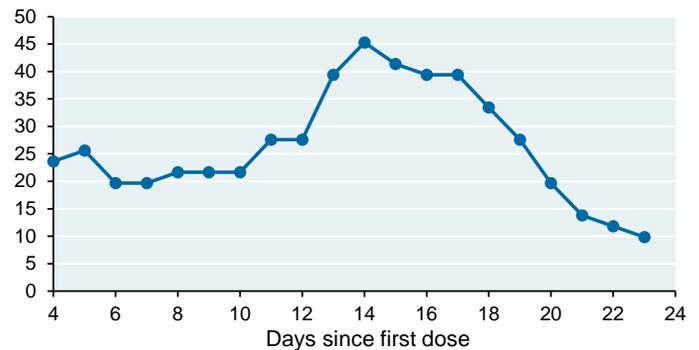
**Infections among Israeli individuals over age 60**

7-day average new daily infections per mm people



Source: KSM Maccabi Research and Innovation Center, JPMAM. January 2021. Includes 480,000 Maccabi healthcare members over the age of 60.

**Hospitalizations among vaccinated Israeli individuals over age 60, 7-day average new daily hospitalizations per mm people**



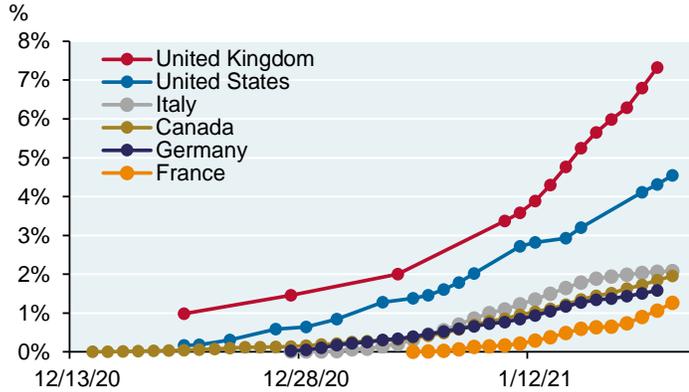
Source: KSM Maccabi Research and Innovation Center, JPMAM. January 2021. Includes 480,000 Maccabi healthcare members over the age of 60.



**Vaccine update by country and US state<sup>2</sup>**

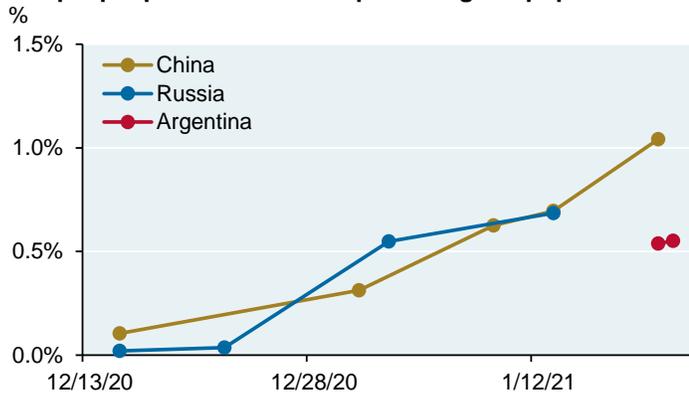
**Country update**

**Unique people vaccinated as percentage of population**



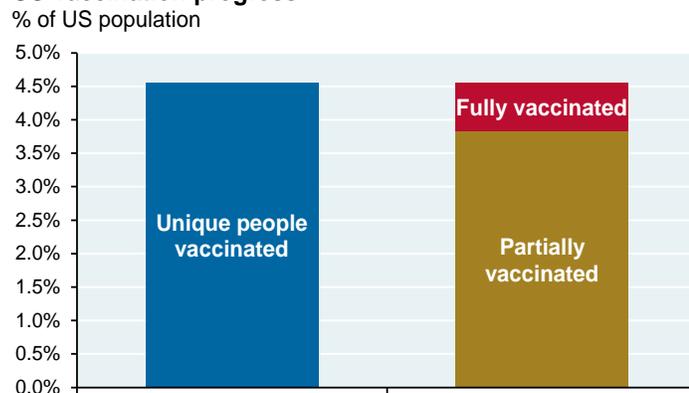
Source: OWID, JPMAM. January 22, 2021.

**Unique people vaccinated as percentage of population**



Source: OWID, JPMAM. January 22, 2021.

**US vaccination progress**



Source: OWID, JPMAM. January 21, 2021.

	Unique people vaccinated	% of pop.
Argentina	249,372	0.6%
Austria	166,956	1.9%
Bahrain	144,130	8.5%
Belgium	141,758	1.2%
Brazil	193,699	0.1%
Bulgaria	20,719	0.3%
Canada	738,864	2.0%
Chile	54,458	0.3%
China	15,000,000	1.0%
Costa Rica	24,804	0.5%
Croatia	54,304	1.3%
Denmark	178,969	3.1%
Estonia	21,985	1.7%
Finland	78,300	1.4%
France	823,567	1.3%
Germany	1,324,091	1.6%
Greece	121,109	1.2%
Hungary	134,554	1.4%
India	1,043,534	0.1%
Ireland	121,900	2.5%
Israel	2,441,379	28.2%
Italy	1,257,118	2.1%
Lithuania	56,358	2.1%
Mexico	534,317	0.4%
Netherlands	100,000	0.6%
Norway	63,727	1.2%
Poland	566,793	1.5%
Portugal	106,000	1.0%
Romania	338,252	1.8%
Russia	1,000,000	0.7%
Saudi Arabia	295,530	0.8%
Singapore	6,200	0.1%
Spain	1,054,245	2.3%
Sweden	146,775	1.5%
Switzerland	110,000	1.3%
United Arab Emirates	1,996,069	20.2%
United Kingdom	4,973,248	7.3%
United States	15,053,257	4.5%

Source: OWID, JPMAM. January 22, 2021.

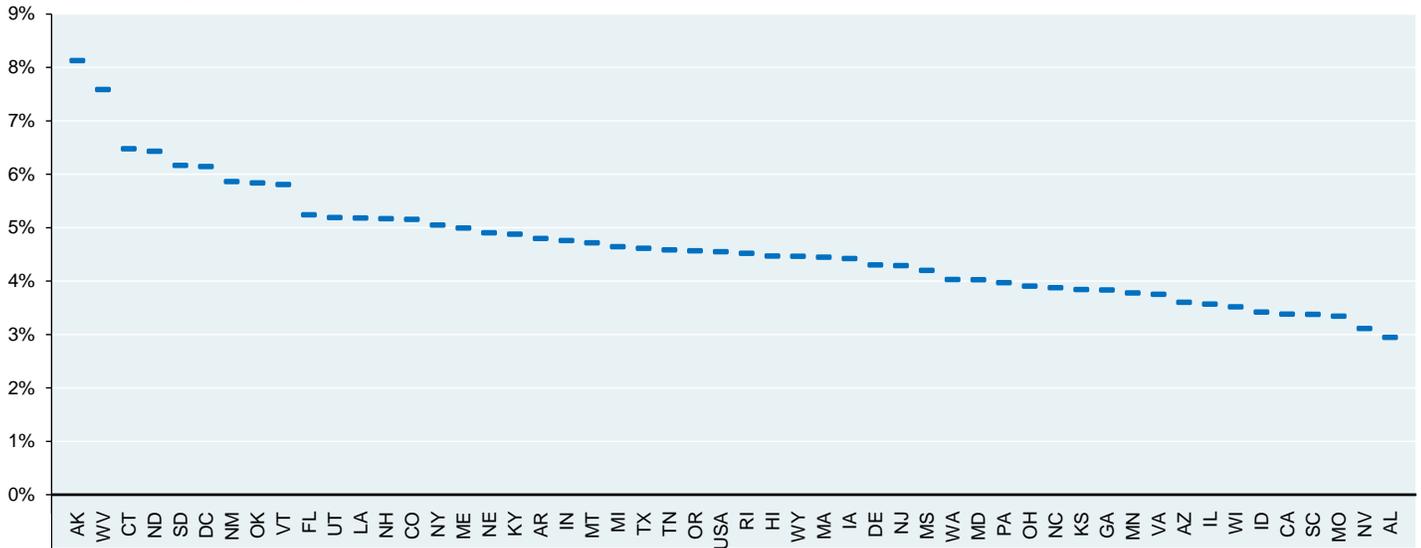
<sup>2</sup> Vaccination data can indicate the number of people that have been vaccinated at all (either with one or two doses), or it can indicate the total number of vaccinations given. The latter number will always be higher because it includes people who received multiple doses. Unless stated otherwise, we show people that have been vaccinated rather than doses.



**US state update**

**Percent of population that received at least one vaccination**

Sorted in descending order by highest vaccination rate

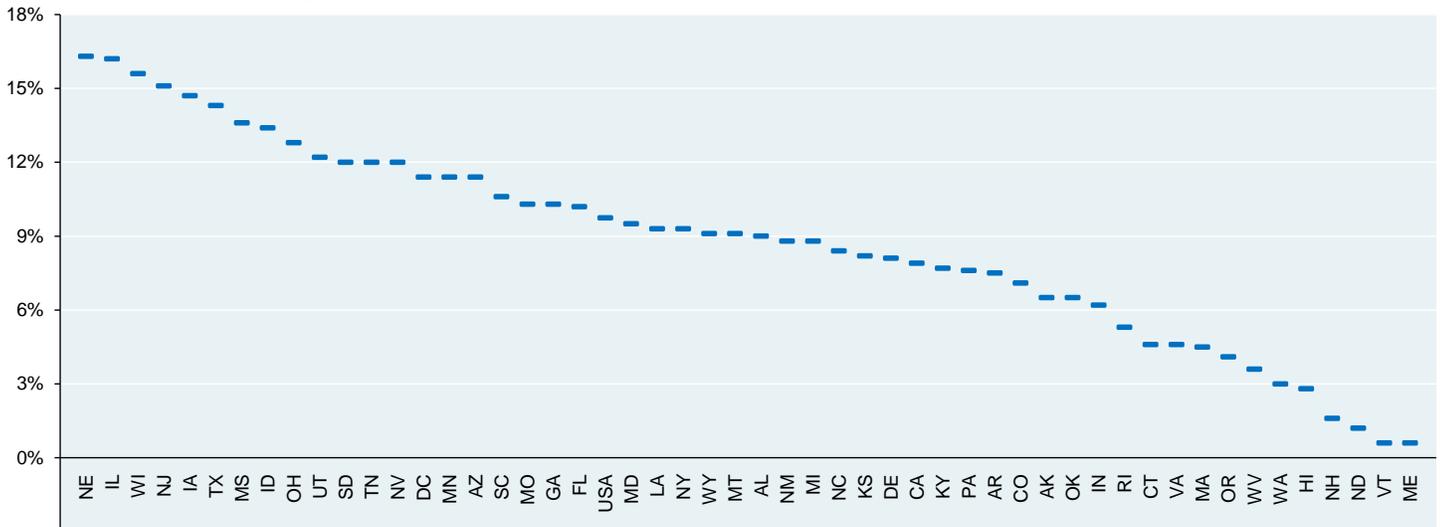


Source: OWID, JPMAM. January 21, 2021.

Estimated COVID antibody prevalence is based on random samples taken by the CDC. To date, prevalence numbers shown below mostly reflect the antibodies from COVID survivors. Over time, vaccinated individuals may show up in here as well since the CDC does not have a sampling process that excludes them. We consider these CDC estimates to be very imprecise since they only involve samples of 900 – 1,000 people each time.

**Estimated COVID antibody prevalence by state**

Sorted in descending order by highest seroprevalence levels



Source: CDC Nationwide Commercial Laboratory Seroprevalence Survey. November 29, 2020.



**Vaccine update: estimated timelines and coverage**

The table shows estimates of vaccine coverage for vulnerable populations (people over 60, medical workers and those with severe co-morbidities) and for total populations by quarter. They reflect vaccine purchases by country based on firm orders and options, vaccine approval timelines and vaccine efficacy. These are very rough estimates that can be derailed by production shortages, safety events and distribution hurdles related to storage and other logistics (i.e. contaminated batches).

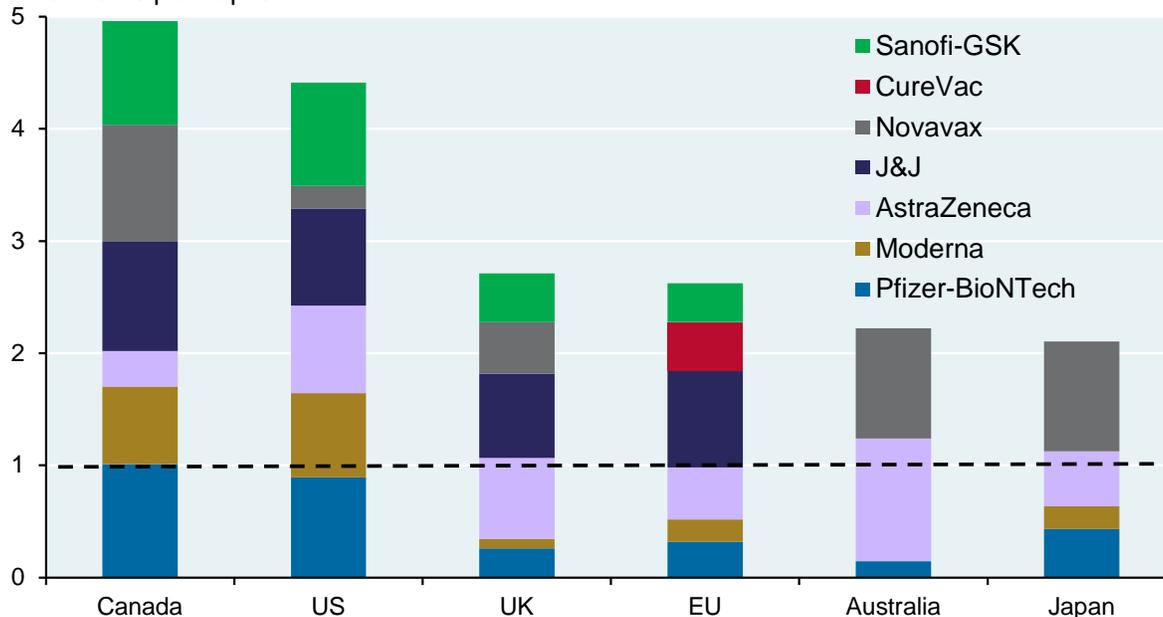
	Vaccine Availability Multiple of Vulnerable Population					Vaccine Availability Multiple of Total Population			
	% of total	Q1 2021	Q2 2021	Q3 2021	Q4 2021	Q1 2021	Q2 2021	Q3 2021	Q4 2021
Australia	26%	0.3x	2.2x	4.1x	6.0x	0.1x	0.6x	1.1x	1.6x
Canada	28%	1.1x	3.0x	6.7x	10.6x	0.3x	0.8x	1.9x	3.0x
France	30%	0.5x	1.3x	3.1x	4.7x	0.1x	0.4x	0.9x	1.4x
Germany	33%	0.4x	1.2x	2.8x	4.2x	0.1x	0.4x	0.9x	1.4x
Japan	38%	0.6x	2.0x	2.9x	3.6x	0.2x	0.7x	1.1x	1.4x
South Korea	24%	0.6x	1.4x	2.0x	2.4x	0.1x	0.3x	0.5x	0.6x
Spain	29%	0.5x	1.3x	3.2x	4.9x	0.1x	0.4x	0.9x	1.4x
United Kingdom	29%	0.5x	1.7x	3.2x	4.6x	0.1x	0.5x	0.9x	1.3x
United States	30%	0.6x	1.5x	3.5x	6.2x	0.2x	0.4x	1.0x	1.8x

Source: Bridgewater. December 2020.

Here’s an estimated breakdown of total vaccine capacity by country, broken down by vaccine type. Note that the total capacity estimates in the chart are quite different from the table. This is due to a large number of divergent assumptions, including on the question of efficacy. However, both tell the same basic story: developed countries are expected to be able to vaccinate their populations in full by the end of 2021, with substantial coverage of at-risk populations much earlier in the year.

**Total estimated vaccine capacity by country and type**

Treatments per capita



Source: Goldman Sachs. December 2020.



## **mRNA vaccines: how they work, who makes them and Phase III results (type 5)**

### **How do mRNA vaccines work?**

“Vaccines train the immune system to recognize the disease-causing part of a virus. Vaccines traditionally contain either weakened viruses or purified signature proteins of the virus. But an mRNA vaccine is different, because rather than having the viral protein injected, a person receives genetic material (mRNA) that encodes the viral protein. When these genetic instructions are injected into the upper arm, the muscle cells translate them to make the viral protein directly in the body.

This approach mimics what the SARS-CoV-2 does in nature, but the vaccine mRNA codes only for the critical fragment of the viral protein. This gives the immune system a preview of what the real virus looks like without causing disease. This preview gives the immune system time to design powerful antibodies that can neutralize the real virus if the individual is ever infected.”<sup>3</sup>

### **What does vaccine efficacy mean?**

Phase III results from Moderna and Pfizer trials point to 80%-90% “efficacy”, which measures the difference between incidence of disease in placebo (P) and vaccinated (V) cohorts. In other words, efficacy is computed as  $(P-V)/P$ . While the residual number of vaccinated patients still got COVID, in trials conducted to date none of these people died or required hospitalization/ supplemental oxygenation. In other words, vaccines appeared to substantially mitigate COVID severity even when people still became sick.

However, Peter Doshi at the British Medical Journal has raised questions about the efficacy numbers using Pfizer as an example. There were 43,538 participants in the Pfizer trials. Pfizer reported 170 PCR-confirmed covid-19 cases, split 8 to 162 between vaccine and placebo groups. Doshi writes that these confirmed COVID cases were dwarfed by “suspected” COVID cases that were not PCR-confirmed. According to the FDA’s report on Pfizer, there were 3,410 cases of suspected but unconfirmed covid-19 (1,594 in the vaccine group and 1,816 in the placebo group). In the extreme case, if these were all really COVID cases, Pfizer efficacy would drop to 25%-30%. As a reminder, PCR sensitivity (the ability of a PCR test to identify disease in an infected person) ranges from 87.5%-100%; meaning that such tests can produce false negatives. To be clear, Doshi was raising questions and *not* saying that Pfizer’s efficacy rate is that low; but in the absence of more data disclosure (Pfizer will only make all of its data public 24 months after study completion), such uncertainty may remain.

### **Will the vaccine work against the new COVID mutations?**

New research suggests that Pfizer’s COVID-19 vaccine can protect against a mutation found in two highly contagious variants of the coronavirus that erupted in Britain and South Africa. Pfizer used blood samples from 20 people who received the vaccine, and their antibodies successfully fended off the new variant in vitro. This is a preliminary finding but reassuring nonetheless; most vaccines are designed to recognize multiple parts of the virus spike protein, making it unlikely that a single mutation could be enough to block them. Furthermore, British scientists have said that the variant found in the UK also seemed to be susceptible to vaccines.

There are still more mutations to test, one of which also originated in South Africa (the E484 mutation). There are concerns that the degree of this mutation relative to the original virus may reduce the efficacy of recently approved vaccines. Testing is underway and if existing vaccines do not provide high levels of efficacy, new rounds of vaccine research, testing and production will be required.

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<sup>3</sup> Sanjay Mishra, Vanderbilt University Medical Center



### What about side effects?

On vaccine history, the CDC maintains a website of historical vaccine safety concerns and outcomes starting in 1955 which you can access here: <https://www.cdc.gov/vaccinesafety/concerns/concerns-history.html>.

The CDC also maintains a database of self-reported adverse events from all vaccines (VAERS). We found that incidence of hospitalization and emergency room visits after COVID vaccines is higher than for the flu, but still very low on an absolute basis and similar to other vaccines and medications. The challenge with this data is that it is not “causal”; adverse events need more analysis to determine if they were actually caused by the vaccine or not. But in the spirit of full disclosure, here’s the data we compiled using VAERS data for 2020.

#### VACCINE SIDE EFFECTS: COVID vs INFLUENZA

Side Effect	COVID			INFLU		
	#	Freq	# per mm	#	Freq	# per mm
Hospitalized	97	0.0035%	34.6	67	0.0000%	0.4
Disability	5	0.0002%	1.8	78	0.0000%	0.4
Dr office visit	464	0.0166%	165.7	283	0.0002%	1.6
ER visit	875	0.0313%	312.5	141	0.0001%	0.8

Doses administered as of 12/31/2020      2,800,000      174,500,000

Sources: CDC Vaccine Adverse Event Reporting System, CDC Vaccine Supply & Distribution

Other vaccine adverse event data:

- Smallpox: 14-52 life-threatening events per mm, encephalitis 12 per mm
- Shingles: 40 serious adverse events per mm
- Measles, mumps, rubella: febrile seizure 850 per mm

### Would an mRNA vaccine alter my DNA?

Scientific consensus: No. Simplified answer: “Think of RNA as a bunch of messages. At any moment a human cell has 5,000+ different RNA messages, and they are all temporary messages, like post-it notes that get torn up by the cells within minutes or hours after being read. Or, actually, like snapchat messages that expire. Temporary messages instructing cells to make one viral protein temporarily, so that it provokes an antibody response”.<sup>4</sup>

Technical answer: mRNA is downstream of the DNA genetic material and all of its editing and replication. Just like the coronavirus itself is not altering your genetic material (it’s also made of RNA), neither would the Pfizer or Moderna vaccines. In contrast, HIV is also a single-stranded RNA virus but is also a “retrovirus”, meaning that it carries RNA to make reverse transcriptase, which it then uses to make DNA from its RNA, and subsequently integrate itself into the host genome. But this is not the case with the coronavirus or the mRNA vaccines being developed to treat it.<sup>5</sup>

### What about DNA messenger vaccines?

RNA vaccines have advantages over DNA: their payloads both enter human cells, but DNA vaccines have to go further and deliver to the nucleus as well. Being DNA, there's also an outside chance for such external sequences to get incorporated into a cell's own genetic material, which isn't possible with foreign RNA. The RNA platform is apparently the better one of the two, which is reflected in the relative amounts of effort that have gone into each.

<sup>4</sup> Shane Crotty, La Jolla Institute for Immunology

<sup>5</sup> Lior Pachter, CalTech, Division of Biology and Biological Engineering



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

- Phase III trial results showed the vaccine demonstrated 95% efficacy compared to the control group in preventing COVID among vaccine participants 7 days after receiving a second dose of the vaccine. There were 170 cases of coronavirus across both the placebo and vaccinated group, with 162 cases in the placebo group compared to only 8 in the group receiving the vaccine
- Protection 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
- In December, the FDA issued an Emergency Use Authorization for the distribution of Pfizer/BioNTech's vaccine in the U.S. 6.4 million doses will be distributed immediately for use in health care workers and nursing home residents, half of which will be reserved for booster shots for the initial recipients. Pfizer plans to file for full FDA approval by April 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 1.3 billion doses globally 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. As a result, the federal government will own 100 million doses of the vaccine

**Moderna** mRNA vaccine announcement. Moderna began Phase III trials in July 2020 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
- Phase III trial results showed the vaccine demonstrated efficacy of 94.1%. In other words, there were only 11 cases of COVID in the group receiving the vaccine compared to 185 cases in the placebo group
- The trial also analyzed the prevalence of severe cases in vaccine trial participants, finding zero severe cases in the group receiving the vaccine compared to 30 severe cases in the placebo group
- In December, the FDA authorized the vaccine for emergency use. 5.9 million doses of the vaccine will be distributed immediately, with another 5.9 million distributed a month later for the administration of booster shots in the initial recipients
- In contrast to the very low temperatures required by the Pfizer RNA vaccine, Moderna expects that its vaccine will remain stable at standard refrigerator temperatures (36°-46°F) for up to 30 days

**CureVac**, a German biopharmaceutical company, is developing a mRNA vaccine and entered Phase 2b/3 trials in December 2020 with 36,500 participants in Europe and Latin America. The only available data is preclinical trial data in mice which showed that the vaccine was effective in producing neutralizing antibodies in all doses. CureVac will provide the EU with 225 million doses and expects to manufacture 300 million doses in 2021. The company has reportedly collaborated with Tesla to create mRNA "micro-factories" which could help produce more doses (Source: NYT).



## **Vector vaccines: how they work, who makes them and Phase III results (type 4)**

**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 of 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. 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 in July 2020<sup>6</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). Older participants not only showed similar antibody and t-cell levels as younger patients, but also had fewer side effects
- Phase II/III trials began in September 2020 in the US, the UK, South Africa, and Brazil with 23,000 participants globally. In September, the trials were paused in the US and UK due to spinal cord inflammation in a vaccine trial participant. Trials resumed in the UK in September and in the US in October, after the FDA found the vaccine was not responsible for the illness
- Initial Phase II/III results from the UK trial showed the vaccine demonstrated 62% efficacy in approximately 8,900 participants receiving two doses of the vaccine one month apart, and there were no hospitalizations or severe cases reported. Due to a manufacturing error, approximately 2,700 participants received a half dose of the vaccine first, followed by a full dose one month later. AstraZeneca reported the vaccine demonstrated 90% efficacy in this group, although there were no participants older than 55 in the trial. More data is to come on whether this efficacy number will hold up in a larger population. AstraZeneca is asking regulators whether the US trial of around 10,000 participants can be modified to include the “low dose, standard dose” regime
- Importantly, the vaccine can be stored, transported and handled at normal refrigerated conditions (36°-46°F) for at least 6 months. The vaccine is approved for emergency use in the UK, India, Argentina and Mexico, but regulatory approval is still pending in the US. AstraZeneca plans to manufacture up to 3 billion doses of the vaccine in 2021

**J&J** announced an ambitious timetable for a COVID-19 vector 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. Phase I/II trials showed that neutralizing antibodies were detected in 90% of participants 29 days after the first vaccine dose, and detected in 100% of participants by day 57. Antibody levels were higher among participants receiving higher doses and among those receiving a second dose. 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. While J&J is expected to move forward with a vaccine that does not require a booster shot, two Phase III trials are currently underway: one with 40,000 participants to study the one-dose regime, and another equally large study to evaluate a two-dose regime (second dose administered 57 days apart). Efficacy data from the Phase III trials is expected soon.

- Update: In early October 2020, 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. In January, J&J announced that its production timeline had fallen as much as two months behind due to manufacturing delays.

<sup>6</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.



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

### **Select vaccine candidates using vaccine types 1, 2 and 3 (attenuated viruses and recombinant proteins)**

Vaccine manufacturers that focus on attenuated and recombinant protein vaccine technologies have a longstanding track record of providing long lasting and safe immunity. Today, state-of-the-art preventive vaccines based on recombinant proteins represent 60% of all vaccines on the market. As these vaccines are produced in controlled bioreactors outside of the body, their structure and purity can be measured and calibrated. In contrast, “genetic” vaccines (DNA and RNA) are providing a genetic *template* to the body which then produces the proteins that trigger an antibody response. Once genetic vaccines are administered to the body, their destination and their protein-generating activity cannot be as tightly controlled.

The disadvantage of recombinant vaccines is the time it takes to develop customized cell lines (bioreactors) to produce a uniform and stable vaccine protein structure. Bioreactors can be based on bacterial, yeast, insect, plant and mammalian systems. Once the cell lines are developed, they can often be scaled quickly and cheaply. The end product: a vaccine that is a partial replica of the virus protein. Once the vaccine protein is administered to the body, the immune system is trained so that if confronted with the *real* virus, antibodies and memory cells are prepared to fight it.

Another complexity: bioreactors based on insect or plant life might produce virus proteins that are not identical to those the body confronts with the actual disease. As a result, antibody responses to some recombinant protein vaccines are sometimes sub-optimal. Some vaccines under development attempt to get around this by using mammalian cells as bioreactors; we expect to know more later in the year as they begin Phase I/II trials.

**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.

- **UPDATE:** GSK suffered a setback recently in its Phase I/II trials. The company announced that while antibody responses from their vaccine were similar to recovered COVID patients, this only held true for trial participants aged 18-49. For participants over 50, the immune response was lower, possibly due to an insufficient concentration of the antigen. The company will now reformulate its vaccine approach and launch a new Phase II trial in February of 2021, aiming to produce its vaccine in Q4 2021



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. A Phase III trial in 15,000 participants launched in the UK in September 2020, and a separate trial of 30,000 participants launched in the US in December after delays in manufacturing the required doses. If trials are successful, Novavax expects to deliver 100 million doses in the US in 2021

**Sinovac/Dynavax** are partnering on development of an inactivated virus vaccine with an adjuvant. In the Phase I trial, no severe side effects were reported but only 80% of participants showed neutralizing antibodies. 95-99% of participants showed neutralizing antibodies in the Phase II trial, however the antibody levels (“titers”) were lower than those seen in recovered coronavirus patients. Phase III trials are currently underway in Brazil, Indonesia and Turkey. The Chinese government has authorized use of the vaccine in high-risk groups

**SinoPharm (China)** is working on a vaccine candidate based on an inactivated virus. Phase I trials demonstrated only mild adverse reactions, and the Phase II trial showed the vaccine produced antibodies in 98% of participants. However, there was no comparison to antibody levels in recovered coronavirus patients. 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. In July, SinoPharm began its Phase III trial in the U.A.E. with 31,000 participants. An initial press release announced the vaccine showed 79% efficacy. The vaccine has been administered to nearly one million government officials, students and Chinese workers abroad as part of the Chinese government’s emergency use authorization



### ***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 6 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.



**Vaccine distribution, production and acceptance 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):

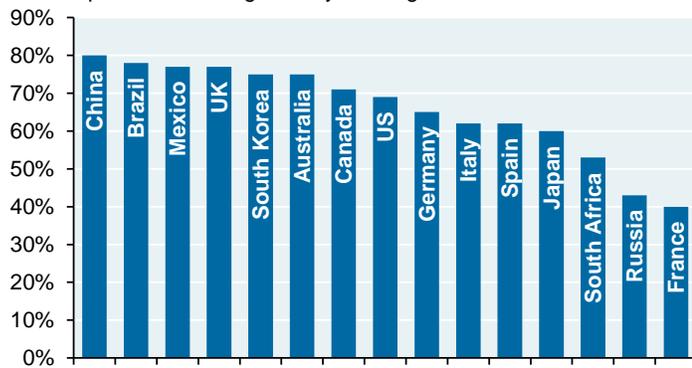
- 20 million healthcare workers
- 60 million essential service workers (food and & agriculture, transportation, education, energy, water/wastewater and law enforcement)
- 100 million individuals with “high risks” other than age (obesity, diabetes, chronic obstructive pulmonary disease (COPD), heart conditions, 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.

- The US ranks below many other developed and developing countries with respect to surveys of COVID vaccine intentions
- However, such resistance in the US appears to be declining, as shown in the second chart

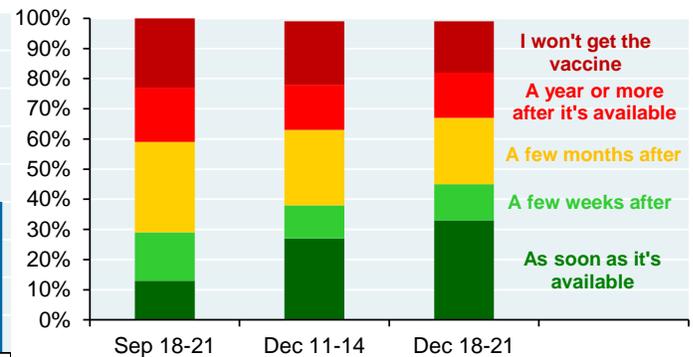
**Willingness to get vaccinated by country**

% of respondents who agree they would get COVID-19 vaccine



Source: IPSOS. December 20, 2020.

**US willingness to get vaccinated after the COVID-19 vaccine becomes available, % of respondents**



Source: IPSOS. December 21, 2020.



## Update on anti-viral, immunomodulator and corticosteroid 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<sup>7</sup> 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>8</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

**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. 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).

The latest results come from the REMAP-CAP study in Europe which involves more than 3,900 COVID patients. Patients receiving tocilizumab and a second immunomodulator called sarilumab experienced a reduced risk of death by 24% when administered within 24 hours of entering intensive care.

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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> “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).** Fujifilm's Phase III trials of 156 COVID patients in Japan demonstrated reduced recovery times for COVID-19 patients with non-severe symptoms. More trials are underway in the US, UK and India. This drug is an existing flu treatment first approved in Japan in 2014.

**Ravulizumab-cwbz (immunomodulator).** Phase III trials are ongoing 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.

**Chloroquine/hydroxychloroquine (anti-viral):** In April 2020, 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>9</sup>.

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<sup>9</sup> <https://blogs.sciencemag.org/pipeline/archives/2020/03/29/more-on-cloroquine-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.**

#### **UPDATE: RECOVERY TRIAL SUSPENDS CONVASCENT PLASMA STUDY, SHOWS NO BENEFITS**

**The convalescent plasma study of the Recovery Arm has been closed since it shows no benefits for hospitalized patients. Early analysis of 1,873 deaths in a study of 10,400 UK patients shows the treatment made "no significant difference". In the group treated with convalescent plasma, 18% of patients died within 28 days - the same figure for the group given standard treatment. January 16, 2021.**

In 2020, 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. In August 2020 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



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 2020, 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. Regeneron also began testing its mAb in Phase II/III trials for treatment of hospitalized and non-hospitalized COVID patients, though in early November it paused its trial in hospitalized patients due to a potential safety concern and what the company called an “unfavorable risk/benefit profile”. However, initial results from the 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. In November 2020, Regeneron received Emergency Use Authorization for the lower dose level, to be used in outpatient settings for people with mild to moderate COVID who are at high risk for hospitalization or developing a severe case. It is not authorized for patients who are already hospitalized or require oxygen. Regeneron plans to produce enough doses of the drug for 300,000 patients by the end of January, and is collaborating with Roche to scale up manufacturing and distribution
- **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 2020: a Phase II trial studying people recently diagnosed with COVID-19 (220 participants) and a Phase III trial on hospitalized patients, which was halted in October because the study did not find any clinical benefit in patients receiving treatment. 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. Our sources tell us that these results are disappointing to say the least. Regardless, Eli Lilly received Emergency Use Authorization from the FDA in November for use of the treatment in high-risk patients in outpatient settings, to be administered in newly infected people within 10 days of developing symptoms. The FDA indicated that the treatment should not be used in hospitalized patients or patients requiring oxygen

**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.



### **Possible benefits of anticoagulants, statins and ACE inhibitors for infected patients**

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>10</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 could explain why ventilation often isn't enough to help patients breathe better. Moving air into the lungs via ventilation can help, but 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 a vascular disease, ACE inhibitors and statins might help protect against endothelial cell damage. However, so far, most studies we have seen assess the outcomes for COVID patients that were *already* taking statins and ACE inhibitors (not studies on such treatments being applied for the first time to infected COVID patients)**
  - A UCSD study found that prior statin use was associated with a lower risk of developing severe COVID disease, and a faster time to recovery with patients with severe disease. Similar results were found in studies from Oxford, the Universitat Rovira i Virgili/Pere Virgili Institut (Spain) and the Policlinico di Modena Hospital (Italy)
- **Blood thinners could help as well.** 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>11</sup>
  - **However, anticoagulation is controversial and a very delicate balance.** COVID physicians we spoke with cite negative side effects such as bleeding (oftentimes brain bleeds that were not recognized until the patients were being considered for extubation), and benefits given the large number of strokes in patients hospitalized with COVID that anticoagulants can prevent. The protocols and research on anticoagulants for COVID patients is still a work in progress

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<sup>10</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>11</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



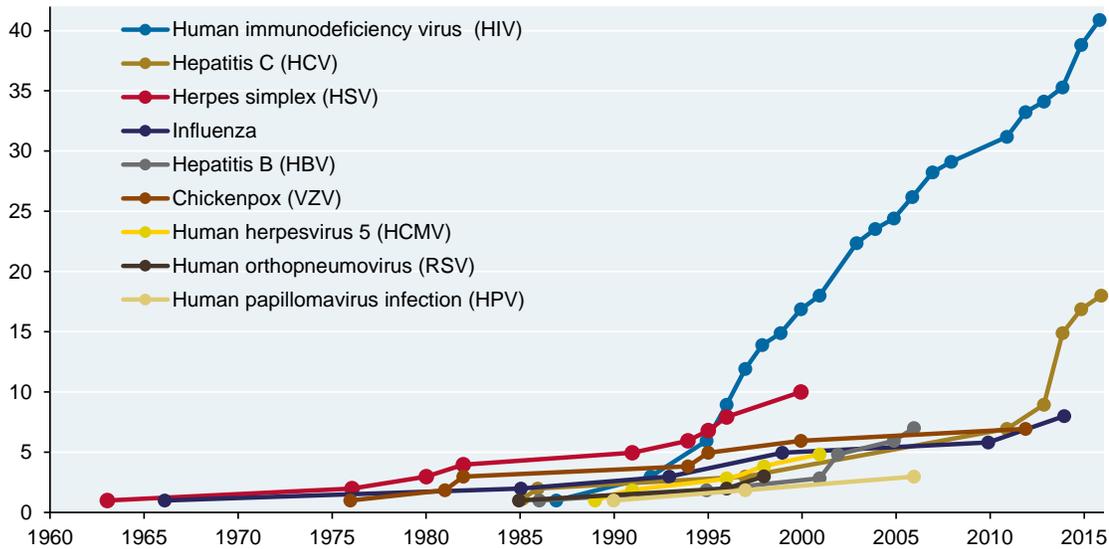
### Additional information on anti-virals

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.



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