THE RACE TO A COVID-19 VACCINE

ABN·AMRO

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- A total of 48 vaccines are currently in clinical trials, with two highly effective vaccines about to get emergency market access

- Emergency use or conditional marketing vaccines to be used to inoculate socially vulnerable groups as soon as early next year

- Detailed timelines and safety assessments suggest Q3 2021 will be the beginning of rollouts to the broader population

- The current wave of lockdown measures will likely be in place for a longer period given seasonal variations common to coronaviruses

- Countries will begin a rapid relaxation of lockdown rules in Q2 and especially Q3 2021, but social distancing will become a thing of the past only in 2022

- Lots of uncertainty in our analysis and several downside risks, including virus mutations or lack of public readiness to get inoculated

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Introduction

In December 2019, a novel coronavirus was identified in a wet market in Wuhan, China. Despite the Chinese government's ability to enact swift lockdowns and a ban on travel, the virus was able to spread throughout the country by infecting thousands. This novel coronavirus could not have come at a worse moment. China was already ten days into the Lunar New Year travel season, which also happens to be the largest annual human migration on the planet. By the time the lockdowns were enacted, much of the region's population was already on the move across the country.

Soon after we came to understand that this novel coronavirus is similar to the bat derived coronavirus that causes Severe Acute Respiratory Syndrome (SARS-CoV), the viral respiratory disease first identified in Guangdong, China which was responsible for the 2002-2004 epidemic. Due to its similarities with SARS-CoV, this coronavirus was named SARS-CoV-2 on 12 February 2020. The virus spreads between people by droplets from coughing and sneezing, causing the respiratory disease known as coronavirus disease 2019, or COVID-19. By using travellers' cells as hosts, SARS-CoV-2 soon reached neighbouring Asian countries, Europe and the Americas. As health services worldwide were overwhelmed with the number of COVID-19 cases, the World Health Organisation (WHO) declared a pandemic on 11 March 2020.

Ever since, the world has been disrupted in all sorts of ways, and the economic shock of the pandemic has been massive, producing the deepest global recession in decades. The economic and human toll has prompted one of the highest stakes scientific races in human history: the race to develop a safe and effective vaccine against COVID-19. Indeed, if we ever intend to return to a resemblance of previous normality, the development of such vaccine is an absolute necessity. While therapeutics can assist vulnerable populations and will certainly play a crucial role in bringing the virus under control, it will only be through a vaccine that we will get out of this pandemic. However, as we explain in this note, a vaccine on its own will not be a silver bullet. While a vaccine will certainly be necessary to get back to 'normal', a combination of non-pharmacological measures (such as social distancing and face masks), as well as therapeutics that will increase the survival rate and lower the treatment time of vulnerable populations infected with COVID-19, will be required. Cheaper and faster testing can also play a role in allowing people to return to work and leisure quickly and be a game changer for the travel and hospitality industries.

In this note, we attempt to answer the important question of when and how will vaccine development take place. Moreover, we lay out the likely path out of this wave of lockdowns around the introduction of vaccines against COVID-19. In addition, we explain the risks to our analysis, as there are more than a dozen moving parts and non-binary outcomes in every one of them.

Timelines for vaccines and restrictions

Before getting stuck in to the detailed analysis, we will get straight to the bottom line: how and when will vaccine developments take place and what will that mean for the restrictions on social and economic life?

We estimate that emergency use or conditional marketing authorisation of vaccines against COVID-19 will likely be granted by respective regulators in the second half of December or early January next year. Initially, due to limited availability of early vaccines, as well as insufficient safety data (particularly on newer, unproven technologies which the frontrunners are based on), vaccines are likely to be available mostly to healthcare and home care workers, and people above the age of 60 who are at high risk of severe disease. As time goes on and health authorities monitor safety on a larger population, it is likely that other parts of the population will have an opportunity to get inoculated. We estimate that the first vaccinations in the US and Europe will begin in January. Considering most vaccine candidates require two doses 28 days apart, it will not be until sometime in Q2 2021 that these socially vulnerable groups build some level of immunity against COVID-19. We expect large swaths of the population to gain access to vaccines starting in Q3 2021, once regulators deem that vaccinating hundreds of millions of healthy individuals is safe and that serious side effects are negligible on a population level.

Stemming from this narrative, we expect lockdowns in Europe to ease gradually starting in the end of Q1 2021 with a more rapid lifting of restrictions in Q2 and especially Q3. Still, some minimal level of stringency measures to remain for the entirety of 2021. Focusing on the near term, we expect the current (soft) lockdown measures which are in place in most major eurozone economies to remain in place for a longer period than in the first wave of lockdowns in March-April primarily due to seasonality patterns common to coronaviruses, as well as governments wanting to avoid potential third waves of virus infections. While vaccination remains our best bet in the long-term, therapeutics, as well as non-pharmacological measures (face masks, quarantines, social distancing) can be powerful weapons in an arsenal to contain COVID-19. Widespread testing will also play a key role in certain regions. We think all of the aforementioned will be necessary to end the pandemic return to 'normal'. See below for our assumptions regarding the likely path for vaccines and lockdown measures.

	Vaccine timeline	Restrictions timeline
Q4 2020	Emergency use vaccine approved by end of the year	Partial lockdown across Europe
Q1 2021	Countries continue preparation of vaccine distribution infrastructure and begin inoculation of socially vulnerable groups around mid Q1	Lockdown restrictions continue from Q4 2020 with varying stringency per region
Q2 2021	Immunity of a large part of socially vulnerable populations is achieved	Countries start lifting restrictions as a large part of vulnerable groups have achieved vaccine induced immunity
Q3 2021	Broader parts of the population gain access to vaccines	More rapid lifting of restrictions as more people get vaccinated and more and better therapeutics become available
Q2 2022	So-called herd immunity, or a situation which allows all level of restrictions to be ignored without any risks of outbreaks is achieved	Stringency index reaches zero and countries return largely to 'normal'

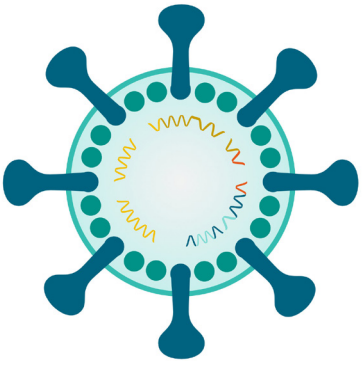
source: ABN AMRO Group Economics

Vaccines currently in development

While there are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19, more than 200 vaccines are being developed according to the WHO, of which 48 are in clinical evaluation. All vaccines currently in development aim to expose the body to an antigen (a molecule that is able to generate antibodies in our immune system) that will not cause disease, but will provoke an immune response that can block or kill the virus if a person becomes infected. There are at least four different types of vaccines currently in pre-clinical and human trials.

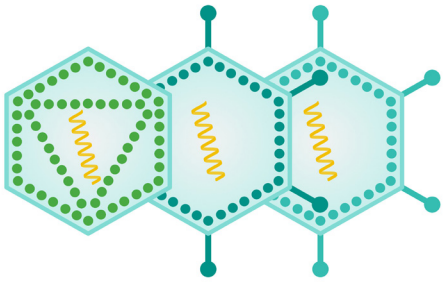
VIRUS VACCINES

The virus is either modified (weakened) by altering its genetic code or completely inactivated (rendered non-infectious) using chemicals. Making them requires large quantities of infectious virus. The advantage of an attenuated live virus is that it induces the same immune response as natural infection. The disadvantage as aforementioned is that large quantities of the virus are required. Most vaccine candidates developed by Chinese firms use this type of technology, which is the same technology used in for example measles, rubella, mumps, yellow fever, and small pox vaccines.



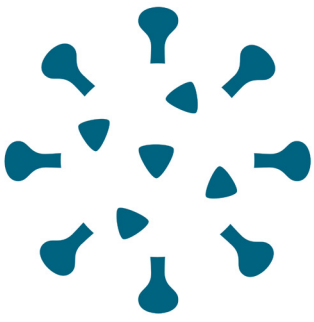
VIRAL VECTOR VACCINES

A virus such as adenovirus is genetically engineered so that it can produce the coronavirus proteins in the body. Like virus vaccines, these viruses are weakened so they cannot cause disease. The safe virus serves as a 'platform' or 'vector' to deliver the protein that triggers an immune response. A vaccine candidate being developed by the University of Oxford and AstraZeneca, as well as a candidate in development by Johnson & Johnson use this technology.



PROTEIN-BASED VACCINES

A protein is extracted from the virus (alive or inactivated), purified, and injected as a vaccine. For coronavirus, this protein is the spike protein. Virus-like particles (VLP) work in the same way. These use fragments of protein shells that mimic the coronavirus's outercoat. These can trigger a strong immune response, but can be challenging to manufacture. To work, these vaccines might require adjuvants (immune stimulating molecules) delivered alongside the vaccine.



NUCLEIC ACID VACCINES

Instead of a virus, a protein antigen, or a virus expressing the protein, nucleic coding for the antigen is injected. DNA plasmid enters the nucleus and gets translated into messenger RNA (mRNA hereafter) for expression of protein. mRNA can also be directly injected (no translation required), but this is less stable than DNA. RNA- and DNA-based vaccines are safe and easy to develop as producing them involves making genetic material only, not the virus itself. However, this technology is new and unproven as no DNA- or RNA-based vaccines have been commercialized in human beings. Finally, while producing nucleic-acid vaccines may be easier, logistically they present challenges as they must be stored at freezing temperatures. For example, the vaccine candidate being produced by Pfizer and BioNTech needs to be stored at -70^{o}C.

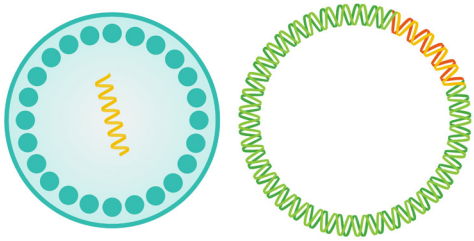


Fig1 Pipeline of COVID-19 vaccine candidates in clinical trials

Developer/manufacturer	Vaccine platform	Number of doses	Timing of doses	Clinical stage
Beijing Institute of Biological Products/Sinopharm	Inactivated	2	0, 21	Phase 3
Bharat Biotech	Inactivated	2	0, 14	Phase 3
BioNTech/Fosun Pharma/Pfizer	RNA	2	0, 28	Phase 3
CanSino Biological Inc./Beijing Institute of Biotechnology	Non-Replicating Viral Vector	2	0, 28	Phase 3
Gamaleya Research Institute	Non-Replicating Viral Vector	2	0, 21	Phase 3
Janssen Pharmaceutical Companies	Non-Replicating Viral Vector	1 or 2	0 or 0, 56	Phase 3
Medicago Inc	VLP	2	0, 21	Phase 3
Moderna/NIAID	RNA	2	0, 28	Phase 3
Novavax	Protein Subunit	2	0, 21	Phase 3
Sinovac	Inactivated	2	0, 14	Phase 3
University of Oxford/AstraZeneca	Non-Replicating Viral Vector	2	0, 28	Phase 3
Wuhan Institute of Biological Products/Sinopharm	Inactivated	2	0, 21	Phase 3
Anhui Zhifei Longcom Biopharmaceutical/Institute of Micro-biology, Chinese Academy of Sciences	Protein Subunit	2 or 3	0, 28 or 0, 28, 56	Phase 2
Beijing Wantai Biological Pharmacy/ Xiamen University	Replicating Viral Vector	1		Phase 2
Curevac	RNA	2	0, 28	Phase 2
Arcturus/Duke-NUS	RNA			Phase 1/2
Beijing Minhai Biotechnology Co., Ltd	Inactivated	2		Phase 1/2
Biological E Ltd	Protein Subunit	2	0, 28	Phase 1/2
Cadila Healthcare Limited	DNA	3	0, 28, 56	Phase 1/2
Genexine Consortium	DNA	2	0, 28	Phase 1/2

Inovio Pharmaceuticals/ International Vaccine Institute	DNA	2	0, 28	Phase 1/2
Institute of Medical Biology, Chinese Academy of Medical Sciences	Inactivated	2	0, 28	Phase 1/2
Israel Institute for Biological Research/Weizmann Inst. Of Science	Replicating Viral Vector	1		Phase 1/2
Kentucky Bioprocessing, Inc	Protein Subunit	2	0, 21	Phase 1/2
Osaka University/ AnGes/ Takara Bio	DNA	2	0, 14	Phase 1/2
Research Institute for Biological Safety Problems, Rep of Kazakhstan	Inactivated	2	0, 21	Phase 1/2
Sanofi Pasteur/GSK	Protein Subunit	2	0, 21	Phase 1/2
SpyBiotech/Serum Institute of India	VLP	2	0, 28	Phase 1/2
CanSino, Biological Inc/Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China	Non-Replicating Viral Vector	2	0, 28	Phase 1
Clover Biopharmaceuticals Inc./GSK/Dynavax	Protein Subunit	2	0, 21	Phase 1
COVAXX	Protein Subunit	2	0, 28	Phase 1
COVAXX / United Biomedical Inc. Asia	Protein Subunit	2	0, 28	Phase 1
FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo	Protein Subunit	2	0, 21	Phase 1
ImmunityBio, Inc. & NantKwest Inc.	Non-Replicating Viral Vector	2	0, 21	Phase 1
Imperial College London	RNA	2		Phase 1
Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme	Replicating Viral Vector	1 or 2	0, 28	Phase 1
Instituto Finlay de Vacunas, Cuba	Protein Subunit	2	0, 28	Phase 1
Instituto Finlay de Vacunas, Cuba	Protein Subunit	2	0, 28	Phase 1
Ludwig-Maximilians - University of Munich	Non-Replicating Viral Vector	2	0, 28	Phase 1
Medigen Vaccine Biologics Corporation/NIAID/Dynavax	Protein Subunit	2	0, 28	Phase 1
Merck Sharp & Dohme/IAVI	Replicating Viral Vector	1		Phase 1
People's Liberation Army (PLA) Academy of Military Sciences/Walvax Biotech.	RNA	2	0, 14 or 0, 28	Phase 1
ReiThera/LEUKOCARE/Univercells	Non-Replicating Viral Vector	1		Phase 1
University Hospital Tuebingen	Protein Subunit	1		Phase 1
University of Queensland/CSL/Seqirus	Protein Subunit	2	0, 28	Phase 1
Vaxart	Non-Replicating Viral Vector	2	0, 28	Phase 1
Vaxine Pty Ltd/Medytox	Protein Subunit	1		Phase 1
West China Hospital, Sichuan University	Protein Subunit	2	0, 28	Phase 1

Source: World Health Organisation, ABN AMRO Group Economics

Why are there so many COVID-19 vaccines currently in development?

There are many different vaccines against COVID-19 currently in development. That is in part because we do not know which ones will be effective and safe. Different vaccine platforms may be good at inducing a different type of immune response and at activating certain arms of the immune system. For example, protein vaccines (such as the Novavax vaccine) do not induce a CD8T cell response, but produce a very high antibody response (B-cells). T-cells, especially CD4T and CD8T, are crucial in eliciting a specific and adequate immune response and producing long-term immunological memory. Given that we still do not know what we need to protect against COVID-19, it is likely that we want to have many options that activate different arms of the immune system. It is highly likely that there will be different vaccines for different people to create different immune responses. For instance, some vaccines may work better in older people, as the immune system weakens with older age. Some vaccines may also work better in certain ethnic groups. Having many vaccines in development maximizes the chances of success by having a broad range of options.

HOW DOES VACCINE DEVELOPMENT WORK?

The typical vaccine development timeframe takes approximately 10-15 years. Certain vaccines such as the rotavirus vaccine took over 25 years to develop, while the first Ebola virus vaccine was developed through an accelerated pathway, which took only 5 years. Luckily, the current situation has allowed vaccine development for COVID-19 to be compressed to an even shorter timeframe of merely 12-18 months. Governments have taken the financial risk away from pharmaceutical companies by fronting a large part of the costs which allows pre-clinical, clinical and manufacturing processes to occur in tandem. Several companies have begun producing vaccines before knowing if the product is safe and effective.

With regards to how vaccine development looks in practice, the typical vaccine development process begins with companies testing potential vaccine candidates in animal models (typically rats and non-human primates) to see if a vaccine can induce an immune response. Safety is also tested to see if no adverse effects occur upon inoculation. Vaccine candidates who are successful can move on to clinical or human trials, where they begin Phase 1, which involves a small group of healthy adult volunteers (typically in ages 18-35) who receive the vaccine to test for dosing and safety. Upon completion, the vaccine candidate enters Phase 2 of clinical trials where the vaccine is given to hundreds of people who have characteristics (such as age and physical health) similar to those for whom the new vaccine is intended for to see if the vaccine remains safe and consistently immunogenic. Phase 3 is when tens of thousands of people get the vaccine (or a placebo) and are allowed to naturally experience the world. It takes time before the trial gets enough individuals enrolled. Trial participants in Phase 3 keep a weekly log of any symptoms or complaints they experience, or they can report these directly. Once enough infections occur within the trial, efficacy and safety is determined. This process actually takes several months. Typically, vaccines get licensed by a regulatory authority after the completion of Phase 3 trials, but emergency authorisation may be issued before the formal completion of clinical trials. Once a vaccine is licensed or approved for emergency use, so-called Phase 4 involves ongoing studies subsequent to approval to monitor adverse events and to study long-term effects of the vaccine in the population.

- Pre-clinical - Vaccine is tested in animal models for efficacy and safety
- Phase 1 - Small groups of healthy adult volounteers receive the vaccine to test for safety
- Phase 2 - Vaccine is given to people who have characteristics (such as age and physical health) similar to those for whom the new vaccine is intended
- Phase 3 - Vaccine is given to tens of thousands of people and tested for efficacy and safety
- Phase 4 - Ongoing studies after the vaccine is approved and licensed, to monitor adverse events and to study long-term effects of the vaccine in the population

WHO IS RESPONSIBLE FOR AUTHORIZING VACCINES?

In the US, the government authority responsible for authorizing vaccines is the Food & Drug Administration (FDA). The EU's equivalent to the FDA is the European Medicines Agency (EMA). The WHO has stated, and the FDA has agreed, that a vaccine against COVID-19 should be at least 50% effective. The EMA has actually not communicated a minimum efficacy threshold for a COVID-19 vaccine, but it is likely to be in line with the recommendation from the WHO.

In the US, the FDA vaccine advisory committee sets out a couple of dates each month to be able to review the data and provide advice. However, the FDA's role is to essentially permit companies to sell or distribute a vaccine. It is the role of the Centre for Disease Control (CDC) to recommend vaccines through the Advisory Committee on Immunization Practices (ACIP). The ACIP will independently review the data following approval by the FDA to make a recommendation. Hospitals and medical practices are likely going to wait for a recommendation by the ACIP, which will not come until a later stage. In addition, several states within the US have or are going to form their own vaccine advisory committees to independently review the data.

In Europe, the EMA can grant a conditional marketing authorisation in situations where vaccines' immediate benefits outweigh the risks with less comprehensive data than normally required. An accelerated assessment reduces the conditional approval timeframe to 150 days. However, a dedicated group—the COVID-19 European Medicines Agency Pandemic Task Force—has been created and provides scientific advice on COVID-19 clinical trials and product development. A 'rolling review' within this setup speeds up the assessment of a vaccine against COVID-19, so essentially the approval timeframe should be under 150 days.

WHICH VACCINES WILL BE READY FIRST?

As shown in Figure 1, 12 vaccine candidates are currently in advanced Phase 3 trials. Several Chinese vaccine candidates have already received emergency use authorisations in China. One of the two vaccines developed by Sinopharm has also been approved in the UAE for emergency use. The EMA's human medicines committee (CHMP) has initiated rolling reviews of the AstraZeneca, Pfizer/BioNTech, and Moderna vaccines on 1 October, 6 October, 16 November, respectively.

Of the vaccine candidates in late-stage development in the West, the closest to approval are the Pfizer/BioNTech and Moderna products. The AstraZeneca vaccine should be next in line, followed by the vaccine in development by Johnson & Johnson's Jansen subsidiary. The protein-based vaccine candidate developed by Novavax should be last amongst these. The Pfizer/BioNTech vaccine hit its case accrual for its final efficacy analyses, while the Moderna and AstraZeneca vaccines hit their case accrual for its first interim efficacy analyses. All three products showed high effectiveness, at 95%, 94.5%, and 70% respectively. The AstraZeneca vaccine candidate did show 90% effectiveness in the one-dose study cohort, but further examination of the clinical data is required before drawing any conclusions. These are high levels of efficacy in comparison to existing vaccines, so these results are extremely encouraging. The Pfizer/BioNTech and Moderna vaccines will likely be granted emergency use authorisation in the US and Europe in the back half of December or early next year. The UK trial of AstraZeneca was the first to begin Phase 3 studies already back in May, and despite being setback temporarily by a pause, could be granted a conditional marketing approval in Europe early next year, and probably earlier in the UK. Data from the Johnson & Johnson and AstraZeneca US trials should be available sometime in Q1 2021 and emergency use authorisation granted shortly thereafter. The Novavax vaccine candidate is currently conducting a Phase 3 study in the UK and will start their larger US study any day now. Novavax could be granted an emergency use license in the first half of 2021.

	Pfizer-BioNTech	Moderna	AstraZeneca	Johnson & Johnson	Novavax
Vaccine platform	mRNA	mRNA	Non-Replicating Viral Vector	Non-Replicating Viral Vector	Protein Subunit
Number of doses	2	2	2	1	2
Trial size (N)	44000	30000	US: 30000 UK: 12330	60000	15000
Randomization	1:1	1:1	US: 2:1 UK: 1:1	1:1	1:1
Number vaccinated	22000	15000	US: 20000 UK: 6335	30000	7500
Doses	Day 0 and 28	Day 0 and 28	Day 0 and 28	Day 0	Day 0 and 21
Number of Events at Trial End	164	151	150	154	152
Interim analyses at	32, 62, 92, 1201	53, 1062	53, 75	Has several criteria	66, 110
Trial start	27 July	27 July	US: 28 Aug UK: 28 May	21 Sep	28 Sep
Trial end	May 2021	Oct 2022	US: Oct 2022 UK: May 2021	Mar 2023	January 2022
First possible date for half of subjects to reach 2 months safety	Third week of November	End November	US: Q1 2021	Q1 2021	Q1 2021
Estimated earliest emergency use authorization granted by regulator	December	December	Q1 2021	Q1 2021	Q1 2021
First possible date for all subjects to reach 2 months safety data	End January	15 Jan	H1 2021	H1 2021	H1 2021
First possible date for all subjects to reach 6 months safety data	End May	May	H2 2021	H2 2021	H2 2021
Expected full licensing of vaccine for broad use	Q3 2021	Q3 2021	Q4 2021	Q4 2021	Q4 2021
Logistics	Tough	Normal3	Normal	Normal	Normal

1) Following discussions with the FDA, Pfizer/BioNTech agreed to drop the 32 case interim analysis and conduct the first interim analysis at the minimum of 62 cases. Upon conclusion of discussions with the FDA, the case count had already reached 94 and the Data and Monitoring Committee (DMC) performed its first interim analysis on all cases.
2) Moderna completed its first interim efficacy analysis at 95 cases. It expects the EUA to be based on the final analysis of 151 cases.
3) Moderna announced that its vaccine candidate is now expected to remain stable at standard refrigerator temperatures of 2°C to 8°C for up to 30 days.
Source: World Health Organisation, Pfizer, Moderna, AstraZeneca, Oxford University, Johnson & Johnson, Novavax, Bloomberg Intelligence

Who will get a shot and when?

It will take time for large swaths of the broad population to get inoculated once one of the aforementioned vaccines is successfully developed. Manufacturing capacity will be initially limited and vaccine availability will be in the hundreds of million doses for the first few months following approval (which is low considering two doses are required under most vaccines). However, production capacity will not be the biggest hurdle to overcome. Instead, it is unlikely that regulators will provide authorisation to give these vaccines to everybody with limited safety data. Initially, vaccines are likely to be used very carefully in people that are at high risk of severe disease. According to health authorities in the US and Europe, these are likely to be frontline health workers, people in care homes, and those with comorbidities such as obesity or diabetes. For example, the European Commission has out guidelines on a strategy to vaccine distribution:

Priority groups to consider by EU states	Considerations
Health care and long-term care facility workers	Essential workers with significantly elevated risk of being infected Carry out essential functions to combat the pandemic
People above 60 years of age	Age-based elevated risk of severe disease or death In particular those living in high risk situations such as long-term care facilities
Vulnerable population due to chronic diseases, co-morbidities and other underlying conditions	Elevated risk of severe disease or death Examples of risk factors: obesity, hypertension, asthma, heart conditions, pregnancy
Essential workers outside the health sector	Teachers, child care providers, agriculture and food sector workers, transportation workers, police officers and emergency responders
Communities unable to physically distance	Dormitories, prisons, refugee camps
Workers unable to physically distance	Factories, meat cutting plants and slaughterhouses
Vulnerable socioeconomic groups and other groups at higher risk	Socially deprived communities to be defined according to national circumstances

Source: European Commission, ABN AMRO Group Economics

In the US, Helene Gayle co-authored a government-commissioned report on how to distribute a coronavirus vaccine (see here). The conclusion of the report is that vaccines should be allocated in a way that maximizes benefits to patients and saves the greatest number of lives possible. The report recommends distributing a vaccine in four phases. Phase 1 would include front line workers followed by older adults living in congregate settings, such as nursing homes and similar settings. The last part of Phase 1 would include select high-risk individuals with underlying conditions. Phase 2 would allow immunization of older adults not included in Phase 2. Phase 3 is when vaccine supplies would become available to a broader set of the population who are essential to restoring full economic activity (including both adults and children). An important caveat is that broad immunization of children (who are at low risk of severe disease, but can spread to virus to the immunocompromised) is dependent on whether new COVID-19 vaccines are tested and approved on children, which is currently not the case with any vaccine candidate in development. Finally, Phase 4 would include all other healthy adults who are not included in Phase 3.

Overall, initial vaccines approved for emergency use will likely only be used on a limited subset of the population which meets this criteria. Only once enough safety data is available (probably six months following the last dose on all trial participants) will the FDA and EMA fully license a vaccine for broad use. There are different levels of evidence that are needed to establish safety in pharmaceuticals, but in the case of a vaccine against COVID-19, where you are potentially going to be vaccinating billions of people, the level of evidence needed is very high. We estimate that vaccines will be fully licensed in the US and Europe beginning in H2 2021 once sufficient data around safety is established. This assumption around safety is built around typical review periods by the FDA and EMA before granting full approval or marketing licenses. The median FDA review period for vaccines in the past 10 years has been 12 months. However, COVID-19 vaccine trials are significantly larger than traditional vaccine trials in the past decade. For instance, the median vaccine trial size approved by the FDA in the past 10 years was around 6,700, while COVID-19 vaccine trials have around 30,000 subjects (Puthumana et al., 2020). More participants to collect safety data from is likely offset by increased safety requirements around newer and unproven technologies such as RNA-based vaccines. The fact that hundreds of millions of people will require vaccinations in Europe and North America alone also implies that safety evidence will need to be large. We think six months of safety data on full trial population seems like a reasonable assumption in this context.

What else will be important to return back to 'normal'?

While a lot of emphasis has been placed on the successful development of a vaccine, additional factors will play a crucial role in containing the virus and allowing society to return closer to 'normal'. While non-pharmacological (social distancing, face masks, quarantines) will likely be required for most of 2021, therapeutics can play a role in increasing the survival rate and lowering the treatment time of those infected with severe disease that require hospitalization. It is also likely that regulators will be more lenient on approving therapeutics as these are typically used in sick populations (whereas vaccines are given to healthy individuals) and thus require less safety evidence. Several companies are developing therapeutics in the form of cocktails of neutralising antibodies, such as Regeneron, GlaxoSmithKline (GSK), and AstraZeneca. Ely Lilly's antibody bamlanivimab and Regeron's casirivimab and imdevimab recently received FDA emergency use authorisation. Also, the FDA and EMA has already granted emergency use authorisation to Remdisivir and Dexamethasone. However, the decision by both regulators to grant an emergency use authorisation to Remdisivir, which not only showed mixed effectiveness in clinical trials, but also was recently recommended against by the WHO, illustrates well our point that regulators are less concerned about safety and efficacy in therapeutics. We do not think any of the aforementioned currently approved therapeutics will be game changers, but certainly more and better therapeutics will become available in upcoming months.

Aside from therapeutics, widespread testing can play a pivotal role in reigning in the virus. Rapid tests can allow people to return to work quicker and can revitalize several industries that rely on close proximity (such as travel and hospitality). The speed and accuracy of rapid tests has improved since the onset of the COVID-19 pandemic and many countries and regions have begun wide implementation of such testing kits. For example, countries such as Slovakia have reportedly been able to test the majority of their population in a matter of a few days. However, rapid testing has some hurdles such as false negatives/positives as was common in the case of Slovakia. Testing may also increase disobedience in other non-pharmacological measures (social distancing and wearing face masks). Logistical hurdles are also something to consider.

What could go wrong?

Lots of factors could affect the timeline of vaccine development and subsequent distribution:
Virus mutations: The ability of SARS-CoV-2 to mutate into strains which could evade antibody dependent immunity, or in other words could make the effect of future vaccines or therapeutics less effective or even ineffective, has always been considered as one of the biggest downside risks since the start of the pandemic. Coronaviruses have a single-stranded RNA genome with a relatively high mutation rate. The longer the virus spreads amongst a large population, the higher the chances that it will mutate. In monitoring the potential for serious mutations, the evolution of the SARS-CoV-2 surface protein, spike (S), which is responsible for viral entry, has been of particular interest. It has also been of particular interest since almost all vaccine candidates against COVID-19 target the spike protein. So far, this part of the virus has shown little change over time. However, recent scientific research has brought forward evidence that a particular mutation of the spike (s) protein, resulted in the mutated virus being able to infect a sizeable fraction of people recovered from infection (see here). In addition, the Prime Minister of Denmark held a press conference recently where he cautioned about 12 cases of COVID-19 identified in the country with a unique variant tied to minks. Minks can act as a reservoir of SARS-CoV-2 and pass the virus to humans. It remains a concern when any animal virus spills in to the human population. On the plus side, the RNA-based approach used by Moderna and Pfizer/BioNTech can be rapidly deployed to produce a different vaccine if the virus mutates enough to evade the current version.

Manufacturing and distribution: Once vaccine safety and efficacy has been established and vaccines have received necessary authorizations, transport and logistics will be the next challenge in reigning in the virus. Vaccine production and distribution is an important step in achieving herd immunity that has been traditionally a bottleneck, particularly in regions with poor infrastructure. Different vaccine platforms have different temperature requirements for storage and transportation. In addition, most vaccine candidates have to be given in two doses, and on a particular schedule (typically 21 or 28 days),

which adds a whole other logistical obstacle. Over time, stringent temperature requirements may be relaxed if vaccine efficacy at higher temperatures is proven by stability testing or formulations are improved that increase stability. For example, Pfizer's vaccines will be formulated and placed in cold storage in its facility in Kalamazoo, Michigan. During shipment and distribution, Pfizer's mRNA vaccine must be kept at -70C. Packaged vaccines will be equipped with a GPS-tracked thermal sensor to monitor location and temperature. However, the company is developing a powder form of the vaccine. Vaccines are often reconstituted with a liquid and then injected. While initially getting Pfizer's vaccine to places with insufficient freezing storage capacity or last mile cooling facilities may present an initial hurdle, future formulations may overcome this challenge. Indeed, it will certainly be a challenge to distribute billions of doses globally in freezing temperatures.

According to a white paper by DHL on vaccine distribution (see here), most countries in Western Europe and North America have advanced logistics systems which make distribution of vaccines with stringent temperature requirements feasible. While logistics and distribution will be challenging, much of the West has adequate infrastructure to cope with vaccines which require deep freeze transportation and storage. Concerns around logistics are more relevant for countries in Africa, South America and Asia which have insufficient cold-chain logistics to supply RNA- and DNA-based vaccines at scale. Public readiness to get vaccinated: Scepticism about vaccines is prevalent among certain parts of the general public. Even if a vaccine is successfully developed and approved, people's unwillingness to get inoculated could represent a significant barrier to achieve herd immunity or bring the virus under control. In a poll conducted by the New York Times and Siena College, 33% of Americans said they would definitely or probably not take a vaccine after FDA approval. A program of public interviews conducted by the Reagan-Udall Foundation for the FDA highlighted the broad scepticism among the US public. In particular, concerns around sacrificing scientific integrity by speeding up the vaccine development process abound. Indeed, the European Commission expects the speed at which COVID-19 vaccines are being developed to make the build-up of trust in such vaccines particularly challenging. Lack of public readiness to get inoculated could seriously diminish the value of vaccination.

What does vaccine developments mean for the return to 'normal'?

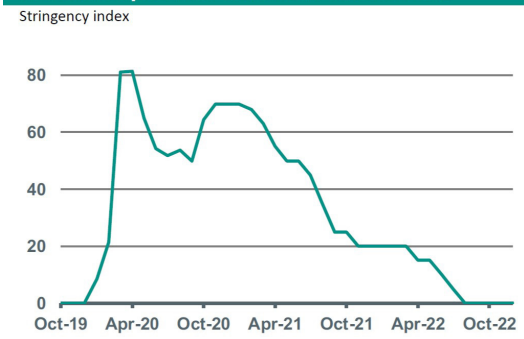
Overall, several vaccine candidates are still undergoing late-stage Phase 3 trials and are unlikely to be approved for broad use in the near term, which means that broad availability and mass inoculation will still take time. What does that mean for the return to 'normal'? Even if vaccines are approved, it will take time for the vulnerable and key workers to achieve immunity so lockdowns across Europe and in parts of the US will remain in place in the near term.

Since the second half of October, all major eurozone countries have entered a partial lockdown. This second round of lockdowns will lead to a deep contraction in the eurozone economy, but will be much less sharp than during the first round of lockdowns earlier this year. The lockdowns are less severe this time, and the most affected sectors are already operating at a lower level of capacity. In addition, manufacturing and trade will be more resilient because factories will remain open, while key Asian economies (that have the virus under control) are currently experiencing a strong recovery. Another reason for the less severe hit is that individuals and companies have adjusted to the virus compared to the first wave. The duration of the second round of lockdowns will vary from country to country. We expect the current restrictions in the eurozone to remain more or less at the current level until February 2021. The reason why we expect the current round of lockdown restrictions to be in place for a longer period than the first wave of lockdown measures in March-April is due to seasonality patterns common to coronaviruses and governments' likely wanting to avoid a potential third wave of COVID-19.

The US is arguably in the third wave of infections and the spectre of regional lockdowns has increased in tandem with rising hospitalizations. We think that states that account for roughly a third of the economy will likely go into lockdown.
The rollout of an effective vaccine to the vulnerable and key workers will coincide with a significant lifting of restrictions in Q2 of next year and especially Q3. Better and faster COVID-19 testing

mechanisms, as well as therapeutics will also help further unwound restrictions. This will trigger rapid economic growth in both Europe and the US from around Q2 onwards. See below for an indicative path for eurozone restrictions:

Indicative path for eurozone restrictions



Source: Oxford University, Bloomberg, ABN AMRO Group Economics

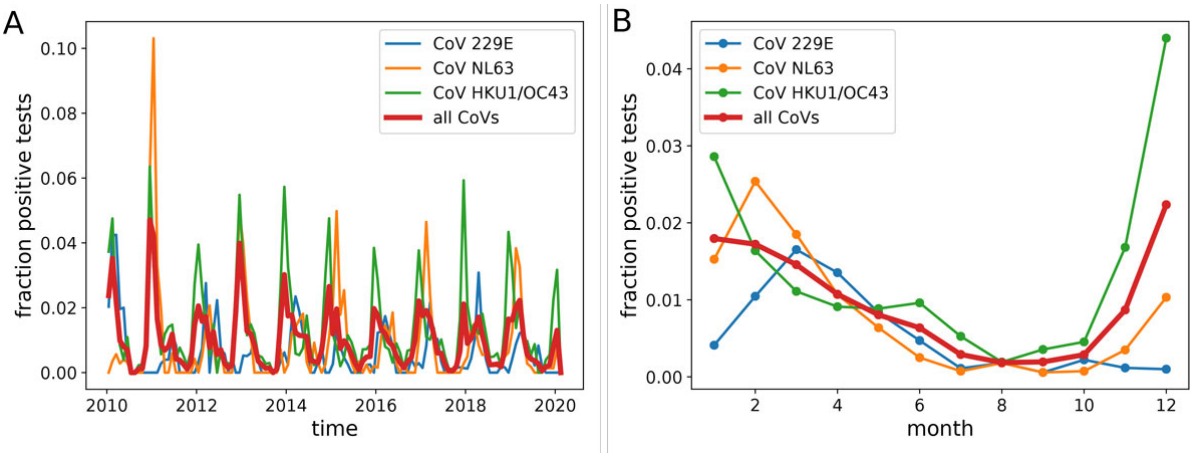
However, to truly get back to 'normal', or a situation in which all concerns around social distancing are eliminated (the stringency index returns back to zero), building herd immunity will be arguably required. Herd immunity refers to "the protection of susceptible individuals against an infection when a sufficiently large proportion of immune individuals exist in a population. In other words herd immunity is the inability of infected individuals to propagate an epidemic outbreak due to lack of contact with sufficient numbers of susceptible individuals" (Omer et al., 2020). Herd immunity is a safe way to protect people who are unable to receive a vaccine—they are either too young or they are immunocompromised. The herd immunity threshold for SARS-CoV-2 is estimated to be ~67% assuming the basic reproductive number (R0) is still three (i.e., one infected individual infects three new individuals). Based on this figure, ~5 billion vaccine doses are required for a single dose vaccine, or possibly ~10 billion in case of two-dose vaccines, assuming a vaccine is 100% effective.

The ability to induce herd immunity on the population will ultimately depend on how effective vaccines are and how many people are willing to accept getting vaccinated. If most vaccine candidates demonstrate 94-95% effectiveness as the Pfizer/BioNTech and Modern RNA-based products have shown in their interim efficacy analyses, then developments on that front look promising.

Coronaviruses and seasonality

Most coronaviruses, like most viral infections, tend to follow seasonal patterns with high incidence during winter in temperate regions and during the rainy season in tropical regions. Despite the fact that SARS-CoV-2 continued to be spread throughout the summer months does not imply that this coronavirus does not exhibit seasonality. In fact, a study by Neher et al. (2020) shows a strong and seasonal variation of four seasonal coronaviruses. The authors found that transmissibility was ten-fold from December to April versus July to September in Sweden.

Four different coronaviruses show a strong and consistent seasonal variation



Seasonal variation in the fraction of positive CoV tests in Stockholm, Sweden. Panel A shows test results between 2010 and 2019. Panel B shows aggregated data for all years. All CoVs show a marked decline in summer and autumn, with HKU1/OC43 peaking January–December, and NL63 and 229E peaking in February–March. Source: Neher et al. (2020)

Thus it is plausible that seasonality played an important role in reigning in SARS-CoV-2 in the summer of 2020 and hence gave a false impression that the virus was under control in Europe and North America. Seasonality alone is unlikely to end the spread of COVID-19, but can slow down a pandemic and thereby provide policymakers a window to loosen lockdown restrictions. That is why we believe this wave of (soft) lockdowns in most large eurozone countries is likely to last longer than the first wave of lockdown measures in March-April.

Another thing to keep in mind, however, is that vaccines may be effective at protecting against severe disease, but they may not protect against shedding. People inoculated with the vaccine may still get mild or asymptomatic infections and be able to spread the virus to others. Given that this is a respiratory virus, it is possible that a vaccine will make people less symptomatic, but they could still be infectious to others. This situation would elongate the return to 'normal' as it would imply that larger parts of the population would require a vaccine in order to protect the immunocompromised.
If in the back half of next year governments are successful in deploying a set of vaccines and are able to reduce disease in the elderly to be similar to that in the young, we can move into something that resembles normality. However, because of all the steps in between related to getting manufacturing capacity and logistics up to speed, as well as convincing the public to get inoculated, it is unlikely that herd immunity will be achieved until at least H1 2022.