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REVIEW

Early approval of COVID-19 vaccines: Pros and cons

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ABSTRACT

The development of safe and effective vaccines has been an overriding priority for controlling the 2019-coronavirus disease (COVID-19) pandemic. From the onset, COVID-19 has caused high mortality and economic losses and yet has also offered an opportunity to advance novel therapeutics such as DNA and mRNA vaccines. Although it is hoped that the swift acceptance of such vaccines will prevent loss of life, rejuvenate economies and restore normal life, there could also be significant pitfalls. This perspective provides an overview of future directions and challenges in advancing promising vaccine platforms to widespread therapeutic use.

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Introduction

Since the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus in December 2019, it has spread throughout most countries in the world, claimed many lives, and wreaked havoc on social and economic structures. Subsequently, the world has seen a large number of vaccine development projects against this deadly pathogen. Plasmid DNA and mRNA vaccines have been touted as potential alternatives to standard vaccines because developing a gene-build coding for the antigen rather than inactivating or attenuating the pathogen is much simpler and quicker, and obviates the hazards of dealing with live pathogens.[1–3] DNA vaccination has recently become the fastest-growing vaccine technology field due its many advantages: high stability, ease of construction and ease of delivery. However, other than for COVID-19, no DNA vaccine has yet to be commercially licensed or even successfully passed phase III clinical trials.[3,4] Moreover, plasmid DNA has the possibility of integration into the host genome, and in many cases DNA vaccination has been hampered by poor efficacy as well as autoimmunity risk.[3,5] In contrast, mRNAs represent a non-infectious, non-integrating platform that is degraded by normal cellular processes and whose in vivo half-life can be controlled by using various modifications and distribution methods.[6–8] RNA vaccines are not completely error free – there are issues with mRNA instability, high innate immunogenicity, and inefficient in vivo-delivery. Despite the fact that a substantial number of mRNA/DNA vaccine candidates are in preclinical and human clinical trials, no licensed vaccine has been seen for human use since 1990, when active protein was detected in a mouse model by mRNA inoculation; mostly due to safety concerns.[1,4] Nevertheless, in 11 January 2021, the first mRNA vaccine against SARS-CoV-2 was approved within just a year after COVID-19 vaccine development projects were initiated. As of 25 May 2021, at least 14 different nucleic acid-based vaccine (in 3 platforms) for SARS-CoV-2 have been issued by the U.S. Food and Drug Administration (FDA) and World Health Organization (WHO).[9] To ensure global immunization against SARS-CoV-2, the COVID-19 Vaccine Global Access (COVAX) initiative has been formed.[10] The primary target of COVAX is to procure and fairly distribute 2 billion doses of COVID-19 vaccines across almost 200 countries, including 92 middle- and lower-income countries that cannot fully afford to pay for COVID-19 vaccines, so that they get equal access as higher-income, self-financing countries do by the end of 2021.[11,12] In this report, the possible effects of the early approval of mRNA/DNA vaccines use against SARS-CoV-2 are summarized.

Significance of the early approval of corona vaccines

The use of face masks, physical separation or social distancing, the testing of exposed or symptomatic individuals, touch tracking, and isolation have proven unsuccessful in preventing the dissemination of SARS-Cov-2. Therefore, several vaccines have been licensed to minimize COVID-19-related morbidity and mortality, despite the possible dangers associated with newly-approved vaccines. Early approval of COVID-19 vaccines might play a great role in controlling the COVID-19 pandemic.

The vaccine will reduce loss of life and will help to recover economic loss

Since the outbreak of COVID-19, the mortality rate has been estimated to be around 2.1%, with nearly 3.5 million people dead by 25 May 2021.[13] Severe/fatal cases of COVID-19 are associated with immune hyperactivation and excessive cytokine release, leading to multiple organ failure.[14–16] It has been estimated that the vaccines against infectious diseases have saved at least 23 million lives over the ten years from 2011 to

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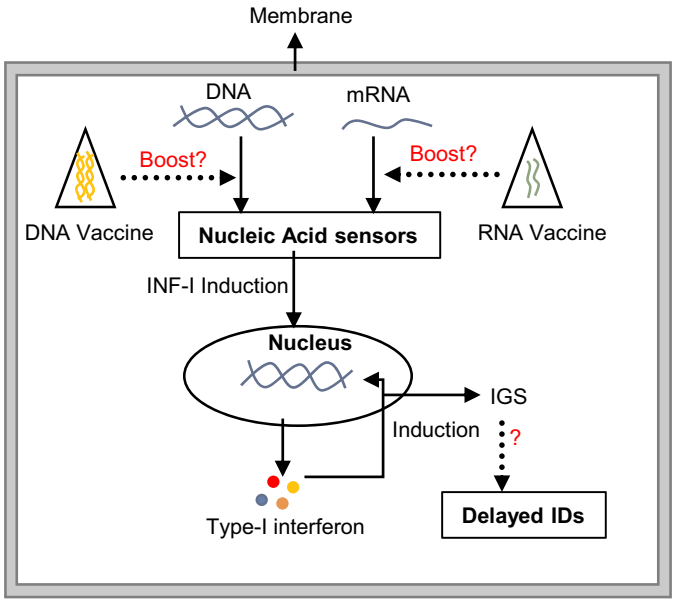

Figure 1. The mechanism of nucleic acid-mediated immune stimulation. The presence of naked mRNA/DNA from any source e.g. infectious organisms, diet or cellular DNA fragments, are sensed by a protein complex. Successive downstream signaling induces type-I interferon, which further stimulates the production of interferon stimulation genes (IGS). Abnormal expression of IGS might link to different immunological disorders (IDs). While second-generation mRNA vaccinations should be safer and may not strongly associated with this mechanism, long-term exposure to any nucleic acid in the form of vaccination may activate the nucleic acid-mediated immune sensing pathway, raising the risk of IDs.

2020.[17] However, identifying, quantifying, and balancing the possible safety risks against possible advantages is an important consideration in approving any vaccine. Despite there being no prior experience of using mRNA/DNA vaccines for human use, the contagious nature and mortality of COVID-19 means vaccines have been approved without long-term clinical follow-up. The efficacy of DNA and mRNA vaccines in producing neutralizing antibodies has already been demonstrated.[4,18,19] Further, several phase-1 mRNA and DNA vaccine clinical studies have provided satisfactory safety and efficacy results, having elicited sufficient neutralizing titer to protect from infectious pathogens. For example, DNA vaccines against West Nile virus can induce neutralizing antibodies in different age groups providing safety and immunogenicity against Ebolavirus, Marburgvirus, Zika virus and HPV infection.[20–24] Additionally, mRNA vaccines against Zika virus, respiratory syncytial virus (RSV), influenza virus, rabies virus, Ebolavirus, H1N1 influenza etc., have already shown satisfactory results in animals.[25–28] Moreover, preclinical and clinical profiles of mRNA vaccines for H10N8, H7N9 influenza virus, rabies virus, and HIV-1 virus can induce protective immunogenicity with acceptable tolerability results.[26,29–31] In the case of COVID-19 vaccines, currently approved mRNA and viral vector vaccines have a vaccine efficacy ranging from around 70% to more than 90%.[32–37] It is hoped that the approved vaccines against SARS-CoV-2 will control COVID-19, as justified by results of their clinical trials.[32,34] Moreover, the vaccination program should promote the herd immunity needed to get back to normal human activities, which will in turn help the global economy to recover.

Cheap, easy, and reproducible

The most important way to control and avoid pandemics is to create prophylactic or preventive vaccines against infectious diseases. Orthodox vaccination methods have often struggled to deliver successful vaccines against complicated viruses like HIV-1, herpes simplex virus, and RSV. Furthermore, commercial vaccine development generally takes many years. Since both mRNA and DNA vaccines are designed and developed independent of cellular processes, they are easily adaptable, relatively inexpensive, and their scalable manufacturing process offers the flexibility to encode virtually every protein as an antigen in a very short period of time. One of the greatest advantages of the new mRNA-based technology is the ease with which nucleotide sequences can be tweaked for revised formulation to combat emerging immune-escape mutants. Recently, a complete mutation map for the SARS-CoV-2 RBD has been developed that might enable rational design of antibody therapeutics using this new technology.[38] In addition, they can be manufactured in the same manufacturing plant using the same manufacturing process. Such vaccines are consistent from batch to batch and reproducible, much as with in vitro-chemical reactions. Thus, with relatively little financial expenditure, innovative vaccines could be produced in a very short period, which is of considerable value for pandemic scenarios with infectious diseases like COVID-19 in addition to of developing cancer vaccines against patient-specific cancer-associated or mutated antigens.[39,40]

Suitable for both infectious and non-infectious disease

One of the greatest advantages of mRNA/DNA vaccines is that the protein is engineered and the vaccine is produced without using the infectious pathogen, and hence no pathogen cultivation or purification steps are required. Once the nucleotide sequences are known, no matter how contagious they are, vaccines can be produced. Moreover, it is equally amenable to non-infectious disease like cancer where antigen purification steps are so difficult. There are many organisms comprising multiple serotypes/genotypes, and in conventional methods, multiple epitope-based vaccine formulation is very difficult, but nucleic acid-based vaccines technology could resolve this problem. While the handling of highly contagious pathogens like SARS, MERS, and Ebola require biosafety level 4 safety cabinets with highly equipped laboratory settings, mRNA/DNA vaccines might be produced in a comparatively low-resource setting. Moreover, using several laboratories around the world should decrease reliance on specialist laboratories, increase production capacity, cut transport and production time and costs, and eventually shorten delays in distribution to the public.

Drawbacks of nucleic acid-based vaccines

The approval of nucleic acid-based vaccines will not only reduce mortality by regulating COVID-19, and reintroduce patients to daily life, but also support research into other diseases. However, there are several serious problems that must be resolved in exposing people to novel nucleic acid

vaccines before they can be deemed a potential therapeutic for long-term use.

First mRNA vaccine without long term safety data

Successful vaccine development needs a long time, usually several years. Until recently, the Mumps vaccine was the fastest vaccine – it was approved in 1960 after approximately four years of initiation. On 11 December 2020, the U.S. Food and Drug Administration issued the first emergency use authorization (EUA) for the prevention of COVID-19 which allows Pfizer-BioNTech's mRNA-based COVID-19 vaccine 'BNT162b2′ to be distributed in the U.S.[41] This was not only the first mRNA vaccine approved for human use but also the fastest formulated vaccine whose development was initiated just 11 months back on 10 January 2020.[34] One week later, the FDA issued an EUA for the another mRNA vaccine, named 'mRNA-1273′, also known as the 'Moderna COVID-19 Vaccine.'[33] Other than these, the first DNA vector-based 'ChAdOx1 nCoV-19 vaccine' (the AstraZeneca/Oxford COVID-19 vaccine), was approved by the WHO on 15 February 2021.[42] Subsequently, another vector-based vaccine from Janssen/Johnson & Johnson was approved on 12 March 2021.

At present, at least 3 different platforms, i.e. mRNA, DNA, and DNA vector-based vaccines comprising 14 candidates are in use worldwide.[9] All these vaccine development projects were launched shortly after the SARS-CoV-2 genetic sequence was determined in January 2020.[43–46] It is obviously not possible to get long-term safety data given this short time. In addition, ethical and practical barriers prevented following placebo recipients for a long time without offering active immunization and thus made it impossible to generate randomized control trial data.[34] The 'BNT162b2′ trail included only 2 months of follow-up of the vaccinated individuals after the second dose of the vaccine for half the trial participants, and up to 14 weeks' maximum follow-up for a smaller subset. The median follow-up of the Moderna vaccine was 56 days for 62% of participants after the second dose.[37] In contrast, the average safety follow-up was 3–4 months for the ChAdOx1 nCoV-19 vaccine produced by Oxford–AstraZeneca. In all cases, vaccinated and non-vaccinated groups developed transient adverse reactions though these were resolved within a couple of days after onset in most of the cases. However, due to early approval more comprehensive information on the vaccine effect and the duration of protection remain to be determined.[34]

Late side effects and duration of protection are unknown

Vaccines are generally safe, *because* they are approved after long clinical and pre-clinical trials. Despite precautions, and an extremely low incidence of serious systemic adverse events, numerous reports have highlighted the occurrence of untoward neurological, articular, and autoimmune effects after single or combined multi-vaccine procedures. For instance, vaccine-associated paralytic poliomyelitis has been associated with oral poliovirus vaccine.[47] In the case of the Yellow Fever (YF) vaccination program, vaccine-associated severe neurotropic diseases such as post-vaccinal encephalitis, acute disseminated encephalomyelitis, and Guillain-Barré syndrome (GBS) have been reported.[48] Although the side-effects are merely associated and causality has never been established, effects including GBS, multiple sclerosis, autism, arthritis, rheumatoid arthritis, systemic lupus erythematosus, and diabetes mellitus, among others, have been reported for other vaccines such as HBV, typhoid/paratyphoid, anthrax, tetanus, MMR, BCG, smallpox, DPT, influenza, pertussis, and polio vaccines.[49] It is supposed that DNA vaccines bear a key risk of genomic integration. Again, this probability is thought to be extremely low and issues about integration are currently theoretical as DNA vaccines are still not licensed for humans. However, if hundreds of millions of effective doses are to be administered to healthy recipients, even a very rare event might become a potentially serious safety problem, particularly in view of vaccination fatigue in many countries.[50]

An mRNA vaccine has no risk of genomic integration, but there are several limitations. The length of antigen expression can last for several months in the case of both DNA and RNA vaccines. In general, mRNA/DNA vaccines serve as a constant long-term antigen production factory, which may not equate with successful immune responses and may even damage the expected immune effect and contribute to T cell exhaustion.[51–53] However, the current mRNA vaccines might be the safer and cleaner than conventional vaccine technologies since mRNA is translated then quickly degrades, leaving nothing behind except vaccine-induced neutralizing antibodies. In contrast, in next-generation mRNA vaccines, the self-amplifying mRNA encodes not only the antigen but also the viral replication machinery leading to high levels of antigen expression, which may provide longer stimulation, hence a long-lasting duration of protection.[4,6]

Another prominent issue might be that certain nucleic acid-based vaccines elicit strong type I interferon responses that have been related to inflammation potentially leading to the development of autoimmune disease.[54–56] Epitope spreading and bystander activation, as well as autoinflammatory dysregulation in genetically prone individuals, can also lead to acute and chronic autoimmunity throughout and after COVID-19 vaccination.[57,58] Additionally, involvement of extracellular naked RNA or DNA results from nucleic acid-based vaccination, which has been shown to increase the permeability of closely-packed endothelial cells and thus may lead to edema.[59] In vivo and in vitro evidence has shown that blood coagulation factors, particularly factors XII and XI, strongly bind to extracellular naked RNAs and activate the proteases involved in the blood coagulation contact process pathway.[59] Different forms of eukaryotic and prokaryotic RNAs serve as promoters of blood coagulation and pathological thrombus formation.[59] During the phase III trials of the AstraZeneca and JNJ vaccines, there were early warning signals whereby serious adverse events following immunization (AEFI), such as multiple sclerosis and transverse myelitis, were reported in like Germany, Austria, USA, and India.[60–63] As of March 2, 2021, more than 51 million dosages of the COVID-19 vaccines from different platforms were administered in the United States and 9,442 adverse reactions had been reported.[64] Common side effects were dizziness, headache, pain, muscle spasms, myalgia,

and paresthesia, while in rare cases, tremors, diplopia, tinnitus, dysphonia, seizures, and reactivation of herpes zoster have been detected. In a few cases, serious events like stroke (17 cases), GBS (32 cases), facial palsy (190 cases), transverse myelitis (9 cases), and acute disseminated encephalomyelitis (6 cases) were observed.[64] Since the evidence is based on passive surveillance, it is subject to reporting bias and might contain errors. Furthermore, due to the high number of patients being vaccinated, certain cases of neurological conditions might arise by chance alone because of background incidence of neurological disorders among the population.

Autoimmune thrombosis associated with the AstraZeneca vaccine mimics heparin-induced thrombocytopenia in different regions such as the United Kingdom, European Union, and Scandinavian countries. The rare cases, cerebral sinus vein thrombosis (CSVT) and thrombocytopenia were reported in patients who received the AstraZeneca COVID-19 vaccine (AZD1222).[60,65] At least 9 patients presented with thrombosis between 4 and 16 days after vaccination. Seven of them had cerebral venous thrombosis (CVT), one had pulmonary embolism, and one had both CVT and splanchnic vein thrombosis; four of them died. While the vaccine-related effects were clinically similar to heparin-induced thrombocytopenia, the serological profile was different.[60] Vaccine-induced immune thrombotic thrombocytopenia (VIITT) and was anxiety-related adverse events such as syncope (fainting) have been reported for the JNJ vector-based vaccine. Syncope was detected for 8.2 per 100,000 doses; nearly 164 times higher than for influenza vaccination, where the reporting rate of syncope was 0.05 episodes per 100,000 doses in July 2019 to June 2020.[61] In contrast, the incidence of VIITT was predicted to be nearly 1 case per 500,000 doses for AstraZeneca vaccine.[65] Overall, VIITT rate for the AstraZeneca/COVISHIELD vaccines have been estimated from 1 case per 26,000 to 1 case per 127,000 however, it greatly varies from one country to another.[60,65–68] Due to safety concerns, vaccine trials were temporarily paused in some countries for both the JNJ and AstraZeneca vaccines. However, the effects were ultimately deemed to be unrelated to the vaccine, as the rate of cerebral venous sinus thrombosis in the general population was estimated at 0.22 to 1.57 cases per 100,000 per year.[60] The benefits of the COVID-19 vaccines were deemed outweigh the risks.[69] Therefore, protection will require ongoing assessment as multiple mRNA/DNA modalities and delivery mechanisms are used for the first time in humans and evaluated in wider populations of patients.

There is no authorized vaccine for human corona viruses, and vaccines against common cold viruses are short-lived and less effective

The *Coronaviridae* family consists of four genera: the alpha, beta, gamma, and delta coronaviruses, and which possess a large (31 kb) single-stranded positive-sense RNA genome. The highly pathogenic SARS-CoV, SARS-CoV-2, and MERS-CoV are all betacoronaviruses. Four other major human coronaviruses (HCoV) are HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, which are responsible for nearly 15% of human common colds.[70] Unfortunately, there are as yet no approved non-Covid coronavirus vaccines for human use; only some ongoing projects.[71] Experimental data show that vaccines against coronaviruses are less effective and less cross-protective than vaccines against many other human viruses, with antibody titers greatly decreasing one year after initial infection, and many are able to re-infect and shed viruses.[72,73] The estimated reinfection rates for HCoV-229E and HCoV-OC43 have been estimated to be 30% and 80%, respectively.[74–76] Accordingly, complete protection from a mRNA/DNA vaccine has yet to be realized.

Similar to coronaviruses, others respiratory viruses such as RSV, influenza viruses, and rhinoviruses impair antibody-mediated protection and defective B-Cell memory due to the short life of the neutralizing antibody and/or presence of numerous serotypes.[77–80] A recent study suggested that a relatively small number of mutations can mediate potent escape of pseudoviruses representing 10 globally-circulating SARS-CoV-2 strains from BNT162b2 or mRNA-1273 vaccine.[81] A number of antibody-resistant SARS-CoV-2 variants have already been reported in the UK and South Africa.[82] A novel SARS-Cov-2 variant CAL.20 C (B.1.427/B.1.429) was originally detected in California and is currently spreading throughout the US and 29 additional countries, has been reported to have escaped from a monoclonal antibody panel.[83]

Another important concern of a COVID-19 vaccine is whether it will generate a sufficient immune response in elderly people. Research demonstrates that elderly people are impaired in generating high-affinity antibodies, have defects in somatic hypermutation and isotype switching, their naive T cells decrease significantly, and have reduced TCR repertoires and poorly responding CD8+ CD28- T cells.[84–89] The most severe risk group for SARS-Cov-2 is the elderly.[90–92] While the overall case fatality rate (CFR) has been estimated to be around 4%, the rate is rapidly increasing in the age group of ≥60 years, reaching 16.9% and 24.4% in the 70–79 years and ≥80 years age groups, respectively.[91,92] More than 85% of the deceased are 65 years or older.[93] Recently, it has been reported that the elderly elicited a strong and persistent antibody response, similar to those younger aged, after a second dose of Pfizer or Oxford-AstraZeneca COVID-19 vaccines in UK and USA.[94–96] However, continuous long-term surveillance is required in spite of initial impressive clinical data because it is unknown how long a new vaccine's immune responses will last.

Nucleotide-mediated ectopic immune stimulation

Type I interferon production is one of the most important, first line, innate, immune defenses against any virus, and essential for the initiation of adaptive immunity. While innate immune responses to DNA viruses are thought to be initiated by pattern-recognition receptors (PRRs), the precise mechanism is unknown.[97] In contrast, immune-sensing mechanisms for RNA viruses are very well studied. It is proposed that both DNA and RNA viruses produce certain RNA species during their replication cycle that are recognized by retinoic acid-inducible gene I (RIG-I).[98–100] RIG-I has been shown to sense viral RNAs derived from a panel of virus families.[98,101] Moreover, previously it was thought that viral replication is required to initiate RIG-I sensing, but surprisingly, viral and

other nucleotide fragments are enough for an RIG-I-mediated immune response (Figure 1).[102–104] Moreover, nucleotide uptake from dietary sources can also elicit immune responses.[105] Among extracellular nucleotides, ATP is the most abundant and is commonly considered a classical danger signal and can act as an immune response initiator or terminator. In addition, signal transduction induced by the association of exogenous nucleotides/nucleosides and their receptors can modulate the expression of a range of genes, some of which can specifically influence the levels of cytokines.[106] As previously discussed, in some platforms, advanced technologies such as mass production, self-expression, rapid degradation, etc., have eliminated the risks associated with nucleic acid-based vaccines. However, COVID-19 vaccines administered on various platforms should be monitored for prolonged periods of time.

The risk of vaccine-associated enhancement

Vaccine-associated enhanced disease (VAED) is very rare but tends to cause serious adverse infection outcomes relative to infection without previous vaccination. VAED is also known as antibody-dependent enhancement (ADE), a disease in which secondary infection is directly facilitated by pathogen-specific antibodies produced by vaccination or primary infection (Figure 2). VAED has been observed for several vaccines such as formalin-inactivated whole-virus vaccines against respiratory syncytial virus (RSV) and measles virus vaccines, and has been reported in rare cases of secondary dengue infection.[107–109] In the context of COVID-19 vaccine production, one of the possible risks posed is whether the immune responses elicited by the vaccine may boost the acquisition of SARS-CoV-2 or make the disease worse during reinfection or when infection occurs after vaccination. Although this phenomenon has not been observed yet in any of the approved vaccine trials including animal studies in non-human primates however, it is too early to settle this question since neither the principles of immunity nor the preclinical trials present a justification claiming the safety of COVID-19 vaccines at this time. Long term follow-up should be provided by post-licensing surveillance to detect adverse events, including the potential for increased severity of COVID-19 illness.

Future perspective

Since 1990, when a successful protein was produced from in vitro-transcribed mRNA-injected animals, researchers have been trying to produce mRNA-based vaccines. To date, several plasmid-based vaccines have already been approved for animals such as a melanoma cancer vaccine for dogs,

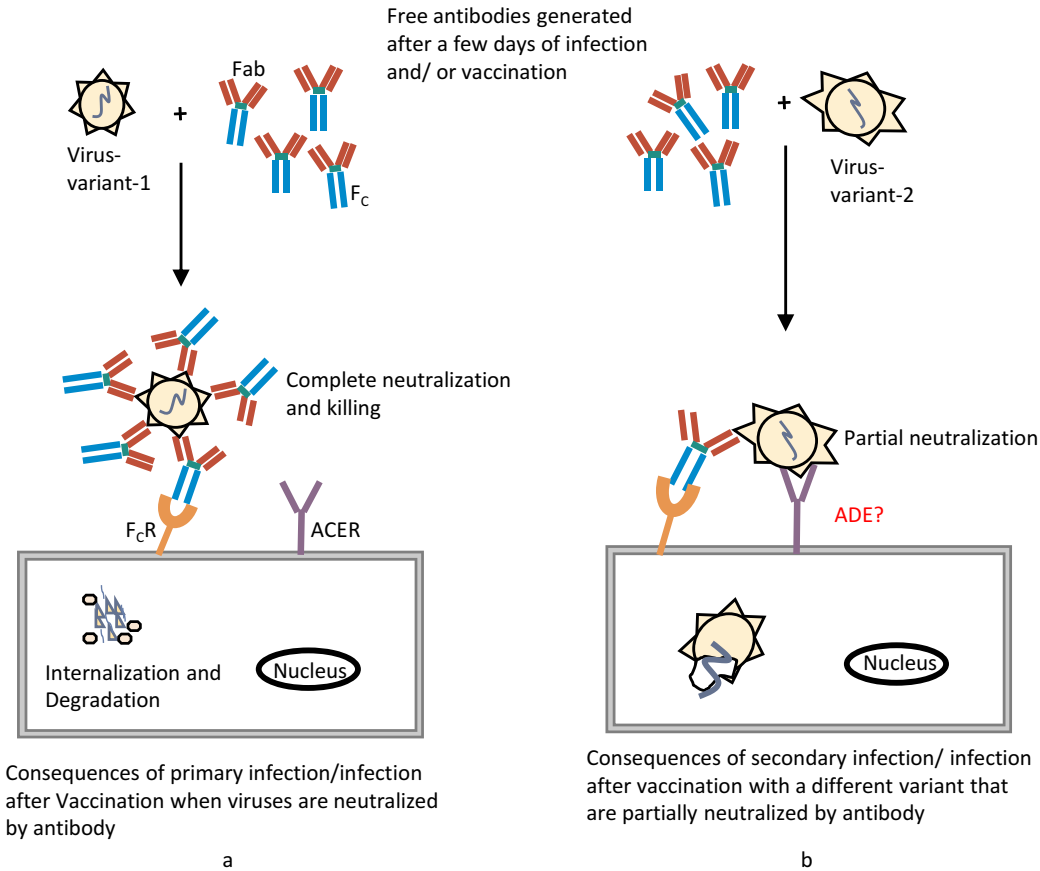

Figure 2. Schematic representation of antibody action and antibody dependent enhancement (ADE) to viral infection. (**a**) Antibodies generated after a few days of viral infection or successful vaccination, which in turn neutralize the viruses, enabling protection from further infection. (**b**) Secondary infection or infection after vaccination with a different viral strain causes failure of complete neutralization by the previously existing antibody. However, due to sharing some antigen similarities, partial neutralization may accelerate viral internalization by antibody-binding Fc receptors. Although nucleic-acid-based COVID-19 vaccines have been successfully approved and have shown no ADE complications in trials, including non-human primate animal studies, vaccinated individuals should be monitored across time.

a West Nile virus vaccine for horses, and an infectious hematopoietic necrosis virus vaccine for fish.[39,110,111] A large number of preclinical vaccine development projects have been published recently, and several have entered into human clinical trials.[4] Although the key ability of nucleic acid-based vaccines to cause cellular T- and B-cell responses in humans has been demonstrated in a number of clinical trials, the production of DNA vaccines for humans has so far not been equally successful. These included a number of HIV vaccines, for Zika virus, influenza virus, rabies virus, and a number of vaccines against different cancers (melanoma, breast cancer, lung cancer, prostate cancer, ovarian cancer, multiple solid tumors, etc.).[4] Unlike therapeutic drugs, vaccines are injected into the healthy individuals and thus safety issues are paramount; none of them have received approval. COVID-19 however, has changed the mind-set and a year after the emergence of the SARS-CoV-2 virus, at least 14 different nucleic acid-based vaccines (3 platforms) have been approved.[9] The approval of several mRNA or vector-based COVID-19 vaccines has had a great impact as it has opened a new era in vaccinology. A billion doses of the Oxford-AstraZeneca vaccine have been ordered already by many countries throughout the world, including the EU, US, China, India, Japan, UK, Brazil, Indonesia, Bangladesh, Australia, Egypt, Argentina, and Canada.[112] These pioneering vaccines can obviously be considered as trials for overall 'nucleic acid-based therapeutics.' Thus, a large trial outcome of nucleic acid-based vaccine, irrespective of gender, ethnicity, and socioeconomic status, will be generated by the COVID-19 vaccination program worldwide. The medical world is no doubt looking forward to seeing the success of these vaccines, as approval of nucleic acid-based vaccines for other diseases will mostly depend on them.

Conclusion

The development of COVID-19 vaccines exemplify the possibilities when key sectors of society, such as the general public, government, scientists, regulators, and industry, collaborate toward a shared objective. The production of COVID-19 vaccines that are safe, reliable, inexpensive, and deployable is vital to ending the pandemic, and restoring normalcy. However, given the low efficacy of previous vaccines against the common cold/influenza viruses and the durability of immune responses, and the questions about new vaccines, the celebrations surrounding early promising results of the COVID-19 vaccines are premature. Longitudinal studies will be required to assess the reliability of the defensive adaptive immune responses following natural infection or vaccination.

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Author contributions

M.A.R conceptualized and designed the study; M.A.R and M.S.I. wrote, reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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