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COVID-19: vaccination problems

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Summary

This minireview addresses problems of financing the vaccine development, regulatory questions, the ethics and efficacy of vaccine prioritization strategies and the coverage of variant viruses by current vaccines. Serious adverse effects observed with adenovirus vectored vaccines and mRNA vaccines in mass vaccination campaigns are reported. The ethical problems of continuing with placebo controlled vaccine trials and alternative clinical trial protocols are discussed as well as concrete vaccination issues such as the splitting of doses, the delaying of the second dose, the immunization with two different vaccine types and the need of vaccinating seropositive subjects. Strategies to increase vaccine acceptance in the population are shortly mentioned.

Vaccine policy

An unprecedented effort has generated over 200 vaccine candidates in various stages of development, with over 50 candidate vaccines in human clinical trials and 18 in efficacy testing, with several vaccines reaching registration by health authorities. Now, a comprehensive post-efficacy strategy is required to ensure vaccination of the global population. With 8 billion people to vaccinate with a two-dose regimen, one might need 10–11 billion doses to end the pandemic. The Coalition for Epidemic Preparedness Innovations (CEPI) estimates global vaccine manufacturing capacity at 2–4 billion doses annually, and that it will take until 2023–2024 before enough vaccine can be manufactured. Several companies have already started increasing production or have sought partners. AstraZeneca has partnered with Serum Institute of India and SK Bioscience from Korea. Johnson & Johnson has engaged Biological E (India). Moderna collaborates with Lonza in Switzerland. Sinovac (China) has partnered with Butantan (Brazil) and Bio Farma (Indonesia). Operation Warp Speed (OWS) invested $1.6 billion in arrangements with 'non-vaccine' manufacturers such as medical glass vials for vaccines (Kim *et al*., 2021).

Vaccine development must now be followed by vaccination campaigns of planetary scale. Currently, several billion doses of vaccines under development from Western manufacturers have been pre-ordered by high-income countries (US: 1.6 billion doses; EU: 1.5 billion doses; UK: 400 million doses; Japan: 300 million doses). As vaccines become available, they will first be scarce. Fair distribution of limiting vaccines is pivotal for worldwide vaccine provision such that resource-poor countries are not disadvantaged compared to resource-rich countries. If high-income countries exclusively acquire the first 2 billion doses without regard for vaccine equity, the number of COVID-19 deaths could worldwide still double in 2021 (Kim *et al*., 2021).

A major stakeholder for fair international vaccine distribution is COVAX (Covid-19 Vaccines Global Access), composed of GAVI (Global Alliance for Vaccines and Immunization), the WHO, and the CEPI which intend to purchase vaccines for fair distribution across countries. COVAX intends to purchase 2 billion doses of WHO prequalification (PQ) approved vaccine by the end of 2021. The European Commission has provided €400 million for COVAX. Some governments might defend vaccine nationalism based on a country's right and duty to prioritize its own citizens, particularly when the government has made substantial financial investments in vaccine development. However, hoarding vaccines is clearly unethical (Emanuel *et al*., 2020).

The Fair Priority Model addresses how to distribute scarce vaccine resources equitably. In phase 1, vaccines should prevent death, particularly premature death using Standard Expected Years of Life Lost averted per dose of vaccine as the metric. This metric regards all deaths as important but earlier deaths as particularly important. In phase 2, vaccines should aim at reducing serious economic and social deprivations (business and school

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closures). In phase 3, vaccines should reduce transmission of the epidemic. Countries should receive donations of vaccine only if they can provide assurance that they can distribute to meet these goals, not just for protecting elites (Emanuel *et al*., 2020).

Financing vaccination

The current and potentially future viral pandemics probably require new models of private–public research funding. Governmental and philanthropic grants fund approximately one-third of the total investment in the life sciences (estimated total investment of $194 billion in 2018 for the United States) and the life sciences industry funds the remainder. During the pandemic, government agencies invested $11 billion in late-stage vaccine development and expansion of manufacturing capacity through Operation Warp Speed. The US government concluded pre-purchase agreements with Moderna, Pfizer, AstraZeneca, Johnson & Johnson, Novamax and Sanofi and GlaxoSmithKline. Pfizer on its own decision was not supported by Operation Warp Speed. Monoclonal antibodies by Regeneron and Lilly have come to market with substantial governmental support. The US government also committed $1.5 billion to supporting development of diagnostic tests related to COVID-19. Vaccine research and development was funded with the understanding that recipient companies will supply vaccines later at prices that only cover the cost of production and committing the manufacturer to prioritize the contracted purchaser over others. The question arises whether these are business models for the future where governments can provide financial incentives for R&D areas which were traditionally not considered as profitable for industry, but represent major public health challenges for the future, such as new antibiotics that address drug-resistant infections, and for the treatment of neglected illnesses prevalent only in low-income countries (Robinson, 2021).

In a *Science* article, economists argue for an accelerated vaccine supply by a double strategy of building more production capacities and stretching the vaccine, which is available. Each 1 month delay in vaccination kills hundreds of thousands of people, reduces global gross domestic product (GDP) by hundreds of billions of dollars, and generates large, accumulating losses to human capital by harming education and health. Increasing vaccine production from 1 to 2 billion doses would confer an estimated GDP benefit of $2 trillion and halve the time to reach a 70% vaccine coverage in both high income countries (from 31 to 16 months) and worldwide (from 66 to 33 months) with a concomitant earlier opening of our societies. The International Monetary Fund (IMF) estimates global GDP losses from COVID-19 of $12 trillion during 2020–2021 and an average monthly GDP loss of $500 billion. Although a large fraction of health benefits may be obtained by vaccinating a small proportion of the population (e.g., health care workers and the elderly = the current strategy), obtaining full economic benefits may require reaching the broader population. The IMF estimates that governments are spending around $1.5 trillion a month on fiscal support during the pandemic. The economists of the *Science* article estimated a benefit of $576 to $989 per vaccine dose for a price of $6–$40 obtained by vaccine producers in current deals, leaving a wide margin for commercial incentives to increase vaccine capacity. To relax supply chain constraints governments should invest in supply-chain like glass vials, lipid particles and bioreactors even if the need may be temporary (or until the next pandemic). Governments should solicit bids from firms for capacity expansion by installing new factories or repurposing existing ones (as done by the Biden administration mediating a deal with Merck to produce the one-shot vaccine from J&J). Since firms are unlikely to accept contracts with substantial penalties (for delayed delivery as tried by EU commission or vaccine side effects), paying higher prices for earlier delivery might be a better incentive. Delaying the second dose or reducing the vaccine dose concentration, preferring one-shot vaccines of lower efficacy with lower logistic needs over two-shot vaccines with higher efficacy, but also more demanding cold-chain needs – could all be strategies to reach an earlier vaccination coverage in order to allow leaving lockdowns (Castillo *et al*., 2021).

The world now needs more doses of COVID-19 vaccines than for any other vaccine in history. Nine companies have said they will be able to produce up to 700 million doses this year, while 10 other manufacturers have set production targets of 1 billion doses for 2021. However, some companies have in the meanwhile declared production problems toward the EU. It is currently not clear what companies can produce the quantities needed for a global coverage. Challenges are manifold since the demand places pressure not only on vaccine companies, but also on global supply chains for glass vials, syringes and stabilizing agents.

Gavi, the Vaccine Alliance, and UNICEF are supposed to get a vaccine dose for $0.6–$0.8, while self-procuring middle-income countries will pay a median of $5 and high-income countries $16 per dose. These prices are within the price range paid for vaccines, but since entire populations of countries need to be vaccinated, the burden will be high for low income countries even at the bargained low prices. The World Bank has earmarked billions of dollars to buy vaccines that have been authorized by stringent regulatory bodies or WHO. It can be foreseen that billions of individuals around the world might not have access to COVID-19 vaccines in 2021,

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which will prolong the pandemic and raise the risk of further viral mutations. Competition for limiting amounts of vaccines can be foreseen, since some high income countries plan to vaccinate their entire adult population in 2021, placing widespread inoculation of their own populations ahead of the vaccination of healthcare workers and high-risk populations in poorer countries, which will create ethical dilemmas.

To these problems come logistic difficulties: 74 of 194 WHO member states had no adult vaccination program for any disease and they are unexperienced in identifying eligible individuals by priority group, send invitations, arrange transport for older subjects and call individuals for the second doses. The need of a cold chain or even freezers will prevent low and middle income countries (LMICs) from using certain types of vaccines. Because of financial and provision challenges, several LMICs have placed orders for COVID-19 vaccines with Russian and Chinese manufacturers, where some vaccines have not yet been approved by stringent regulatory authorities (Wouters *et al*., 2021).

Regulatory questions

Good Clinical Practice, Good Manufacturing Practice and Good Laboratory Practice form a common basis for quality and regulatory compliance. Lapses have already surfaced with unscheduled differences between viral lots in trials of AstraZeneca and Sinovac vaccines. Vaccines are approved in the country of manufacture by a national regulatory authority (NRA). Not all NRAs meet the WHO requirements to be a 'stringent' regulatory authority. Those of the United States, Europe, the United Kingdom and Japan are stringent; those in India, South Korea, Brazil and Indonesia are deemed functional, but not stringent. Others have not yet been rated. WHO can pronounce a PQ approval (currently under investigation in China). PQ approval allows United Nations agencies to purchase the vaccines for global health use by organizations like GAVI, the Vaccine Alliance. NRAs that lack the technical capacity to review dossiers will seek relief from COVID-19 by directly licensing vaccines without WHO review and purchase those vaccines directly from manufacturers through bilateral deals. The United Arab Emirates struck a deal for whole-inactivated vaccine from Sinopharm, approved only in China, in the absence of published evidence of efficacy or WHO approval.

On 2 December 2020, UK regulators granted emergency-use authorization (EUA) to the Pfizer vaccine (Ledford, 2020a). The FDA advisory committee voted 17 to 4 to recommend this vaccine and issued an EUA. The European Medicines Agency (EMA) looks for a standard approval, not for an EUA to instill vaccine confidence in the population. The regulators are now looking more deeply into side effects to reassure the public and to work against unfounded associations by anti-vaccination movements. The CDC will roll out a new program called v-Safe asking health-care workers who received the vaccine about any possible adverse events. Most events are expected within 6 weeks from injection. The more time elapses between the vaccination and the event, the more cases are needed to suggest causality. Pfizer reported four cases of Bell's palsy, a condition that temporarily weakens some muscles in the face, among those who received the vaccine, compared with none among those who received the placebo. Bell's palsy is not unusual in the general population, and one of the study participants had it already in the past. In the UK, two recipients with a history of severe allergic reactions, experienced an anaphylaxis episode after getting the vaccine. FDA advisers were not dissuaded by the reports since the vaccinator should be able to handle anaphylactic reaction. Freshly vaccinated persons are requested to wait 30 min on site before going home (Ledford, 2020b). The Nature editors deplore a lack of global coordination for vaccine regulation. China, Russia and the United Arab Emirates began administering vaccines that have not yet finished phase 3 trials. Different Western regulators are assessing the same data independently without exchanging documents (increasing the work load both for drug companies and the regulators). WHO will establish the International Coalition of Medicines Regulatory Authorities (ICMRA) to reach a consensus on the best animal models for testing COVID-19 vaccines, the ideal clinical-trial end-points and the complicated issue of continuing placebo-controlled trials after vaccine roll out begins (Anonymous, 2020).

Continued placebo-controlled trials?

The WHO Ad Hoc Expert Group on COVID-19 vaccines made a strong argument for continued placebo-controlled trials for further vaccine candidates and even for vaccines that are already used for vaccination. Early vaccine deployment could use the Expanded Access/Compassionate Use (EA/CU) legislation that would allow conducting placebo-controlled vaccine trials in the future. If this is not done and definitive approval is granted for available vaccines, it will be difficult to obtain ethical approval for placebo-controlled trials with alternative vaccine candidates, some of which might represent important sources of second generation vaccines. Randomized, placebo-controlled trials are the bedrock of modern clinical decision making and should not be given-up due to emergency use of vaccines. Also the currently started clinical trials should be continued (instead of switching the placebo recipients to vaccine injection). Important data will be derived from such follow-ups, e.g., whether waning of vaccine-induced protection may

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lead to vaccine-enhanced disease after natural exposure to the pathogen (Krause *et al*., 2021).

Members of the department of bioethics from NIH concur in a *Science* article with that view. A single finding of safety and efficacy may not be sufficient for a vaccine candidate to receive FDA approval. FDA frequently requires a finding of efficacy in two phase 3 trials before approving medical interventions in millions of people. However, this argument means that a decision is only postponed. Limitations on current treatment options mean that it is in each individual's interests to receive the first vaccine found to be safe and efficacious, rather than participate in vaccine trials where they might receive placebo or an unproven vaccine candidate. The authors argue that several vaccines may be needed production-wise to meet the global need, which highlights the potential social value of conducting additional trials. Other vaccine candidates than those that were tested so far in phase 3 trials might be more effective, generate longer-lasting immunity, work better in certain subpopulations, provide greater protection against severe disease, prevent infection transmission better or will be cheaper. Researchers might consider redesigning the trial, for example, to include a crossover in which the blind is maintained and those on the placebo arm receive the vaccine after they completed the placebo arm. The NIH experts disagree that there is an ethical obligation not to conduct further placebo-controlled vaccine clinical trials once the first trials showed efficacy and safety. They admit that participants in the placebo arm are known to be at higher risk of symptomatic disease. However, it can be ethically appropriate to invite research participants to accept some risks to collect socially valuable data. They stress that the obligations researchers have to their participants are distinct from the obligations that clinicians have to their patients. On a practical side vaccines will be in limited supply and for the next half a year prioritized to risk groups, which do not apply to the classical participants of clinical trial. Trial participants receiving placebo will not be at an increased risk since they cannot obtain for the next few months a vaccine outside of the trial protocol. Regulatory authorities have therefore a great responsibility when deciding on emergency use approval or full approval. Ethics need to weigh the risk of a few ten thousand placebo recipients against the risk of hundred millions of future vaccine recipients. One possibility out of an ethical dilemma could be to conduct future trials with new vaccine candidates not against placebo, but against the approved vaccines. However, ethical committees should take into account that an active comparison trial is likely to require larger sample sizes and extend the duration of the trial to accumulate the necessary cases of infections and diseases for an evaluation (Wendler *et al*., 2020).

Alternative efficacy trials?

Others suggested using immune markers for protection as done for new influenza or rabies vaccines, evaluating 'correlates of protection' instead of clinical protection. However, these correlates of protection are not yet known for COVID-19 and typically derived from breakthrough infections in previous vaccine trials. As very few breakthrough infections were observed in the mRNA trials, this approach is difficult. Still other suggest trials in experimentally challenged volunteers, but many scientists consider this as even more ethically problematic and not practical since attenuated SARS-CoV-2 strains have not been described yet (Dolgin, 2021). The Human Challenge Consortium has received £33 million of funding from the UK Government. A Dublin-based commercial clinical-research organization will recruit 30–50 healthy adults aged 18–30 who will receive increasing doses starting with a very low dose of a SARS-CoV-2 challenge strain derived from a currently circulating virus to determine the infectious dose leading to infection in most of the human volunteers. In a next step, human volunteers will receive vaccine candidate strains and subsequently the challenge virus to test vaccine efficacy. The tests could begin in 2021. Proponents of this trial argue that valuable human data can be obtained (infectious dose) crucial for vaccine development and public health protection measures at a risk comparable to the annual likelihood of a car accident. Sceptics argue that a zero risk cannot be given and that data obtained in a low risk age group cannot be easily transferred to elderly persons with comorbidity who are in greatest need of a vaccine (Callaway, 2020; Kirby, 2020).

Vaccine prioritization

Vaccine allocation is also a problem for rich countries in the initial roll out of vaccines when doses are still scarce. Guidelines for vaccine prioritization have been elaborated by the Strategic Advisory Group of Experts of the WHO (WHO, 2020) and the US Advisory Committee on Immunization Practices (ACIP) of CDC (Dooling *et al*., 2021). CDC recommendations prioritize: (i) health care personnel; (ii) residents of long-term care facilities; (iii) persons aged 75 years and over and frontline essential workers; (iv) persons aged 65 years to 74 years, and persons aged 16 years to 64 years with high-risk medical conditions, and essential workers; and (v) everyone aged older than 16 years (McClung *et al*., 2020). The European CDC and the European Health Security Committee have prioritized elderly people (with various lower age cut-off across countries), healthcare workers and persons with certain comorbidities (ECDC, 2020).

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From a public health perspective there are two main approaches to vaccine prioritization: (i) directly vaccinate those at highest risk for severe outcomes and (ii) protect them indirectly by vaccinating those who mostly transmit the infection. US scientists developed a computer model exploring different vaccination strategies, which accounted for country-specific age structure, age-contact structure, infection fatality rates and seroprevalence as well as different transmission rates (R values). Three possible goals of vaccination were considered – minimizing cumulative incidence, mortality, or years of lost life (YLL). The model showed that across countries those aged 60 and older should be prioritized to minimize deaths. However, the model identified three general regimes in which prioritizing adults aged 20–49 would provide greater mortality benefits than prioritizing older adults. This would be the case if (i) infection is well controlled by nonpharmaceutical interventions ($R \leq 1.15$), (ii) with a vaccine displaying 80% or higher transmission blocking effects; or (iii) if vaccine efficacy is substantially lower in older than younger individuals. Otherwise, as the infection fatality rate steeply increases with age, it is favourable to target older people. If infection-minimizing strategies are targeted and not mortality, the model recommends to prioritize adults 20–49 for vaccination (Bubar *et al*., 2021; Fitzpatrick and Galvani, 2021).

Canadian researchers compared projected COVID-19 mortality under four strategies for the prioritization of COVID-19 vaccines: older individuals first, children first, uniform allocation and a novel strategy based on the contact structure of the population. In their model, vaccinating people aged 60 years or older first prevents the most deaths out of all four strategies if vaccination begins on 1st January, 2021. A third wave in the autumn of 2021 or winter of 2022 is thereby prevented. If vaccine roll-out is done much later in the pandemic, use of vaccines to interrupt transmission might prevent more deaths from COVID-19 than use of the vaccines to target those aged 60 years and older (Jentsch *et al*., 2021).

Mortality reduction cannot be the only societal goal. Social values such as returning to school, to work and social life are also important to consider. In that context, it might become essential to target essential workers who are the least able to participate in non-pharmaceutical interventions (NPI) such as social distancing and thus are the most at risk for infection and of transmitting infections. If allowing children to return to school is a high societal priority, then allocation strategies might be tilted toward targeting school-age children and teachers (Buckner *et al*., 2021). Priority setting for vaccination strategies thus depends on a multitude of factors defined by the dynamic of the pandemic, the timing of mass vaccination campaigns, political and societal priorities. Giving priority to risk groups has the advantage that it can be based on disease protection demonstrated in phase 3 clinical trials, while data on vaccination blocking infection transmission are still scarce and were assumed in the computer models at 75% efficiency for which sound data are still lacking.

Practical vaccination problems

Splitting doses

A number of solutions have been proposed to cope with the initial scarce vaccine supply. Fractional dosing might be an approach since it has already been used to extend the supply of yellow fever vaccine in the past and lower doses of the AstraZeneca vaccine have shown higher efficacy (Kim *et al*., 2021). Using six doses instead of five from a BioNTech vial seems to be a safe way to exploit the available supply. In addition, the Moderna vaccine dose contains 100 μg mRNA compared to 30 μg mRNA in the BioNTech dose. Moderna has data showing that its vaccine stimulated a strong immune response in people between ages 18 and 55 at half the usual dose. One might therefore consider to vaccinate people with 50 μg of RNA in Moderna's vaccine. However, FDA is against deviations from the published protocols with dosing (Cohen, 2021; Anonymous, 2021a; Ledford, 2021a; Anonymous, 2021b; Ledford, 2021b; Ledford, 2021c).

Delaying the second dose

The UK Medicines and Healthcare Products Regulatory Agency (MHRA) decided that the second shot can be given up to 12 weeks later instead of 3 weeks later as in the published trials. Pfizer–BioNTech scientists said they do not have evidence of what happens to immunity beyond 21 days after the first dose. Authorities must be transparent about their decisions to allow the public to follow the arguments and thus keep the confidence into vaccination (Cohen, 2021; Anonymous, 2021a; Ledford, 2021a; Ledford, 2021b; Ledford, 2021c). The rationale for this approach is to reduce more preventable deaths with a delayed second injection which transiently liberates vaccine for twice as many people. If 95% of people are protected from disease after two doses (PfizerBioNTech trial data) and 90% are protected after one dose (Joint Committee on Vaccination and Immunization estimate), then 19 of 20 people will be protected by two doses, but when given to 40 people as single shot, 36 will be protected (Wadman, 2021a; Anonymous, 2021b; Wadman, 2021b). However, this calculation is based on a high 90% single-shot protection rate, while other scientists estimated a 50%–60% protection rate (Robertson *et al*., 2021), which would reduce the mortality sparing effects.

Scientists are split with respect to these modifications. Some argue that the vaccine shortness occurred at a

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critical moment when COVID-19 is killing approximately 3000 people in the United States per day. Protecting more people from death is thus a priority. This strategy would anyway be transient since vaccine shortage is likely to ease later in 2021 in rich countries. The UK endorsed the delayed-second-dose approach (up to 12 weeks) and CDC liberalized its position to a 6 week interval between the two injections. Experts opposing this delay of the second shot argue that no data inform us on how long a second dose could be delayed without compromising effectiveness and frontline health care personnel need assurance that if they get vaccinated, they can work more safely. Changing the vaccination schedule could put public confidence at risk and a waning immunity could lead to subinhibitory levels of antibody favouring the selection of antigenic variants. These experts argue that adherence to basic public health measures will save 1.5 times as many lives as vaccines and one should vaccinate with the standard delay and protect the unvaccinated vulnerable parts of the population with containment measures (Kadire *et al*., 2021).

Support for a delayed vaccination schedule came from evaluations of phase 3 studies by AstraZeneca with the adenovirus vectored vaccine. These studies were initially planned as single-dose studies but were amended to incorporate a second dose after review of insufficient immunogenicity in a phase 1 trial. However, some participants chose not to receive the second dose. Due to vaccine production problems, there were in addition delays in administration of the second dose for a large number of trial participants. These peculiar conditions allowed to explore the effect of the time interval between prime and boost injection or of a single injection. Vaccine efficacy after two standard doses was 55% when given with an interval of less than 6 weeks, but 81% when the two injections were given more than 12 weeks apart. A single injection provided protection against primary symptomatic COVID-19 in the first 90 days with an efficacy of 76% alleviating concerns that subjects with a single injection are sub-optimally protected with the adenovirus-vectored vaccine (Voysey *et al*., 2021).

Heterologous vaccination

In order to quickly immunize the maximum of vulnerable population sectors with the available vaccine doses, a mix and match strategy might in the beginning phase be necessary. Such a 'heterologous vaccination' strategy might not be a disadvantage. One vaccine might confer a better antibody immune response, while another might achieve a better cellular immune response; or one might provide a better protection against disease when naturally infected ('protecting immunity'), while another has a better potential to suppress transmission of the virus if a vaccinee is infected ('sterilizing immunity').

Scientists at the Jenner Institute of Oxford University where the AstraZeneca vaccine was developed are now actively exploring this approach. They immunized mice with the chimpanzee adenovirus vector expressing the SARS-CoV-2 spike protein and a self-amplifying RNA vector encoding the alphavirus replicase and the SARS-CoV-2 spike gene. Heterologous (adenovirus/alphavirus) and homologous two-dose strategies induced irrespective of sequential order comparable antibody titers (Spencer *et al*., 2021). Oxford University will recruit 820 participants for AstraZeneca adenovirus and Pfizer mRNA vaccines given in two different sequential orders and with two dosing intervals (4 and 12 weeks) and measure levels of antibodies and investigate immune cells. Data are expected in June 2021 (Ring, 2021; Ledford, 2021a; Ledford, 2021b; Ledford, 2021c).

Mixing two different vaccines is not a new concept: precedence exists for Ebola virus vaccine trials. Scientists from Oxford University expressed the Zaire Ebola virus glycoprotein in adenovirus vectors also used in COVID-19 vaccines and explored the effect of boosting half of the subjects with a modified vaccinia Ankara vector expressing Zaire Ebola virus glycoprotein (MVA-BN-Filo) in 180 adults from Mali, UK and Senegal (Tapia *et al*., 2016). A good antibody response to the Ebolavirus glycoprotein was seen with heterologous vaccination, irrespective of sequence and time intervals between the two injections (Milligan *et al*., 2016). Cellular immunity by ELISpot gave a better boost response when applied to the ipsilateral instead of the contralateral arm (Venkatraman *et al*., 2019). In a phase 2 heterologous vaccination trial 423 adults from UK and France received an intramuscular injection of Ad26. ZEBOV on day 1, followed by intramuscular injection of MVA-BN-Filo at either 28, 56, or 84 days after the first vaccine. ELISA and neutralizing antibody titers increased with increasing interval length between both injections. One year later, ELISA and neutralizing antibody titers as well as CD4+ and CD8+ T cells expressing a cytokine remained elevated over 1 year, irrespective of the interval between the two injections (Pollard *et al*., 2020).

Seropositive subjects' vaccination needs

The PARIS (Protection Associated with Rapid Immunity to SARS-CoV-2) study collected data for at baseline 67 seronegative and 43 seropositive participants who received a mRNA vaccine dose. After the first injection, the majority of seronegative participants had variable and relatively low SARS-CoV-2 IgG responses while the subjects who were seropositive due to a prior natural SARS-CoV-2 infection rapidly developed uniform, high antibody titers within days after vaccination. After the second dose

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the IgG titers increased in the vaccinees that were seronegative at baseline, but not in those seropositive at baseline (Krammer *et al*., 2021).

Previously infected health care workers showed at baseline an antibody titre comparable to that achieved by naive subjects after the prime injection of the mRNA vaccine. After one immunization with the mRNA vaccine the antibody titre rose in the naturally infected ('seropositive at baseline') subjects by 140-fold. The physicians recommended that for a more efficient vaccine roll-out, previously infected subjects as determined by a serological test need only one dose of vaccine (Manisty *et al*., 2021). Another study from UK HCW confirmed a strong antibody and T cell response in seropositive subjects after one immunization (Bernal *et al*., 2021). Scientists from Israel who studied antibody response after natural infection and before and after one dose of Pfizer mRNA vaccine added an important aspect to this topic. After natural infection with the previously circulating sub-lineage B1 virus, they showed mean neutralizing titers of 450, 250, 70 and 8 against the original virus and the B.1.1.7, P.1 and B.1.351 viruses, representing the 'UK', 'Brazil' and 'South Africa' (SA) virus variants respectively. The corresponding titers were 9000, 8000, 2900 and 1600 after vaccination, indicating that vaccination conferred an increased protection to naturally infected subjects against variant viruses (Lustig *et al*., 2021).

Low responders

After one injection with mRNA vaccine particularly older naive subjects showed a weaker antibody response than younger subjects. Some vaccinees mount very little demonstrable response to single-dose vaccination which might not persist for the 12-week interval to the second vaccination under UK policy. Indeed, one individual developed symptomatic, PCR-proven COVID-19 infection 5 weeks after one dose of vaccine. Furthermore, two out of 72 subjects enrolled did not seroconvert, and eight participants generated antibody titers considered insufficient for virus neutralization (Bernal *et al*., 2021; Manisty *et al*., 2021). Their research recommends that after the first vaccine injection, vaccinees still have to follow hygiene rules and HCW need personal protection use.

Precautions for vaccinated subjects

CDC recommends that fully vaccinated people should keep taking precautions in public places like wearing a mask, staying 6 ft apart from others and avoiding crowds and poorly ventilated spaces. However, CDC states that fully vaccinated people can gather indoors with fully vaccinated people without wearing a mask and can gather indoors with unvaccinated people from another household without masks, unless any of those people or anyone they live with has an increased risk for severe illness from COVID-19 (CDC, 2021).

Excluded groups

Children and pregnant women were so far excluded for safety reasons from SARS-CoV-2 vaccination trials. Since a quarter of the U.S. population is under 18 years old, herd immunity will require paediatric vaccination. Children are with the exception of the rare multisystem inflammatory syndrome in children (MIS-C) clinically not much affected by the pandemic. Their vaccination can ethically be justified by analogy with the measles–mumps–rubella (MMR) vaccine which reduces severe measles cases in young adults, and protects young male adults from sterility (mumps) and pregnant women from delivering malformed children (rubella). Childhood vaccination with SARS-CoV-2 needs, however, particularly robust safety data in children before a roll-out can be considered (Klass and Ratner, 2021).

Waning immunity

The durability of vaccine-induced protection is currently unknown and we ignore whether and when further booster vaccinations are needed. Participants of a phase 1 trial with the Moderna mRNA trial reached now a 6 month follow-up. Serological evaluation showed a half-life of 50 to 100 days for ELISA antibodies and 70 to 200 days for neutralizing antibodies in the sera of vaccinees (Doria-Rose *et al*., 2021). As measured by standardized ELISA, anti-SARS-CoV-2 spike IgG responses to a single dose of AstraZeneca adenovirus-vectored vaccine decayed log-linearly over a 6-month period. Compared to day 28, antibodies showed a decrease of 34% by day 90 and a decrease of 64% by day 180 (Voysey *et al*., 2021).

Coverage of novel variant viruses

The emergence of variant viruses raised the concern that current vaccines might display a diminished efficacy because many vaccines present the spike protein from the original Wuhan virus isolate to the immune system. Immunologists noted that historically few viruses have managed to evolve resistance to vaccines, influenza virus is a notable exception. Vaccine developers assured that even if an adaptation of the vaccine to a new variant virus strain should become necessary in the future, such an adaptation would be facilitated by the flexibility of mRNA-based vaccine technology (Muik *et al*., 2021). Nevertheless, in the vaccine race against the unfolding of the pandemic it is important to assess whether current

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vaccines are still protective. That this is not a moot point is demonstrated by vaccine trials where the AstraZeneca adenovirus vectored vaccine showed a good protection against the UK variant, but not against the South African variant. Therefore, many researchers tested the sera of vaccinees (mostly having received mRNA vaccines) for in vitro neutralizing activities against various variant viruses. US immunologists tested plasma from 20 volunteers who received either the Moderna or Pfizer-BioNTech mRNA vaccines against a panel of 10 mutant pseudotype viruses including the B1.1.7 and 501Y.V2 variants as well as several single substitutions including E484K. There was a small (≤ threefold), but statistically significant neutralization titre decrease against the variants (Wang *et al*., 2021a; Wang *et al*., 2021b). Sera from Pfizer vaccine recipients in Germany neutralized the UK variant virus B.1.1.7 as efficiently as against pseudovirus with the spike protein from the Wuhan virus which is the basis of the mRNA vaccine (Muik *et al*., 2021). Sera from 23 elderly vaccinees (mean age 82 years) who received the Pfizer vaccine also neutralized both wild type and mutated viruses (N501Y, A570D, 69/70 deletion) similarly (Collier *et al*., 2021). Subjects immunized with the Moderna mRNA vaccine showed a minimal neutralization decrease against the UK variant, but a 6.4-fold reduction in neutralizing titers against the South African B.1.351 variant, while neutralizing titers remained generally high (Wu *et al*., 2020a; *Wu et al*., 2020b). Sera from 15 participants of the Pfizer-BioNTech mRNA vaccine trial in the US showed mean neutralization titre of 500 against the reference US virus isolate and 180 against the South African variant. Since the immunization also elicits CD8+ T-cell responses, part of the clinical protection will probably also be conferred by the cellular immune response, which provides a second line of defence against immune escape by variant viruses (Liu *et al*., 2021). Interestingly, the N501Y mutation that is shared by both the UK and SA variant viruses was even better neutralized than the US wild type virus suggesting that some mutations might improve viral fitness (titre, transmission), but not necessarily immune escape (Xie *et al*., 2021).

The low protection rate observed in the AstraZeneca vaccine trial from South Africa where the variant B.1.351 was dominant, motivated a number of studies to explore the capacity of sera from vaccinees to neutralize this variant virus. Subjects vaccinated with the Moderna mRNA vaccine, taken 1 week after the second immunization, neutralized B.1.351 with a 6-fold lower titre than the reference virus, but mean neutralizing titre against B.1.351 was with 290 still high (Wu *et al*., 2021a; Wu *et al*., 2021b). Sera from people vaccinated with the Pfizer-BioNTech and the Oxford-AstraZeneca (AZ) vaccine showed eightfold and ninefold lower neutralization titers against B.1.351 compared to the Wuhan-like isolate, but since the AZ vaccine showed already a fourfold lower neutralization titre against the Wuhan-like virus, the effect of the titre decrease against B.1.351 was greater such that a third of the AZ vaccinees had only low neutralizing titre against the South African variant (Zhou *et al*., 2021). Individuals who received only one dose of either Pfizer or Moderna mRNA vaccine showed titers of about 200. The UK variant B.1.1.7 (N501Y), Danish mink variant B.1.1.298 (Y453F) and California variant B.1.429 (L452R) exhibited neutralization that was generally similar (about 2-fold decrease) to that of wild-type virus. The Brazilian P.2 variant, whose spike receptor binding domain contains an E484K mutation, showed an about 5-fold titre decrease. Strikingly, neutralization of South African B.1.351 strains was substantially decreased by 40-fold, a similar decrease as seen for distantly related coronaviruses such as SARS-CoV from the 2003 outbreak. The researchers concluded that single dose immunization with the existing mRNA vaccines may be insufficient to induce a sufficiently cross-neutralizing antibody responses to the South African variant virus (Garcia-Beltran *et al*., 2021). Sera from 19 individuals vaccinated twice with Pfizer vaccine were similarly potent against B.1.1.7 but less efficacious against B.1.351, when compared to D614G. Neutralizing titers increased after the second vaccine dose, but still remained 14-fold lower against B.1.351 (Planas *et al*., 2021). The reduction in neutralization of the South African variant by sera of mRNA vaccine recipients differed between studies: fourfold decreases were reported (Pfizer: Liu *et al*., 2021; Moderna: Edara *et al*., 2021), as well as 12-fold lower titers for Moderna and 10-fold lower titers for Pfizer vaccinees against B.1.351 compared to wild type virus (Wang *et al*., 2021a; Wang *et al*., 2021b). The differences in neutralization of the South African variant reported in these publications might reflect technical test details with respect to reference virus (Wuhan vs. Washington SARS-CoV-2 isolate), the engineering of the variant test viruses (pseudo-typed lentivirus vs. engineered infectious cDNA clone) and the number of tested sera ranging from 10 to 100 in different studies, making direct comparisons of results difficult.

Adverse events

Vaccine side effects

Common side effects of mRNA vaccines were fever, chills and muscle ache. Some researchers suspect that the immune system's response to lipids in the nanoparticle delivery vehicle is causing the short-term side effects because of the release of inflammatory mediators in the muscle. However such short term side effects should be accepted since they might be essential for activating the

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immune system (Wadman, 2021a). By 21st February, 2021, more than 46 million persons had received at least 1 dose of an mRNA-based COVID-19 vaccine in the United States. CDC enrolled 3.6 mio persons in v-safe health surveys. Reactions after the first dose of COVID-19 vaccine were injection site pain (68%), fatigue (31%), headache (26%) and myalgia (19%). Reactogenicity was substantially greater after the second dose, greater with Moderna than with Pfizer vaccine and greater in younger than in older vaccinees. Systemic reactions were highest on day 1 after vaccination and declined markedly through day 7 (Chapin-Bardales *et al*., 2021). Up to 0.8% of the vaccinees experienced a delayed type or T-cell mediated hypersensitivity near the injection site with an onset after a week, which resolved within days and sometimes recurred after the second injection, but did not represent a contraindication against immunization with the mRNA vaccines (Blumenthal *et al*., 2021).

Vaccine accidents

Historically severe vaccine accidents have occurred (Knipe *et al*., 2020). In 1955 two batches of insufficiently formalin-inactivated Salk polio vaccine resulted in 51 cases of permanent paralysis and 5 deaths. In the 1960s, a formalin-inactivated respiratory syncytial virus vaccine enhanced disease after exposure to the wild virus because the vaccine did not induce neutralizing antibodies in vaccinees and induced a T helper cell 2 (TH2)–biased CD4+ T cell response, a hallmark for vaccine-enhanced disease. More recently, antibody-dependent enhancement (ADE) of disease has been observed with dengue virus vaccines. ADE is caused by non-neutralizing antibodies that promote infection by enhancing uptake of viral particles into host cells. The first rotavirus vaccine was licensed in the United States in 1998. After the approval of rotavirus vaccines in the late 1990s and in the first year of vaccine use, 15 cases of intussusception were reported in vaccinees, in contrast to only four cases in the 7 years preceding vaccination. Intussusception is a painful form of bowel obstruction due to bowel prolapse that can be fatal if left untreated.

These examples illustrate the importance of careful evaluation of any adverse reaction and of post-licensure surveillance to ensure vaccine safety. In contrast, a report linking childhood vaccines to autism was a case of scientific fraud. Likewise reports about the adverse effects of hepatitis B vaccine are scientifically unfounded. Real risks must be communicated in perspective. Vaccines are among the most successful medical and public health measures ever implemented. It is estimated that vaccines prevent 6 million deaths globally per year. Against this background severe adverse vaccine events should be considered. For example, vaccines developed against swine flu in 1976 and more recently against the Mexican swine flu were linked to paralytic Guillain–Barré syndrome (GBS) disease and narcolepsy respectively. Careful analysis noted statistically increased associations with some flu vaccine batches, but not others and associations in some countries, but not in others. These adverse events counted in the hundreds without subtracting the background level of their occurrence in the population and compare with ten thousands of deaths annually claimed by influenza in the United States alone (CDC, 2020; Evans *et al*., 2009).

Severe adverse events: anaphylaxis and mRNA vaccines

Quickly after the start of the UK mass vaccination program for health care workers and elderly adults, the program reported cases of anaphylaxis in two women with known food and drug allergies. Further cases of anaphylaxis associated with the Pfizer mRNA vaccine have been reported in the United States. Anaphylaxis in vaccinees occurred within minutes after the injections and all responded to epinephrine. The mRNA vaccines developed by Pfizer-BioNtech and Moderna use a lipid-based nanoparticle carrier system that prevents the rapid enzymatic degradation of mRNA and facilitates in vivo delivery. This lipid-based nanoparticle carrier system is further stabilized by a polyethylene glycol (PEG) 2000 lipid conjugate that provides a hydrophilic layer, prolonging half-life. CDC recommended to exclude patients with a history of immediate reactions associated with PEG from vaccination with mRNA vaccines. It is currently unknown whether for these subjects the adenovirus vectored vaccine which is formulated with polysorbate 80, a nonionic surfactant and emulsifier that has a structure similar to PEG, is an alternative (Castells *and Phillips, 2021*).

The Vaccine Adverse Event Reporting System identified 21 cases of anaphylaxis after application of 1.8 mio doses of Pfizer-BioNTech mRNA vaccine corresponding to an estimated rate of 11 cases per million doses administered. Seventeen had a documented history of allergies to drugs or medical products, foods and insect stings; seven had experienced an episode of anaphylaxis in the past. CDC guidance recommends that vaccination locations should have epinephrine in prefilled syringes available and implement recommended observation periods of 15 or 30 min at these centres (Shimabukuro *et al*., 2021). After 10 mio doses of Pfizer and 7.6 mio doses from Moderna mRNA vaccines were applied in the United States, CDC identified 66 cases of anaphylaxis yielding a rate of 4.7 and 2.5 cases/million doses of the Pfizer and Moderna vaccine respectively; 92% of the patients received epinephrine, 48% were hospitalized, but no death occurred. Common signs were

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urticaria, rash, angioedema, respiratory and airway obstruction symptoms and nausea. Median time to symptom onset was 6 min. CDC concluded that benefits of vaccination far outweigh the risk of anaphylaxis (Shimabukuro and Nair, 2021).

Severe adverse events: cerebral thrombosis and adenovirus vaccines

Until end of March, EMA had collected 86 reports of people who had experienced unusual cerebral blood clots in previously healthy young adults which occurred within 2 weeks after receiving the AstraZeneca vaccine. Linking a rare, but severe adverse event to a vaccine is challenging. More data about cerebral thrombosis in young adults are needed in people who did not receive the vaccine because awareness about this condition and its link to vaccination could increase reporting in vaccinated over unvaccinated subjects (Ledford, 2021a; Ledford, 2021b; Ledford, 2021c). By mid-March 2021, about 10% of the German population (80 mio) had received at least one injection of a vaccine, a quarter received the AstraZeneca vaccine. Clinicians reported 11 cases of unusual thrombotic events in combination with thrombocytopenia for Germany and Austria. Cerebral venous thrombosis and splanchnic-vein thrombosis in association with a positive test for antibodies against platelet factor 4 (PF4)–heparin were characteristic. Laboratory data indicated that platelet activation had occurred through platelet Fcγ receptors for these antibodies while it remains unclear whether they represent auto-antibodies or vaccine-induced antibodies. Platelet activation was inhibited by high levels of heparin, Fc receptor-blocking monoclonal antibody and immune globulin. The median age of the previously healthy subjects was 36 years, 9 of 11 were women, 6 of them died. The condition resembles autoimmune heparin-induced thrombocytopenia (a prothrombotic thrombocytopenic disorder that can be triggered by heparin), but none of the patients had received heparin. The condition occurred 5–20 days after vaccination (Greinacher *et al*., 2021). Very similar clinical observations were reported for five cases noted in Norway among 130 000 vaccinated subjects. All five patients had high levels of IgG antibodies to PF4–polyanion complexes, platelet aggregation was efficiently reduced by high heparin levels and the outcome was fatal in three. While 5%–7% of blood donors have detectable PF4–heparin antibodies, titers are not so high as in these patients. The clinicians noted early treatment with intravenous immune globulin as a potential option. In view of the devastating effects in healthy young adults, the clinicians requested a thorough risk–benefit analysis for this population (Schultz *et al*., 2021). Also British haematologists reported 23 cases with rare blood clotting disorders shortly after immunization with the AstraZeneca vaccine that resembled clinically closely the German and Norwegian cases. Testing for antibodies to PF4 was positive in 22 patients; 30% of the patients died. Rapid identification of this rare syndrome is important because of the therapeutic implications (use of a non-heparin anticoagulant agent, intravenous immune globulin; Scully *et al*., 2021). After their initial reviews, the MHRA and the EMA confirmed that the risk of venous thromboembolism associated with the vaccines was not higher than the background risk in the general population and emphasized the overwhelmingly favourable risk–benefit ratio for vaccines against SARS-CoV-2. Also US clinicians reported a case of splanchnic vein thrombosis in a patient who received the Ad26.COV2.S vaccine from Johnson & Johnson/Janssen and suggested a link to vaccination with adenovirus vectors because no such cases were reported for recipients of the mRNA vaccine (Muir *et al*., 2021). Scientists from Janssen answered that a post-authorization pharmacovigilance program by Janssen noted six cases of cerebral venous sinus thrombosis (CVST) with thrombocytopenia occurring 7 to 14 days after vaccination among more than 7.2 million persons who had been vaccinated with Ad26.COV2.S globally. With a rate of 1 case per 1 million vaccinees it is within the range of published background incidence for CVST (but not of this new PF4 antibody phenotype). They also noted that the AstraZeneca and Janssen adenovirus vectors belong to different adenovirus species, which does not suggest a common causal mechanism, but agree that further investigation is needed (Sadoff *et al*., 2021).

Outlook

The only way-out of the current health and economy crisis is widespread vaccination to stop the epidemic. Now the task for industries is to produce vaccines for billions of people and governments and international organizations to organize their distribution and vaccination campaigns. In contrast to countries such as Israel, UK and the United States, the EU has bargained with pharma companies about prices and producer's liability for side effects of vaccines. The savings made are now more than compensated by the cost of delayed economic recovery by slower vaccine delivery. The EU was also hesitant to support an increase in production capacities by financial incentives to the private industry. According to *The Economist* news from 19th of April, 1 billion doses of COVID-19 vaccines were produced by mid-April 2021 and a second billion could be produced in enlarged industrial production sites were it not for export restrictions of essential ingredients and machines imposed by the US government. A fire in India's largest vaccine production site (SII, the Serum Institute of India) has reduced the 400 mio doses promised to COVAX to a mere 28 mio doses. The recent surge of cases in India (>300 000 new

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infections on a single day) will also increase political pressure to diverge a major part of the Indian vaccine production for domestic needs (Padma, 2021). To these industrial vaccine production problems, psychological problems of vaccine acceptance further complicate the situation. The decisions of European governments to suspend vaccination with AstraZeneca vaccine in older citizens for lacking efficacy data, followed by the decision to recommend the same vaccine in older subjects (thrombosis events became known in younger vaccinees) probably contributed to the confusion of the public, as did the discordant risk assessment of the AstraZeneca vaccine by the EMA and national health authorities. Successful vaccine roll-out will only be achieved by ensuring effective community engagement and by building vaccine confidence. Wide-scale social mobilization of community and faith leaders, teachers, sports and youth clubs and online communities and networks are needed for confidence building (Burgess *et al*., 2020). Already in 2019, WHO named vaccine hesitancy one of the top 10 threats to global health alongside climate change. It will need psychological and sociological approaches to cope with vaccine hesitancy. It will be important to distinguish between people wholly opposed to vaccination (anti-vaxxers) and individuals who have genuine vaccine concerns and questions (vaccine hesitaters). In conflating both groups and developing an aggressive position against anti-vaxxers, authorities might fail to develop trust among vaccine hesitaters. This problem shows parallels with the use of condoms in the early phase of the AIDS pandemic where doctors had to realize that recommending condoms met high psychological barriers in some populations which led to the involvement of social scientists to increase the acceptance of condoms. Another example from the current pandemic is the use of face masks which in the United States got a symbolic importance of political identity instead of being used across the population as a low cost item with high public health efficacy. Marketing specialists argue against the use of scientific and statistical arguments since more than half of Americans score 2 or lower on the 5-point numeracy scale. If confronted with individual vaccine side effects, counter with individual success stories. Narratives are more important than numbers. Consumers' ability to observe others' choices can increase an innovation's rate of adoption, wearable tokens or electronic stickers or immunity passports allowing greater social mobility for vaccinated people (once their decreased transmission potential demonstrated) could increase acceptance and create a visible sign of in-group/out-group attribution. In consumer markets, scarcity often signals exclusivity and prompts greater interest and the initial shortage of supply should here be used to frame early access to vaccines as a mark of social honour or respect (elderly and health care workers). If a product runs out quickly, people might assume it is highly desirable. People dislike missing out on fun things, therefore working with reward is legitimate, e.g., employers could offer a day off to reward an employee's contribution to a safe workplace (this will also help people to rest and recover from side effects if any; Wood and Schulman, 2021). Imaginative approaches are needed to motivate the population to get the jab once the vaccine becomes available in sufficient numbers.

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