Mass vaccination in 2021: What could possibly go wrong?

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- The single most important determinant of the economic outlook is health policy and, ultimately, the way out of the pandemic is mass vaccination. Our base case is that, in the US and Europe, the vaccination programs go reasonably well and herd immunity is approached by year-end. But there is a lot that can go wrong.
- There are three main concerns. First, how many people will get the vaccine? The rollout has so far been underwhelming, although the pace is picking up. For herd immunity, a high bar of at least 60% of the population would need to be vaccinated (or infected), and the bar is higher if vaccines with lower efficacy are used and for more infectious variants of the virus. But most worryingly of all, a significant proportion of people still say they would decline a vaccine, which could make herd immunity unachievable in some cases.
- Second, there is uncertainty regarding how long immunity lasts for, both via vaccination and past infection, and whether the current suite of vaccines can protect against new, more infectious, variants. Once immunity wanes, the vaccination process must start over again.
- Third, several emerging economies are lagging behind in terms of pre-ordered vaccines. This means that different parts of the world are likely to achieve herd immunity at different times.

Vaccines are the way out of this crisis

The single most important determinant of the economy last year was the prevalence of the new coronavirus (causing the disease COVID-19). Due to the absence of vaccines or effective treatments at the time, efforts to control the spread of COVID-19 focused on non-pharmaceutical interventions (NPIs), such as lockdowns, social distancing, quarantines and self-isolation, which weighed significantly on economic activity. The way out of this crisis is through health policy, via new medical treatments and, above all, vaccination to control the spread of the virus.[1] The ultimate goal is to reach so-called herd immunity, which is achieved when a sufficient proportion of the population has immunity so that the virus is unlikely to spread.

Mass vaccination, therefore, will reduce the need for future NPIs, and facilitate a return to something close to life as we knew it. This could unlock huge savings balances accumulated as a result of curbs to social consumption and strong fiscal support for incomes.

The news last November that Pfizer and BioNTech's COVID-19 vaccine had an efficacy rate of 95% (in preventing the COVID-19 disease among vaccinated people in trials) was a game-changer. Until then, while vaccines were likely to be developed, uncertainty was very high as to how effective they would be.[2] The actual result was better than anyone could have expected.[3] Following the positive vaccine news, market sentiment improved dramatically, lifting the prices of risky assets.

Our baseline assumption is that, in the US and advanced Europe, the mass vaccination program goes well and a sufficient number of individuals will be vaccinated by the winter to avoid the need for lockdowns. While this remains the most likely outcome, there are substantial uncertainties, which markets appear to be under-pricing. In what follows, we discuss what could go wrong. The concerns pertain to how many people will get the vaccine (and by when), whether this is enough to reach herd immunity, and how long immunity lasts for.

The bar for herd immunity is high (and variable)

The bar to reach herd immunity is high and in part depends on the efficacy of the vaccines deployed, as well as the transmissibility of the COVID-19 strain (the so-called basic reproduction number, or Ro).[4] Using a vaccine with a lower efficacy, and/or a more infectious variant of the disease, needs a higher proportion of the population to be vaccinated (or infected) to reach herd immunity.

At the time of writing, only vaccines developed by Pfizer-BioNTech and Moderna have obtained regulatory approval in the US (authorized for emergency use) and in the EU (conditional marketing authorisation). In the UK, a vaccine developed by Oxford University and AstraZeneca has also been approved. The EU's medicines regulator has said it could issue an opinion on the marketing authorisation of the Oxford-AstraZeneca vaccine by 29 January. All the vaccines approved so far are a two-dose regimen.

[1] To be sure, pandemics always end, even without vaccines. In the classic Susceptible-Infected-Removed (SIR) model of the spread of a virus, the susceptible population decreases towards zero, because the infected population either survive and gain immunity from infection or die. Nevertheless, clearly, the letting–the-virus-rip approach to achieving herd immunity is much riskier and would result in many more deaths than the achievement of herd immunity via vaccination.

[2] The US Food and Drug Administration said that once a vaccine is shown to be at least 50% effective and safe then it could be approved for use in the US.

[3] For comparison, the effectiveness of the common flu vaccines range from 40% to 70%, varying year-by-year.

[4] The basic reproduction number, or Ro, is defined as the number of secondary cases generated from primary cases throughout its whole infectious period without any intervention.

Several others are in late stage (phase-3) trials. Johnson & Johnson has two phase-3 trials ongoing: one testing a single-dose vaccine, the other testing a two-dose vaccine. If things go smoothly, these might obtain emergency approval in the spring.

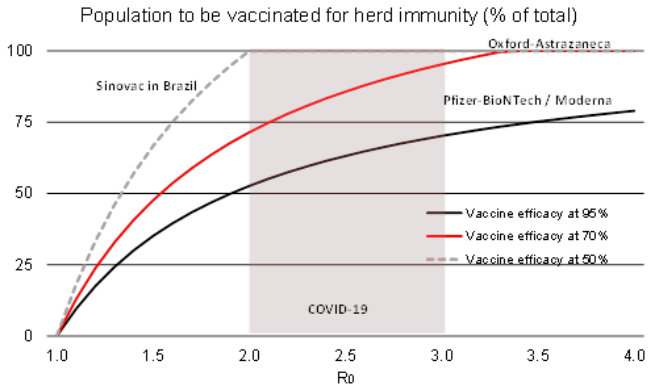
Each vaccine differs in terms of technology utilized, storage requirements and efficacy. The Pfizer-BioNTech vaccine, which uses mRNA technology, has achieved the highest efficacy rate (95%) in trials, but it poses the greatest logistical challenge as it can be stored for only up to five days at regular refrigerator temperatures, and at ultra-cold -70 degrees beforehand. The ultra-cold storage requirement is mostly a problem for emerging markets, which lack the "cold chain" capacity. The Moderna vaccine uses technology similar to that utilized by the Pfizer-BioNTech vaccine and was found to also have an efficacy rate of around 95%. It can be stored in a regular refrigerator for up to 30 days, but it is relatively expensive. The Oxford-AstraZeneca vaccine, which is an adenovirus viral vector vaccine, can be stored at temperatures achieved by typical refrigerators and is cheap, but it has been shown to have an efficacy rate of "only" around 70%. Varying efficacy rates – i.e. the percentage associated with the reduction of the disease in a vaccinated group of people compared to an unvaccinated group during trials – pose two challenges.

First, as shown in Chart 1 – and assuming a reasonable range for the basic reproduction number (R_0) of COVID-19 (the herd immunity threshold is an estimate, the precise figure varies from location-to-location depending on the features of the local population, including population mixing and demographics, as well as variants of the virus) – the Oxford-AstraZeneca vaccine would require 70-90% of the population to be vaccinated in order for herd immunity to be achieved.[5] The Pfizer-BioNTech and Moderna vaccines, instead, require that 60-70% of the population be vaccinated – a non-negligible difference for governments that have to mobilize a large amount of human, financial and physical resources to carry out vaccination campaigns.

Second, at least within the EU, citizens will be informed about the type of vaccine that they are being inoculated with. Given the sizable difference in efficacy between the vaccines, it is possible that people will agree to be inoculated only with those vaccines that are associated with the highest efficacy rates. This could create delays in take-up and put strains on the ability of producers to meet demand. Around 20% of the 2 billion vaccine doses pre-ordered by the European Commission are of the Oxford-AstraZeneca vaccine.

[5] Our estimates are based on the following theoretical formula for herd immunity: $p(t)=(1-1/R0)/\varepsilon$, where p(t) represents the percentage of the population to be vaccinated for herd immunity, R0 is the basic reproduction number and ε is the vaccine efficacy. For more detail, see *Challenges in creating herd immunity to SARS-CoV-2 infection by mass vaccination,* https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32318-7/fulltext and our *Chart of the Week* on this topic.

CHART 1: DIFFERENT HERD IMMUNITY THRESHOLDS



Source: The Lancet, UniCredit Research

The UK is taking an unorthodox approach to vaccination. In order to vaccinate as many people as quickly as possible, people will wait up to 12 weeks to get their second dose of the two-dose regimen, much longer than the recommended 3-4 weeks between doses used during the clinical trials. The US Food and Drug Administration (FDA) has said there is no data to demonstrate vaccine efficacy if the second dose is delayed.

Another uncertainty is whether vaccinated people can still infect others or not. In clinical trials, the efficacy rate measures whether vaccines protect people from becoming ill from COVID-19. That is, only those people that developed COVID-like symptoms were actually tested for the virus. We know asymptomatic people can still spread the virus to others, we don't know whether vaccination prevents this. In the extreme, vaccinated people could feel they no longer need to take precautions such as mask wearing and, inadvertently, could increase the spread of the virus. All this would make herd immunity harder to achieve.

New, more infectious, variants of COVID-19 have recently been reported in the UK, South Africa and Brazil. This led to a surge in new cases of COVID-19 in these countries. In the case of the UK variant, early evidence suggests it's between 50% and 70% more infectious than the original strain, but not more deadly. It means the R_0 number is higher and, as you can infer from Chart 1, so is the bar to reach herd immunity.

Efficacy is not the same as effectiveness

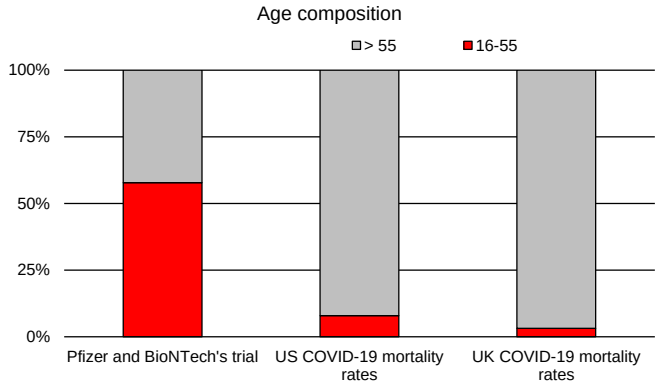
The published efficacy rates are the performance of a vaccine under ideal, clinical trial, conditions. The participants tend to be healthy and can differ in their demographics from the people that are most vulnerable to the COVID-19 disease. In contrast, effectiveness measures performance of the vaccine under real-world conditions, which is gathered from data as the vaccine is rolled out to the wider population.

Some of the most important demographics, judging by mortality rates from COVID-19, are age, ethnicity and the presence of underlying health conditions.

Typically, effectiveness of the vaccine turns out to be lower than efficacy in trials because of differences between the clinical trial sample and the population.

For example, in the case of the trials conducted on the Pfizer-BioNTech vaccine, 42% of participants were aged 55 plus, but, as shown in Chart 2, more than 90% of COVID-19-related deaths in the US and UK have been concentrated in the 55-plus age group. Around 60% and 75% of such deaths in the US and the UK have involved people older than 75, respectively. The age of the participants in clinical trials is known, and age-specific efficacy rates have been published, but the relatively small sample sizes of the older age groups make these age-specific estimates less reliable. Of course, it is possible that efficacy reported in trials for the most vulnerable individuals will be confirmed in real-world conditions, but the scientific community cannot yet guarantee this.

CHART 2: NOT SO HOMOGENOUS POPULATIONS



Source: Pfizer, CDC, UniCredit Research

Even in clinical trials the same vaccine can yield very different efficacy results in different locations. The COVID-19 vaccine developed by China's Sinovac was found to have an efficacy rate of 50% in the Brazil clinical trial, around 60% in the Indonesia trial, and above 90% in the Turkey trial.[6]

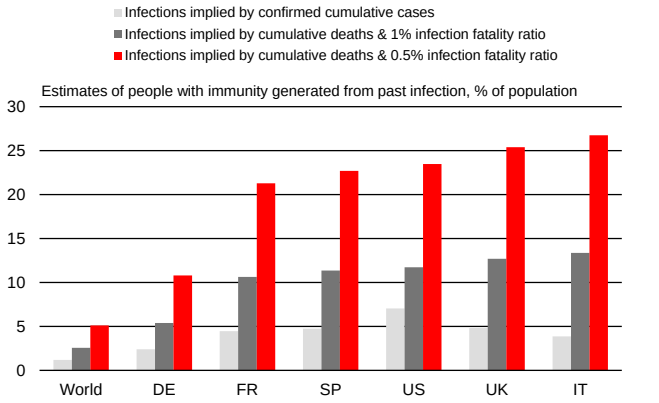
To be sure, while herd immunity is the ultimate goal, failure to reach herd immunity levels doesn't mean vaccination is not helpful. Even when the vaccine does not stop some people from getting ill, it may still reduce the worst symptoms of the disease, reducing the need for hospitalisation.

Immunity of those previously infected

People infected in the past with the virus will also have built up some immunity (via antibodies) to COVID-19 and, to the extent immunity from infection is comparable with that gained from vaccination, progress towards herd immunity should be measured against the share of the population that has either been infected or vaccinated.

Chart 3 plots estimates of the number of past infections for selected countries as a proportion of that country's population. One measure of infections is the number of confirmed cumulative cases of COVID-19. On this measure, infections total just over 1% of the world population, a little more than 2% in Germany, 4-5% in Italy, France and Spain, 5% in the UK, and 7% in the US. However, since mass testing for COVID-19 did not start in earnest until after the first wave of the virus, the cumulative number of confirmed COVID-19 cases is likely to be a gross underestimate of the number of past infections.

CHART 3: IMMUNITY GENERATED FROM INFECTION



Source: Our World in Data, UniCredit Research

A more reliable measure of the number of past infections can be computed using the number of cumulative confirmed deaths from COVID-19 (which are not really affected by the prevalence of testing) and an estimate of the so-called Infection Fatality Ratio (IFR, defined as the number of deaths divided by the number of infected persons expressed as a percentage). Based on several studies, the World Health Organisation has said the IFR is in the range of 0.5-1%.[7] Chart 3 shows the estimates of the share of the population infected in the past using these upper and lower bounds for the IFR. Using the lower bound estimate for the IFR, infections would total 5% of the world population, 10% in Germany, 21% in France, 23% in Spain and the US, 25% in the UK and 27% in Italy. This is a sizable share of the population and, to the extent immunity from infection is comparable to immunity from vaccination, it could reduce the burden on vaccination to meet herd immunity. However, in addition to using the lower bound estimate for the IFR, these figures are likely to be an overestimate of the number infected. Indeed, this is the total number of infections, not persons infected (the same person can be infected more than once).

[6] https://www.bbc.co.uk/news/world-latin-america-55642648

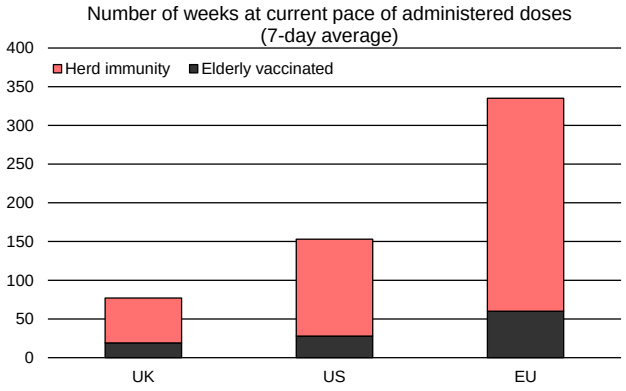
[7] https://www.who.int/news-room/commentaries/detail/estimating-mortality-from-covid-19

There are other issues to consider with immunity derived from infection. In order to not double-count when measuring progress towards herd immunity, the vaccinated must not be drawn from the previously infected group. Also, it's not clear that previous infection provides the same level of immunity (both in terms of strength and length of protection) as vaccination (an issue we will come back to later).

A slow rollout so far, but the pace is accelerating

The distribution of millions of doses of vaccine will strain human and physical resources. So far, the roll-out of the vaccination campaign in Europe and the US has been underwhelming, proceeding at a slower pace than originally expected. However, the pace of the campaign is accelerating, and it is still early days. Currently, the issue is not to do with the production of doses but rather their administration, with governments struggling to administer the doses they receive. For example, at the current pace,[8] it would take about 80 weeks for the UK and around 150 weeks for the US to achieve herd immunity (see Chart 4, which assumes that herd immunity is reached when 75% of a population has been vaccinated). At their current paces, the US and the UK would manage to completely vaccinate people aged 65 and more, who are most vulnerable to the disease, by the fall.

CHART 4: VACCINATION ROLLOUT HAS BEEN SLOW SO FAR



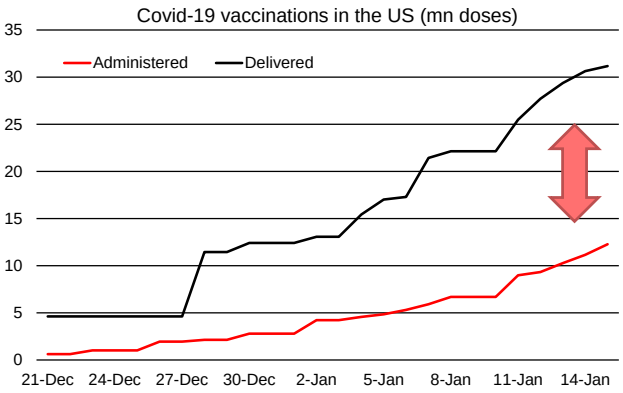
Source: Our World in Data; UniCredit Research

On the other hand, the EU, which approved a vaccine with a delay of a few weeks and started a vaccination campaign only in late December, would need 335 weeks (or eight years) to achieve herd immunity if the current pace is maintained. This merely reflects the fact that the EU has lagged the US and the UK in terms of rollout, particularly in France (there are large differences across EU member states in terms of the vaccination rollout, despite the ordering of vaccine doses being centrally managed by Brussels), but the expectation is for some catch up.

[8] Data are, depending on their availability, from between January 15 and January 17.

Indeed, the US, for example, is currently administering around 1.1mn doses a day, up from around 450,000 doses in mid-December. Chart 5 shows the acceleration in the number of vaccinations administered in the US, although this figure has not kept pace with vaccine deliveries.

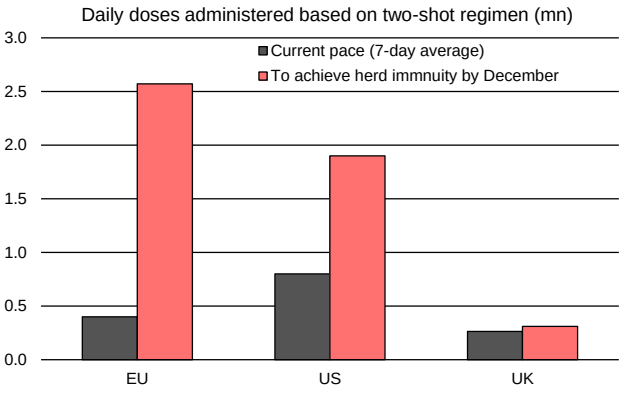
CHART 5: THE PACE IS ACCELERATING, ALTHOUGH NOT AS FAST AS PRODUCTION



Source: Our World in Data; UniCredit Research

In order for the US to achieve herd immunity by the end of the year, and thereby reduce the risk that a new round of restrictions will be necessary when temperatures drop – the virus survives longer in colder temperatures, and as the temperature drops, people tend to move indoors, where the virus is transmitted more easily – the number of doses administered there daily would have to rise from around 800k (7-day average) to 1.9mn (Chart 6). The EU would need to achieve a daily vaccination rate of about 2.5mn, and the UK of about 400,000. These estimates are based on an assumed vaccine efficacy of 75% and the assumption that two shots will have to be administered. They take into account all members of the population, including those who have contracted COVID-19 in the past.

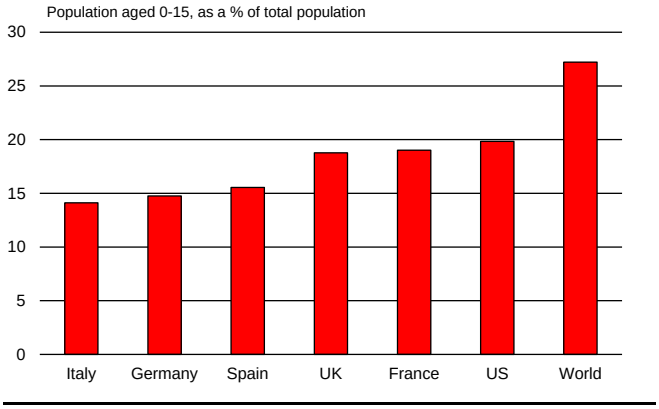
CHART 6: THE NEED TO SPEED UP THE CAMPAIGN



Source: Our World in Data; UniCredit Research

The COVID-19 vaccine trials were not tested on children and so have not been approved for use in this age group. The Pfizer-BioNTech vaccine has been approved for those aged 16 and over, while the Moderna vaccine is approved for ages 18 and over, reflecting the different age samples of the clinical trials. As a result, vaccination of this group will come later, once trials can be completed and approval obtained, which is unlikely to be before the autumn, which excludes a sizeable proportion of the population from contributing to reaching the herd immunity threshold (at least for those children that have not acquired immunity from previous infection). Chart 7 shows that the share of the population aged 0-15 accounts for around 15% of the population in Italy, Germany and Spain, just under 20% in the UK and France, 20% in the US, and more than 27% of the world population.

CHART 7: SHARE OF THE POPULATION AGED 0-15

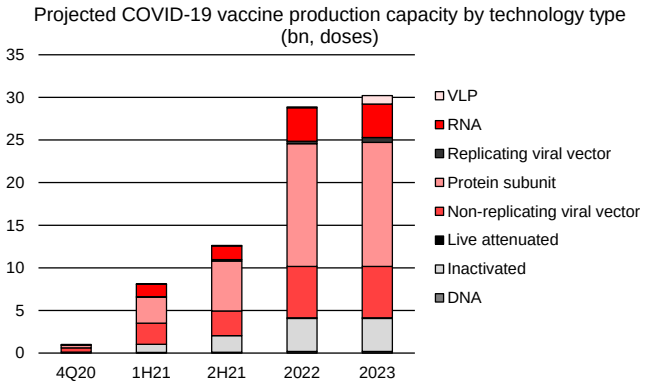


Source: United Nations, UniCredit Research

Decoupling between emerging and advanced economies

One of the main questions before the vaccination campaign started had to do with the ability of pharmaceutical companies to produce enough doses of vaccine, given huge global demand. It appears now that the risk posed by production shortfalls (of total vaccines) is likely to be low. While some constraints might emerge going forward, companies are implementing plans to expand production capacity by opening new plants across the world and expanding staff. Moreover, new vaccines will likely be released in the coming months. Therefore, more doses should be made available. According to UNICEF, in 2021 there will be around 20 billion doses available – based on forecasted production capacity by companies and on the assumption that more vaccines will be approved – more than enough to vaccinate the world population, assuming a two-dose regimen (Chart 8).

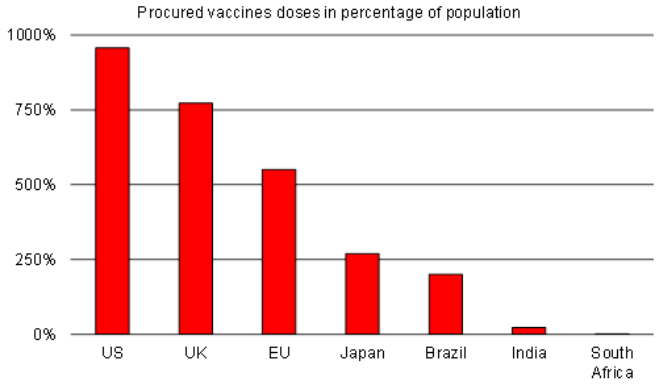
CHART 8: PRODUCTION CAPACITY NOT AN ISSUE



Source: UNICEF, UniCredit Research

However, emerging markets are likely to significantly lag behind advanced economies in vaccinating their populations, and it is hard to envision a full recovery by the global economy (including in advanced economies) until this happens. There is a large gap between advanced and emerging economies in terms of the number of pre-ordered doses of vaccine (Chart 9). Moreover, in many emerging and developing economies, cold storage chains are not sophisticated enough to manage the Pfizer/BioNTech or Moderna vaccines. Therefore, many countries are likely to need to wait for other vaccines to become available or to opt for those with lower efficacy (like the Oxford/AstraZeneca or Sinovac vaccines). This implies that different parts of the world are likely to achieve herd immunity at different times. As a result, flows of people travelling across the world might remain impaired beyond the end of 2H21.

CHART 9: EMERGING ECONOMIES HAVE INADEQUATE VACCINE PROCUREMENT



Source: UNICEF, UniCredit Research

The biggest risk is low take-up of vaccines

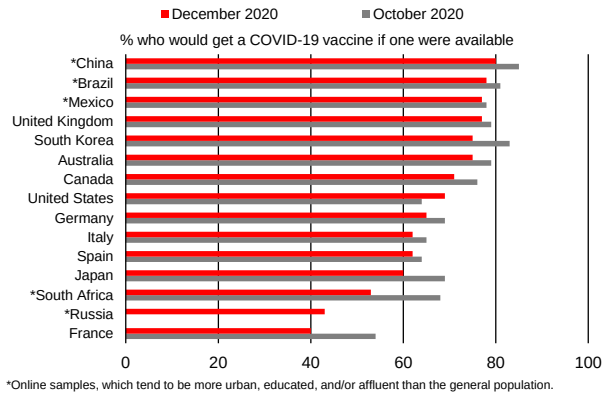
Significant proportions of the population say they would turn down a vaccine if one were offered to them, and there are large differences across countries.

Ipsos, a polling company, has regularly surveyed public opinion in several countries on the intent to get a COVID-19 vaccination. The latest survey was conducted on 17-20 December.[9] The figures are worrying, particularly for several advanced economies. Less than half of adults in France (40%), only around three-fifths in Japan (60%), Spain (62%) and Italy (62%), and around two-thirds in Germany (65%) and the US (69%) would get the vaccine if it were available (Chart 10). If so, for these countries it could mean herd immunity is out of reach.

Among advanced economies, Australia (75%), South Korea (75%) and the UK (77%) report relatively high intent to get vaccinated.

Adults in some emerging markets report higher intent to get vaccinated, including Mexico (77%), Brazil (78%), China (80%) and India.

CHART 10: COVID-19 VACCINATION INTENT



Source: Ipsos, UniCredit Research

In a separate opinion poll by the Pew Research Center specifically for the US (conducted in November 2020), 60% of respondents reported they would get a COVID-19 vaccine if it were available today, up from 51% in September 2020. The good news is that almost half of those that said they would not get a vaccine added that it's possible they would get vaccinated once people start getting a vaccine and more information becomes available.[10] Still, that leaves 21% of the US adult population who do not intend to get vaccinated and are "pretty certain" they won't change their mind.

According to a recent poll by Odoxa-Backbone, on 13-14 January, 56% of French people are now in favour of COVID-19 vaccination.[11] This is 14 points higher than the last poll it carried out on 23 December. And 77% of people aged over 65 want the vaccine. Similar to the US, 23% of people who do not yet want the vaccine say they would be more encouraged to do so if many people in France were vaccinated before them.

Currently, it seems governments are mostly against encouraging vaccination through limiting the freedoms of those people that refuse vaccination.

Uncertainty over how long immunity lasts for

Aside from how many people will get the vaccine, the other big uncertainty is how long immunity lasts for.

The CEO of Moderna, Stephane Bancel, has said that the company's COVID-19 vaccine should provide immunity for at least one year after vaccination, but uncertainty remains, given that trials are only a few months old.

There is concern that new variants of the virus (following mutations) could compromise vaccination efforts. Pfizer-BioNTech's Covid-19 vaccine is thought to be effective against a key mutation first identified in the UK and South Africa[12]. While this is welcome, experts have cautioned that the findings only look at one mutation (N501Y) found in the new variants and not at all mutations. And there is now greater concern regarding the new variant originating from Brazil. More studies and data will be needed.

[9] https://www.ipsos.com/en/global-attitudes-covid-19-vaccine-december-2020

[10] https://www.pewresearch.org/science/2020/12/03/intent-to-get-a-covid-19-vaccine-rises-to-60-as-confidence-in-research-and-development-process-increases/

[11] https://www.francetvinfo.fr/sante/maladie/coronavirus/vaccin/covid-19-56-des-francais-desormais-favorables-au-vaccin-selon-notre-sondage_4257599.html

[12] https://www.cnbc.com/2021/01/08/pfizer-biontech-vaccine-appears-effective-against-mutation-in-new-strains.html

It is normal for viruses to mutate and vaccines can be altered to be effective against new strains of the virus. The CEO of BioNTech, Uğur Şahin, has said that the sequence of the Pfizer-BioNTech vaccine can be adapted within a few days and the new vaccine delivered within six weeks. However, such changes would need to be approved by regulators and, moreover, the entirety of the vaccine's production and administration would then have to start all over again

As for immunity derived from past infection, which generates antibodies, there is mixed evidence as to how long immunity lasts for and whether the immune response is strong enough to protect against reinfection. Researchers at the University of Oxford find that acquired immunity from an initial COVID-19 infection offers protection against reinfection for six months or maybe longer.[13] Another study, published in the journal Science, found that immunity can last up to 8 months.[14] But more studies will be needed to verify this, particularly for different groups. Time will tell.

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[13] https://www.medrxiv.org/content/10.1101/2020.11.18.20234369v1
[14] https://science.sciencemag.org/content/early/2021/01/06/science.abf4063

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