The table outlines the different approaches that vaccine companies are taking to provoke a lasting antibody response. Vaccines train the immune system to recognize the disease-causing part of a virus so that when people are infected, their bodies are prepared to fight the virus with a combination of antibody and T-cell responses. Historically, most vaccines contained either weakened viruses or the signature proteins of the virus (Types 1, 2 and 3), but the first approved vaccines for COVID were genetic (Types 4 and 5).

<table>
<thead>
<tr>
<th>Type</th>
<th>Method of provoking antibody response to SARS-CoV-2</th>
<th>Drug companies (bold = approved)</th>
<th>Existing licensed vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Attenuated</td>
<td>Codagenix</td>
<td>Measles, yellow fever, mumps, smallpox, polio</td>
</tr>
<tr>
<td>2</td>
<td>Attenuated</td>
<td>Sinovac¹, Sinopharm²</td>
<td>Polio (dev countries)</td>
</tr>
<tr>
<td>3</td>
<td>Recombinant</td>
<td>GlaxoSmithKline/Sanofi, Novavax³</td>
<td>Tetanus, pertussis, flu, shingles</td>
</tr>
<tr>
<td>4</td>
<td>Genetic (vector vaccines)</td>
<td>CanSino⁴, Oxford/AstraZeneca⁵, J&amp;J⁶, Gamaleya⁷</td>
<td>Ebola</td>
</tr>
<tr>
<td>5</td>
<td>Genetic</td>
<td>Moderna, Inovio, BioNTech/Pfizer</td>
<td></td>
</tr>
</tbody>
</table>

1: Sinovac has been approved for use in China, Hong Kong, Indonesia, Philippines, Brazil, Chile, Mexico, and Turkey and several other countries
2: Sinopharm has been approved in China, UAE, Bahrain, Egypt, Hungary and Jordan. No Phase III trials released by the company
3: Protein vaccines are not new, but the Novavax vaccine is combined with a proprietary adjuvant which has not been approved for use before
4: CanSino has been approved for use in China, Mexico and Pakistan
5: Oxford/AstraZeneca's vaccine has been approved for use in the UK, Europe, South Africa, Brazil, Chile, and several other countries
6: J&J's vaccine has been approved for use in the US and Bahrain
7: Gamaleya's vaccine has been approved in Russia, Argentina, Venezuela, Mexico, Hungary, Iran, UAE, and several other countries

US vaccination overview

First, the good news: approved vaccines (Pfizer, Moderna, AstraZeneca, J&J) and pending vaccines (Novavax) report 70%-90% efficacy against the COVID strains that prevailed throughout 2020. In addition, even people who got sick during the trials experienced extremely low rates of hospitalization and mortality. Finally, vaccines appear to work almost as well against some new variants (see table on page 3). The bad news: even when vaccines work just as well, if new variants are more infectious, more people will die given gradual pace of vaccination in many countries; and there are some variants which pose challenges for existing vaccines.

B.1.1.7 variant. Scripps Research expects the B.1.1.7 variant to become the dominant strain in the US by end of March, and practically the only circulating strain in the US by May (first chart). The lethality of this new strain is seen by some scientists as being higher than other variants, although this is a preliminary finding. One thing is clear: when B.1.1.7 hit the UK, mortality rose sharply.

The US and other countries are now in a race against time: vaccinations are rising just as B.1.1.7 is spreading. Let’s avoid the phrase “herd immunity” since there is no agreed upon definition of what that means. Instead, the chart above looks at the pace of vaccination and the number of non-vaccinated COVID survivors in the US (derived from estimated infection fatality rates). By mid-May, this combined figure should approach 70%, in which case we would expect a sharp and sustained decline in hospitalization and mortality.

While the B.1.1.7 sprain is seen as being more contagious, it is notable that infections, hospitalizations and mortality in the UK continue to decline even as B.1.1.7 spreads. However, as we explain in Section 2 of our web portal, the UK has much more stringent lockdowns than the US, which may mask the potential impact of B.1.1.7 when/if the UK reopens. The best news might be from Israel, where Pfizer vaccinations approaching 60% of the population have contributed to declines in infection, hospitalization and mortality.
Coronavirus

Vaccine update by country and US state

Country/Region vaccination rates
Unique people vaccinated as % of population

Country vaccination rates: Europe/Canada
Unique people vaccinated as % of population

Country vaccination rates
Unique people vaccinated (or doses administered*) as % of population

1 Vaccination data can indicate the number of people that vaccinated (either with one or two doses), or the total number of vaccinations given. The latter 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 vaccination progress

% of US population

0% 5% 10% 15% 20% 25% 30%

Unique people vaccinated
Fully vaccinated
Partially vaccinated


US daily vaccinations

Millions of people, 7-day average

0.0 0.5 1.0 1.5 2.0 2.5

1/1 1/15 1/29 2/12 2/26 3/12

Full vaccinations (1st of 2 doses)
Partial vaccinations (1st of 2 doses)
Full vaccinations (2nd of 2 doses)


Percent of population that received at least one vaccination

Sorted in descending order by highest vaccination rate

## Vaccine efficacy by variant

The table below reviews vaccine efficacy against known variants. Note that efficacy is often not comparable across vaccines; some trials and studies measure prevention of severe disease, while others measure mild/moderate disease prevention. **By far the worst news so far is that Pfizer, Moderna and Oxford vaccine efficacy shrinks substantially against the South Africa variant, so much so that these companies are reportedly reconfiguring their vaccines to see if they can boost results.** While this variant has minimal spread so far in the US, it has begun to spread more widely in both France and Japan.

<table>
<thead>
<tr>
<th>Type</th>
<th>Moderna</th>
<th>Pfizer</th>
<th>AstraZeneca</th>
<th>J&amp;J</th>
<th>Novavax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>mRNA</td>
<td>mRNA</td>
<td>Vector</td>
<td>Vector</td>
<td>Recombinant</td>
</tr>
<tr>
<td>Efficacy vs prevailing 2020 variants</td>
<td>94%; 100% vs severe infection, hosp. and deaths [T]</td>
<td>95% [T]</td>
<td>US study: 76% vs symptomatic 100% efficacy vs severe infection, hosp. and deaths [T]</td>
<td>72%; 86% vs severe infection [T]</td>
<td>95.6% [T]</td>
</tr>
<tr>
<td>Efficacy vs B.1.1.7 (UK variant)</td>
<td>2x reduction in neutralization [V]</td>
<td>&quot;modest decline in neutralization&quot; [V]</td>
<td>75% vs symptomatic 27% vs asymptomatic [T]</td>
<td></td>
<td>85% [T], 2x reduction in neutralization [V]</td>
</tr>
<tr>
<td>Efficacy vs B.1.351 (South Africa variant)</td>
<td>6x reduction in neutralization [V]</td>
<td>U. of Texas: 2/3 decline in neutralization [V]</td>
<td>Johannesburg study: 10% efficacy vs mild/moderate illness [T]</td>
<td>Oxford: 9x reduction in neutralization [V]</td>
<td>64%; 82% vs severe infection [T]</td>
</tr>
<tr>
<td>Efficacy vs P.1 (Brazil variant)</td>
<td>Effectiveness cut in half</td>
<td>3x reduction in neutralization [V]</td>
<td></td>
<td></td>
<td>60%[T]</td>
</tr>
<tr>
<td>Efficacy vs B.1.427/9 (California variant)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy vs B.1.526 (NY variant)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storage</td>
<td>Normal refrigerated conditions</td>
<td>Ultra-cold storage (-94˚F)</td>
<td>Normal refrigerated conditions</td>
<td>Prevented 100% of severe infection, hosp. and deaths in UK, Brazil and S Afr trials [T]</td>
<td>Normal refrigerated conditions</td>
</tr>
<tr>
<td>Additional trial data</td>
<td>No COVID-related deaths in trials (across U.S., Ger., Turkey, S Afr, Brazil and Arg.)</td>
<td></td>
<td>Prevented 85% of severe infection and 100% of deaths in US, LatAm and S Afr trials [T]</td>
<td></td>
<td>No hospitalizations or deaths reported in trial participants receiving vaccine</td>
</tr>
<tr>
<td>Roll-out observations</td>
<td>Pfizer: In Israel, 60+ infections fell by 2/3 after first shot; after 2nd dose, only 0.1% infection rate. UK study: 75% reduction in hospital admission &amp; death after single shot; 70% infection decline after first dose, 85% after second dose (57% and 88% for people over 80). Germany study: no neutralizing antibodies in 31% of people over 80 compared to 2% in people under 60</td>
<td>Moderna: UK, 76% vs symptomatic 100% efficacy vs severe infection, hosp. and deaths [T]</td>
<td>AstraZeneca: In Scotland, reduced risk of hospital admission by 94%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: efficacy refers to the decline in infection probability relative to a placebo or control group. Declines in neutralization do not map directly into efficacy declines. For example, for the flu vaccine, a 4x reduction in neutralization is generally seen as the level at which reformulation of a new vaccine is required.

T = clinical trial (researchers observe treatment efficacy in human subjects); V = in vitro study (researchers isolate cells outside of human subjects)

Sources: Company press releases, Duke University, University of Cambridge, University of Oxford, University of Strathclyde, University of the Witwatersrand (Johannesburg), University of Texas, New England Journal of Medicine, Public Health/England, Heinrich Heine University. 2021.
Variant prevalence by country and for the US

The table shows variant prevalence for select countries from GISAID, an open-source global science information sharing initiative. Only a handful of countries are sequencing more than 250 people per month, which is the threshold we use for inclusion. As shown on the prior page, the South Africa variant (B1351) creates the most significant challenges for existing vaccines so we also include a bar chart on countries with the largest penetration of that variant. GISAID data may reflect data aggregated two weeks prior. In a world of rapidly changing variant shares, the numbers can change a lot when they’re updated. For example, the CDC showed B117 at 9% in the US at the end of February, while Helix (a PCR test provider) reports B117 prevalence in the US at 44% as of late March. This rise conforms to the chart on page 2 predicting a rapid transition to this variant.

Variant shares can also differ substantially by state; in mid-March, the NY variant B1526 was already accounting for 39% of NYC infections even though the CDC reported that strain as only 3% prevalent across the entire US.

Prevalence of variants of interest or concern in select highly infected countries with significant sequencing in past 4 weeks

<table>
<thead>
<tr>
<th>Country</th>
<th>B.1.1.7 (UK variant)</th>
<th>B.1.351 (South Africa variant)</th>
<th>P.1</th>
<th>B.1.427 + B.1.429 (CA variant)</th>
<th>B.1.529 (Nigeria variant)</th>
<th>B.1.526 (NY variant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>55.7%</td>
<td>8.8%</td>
<td>2.9%</td>
<td>0.0%</td>
<td>0.4%</td>
<td>?</td>
</tr>
<tr>
<td>France</td>
<td>65.4%</td>
<td>4.2%</td>
<td>0.1%</td>
<td>0.0%</td>
<td>0.2%</td>
<td>?</td>
</tr>
<tr>
<td>Germany</td>
<td>59.5%</td>
<td>1.9%</td>
<td>0.2%</td>
<td>0.0%</td>
<td>0.4%</td>
<td>?</td>
</tr>
<tr>
<td>Ireland</td>
<td>93.1%</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.0%</td>
<td>2.0%</td>
<td>?</td>
</tr>
<tr>
<td>Italy</td>
<td>65.2%</td>
<td>0.1%</td>
<td>2.5%</td>
<td>0.0%</td>
<td>0.6%</td>
<td>?</td>
</tr>
<tr>
<td>Netherlands</td>
<td>81.2%</td>
<td>2.3%</td>
<td>0.6%</td>
<td>0.0%</td>
<td>0.4%</td>
<td>?</td>
</tr>
<tr>
<td>Spain</td>
<td>68.3%</td>
<td>0.2%</td>
<td>0.6%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>?</td>
</tr>
<tr>
<td>Sweden</td>
<td>61.4%</td>
<td>1.8%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.2%</td>
<td>?</td>
</tr>
<tr>
<td>Switzerland</td>
<td>78.7%</td>
<td>1.3%</td>
<td>0.5%</td>
<td>0.1%</td>
<td>0.2%</td>
<td>?</td>
</tr>
<tr>
<td>Turkey</td>
<td>4.4%</td>
<td>3.4%</td>
<td>0.1%</td>
<td>0.0%</td>
<td>0.7%</td>
<td>?</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>97.8%</td>
<td>0.2%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.3%</td>
<td>?</td>
</tr>
<tr>
<td>United States</td>
<td>44.2%</td>
<td>0.2%</td>
<td>0.2%</td>
<td>12.2%</td>
<td>0.2%</td>
<td>?</td>
</tr>
</tbody>
</table>

Source: GISAID. March 23, 2021. Includes countries with 250 or more total genomic sequences analyzed over trailing 4 weeks. Table does not show prevalence of specific mutations e.g. the D614G mutation, which was found in many circulating variants in 2020.

B.1.351 (South Africa variant) prevalence by country

% of sequenced genomes in last 4 weeks

Source: GISAID. March 25, 2021. Only includes countries with 250 or more total genomic sequences analyzed over trailing 4 weeks.
mRNA vaccines: how they work, efficacy, side effects and other Q&A (type 5)

How do mRNA vaccines work?

Messenger RNA is a single-stranded molecule present in all cells. It carries instructions for making proteins from the cell nucleus to the cytoplasm, which in turn translates information stored in mRNA and makes proteins. Rather than injecting the virus or a viral protein (which is a part of the virus), an mRNA vaccine contains genetic material that encodes the viral protein. When these genetic instructions are injected into the arm, muscle cells translate them and make the viral protein directly in the body. This gives the immune system a preview of what the real virus looks like, allowing it to generate antibodies and T-cells that can fight the virus if the individual is infected. mRNA are packaged inside lipid nanoparticles to prevent them from being immediately destroyed by the body’s immune system; eventually, the body’s enzymes degrade the mRNA after it delivers its instructions.

Moderna and Pfizer mRNA vaccines for COVID are the first mRNA vaccines ever approved in Western countries. As shown below, 60% of the current vaccine market is made up of recombinant protein vaccines (which we discuss later), with the rest mostly divided between the two attenuated virus types. As for COVID vaccines under development, they were more evenly split by type as of April 2020.

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 (i.e., the people upon who the vaccine was not “effective”), in most trials conducted to date none of these people died, or required hospitalization or supplemental oxygenation. In other words, vaccines appeared to substantially mitigate COVID severity even when people still became sick.

However, trials are just that: a small sample size relative to the millions of people that will be vaccinated. Some things to keep in mind:

- In some trials (i.e., Pfizer), large numbers of “suspected” COVID cases were not included when vaccine subjects had a negative PCR. If the suspected cases were included, reported efficacy numbers could drop substantially. 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.
- Most trials excluded pregnant women, children and people with certain immune disorders
- Trials cannot test all the permutation of clinical and behavioral conditions which exist in broad populations

As a result, the best way to monitor efficacy is through the actual infection, hospitalization and mortality results in populations that have received the vaccines.
What about side effects?

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.

### VACCINE SIDE EFFECTS: COVID vs INFLUENZA

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>COVID #</th>
<th>Freq %</th>
<th># per mm</th>
<th>INFLU #</th>
<th>Freq %</th>
<th># per mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized</td>
<td>4024</td>
<td>0.0041%</td>
<td>41.0</td>
<td>368</td>
<td>0.0002%</td>
<td>2.1</td>
</tr>
<tr>
<td>Disability</td>
<td>756</td>
<td>0.0008%</td>
<td>7.7</td>
<td>174</td>
<td>0.0001%</td>
<td>1.0</td>
</tr>
<tr>
<td>Dr office visit</td>
<td>4972</td>
<td>0.0051%</td>
<td>50.6</td>
<td>2816</td>
<td>0.0016%</td>
<td>16.1</td>
</tr>
<tr>
<td>ER visit</td>
<td>5698</td>
<td>0.0058%</td>
<td>58.0</td>
<td>1065</td>
<td>0.0006%</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Doses administered as of 3/11/2021: 98,203,893

Doses administered in 2020: 174,500,000


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”.

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.

What about DNA messenger vaccines?

RNA vaccines have advantages over DNA vaccines: 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 RNA. The RNA platform is the better of the two, reflected in the relative amounts of effort that have gone into each.

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2 Shane Crotty, La Jolla Institute for Immunology
3 Lior Pachter, CalTech, Division of Biology and Biological Engineering
Are there other mRNA vaccines under development?

CureVac, a German biopharmaceutical company, is developing an 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 (type 4)

Vector vaccines are also “genetic” but they work differently. 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 the gene for SARS-CoV-2 spike proteins (i.e., only the spike protein and not the virus itself; you cannot get COVID from the spike protein alone). Once these genes are injected via vaccine, the body transcribes the genes into mRNA, which in turn prompts the cell’s cytoplasm to produce the SARS-CoV-2 spike proteins which provoke an antibody response (i.e., the latter step is the same as for the mRNA vaccines).

Oxford’s vector vaccine uses a chimpanzee virus that is altered to be harmless to humans, and for which humans have no antibodies. J&J’s vaccine uses a vector approach as well, but with a human adenovirus as the carrier. The adenovirus is altered to be non-replicating, effectively preventing it from causing adenovirus infections.

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. 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.

Genetic vaccines: the future

Genetic vaccines are a remarkable breakthrough, particularly compared to traditional vaccine types made from attenuated viruses and recombinant proteins. Both development timeframes and the time required to address evolving mutations and variants are much faster for genetic vaccines. However, there’s a big unknown: the risk of declining efficacy as the human body starts to recognize delivery mechanisms of genetic vaccines, attacking them before they have a chance to complete their mission. This is very unlikely to be a problem for annually delivered vaccines with small doses for diseases like COVID, but could become an issue for more frequent treatment applications with much larger doses (i.e., weekly delivery with doses that are 800x higher than those used in COVID vaccines).

Genetic vaccines package instructions inside something else: in the case of vector vaccines, adenoviruses or chimpanzee viruses that are harmless to humans; and in the case of mRNA vaccines, cationic phospholipids. The word “cationic” is important; neutral lipids would not provoke the body’s immune system, but lipids used for mRNA vaccines are positively charged (cationic) to offset the negative charge of the RNA. On its own, negatively charged RNA would be destroyed by the immune system, but positively charged lipids appear to eventually be recognized by the immune system as well. Moderna wrote a paper about this in 2019⁴, citing increased antibody responses to the lipid surface coating and the structural lipid layer. To reiterate, this issue pertains to very high-frequency therapeutic treatments with very large dosages, and should not be an issue for annual treatments with small dosages such as COVID vaccines.

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⁴ “Accelerated Blood Clearance of Lipid Nanoparticles Entails a Biphasic Humoral Response of B-1 Followed by B-2 Lymphocytes to Distinct Antigenic Moieties”, Besin et al, Moderna Inc. June 2019
Select vaccine candidates using vaccine type 3 (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, and require the addition of an “adjuvant” to provoke a stronger antibody response. 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 has reformulated its vaccine approach and launched a new Phase II trial of 720 participants in February of 2021, aiming to produce its vaccine in Q4 2021.
Select vaccine candidates using vaccine types 1 and 2 (attenuated viruses)

Unlike genetic vaccines and recombinant protein vaccines, attenuated vaccines contain the entire SARS-CoV-2 virus. The virus is chemically modified to inactivate it so that it cannot cause disease. There are two different types of attenuated vaccines: live and inactivated. Live attenuated vaccines elicit strong immune responses but are not suitable for people with weakened immune systems. In an inactivated vaccine, the virus is killed so that it is unable to replicate. Inactivated vaccine responses are usually not as strong as live vaccines, so booster shots are often used to ensure ongoing protection.

Sinovac’s vaccine is 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 in 25,000 participants across Brazil, Indonesia, Turkey and Chile demonstrated efficacy of 50.65% in preventing all cases, but was 100% effective in preventing severe cases, hospitalizations or deaths. In the trials based in Turkey, the vaccine had an efficacy of 91.25%

SinoPharm’s vaccine candidate is 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 2020, SinoPharm began its Phase III trial in the U.A.E. with 31,000 participants. A company press release announced the vaccine showed 79% efficacy

Some caveats and challenges for Chinese and Russian vaccine developers

Chinese vaccine companies 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 diptheria, 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, July 31, 2020

As for the Russian vector vaccine, it comes from the Gamaleya Research Institute. Members of my science advisory group were skeptical given that it was only in human trials for less than two months when it received regulatory approval in Russia. However, Phase III trial results published in February by The Lancet showed the vaccine demonstrated 91.6% efficacy against symptomatic coronavirus. The vaccine was equally effective for participants aged 60 and older, for whom the vaccine showed 91.8% efficacy. Results were based on a trial of 20,000 adults (15,000 in the vaccine group vs 5,000 in placebo group) who received two injections 21 days apart, though the ongoing Phase III trial plans to ultimately enroll a total of 40,000 participants. Side effects were mild and no serious adverse events were linked to the vaccine. Researchers also noted that efficacy after only one dose of the vaccine was 73.6%, though they plan to initiate trials to test a one-dose regime in the coming weeks. 1.4bn doses of the vaccine, which can be stored and distributed at regular refrigerator temperatures, are expected to be produced in 2021.
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 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. 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.

5 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”.

**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).** The drug 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. 

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**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 CONVALESCENT 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).** Phase II/III results from Regeneron’s 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. Final Phase III data indicated that the drug reduced risk of hospitalization or death by 70%. Regeneron received Emergency Use Authorization in November 2020 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.

- **Eli Lilly/AbCellera (LY-COV55).** 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. Eli Lilly received Emergency Use Authorization from the FDA in November 2020 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.

- **GSK/Vir (VIR-7831).** In March, GSK/Vir’s Phase III trial of its monoclonal antibody demonstrated 85% efficacy in reducing hospitalization and death among 583 high-risk participants with mild or moderate COVID. A forthcoming in vitro study from GSK/Vir found that the treatment demonstrates efficacy against the UK, South Africa and Brazil variants. Like other monoclonal antibodies, the treatment must be administered intravenously to patients early in the disease, though the company is initiating Phase III trials to test efficacy both as an intramuscular injection and as a preventative measure against COVID in high-risk adults. Based on these results, the companies are seeking Emergency Use Authorization from the FDA and global regulatory authorities.

**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)⁸:

- 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 not⁹

- **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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⁸ “Endothelial cell infection and endotheliitis in COVID-19”, Z. Varga et al. Department of Pathology and Molecular Pathology, University Hospital Zurich. April 20, 2020

⁹ “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
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