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Available COVID-19 vaccine platforms: A roadmap to eclipsing the SARS-CoV-2 viral saga

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Abstract

The coronavirus disease of 2019 (COVID-19) has devastated the globe and continues to be a protracted health and economic saga. In the absence of specific efficacious medical remedies, efforts to encounter and contain this emerging virus concentrated on vaccine production. A plethora of novel vaccines has been under development by major companies in different countries. To date, around 60 vaccines are in clinical trials with many others continuously added to the pipeline. The variety of vaccine types, in their design, platform and trial phases, requires an understanding of what is being presented in the literature and launched into the market.

Thus, this study is intended to enlighten and educate the medical community by reviewing the different vaccine platforms, and briefly explaining their mechanisms of action, with an emphasis on those vaccines that have reached the most advanced stages.

Keywords
COVID-19, Novel Vaccine, Platforms, Antibodies, SARS-CoV-2 Immunity

Introduction

The coronavirus disease of 2019 (COVID-19) outbreak was first reported in Wuhan, China, in December 2019 [1]. On 11 March 2020, the World health Organization (WHO) declared COVID-19 a pandemic, and until now, the health sector is struggling to fight this rapidly expanding virus, with a total of 88 million cases and around 2 million deaths worldwide at the time of writing this article. Non compliance with social distancing, hand washing, wearing of face masks and other public health measures has dramatically increased the infectivity rates and depleted essential health sector resources [2].

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As a consequence to this high-pressure situation and its global impact, many aspects related to our everyday life have been altered or disrupted. These include economic matters, lockdowns and medical-related burdens entailing shortages of hospital beds, health care workers due to illness, soaring hospitalization costs, and the absence of a clear treatment algorithm or a treatment drug, as well as the burden of molecular and serological testing, and continuous contact tracing [3].

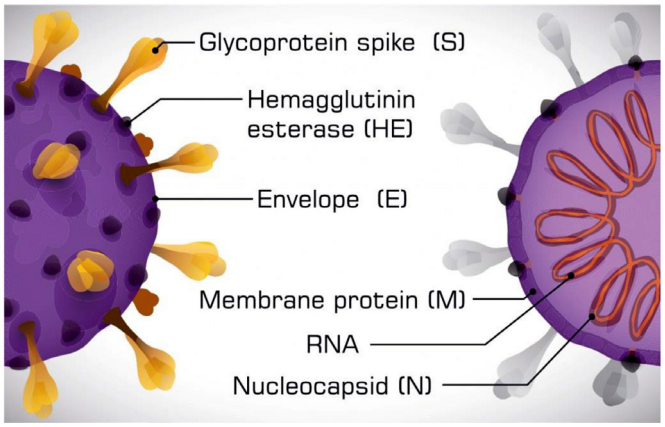
Major efforts have been directed towards a thorough understanding of the immune response involved in this viral infection as well as in vaccine development. In addition, many research laboratories, mainly sponsored by large pharmaceutical companies, have labored to develop an effective vaccine against this devastating virus.

In order to better understand the current vaccine status and its milestones features, this manuscript will address the antigenic structures of the virus, the human immune response against it and the various novel approaches to vaccine development.

COVID-19 antigenic structure

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) consists of a positive sense single stranded RNA genome coated by a nucleocapsid protein (N-protein) enclosed in a lipid envelope derived from the host membrane, onto which are inserted 3 other proteins: The glycoprotein spike (S-protein), the envelope protein (E-protein), and the membrane/matrix protein (M-protein) **(Figure 1)** [3]. The SARS-CoV-2 receptor binding domain (RBD), being part of the S-protein domain, binds to the angiotensin converting enzyme-2 (ACE 2) receptor in host cells mainly via the S1 subunit, allowing viral entry into the host cell [4]. Moreover, many studies found that neutralizing antibodies were directed against the S-protein responsible for cell attachment, but not exclusively, because antibodies against N-protein were also protective [5].

Figure 1: SARS-CoV-2 antigenic determinants: The glycoprotein spike (S-protein), the envelope (E-protein), and the membrane/matrix (M-protein).



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Immunity against SARS-CoV-2 and its duration

SARS-CoV-2 infection is acquired via the respiratory route, after interaction of the S-protein-RBD with ACE2 receptor. Subsequently and like other respiratory viruses, the immune response will initiate mobilization of its different arms starting with the innate immune system. However, SARS-CoV-2 plays a major role in the suppression of dendritic cell activity along with a dampening of interferon type I and type III responses, and the elevation of systemic cytokines, mainly interleukin-6 [6-7]. Thus, adaptive immunity, as a second line of defense, will gear up with its two components: Th1 cellular immunity and Th2 humoral immunity. Antibody-mediated immunity is fundamental for virus neutralization, mainly via antibodies directed against the S-protein, which makes the antigenic epitope the basis for most serologic rapid diagnostic tests targeting IgM and IgG detection [8].

The exact magnitude and duration of the protective immunity remain under investigation. Many studies have shown that the antibody response is positively related to disease severity. That is, the more the severe the SARS-CoV-2 infection, the hig-

her the antibody titer [9]. So far, evidence reported from Arizona [9] suggests that the spike-RBD, S2 and neutralizing antibodies remain detectable for up to seven months post infection. A Korean study showed that out of millions of COVID-19 cases since December 2019, there have been only ten confirmed reinfections [10]. These studies provide comfort about the potential for developing vaccines that have the ability of stimulating the natural immune response and producing neutralizing antibodies, for up to eight months [4, 11].

In natural infection or whether using a vaccine, antibodies are not the only modality the immune system fight COVID-19 virus. Another important role is cellular immunity via CD8 positive T-cells, that will also take a lead in viral clearance [12]. Noteworthy, is the coordinated interaction between CD4 positive and CD8 positive T-cells, Th17, and the memory cells that play a major role in the immune defenses against invading pathogens. So far, this complex immunologic interaction in response to a SARS-CoV-2 infection is not well explained, and many hidden facts need to be elucidated for future therapeutic approaches and vaccine optimization strategies.

Vaccine development

Normally, a vaccine takes 10 to 15 years to be developed safely and efficaciously, but in pandemics vaccine development is expected to occur at higher rates, with overlapping clinical stages and simultaneous ongoing processes [13]. The first step of designing a vaccine requires the selection of antigens capable of inducing an immune response, followed by the selection of a platform, a route of administration along with a safe regimen of doses [14].

In the following section, we will discuss the current status of available platforms under investigation and development for SARS-CoV-2 vaccine, their pros and cons, and their phases. Until 29 December 2020, it was reported that there are 172 vaccine candidates in pre-clinical evaluation, and 60 vaccine candidates in clinical evaluation, and some were granted the emergency use authorization (EUA) by the USA FDA, and this can be tracked on WHO link [15].

Different vaccine platforms

Six different platforms are being investigated for SARS-CoV-2 vaccine development: protein subunits, recombinant viral vectored vaccines, nucleic acid-based vaccines, inactivated virus vaccines, virus-like particles (VLP) vaccines, and live attenuated virus. A brief description of each platform is given below, along with a note of its current clinical trial phase, and its pros and cons. The listing is based on the most common platforms in clinical trials with examples:

Protein subunit vaccines (example: Novavax company, UK):

These consist of one or more viral antigenic epitopes, but lack the viral nucleic acids. Because proteins alone are rarely immunogenic, they usually require the addition of adjuvants, and repeated doses for the adequate eliciting of a suitable immune response, mostly antibodies [3]. To date, there are 19 protein subunit vaccine candidates in clinical trials. Two vaccines have reached Phase 3 clinical trial: the"NVX-CoV2373" developed by "Novavax" company (UK), which is a SARS CoV-2 recombinant glycoprotein nanoparticle adjuvanted with Matrix M. The other vaccine is being developed by Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences, and consists of a RBD-dimer. The remaining protein subunit vaccine candidates still in Phase 1/2 of clinical trials and they are working on different epitopes of the spike S-protein [15].

Recombinant viral vectored vaccines (examples: Oxford/AstraZeneca, UK; Sputnik V, Russia, Janssen, Belgium)

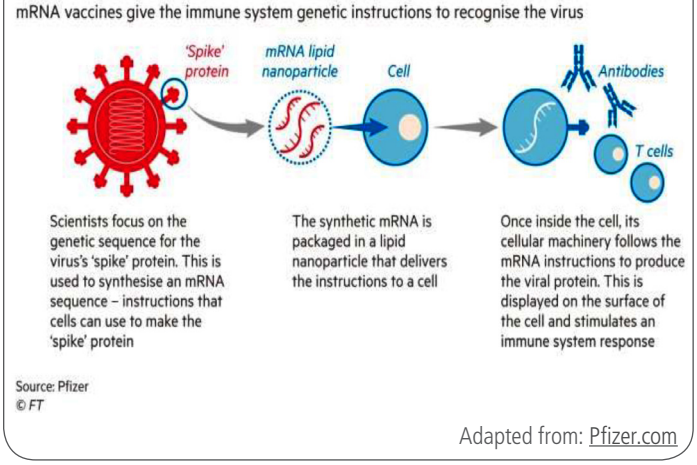
This platform uses a defective virus, mostly human or chimpanzee adenovirus, as the vector to carry

and deliver genes to the targeted cells for expressing antibodies. Such vaccines are highly specific in delivering the genes to the target cells. These models are built on either a replication deficient viral backbone or an attenuated competent viral backbone that is bioengineered to express antigens derived from the target pathogen [16, 17]. When the virus infects a cell, they administer this foreign gene into the cell. The cell then transcribes and translates the gene to produce the antigen and display this antigen on the cell surface to stimulate an immune response. Although 16 candidates are now in clinical trial, only four vaccines are in Phase 3 trials: ChAdOx1-S by the University of Oxford/AstraZeneca, UK, achieving a 70% efficacy, Adenovirus Type 5 Vector by CanSino Biological Inc./Beijing Institute of Biotechnology, Adeno-based (rAd26-S+rAd5-S) trade-named "Sputnik V" by Gamaleya Research Institute, Russia, achieving so far a 91.4% efficacy, and Adenovirus Type 26 vector by Janssen Pharmaceutical Companies, reporting efficacy rates greater than 90%. Moreover, there is one intranasal flu-based-RBD replicating vaccine developed by Beijing Wantai Biological Pharmacy/Xiamen University in Phase 2 clinical trials [15].

Nucleic acid-based vaccines (examples: Pfizer and Moderna, USA)

This platform relies on usingei ther DNA or RNA. Both of the nucleic acid approaches can be easily and expeditiously developed at an accelerated pace, they are safe to administer on immunosuppressed people in the absence of infectious components. This explains the rapid pace of development and launch of vaccines marketed by Pfizer and Moderna companies. DNA vaccines are more stable than RNA vaccines, but they have the possibility of insertion in the host genome [18]. To date there are eight DNA vaccine candidates in clinical trials. Four of them are at Phase 1/2. These include, but are not limited to, a DNA plasmid vaccine with electroporation developed by Inovio Pharmaceuticals/International Vaccine Institute, a DNA plasmid vaccine coupled to an adjuvant developed by Osaka University/AnGes/Takara Bio and others less well advanced in the vaccine pipeline [15]. Messenger RNA (mRNA) vaccines are considered non-infectious platforms and minimally immunogenic with no potential risk of insertional mutagenesis [19]. Their biggest drawback remains in RNA instability, as naked genetic material can be quickly degraded and the necessity of very low storage temperature (e.g. at -80°C for Pfizer vaccine) which is a limitation in many countries, where hospitals/clinics are not well equipped with these freezers. The two approved mRNA vaccines are (i) the "mRNA-1273" vaccine developed by Moderna/NIAID and consisting of a synthetic mRNA encapsulated in a lipid nanoparticle (LNP). This vaccine yields a high antibody response similar to those detected in convalescent serum specimens [20], and (ii) the "BNT162b" vaccine developed by BioNTech/Fosun Pharma/Pfizer. This is a codon-optimized mRNA vaccine encoding for the trimerized SARS-CoV-2 RBD. Promising elevated IgG antibodies have been obtained, with an efficacy rate above 90%, seven days after the second dose of Pfizer vaccine administration **(Figure 2)**. Another mRNA vaccine in the pipeline is the "CVnCoV" vaccine developed

Figure 2: Pfizer's vaccine mechanism of action.



Adapted from: Pfizer.com

by CureVac AG, and still is in Phase 2/3 clinical trial. Moreover, seven RNA vaccines and eight DNA vaccines are in the pipeline and are in Phase 1 or 1/2 clinical trials.

Inactivated virus vaccines (examples: Sinopharm and Sinovac, China)

These vaccines are composed of an entire virus that is killed by exposure to chemical or physical agents [21]. Such treatment/manipulation eliminates the possibility of the pathogen infectivity, but maintains the antigenicity required to initiate an immune response in the host. Adjuvants (e.g. aluminum salts) can be added to increase immunogenicity. Such vaccines can be stored at room temperature as the pathogen is dead. Currently, eight vaccine candidates are in clinical trial, four of them have reached Phase 3: "CoronaVac" which is a SARS-CoV-2 inactivated virus from Sinovac, inactivated SARS-CoV-2 (Vero cell) developed by the Wuhan Institute of Biological Products/Sinopharm and another one by the Beijing Institute of Biological Products/Sinopharm, achieving a 90% efficacy, in addition to the BBV152 vaccine, known as Covaxin, achieving 95% efficacy, by Bharat Biotech International Limited, India [15]. The remaining four vaccine candidates are in Phase 1/2 to date.

Virus-like particle(VLP) vaccines (example: SpyBiotech, India; GlaxoSmithKline, USA):

These vaccines consist of self-assembling virus structural subunits lacking nucleic acids. VLP has been an effective way of creating vaccines against diseases, such as human papillomavirus (HPV), hepatitis and malaria. In the case of SARS-CoV-2, VLP forms when the viral proteins S, M and E are co-expressed in eukaryotic producer cells, resulting in virus budding with absent genetic material [22, 23]. To date, there are only two vaccine candidates in clinical trial: RBD SARS-coV-2 HBsAg VLP vaccine developed by SpyBiotech/Serum Institute of India, and a plant-derived VLP adjuvanted with GlaxoSmithKline (GSK) or Dynavax adjuvants, but none of them, until now, have reached Phase3 [15].

Live attenuated virus vaccines (example Codagenix, India):

Attenuated strains are obtained after several *in vitro* viral passages, resulting in loss or mutation of virulence genes [24]. The production of live attenuated vaccines requires high biosafety-level facilities and they cannot be administered to immunocompromised patients. The main challenge of such platform in regard to SARS-CoV-2 is the potential for such strains to revert back to its pathogenic form, and since coronaviruses tend to recombine in nature, such theoretical risk of regaining of pathogenicity cannot be underestimated [25]. This explains the presence of only one live attenuated vaccine in clinical trial, the COVI-VAC vaccine developed by Codagenix/Serum institute of India. A brief summary of advantages and disadvantages of the above-mentioned platform is presented in **Table 1**.

Table 1. Brief summary of the major vaccine type and their associated Pros and Cons.

Vaccine type	Pros	Cons
Protein subunit	Strong antibody response Safe to administer Simple and cheap to produce Convenient storage (2-8^{O}C)	Memory of future responses is doubtful Need of repeated doses and adjuvants+
Recombinant viral vector vaccine	Strong antibody and T cell response Easy to produce Convenient storage (2-8^{O}C)	Safety is not clear in severely immunocompromised patients Efficacy in individuals with prior antibodies against Adv is diminished*

Vaccine type	Pros	Cons
DNA vaccine	Safe to administer to immunosuppressed patients Cheap and easy to produce	Might incorporate into host genome Require special mode of delivery (electroporation) Need for adjuvants+
RNA vaccine	Safe to administer to immunosuppressed patients Cheap and easy to produce No genomic integration	Unstable, need for complexing with lipids Needs storage under ultra-low temperature (ULT)
Inactivated virus	Stable and safe Convenient storage (2-8^{o}C)	Require booster shots to maintain immunity Need for adjuvants+
Virus-like particles	High humoral and cellular immune response Lack viral genome Convenient storage (2-8^{o}C)	Need for repeated dosages
Live attenuated virus	Long lasting immunity Convenient storage (2-8^{o}C)	High biosafety levels are needed in production Possibility to revert to infective wild form

*: The use of non-human adenoviral vector (simian) is an alternative. +: Concerns about adjuvants.

Insightful thoughts

Developing, approving and utilizing a successful-SARS-CoV-2 vaccine is a major step in controlling the current coronavirus pandemic, alleviating human suffering and beginning to return our lives to normalcy. However, the success of the vaccines in preventing morbidity and mortality depends on the success of vaccination, which in turn is dependent on many factors some of which include the health system but also the recipient. While this issue is beyond the scope of this paper, it should also be a subject of further study in our region in order to assure that the public is well informed about the vaccines and their effectiveness so as to gain the trust which is needed for the success of the effort. Essentially, the development of vaccines undergoes strict national and international regulation, but minor side-effects have always been encountered and the 100% efficacy of a vaccine is not always achieved. The same applies to the rapidly developed COVID-19 vaccines which have gained EUA. The developing apprehension among the medical community and public about taking the SARS-CoV-2 vaccine, especially the novel RNA based vaccines, is a prejudgment lacking scientific based evidence. No doubt the choice is debatable between some potential vaccine side effects or contracting the virus itself with all its related complications and associated damage. Whatever the government in any country chooses, it should take into consideration the cost, logistics and ensure equality and transparency aiming to embark on a national immunization plan to reach community protection antibody levels. Moreover, these vaccines are promising to have affectiveness against the emerging new variants.

Conclusion

The COVID-19 pandemic has taken the world by surprise and resulted in a significant health and economic burden. Moreover, it has affected all aspects of our lives, disrupting communities and resulting in severe economic, social, educational and cultural repercussions. In order to salvage this dismal situation, the world is in dire need of a vaccine to be implemented to achieve adequate levels of artificial herd immunity. This article briefly exposes the different available COVID-19 vaccine platforms, essentially focusing on those in late phases of clinical trials and clarifying the active mechanisms of the different novel vaccines. Such vaccines will complement

each other in order to target various sections of the community including those at high risk and the severely immunocompromised. Moreover, a global vaccination coverage will only be achieved by collaboration among various international organizations to operationalize an equal delivery of these vaccines so as to stop the virus spread and its devastating consequences.

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