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The EFIS vaccination task force expert report

An important task of immunologists is to educate the public about our field of expertise. As vaccine hesitancy is increasing, EFIS has recently formed a task force that aims to counter misinformation and improve understanding of the benefits of vaccination. Its purpose became acutely pressing with the emergence of the COVID-19 pandemic and the rapid development of vaccines against this disease. To aid the European vaccination effort with a position statement of the scientific community, the EFIS vaccination task force (EVTF) has formulated an expert report. In this statement we describe which scientific considerations should guide vaccination strategies, what the limitations of vaccination are, how this should be communicated to the public and how we should proceed as our knowledge on the SARS-CoV-2 virus and its vaccines increases. Below, we will provide a summary of the report. The full version can be downloaded here. Cumulative recommendations of the report are incorporated in Figure 1.

COVID-19 and the vaccination effort

The COVID-19 pandemic has defined the year 2020 and the response from the scientific community has been overwhelming. Countless researchers from across the world have postponed work on their projects to shift focus to some aspect of COVID-19 biology. As a result, great progress has been made in our understanding of the disease and the first vaccine candidates entered the initial stages of human testing within months after the emergence of COVID-19 [1]. At the beginning of 2021, several vaccines are approved for the European market. In addition to the collective research effort, collaboration between funders and researchers has been essential for generating rapid results. By taking on much greater financial risks, 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. Nevertheless, the speed with which COVID-19 vaccines have been developed comes with a certain risk. Monitoring bodies and scientists should closely follow how these products perform as they are distributed amongst the population. This will ensure safety and efficacy of the current vaccines and will provide valuable new information on how we should approach the next generation of therapies.

Immunological consequences

The immune response against SARS-CoV-2 comprises several innate and adaptive mechanisms during the early and late stages of infection [2]. Most infected individuals appear to develop protective immunity [3]. Nevertheless, cases of SARS-CoV-2 reinfections have been described [4]. Importantly, the duration of protection after infection or vaccination is still unclear. Infection with the related SARS-CoV-1 virus induces production of neutralizing antibodies that persist for months whereas virus-specific T cells can be detected for many years after recovery, providing hope for COVID-19 [5]. Nevertheless, the critical immune correlates of protection against SARS-CoV-2 in humans have not yet been listed. Despite rapid progress in this field, the immunological differences registered between young and old patients and between patients with asymptomatic versus severe COVID-19 syndrome, also largely remain to be characterized.

Vaccine-induced immunity may differ from natural immunity after infection. Several vaccines using different platforms are currently being used and/or are under development for COVID-19 [6]. 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 typically use the SARS-CoV-2 spike protein as antigen to induce host immunity, with promising results with regards to induction of neutralizing antibodies. For some of the currently developed vaccines there is also evidence for vaccine-induced Th1 and $CD8^+$ T-cell immunity and our basis of knowledge on these topics is rapidly increasing [7]. Published reports, as well as documents from regulatory agencies, assert that the vaccines show good-to-excellent short-term effectiveness (70–95%). To further ascertain the immunogenicity and corroborate the safety of current and future COVID-19 vaccines, we recommend the prospective evaluation of the following parameters:

1. SARS-CoV-2 specific antibody titers, time period of detection, antigen specificity/neutralization
2. Antigen-specific Th1 cell and $CD8^+$ T-cell responses in those vaccinated.
3. The impact of immune senescence and immunosuppression on vaccine effectiveness and protective immune responses.
4. The effects of vaccination in seropositive individuals due to prior asymptomatic or symptomatic SARS-CoV-2 infection.
5. The immunological phenotype in those vaccinated with primary vaccine failure.

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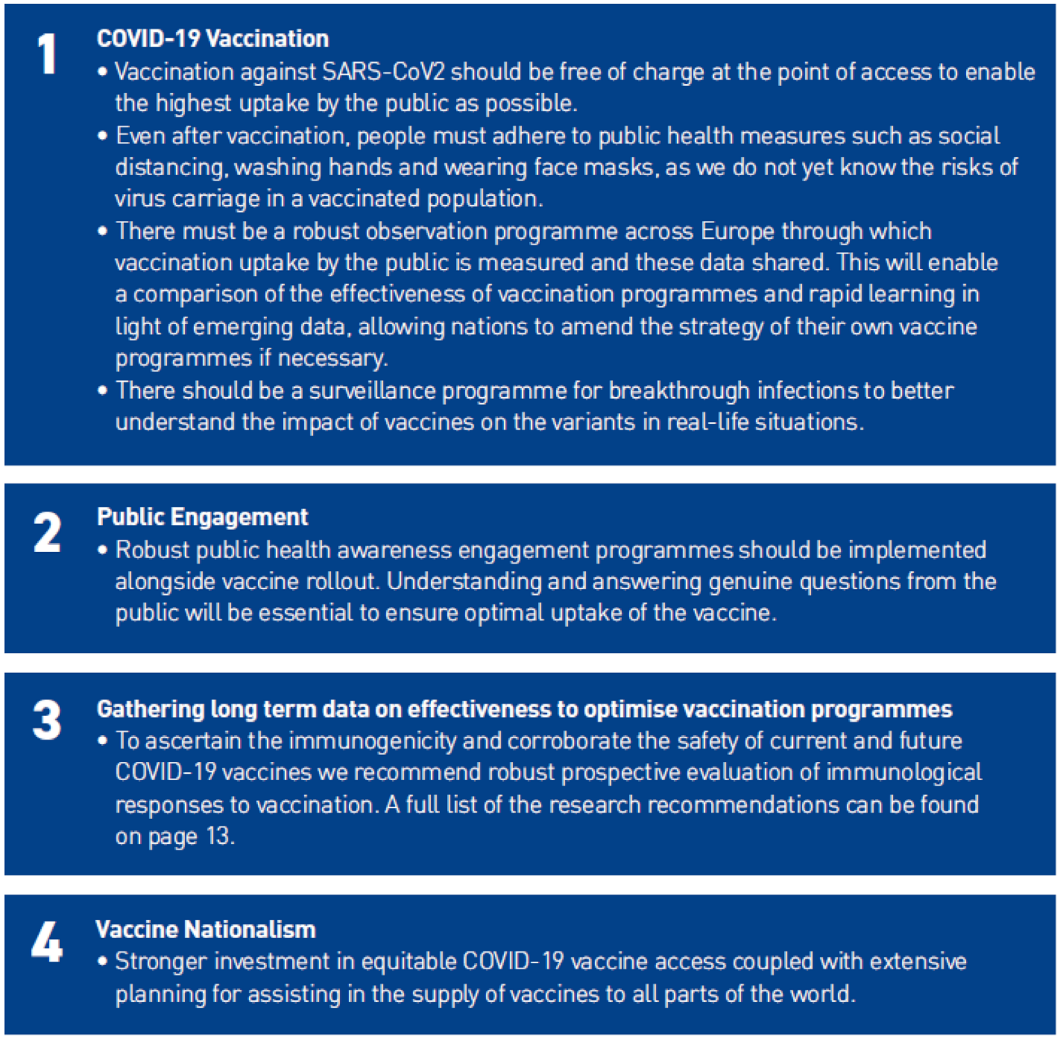

Figure 1. Recommendations by the EFIS Vaccination Task Force

6. The impact of type-I interferon autoantibodies or inborn errors of innate immunity on vaccine effectiveness.
7. Non-specific effects of COVID-19 vaccines against other respiratory viral infections.
8. Potential immunological side effects of COVID-19 vaccines.
9. Potency of SARS-CoV-2 antigens and potential adjuvants to improve immunogenicity and safety.
10. Proper monitoring of viral variants and the effectiveness of COVID-19 vaccines against them.

Challenges in testing the effectiveness of vaccines

Current phase 3 clinical trials will provide vaccine 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. Bridging studies, monitoring correlates of protection, will therefore become more important. The results of the Phase 3 trials will only provide information on the direct effectiveness of the vaccine to prevent disease symptoms. However, as more people are vaccinated, data is emerging on its ability to reduce transmission. Currently available data from various phases of clinical trials indicates a highly divergent immune responses between vaccine platforms.

However, procedures to evaluate and monitor the levels of neutralizing antibodies are not uniform. Some studies use a pseudovirus-based assay, whereas others use the wild-type virus [8]. In addition, timepoints for analysis vary greatly between studies. Also, the methods to evaluate T-cell responses induced by vaccine candidates are variable. This limits our ability to compare the effectiveness of the various vaccines and therefore more standardized assays should be introduced.

SARS-CoV-2 is characterized by a relatively low mutation rate compared to some other RNA viruses. Nevertheless, a large fraction of mutations is observed in the spike protein, responsible for biding and entry of host cells. Viral mutants such as the B.1.1.7 ('British') strain or the B.1.351.6–8 ('South African') strain have accumulated several mutations in the receptor binding domain (RBD) of the Spike molecule, some of which greatly increase virulence [9]. Importantly, several of the mutants appear to escape neutralization when using serum of vaccinated people. This also complicates our ability to assess vaccine efficacy and the

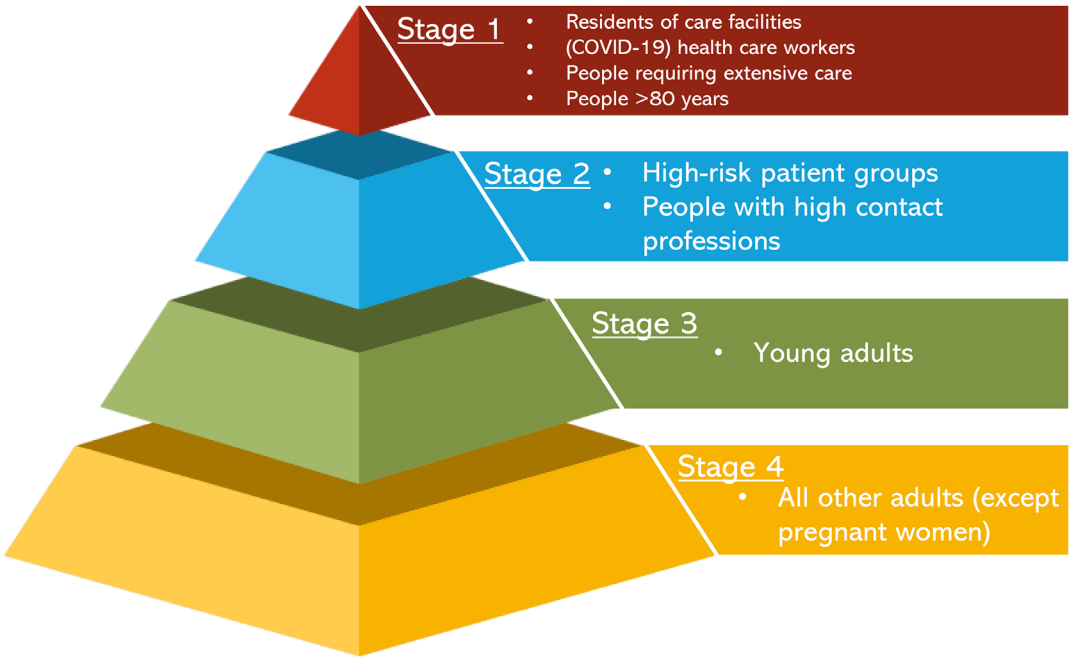

Figure 2. Common stages of European vaccination strategies.

use of convalescent serum or monoclonal antibody treatment. Fortunately, recent reports indicate that dominant T cell epitopes are rarely mutated in the various virus strains and that the T cell response against these variants is not greatly reduced compared to those against the wild type virus in vaccinated individuals. Nevertheless, the immune response against variants should be closely monitored and considered when assessing the impact of vaccination.

How a vaccination strategy emerges

Vaccination strategies should prioritize in reducing mortality, increasing healthy life years, and alleviating pressure on the healthcare system. If the vaccine does not protect against transmission, or if this is not known, then vaccination should include those groups at highest risk of severe disease. If vaccines are effective against infection and transmission, healthcare and elderly-care workers should be among the first groups to be vaccinated. Clinical trials generally only investigate the protective effect of COVID-19 vaccines against developing disease symptoms and not against transmission. Therefore, most countries prioritize vaccination based on age and professional exposure to COVID-19. In general, three principles are taken into consideration: **necessity**, i.e. scientific evidence that an individual is at high risk of death; **equity**, i.e. groups that are highly vulnerable and **reciprocity**, meaning protection of those facing the highest risks through taking care of others. Therefore, most European vaccination programs use the stages outlines in Figure 2.

Nevertheless, this strategy is a general consideration. National vaccination policies may adopt to better comply with distinctive population qualitative parameters, as described below. Two groups are currently not covered by the above-mentioned strategies: children, and pregnant/lactating women. Vaccine trials are only now including these groups. Therefore, they are currently not considered for routine vaccination. Trials specific for these groups are currently ongoing.

Practical requirements are also an important consideration when defining the best vaccination strategy. Many vaccines require two doses. Some vaccines need to be stored at −70°C, whereas other can be kept at −20°C, or +4°C. Logistics for vaccine delivery and storage must therefore be taken into consideration when designing a plan for population-wide distribution.

Finally, vaccination strategies should not stop at national borders. Beyond the appalling cost of human lives, the COVID-19 pandemic has a major negative impact on the world economy. Most wealthy countries have ordered many more vaccines than their population size requires, limiting the availability to countries with less purchasing power. However, even if wealthy countries vaccinate their entire population, the persistence of SARS-CoV-2 in less developed countries impairs the global economy and increases the probability that viral mutants emerge. Global redistribution of COVID-19 vaccines will therefore be of paramount importance for ensuring that everyone in the world has access to them. Currently, the best platform for achieving this goal is the COVAX initiative. COVAX acts as a platform to support research, development and manufacturing of vaccines and negotiates their pricing. COVAX provides a separate funding mechanism to support access to vaccines by low-income economies. Global crises require global solutions, especially for the COVID-19 pandemic. The EVTF therefore makes the recommendation shown in section 4 of Figure 1.

Vaccination strategies across Europe

Several similarities are observed in the vaccination strategies of countries within Europe (Figure 2). For example, most strategies prioritize high-risk groups for vaccination to reduce mortality and reduce the burden on healthcare services. However, there are important differences with

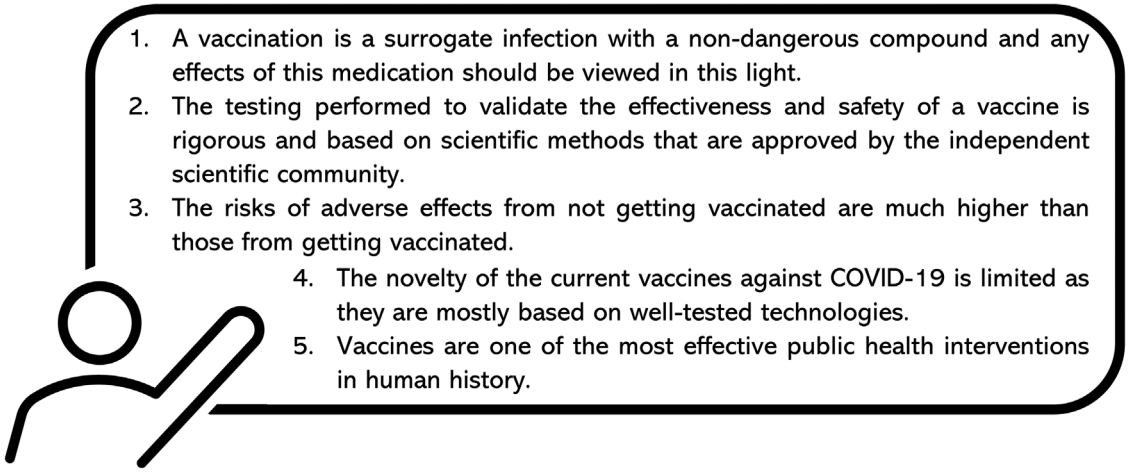

Figure 3. Important concepts regarding vaccine communication.

regards to the location where is being vaccinated, which professionals can administer the vaccine and which dosing schedule is being used. The final strategy is a result of the cumulative input from local scientists, doctors and policy makers, which have to make difficult judgement calls about the demographics of their respective populations, the supply and kind of vaccines available and the capacity of their public health sectors. As a result, the share and demographics of the population fully vaccinated against COVID-19 in EFIS associated countries varies substantially. An unforeseen opportunity of these differences is that it allows for in-depth comparisons between nations and rapid assessment of the most optimal vaccination strategy for a given population. To optimize the use of this wealth of information, the EVTF makes the recommendations shown in section 1 of Figure 1.

Gathering long-term data on safety and effectiveness

The COVID-19 pandemic is unique because it is the first time that so many vaccines are developed in such a short period of time. Moreover, it is one of the first times that mRNA vaccine technologies are widely implemented. This outburst of immunological research was inevitably accompanied by raised public awareness. Common interest sparked the need for a critical re-appraisement of vaccine effectiveness and safety. Preliminary results from Phase 3 clinical trials show a high degree of effectiveness, reaching up to 95% for some mRNA vaccines without serious side effects. However, many questions remain: How long will the protection last? How safe are these vaccines in the long run? How effective are the vaccines against emerging variants? It is up to the scientific community to provide answers.

Data on the effectiveness and reactogenicity of some vaccine candidates have been reported, but the long-term safety profile is currently unknown. As vaccines are being rolled out, this needs to be carefully monitored. All Phase 3 trial participants will be followed for at least one year, providing some answers to these questions. The perspective method of assessing safety issues renders vaccination campaigns against COVID-19 mandatory to identify the level of acceptability by people of immunization as well as the level of accessibility of people to vaccines.

It is crucial that scientific information on potential side effects observed during vaccination campaigns is delivered in a transparent and timely manner. European regulatory authorities have announced plans to widely distribute the scientific knowledge obtained on vaccination effectiveness and safety issues. Immunologists face additional challenges in ascertaining the correlates of protection and disease. We need to identify which immune markers (e.g. antibodies, antigen-specific memory B and T cells etc.) predict who is immune to COVID-19 and who is susceptible to either mild or severe disease. These biomarkers will allow us to identify high-risk immune phenotypes, figure out how often booster vaccinations might be needed and will speed up development of even better therapies. This will require long-term, detailed studies of the immune response generated in vaccinated individuals and those who were naturally infected with severe, mild or asymptomatic disease. The immunological parameters that have been so far studied are mostly IgG antibody levels, with some papers also reporting IgA, IgM and neutralizing antibodies [10]. A few papers have reported memory B and T cell responses [3]. Follow-up of these cohorts is needed to determine which metrics correlate with protection. Moreover, further studies are required to investigate whether humoral and/or cellular immunity is sufficient or required for providing protection against reinfection and to see how these immunological parameters respond to antigen re-encounter (e.g. through re-infection or booster immunization). EFIS therefore makes the recommendation shown in section 3 of Figure 1.

Communicating with the public

Many people are hesitant to take an injection if they are healthy. Proper communication about the benefits and risks of vaccines is therefore crucial to improve their adoption. By being open and honest it should become clear that negative effects of vaccines are outweighed enormously by their benefits. According to a recent IPSOS survey, the most common reasons not to get vaccinated against COVID-19 are (1) fear of side effects, (2) questionable effectiveness and (3) respondents do not consider themselves at risk for contracting severe COVID-19. When communicating about vaccines, the scientific community should therefore consider explaining the aspects noted in Figure 3. In addition, the EVTF makes the recommendation noted in section 2 of Figure 1.

Concluding remarks

The COVID-19 crisis is a major challenge for our society at large and for immunologists in particular. One positive outcome of this pandemic is that it has revolutionized vaccination practices. Introduction of new technologies, engagement of public awareness to the benefits of vaccination and implementation of vaccination as a cornerstone for public health strategies, have the potential of great long-term benefits to public health, but only if new knowledge is properly aggregated, interpreted and applied. Clinical immunologists and epidemiologists are required to assess disease in patients infected with SARS-CoV-2 and document side effects of vaccination. Diagnostic specialists are expected to provide optimum protocols for large-scale population studies, as well as mapping the real-life mutational burden of SARS-CoV-2. Basic scientists should build on our current knowledge to deliver effective new vaccines against emerging viral mutations. In summary, whereas the COVID-19 pandemic is still a work in progress, it has led us to a new chapter of immunology research.

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