[1] COVID vaccination update

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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).

Type	Method of provoking antibody response to SARS-CoV-2	Drug companies (bold = approved)	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 Attenuated	A "killed" coronavirus that will get recognized as foreign matter by the immune system	**Sinovac[1], SinoPharm[2], Covaxin[3]**	Polio (dev countries)
3 Recombinant	Recombinant coronavirus proteins, produced industrially in outside cell cultures, which are recognized as foreign matter by the immune system	GlaxoSmithKline/Sanofi, Novavax[4]	Tetanus, pertussis, flu, shingles
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 produce them	**CanSino[5], Oxford/AstraZeneca[6], J&J[7], Gamaleya[8]**	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**	

1: Sinovac has been approved for use in China, Hong Kong, Indonesia, Philippines, Brazil, Chile, Mexico, 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: Covaxin has been approved for emergency use in India, Iran, Philippines, Paraguay, Guatemala and several other countries
4: Protein vaccines are not new, but the Novavax vaccine is combined with a proprietary adjuvant which has not been approved for use before
5: CanSino has been approved for use in China, Mexico and Pakistan
6: Oxford/AstraZeneca's vaccine has been approved for use in the UK, Europe, South Africa, Brazil, Chile, and several other countries
7: J&J's vaccine has been approved for use in the US and Bahrain
8: Gamaleya's vaccine has been approved in Russia, Argentina, Venezuela, Mexico, Hungary, Iran, UAE, and several other countries

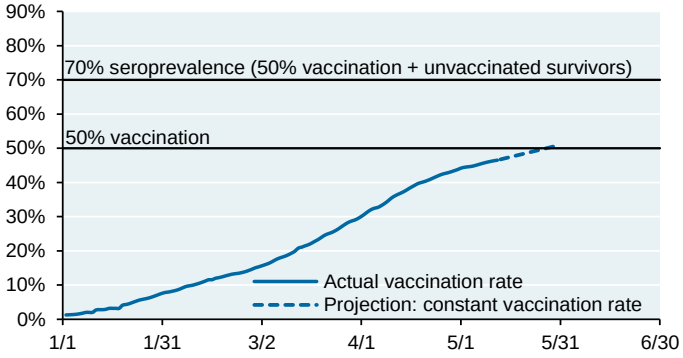
Source: J.P. Morgan Asset Management. 2021.

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 8). 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.

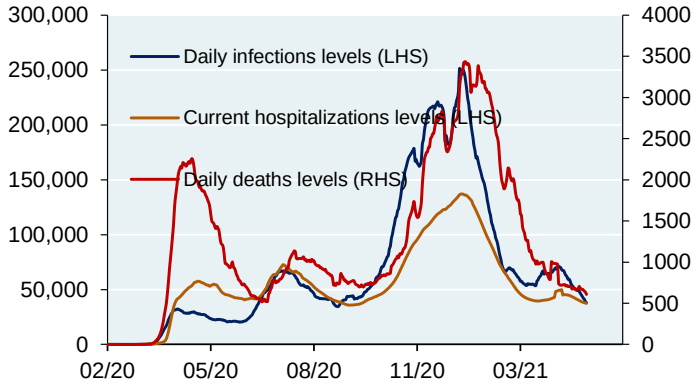
The first chart looks at the pace of vaccination plus the estimated number of non-vaccinated COVID survivors in the US (derived from estimated infection fatality rates). By mid-May, this combined figure could reach 70%, in which case we would expect a sustained decline in hospitalization and mortality. We stop plotting this series in late May since at some point, the population of vaccine seekers will be depleted, leading to a flattening in this curve. As shown in the last chart, the pace of vaccinations in the US is already slowing, although the eventual resumption of J&J vaccinations may reverse part of the decline.

US vaccinated individuals and survivors
Unique people vaccinated as % of US population



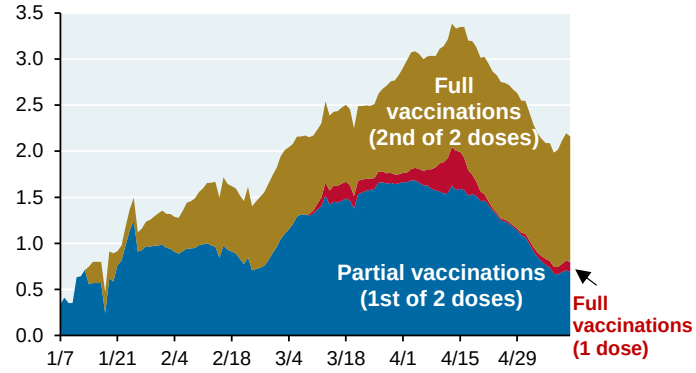
Source: OWID, JPMAM. May 12, 2021. Estimated vaccination rate is based on trailing 7-day average vaccination rate.

US



Source: JHU, IMF, HHS, JPMAM. May 11, 2021. 7 day smoothing.

US daily vaccinations
Millions of people, 7-day average



Source: OWID, JPMAM. May 12, 2021.

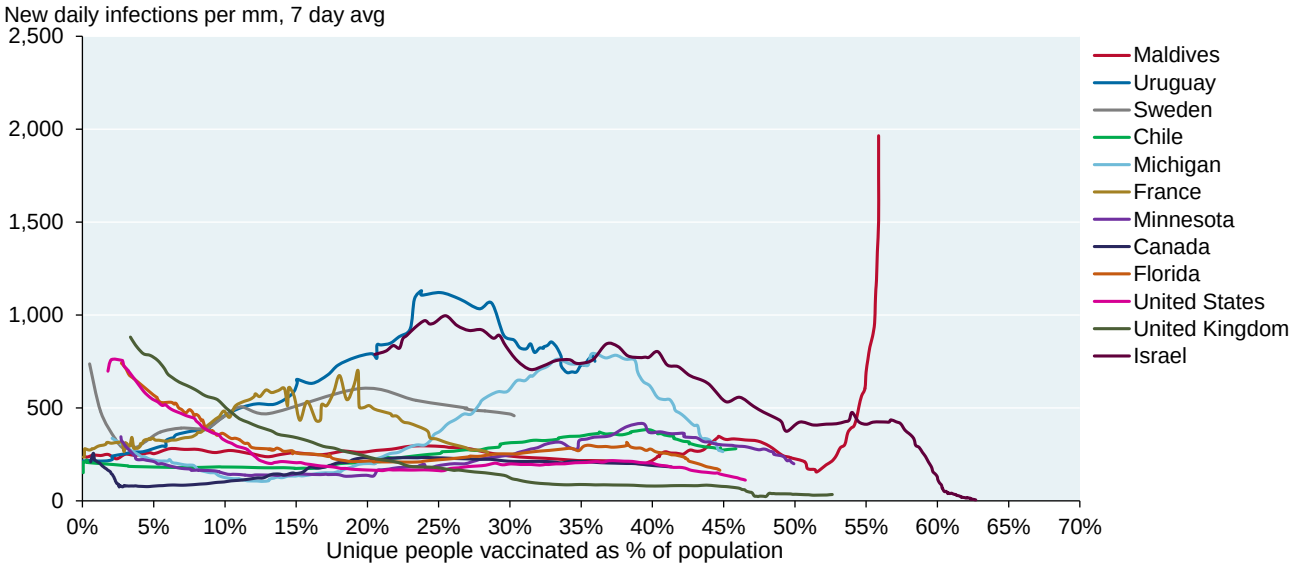
Herd immunity and the return to normalcy

Vaccine hesitancy, emergence of new variants, reduced vaccine efficacy (i.e., vs South Africa & Brazil variants), delayed vaccinations for children, low vaccination rates in emerging countries and uncertainty on whether vaccines prevent asymptomatic spread all make textbook herd immunity a practically unreachable goal. It looks like COVID will become an endemic disease like the flu, and will need to be treated accordingly.

The good news: a return to normalcy can still be attained when/if seroprevalence (prior exposure + vaccines) drives infection, hospitalization and mortality down on a sustained basis. We're looking for signs of a "path to normalcy" and wanted to share the results so far. The challenge: most gov'ts are not conducting widespread antibody testing and do not publish a breakdown of vaccinations between previously infected and uninfected people. As a result, we cannot track total seroprevalence and can only plot COVID outcomes vs vaccination.

Let's start with vaccinations vs infection for select countries/states. Given the disparity in lockdowns, vaccines and variants, and the natural fall-off in respiratory infections in the spring, we are not drawing a lot of hard and fast conclusions from this data. That said, here's what we are seeing so far.

Infections vs vaccinations



Source: OWID, JPMAM. May 12, 2021.

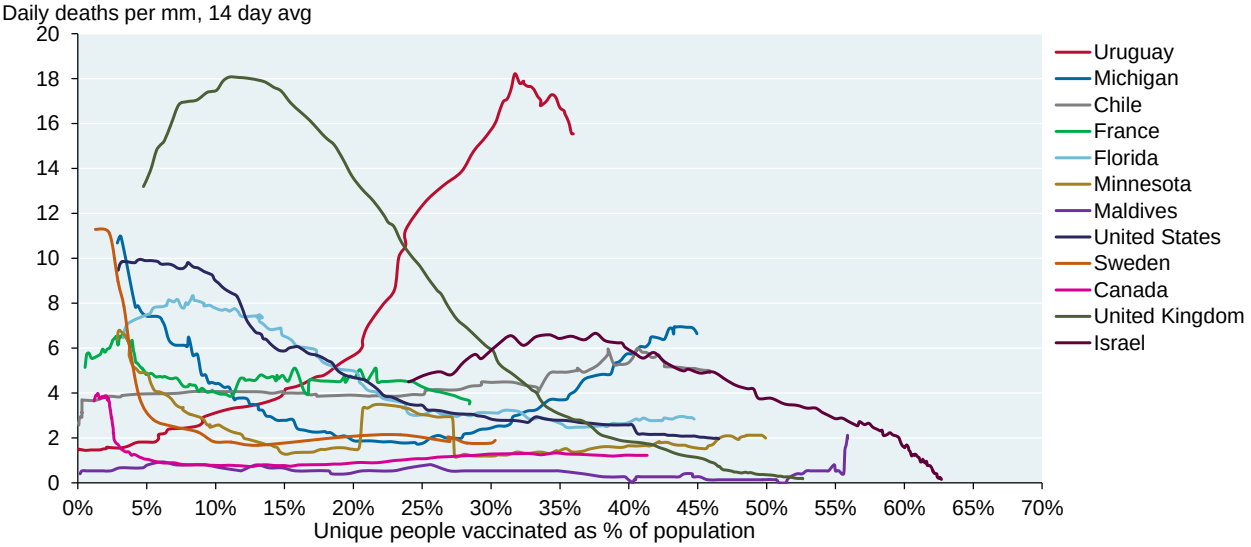
- While **UK** infections started declining almost as soon as vaccinations began, the UK also had one of the more restrictive lockdowns in the world which makes it difficult to isolate the impact of vaccinations on infection
- **Israel** did not experience a sustained decline in infections until vaccinations hit 60%. We estimate that Israel had a COVID survivor population of ~10% before its vaccinations began, but we don't know how many of these people were then vaccinated or not. If we split the difference, herd immunity may have started to appear at around 65% total "seroprevalence" (antibodies from vaccines + unvaccinated survivors combined)
- At a ~45% vaccination level, **Minnesota, Chile, Florida and Michigan** were still experiencing high levels of infection. Let's take a closer look at **Michigan**. At the end of 2020, CDC sampling showed survivor antibodies of 18% in Michigan. If we assume that half of this population is still not vaccinated, **Michigan's high levels of infection, hospitalization and mortality were occurring at seroprevalence levels of over 55%.**
- High infection rates in **Uruguay** at 35% vaccination levels are also concerning and most likely reflect highly infectious variants imported from Brazil
- Concerns about the Maldives and the Seychelles: spiking infection rates despite vaccination levels over 55% could indicate a problem with India variants and/or the Sinopharm vaccine

Vaccines have reduced mortality and hospitalization in many locations. Both have declined by 70% in the US despite minimal mobility restrictions. Even so, there are exceptions: in Michigan and Florida, mortality and hospitalization are flat or rising despite 40% vaccination. The same is true in Uruguay whose COVID situation is now as bad as Brazil despite 30%-35% vaccination. Note how stable some of the hospitalization data is despite vaccinations increasing from 20% to 45% of populations. Also: while mortality and hospitalizations are important metrics, so are infections given long term COVID survivor risks.

Bottom line: the only country that might be close to COVID normalcy is Israel, and its total seroprevalence is probably 65%+. In contrast to wildly uninformed projections I saw last year[1], herd immunity almost certainly does not occur at seroprevalence below 40%. If that's the case, governments around the world will need to push harder to overcome existing pockets of vaccine resistance.

Mortality vs vaccinations

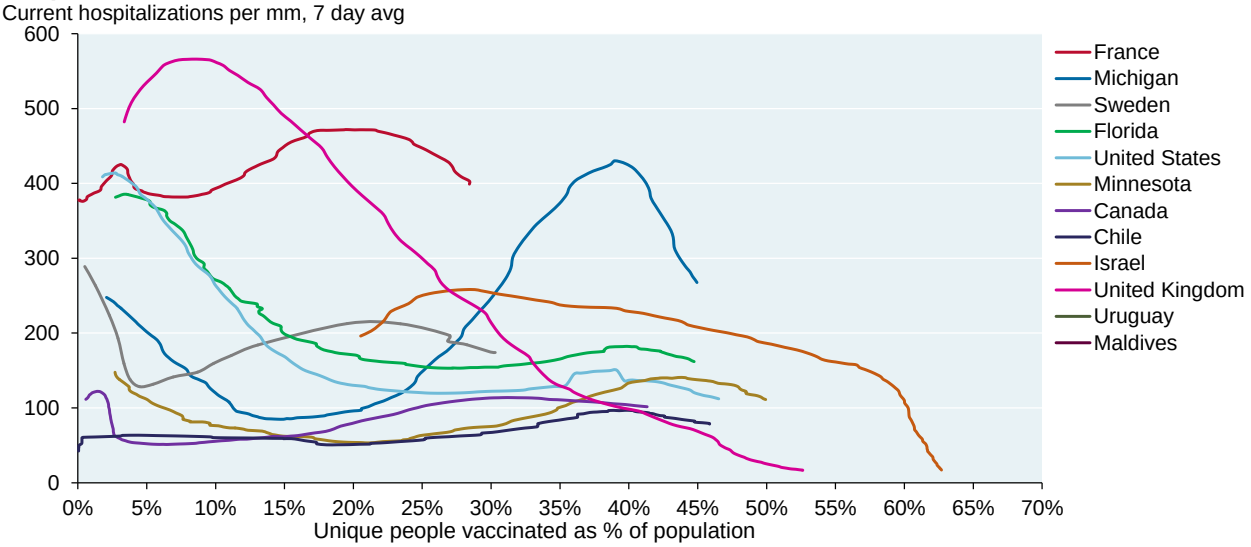
Daily deaths per mm, 14 day avg



Source: OWID, JPMAM. May 12, 2021.

Hospitalizations vs vaccinations

Current hospitalizations per mm, 7 day avg

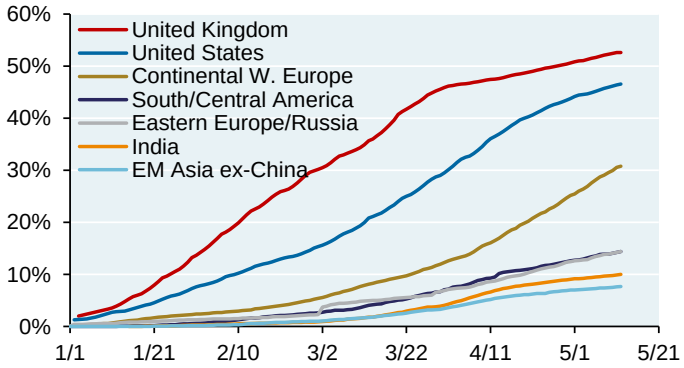


Source: OWID, JPMAM. May 12, 2021.

[1] Last August I wrote about Fundstrat Research which based its 10%-20% herd immunity estimate on a former ophthalmologist whose COVID videos were pulled by social media, who has a "not medical advice" caveat on his Twitter profile, who has no known experience treating COVID-19, whose medical license expired in 2019 and who was part of the hydroxychloroquine misinformation chain. There's a lot of really bad COVID stuff out there.

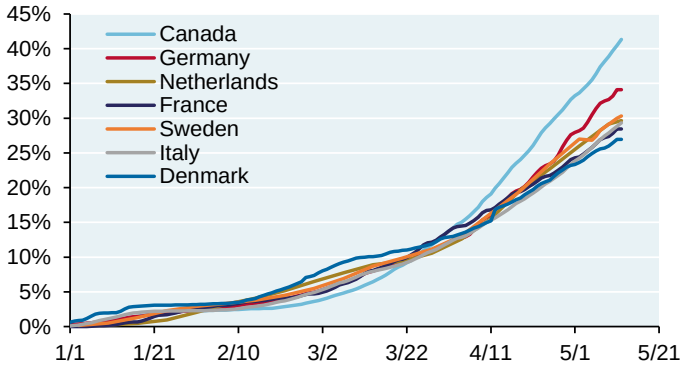
Vaccine update by country and US state[2]

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



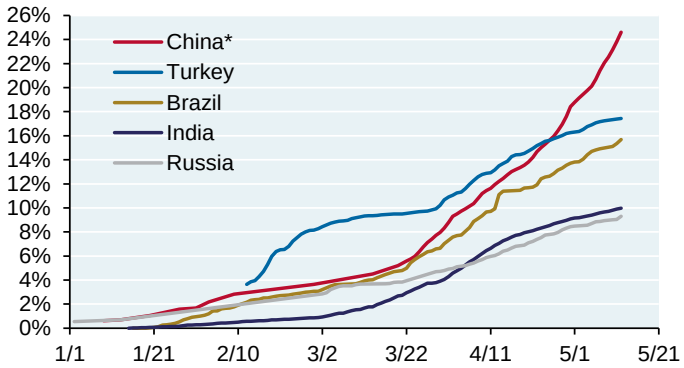
Source: OWID, JPMAM. May 12, 2021.

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



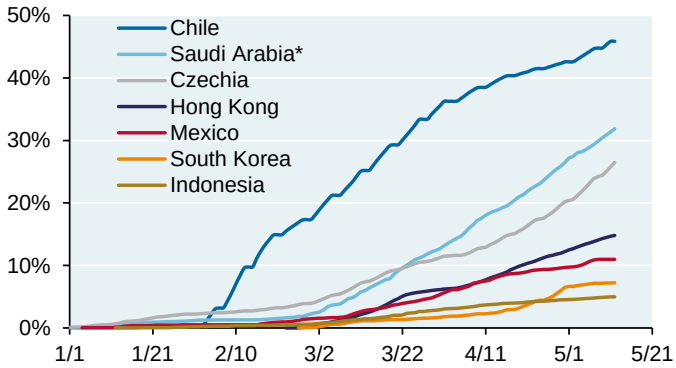
Source: OWID, JPMAM. May 12, 2021.

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



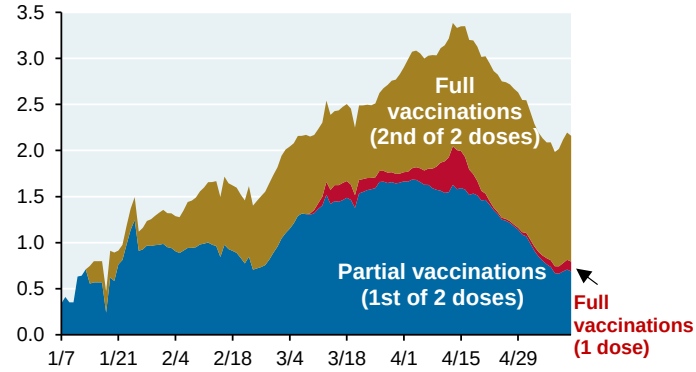
Source: OWID, JPMAM. May 12, 2021.

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



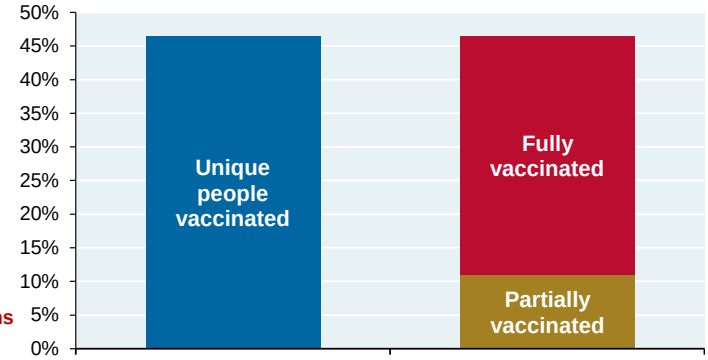
Source: OWID, JPMAM. May 12, 2021.

US daily vaccinations
Millions of people, 7-day average



Source: OWID, JPMAM. May 12, 2021.

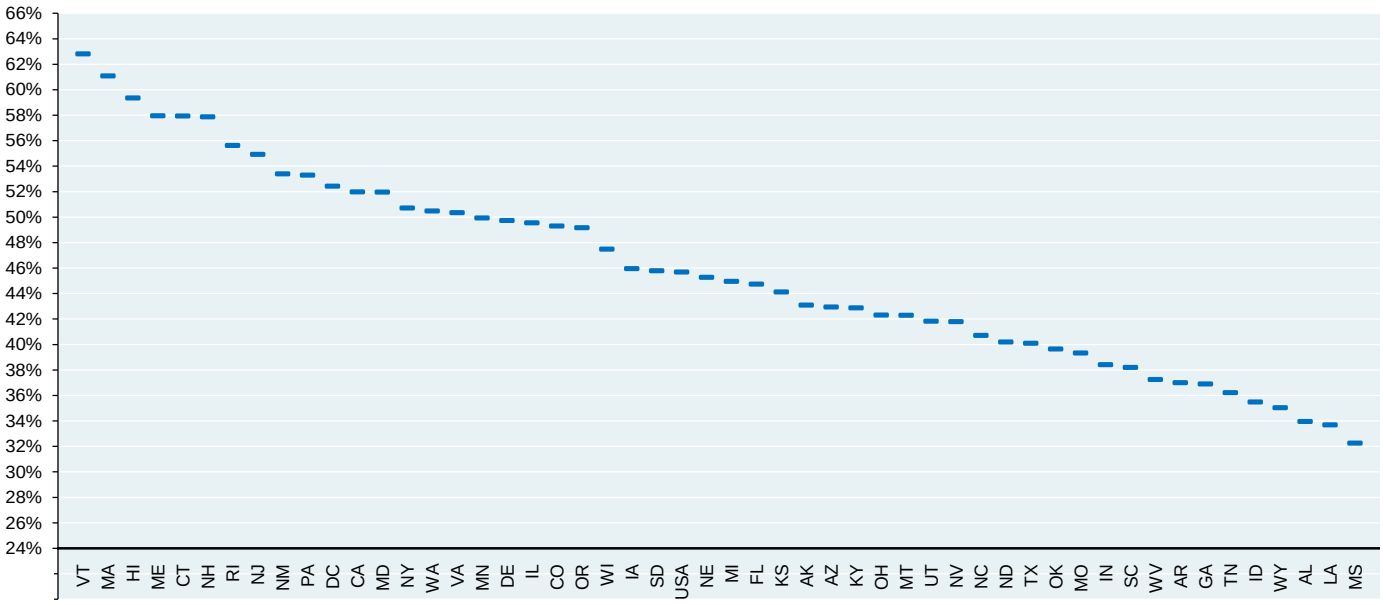
US vaccination progress
% of US population



Source: OWID, JPMAM. May 12, 2021.

[2] 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.

Percent of population that received at least one vaccination
Sorted in descending order by highest vaccination rate



Source: OWID, JPMAM. May 12, 2021.

Unique people vaccinated as percent of population

State	VT	MA	HI	ME	CT	NH	RI	NJ	NM	PA	DC	CA	MD
Total population	63%	61%	59%	58%	58%	58%	56%	55%	53%	53%	52%	52%	52%
18-64 population	69%	69%	67%	62%	65%	62%	61%	64%	61%	57%	61%	60%	60%
18+ population	76%	74%	74%	70%	71%	70%	68%	69%	68%	66%	64%	66%	65%
65+ population	97%	93%	96%	92%	92%	96%	92%	88%	88%	96%	80%	89%	86%

State	NY	WA	VA	MN	DE	IL	CO	OR	WI	IA	SD	NE	MI
Total population	51%	50%	50%	50%	50%	50%	49%	49%	47%	46%	46%	45%	45%
18-64 population	58%	58%	57%	57%	53%	56%	56%	54%	52%	51%	51%	52%	49%
18+ population	63%	64%	63%	64%	62%	62%	62%	61%	60%	59%	60%	59%	56%
65+ population	81%	87%	85%	89%	90%	86%	84%	82%	88%	86%	89%	85%	81%

State	FL	KS	AK	AZ	KY	OH	MT	UT	NV	NC	ND	TX	OK
Total population	45%	44%	43%	43%	43%	42%	42%	42%	42%	41%	40%	40%	40%
18-64 population	44%	49%	51%	47%	47%	46%	45%	52%	47%	44%	44%	47%	44%
18+ population	55%	57%	56%	55%	55%	53%	53%	57%	53%	51%	52%	53%	52%
65+ population	86%	89%	79%	81%	82%	80%	79%	85%	78%	78%	82%	79%	81%

State	MO	IN	SC	WV	AR	GA	TN	ID	WY	AL	LA	MS	USA
Total population	39%	38%	38%	37%	37%	37%	36%	35%	35%	34%	34%	32%	46%
18-64 population	42%	41%	38%	36%	40%	41%	38%	39%	37%	34%	35%	33%	52%
18+ population	50%	49%	48%	45%	48%	48%	46%	47%	45%	43%	44%	42%	59%
65+ population	77%	80%	81%	71%	74%	78%	75%	78%	74%	74%	76%	74%	84%

Source: OWID, CDC, JPMAM. May 12, 2021.

	Unique people vaccinated	% of pop.	7d avg inf/mm	7d avg mort/mm
Algeria	75,000*	0%	5	0.2
Argentina	7,866,933	17%	455	9.3
Aruba	56,594	51%	121	5.2
Australia	159,294	1%	0	0.0
Austria	2,749,793	31%	122	1.9
Bahrain	821,210	48%	921	3.4
Bangladesh	5,819,900	4%	9	0.3
Belgium	3,704,273	32%	245	2.8
Belize	47,675	12%	10	0.0
Bermuda	32,877	55%	62	2.4
Bolivia	741,658	6%	147	2.8
Botswana	53,375	2%	72	1.6
Brazil	33,332,789	16%	288	9.2
Brunei	15,043	3%	1	0.0
Bulgaria	673,441	10%	103	7.7
Canada	15,596,419	41%	182	1.2
Chile	8,767,853	46%	280	4.9
China	354,272,000*	25%	0	0.0
Colombia	4,140,197	8%	320	9.1
Costa Rica	657,301	13%	459	4.4
Croatia	919,139	22%	267	9.5
Czechia	2,835,307	26%	126	4.1
Denmark	1,560,879	27%	189	0.2
Dominican Rep.	1,825,500	17%	65	0.6
Ecuador	1,024,121	6%	94	3.6
Egypt	1,133,956	1%	11	0.6
Estonia	379,288	29%	245	2.9
Ethiopia	1,215,934*	1%	5	0.2
Finland	2,014,653	36%	38	0.3
France	18,550,890	28%	252	3.3
Germany	28,572,376	34%	136	2.2
Greece	2,615,123	25%	240	6.1
Guatemala	230,431	1%	51	1.4
Honduras	55,000	1%	87	6.0
Hong Kong	1,112,120	15%	0	0.0
Hungary	4,420,767	46%	116	10.6
Iceland	144,775	43%	12	0.0
India	137,805,245	10%	272	2.9
Indonesia	13,647,777	5%	19	0.7
Iran	1,475,436	2%	198	4.0
Ireland	1,376,583	28%	85	0.6
Israel	5,429,023	63%	4	0.1
Italy	17,714,182	29%	143	3.6
Jamaica	135,473	5%	35	1.3
Japan	3,844,717	3%	49	0.7
Kazakhstan	1,757,407	9%	124	0.2
Kenya	853,081	2%	8	0.3
Kuwait	822,000	19%	256	2.0
Laos	405,200	6%	7	0.0
Lebanon	325,383	5%	87	3.3
Lithuania	823,512	30%	443	3.5
Malaysia	1,166,737	4%	127	0.8
Maldives	301,707	56%	1,965	3.4
Malta	268,118	61%	19	0.3
Mexico	14,176,406	11%	17	1.8
Morocco	5,994,379	16%	7	0.2
Myanmar	1,900,000	3%	0	0.0
Nepal	2,091,511	7%	308	3.8
Netherlands	5,075,865	30%	385	1.4
New Zealand	268,787	6%	0	0.0
Nigeria	1,713,306	1%	0	0.0
Norway	1,505,957	28%	81	0.2

Source: OWID, JPMAM. May 12, 2021. * indicates doses administered.

	Unique people vaccinated	% of pop.	7d avg inf/mm	7d avg mort/mm
Pakistan	2,811,726	1%	19	0.6
Panama	520,260	12%	98	1.1
Paraguay	159,422	2%	319	11.2
Peru	1,476,921	4%	203	9.6
Philippines	2,024,953	2%	58	1.2
Poland	10,609,955	28%	115	8.3
Portugal	3,059,886	30%	33	0.2
Qatar	1,149,854	40%	161	1.5
Romania	3,711,304	19%	59	4.6
Russia	13,566,658	9%	55	2.3
Saudi Arabia	11,091,242*	32%	29	0.4
Serbia	2,169,340	25%	125	2.2
Seychelles	68,512	69%	2,570	0.0
Singapore	1,852,684	32%	4	0.0
Slovakia	1,289,359	24%	58	5.5
Slovenia	512,316	25%	256	1.7
South Africa	430,730	1%	33	1.0
South Korea	3,711,023	7%	11	0.1
Spain	14,318,348	31%	127	2.0
Sri Lanka	996,445	5%	107	0.8
Sweden	3,060,144	30%	457	1.6
Switzerland	2,155,259	25%	162	0.7
Taiwan*	32,389	0%	0	0.0
Thailand	1,395,130	2%	29	0.3
Trinidad	60,585	4%	236	4.7
Tunisia	372,240	3%	103	6.2
Turkey	14,711,273	17%	198	3.3
Ukraine	901,105	2%	127	6.4
UAE	5,081,853	51%	165	0.3
United Kingdom	35,722,461	53%	34	0.1
United States	153,986,312	47%	111	1.9
Uruguay	1,247,977	36%	751	13.8
Uzbekistan	1,057,094	3%	12	0.0
Venezuela	250,000	1%	42	0.6
Vietnam	887,705	1%	1	0.0
Zambia	90,916	0%	3	0.0
Zimbabwe	539,526	4%	1	0.0

Source: OWID, JPMAM. May 12, 2021. * indicates doses administered.

Top 15 countries by vaccination rate

	Unique people vaccinated	% of pop.	7d avg inf/mm	7d avg mort/mm
Seychelles	68,512	69%	2,570	0.0
Israel	5,429,023	63%	4	0.1
Malta	268,118	61%	19	0.3
Maldives	301,707	56%	1,965	3.4
Bermuda	32,877	55%	62	2.4
United Kingdom	35,722,461	53%	34	0.1
Aruba	56,594	51%	121	5.2
UAE	5,081,853	51%	165	0.3
Bahrain	821,210	48%	921	3.4
United States	153,986,312	47%	111	1.9
Chile	8,767,853	46%	280	4.9
Hungary	4,420,767	46%	116	10.6
Iceland	144,775	43%	12	0.0
Canada	15,596,419	41%	182	1.2
Qatar	1,149,854	40%	161	1.5

Source: OWID, JPMAM. May 12, 2021. * indicates doses administered.

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.

	Moderna	Pfizer	AstraZeneca	J&J	Novavax
Type	mRNA	mRNA	Vector	Vector	Recombinant
Status	Approved	Approved	Approved	Approved	Pending
Efficacy vs prevailing 2020 variants	94%; 100% vs severe infection, hosp. and deaths [T]	95% [T]	US study: 76% vs symptomatic 100% efficacy vs severe infection, hosp. and deaths [T]	72%; 86% vs severe infection [T]	95.6% [T]
Efficacy vs B.1.1.7 (UK variant)	2x reduction in neutralization [V]	"modest decline in neutralization" [V]	75% vs symptomatic 27% vs asymptomatic [T]		85% [T], 2x reduction in neutralization [V]
Efficacy vs B.1.351 (South Africa variant)	**6x reduction in neutralization [V]**	**U. of Texas: 2/3 decline in neutralization [V] Oxford: 8x reduction in neutralization [V]**	**Johannesburg study: 10% efficacy vs mild/moderate illness [T] Oxford: 9x reduction in neutralization [V]**	**64%; 82% vs severe infection [T]**	**60% [T]**
Efficacy vs P.1 (Brazil variant)		3x reduction in neutralization [V]	3x reduction in neutralization [V]		
Efficacy vs B.1.427/9 (California variant)	Effectiveness cut in half	Effectiveness cut in half			
Efficacy vs B.1.525 (Nigeria variant)					
Efficacy vs B.1.617 (India variant)					
Efficacy vs B.1.526 (NY variant)					
Storage	Normal refrigerated conditions	Ultra-cold storage (-94˚F)	Normal refrigerated conditions	Normal refrigerated conditions	Normal refrigerated conditions
Additional trial data		No COVID-related deaths in trials (across U.S., Ger., Turkey, S Afr, Brazil and Arg.)	Prevented 100% of severe infection, hosp. and deaths in UK, Brazil and S Afr trials [T]	Prevented 85% of severe infection and 100% of deaths in US, LatAm and S Afr trials [T]	No hospitalizations or deaths reported in trial participants receiving vaccine
Roll-out observations	**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 & 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. **Pfizer/Moderna:** CDC study: efficacy after 1st dose of either Pfizer or Moderna vaccines was 80%; 90% effective after 2nd dose **AstraZeneca**: In Scotland, reduced risk of hospital admission by 94% **CDC**: As of mid-April, out of more than 75 million fully vaccinated people, CDC reported 5,800 infections, 396 hospitalizations and 74 deaths				

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, CDC, 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 67% as of late April.

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.

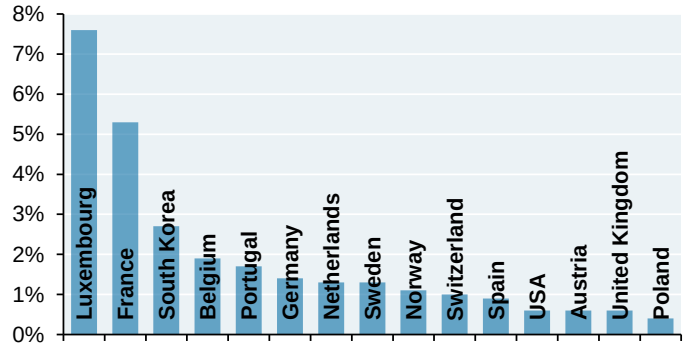
Prevalence of variants of interest or concern in countries with significant sequencing in past 4 weeks

	B.1.1.7 (UK variant)	B.1.351 (South Africa variant)	P.1 (Brazil variant)	B.1.429 + B.1.427 (CA variant)	B.1.525 (Nigeria variant)	B.1.617 (India variant)	B.1.526 (NY variant)
Austria	27.1%	0.6%	0.2%	0.0%	0.0%	0.2%	?
Belgium	71.3%	1.9%	9.2%	0.0%	0.2%	0.7%	?
France	78.6%	5.3%	1.0%	0.0%	2.2%	0.4%	?
Germany	95.7%	1.4%	0.2%	0.0%	0.4%	0.3%	?
India	2.2%	0.0%	0.0%	0.0%	0.0%	88.8%	?
Ireland	93.4%	0.1%	0.1%	0.2%	0.8%	2.2%	?
Italy	76.1%	0.2%	5.2%	0.0%	1.4%	0.9%	?
Netherlands	94.3%	1.3%	1.7%	0.0%	0.2%	0.5%	?
Poland	87.5%	0.4%	0.2%	0.0%	0.0%	0.3%	?
Spain	76.1%	0.9%	4.3%	0.0%	2.0%	0.5%	?
Sweden	91.5%	1.3%	0.0%	0.0%	0.0%	0.1%	?
Switzerland	91.7%	1.0%	0.5%	0.0%	0.3%	0.8%	?
United Kingdom	91.3%	0.6%	0.3%	0.0%	0.3%	6.4%	?
United States	72.1%	0.6%	7.7%	3.7%	0.3%	0.8%	?

Source: GISAID, Helix. May 11, 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. May 11, 2021. Only includes countries with 250 or more total genomic sequences analyzed over trailing 4 weeks.

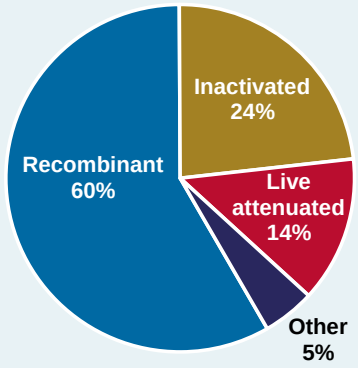
mRNA vaccines: how they work, efficacy, side effects and other Q&A (type 5)

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.

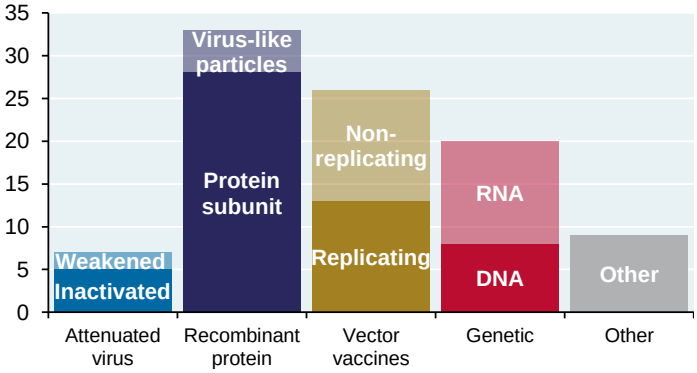
Moderna and Pfizer mRNA vaccines for COVID are the first mRNA vaccines ever approved in Western countries. As shown below, 60% of the current vaccine market is made up of recombinant protein vaccines (which we discuss later), with the rest mostly divided between the two attenuated virus types. As for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

Breakdown of existing vaccine types
% of global market share



Source: Fortune Business Insights. 2019.

COVID vaccines in development
Number of COVID vaccines



Source: *"The Race for Coronavirus Vaccines"*, Nature. 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

	COVID	COVID	COVID	INFLU	INFLU	INFLU
Side Effect	#	Freq	# per mm	#	Freq	# per mm
Hospitalized	7199	0.0032%	32.4	368	0.0002%	2.1
Disability	1443	0.0006%	6.5	174	0.0001%	1.0
Dr office visit	15527	0.0070%	69.8	2816	0.0016%	16.1
ER visit	13046	0.0059%	58.7	1065	0.0006%	6.1

Doses administered as of 4/23/2021	222,322,230	Doses administered in 2020	174,500,000

Sources: CDC Vaccine Adverse Event Reporting System, CDC Vaccine Supply & Distribution. April 23, 2021.

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".[3]

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.[4]

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.

[3] Shane Crotty, La Jolla Institute for Immunology

[4] 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. *Update: In early April, a UK regulatory agency announced that the Oxford/AstraZeneca vaccine should not be administered to patients under age 30 due to evidence suggesting a link between the vaccine and blood clots.*

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. *Update: In late April, the CDC recommended use of J&J vaccines following a temporary pause which was implemented in order to investigate linkages between the vaccine and blood clots.*

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. CanSino initiated Phase III trials in August 2020, and initial results indicate an efficacy rate of 65% in preventing symptomatic COVID cases. Like J&J, CanSino's vaccine only requires one dose, but the company is considering the use of a booster shot in light of evidence that the efficacy of the vaccine could wane over time.

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 2019[5], citing increased antibody responses to the lipid surface coating and the structural lipid layer. To reiterate, this issue pertains to very high-

[5] *"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

frequency therapeutic treatments with very large dosages, and should not be an issue for annual treatments with small dosages such as COVID vaccines.

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 2020, but suffered a setback in December. 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 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. 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, and announced an efficacy rate of 86%, leading the UAE and several other countries to authorize the vaccine for use. In December, a company press release from SinoPharm announced the vaccine showed 79% efficacy, though no trial data has yet been published.

Covaxin's vaccine candidate, also based on an inactivated virus, was developed by India-based Bharat Biotech in partnership with Ocugen, a US biopharmaceutical company. The vaccine entered Phase III trials in October 2020 after Phase I/II trials demonstrated safety and production of antibodies. Interim results from their Phase III trials among 25,000 volunteers showed the vaccine demonstrated 78% overall efficacy and 100% efficacy against severe infection. The vaccine has been approved for emergency use in India and several other countries.

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 2021 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. 1.4bn doses of the vaccine, which can be stored and distributed at regular refrigerator temperatures, are expected to be produced in 2021. Researchers also noted that efficacy after only one dose of the vaccine was 73.6%. Russian officials report that a one-dose regime may soon be registered for use.

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