Journal of High Institute of Public Health 2021;51(1):1-9.

Review Article

Merits and Demerits of COVID-19 Vaccines

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Abstract

The COVID-19 pandemic caused by the novel coronavirus (SARS-CoV-2) continues to reshape the globe. It is more than a year since the virus first emerged, yet the vast majority of people are still vulnerable. The current response to the COVID-19 pandemic involves aggressive implementation of containment, suppression, and mitigation strategies causing devastating social, economic and political crises. The restrictions on our lives are the only thing holding the virus in check. The world cannot return to normal without safe and effective vaccines against COVID-19 along with a coordinated global vaccination program. Vaccines remain the safest, most cost-effective protection against disease. Unprecedented data sharing and collaborative team efforts are breaking down barriers in an attempt to reduce the time of vaccine development. An ideal COVID-19 vaccine should be safe, provide long-lasting protection, protect not only against disease but prevent virus transmission to others, be able to be produced quickly and in large quantities, be easily stored, transported and administered. The global COVID-19 vaccine pipeline is currently expanding on a daily basis. Multiple platforms are being used for producing vaccines at pandemic speed. Each platform has its own merits, demerits and challenges and it is unlikely that any single platform on its own will constitute a solution for the ongoing COVID-19 pandemic.

Keywords: COVID-19, vaccines

Available on line at:
jhiphalexu.journals.ekb.eg

Print ISSN: 2357-0601
Online ISSN: 2357-061X

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Suggested Citations: El-Nimr NA. Merits and demerits of covid-19 vaccines. JHIPH. 2021;51(1):1-9.

Overview

The coronavirus disease (COVID-19) pandemic is the biggest challenge we have faced since World War Two. Since late December 2019, COVID-19 was first reported in Wuhan, China, and subsequently spread to every continent except Antarctica.[1, 2] COVID-19 is much more than a health crisis. It can create catastrophic social, economic and political problems by stressing each of the countries it affects, which will leave deep scars. Countries are taking extreme measures to slow the spread of the disease by testing and treating patients, carrying out contact tracing, limiting travel, quarantining citizens, and cancelling large gatherings such as sporting events, concerts, and schools.[2] Science and medical communities are making serious efforts by creating preventive vaccines and repurposing existing medicines as possible treatments to reduce this pandemic and subsequent waves of viral spread.[3] Their efforts are beginning to bear fruit. A handful of vaccines now have been authorized around the globe; many more remain in development.[4, 5]

COVID-19 is the disease caused by a new coronavirus called SARS-CoV-2. It was first reported in December 2019, following a report of a cluster of cases of 'viral pneumonia' in Wuhan, China.[6] Coronaviruses (CoVs), including SARS-CoV, MERS-CoV, and SARS-CoV-2, are cytoplasmically replicating, positive-sense, single-stranded RNA viruses with four structural proteins [namely spike (S) protein, envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein]. Generally, the S protein plays a crucial role in eliciting the immune response during disease progression.[7]

The most common symptoms of COVID-19 are fever, dry cough and fatigue. Other symptoms that are less common and may affect some patients include loss of taste or smell, nasal congestion, conjunctivitis, sore throat, headache, muscle or joint pain, different types of skin rash, nausea or vomiting, diarrhea, and chills or dizziness. Symptoms of severe COVID-19 disease include shortness of breath, loss of appetite, confusion, persistent pain or pressure in the chest and high temperature (above 38 °C).[6] The virus spreads mainly from respiratory droplets of infected individuals in confined spaces to mucosal epithelial cells in the upper airway and oral cavity, and to a much lesser degree through fomites.[3, 6]

The current response to the COVID-19 pandemic involves vigorous implementation of containment, suppression, and mitigation strategies. Such an approach includes introducing a range and combination of public health measures including hand hygiene and respiratory

etiquette, disinfection, case identification, isolation of sick people, tracing and quarantine of contacts, and unparalleled restrictions on the mass population. A vaccine represents the most promising strategy for combating the COVID-19 pandemic by primary prevention, in addition to substantial investment in transmission containment interventions and in diagnostics and therapeutic testing.[8]

The vaccines success story

Among the most cost-effective preventive procedures available are vaccines. Through vaccination, there are currently between 2 and 3 million lives saved per year. The influence of vaccines goes far beyond saving lives and improving health. Vaccination programs often target population or herd immunity, in addition to offering individual protection.[9]

Throughout history, humans have successfully developed vaccines for a number of diseases.[10] During the 18th and 19th centuries, the widespread introduction of mass smallpox immunization resulted in its worldwide eradication in 1979. Viral tissue culture methods developed from 1950-1985, and led to the advent of the Salk and Sabin polio vaccines. Mass polio immunization has now eradicated the disease from many regions around the world. Measles is currently the next possible target for elimination via vaccination.[11] We now have vaccines to prevent more than 20 life-threatening diseases, helping people of all ages live longer, healthier lives.[12]

Molecular genetics is setting the stage for vaccinology for a promising future, including the development of new vaccine delivery systems (e.g. nucleic acid vaccines, viral vectors, plant vaccines and topical formulations), new adjuvants, the development of more effective tuberculosis vaccines, and vaccines against cytomegalovirus, herpes simplex virus, respiratory syncytial virus, staphylococcal disease, streptococcal disease, pandemic influenza, shigella, HIV and schistosomiasis among others. Therapeutic vaccines may also soon be available for allergies, autoimmune diseases and addictions.[11]

The wealth of expertise gained over decades by WHO and its partners is now being deployed to accelerate the production and delivery of COVID-19 vaccines. Vaccines remain the safest, most cost-effective protection against disease and will provide a powerful tool to address the COVID-19 pandemic.[13]

Accelerated vaccine development timeline

The development of a vaccine against a disease is a combined effort from academicians and industries.[14] A typical vaccine development timeline takes 5 to 10 years, and sometimes longer, to assess whether the vaccine is safe and efficacious in clinical trials, complete the regulatory approval processes, and manufacture sufficient quantity of vaccine doses for widespread distribution.[15]

Considering the global magnitude of the COVID-19 pandemic, the speed, scale, magnitude of the initiative, financial contributions and scientific collaborations to develop COVID-19 vaccines have been unprecedented. In an attempt to reduce the time for vaccine production, unparalleled data sharing and collaborative team efforts are breaking down barriers.[3] The traditional milestones of vaccine development are compressed from a period of 10-15 years to 1-2 years, with simultaneous overlapping preclinical, clinical and scale-up production processes, while maintaining strict clinical and safety standards.[16,17]

Different companies have already taken initiatives to develop a vaccine against COVID-19.[14] The ongoing global effort draws upon decades of research into both endemic and epidemic human coronaviruses, in particular the structure of the Spike (S) protein and its role in coronavirus pathogenesis, the importance of neutralizing antibodies directed against different S protein epitopes to provide protective immunity, and the theoretical risk of vaccine-enhanced disease in animal models. The effort also draws upon decades of vaccine and adjuvant development, both conventional and novel platform approaches.[18]

Economic impact of COVID-19 vaccination

The vaccination of COVID-19 is estimated to be cost-effective from the perspective of the healthcare sector. Vaccination could avert US$151-$738 billion in direct medical costs and US$527–$2,355 billion in productivity losses across various vaccine effectiveness and coverage levels.[18]

Analyses of the economic effects of the COVID-19 vaccine, which eliminates the need for physical distancing or lockdowns and restores economic development, have shown that the averted gross domestic product losses are of high socioeconomic importance. If vaccination was scaled up, social distancing will be wound back in 2021, resulting in 5.2% global growth in 2021; growth might otherwise be 3% lower if vaccination (and other disease control measures, e.g., therapeutics) are less widely or quickly available. It has been projected that the supply of vaccines to low-income countries would produce an almost fivefold return on investment in terms of averted gross domestic product losses alone.[18]

Safety concerns regarding COVID-19 vaccines

In general, the safety of a vaccine is determined by the nature of the vaccine platform, the choice of adjuvant, the mode and route of vaccine administration, the age of the vaccine recipient and the status of pre-existing vaccine immunity. Vaccine strategies for COVID-19 require additional safety considerations related to the potential antibody-dependent enhancement of disease and the role of over production of pro-inflammatory cytokines in lung immunopathology.[17] Previous experience from the development of SARS-CoV and MERS-CoV vaccines has raised questions about pulmonary immunopathology correlating with Th2 responses (a subgroup of T cells that can secrete Th2-type cytokines).[7] Standard templates for

benefit-risk assessment of vaccine technologies for the main COVID-19 platforms has been developed by the Brighton Collaboration (BRAVATO). The Global Advisory Committee on Vaccine Safety (GACVS) has recommended that any review of the safety of new vaccines be based on these templates because they provide a standardized approach to the safety evaluation of new vaccines.[18]

Vaccine manufacture

Without safe and effective vaccines against COVID-19 along with a coordinated global vaccination program, the world cannot return to normal. Due to the complexity of the product, vaccine development and manufacture of adequate doses to induce herd immunity is one of the most difficult tasks within biopharmaceutical companies.[19]

It is estimated that a threshold value of ~67% is adequate to achieve SARS-CoV-2 herd immunity, assuming that the basic reproductive number (Ro) of the virus is three. Based on this estimate, ~5.3 billion vaccine doses are required for a single-dose vaccine, or possibly 12–16 billion in case of a multi-dose vaccine. It is clear that triggering herd immunity by mass vaccination would be an immensely effective weapon to control the COVID-19 pandemic, but it is also a huge challenge.[17]

The most basic requirements for manufacturing vaccines in a way that is safe, effective yet consistent from batch to batch are difficult to implement. Scale up and safety of vaccine formulations are equally important for maintaining a successful production process. Improved technologies for streamlining the development and distribution of vaccines are therefore critical.[19]

The "ideal" vaccine for COVID-19 prevention

The criteria of an ideal SARS-CoV-2 vaccine, listed by the coronavirus resource center at the Johns Hopkins University and Medicine, are as follows: [20]

1. Be safe and associated with only mild, transient side effects (e.g. soreness and low-grade fever).
2. Confer long-lasting protection (more than a season) in a high proportion of vaccine recipients (e.g. >80%), particularly in vulnerable populations such as the older adults and those with other underlying medical conditions or risk factors such as obesity.
3. Protect not only against disease but prevent virus transmission to others.
4. Be administered as a single dose.
5. Be able to be produced quickly and in large quantities.
6. Be easily stored (e.g., not at ultra-low temperatures, in packaging that does not require a lot of space).
7. Can be easily transported (e.g., outside of the cold-chain or even through the mail).
8. Can be easily administered (does not require special devices, self-administered or administered by those who do not require much training).

The WHO has proposed a number of attributes and criteria that provide considerations for the evaluation and prioritization of COVID-19 candidate vaccines to be considered for further development. These attributes include safety profile (25 points), potential for efficacy (25 points), vaccine stability (10 points), vaccine implementation (15 points) and vaccine availability (25 points).[21]

The platforms used for SARS-CoV-2 vaccine development

Diverse SARS-CoV-2 vaccine types are currently under development.[7] Currently, there are 179 vaccines for COVID-19 in pre-clinical development and 63 vaccines in clinical development (18 in phase 1, 18 in phase 1/2, 6 in phase 2, 5 in phase 2/3, and 16 in phase 3).[22]

(1) Inactivated vaccines

Inactivated viruses are made non-infectious via physical or chemical approaches. Traditionally, purified inactivated viruses have been used to produce vaccines and have been shown to be effective in preventing viral diseases, such as influenza.[7]

(2) Live-attenuated vaccines

Live attenuated vaccines have demonstrated success in infections such as smallpox and poliomyelitis.[7]

(3) Nucleic acid vaccines

Nucleic acid vaccines, such as mRNA vaccines and DNA vaccines, are other popular vaccine forms. Nucleic acid-based vaccines use the hosts own cell machinery where they will then be transcribed into viral proteins, which is then presented to the immune system. While RNA is encapsulated into lipid nanoparticle and injected, DNA is fired directly in the host cells using a brief electrical pulse.[11,19,20,23,24] Among the CoV proteins, S protein has been the most common candidate.[7]

(4) Protein-based "subunit" vaccine

Currently, there are 20 COVID-19 subunit vaccines in clinical trials, with 100 other candidates under preclinical development, making this the most common platform.[22] A subunit vaccine is the one which is based on the synthetic peptides or recombinant antigenic proteins.[7, 20, 25] Subunit vaccines primarily induce CD4+T cell and antibody responses. Therefore, most of these vaccines contain full-length SARS- CoV-2 S protein or portions of it with the goal of inducing neutralizing antibodies.[17]

(5) Viral vector based vaccines

Vector vaccines are generally constructed from a carrier virus (viral vector) and are engineered to carry a relevant gene from the virus, usually the S gene for CoVs.[7, 19, 20] A wide variety of replicating and non-replicating viral vectors are available. Adenoviruses and poxviruses represent examples of viral vectors, of which both replicating and non-replicating forms are available. Vectors designed primarily as replication-defective or non-replicating viral vectors include adeno-associated virus, alphavirus, and herpesvirus, while replicating vectors include measles virus, vesicular stomatitis virus, poliovirus, and yellow fever virus.[19]

(6) Virus like particle (VLP) vaccine

VLPs are spontaneously forming particles composed of several structural viral proteins that are co- expressed or admixed. Several commercial vaccines, such as hepatitis B and human papillomavirus vaccines, are based on VLPs.[17] Currently, there are only 2 VLP vaccines in clinical trial.[22]

Comparison between different COVID-19 vaccine platforms [3, 7, 19, 20, 25]

Platform	Immune response and no. of doses	Vaccine Candidate (Manufacturer)	Advantages	Disadvantages
Inactivated vaccines	Humoral Cellular (2 doses)	SARS-CoV-2 vaccine (Sinovac) Inactivated SARS-CoV-2 vaccine (Vero cell) (Sinopharm)	• Proven technology with infrastructure required for its development. • Has already been tested for SARS-CoV and various other diseases. • Stable and safer as compared to the LAVs. • Can be easily produced in large quantities. • Strong immune response. • Multivalent. • Simple formulation, not requiring adjuvants. It can be used along with adjuvants to increase their immunogenicity.	• Require the booster shots to maintain the immunity. • Needs the biosafety level 3 growth of pathogen (requires dedicated biosafety level facilities). • Large amounts of viruses need to be handled and the integrity of the immunogenic particles must be maintained. • Relatively expensive.
Live attenuated vaccines	Humoral Cellular		• Proven technology. • The intrinsic ability to stimulate the immune system (strong immune response). • Multivalent. • Simple formulation, not requiring adjuvants. • Proven track record for economical large-scale manufacturing.	• Requires dedicated biosafety level facilities. • Risk for attenuated virus to regain virulence. • Can be complicated to scale up manufacturing. • Not suitable for immunocompromised patients.
RNA vaccines	Humoral Cellular (2 doses)	BNT-162b2 (Pfizer, BioNTech) mRNA-1273 (Moderna)	• No handling of infectious material. • Rapid design and production. • High potency. • Have potential for low-cost manufacture (cost-efficient production). • The translation of mRNA occurs in the cytosol of the host cell averting the risk of any sort of integration into the host genome. • Strong early antiviral responses, both humoral and cell-mediated. • Options for multivalent formulation. • Scaling up to global-wide production appears feasible but not yet tested.	• No approved RNA vaccines, but some clinical testing for other viruses (rabies, influenza) • The physiochemical properties of mRNA may influence its cellular delivery and organ distribution. • Inflammatory reactions possible. • Most formulations require a cold chain for longevity and stability. • Ubiquitous ribonucleases require careful design with substituted nucleosides and skilled formulation of lipid nanoparticle carriers for effective delivery. • Boosting likely necessary to achieve robust and long-lasting immunity. • Whether it is safe or not in humans remains unknown.

DNA vaccines	Humoral Cellular (2 doses)	INO-4800 (Inovio)	• No handling of infectious material. • Enhances humoral and cellular immune responses (enhance T-cell induction and antibody production). • Rapid design and production (Rapid and scalable manufacturing). • Low-cost manufacturing. • Long shelf life. • Can be used in immunocompromised subjects. • Options for multivalent formulation. • Oral formulation possible.	• No approved DNA vaccines, along with real-world experience in the global population. • Some require special tools for delivery to the sub-dermal layer. • The safety and efficacy of vaccines for use in humans remain unknown. • Though it elicits both cytotoxic and humoral immunity, the titers remain low. • Potential risk for host cell genomic integration. • May induce the antibody production against itself.
Protein based Subunit vaccines	Humoral (2 doses)	NVX-CoV2373 (Novavax)	• Do not have any live component of the viral particle. Thus, it is safe with fewer side-effects. • No handling of infectious material. • Strong antibody response. • Precedent for successful vaccines of this platform. • Viral protein complexes can be formulated to simulate virus patterning (VLPs).	• Given that only a few viral components are included which do not display the full antigenic complexity of the virus, their protective efficacy may be limited and memory for future responses is doubtful. • May cause unbalanced immune responses. • Need for adjuvants. • Scale up of manufacturing can be challenging.
Viral vector based vaccines	Humoral Cellular (1 or 2 doses)	AZA-1222 Ad5-CoV (AstraZeneca; Oxford University); Ad26.COV2.S (Johnson & Johnson) Gam-COVID-Vac Adeno-based (rAd26-S+rAd5-S) (Gamaleya)	• A well-tested technology platform with substantiated, long-term safety. • Years of experience in the gene therapy field studying safety, immune responses. • Can infect antigen presenting cells directly. • Physically and genetically stable. • Strong antibody and cellular responses. • Show a highly specific gene delivery into the host cell with a vigorous immune response. • Avoids handling of any infectious particle. • It has been used widely for MERS-CoV with positive results from the trials.	• Limited to presenting only a small number of CoV antigens to the host immune system. • Risk for chromosomal integration and oncogenesis. • Cannot be used in immunocompromised subjects. • Potential for inflammatory adverse events. • Variable immunogenicity. • Significant manufacturing hurdles at scale. • The host may possess immunity against the vector due to prior exposure, reducing the efficacy.
Virus like particle vaccines	Humoral		• Non-infectious. • Potent antibody induction. • Well-established platform for several commercial human vaccines.	• Assembly into stable particles is challenging. • Quality control. • Potential contaminants. • Heterogeneity. • Cold chain transfer and storage as they are sensitive to the external environment.

Comparison between 4 COVID-19 vaccine candidates

	Pfizer-BioNTech [26-29]	Moderna [29-33]	Oxford/AstraZeneca [29,34-36]	Sinopharm [37, 38]
Efficacy	95%	94.1%	70% (62-90%) 62% effective rate was observed in people who received the full vaccine dose compared with 90% in those who received the half dose	79.34%
Type (platform)	mRNA-based	mRNA-based	Adenovirus vector (Chimpanzee Adenovirus)	Inactivated virus
Shelf life, storage and transportation	Can be kept in a standard refrigerator for up to 5 days, in a dry-ice chest for up to 30 days, or in an ultra-cold freezer (-94 degrees Fahrenheit/-70^{o}C) for up to 6 months. Room temperature stability: 2 hours	Can be kept at room temperature for up to 12 hours, a standard refrigerator for up to 30 days, and a standard freezer for up to 6 months (-20^{o}C).	Can be kept in a standard refrigerator for at least 6 months.	Easy to preserve Temporary preservation at 2-8^{o}C and long term preservation at -20 to -18^{O}C Stable for up to 3 years
How to administer	2 shots, 3 weeks apart	2 shots, 4 weeks apart	2 shots, 4 weeks apart	2 shots, 3 weeks apart
Regulatory status (When approved/ expected approval)	On December 2, 2020 the UK became the first Western country to approve any COVID-19 vaccine when it authorized the Pfizer-BioNTech. FDA issued the first emergency use authorization Dec. 11, 2020 Received Emergency use listing by the WHO Dec. 31, 2020	FDA issued the first emergency use authorization Dec. 18, 2020 On January 8, 2021 the UK approved its use	Approved in United Kingdom Dec. 29, 2020. Has not submitted application for emergency use authorization in U.S. Will seek early authorization globally, including emergency listing from WHO	**China approved Sinopharm vaccine for general use in Dec. 31, 2020** The UAE approved the vaccine on Dec. 9, and Bahrain followed days later. Submitted a conditional listing application to the FDA.
Adverse effects	Soreness or redness at the site of injection (84% of vaccine recipients), fatigue (63%), headache (55%), muscle pain (38%), chills (32%), joint pain (24%), and fever (14%). Severe adverse reactions occurred in less than 5% of vaccine recipients and were more common after the second dose and less common in adults older than age 55. Most severe adverse reactions were not thought to be associated with the vaccine, with the possible exception of swollen lymph nodes, although this was quite rare (0.3% of vaccine recipients).	Soreness or redness at the site of injection (92%), fatigue (69%), headache (63%), muscle pain(60%), joint pain (45%), and chills (43%). Effects worse after second dose. Severe adverse reactions occurred in less than 10% of vaccine recipients and also were more common after the second dose and less common in adults older than age 65. Most severe adverse reactions were not thought to be associated with the vaccine, with the possible exception of swollen lymph nodes, although this was quite rare (1.1% of vaccine recipients). Slightly more vaccine recipients (1.5%) developed an allergic reaction compared to placebo recipients (1.1%), although none were severe.	Potential injection site pain and flu-like symptoms, including fever, fatigue, headaches, and muscle pain. There was one case of hemolytic anemia and a three cases of transverse myelitis in people who received the vaccine. These illnesses were determined to be unlikely to have been caused by the vaccine, according to the trial report. A number of deaths were also reported in the study group, but those deaths were unrelated to the vaccine	Data are not yet available
Contraindications	People with a history of serious allergic reactions, anyone with a history of allergic reactions to vaccine ingredients including polyethylene glycol, and anyone with a history of allergic reactions to polysorbate.		Data are not yet available	Data are not yet available

Egypt and COVID-19 vaccines

To date, Egypt has joined 100 countries in the WHO solidarity clinical trial, with the largest number of clinical trials being performed in the Middle East and Africa. Of a total of 30 trials carried out in Africa and 44 in Middle Eastern countries, Egypt conducted 22 trials.[39] Egypt, along with three other Arab nations, the UAE, Bahrain and Jordan, are also taking part in international efforts to find a vaccine for COVID-19.[40] The Sinopharm vaccine has been tested in more than six countries, including Egypt, on 45,000 volunteers, after verifying its effectiveness and safety.[41]

Egypt has arranged with American Pfizer and British-Swedish AstraZeneca to get batches of coronavirus vaccines and contracts were signed to purchase 20 million doses of the Pfizer BioNTech and 30 million doses of the AstraZeneca COVID-19 vaccines.[42,43] The number of vaccine doses that Egypt purchased up till now amounted to 55 million doses, representing 0.8% of the global share.[44]

It has been announced that, in collaboration with the WHO and the Sinovac Manufacturing Company, there are plans to start a new production line for COVID-19 vaccine as soon as the final results of the Chinese vaccine appear.[45] At VACSERA, a production line has been prepared to manufacture a Chinese COVID-19 vaccine once approved by the organization. A WHO team assessed the line and stated that it was ready to start production.[46]

A plan to coordinate the vaccination process for Egyptians is also being carried out by the Ministry of Health and Population (MOHP). People aimed at obtaining the vaccine will be registered via an online registration website connected to a particular operating system, as the first stage of registration involves medical personnel. After registration, the vaccine will be issued to healthcare workers and then tracked for 21 days before getting the second one. The vaccine would then be given to citizens according to the 'deserving categories of patients', based on the recommendations of the Scientific Committee to Combat Coronavirus.[41]

On the 29th of December 2020, the Egyptian Center for Public Opinion Research (Baseera) conducted a survey on the Expectations of Egyptians for the year 2021 in the presence of the COVID-19 pandemic. A question about the willingness of respondents to take the Coronavirus vaccine if it is proven safe and effective showed that 67% of Egyptians strongly agreed to taking the vaccine, 25% agreed, 3% Disagreed, 4% strongly disagreed, while 1% said they could not specify. [47]

CONCLUSION AND RECOMMENDATIONS

COVID-19 is currently spreading and raising a major economic and public health concern globally. The design and production of safe and effective vaccines to prevent further spread of COVID-19 and to establish vaccine-induced herd immunity is urgent. The global COVID-19 vaccine pipeline is currently expanding on a daily basis, and our responses to the COVID-19 pandemic can be can be greatly reinforced by radical rethinking of the development and production processes of vaccines.

Several novel platforms have been developed over the past decades for the manufacture of vaccines at pandemic speed. The scope of these platforms has been expanded and the period from pathogen identification to the deployment of vaccine candidates for clinical testing has been shortened. Each platform has its own merits, demerits and challenges related to its ability to induce potent immune responses, manufacturing capacity, and safety for clinical use.

Therefore, it is unlikely that any single platform on its own will, in the future, constitute a solution for the ongoing COVID-19 pandemic or a pandemic situation. The implementation of vaccination programs is likely to be uneven, asynchronous and complex, involving numerous vaccine platforms and strategies across the globe, given the challenges in resources, development and issues associated with distribution and regional protectionism.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

FUNDING

Author's own work. No funding sources.

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