COVID-19 Vaccines
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The main goals of EFIS are to support immunological research and education, as well as to strengthen scientific interaction amongst its members.

As this has been a rapid review, it is a summary of the research at time of writing; it is not an exhaustive literature review. It is the considered input of the advisory group and does not necessarily represent the position of EFIS, its members or the individual members of the taskforce.

All web references were accessed in February 2021.
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An asterisk (*) denotes words that appear in the glossary (Annexe 2)
Executive Summary

Last year saw Europe, and indeed most of the world, shuttered and closed in response to the spread of the SARS-CoV-2 virus that, within a matter of a couple of months, had spread across the world. Most nations closed businesses, stopped children from going to school, and confined people to their homes, in an unprecedented attempt to protect public health. From the beginning however, there was a light on the horizon: to free people’s lives, and whole countries, across Europe and the world, a vaccine to protect people against COVID-19 would be required.

After many months of intensive and rigorous endeavour by scientists in labs the world over, most countries in Europe are now at a point where they can begin to vaccinate their citizens. This, however, comes with its own challenges. It means shoring up confidence in vaccines, which can be vastly different when crossing national borders, and providing people with the information that they need to make the right choices. Vaccine hesitancy will not disappear overnight, but what this report makes clear, is that it is not an immoveable obstruction, and that given time and engagement on scientific issues, people’s fears and concerns can be allayed and assuaged.

The role of the scientific community does not end, however, after a vaccine has been developed. Robust immune monitoring and long-term, detailed studies of the immune responses of vaccinated individuals must be carried out. The outcome of these studies will determine the answers to questions around the longevity and durability of vaccine-mediated immunity so that we might be able to properly formulate policy around ending or easing national lockdowns, and to see if there will be a need for an annual vaccination along the lines of the influenza vaccination programme seen in many countries.

In Europe, we stand closer to the finish line that we did eleven months ago, but we must remember that many countries outside of Europe are not as far along the road as we are. We must now ensure that we do not forget about our neighbours and partners at the time when they need our friendship and co-operation the most. Vaccine nationalism will not bring the world any closer to ending this pandemic but instead will foster resentments and deepen economic pain on all sides. Equitable access to vaccines for all nations must be a European mantra as we continue during 2021.
EFIS makes the following recommendations:

1. **COVID-19 Vaccination**
   - Vaccination against SARS-CoV2 should be free of charge at the point of access to enable the highest uptake by the public as possible.
   - Even after vaccination, people must adhere to public health measures such as social distancing, washing hands and wearing face masks, as we do not yet know the risks of virus carriage in a vaccinated population.
   - There must be a robust observation programme across Europe through which vaccination uptake by the public is measured and these data shared. This will enable a comparison of the effectiveness of vaccination programmes and rapid learning in light of emerging data, allowing nations to amend the strategy of their own vaccine programmes if necessary.
   - There should be a surveillance programme for breakthrough infections to better understand the impact of vaccines on the variants in real-life situations.

2. **Public Engagement**
   - Robust public health awareness engagement programmes should be implemented alongside vaccine rollout. Understanding and answering genuine questions from the public will be essential to ensure optimal uptake of the vaccine.

3. **Gathering long term data on effectiveness to optimise vaccination programmes**
   - To ascertain the immunogenicity and corroborate the safety of current and future COVID-19 vaccines we recommend robust prospective evaluation of immunological responses to vaccination. A full list of the research recommendations can be found on page 13.

4. **Vaccine Nationalism**
   - Stronger investment in equitable COVID-19 vaccine access coupled with extensive planning for assisting in the supply of vaccines to all parts of the world.
Section 1: Development of COVID-19 vaccines

The COVID-19 pandemic has defined the year 2020 and the response from the scientific and research community has been overwhelming. Countless scientists from across the world have put on hold the projects that they would normally be working on, to shift their focus to some aspect of research to do with COVID-19. None, however, will have had such a titanic impact on the world as those working on the development of COVID-19 vaccines. We are beginning to see medicines regulators and other national competent authorities around the world approving the first vaccines for use, which, as rollouts continue, will start to turn the tide and allow people to slowly return to their lives with some semblance of normality this year.

Immense progress has been made since the beginning of the pandemic. The genetic sequence of SARS-CoV-2, the virus that causes the disease COVID-19, was published on 11 January 2020. This fired the starting shot on the race to develop a vaccine. With unparalleled speed, just two months later, on 16 March 2020, the first vaccine candidate was entering the first stages of human clinical testing. By April 2020, a Nature review found that there were 115 vaccine candidates being worked on around the world. A subsequent review found that by September 2020, this number had increased over 2.5-fold to 321 vaccine candidates, 33 of which were in clinical trials involving 280,000 participants from at least 470 sites in 34 countries. This enormous scale-up is an unprecedented effort and is the manifestation of the drive, dedication and resolve of researchers across Europe and worldwide, all working towards a common goal. The collaboration between funders and researchers is also self-evident. By taking on much greater financial risk, funders have allowed an acceleration of the vaccine development pipeline that would not normally be possible; running safety trials simultaneously rather than sequentially to speed up the process without compromising any of the safety aspects.

Several resources have been developed by many organisations to allow the general public to track the progress of each vaccine candidate. These include vaccine trackers from The New York Times, the World Health Organization (WHO) and the Regulatory Affairs Professionals Society (RAPS). While none of these trackers is exhaustive, each provides a good and up-to-date overview of preclinical and clinical vaccine candidates across the development landscape.

The multitude of vaccines that are under development, or have already been approved for use, come in different types. These include viral vector, DNA, RNA, inactivated virus, and protein-based vaccines. Each of these broad types of vaccine has a different mechanism of activating an immune response, with individual vaccines having different operative characteristics within these overall mechanisms. There are also advantages to each with regards to production, storage and delivery. Vaccine development will continue to see more new vaccines brought to market, as well as the production of second and third generation candidates in the future.
Section 2: Vaccination strategies across Europe

Public health science requires large-scale vaccination projects to be implemented through a strategic national plan, delivered by the respective scientific, regulatory or administrative authorities. As is currently emerging, the vaccination strategies employed by European countries are varied in terms of timing, policy and type of vaccine(s) rolled out.

Most European countries are prioritising high-risk groups for vaccination to reduce the burden on healthcare services and the number of deaths due to COVID-19. However, there are differences; for example, in the UK, in addition to doctors, the government also allows nurses, pharmacists and allied health professionals to administer the vaccine, whereas other European nations will insist that vaccinations are supervised by a qualified doctor only. It is not just the personnel administering the vaccines that differs among countries, but also the setting in which it occurs. Some will require that vaccinations take place in a medical facility, such as a primary health setting, whereas others will also extend vaccine deployment to community pharmacies.

Dosing schedules are also likely to differ from country to country. This will be a result of advice from each nation’s scientists and doctors, which make difficult judgement calls about the demographics of their respective populations, the rate and modes of transmission (in part founded on population density), the supply of vaccines available, and the capacity of their public health sectors. The UK, for example, has opted to lengthen the time between the first and second doses to 12 weeks for all vaccines being administered currently; this is to vaccinate as many people as possible with the first dose of a vaccine, to ensure that more people have at least some immunity as opposed to only half as many being fully protected having had both doses.

The variety of deployment methods will allow for in-depth comparisons between nations and allow each one to assess what is working and what is not.

EFIS makes the following recommendations for COVID-19 vaccination:
1. Vaccination against SARS-CoV2 should be free of charge at the point of access to enable the highest uptake by the public as possible.
2. Even after vaccination, people must adhere to public health measures such as social distancing, washing hands and wearing face masks, as we do not yet know the risks of virus carriage in a vaccinated population.
3. There must be a robust observation programme across Europe through which vaccination uptake by the public is measured and these data shared. This will enable a comparison of the effectiveness of vaccination programmes and rapid learning in light of emerging data, allowing nations to amend the strategy of their own vaccine programmes if necessary.
4. There should be a surveillance programme for breakthrough infections to better understand the impact of vaccines on the variants in real-life situations.

How a vaccination strategy emerges

Vaccination strategies should prioritise reducing mortality, increasing healthy life years, and reducing the pressure on the healthcare system. Priorities also depend on the characteristics of the vaccine to be administered. If the vaccine does not protect against transmission, or its ability to block transmission is not known, then vaccination should include those groups at highest risk of severe disease and death. In this regard, the elderly, and patients with co-morbidities at high risk of COVID-19 should be included in the first groups for vaccination. If vaccines are effective against infection and transmission, healthcare and elderly-care workers should be among the first groups to be vaccinated, since this would provide indirect protection to patients in hospitals and health centres, as well as residents of long-term care facilities or other high-risk individuals.

Although emerging, there is limited data available on the ability of licensed vaccines to block the transmission of SARS-CoV-2 infection. Instead, the proven effect is on protecting against COVID-19 disease symptoms. For these
reasons, most countries have based their vaccination strategies on stratification by age and professional exposure to COVID-19, and specify several stages of vaccination prioritisation. In general, three principles are taken into consideration for vaccination: necessity, meaning that there is scientific evidence that an individual is at high risk of death; equity, meaning those groups that are highly vulnerable; and reciprocity, meaning protection of those facing the highest risks through taking care of others’ health. Therefore, most but not all (e.g. the UK), European programmes of vaccination show the following stages:2

- In the first stage, group 1 are residents of long-term care facilities and their health and social care workers. Group 2 corresponds to all other health and social care personnel at the frontline against COVID-19. Group 3 consists of other health personnel. And group 4 includes people with high levels of disability or dependency, meaning they require intensive measures of care. Group 5 consists of those persons older than 80 years.
- In the second stage, patients with co-morbidities who are at high risk of COVID-19, alongside teachers and professors.
- In the third stage, young people are vaccinated.
- The fourth stage covers the rest of the population, mainly adults.

There are two groups of persons not covered by these strategies: children, and pregnant and lactating women. Vaccine trials have not included these groups initially; currently, only the Pfizer and Moderna trials have included a group of teenagers and pregnant women. Therefore, since manufacturers have not released trial results regarding these two groups, they are not considered yet for routine vaccination; they will be included in next stages.

Another important issue to take into consideration is the characteristics of the available vaccines regarding doses, supply and storage conditions. Pfizer and Moderna vaccines require two doses of vaccination. Whereas the Pfizer vaccine requires cold-chain storage at −70°C, the Moderna vaccine requires less stringent conditions, and can be refrigerated for several weeks. Logistics for vaccine delivery are also important in the design of vaccination strategies, since supplies may be interrupted for any number of reasons.

Section 3: Informing and engaging the public

Introduction

Immunologists – those working in the field of fundamental science that focuses on the workings of the immune system – have great confidence in vaccination as the best strategy for protecting our society against the spread of SARS-CoV-2. We believe that this method is both effective and safe and we therefore support the national and international efforts to distribute vaccines widely in the battle against COVID-19. This confidence is grounded not in the reputation of any single developer of vaccines, but on the scientific method that is required by these developers to demonstrate that a vaccine both works and is safe. Nevertheless, it is understandable that people have a natural hesitancy to receive an injection if they are healthy, even though its purpose is to ensure that they stay healthy. When distributing a vaccine, it is therefore important also to discuss in a transparent way what the negative aspects of vaccination are. By being open and honest it should become clear that these negative effects are outweighed enormously by the benefits of vaccination. In addition, when talking about a ‘new’ vaccine, it should be communicated that many aspects of such vaccines are not new individually but are in fact based on established and well-known platforms and technologies. As such, only a small component of a new vaccine is usually new, which should give further confidence about its safety after trials have been carried out.
How can we communicate the science behind vaccines?

When communicating what a vaccine does, it should first be clear what it intends to do. The underlying molecular mechanisms are quite complex, but the basic principle is not. The purpose of a vaccine is to familiarise and to train the immune system with a dangerous micro-organism (a ‘pathogen’), so that when that pathogen is actually encountered, the immune system can easily find and destroy it before it makes the infected person sick. In order to do that, a vaccine uses a piece of the pathogen to activate the immune system, so that it prepares itself for the actual infection. Using a piece of the pathogen is safe because it is not a replicating (live) pathogen. Various techniques are available, but in all of them, usually only a small piece of the pathogen is used. Typical techniques commonly include a co-factor (an adjuvant*) that helps to stimulate the immune system. Some of the latest COVID-19 vaccines make use of a recent technique, which is based on injection of messenger RNA. This technique does not require additional co-factors and should be even more specific in generating an immune response, with fewer side effects.

How can we communicate the limits of a vaccine in a scientific way?

According to a recent survey conducted by IPSOS on willingness to receive a COVID-19 vaccination, the most common reasons not to get vaccinated cited by respondents are that (1) they fear side effects, (2) they question its effectiveness and (3) they do not consider themselves at risk for contracting severe COVID-19 disease. How should the immunological community respond to these objections?

(1) The fear of side effects. First, it should be noted that what many people experience as ‘side effects’ of a vaccine – for example, nausea, chills, pain around the site of injection – are in fact signs of immune activation. This is what normally happens during an infection and since a vaccine mimics an infection, these events also happen following vaccination. As such, many side effects are not adverse effects, since they stimulate a reaction other than which is planned. They may indeed be unpleasant, but they typically do not cause harm. Of course, in very rare cases (i.e. 1 per 10,000 or rarer), vaccination can cause severe adverse effects, such as severe allergic reactions to the vaccine. Usually, these cases can be detected quickly as they occur rapidly after vaccination and the practitioner administrating the vaccine can prevent complications. One of the reasons why the vaccine is tested on thousands of people is to see whether they have these kinds of adverse effects. When mass-vaccinating the population, rare adverse effects may occur that could not be detected in fewer people in the trials. We should keep in mind however, that after SARS-CoV-2 infection, even in low-risk groups such as children, people develop severe disease or even die with a frequency that is much higher than they ordinarily experience severe adverse effects following vaccination. This has been shown by the Phase 3 trials of current vaccines where no severe adverse effects have been detected among more than 20,000 vaccinated people. Considering that the virus will not disappear by itself, most of the population will either get the virus or be vaccinated and be protected. As such, those choosing not to get vaccinated will have a much higher chance of experiencing severe symptoms from COVID-19 than those who choose to be vaccinated.

(2) Effectiveness. The effectiveness of a vaccine is determined only after rigorous testing and is an illustration of the validity of the scientific method. In a Phase 3 trial, tens of thousands of people are vaccinated, and an equal number receives a control substance (placebo). People are randomised, meaning that there is no difference between the test group and the control group in terms of age, sex and other confounding variables. After a pre-determined period, the number of clinically confirmed sick people in the two groups are compared and we can say with a certain probability based on the statistics whether the vaccine works. This scientific method has been used many times before to determine the effectiveness of vaccines. The method is sound and has objectively been used by the scientific community to test every pharmaceutical currently on the market. As such, we have no reason to doubt its validity. As a result of vaccination, smallpox has been eradicated, polio has almost been eliminated, and many other childhood diseases are increasingly rare.
(3) Usefulness. As mentioned above, the risk of adverse effects caused by a vaccine are much smaller than the risk of severe disease for those who contract the viral infection. Since it is likely that a large majority of those who are not vaccinated sooner or later will contract COVID-19, it is therefore a much safer choice to get vaccinated than not to get vaccinated. However, getting vaccinated is not only for your own safety, but also for the safety of others. Governments should communicate clearly that the aim of mass vaccination is both to protect the individual and also to protect the most vulnerable: older people, those in hospitals and those who cannot be vaccinated such as the immunocompromised. By vaccinating everyone who can be vaccinated, we stop the spread of the virus by generating herd immunity; this prevents suffering among those who can cope with suffering the least.

Advice from the scientific community to governments on how to communicate the risks and benefits of vaccination, should focus on these aspects:
1. A vaccination is a surrogate with a non-dangerous compound and any effects of this medication should be viewed and understood in this light.
2. The testing performed to validate the effectiveness and safety of a vaccine is rigorous and based on scientific methods that are approved by the independent scientific community.
3. The risks of adverse effects from not getting vaccinated are much higher than those from getting vaccinated.
4. The novelty of the current vaccines against COVID-19 is limited as they are mostly based on well-tested technologies.
5. Vaccines are one of the most effective public health interventions in human history.

EFIS makes the following recommendation:
- Robust public health awareness engagement programmes should be implemented alongside vaccine rollout.
  Understanding and answering genuine questions from the public will be essential to ensure optimal uptake of the vaccine.

Section 4: De-risking and enhancing COVID-19 vaccination

Gathering long-term data on safety and effectiveness

The preliminary results from Phase 3 clinical trials, as announced by the consortia developing the vaccines, show a high degree of effectiveness, reaching 95% for the mRNA vaccines*, without serious side effects. Many questions remain, however: How long will the protection last? How safe are these vaccines? How effective are the vaccines against emerging variants?

Data on the effectiveness were provided by at least three vaccine manufacturers that either completed Phase 3 clinical trials or provided interim results. Data on the reactogenicity* of some vaccine candidates were also reported. However, the long-term safety profile is currently unknown with all the vaccines being rolled out and needs to be carefully monitored. All Phase 3 trial participants will be followed for at least one year, providing some answers to these questions, in particular for safety. The possibility of adverse events too rare to be identified in clinical trials exists for all licensed vaccines and is not limited to those being developed for COVID-19. However, millions, or even billions, of people will be vaccinated against COVID-19 before this long-term follow-up will be completed. In addition, even in the same country, people will receive different types of vaccines with potentially different side effects.

Thus, the success of vaccination campaigns against COVID-19 relies on the acceptability by people of immunisation and it will be crucial to communicate in a very transparent and timely manner on potential side effects that will be observed during these vaccination campaigns.
The European Medicines Agency (EMA) and the national competent authorities (NCAs) in EU Member States have prepared a safety monitoring plan and guidance on risk management planning for COVID-19 vaccines. The safety of COVID-19 vaccines will be monitored according to the guidance that applies to all medicines but EU authorities have also planned several activities that will apply selectively to COVID-19 vaccines; for instance, information on vaccine safety in special populations.

The EMA is also implementing exceptional measures to maximise the transparency of its regulatory activities on treatments and vaccines for COVID-19 that are approved or are under evaluation. It is achieving this by shortening its standard publishing timeframes and publishing information it does not normally publish for other medicines. It will be essential that EU Member States strictly follow these recommendations. In addition, the involvement of citizens’ committees in the preparation and follow-up of future vaccination campaigns could help to fight the vaccine hesitancy which will be a major challenge for COVID-19 vaccines.

There are challenges in ascertaining the correlates of protection* and disease. We need to identify which immune markers (antibodies*, memory B* and memory T cells* etc.) predict who is immune to COVID-19 and who is susceptible to either mild or severe disease. These markers will allow us to identify people who are at particular risk, figure out how often booster vaccinations might be needed, and to speed up the development of even better vaccines and immunotherapies. This will require long-term, detailed studies of immune response generated in vaccinated individuals and those who were naturally infected with severe, mild or asymptomatic disease. The immunological measurements that have been made so far have mostly been of total IgG* antibody* levels, with some papers also reporting IgA*, IgM* and neutralising antibody* levels. A few papers have reported memory B* and T-cell* levels. Follow-up of these cohorts is needed to determine which metrics correlate with protection. In addition, there are more detailed immunological metrics that are candidates for correlate of protection* which have not yet been fully investigated.

We also note that even if antibodies* are lost, immunity can be reactivated. Antibody-secreting cells can be renewed from the memory B cell* population, with help from memory T cells*, if the person encounters the virus again (either naturally or by vaccination, or booster vaccination). So, while measuring antibodies* is one good indicator of immunity, it may be that measurements of memory lymphocytes* of different types would provide a better correlate of protection*.

Challenges in testing the effectiveness of vaccines

The current wave of COVID-19 is associated with a high incidence of infection, in particular in European countries and the US, thus providing the capacity to perform Phase 3 clinical trials of the more advanced vaccine candidates under appropriate conditions in the following months. These Phase 3 clinical trials will provide efficiency data for different age groups. As the approved vaccines are rolled out into the population, Phase 3 studies of new or adapted vaccines will become more difficult to carry out and bridging studies, monitoring correlates of protection*, will become more important.

The effectiveness of vaccines could be direct (prevention of the disease) or indirect (reduction of the contagiousness of the virus). The results of the Phase 3 trials will only provide information on the direct effectiveness, that is, the number of people who have developed COVID-19 disease. Data are now emerging from vaccine rollout and indicate an impact on reducing viral transmission.

Data on the different vaccine candidates already available from preclinical and Phase 1–2 clinical trials indicate highly divergent immune response profiles depending on the vaccine platform*. As expected, spike protein*-based adjuvant* vaccine candidates induce a strong B cell* response with high IgG* titres* exceeding those in convalescent sera*. In contrast, adenovirus- and mRNA-based vaccine* candidates induce only a moderate IgG* response. Titres* of neutralising antibodies* seem to correlate with IgG* titres*. However, there are no standardised procedures to evaluate and monitor the levels of neutralising antibodies* – different strategies based on the use of either the pseudovirus* or wild-type virus* are applied and different convalescent sera are used. The procedures to evaluate T-cell* responses induced by vaccine candidates are also non-standardised – different cytokine* profiles are measured.
Immune responses induced by a vaccine could enhance the severity of the COVID-19 disease. Vaccine-associated enhanced disease could be linked to the induction of specific antibodies* and has been described in several infections such as dengue in humans, and for SARS-CoV-1 and MERS-CoV in animal models. Although no immune enhancement of COVID-19 disease was observed in animal models, or in humans treated with convalescent plasma, these potential side effects merit further investigation. In this respect, reinfections, although still rare, could provide clues on immunity against COVID-19, particularly when the second episode is much worse.

SARS-CoV-2 is prone to make errors in its genetic code during replication, accumulating a small number of nucleotide changes per month. Given that coronaviruses are able to proofread during replication, mutation rates are lower than in some other RNA viruses. A SARS-CoV-2 variant with substitution D614G emerged in late January 2020 and replaced the original SARS-CoV-2 strain identified in China and became the globally dominant form by June 2020.

In early December 2020 a new variant – B117 – was identified in the UK, containing 8 changes in the spike glycoprotein and N501Y changes in the receptor binding domain. Early epidemiological analyses performed in the UK suggest a transmission advantage over other co-circulating variants. The substitution at position 501 has been associated with reduced viral neutralisation to monoclonal antibody* LY-CoV016.

At the beginning of October, a different variant was identified in South Africa (B.1.351) with a large number of mutations in the spike protein*, including 3 in the receptor binding domain. Variants with alterations in the spike protein* have a different significance for control and prevention, as this may affect vaccine efficacy, background immunity, use of monoclonal antibodies* for treatment and convalescent plasma therapy.

Laboratory studies indicated that adeno-based and mRNA vaccines* induced neutralising antibodies* against B117 spike mutants by assessing the neutralising capacity of sera from human subjects that received mRNA COVID-19 vaccines*. Reduced but still significant neutralisation was measured with the mRNA COVID-19 vaccines* against the mutations present in B.1.351.

Recently, researchers of the University of Witwatersrand (South Africa) and University of Oxford observed in clinical studies that viral neutralisation by sera induced by the ChAdOx1 nCov-19 vaccine against the B.1.351 variant was substantially reduced when compared with the original strain of the coronavirus.

We should bear in mind that in real life T-cell* immunity will play a role, and vaccines provide antibodies* that target different regions of the spike protein*. The concentration of antibodies* can also play a role and must be taken into account in the interpretation of these data.

The role of challenge studies*

A large number of vaccine candidates (around 300) are under preclinical and/or clinical development. In preclinical studies, some, but not all, of these candidates were tested in challenge experiments* on non-human primate (NHP) models before entering Phase 1–2 clinical trials. The effectiveness results were variable – complete versus partial protection – and were obtained under different experimental conditions, limiting our capacity to compare the potential effectiveness of these vaccine candidates.

Human challenge studies* (HCS) could be instrumental in prioritising the best vaccine candidates to be tested in large clinical trials but also to increase our understanding of COVID-19 pathogenesis, as demonstrated in diseases such as typhoid fever or cholera.

However, the infection of healthy volunteers with COVID-19 raises several ethical and scientific issues. HCS are likely to be conducted in young healthy volunteers with no risk factors. Even young individuals, however, could suffer severe COVID-19 disease with the potential for neurological and/or cardiovascular effects, among others, resulting from severe sequelae and/or ‘long COVID’.
One possibility will be to use minimally pathogenic virus or efficient anti-viral treatments. However, the results of protection using attenuated strains will not be comparable with those obtained in Phase 3 clinical trials, strongly limiting the scientific interest of these HCS.

Thus, these studies could be considered ethically acceptable only if they can be expected to accelerate or improve vaccine development and would have to be designed to strongly limit the participants’ risk.

**Immunological consequences**

The immune response against SARS-CoV-2 infection comprises several innate* and adaptive* mechanisms during the early and late stages of infection. Although cases of SARS-CoV-2 reinfections have been described,11 most infected persons appear to develop protective immunity. Naturally acquired protection against SARS-CoV-2 seems to be mediated by type I interferons*, neutralising antibodies* against the spike (S)-protein* of SARS-CoV-2 and by virus-specific CD4+ (particularly Th1) and CD8+ T cells*, including tissue-resident memory T cells*.12–16 For obvious reasons, the duration of protection to SARS-CoV-2 is currently unknown. Following infections with the related SARS1* virus, neutralising antibodies* lasted for months and SARS1*-specific T cells* were found many years after recovery of the patients.17 The critical immune correlates of protection* against SARS-CoV-2 in humans have not yet been formally established. Pre-existing CD4+ SARS-CoV-2-reactive memory T cells* in individuals who have not contracted COVID-19 (which might or might not be due to prior infections with human endemic ‘common cold’ coronaviruses) may contribute to the control, but also to the pathology of SARS-CoV-2 infections.18, 19 The immunological differences between young and old patients, and patients with asymptomatic versus severe COVID-19 infections, also remain to be characterised in detail.

Vaccine-induced immunity may differ from natural immunity after infection. Several vaccines using different platforms* are being used and/or in development for COVID-19. These include inactivated SARS-CoV-2 viruses, vaccines based on the use of non-replicating adenoviral vectors* and mRNA vaccines*. The vector*- and mRNA-based vaccines* use the SARS-CoV-2 spike protein* as a target for immunity.

Phase 1 and 2 trials of these vaccines have demonstrated safety and immunological effects and the induction of high anti-spike protein* IgG* titres* [similar to those induced by infection] and of antibodies* with virus-neutralising activity.20–26 For some of the currently developed vaccines there is also evidence for vaccine-induced Th1 and CD8+ T-cell* immunity.24–27 As the COVID-19 vaccine effectiveness trials have only started recently, there is very limited peer-reviewed, published information on the extent and duration of vaccine-induced protection or on the characteristics of the induced immune responses. Papers published in journals, as well as applications to regulatory agencies, assert that the vaccines show good-to-excellent short-term effectiveness (70–95%) in the completed or still ongoing Phase 3 trials.

To further ascertain the immunogenicity* and corroborate the safety of current and future COVID-19 vaccines, we recommend the prospective evaluation of:

- the persistence of IgG* anti-SARS-CoV-2 titre* and neutralising activity after vaccination, and how antibodies* against different antigens*/epitopes might differ.
- antigen*-specific Th1 cell and CD8+ T-cell* responses in those vaccinated.
- the impact of immune senescence* and immunosuppression on vaccine effectiveness and protective immune responses.
- the effects of vaccination in individuals that were seropositive* due to prior asymptomatic or symptomatic SARS-CoV-2 infection.
- the immunological phenotype* in those vaccinated with primary vaccine failure as this may help establish correlates of protective* immunity.
- the impact of type I IFN autoantibodies* or inborn errors of innate immunity* on vaccine effectiveness.
- non-specific effects of COVID-19 vaccines against other respiratory viral infections (role of trained immunity).
- potential immunological side effects of COVID-19 vaccines, such as vaccine-associated enhanced disease by non-neutralising antibodies* or triggering of autoimmune reactions by antigen* mimicry.3
- SARS-CoV-2 antigens* and potential adjuvants* to improve immunogenicity* and safety.
- proper monitoring of viral variants and the effectiveness of COVID-19 vaccines against them.
Section 5: Tackling vaccine nationalism

Nations with an excess of supply must work to ensure that every country around the globe is able to access vaccines. Highly economically developed countries (HEDCs) have over-ordered the number of COVID-19 vaccines that they require, with the Wall Street Journal reporting in September 2020 that the USA, Japan, the EU and the UK had, between them, ordered 3.7 billion doses of COVID-19 vaccines.29 Obviously, these respective governments ordered speculatively: there were and are no guarantees that all the vaccines under order would prove safe and/or effective – but to put the numbers into perspective, if these doses were all delivered, then this group of nations could vaccinate almost every citizen four times over. The pivot from rollout to their own citizens to distribution to the world’s middle- and less-economically developed countries will therefore be of paramount importance for ensuring that everyone in the world has access to a COVID-19 vaccine.

Currently the best bet for achieving this is through the COVAX initiative. A product of the World Health Organization (WHO); Gavi, the Vaccine Alliance; and the Coalition for Epidemic Preparedness Innovations (CEPI), it acts as a platform to support the research, development and manufacturing of a wide range of COVID-19 vaccine candidates and negotiate their pricing. It aims to have two billion doses by the end of 2021, or enough to vaccinate frontline healthcare workers and the most vulnerable. The associated COVAX Advance Market Commitment (AMC) provides a separate funding mechanism to support access to the vaccines for lower-income economies, making possible the participation of all countries, regardless of their ability to pay. We are pleased by the news that the COVAX programme could begin the rolling out of vaccines by the end of February 2021.30

Beyond the appalling human cost, one study has shown that for every year that the pandemic continued without a vaccine, the worldwide economy would have lost $3.4 trillion per year, but even with a vaccine, its inequitable distribution could still result in annual losses of $1.2 trillion;31 this would see a 5.6% loss of annual GDP for the EU and a 4.3% loss for the UK. Instead, for every $1 spent by high-income countries on supplying vaccines to low-income countries, they could expect an average $4.80 return. The danger is that we are investing too little in equitable vaccine access compared with the vast potential economic losses that could be consequent across the planet. In today’s globalised world we all rely on each other whether we know it or not, so global crises really do demand global solutions, and this pandemic is no exception. We strongly urge governments across Europe to plan extensively for assisting in the supply of vaccines to all parts of the world, and to act on these plans when the moment comes.
Annexe 1: References

1. European Centre for Disease Prevention and Control 2020 COVID-19 vaccination and prioritisation strategies in the EU/EEA.
Annexe 2: Glossary

**Adaptive immunity** – a subsystem of the immune system, which comprises specialised cells and processes, that can adapt to provide immunity specific for individual pathogens.

**Adenoviral vector** – an unrelated harmless adenovirus (the viral vector) which delivers SARS-CoV-2 genetic material. When administered, our cells use the genetic material to produce a specific viral protein, which is recognised by our immune system and triggers a response.

**Adjuvant** – an agent that boosts the immune response to a vaccine.

**Antibodies** – large Y-shaped proteins produced by B cells*. They act to neutralise invading pathogens such as the SARS-CoV-2 virus. They can also signal to other cells to help them recognise pathogens.

**Antigen** – a substance that triggers the body to produce antibodies* against it

**B cell** – a type of white blood cell that produces antibodies* as part of the adaptive immune system*.

**Autoantibodies** – an autoantibody is an antibody produced by the immune system that can bind to one or more of the individual’s own antigens.

**Challenge study** – a type of clinical trial for a vaccine or other pharmaceutical in which a subject is purposely exposed to the condition being tested, in this case the virus.

**Correlate of protection** – A specific immune marker, or measurable sign, that is associated with protection from becoming infected and/or developing a disease.

**Cytokines** – signalling proteins that regulate a wide range of biological functions including innate and acquired immunity, haematopoiesis, inflammation and repair, and proliferation, mostly through extracellular signalling. They are secreted by many cell types and are involved in cell-to-cell interactions.

**IgA** – immunoglobulin A is an antibody associated with mucosal surfaces such as you find in the nose and mouth. It can inhibit pathogen adhesion to epithelial cells

**IgG** – immunoglobulin G is the commonest form of antibody found in the blood and extracellular fluid and binds many kinds of pathogens.

**IgM** – immunoglobulin M is the first antibody made in response to a new antigen.

**Immune senescence** – the changes in the immune system that occur with age.

**Immunogenicity** – the ability of a foreign substance to provoke an immune response.

**Innate immunity** – the immune system’s defences that are rapid but non-specific to individual pathogens.

**Interferons** – a group of signalling proteins that are made and released by host cells in response to the presence of certain viruses.

**Lymphocyte** – a type of white blood cell; subtypes include T cells*, B cells* and natural killer cells.

**mRNA vaccine** – a type of vaccine that enables cells of the body to create a protein or piece of a protein that will provoke an immune response in the body.

**Phenotype** – an observable genetic trait or characteristic.

**Pseudovirus** – a virus that has the characteristics of the infectious virus but does not have the virulence, it can only replicate once. Thus it is safer to use in laboratory tests.

**Reactogenicity** – the ability of a vaccine to elicit a reaction in an individual after vaccination.

**SARS1** – Severe Acute Respiratory Syndrome caused by the coronavirus known as SARS-CoV, which caused two outbreaks between 2002 and 2004.

**Seropositive** – generally refers to the state of having detectable antibodies against a specific antigen.

**Serum** – the liquid part of the blood that does not contain either blood cells or clotting factors.

**Spike protein** – the main antigen on the surface of the SARS-CoV-2 virus and present in the vaccines.

**T cell** – also known as T lymphocytes, T cells are a type of white blood cell that determines the specificity of immune response to antigens* in the body.

**Titre** – a measure associated with the concentration of an antibody.

**Vaccine platform** – a technology to carry antigens, such as a nucleic acid, viral vector or liposome, which can be modified when the target antigen of the pathogen changes.

**Wildtype virus** – the naturally occurring, non-mutated form of a virus.
Annexe 3: Taskforce membership

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