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Some questions on the future of R&D on Covid-19 vaccines. A conversation between Massimo Florio and Giuseppe Remuzzi

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Abstract

The paper highlights the need for continued public support for R&D for Covid-19 vaccines. It is structured as a conversation between Professor Giuseppe Remuzzi, scientific director of the "Mario Negri" Institute for Pharmacological Research, and Professor Massimo Florio, economist principal investigator of the study "Mapping of long-term public and private investment in the development of COVID-19 vaccines", for the European Parliament. Questions dealt with include a) virus mutations and vaccine adaptation, b) Efficacy and duration, c) Clinical effectiveness, d) Safety, and e) target population. The paper is concuded by some social cost-benefit analysis remarks about the creation in the EU of a public infrastructure for R&D and delivery of drugs and vaccines in the public interest.

Keywords: Covid-19 Vaccines; Pandemics; R&D and public investment

JEL codes: I18, H43, H51

Contents

1. Introduction

In 2023, the European Parliament (EP) established the Special Committee "COVID-19 Pandemic: Lessons Learned and Recommendations for the future" (COVI), and the EP Policy Department for Economic, Scientific and Quality of Life Policies requested the independent study "Mapping of long-term public and private investments in the development of COVID-19 vaccines" to support the COVI Committee and to provide a mapping of funds contributed by different actors for the R&D and the expansion of the production capacity of COVID-19 vaccines, with a focus on those authorised in the EU[1].

The methodology employed to draft the study combined desk research, statistical analysis and interviews involving 30 expert stakeholders. Professor Giuseppe Remuzzi, Director of Mario Negri Institute for Pharmacological Research, has answered in written form several questions asked to him by Professor Massimo Florio. While the above-mentioned report summarises some of the answers, we report here the full text of the conversation (24 January 2023) as it was considered for the Florio et al. (2023) study for the EP.

In this paper, possible directions for R&D on Covid–19 are presented, focusing on the following issues: a) Virus mutations and vaccine adaptation; b) Efficacy and duration; c) Clinical effectiveness; d) Safety; e) Target population. While several advances were made after the delivery of the above-mentioned study, we report here the interview for the data available.

The paper is concuded by some social cost-benefit analysis remarks about the creation in the EU of a public infrastructure for R&D and delivery of drugs and vaccines in the public interest.

[1] The full report (Florio, Gamba, Pancotti 2023) is available at: https://www.europarl.europa.eu/RegData/etudes/STUD/2023/740072/IPOL_STU(2023)740072_EN.pdf.

2. Some questions for future R&D

2.1 Virus mutations and vaccine adaptation

MASSIMO FLORIO:

Given that Sars Cov 2 so quickly and so extensively mutates, should R&D focus on vaccines adapted to major mutations over time, or should vaccines target some more stable features of the virus?

GIUSEPPE REMUZZI:
The spike protein of SARS-CoV-2 has been identified as the most targetable viral component to limit viral infection due to its critical role in mediating viral infection in target cells. However, its extensive mutation rate poses some challenges to vaccine protection from breakthrough infections with highly mutated viral variants. For this reason, reformulating SARS-CoV-2 vaccines with variant strains (bivalent vaccine) is being pursued to combat the global surge in infections.

However, recent data suggest that the efficacy of updated bivalent vaccine boosters may not be as effective in preventing viral infection against different variants. This finding could be explained by the so-called '*immune imprinting*', a phenomenon in which an initial exposure to a virus — such as the original strain of Covid, by infection or vaccination — limits a person's future immune response against different variants by triggering the antibody response against the initial viral strain encountered during vaccination or infection[2]. This concern is supported by the research by Roltgen K et al., which found that "Viral variant infection elicits variant-specific antibodies, but prior mRNA vaccination imprints serological responses toward Wuhan-Hu-1 rather than variant antigens"[3]. Prior infections have also been observed to cause imprinting. Reynolds et al. found that "Omicron infection after previous Wuhan Hu-1 infection failed to boost neutralising antibody and T cell responses against Omicron, revealing a profound imprinting effect and explaining why frequent reinfections occur"[4]. Even more important, a recent study suggested that boosting with new bivalent mRNA vaccines targeting both the BA.4–BA.5 variant and the D614G strain did not elicit a discernibly superior virus-neutralising peak antibody response as compared with boosting with the original monovalent vaccines[5]. Similarly, among the different viral variants, BQ.1, BQ.1.1, XBB, and XBB.1 have been shown to escape serum neutralisation of individuals with bivalent boosters, as well as all clinical monoclonal antibodies developed so far[6].

Based on this finding, R&D should focus on developing a novel vaccine platform to target some more stable features of the virus in order to induce durable sterilising immunity. These approaches might include, among many other methods, targeting S protein viral sequences that are immutable, immunogenic, and accessible to neutralising antibodies; including other targets from the virus such as portions of the membrane, envelope, or nucleocapsid proteins; targeting conserved or occluded (structurally hidden) epitopes using nanoparticles of randomly arrayed receptor binding domains; and developing vaccines based on T-cell receptor constructs that specifically recognise the SARS-CoV-2 RNA-dependent RNA polymerase[7].

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[2] Brazil, 2023.
[3] Röltgen et al., 2022.
[4] Reynolds et al., 2022; Chemaitelly et al., 2022.
[5] Wang et al., 2023a.
[6] Wang et al., 2023b.
[7] Marks et al., 2023.

2.2 Efficacy and duration

MASSIMO FLORIO:

Current vaccines' efficacity against infection is overall limited to some months: is it possible to improve the duration? This question may or may not be related to the previous one.

GIUSEPPE REMUZZI:
Researchers are ramping up efforts to figure out why some vaccines protect for mere weeks, but others work for life. To date the answer to this question is that we simply don't know which are the rules to induce long-lasting immunity. Indeed, for years, most vaccines were developed empirically, while the deep immunological mechanisms underlying the longevity of vaccine-induced protection have not been systematically measured.

Some vaccine designers hold fast to the idea that a live and weakened pathogen-based vaccine induces the longest-lasting, most robust responses. This is true for measles, smallpox, and poliomyelitis vaccines, for example, which protect for life.

But this notion may be simple-minded. Indeed, for the flu, both live and killed virus vaccines exist—and neither offers durable protection. Even when they closely match the circulating strains of influenza viruses, both types protect only about 60% of vaccinated people. And those modest immune responses rapidly wane. In a 2018 review of 11 recent studies on the durability of influenza vaccines, researchers concluded that effectiveness can vanish as soon as 90 days after vaccination.

For the COVID-19 mRNA vaccine, data suggest that protection against viral infection may last three months or shorter despite a remarkable and durable protection against hospitalisation, severe disease and death. To overcome this limitation, multiple booster shots have been authorised to restore antibody waning and confer additional protection. As described in question 1, this may not be the preferred road to generate a broad, long-lasting sterilising immunity.

To date, one of the most compelling findings that can justify the short duration of mRNA vaccines is that they are not able to induce a sufficient mucosal IgA response that could, in part, explain the limited efficacy of mRNA vaccination in limiting the transmission chain, prevent the frequent breakthrough infections, and achieve high levels of durable protection against severe disease. Based on these findings, nasal vaccines, with their allure for achieving mucosal immunity, have received the spotlight for the possibility of complementing and likely bolstering the circulating immunity achieved via intramuscular shots. Fortunately, there are at least 12 nasal vaccines that are in clinical development, and four have reached phase 3 randomised, placebo-controlled trials with promising results. Despite these encouraging data, the challenges of validating a clinically effective and safe nasal vaccine for which there has been limited success. For this reason, R&D teams and research immunologists should cooperate together to achieve a successful, life-long, effective COVID-19 vaccine[8].

To this aim, some clues may arise from unusually successful vaccines that drive the immune system to mount effective responses for decades, if not an entire human life. One comes from the vaccine against the cancer-causing, sexually transmitted human papillomavirus (HPV), which has proved remarkably durable since it debuted about a decade ago, spotlighting a novel mechanism of long-lasting protection.

Concerned that an attenuated or an inactivated HPV vaccine might still contain viral components that can cause cancer, researchers genetically engineered another virus to manufacture copies of

[8] Topol, Iwasaki, 2022.

a harmless HPV surface protein that self-assembles into what's called a virus-like particle (VLP). Trials have shown that nearly everyone vaccinated with that noninfectious VLP develops high levels of HPV-neutralizing antibodies. Those levels decline moderately after two years but then remain stable for at least a decade. VLPs challenge the widely held notion that durability depends primarily on memory B cells waking and expanding when an infection occurs. Indeed, the HPV vaccine leads to consistent blood levels of neutralising antibodies for years on end, but if it were memory B cells, you should see spikes and blips up and down in the antibody response. Studies suggested that VLPs trigger the production of a different set of B cells called long-lived plasma cells (LLPCs), which reside in the bone marrow and continually produce antibodies specific to different foreign antigens. Almost 25 years ago[9], it was reported that dense, highly repetitive proteins on the surfaces of viruses trigger the strongest antibody responses. A VLP is just such a structure. In theory, that allows the viral antigens to "cross-link" to many receptors on the surface of B cells. That, in turn, triggers a cascade of signals in immune cells that lead to strong, durable antibodies.

Although mRNA vaccines have been demonstrated to induce antigen-specific memory B cells (MBCs) in the human population, there is no evidence that these vaccines induce the production of sufficient and efficient LLPCs in the bone marrow.

In the wake of the HPV vaccine's success, VLPs have become a trendy vaccine strategy and experimental influenza, norovirus, chikungunya, encephalitis, malaria, and dengue VLP vaccines are in development. Also, for COVID-19, VPL-based vaccines could be the next future strategy to induce a long-lasting protective effect by assessing the most effective conformational structures and number of spike proteins on the VPLs surface to sustain a wide and durable LLPC generation.

The existing COVID-19 vaccines have had a profoundly positive effect during the pandemic, reducing both hospitalisation and death. However, the documented emergence of a new dominant SARS-CoV-2 variant approximately every 3 to 4 months presents a public health dilemma. Continuing along the current path of the generation and administration of variant-specific vaccine boosters is inadequate as a long-term strategy for addressing COVID-19 in populations globally. Serious consideration, therefore needs to be given to the development of a distinctly improved generation of SARS-CoV-2 vaccines offering longer protection with greater scope[10]. Possible approaches to achieve more durable SARS-CoV-2 vaccine immunity include the generation of the following: i) variant-proof SARS-CoV-2 vaccines; ii) pan-sarbecovirus vaccines (i.e., against sarbecoviruses, the subgenus that includes all the SARS-like viruses); iii) pan-betaCoV vaccines (i.e., against betacoronaviruses, which include sarbecoviruses, merbecoronaviruses like the one that causes Middle East Respiratory Syndrome (MERS), and two that now trigger the common cold); iv) pan-CoV vaccines. Regarding the first objective, different approaches aim to yield a variant-proof vaccine: multivalent platforms or formulations with distinct variants (with or without the ancestral SARS-CoV-2 Spike strain); inserts designed to elicit cellular responses (such as Nucleocapside, that is an internal RNA-binding protein which has long been viewed as an important target for T cell response, that may eventually confer broad protection); or the ancestral SARS-CoV-2 Spike strain in a platform deemed to elicit broader and more potent immunity. It is important to note that these variant-proof strategies do not necessarily include distinct variant sequences because it is argued that a given vaccine candidate based on the ancestral SARS-CoV-2 antigen could offer superior immune responses that would cover a broad array of viruses. In this regard, researchers at Duke University have developed a vaccine candidate based on the ancestral SARS-CoV-2 strain and aimed to be variant-proof. The administration of this vaccine candidate in nonhuman primates has recently been reported to induce neutralising antibodies against eight

[9] Bachmann et al., 1993.
[10] Marks et al., 2023.

SARS-CoV-2 variants, including Beta, Delta and Omicron[11]. Other strategies seek to cover incrementally broader CoV space. The feasibility of a pan-sarbecovirus vaccine strategy is supported by evidence that people with 20-year-old SARS-CoV-1 infection who received mRNA-based COVID-19 vaccine produced a swathe of pan-sarbecovirus neutralising antibodies[12]. A leading strategy seeking to confer pan-sarbecovirus coverage is the nanoparticle vaccine developed by Cohen et al. (Mosaic-8b), which includes eight receptor-binding domain (RBD) sequences (i.e., SARS-CoV-2 RBD plus seven animal sarbecoviruses RBDs). When Mosaic-8 nanoparticles were used to immunise mice and nonhuman primates, the animals were protected against SARS-CoV-1 and SARS-CoV-2, including Omicron[13].

Finally, there are ongoing studies testing pan-betaCoV vaccines, but details on the vaccine inserts are not available[14].

As yet, there has been little breathing space for comparative evaluations of these options.

Box 1: Variant-proof SARS-CoV-2 vaccines: summary of approaches

a) multivalent platforms or formulations with distinct variants (with or without the ancestral SARS-CoV-2 Spike strain);
b) inserts designed to elicit cellular responses (such as Nucleocapsid, which is an internal RNA-binding protein which has long been viewed as an important target for T-cell response that may eventually confer broad protection);
c) or the ancestral SARS-CoV- 2 Spike strain in a platform deemed to elicit broader and more potent immunity.
d) It is important to note that these variant-proof strategies do not necessarily include distinct variant sequences because it is argued that a given vaccine candidate based on the ancestral SARS-CoV-2 antigen could offer superior immune responses that would cover a broad array of viruses. In this regard, researchers at Duke University have developed a vaccine candidate based on the ancestral SARS-CoV-2 strain and aimed to be variant-proof[15].

2.3 Clinical effectiveness

MASSIMO FLORIO:

In terms of clinical effectiveness, is there conclusive evidence of which technology is superior? Rigorous comparative studies in this perspective are not frequent, while in a public health perspective, this information would be important.

GIUSEPPE REMUZZI:
The four major platforms employed for the development of SARS-CoV-2 vaccines include the use of non-replicating viral vector vaccine (e.g., AstraZeneca-Oxford ChAdOx1 nCov-19 and Johnson & Johnson/Janssen Ad26.COV2.S), mRNA vaccines (e.g., Pfizer-BioNTech BNT162b2 and Moderna-US National Institute of Health mRNA-1273), inactivated whole-virus vaccines (e.g., Sinovac CoronaVac) and protein subunit vaccines (e.g., Novavax NVX-CoV2373). Estimates of efficacy have varied widely. In particular, regarding non-replicating viral vector vaccines, AstraZeneca-Oxford's trial produced estimates of efficacy of 62% with the standard dosing and 90% with the lower

[11] Li et al., 2022.
[12] Tan et al., 2021.
[13] Cohen et al., 2022.
[14] Dolgin, 2022.
[15] Li et al., 2022.

primer dosing[16], whereas Johnson & Johnson/Janssen's vaccine was found to be 67% effective[17]. As for mRNA vaccines, effectiveness was estimated at approximately 95% for both Moderna and Pfizer-BioNTech clinical trials[18]. The estimates of efficacy of Sinovac CoronaVac were found to vary across trials, namely 50.65% in Brazil, 65.30% in Indonesia, and 83.50% in Turkey[19]. Regarding two other Chinese inactivated vaccines, HB02 and WIV04, estimates of efficacy were reported to be 78.1% and 72.8%, respectively[20]. Finally, Novavax NVX-CoV2373 trials produced estimates of efficacy of 90%[21].

Thus, point estimates of vaccine efficacy from phase 3 trials – often with relatively wide and overlapping confidence intervals - varied considerably, both within and between technologies. Moreover, such point estimates cannot be compared directly because efficacy trials were performed in different epidemiologic settings and used different case definitions, clinical endpoints, and protocols for ascertainment of such endpoints.

In addition, the concept that vaccine efficacy is not a static value has become particularly salient, as real-world effectiveness has changed with location and over time. In this regard, COVID-19 vaccines have been especially challenged by the emergence of variants of concern.

Accordingly, there is no conclusive evidence of which technology is superior in terms of clinical effectiveness. Formal comparative trials regarding the efficacy of vaccines are not available, but probably such studies are not necessary. Indeed, in all cases, irrespective of underlying technology, vaccine efficacy against severe illness and death appeared to be very high, both in clinical trials and in real-world settings. Thus, even vaccines with lower effectiveness in preventing symptomatic COVID-19 may still have a substantial effect on public health[22]. Moreover, each vaccine has different attributes, advantages and disadvantages, and multiple factors have to be considered in guiding policy decisions. These include, amongst others, vaccine availability, costs, logistics, side effects and patient acceptability.

2.4 Safety

MASSIMO FLORIO:

The safety of vaccines is overall good for those approved by the major agencies, but even if rare adverse effects have been recorded, comparative evidence across technologies is not firmly established: are comparative studies needed and/or more in depth studies on adverse effects?

GIUSEPPE REMUZZI:
Formal comparative studies on the safety of vaccines are scanty, but probably no further such studies are necessary, given the large number of reassuring information collected so far with the administration of different COVID-19 vaccine platforms.

Overall, COVID-19 vaccines are safe and effective: Local and systemic adverse events are relatively common with these vaccines (at least for the four mostly used in Europe, including Pfizer-BioNTech BNT162b2 and Moderna-US National Institute of Health mRNA-1273, both mRNA vaccines; and Johnson & Johnson/Janssen Ad26.COV2.S and AstraZeneca-Oxford ChAdOx1 nCov-19, both non-replicating viral vector-based vaccines). Most of the adverse events that occurred during vaccine

[16] Voysey et al., 2021.
[17] Sadoff et al., 2021.
[18] Pollack et al., 2020; Baden et al., 2021.
[19] Wilder-Smith et al., 2021.
[20] Al Kaabi et al., 2021
[21] Dunkle et al., 2022.
[22] Wilder-Smith et al., 2021; Jara et al., 2021.

trials were mild or moderate in severity (i.e. they did not prevent vaccinated people from engaging in daily activities) and resolved after 1 or 2 days. Among the most commonly reported side effects are fatigue, headache, myalgia, fever, pain and/or redness at the injection site[23]. On the other hand, there are some rare adverse events reported, such as allergic and anaphylactic reactions following mRNA vaccination, and thrombosis and thrombocytopenia following non-replicating viral vector vaccination[24]. Other rare adverse events described were myocarditis, Bell's Palsy, Transient Myelitis, Guillen-Barré syndrome, recurrences of herpes-zoster, autoimmunity flares, epilepsy, and orthostatic tachycardia. Of note, most of these adverse events are considered mild to moderate in severity, indicating that COVID-19 vaccines are actually safe.

Regarding the relationship with particular vaccine platforms, COVID-19 adenoviral vector vaccines (Johnson & Johnson/Janssen vaccine and AstraZeneca Oxford vaccine) have been associated with an increased risk of thrombosis with thrombocytopenia syndrome (TTS) in adults. Cases of thrombosis and thrombocytopenia have also been reported, rarely, following COVID-19 mRNA vaccination, such as the Moderna vaccine, although no association has been established so far. TTS is a rare but serious condition that causes blood clots in large blood vessels and low platelet levels. Women aged 30 to 49 years should be aware of the increased risk of TTS.

Concern has been put forward also for myocarditis and pericarditis, but these adverse events after COVID-19 vaccination are rare, and most of the reported cases were very mild and self-limiting[25]. These conditions have occurred most often in male adolescents, young adults, and people who have received mRNA vaccines. The risk rate seems to be about threefold to four-fold higher for Moderna mRNA-1273 compared to Pfizer-BNT162b2[26]. The discrepancy regarding the frequencies of myocarditis occurrence for the two vaccines could probably be explained by the different time span between the two doses, the differences in composition (lipid nanoparticles) and the purity of the materials, as well as in the production protocols.

After the initiation of the mass vaccination program against COVID-19, reports concerning neurological adverse events of vaccines also started to emerge. Among these neurological adverse events, the most commonly observed were Guillain-Barré syndrome, transverse myelitis and Bell's Palsy, although no association with COVID-19 vaccines has been confirmed yet[27]. Guillain-Barré syndrome is a neurologic disorder that causes muscle weakness and sometimes paralysis. It has been linked with viral vector vaccine, although in people who received the Johnson & Johnson/Janssen vaccine is rare. Most people with Guillain-Barré syndrome fully recover, but some have permanent nerve damage. Onset typically occurs about two weeks after vaccination. It has mostly been reported in men aged ≥ 50 years.

In summary, the available evidence indicates that approved COVID-19 vaccines are safe, and adverse events are rare and, in most cases, with full recovery. However, some of these rare events occur primarily with mRNA vaccines, whereas others occur with viral vector-based platforms. Thus, a better understanding of the underlying mechanisms, according to which the vaccines cause side effects, in conjunction with the identification of the vaccine components and/or platforms that are responsible for these reactions in terms of pharmacovigilance, could probably enable the improvement of future vaccines against COVID-19 and/or even other pathological conditions.

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[23] Pollack et al., 2020; Sadoff et al., 2021.
[24] Lin et al., 2021; Mehta et al., 2021.
[25] Centers for Disease Control and Prevention, 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html
[26] Heinz, Stiasny, 2021; Husby et al., 2021.
[27] Lu et al., 2021.

2.5 Target population

MASSIMO FLORIO:

Are there differences in responses to vaccines by gender, age, ethnicity, and previous health conditions that should be considered more in-depth, given that some trial samples were not balanced to represent subgroups in detail?

GIUSEPPE REMUZZI:
In general, responses to vaccines are comparable in male and female adults. There are, however, particular conditions that until recently have not been considered in depth in trials. For example, pregnant and lactating individuals were not included in the initial COVID-19 vaccine trials. However, the CDC, the American College of Obstetricians and Gynecologists, and the Society of Maternal-Fetal Medicine[28] in the USA recommend vaccination for pregnant and lactating people based on the accumulated safety and efficacy data on the use of these vaccines in pregnant people, as well as the increased risk of severe disease in pregnant individuals with COVID-19[29].

Indeed, the morbidity and mortality from SARS-CoV-2 infection are higher in pregnant women compared to their non-pregnant counterparts[30]. Ongoing post-authorisation surveillance of COVID-19 vaccine use in pregnant women has enabled further characterisation of vaccine safety in pregnant women and confirms that Covid-19 vaccination during pregnancy produces a good immunological response with no increased risk of adverse maternal and neonatal outcomes. However, vaccine hesitancy is a barrier to uptake, especially among the younger population and individuals of ethnic minority backgrounds; pregnant women have additional concerns. Trust in the importance and effectiveness of the vaccine, trust in public health agencies and science, together with good communication methods regarding the safety of COVID-19 vaccines, are strong factors for vaccination acceptance in pregnancy. The lack of trust in the health system was worsened by initial knowledge gaps in the information provided about COVID-19 infection and the safety and immunogenicity of COVID-19 vaccines. This was exacerbated by access to incorrect information and misinformation to fill in those knowledge gaps, especially with the increased use of social media. Thus, communication is crucial: clinical pharmacologists have the expertise to appraise and synthesise emerging pharmacovigilance data, which can inform and support risk-benefit communication by other clinicians.

A particular issue related to vaccines, in terms of efficacy and safety, is their administration to individuals with autoimmune diseases or organ transplantation who are on chronic immunosuppressive therapy. Since activation of innate and adaptive immunity by SARS-CoV-2 vaccines is essential for triggering host immune response, immunosuppressive agents given chronically to these patients might restrict such response, eventually reducing the efficacy of vaccine treatment in preventing viral infection or limiting the severity of the illness. An example is the case of people with multiple sclerosis who are considered at high risk for COVID-19-related complications and at increased risk of disease relapse induced by the infection[31]. Although the acceptability of COVID-19 vaccines has progressively increased in the last year, a small but significant part of patients with multiple sclerosis still have relevant concerns about vaccination that make them hesitant about receiving the COVID-19 vaccine. Overall, available data suggest that

[28] Centers for Disease Control and Prevention. 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html. Society for Maternal-Fetal Medicine, 2022. Available at: https://www.smfm.org/covidclinical.
[29] Shimabukuro et al., 2021; Ai-ris et al., 2021.
[30] Villar et al., 2021; Shimabukuro et al., 2021.
[31] Capone et al., 2023.

COVID-19 vaccination is safe and effective in multiple sclerosis patients, even though some pharmacological treatments, such as anti-CD20 therapies, can reduce the immune response to vaccination. Accordingly, COVID-19 vaccination should be strongly recommended for people with multiple sclerosis, including those treated with anti-CD20 therapies. This is because the risk of morbidity, mortality and neuro-inflammation associated with COVID-19 largely outweighs the low percentage of serious neurologic and non-neurologic adverse events associated with vaccines. Nonetheless, further studies are necessary to understand the role of cellular immunity in COVID-19 vaccination and the possible usefulness of booster jobs. Meanwhile, long-term post-marketing surveillance is necessary to confirm the safety of COVID-19 vaccines also in real-life scenarios.

This approach should also be applied to patients with organ transplantation or other immune diseases.

On the side of safety, given that vaccines from multiple platforms are now widely available, people at increased risk of a specific severe adverse event may have options to pursue vaccination with a platform that does not carry such risks.

3. Concluding remarks and policy implications

Epidemics are part of human history (see Alfani, 2022, for a review of the literature). According to some studies, there have been 476 reported epidemic events since 1600 (Marani *et al.*, 2021), not to mention what we know about major pandemics in the ancient world.

In this context, the social value of being prepared for the next pandemic cannot be exaggerated. This implies public investment in the advanced production capacity of vaccines (Glennerster *et al.*, 2022) and in R&D, as the private sector tends to postpone such investment until risk and profitability are convenient to companies. The mismatch between private and public priorities should be duly considered in a social cost-benefit perspective. Let us consider the social cost of Covid-19 until 2022:

Firstly, excess mortality has been highly significant. There is large uncertainty on mortality data, which range from over 5.43 million confirmed Covid-19 deaths (to December 2021) for the WHO, to be compared with 14.9 excess deaths (mean estimate) by the WHO itself, for example, because of economic disruption, not only in less developed economies. According to a detailed model by The Economist, Covid-19 confirmed deaths were 7.05 million to June 2024, while global excess deaths in their central estimate are about 27 million[32].

By comparison, the flu pandemic of 1918, often called the Spanish flu, is supposed to have killed 50 million worldwide:

> "The virus infected roughly 500 million people—one-third of the world's population—and caused 50 million deaths worldwide (double the number of deaths in World War I). In the United States, a quarter of the population caught the virus, 675,000 died, and life expectancy dropped by 12 years.[33]"

Secondly, from a social cost-benefit analysis perspective[34], the prevention of death is valued in terms of the value of a statistical life:

> "The value of a statistical life (VSL) [...] defines the monetary value of a (small and similar among the population) mortality risk reduction that would prevent one statistical death and, therefore, should not be interpreted as how much individuals are willing to pay to save an identified life."[35]

While VSL is clearly a conservative concept, as it does not include a number of indirect social costs (for relatives and third parties) of a statistical loss of life, and the estimates of VSL hugely vary across counties and age groups, and across estimation methods, the social cost worldwide of the Covid 19 pandemics in VSL terms would be in the range of tens of trillions USD. For example, the US government Department of Health and Human Services used a central value of VSL of 11.4 million USD in 2020[36]. As in the US, the confirmed Covid-19 deaths are well over 1.1 million to date (and the excess mortality is correspondingly higher); the social cost of the pandemic in the USA could be of not less than 12,5 billion USD, or 12.4 trillion.

Thirdly, estimates of the loss of GDP are about USD 13.5 trillion (relative to a no-pandemic counterfactual), or 3.6% per year for some years:

> "The global COVID-19 coronavirus pandemic had severe negative impacts on the global economy. During 2020, the world's collective gross domestic product (GDP) fell by 3.4 per cent. To put this number in

[32] For details see Mathieu et al., 2024.
[33] https://www.archives.gov/news/topics/flu-pandemic-1918
[34] Florio and Pancotti, 2023.
[35] The concept in the context of Covid 19 public health considerations is discussed e.g. by Colmer, 2020.
[36] https://aspe.hhs.gov/sites/default/files/2021-07/hhs-guidelines-appendix-d-vsl-update.pdf

perspective, global GDP reached 84.9 trillion U.S. dollars in 2020 – meaning that a 3.4 per cent drop in economic growth results in over two trillion U.S. dollars of lost economic output. However, the global economy quickly recovered from the initial shock, reaching positive growth levels again in 2021[37]".

It is indeed difficult to estimate a counterfactual world growth in a "without Covid-19" scenario, but it seems uncontroversial that there was a long-term loss because of decreased human capital (school lockdowns and other disruption of education), again in the cumulative range of USD trillions.

The research work suggested in the previous section, while costly in the range of some USD billions, is orders of magnitude less costly than the benefits of avoiding or -more realistically- containing future pandemics.

It seems that a social cost benefit analysis of preparation for a future pandemic (public investment for production capacity of existing vaccines and R&D for new ones) would lead to interesting results. According to Glennerster *et al*. (2022), excluding HIV, future pandemics would cost – with the social discount rate (4%) and long-term yearly output increase (1.6%) – a total loss per year in future of about USD 808 billion (within an interval of 400 billion -2423 billion). They suggest that a program of USD 60 billion of public expenditure given upfront to expand the production capacity of vaccines and their inputs (with both mRNA and non-mRNA technologies) and USD 5 billion yearly for maintenance of such capacity would create considerable net benefits. In their CBA Baseline scenario, the net present value (discounted benefits less cost) would be about USD 409 billion NPV.

We suggest that a program for the EU would have, in any case, a positive NPV and positive externalities, even if there is no agreement on such a grand design at the global level. Moreover, advanced production capacity should work better if, at the same time, there is a public investment in R&D for future vaccines before the actual pandemic, looking at different kinds of pathogens, possible zoonosis, and bacteria resistant to antibiotics. Simply redoing the Glennerster *et al.* (2022) model for the EU, advance public investment would generate an NPV (against the counterfactual of waiting) of Euro 59,4 billion (current exchange rate).

There is no doubt that a long-term vaccine strategy for COVID-19 would be needed, as the SARS-CoV-2 virus is still with us, with a plethora of variants. Cost Benefit-Analysis of preparedness suggests hence that a large Net Present Value (NPV) of public investment would arise from advanced vaccine production capacity, and probably from new R&D.

The United States has responded to COVID-19 by leveraging on a strong public infrastructure, including the U.S. Department of Health and Human Services (HHS), National Institute of Health (NIH), Administration for Strategic Preparedness and Response (ASPR) and Biomedical Advanced Research and Development Authority (BARDA). On the other side, while the EU is not a federal government, it has the ambition of designing a European Health Union with its own polices and institutions. Until now, however, Pharma companies captured huge rents from lack of preparedness and public ownership of R&D on Covid-19; see Florio, Gamba, and Pancotti (2023) for details. Recently the European Parliament has voted that the existing Health Emergency Preparedness and Response (HERA)[38], a department of the EC, should be radically re-designed in terms of mission, governance, operations and budget.

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[37] https://www.statista.com/topics/6139/covid-19-impact-on-the-global-economy/#topicOverview

[38] Article 175a -Amendments to Regulation (EC) No 851/2004 Regulation (EC) No 851/2004 is amended as follows: (1) the following Article 11a is inserted: Article 11a European Health Emergency Preparedness and Response Authority. 1. The Health Emergency Preparedness and Response Authority (here after 'HERA' or

In our view, more ambition is needed: the EU should create «Biomed Europe»: a large-scale public infrastructure for R&D (see Florio and Gamba, 2021)[39]. In any case, the US, EU and other countries should re-think the incentive mechanisms for pharma innovation before emergencies, see Gamba et al. 2023 and Florio et al. 2021.

Moreover it would be important to involve African researchers and health authorities in a new long-run project for vaccines and drugs in the public interest. See in the Appendix a proposal by Florio and Remuzzi.

Box 2: European Parliament, COVI Committee - Report on the COVID-19 pandemic lessons learned and recommendations for the future (2022/2076(INI)), 26 June 2023

"Calls on the Commission and the Member States to create a large-scale, mission-oriented, public European health R&D infrastructure which operates in the public interest to manufacture medicinal products of health and strategic importance for healthcare, in the absence of existing industrial production, in order to support the EU to overcome market failure, guarantee security of supply and prevent possible shortages of medicines, while contributing to greater preparedness for facing new health threats and emergencies[40];"

'the Authority') is hereby established as a separate structure under the legal personality of the European Centre for DiseasePrevention and Control (ECDC). 2. The Authority shall be responsible for creating, coordinating and implementing of the long-term European portfolio of biomedical research and development agenda for medical countermeasures against currentand emerging public health threats as well as the, production, procurement, stockpiling and distribution capacity of medical countermeasures and other priority medical products in the EU. 3. The Authority is represented by the Executive Director of the European Centrefor Disease Prevention and Control.

[39] The concept was supported by an amendament to pharma regulation, that did not reach the majority in the plenary session. This is the text: Article 40a - Establishment and role of the European Medicines Facility. 1. The European Medicines Facility ('EMF') is hereby established. 2. The main missions and responsibilities of the EMF shall be: (a) setting out a long-term vision of health priorities in the public interest at a Union level in the form of a strategic roadmap with a number of specific purpose-led R&D projects; in the elaboration of the strategic roadmap, theEMF shall engage in transparent consultation with relevant stakeholders,including scientific communities, Unionpublic health authorities, patient and consumer organisations as well as the relevant agencies established at Unionlevel; (b) establishing, as a priority, a portfolio of priority pharmaceutical R&D projects addressing at least the following therapeutic areas: (i) the development of priority antimicrobials provided for in the 'WHO priority pathogens list for R&D of new antibiotics', specifically those listed as priority 1 (critical) or priority 2 (high), or taking into account as a priority any equivalent list of priority pathogens adopted at Union level; (ii) the development of medicinal products for high unmet medical needs as referred to in Article 70(1) of this Regulation and unmet medical needs as referred to in Article 83 of [revised Directive 2001/83/EC], in particular for conditions not sufficiently addressed by the private sector and where the private R&D pipeline is unlikely to deliver on medicinal products and therapies; (iii) the development of medicinal products for which the private sector charges excessive prices and for which alternatives or generic alternatives are non-existent or unaffordable;

[40] Report available at: https://www.europarl.europa.eu/doceo/document/A-9-2023-0217_EN.pdf

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Professor Massimo Florio has written Sections 1 (Introduction) and 3 (Conclusions) and the questions to Professor Remuzzi. Professor Giuseppe Remuzzi has written the answers to the questions[41].

Part of the paper was also presented by Professor Florio at the Society for Benefit-Cost Analysis 2023 Annual Conference (Washington D.C., March 9-10, 2023) and at 3rd Edition of International Vaccines Congress - IVC 2023 (Boston, October 23-25, 2023).

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[41] Professor Remuzzi also suggested some relevant papers about heterologous vaccination and nasal administration of vaccines: Accorsi et al., 2022; Richardson, 2021; Waltz, 2022 (see References section).

Appendix: Proposal for a solidarity fund between the European Union and Africa for an urgent Covid-19 vaccine programme

7 FEBRUARY 2022, MASSIMO FLORIO AND GIUSEPPE REMUZZI[42]

The data concerning the administration of vaccines against the SARS-CoV-2 virus in low-income countries (World Bank definition) are alarming: only 10% of the population has received at least one dose of the 1.37 billion inhabitants of the 55 African Union countries, which also include some middle-income countries, almost 90% have yet to be fully vaccinated. In countries like Burkina Faso, Burundi, Cameroon, Chad, Ethiopia, Madagascar, Malawi, Mali, Niger, Nigeria, Democratic Republic of Congo, Somalia, South Sudan and Tanzania, fewer than 10 doses per 100 inhabitants have been administered. In some of these countries, the rate is lower than 5 doses per 100 inhabitants (Our World in Data, Oxford).

The data on the spread of the pandemic in Africa are unclear, and the figures available so far (roughly 11 million cases and over 241,000 deaths, Africa CDC data) may underestimate the true figure due to a lack of systematic diagnosis, infection tracing and variant sequencing in many countries. We cannot rule out the possibility that a pandemic time bomb could explode from the Mediterranean coast down to Southern Africa, although the low average age of the population may be a protective factor against serious disease.

As the Omicron variant case shows, when it replicates on a large scale among non-vaccinated populations, the SARS-CoV-2 virus creates mutations that are potentially capable of partially evading immunity, even in the vaccinated population. Given its geographical proximity and historical ties, the European Union could demonstrate concrete solidarity and offer the population of its own Member States greater protection by contributing to the vaccination of the entire African population.

Existing solidarity tools, such as the COVAX mechanism and bilateral agreements between countries, are not working well enough. In spite of momentous announcements, in 2021, the number of doses administered in the countries that needed them the most was very limited. We propose that national governments urgently ask the Council of the European Union through the rotating presidency of France (1 January to 30 June 2022 semester) to include an extraordinary Europe-Africa solidarity plan for a vaccination campaign in its agenda. The plan would involve creating a dedicated fund, amounting to about €8 per African citizen, for a total of €10 billion.

This fund should directly finance African countries' own vaccination plans through three axes:

a) Vaccine availability: the range of vaccines available on a global scale is evolving rapidly. A good example is the Corbevax open-source vaccine initiative developed by Peter Hotez, Maria Elena Bottazzi and other scientists from Baylor College of Medicine (Texas) who waived any intellectual property rights. This vaccine has been emergency-approved in India (and elsewhere), where production has already started. It is, therefore, possible to manufacture it wherever capacity and infrastructures allow. Should this option prove not to be available in the short term (or if there is a preference not to be bound to a single option), African countries should be allowed to purchase at least two billion doses of vaccines at affordable prices. The contracts with suppliers should

[42] https://www.change.org/p/vaccini-covid-19-proposta-di-un-fondo-di-solidariet%C3%A0-fra-unione-europea-ed-africa?recruiter=539578013&recruited_by_id=76aaa950-174f-11e6-81a6-a5f984be6f5d&utm_source=share_petition&utm_medium=copylink&utm_campaign=petition_dashboard

favour, completely or at least in part, vaccines that are suitable for manufacture in emerging countries. Priority should be given to pharmaceutical companies that are committed to completing technology transfers and/or direct investments in Africa, where a potential production base already exists for both mRNA and other types of vaccines (possibly with production licenses or with the temporary suspension of patents).

b) Local storage logistics and widespread distribution of the vaccines: the organisations already on the ground should receive funding, and a contingent of volunteers could be dispatched under the aegis of the European Union (where local resources cannot be found and trained fast enough). All personnel must be equipped with personal protective equipment and means of transport and support for vaccination activities.

c) Extensive information campaign for the population: this should be financed with the involvement of local communities and health communication experts in individual countries who, with their in-depth knowledge of the contexts, can help local health authorities implement the vaccination programme.

The European Solidarity Fund for Africa that we propose should not replace the European Union's and individual countries' participation in other solidarity mechanisms. It should be an additional measure, managed directly by the European Commission with individual African countries, in consultation with the World Health Organization, the African Union and other international bodies.

For the longer term, the European Parliament (Science and Technology Options Assessment STOA-Panel) recently launched a study proposing a supranational public infrastructure as a European Union initiative for research into and the development of vaccines and drugs to plan for future pandemics and other health risks. We suggest that this project, which we hope will be adopted, should focus particularly on collaboration with researchers from the African continent and on mechanisms that address the prohibitive cost of drugs, particularly for treating rare diseases, which can cost as much as US$ 400,000 per patient per year[43].

[43] Sources:
1) https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups; 2) https://ourworldindata.org/covid-vaccinations; 3) https://www.statista.com/statistics/1221298/covid-19-vaccination-rate-in-african-countries/; https://africacdc.org/covid-19-vaccination/; 4) https://africacdc.org/covid-19/, 5) https://www.who.int/initiatives/act-accelerator/covax; 6) https://www.unaids.org/en/resources/presscentre/featurestories/2021/october/20211021_dose-of-reality; 7) Wouters, O. J., Shadlen, K. C., Salcher-Konrad, M., et al. (2021). Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. The Lancet. https://doi.org/10.1016/S0140-6736(21)00306-8; 8) Hotez Peter J., Bottazzi Maria Elena /Scientific American, CORBEVAX, un vaccino anti COVID per tutti, 04 gennaio 2022 https://www.lescienze.it/news/2022/01/04/news/vaccino_covid_ricombinante_corbevax_immunizzare_mondo_produzione_paesi_poveri-7392183/; 9) Prabhala A, Alsalhani A., Pharmaceutical manufacturers across Asia, Africa and Latin America with the technical requirements and quality standards to manufacture mRNA vaccines https://www.medicisenzafrontiere.it/wp-content/uploads/2022/01/Manufacturing-mRNA-Report-10DEC2021.pdf; 10) https://www.europarl.europa.eu/RegData/etudes/STUD/2021/697197/EPRS_STU(2021)697197_EN.pdf; 11) Luzzatto, L., & Makani, J. (2021). Treating Rare Diseases in Africa: The Drugs Exist but the Need Is Unmet. Frontiers in Pharmacology, 12, 770640-770640.

References

Accorsi, E. K., Britton, A., Shang, N., Fleming-Dutra, K. E., Link-Gelles, R., Smith, Z. R., ... & Verani, J. R. (2022). Effectiveness of homologous and heterologous Covid-19 boosters against Omicron. *New England Journal of Medicine*, *386*(25), 2433-2435.

Ai-ris, Y. C., McMahan, K., Yu, J., Tostanoski, L. H., Aguayo, R., Ansel, J., ... & Barouch, D. H. (2021). Immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women. *Jama*, *325*(23), 2370-2380.

Al Kaabi, N., Zhang, Y., Xia, S., Yang, Y., Al Qahtani, M. M., Abdulrazzaq, N., ... & Yang, X. (2021). Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomised clinical trial. *Jama*, *326*(1), 35-45.

Alfani, G. (2022). Epidemics, inequality, and poverty in preindustrial and early industrial times. *Journal of Economic Literature*, *60*(1), 3-40.

Andersson, H. and N. Treich: 2011, Handbook in Transport Economics, Chapt. 'The Value of a Statistical Life', pp. 396-424, in de Palma, A., R. Lindsey, E. Quinet and R. Vickerman (eds.) Edward Elgar, Cheltenham, UK.

Bachmann, M. F., Rohrer, U. H., Kündig, T. M., Bürki, K., Hengartner, H., & Zinkernagel, R. M. (1993). The influence of antigen organisation on B cell responsiveness. *Science*, *262*(5138), 1448-1451.

Baden, L. R., El Sahly, H. M., Essink, B., Kotloff, K., Frey, S., Novak, R., ... & Zaks, T. (2021). Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *New England journal of medicine*, *384*(5), 403-416.

Brazil, R. (2023). How your first brush with COVID warps your immunity. *Nature*, *613*(7944), 428-430.

Capone, F., Rossi, M., Cruciani, A., Motolese, F., Pilato, F., & Di Lazzaro, V. (2023). Safety, immunogenicity, efficacy, and acceptability of COVID-19 vaccination in people with multiple sclerosis: a narrative review. *Neural Regeneration Research*, *18*(2), 284-288.

Chemaitelly, H., Ayoub, H. H., Tang, P., Hasan, M. R., Coyle, P., Yassine, H. M., ... & Abu-Raddad, L. J. (2022). Immune imprinting and protection against repeat reinfection with SARS-CoV-2. *New England Journal of Medicine*, *387*(18), 1716-1718.

Cohen, A. A., van Doremalen, N., Greaney, A. J., Andersen, H., Sharma, A., Starr, T. N., ... & Bjorkman, P. J. (2022). Mosaic RBD nanoparticles protect against challenge by diverse sarbecoviruses in animal models. *Science*, *377*(6606), eabq0839.

Colmer, J. (2020). What is the meaning of (statistical) life? Benefit–cost analysis in the time of COVID-19. *Oxford Review of Economic Policy*, *36*(Supplement_1), S56-S63. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7499700/

Dolgin, E. (2022). Pan-coronavirus vaccine pipeline takes form. *Nat. Rev. Drug Discov*, *21*(5), 324-326.

Dunkle, L. M., Kotloff, K. L., Gay, C. L., Áñez, G., Adelglass, J. M., Barrat Hernández, A. Q., ... & Dubovsky, F. (2022). Efficacy and safety of NVX-CoV2373 in adults in the United States and Mexico. *New England Journal of Medicine*, *386*(6), 531-543.

Florio, M., & Gamba, S. (2021). Biomed Europa: after the coronavirus, a public infrastructure to overcome the pharmaceutical oligopoly. *Annals of Public and Cooperative Economics*, *92*(3), 387-409.

Florio, M., Pancotti, C., Prochazka, D. A. (2021). European pharmaceutical research and development. Could a public infrastructure overcome market failures?. *European Parliament, Study: Panel for Future of Science and Technology, STOA.*

Florio, M., Gamba, S., & Pancotti, C. (2023). Mapping of long-term public and private investments in the development of Covid-19 vaccines. *Eur Parliament COVI Committee.*

Florio, M., Pancotti, C. (2023). Applied Welfare Economics. Cost-Benefit Analysis of Projects and Policies. 2nd Edition, Routledge.

Gamba, S., Magazzini, L., & Pertile, P. (2023). Improving access to medicines and promoting pharmaceutical innovation, Study prepared for the Panel for the future of Science and technology.

Glennerster, R., Snyder, C. M., & Tan, B. J., 2022, Calculating the Costs and Benefits of Advance Preparations for Future Pandemics, Working Paper 30565, National Bureau of Economic Research.

Heinz, F. X., & Stiasny, K. (2021). Distinguishing features of current COVID-19 vaccines: knowns and unknowns of antigen presentation and modes of action. *npj Vaccines*, *6*(1), 104.

Husby, A., Hansen, J. V., Fosbøl, E., Thiesson, E. M., Madsen, M., Thomsen, R. W., ... & Hviid, A. (2021). SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study. *bmj*, *375*.

Jara, A., Undurraga, E. A., González, C., Paredes, F., Fontecilla, T., Jara, G., ... & Araos, R. (2021). Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. *New England Journal of Medicine*, *385*(10), 875-884.

Li, D., Martinez, D. R., Schäfer, A., Chen, H., Barr, M., Sutherland, L. L., ... & Haynes, B. F. (2022). Breadth of SARS-CoV-2 neutralisation and protection induced by a nanoparticle vaccine. *Nature communications*, *13*(1), 6309.

Lim, X. R., Leung, B. P., Ng, C. Y. L., Tan, J. W. L., Chan, G. Y. L., Loh, C. M., ... & Leong, K. P. (2021). Pseudo-anaphylactic reactions to Pfizer BNT162b2 vaccine: report of 3 cases of anaphylaxis post Pfizer BNT162b2 vaccination. *Vaccines*, *9*(9), 974.

Lu, L., Xiong, W., Mu, J., Zhang, Q., Zhang, H., Zou, L., ... & Zhou, D. (2021). The potential neurological effect of the COVID-19 vaccines: a review. *Acta Neurologica Scandinavica*, *144*(1), 3-12.

Marani, M., Katul, G. G., Pan, W. K., & Parolari, A. J. (2021). Intensity and frequency of extreme novel epidemics. *Proceedings of the National Academy of Sciences*, *118*(35), e2105482118.

Marks, P. W., Gruppuso, P. A., & Adashi, E. Y. (2023). Urgent need for next-generation COVID-19 vaccines. *Jama*, *329*(1), 19-20.

Marks, P. W., Gruppuso, P. A., & Adashi, E. Y. (2023). Urgent need for next-generation COVID-19 vaccines. *Jama*, *329*(1), 19-20.

Mathieu, E., H. Ritchie, L. Rodés-Guirao, C. Appel, C. Giattino, J. Hasell, B. Macdonald, S. Dattani, D. Beltekian, E. Ortiz-Ospina and M. Roser (2020) - "Coronavirus Pandemic (COVID-19)". Published online at OurWorldInData.org. Retrieved from: https://ourworldindata.org/coronavirus

Mehta, P. R., Mangion, S. A., Benger, M., Stanton, B. R., Czuprynska, J., Arya, R., & Sztriha, L. K. (2021). Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination–A report of two UK cases. *Brain, behavior, and immunity*, *95*, 514-517.

Polack, F. P., Thomas, S. J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., ... & Gruber, W. C. (2020). Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *New England journal of medicine*, *383*(27), 2603-2615.

Reynolds, C. J., Pade, C., Gibbons, J. M., Otter, A. D., Lin, K. M., Muñoz Sandoval, D., ... & Moon, J. C. (2022). Immune boosting by B. 1.1. 529 (Omicron) depends on previous SARS-CoV-2 exposure. *Science*, *377*(6603), eabq1841.

Richardson, C. D. (2021). Heterologous ChAdOx1-nCoV19–BNT162b2 vaccination provides superior immunogenicity against COVID-19. *The Lancet Respiratory Medicine*, *9*(11), 1207-1209.

Röltgen, K., Nielsen, S. C., Silva, O., Younes, S. F., Zaslavsky, M., Costales, C., ... & Boyd, S. D. (2022). Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination. *Cell*, *185*(6), 1025-1040.

Sadoff, J., Gray, G., Vandebosch, A., Cárdenas, V., Shukarev, G., Grinsztejn, B., ... & Douoguih, M. (2021). Safety and efficacy of single-dose Ad26. COV2. S vaccine against Covid-19. *New England Journal of Medicine*, *384*(23), 2187-2201.

Shimabukuro, T. T., Kim, S. Y., Myers, T. R., Moro, P. L., Oduyebo, T., Panagiotakopoulos, L., ... & Meaney-Delman, D. M. (2021). Preliminary findings of mRNA Covid-19 vaccine safety in pregnant persons. *New England Journal of Medicine*, *384*(24), 2273-2282.

Tan, C. W., Chia, W. N., Young, B. E., Zhu, F., Lim, B. L., Sia, W. R., ... & Wang, L. F. (2021). Pan-sarbecovirus neutralising antibodies in BNT162b2-immunized SARS-CoV-1 survivors. *New England Journal of Medicine*, *385*(15), 1401-1406.

Topol, E. J., & Iwasaki, A. (2022). Operation nasal vaccine—lightning speed to counter COVID-19. *Science immunology*, *7*(74), eadd9947.

Villar, J., Ariff, S., Gunier, R. B., Thiruvengadam, R., Rauch, S., Kholin, A., ... & Papageorghiou, A. T. (2021). Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: the INTERCOVID multinational cohort study. *JAMA pediatrics*, *175*(8), 817-826.

Voysey, M., Clemens, S. A. C., Madhi, S. A., Weckx, L. Y., Folegatti, P. M., Aley, P. K., ... & Bijker, E. (2021). Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet*, *397*(10269), 99-111.

Waltz, E. (2022). How nasal-spray vaccines could change the pandemic. *Nature*, *609*(7926), 240-2.

Wang, Q., Bowen, A., Valdez, R., Gherasim, C., Gordon, A., Liu, L., & Ho, D. D. (2023a). Antibody response to omicron BA. 4–BA. 5 bivalent booster. *New England Journal of Medicine*, *388*(6), 567-569.

Wang, Q., Iketani, S., Li, Z., Liu, L., Guo, Y., Huang, Y., ... & Ho, D. D. (2023b). Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants. *Cell*, *186*(2), 279-286.

Wilder-Smith, A., & Mulholland, K. (2021). Effectiveness of an inactivated SARS-CoV-2 vaccine. *New England Journal of Medicine*, *385*(10), 946-948.