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An Overview of COVID-19 Vaccines: Challenges of the Discovery and Development by the Pharmaceutical Industries

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Authors' contributions

This work was carried out in collaboration among all authors. Authors ANB, RD, CNF and EATF designed the study. Authors JF, DJF, KNK and ST did data mining and organization. Authors LBF, BEE and ZNI sorted information and wrote the first draft. All authors read and approved the final draft.

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Review Article

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ABSTRACT

The coronavirus (COVID-19) took the world by storm and triggered intensive research mobilization and action towards vaccines and drug repurposing. This pandemic triggered an emergence therapy intervention of which the development of new vaccine and drug repurposing were good options that was to be validated by regulatory authorities for potential use for enhancing acquired immunity for the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Prior to the outbreak that led to the global health emergency intervention, an understanding of the viral architecture, pathophysiology and mechanism of action and functions were well established. The global health disaster caused by COVID-19 has generated significant interest globally for research in vaccine discovery and development by many research institutions and Pharmaceutical sectors since 2019. So far, the approval of many clinical trials tested vaccines by the regulatory authorities have led to the need for post approval concerns of efficacy, safety and quality of these approved vaccines. This review paper attempts to explore the vaccines approved for global access to the population discovery and development process, the potential safety implications. An insight into other therapy options such as the convalescence plasma treatment and management for the global COVID-19 pandemic has been reviewed.

Keywords: Coronavirus; COVID-19; vaccine; SARS-COV-2; immunity; China.

1. INTRODUCTION

It was since 10th of January 2020 that the world came to witness the SARS-CoV-2 genetic sequence availability thanks to the genomic platform of the Global Initiative for Sharing the Avian Influenza Data (GISAID), and from the 19th of March 2020, the worldwide pharmaceutical industry declared a major engagement to research and provide a therapeutic solution for COVID-19 treatment/management [1,2]. Currently there are many developed and approved COVID-19 vaccines that have proven to be 95% efficacious in the prevention of symptomatic COVID-19 infections, and some vaccine are in progress at the clinical trials phase III studies [3]. As far back as March 2021, more than a dozen vaccines have successfully gone through regulatory approval for global use, most popular the two marketed RNA vaccines, (Pfizer-BioNTech vaccine and the Moderna vaccine), some four conventional inactivated vaccines, the Beijing Institute of Biological Products, Sinopharm (BIBP-CorV, CoronaVac, Covaxin, and coviVac) [3,4].

Some more vaccines that gained approval in the global market include; the four viral vector vaccines such as (Oxford-AstraZeneca vaccine, the Johnson and Johnson vaccine, Sputnik V, and the Convidicea), including the two protein subunit vaccines (EpiVacCorona and RBD-Dimer) [4-6]. It is worth noting that from March 2021, about 308 documented vaccine candidates have been reported, at different stages of development, with 73 in clinical research, some 24 more in phase 1 trials, 33 in phase I-II clinical trials, and 16 in Phase III clinical trials development [6-9].—The COVID-19 vaccines following their approval have been introduced and marketed in many countries worldwide. Some of the regulatory guidelines developed to determine a good vaccine before potential approval for human health and safety use includes the following;

- The vaccines have to show proof of efficacy (POE) and safety (POS) in a phase III multicenter clinical trials study [10-13]. Some COVID-19 vaccine candidates successfully gone through the phase III clinical trials for the development of many other potential vaccines.
- An independent institutional review board (IRB), for approval of study of the evidence of proof of efficacy (POE) and proof of safety (POS) is required for each vaccine candidate study, and also include regulatory review and approval of vaccines in the country where the vaccine was manufactured, before WHO can recommend the use of the vaccine candidate for prequalification approval. The Global Advisory Committee on Vaccine Safety (GACVS is considered to be involved or are part of the vaccine candidate review and approval process [11-13].
- The evidence of quality are requirements for review, for the purpose of supporting policy recommendations on developing the guide on how the vaccines should be used. This is in support of the vaccine data for regulatory requirements,

- The WHO external team of experts known as the Strategic Advisory Group of Experts on Immunization (SAGE), are required to analyzes the vaccine clinical trials results, together with the evidence on the disease state, the infected age groups, the disease predisposed risk factors, rational good use, and other important health information needed. SAGE can proceed in recommending how and when the vaccines should be used for possible disease interventions.
- Public Health personnel within their national regulatory policy within the different countries may take decisions on whether or not to approve the vaccines for national use and in developing policies on how the vaccine can be used in their country following the WHO recommendations.
- The vaccines requirement of scale up production to produce large quantities is mandatory, although large production has been a major challenging process so far, and also the management of cold particularly in low medium income countries (LMIC).
- The last step in vaccine development, necessitates that all vaccines approved must require quality distribution through a validated complex logistical process, with better stock management, temperature regulation in the cold chain management for quality process) [14].

Many countries currently have in place the implementation of structured distribution plans that gives priorities to those at highest risk of vaccine complications, such as the elderly, and those with predisposed high-risk factor of exposure and transmission, such as the healthcare workers community [15-17]. As from the 15th of March 2021, about 381.34 million doses of COVID-19 vaccine have been administered worldwide following the official reports from the National Health Agencies (NHA) [7,18]. AstraZeneca-Oxford are scheduled to produce about 3 billion doses of the vaccines by 2021, the Pfizer-BioNTech production anticipated production of about 1.3 billion doses, and Sputnik V, Sinopharm, Sinovac, and Johnson & Johnson about one billion doses each respectively.

The Moderna production targets was around 600 million doses and Convidicea 500 million doses in 2021 [18-22]. By the close of December 2020, more than 10 billion vaccine doses were preordered worldwide by many countries [23], with about half of the doses purchased and delivered for the developed nations which constitute just about 14% of the world's population [9, 24].

Before the emergence of COVID-19, there was no approved vaccine for an infectious disease therapy produced in less than 10 years [25], and no known vaccine discovered for the prevention of coronavirus infection in humans [26]. There have been vaccines developed for the prevention of many pathogens such as the infectious bronchitis virus in avian, canine coronavirus, and the feline coronavirus [2,27-29]. More studies for the discovery of vaccines for the viruses in the family Coronaviridae affecting humans have targeted the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) [6,30]. The vaccines for protection against SARS [31] and MERS [32] have been tested in non-human animals in preclinical studies [33].

Clinical trials studies conducted in 2005 and 2006, showed that the identification and development of new potential vaccines and drugs for the treatment and management of SARS became a priority for governments and state institutions [9,34-36]. As from 2020, a cure or protective vaccine has been developed with proven safety and efficacy against SARS in humans [3,37]. It is important to note that when MERS was reported, it was postulated that the existing SARS research may provide a useful platform for developing vaccines and therapeutic solution against a MERS-CoV infection [38-41]. As from March 2020, only one DNA based MERS vaccine has gone through the Phase I clinical trials in humans [42], and three other vaccines viral vectored vaccines were in progress, two adenoviral-vectored (ChAdOx1-MERS, BVRS-GamVac) and one MVA- vectored (MVA-MERS-S) [43, 89].

2. BACKGROUND HISTORY OF THE CORONAVIRUS VACCINE

After the isolation of the coronavirus 2019 [22], its genetic sequence was also published on the 11th of January 2020, to address the international emergency response in preparation of the effect of the outbreak and stimulate the development of a preventive COVID-19 vaccine [3,17,33]. From the onset of the early months of 2020, vaccine development was expedited via unprecedented collaboration within the multinational pharmaceutical industry and between governments support structures [20]. As of June

2020, tens of billions of dollars were put together to support investment by corporate organizations, governments, international health organizations, and university research institutions for vaccine candidates development research and to prepare for global vaccination programs for immunization against COVID-19 infection [15, 27,44].Through the Coalition for Epidemic Preparedness Innovations (CEPI) programme, the geographic distribution of COVID-19 vaccine development showed the North American communities having about 40% of the research activity when compared to 30% in Asia and Australia, 26% in Europe, and a few in significant projects in South America and Africa [3,28,41].

As from February 2020, the World Health Organization (WHO) made a declaration that the availability of a new vaccine for the management of acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was to be available in less than 18 months [9]. The concern of the COVID-19 pandemic fast rate of global infection during the early part of 2020 was a public health concern which led to the appeal for international alliances and government mobilization initiative to urgently organize resources to the development of multiple vaccines as a priority on a short-term agenda [25], with the declaration of four vaccine candidates progressing into clinical trials evaluation during the month of March 2020. Emergency use authorization for 12 vaccines were granted to National regulatory. Six of the twelve were approved for emergency or full use by WHO-with recognized stringent regulatory authorities.

By the 24 June 2020, China approved the CanSino vaccine for limited use in the military and two inactivated virus vaccines for emergency use in high-risk occupations [45]. As of 11 August 2020, Russia regulator approved the Sputnik V vaccine for emergency use, and one month later only a only small amounts of the vaccine were successfully, distributed for use outside of the phase 3 trial in Russia [9,46]. The Pfizer–BioNTech partnership on the 20 November, 2020, also filed for an Emergency Use Authorization (EUA) request to the FDA for the mRNA vaccine BNT162b2 (active ingredient lozinameran) [33,47]. The United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) on December 2020, gave a temporary regulatory approval for the Pfizer-Biotech vaccine [48,49], that became the first country to approve this vaccine and the first country in the Northern Hemisphere 21 December, many countries and the European Union [51] have authorized or approved the Pfizer–BioNTech COVID-19 vaccine. On the 11th of December 2020, the United States Food and Drug Administration (FDA) approved an Emergency Use Authorization (EUA) for the Pfizer–BioNTech COVID-19 vaccine [52] and a week later, they granted approval for an EUA for mRNA-1273, the Moderna vaccine [53]

2.1 The Potential Evaluation of Covid-19 Vaccine Efficacy

An understanding of the efficacy of a new vaccine is defined by its effectiveness during clinical trials evaluation process [14]. The efficacy is the risk of infection by the disease by vaccinated participants in the trial compared with the risk of getting the disease by unvaccinated participants [13]. An efficacy of 0% indicates that the vaccine is not effective (identical to placebo). An efficacy of 50% implies that there are half as many cases of infection as in unvaccinated participants [35]. It is quite challenging to compare the efficacies of the different vaccines considering that the clinical trials were conducted with different populations, geographic locations, and variants of the virus [23,36]. For the case of COVID-19, a vaccine efficacy of 67% may be enough to slow the pandemic, but this has to consider that the vaccine can perform sterilizing immunity necessary to prevent transmission [16].

Vaccine efficacy is a proof of efficacy (POE) of disease prevention, and indicates a poor transmissibility of SARS-CoV-2 considering that asymptomatic patients are known to express high infection rate [7,13]. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) developed a cutoff of 50% as the efficacy needed for the approval for a COVID-19 vaccine [1,17] which aims at a meaningful vaccination coverage rate of 75% of the population, while taking into consideration the actual basic reproduction number. The POE of a COVID-19 vaccine is projected to be at least 70% to achieve epidemic prevention of about 80% that may not necessitate implementation of barrier measures, such as social distancing [30]. To calculate the vaccine efficacy, symptomatic COVID-19 is globally defined as having done both the positive PCR test and at least one or more of the WHO recommended lists of COVID-19 symptoms, taking into consideration the variability in the exact specification between clinical trials [3]. The site of trial, study design can affect the reported vaccine efficacy

considering that there are country specific incidence and prevalence of SARS-COV-2 variants.

3. TYPES OF COVID-19 VARIANTS

The upsurge of a SARS-CoV-2 variant showing moderate or full resistant to an antibody response expressed by the new generation of COVID-19 vaccines may need a modification of the vaccines in development [36]. Clinical trials studies have confirmed that many vaccines developed for the initial COVID-19 strain have reduced efficacy for some emerging variants against symptomatic COVID-19 [5]. As reported since February 2021, the FDA consideration is that all FDA authorized vaccines showed efficacy in the protection of the circulating strains of SARS-CoV-2 [34].

3.1 SARS-COV-2 COVID-19 variant B.1.1.7

Reports published in December 2020, showed a new SARS-CoV variant B.1.1.7, that was first identified in the UK [4,19] and the early trials results of study indicated that there was protection of the UK variant using the existing Pfizer and Moderna vaccines [11,21,35]. Another study reported that the Oxford-AstraZeneca vaccine had an efficacy of 42–89% against the B.1.1.7 variant, with respect to 71–91% against non-B.1.1.7 variants [9,45]. Early preliminary data from a clinical trial on NovaVax vaccine showed that the vaccine reported about 96% efficacy for symptoms against the original variant, approximately 86% against B.1.1.7, and, 60% against the "South African" B.1.351 variant [21,28]

3.2 The SARS-COV-2 COVID-19 501.V2 variant

Moderna launched a clinical trial for the discovery and development of a new vaccine address the South African 501.V2 variant also known as the B.1.351 [14,37]. It was on 17 February 2021 that Pfizer reported that the neutralization activity of vaccine was capable of reducing by two-thirds the 501.V2 variant, without indicating any claims whether the efficacy of the vaccine in the prevention of illness for this variant be possible [42]. Johnson & Johnson on the other hand, in January 2021 conducted trials for its new Ad26.COV2. S vaccine in South Africa, and the report indicated that the level of protection shown on the moderate to severe COVID-19 infection was 72% in the United States and 57% in South Africa [41]. The Financial Times also published on 6 February 2021 that provisional trial data from a study conducted by South Africa's University of the Witwatersrand in collaboration with the Oxford University demonstrated reduced efficacy of the Oxford-AstraZeneca COVID-19 vaccine against the 501.V2 variant [23,40]. The study further indicated that with a sample size of 2,000 volunteers that participated in a study of the AZD1222 vaccine only a minimal protection was seen in all but the most severe cases of COVID-19 [2,7]. The Minister for Health for South Africa reported on 7 February 2021 the suspension of the planned deployment of around 1 million doses of the vaccine while there was examination of the data and awaiting expert advice before proceeding. [9].

4. COVID-19 VACCINE FORMULATION PROCESS

Eleven of the vaccine candidates in clinical development as of September 2020 were using adjuvants to enhance immunogenicity [12]. An immunological adjuvant is a substance formulated with a vaccine to enhance the immune response to an antigen [42], such as the case of COVID-19 virus or influenza virus [8]. An adjuvant may be used in a more specific manner in formulating a COVID-19 vaccine candidate to boost its immunogenicity and efficacy and to reduce or prevent COVID-19 infection in vaccinated patients [45]. Adjuvants used in COVID-19 vaccine formulation may be particularly used effectively for technologies that use the inactivated COVID-19 virus and recombinant protein-based or vector-based vaccines [19]. There are reported cases of the use of aluminum salts, known as *alums,* that were the first reported adjuvant used for licensed vaccines, and are the gold standard adjuvant of choice in some 80% of adjuvant vaccines [37]. The alum adjuvant is known to initiates a series of diverse molecular and cellular mechanisms to boost immunogenicity, and the release of proinflammatory cytokines [42].

5. PLANNING AND DEVELOPMENT OF COVID-19 VACCINES

Vaccine development from the early 2020, has been fast-tracked thanks to emergency collaboration in the multinational pharmaceutical industry, multiple stakeholders and the governments in some cases [45]. Following the declaration by the Coalition for Epidemic Preparedness Innovations (CEPI), the geographical distribution of COVID-19 vaccine

development shows that North American entities having about 40% of the trial with respect to 30% in Asia and Australia, 26% in Europe, and a few least documented projects in South America and Africa [46-48]. Many regulatory procedures following the complete vaccine development process have been evaluated, and considers the following aspects during the evaluation [13, 49, 50]

- Consideration of the safety based on the level of acceptable toxicity of the vaccine.,
- Issues of the vulnerability of the populations who are the main actors in clinical trials study participation,
- priority should be given for the vaccine efficacy breakthroughs,
- emphasis must be placed on the duration of vaccination protection capacity,
- Consideration on a special develop delivery systems such as oral or nasal, rather than by injection,
- A clear dose response regimen must be in implementation,
- Special consideration on the importance of the vaccine stability and storage condition specificity characteristics such as the cold chain quality assurance,
- An emphasis must be placed on the emergency use authorization before formal licensing is granted,
- There should be a developed platform for optimal manufacturing for scale up production of billions of doses [50],
- A well-developed structure channel for the dissemination and rapid distribution channel and access of the approved vaccine.
- The clinical dosing trials must run simultaneously over months, and potentially compromising efficacy, safety and quality assurance [6,53,54].

6. CASE STUDY OF THE CHINESE VACCINE DEVELOPMENT AS A MODEL FOR THE LOW MEDIUM INCOME COUNTRIES

The Chinese is considered as a vaccine in this case study within the regulatory point of view for a low middle income country (LMIC). It was reported that the Chinese vaccine developers and the Chinese government through the Chinese Centre for Disease Control and Prevention began their COVID-19 vaccine development mobilization research in January 2020 [55, 56]. By March 2020 there were promising mobilized progress and follow up of many vaccine candidates, which demonstrated the Chinese state of the art drug discovery technology strength [56, 57]. The objective of the Chinese vaccine developers was to reassure the Chinese population on the hope of producing a new vaccine to address the pandemic, and guarantee the potential efficacy, safety quality of the vaccine [58-60]. The rapid development and the urgent need to produce a vaccine for the COVID-19 pandemic in China have potential risk implication of adverse risks and failure rate of delivering a safe, effective vaccine [4,61]. In addition, preclinical and clinical research at the universities and research institutions have been hindered by physical distancing and closing of laboratories [21,49,62]. The vaccines development made progress through several phases of clinical trials to evaluate for safety, immunogenicity, efficacy, dose range and drug interactions, adverse effects [11,17,63]. The Chinese vaccine developers had obligation to invest much resources internationally to source out enough participants for Phase II–III clinical trials when the virus was proven to be a moving target and changing transmission rate across and within countries, now that effect forced companies to compete for trial participants [64-66]. China has also taken a step forward to provide low-rate loans to vaccine developers through its central bank and has readily made land available for the company to build production plants [27,77]. Three Chinese vaccine companies and research institutes are supported by the government for financing research, conducting clinical trials, and manufacturing [40].

The Clinical trial organizers had other challenges of having participants in the community not consenting to be vaccinated due to vaccine hesitancy, and with no spirit of voluntarism there was no will to be *guinea pigs,* for a very new vaccine to hit the market and with no long history of safety yet [19,68]. There was also the tendency of disbelieving the science of the vaccine technology and the ability to prevent COVID-19 infection [3,69]. Even though, new vaccines have been developed during the COVID-19 pandemic, regulatory approval/licensure of COVID-19 vaccine candidates still require submission of a full dossier of information on the discovery, development and manufacturing quality to the competent regulatory authority, and this has been a major challenge especially for resource limited countries [23,70-71].

7. COVID-19 VACCINE DEVELOPMENT CHALLENGES

Several potential challenges have been reported with the development of COVID-19 vaccine. The need for an emergency development of a vaccine for COVID-19 has led to fast tracking schedules that shortened the standard vaccine development timeline, and in many cases the obligation of combining clinical trial process over months, a process that normally takes over 10 years in a typically conducted sequential vaccine studies [51,52]. The timelines for the conduct of clinical research is a sequential process which requires many years of studies, now compressed for a short duration to generate efficacious, safe and quality vaccines.

8. COVID-19 VACCINE ORGANIZATIONS

Globally, the access to COVID-19 tools accelerator is a G20 and World Health Organization (WHO) initiative that was put in place as of April 2020 [46,72]. This is composed of a multidisciplinary support structure to facilitate partners to share resources and knowledge. They as made up of four main actors, each coordinated by two to three collaborating partners: Vaccines known as 'COVAX', Diagnostics, Therapeutics, and Health Systems Connector [44,61,73].The WHO's April 2020 research and development Blueprint for the novel Coronavirus reported a large international, multi-site, individually randomized controlled clinical trial that permits the progressive evaluation of the benefits and risks of each potential promising vaccine candidate within 3–6 months of consideration for the clinical trial [29,74]. The WHO vaccine coalition has prioritized which vaccines should go into Phase II and III clinical trials, and put in place a framework for the harmonization of Phase III protocols for all vaccines that have gone through the pivotal development stage [45,75].

National governments in developed countries are implicated in vaccine development. For example, Canada engaged in funding 96 research vaccine projects at Canadian companies and universities, with plans of developing a *vaccine bank* that could be used for future coronavirus outbreaks [46,76], and also to encourage clinical trials, develop manufacturing and supply chains for new vaccines [3,47,76]. Great Britain on the other hand formed a COVID-19 vaccine task force in the month of April 2020 to boost local efforts for accelerated development of a vaccine through collaborations with the industry, universities, and government agencies, integrating every phase of development from research to manufacturing [14,78]. [49]. In the United States also, the Biomedical Advanced Research and Development Authority (BARDA), which is a federal agency funding disease-fighting technology, announced potential funding mobilization investments to support American COVID-19 vaccine development and manufacture of the most promising COVID-19 vaccine candidates [27,79]. Most pharmaceutical companies with track record in vaccine discovery and development such as Pfizer, Johnson & Johnson, AstraZeneca, and GlaxoSmithKline (GSK), have formed alliances with biotech companies, governments, and universities to accelerate progression in developing an effective COVID-19 vaccine [41,80].

9. MAJOR TYPES OF COVID-19 VACCINE

To date there are four major categories of vaccines in clinical trials namely; the whole virus, protein subunit, viral vector and nucleic acid (RNA and DNA) [5,14,81]. Some of the vaccine functions by ingress of the antigen into the body, others use the body's own cells (biologics) to make the viral antigen.

9.1 Whole Virus

Most conventional vaccines exploit the whole viruses to trigger an immune response, using two main strategic approaches. The live attenuated vaccines which uses a weakened form of the virus (avirulent), that can still replicate without causing illness [83]. The inactivated vaccines which use viruses whose genetic material composition has been destroyed so that they cannot replicate, but are capable of triggering an immune response. Both types of viruses can use well established technology and pathways for regulatory approval, but live attenuated vaccines have the risk of causing disease in subjects predisposed with weak immune system [1, 14, 33] and the vaccine will always require careful cold storage, making their use in most cases more challenging, especially in low-resource countries [84]. Inactivated virus vaccines can however, be given to patients with compromised immune systems, but might also need cold storage [17].

9.2 Protein Subunit

The protein subunit vaccines are well developed by using the fragments of the pathogen like protein to necessitate trigger of an immune

response thereby minimizing the risk of adverse effects, although in most cases may weaken the immune response [12, 85] and therefore will require adjuvants, to boost the immune response. An example of the protein subunit vaccine is the hepatitis B vaccine.

9.3 The Nucleic Acid Vaccine

Nucleic acid vaccines development exploits the use of the genetic material of RNA or DNA to provide the cells with the genetic instructions use for producing antigens. In the case of COVID-19 vaccines, the vaccine target is usually the viral spike protein [29]. Once this genetic material gain access into the human cells, it uses the cells' protein factories to make the antigen that has the capability to trigger an immune response [86]. The advantages of the nucleic acid vaccine are the fact that they are cheap and readily available and their ease to use. Since the antigen is produced inside the human cells in large quantities, the immune reaction is usually strong. The disadvantage of nucleic acid vaccine is that no DNA or RNA vaccines till date have been approved for human use, which is a major challenge for regulatory approval. Furthermore, the RNA vaccines require storage under ultra-cold temperatures, -70 ºC or lower, which poses a big challenge for countries that do not have specialized cold chain facilities, particularly in low resource countries.

9.4 Viral Vector

Viral vector vaccines work mainly by providing cells genetic instructions to produce antigens. However, this vector differs from others due to the fact that they use an avirulent virus, different from the one the vaccine is targeting, to deliver these instructions into the cell [27]. One type of virus well reported for use as a vector is the adenovirus, which causes common cold. Nucleic acid vaccines differ from viral vector vaccines in that the human cellular machinery is hijacked to produce the antigen from those instructions, in order to trigger an immune response, while the viral vector vaccines can act like the natural viral infection and likely to trigger a strong immune response. There are possibilities that many people may have already been exposed to the viruses being used as vectors, while some may be immune to it, rendering the vaccine less effective [70]. The three main types of vaccine responses for: (1) RNA vaccine, (2) subunit vaccine, (3) viral vector vaccine are well illustrated in Fig. 1.

Since January 2021, nine different technology platforms of numerous candidates still undefined have been under research and development for developing effective vaccines against COVID-19 [30]. Most of the vaccine candidate's platform in clinical trials are focused on the coronavirus spike protein and its variants as the primary antigen of COVID-19 infection [60,82]. Platforms developed in 2020 involved the nucleic acid technologies, (nucleotide-modified messenger RNA and DNA), non-replicating viral vector, peptides, recombinant proteins, live attenuated viruses, and inactivate viruses [17,45,72].

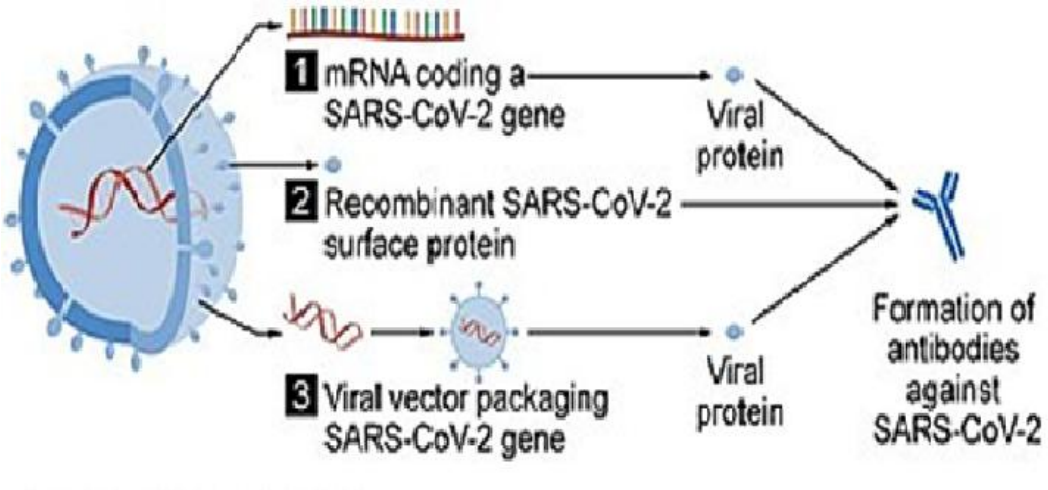

Fig. 1. Shows the three vaccine types that forms the SARS-CoV-2 proteins to produce an immune response: (1) RNA vaccine (2) subunit vaccine, (3) viral vector vaccine [17]

Many vaccine technologies in development for COVID-19 are not like vaccines already in use to prevent influenza, but rather they are using the next generation strategies for precision on COVID-19 infection mechanisms [11]. Vaccine development platforms may enhance the chances of antigen manipulation and effectiveness for targeting mechanisms of COVID-19 infection in susceptible population subgroups, such as healthcare personnel, the elderly, pediatrics, pregnant women (vulnerable groups), and people with existing weakened immune systems [84].

9.4.1 RNA vaccines

The RNA vaccine contains RNA which when introduced into a tissue can act as a messenger RNA (mRNA) that is capable of causing the cells to build the foreign protein and stimulate an adaptive immune response which controls the body to identify and destroy the target pathogen or cancer cells [49]. RNA vaccines often use nucleoside-modified messenger RNA which is achieved by a coformulation of the molecule into lipid nanoparticles and protect the RNA strands to enhance their absorption into the cells [88]. RNA vaccines were reported as the first COVID-19 vaccines to be authorized in the United States and the European Union [23, 86]. Since January 2021, the authorized RNA vaccines were the Pfizer-BioNtech COVID-19 [90] and the Moderna COVID 19 vaccine [91]. As of February 2021, the CVnCoV RNA vaccine from CureVac was in progress for approval in the EU [91,92]. The RNA vaccine (Messenger RNA) is illustrated in Fig. 2.

9.4.2 Adenovirus vector vaccines

These vaccines belong to the non-replicating viral vectors, and uses an adenovirus shell containing DNA that encodes a SARS-CoV-2 protein [35, 93]. The viral vector-based vaccines for COVID-19 protection and management are non-replicating in nature, and thus they do not make new virus particles, instead they rather produce only the antigen which triggers a cascade of systemic immune response [17, 93]. Since January 2021, the known approved adenovirus vector vaccines are the British Oxfors-AsraZeneca COVID-19 vaccine 94], Russian Sputnik V [95], Chinese Convidicea, and the Johnson & Johnson COVID-19 vaccine [90, 96]. The Convidicia and Johnson and Johnson vaccine on one hand are both one-shot vaccines which offer less complication in management; and has the advantage that they can be stored under ordinary refrigeration for several months [97]. Sputnik V on the other hand, uses the Ad26 for the first dose similar to Johnson & Johnson vaccine and Ad5 for the 2nd dose the same as Convidicea with a similar single dose efficacy and full clinical trial was conducted on single dose effectiveness [95].

9.4.3 Inactivated virus vaccines

Inactivated vaccine is made up of virus particles that have been cultured and then killed using heat or formaldehyde method to render virus avirulent (reduce disease producing capacity) but still capable producing an immune response [25]. Since January 2021, the approved inactivated virus vaccine type is the Chinese CoronaVac [97], BBIBP-CorV, [98] the Indian Covaxin, and also including the CoviVac [99]. The other vaccines with clinical trials in progress include the Valneva COVID-19 vaccine [78,100].

9.4.4 Subunit vaccines

This group of vaccine have one or more antigens without introducing whole pathogen particles. The antigens in this group are usually protein subunits, but can also be any molecule that constitutes a fragment of the pathogen [101]. Since January 2021. So far, the only approved vaccine of this subunit is the peptide vaccine EpiVacCorona [23, 102]. Some of the vaccines under progress in clinical trials include the Navavax COVID-19 vaccine [12,44] and RBD-Dimer [3,103]. The V451 vaccine progressed to clinical trials but was met with major challenges that led to attrition and terminated for safety issues as it was reported that the vaccine could potentially cause false or incorrect results for subsequent HIV testing [67, 85].

9.4.5 Other types

Other types of vaccines that are reported in clinical trials include multiple DNA plasmid vaccine [94, 98] at least two lentivirus vector vaccines [98] a conjugate vaccine, and a vesicular stomatitis which has the SARS-CoV-2 spike protein [99]. Scientists investigated if existing vaccines for unrelated conditions could enhance the immune system and lessen the severity of COVID-19 infection [83]. There is experimental evidence that the BCG vaccine for tuberculosis has non-specific effects on the immune system, but show no evidence that this vaccine is effective against COVID-19 [29].

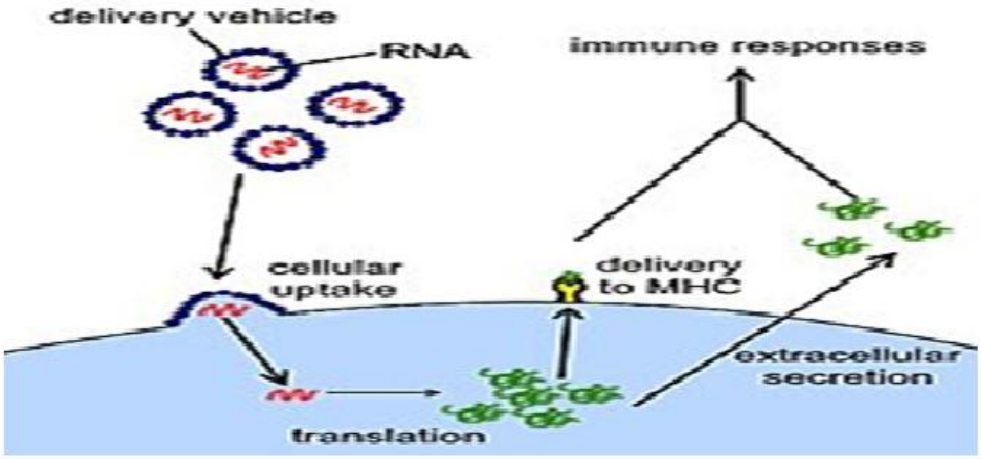

Fig. 2. Schematic diagram to illustrate the operation of an RNA vaccine. The mRNA contained in the vaccine enter the cells and is translated into foreign proteins, which trigger an immune response [27]

10. OVERVIEW OF THE VACCINE APPROACH FOR THE MANAGEMENT OF COVID19 PANDEMIC

10.1 Post-Vaccination Embolic and Thrombotic Clinical Adverse Events

Post-vaccination embolic and thrombotic events, also termed vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) [101] or vaccine-induced immune thrombotic thrombocytopenia (VITT) [102, 103] are reported rare types of blood clotting event that were initially observed in a very small number of people who had previously received the Oxford-AstraZeneca COVID-19 vaccine (AZD1222) during the COVID-19 pandemic [101, 104]. It was later also described in the Johnson & Johnson COVID-19 vaccine [108], leading to suspension of its use until its safety had been reassessed [105-107].

In April 2021, AstraZeneca and the EMA updated their information for healthcare professionals about AZD1222, saying that it was important that there was a causal relationship between the vaccination and the occurrence of thrombosis in combination with thrombocytopenia and that even though such adverse reactions were very rare, they exceeded what would be expected in the general population [105, 106]. Guidelines from professional societies recommend treatment with alternative anticoagulants instead of heparin, as there is a possibility that it may aggravate the phenomenon [100].

11. SIGNS AND SYMPTOMS

11.1 Thrombosis

The thrombosis events linked to the COVID-19 vaccine may occur 5-28 days after its administration to patients. Several unusual types of thrombosis have been frequently reported in patients [109]: There has been cerebral venous sinus thrombosis and thrombosis of the splanchnic veins. Cerebral venous sinus thrombosis is known to cause severe headache, stroke-like symptoms (weakness of the limb and/or facial muscles), seizures and coma [15, 107]. The Splanchnic vein thrombosis may cause abdominal pain accumulation of fluid in the abdominal cavity and gastro intestinal bleeding [107,110].

Other forms of thrombosis, such as the pulmonary embolism and arterial thrombosis are known to occur and has been well documented [108]. The low platelet count seen in patients may manifest as tiny blood spots under the skin beyond the site of the injection [108]. Disseminated intravascular coagulation (DIC), diffuse formation of blood clots throughout the blood vessels of the body, has been shown as part of the syndrome [109]. DIC may cause many types of symptoms, such as abnormal bleeding, breathlessness, chest pain, neurological symptoms, low blood pressure, or swelling [21, 110]. COVID-19 vaccines have demonstrated some adverse effects that are listed as common in the two- or three-days following vaccination which are often mild and temporary in nature [19]. The rare simultaneous occurrence of

thrombocytopenia (low blood platelets) with blood clots after vaccination raised the original concern about this condition [47, 111]. In many cases where acute thrombosis and thrombocytopenia have been reported together after COVID-19 vaccination, an antibody against platelet factor has been identified [22, 112]. This phenomenon is mostly seen in patients who have been administered heparin, but none of the reported cases had received heparin [24]. Very rarely, this phenomenon had been described as an autoimmune phenomenon in patients not yet exposed to heparin [19, 57, 113].

One striking feature of thrombocytopenia in the presence of anti-PF4 antibodies is the ability of some patients to develop thrombosis, a phenomenon called heparin-induced thrombocytopenia, where heparin administration is involved [30, 114]. Thrombocytopenia is generally a common symptom after many viral infections [9] and it has generally been reported after administration of adenoviral gene transfer vectors [11, 66, 115], even though the mechanisms of action are not well understood. There is no confirmed causal relationship to the syndrome and any COVID-19 vaccination [45]. However, EMA has launched studies for the investigations into AZD1222 and the Johnson and Johnson COVID-19 (Janssen) vaccine (J&J) for possible causal links [88]. On 7th of April 2021 the EMA noted one plausible explanation for the combination of blood clots and low blood platelets is an immune response, leading to a condition similar to the one seen most often in patients treated with heparin, that is heparin induced thrombocytopenia (HIT) [109].

12. CONVALESCENCE PLASMA THERAPY APPROACH

Convalescent plasma has increased more interest during the early days of the coronavirus disease in 2019 (covid-19) pandemic because of some understanding of its mechanism of cation. In addition, the impact and importance of its100-year history of use in the treatment of other infectious diseases, and coupled with the easy availability to get from voluntary donors [111,113]. In a related PLACID clinical Trial, Agarwal and collaborators evaluated convalescent plasma for the treatment of moderate covid-19 in patients admitted into hospitals in India [107,112]. The PLACID Trial was a rigorous randomized controlled study of global importance, ethically designed and implemented given the contemporaneous state of scientific knowledge about SARS-CoV-2. The strengths of the study included a primary hard outcome meaningful to patients, proper patient enrollment with no exclusions for comorbidities, careful consideration of donor selection and safety screening of donated plasma, post facto quantitative testing of antibody titers in all plasma samples, assessment of secondary patient outcomes, and evaluation of the efficacy of the subsample of plasma donations that consisted of the detectable titers of antibodies to severe acute respiratory coronavirus 2 (SARS-CoV-2), the causal agent of covid-19 [32,115].

In a prespecified with the intention-to-treat analyses of the PLACID Trial, investigators reported no net benefit associated with convalescent plasma in patients admitted to at the hospital with moderate covid-19 [114, 115]. The main primary outcome (progression to severe disease or all-cause mortality at 28 days) occurred in 19 % (44/235) of patients in the intervention arm and 18 % (41/229) of patients in the control arm (risk ratio of 1.04, 95 % confidence interval 0.71 to 1.54) [107, 115]. Limitation of the comparison to the subset of patients who received plasma with detectable antibody titers did not change the outcome. The primary hypothesized mechanism of benefit from convalescent plasma is based on direct antiviral action of neutralizing antibodies on SARS-CoV-2 RNA [105, 115] In the PLACID Trial, there as a significant statistical difference, at 20 % higher rate of conversion with respect to a negative result for SARS-CoV-2 RNA occurring on day 7 among patients in the intervention arm.

The most common use of therapeutic plasma, which contains more than 1000 different proteins, is for the management of acute bleeding and complex coagulopathies [5, 106, 112]. Despite the presence in plasma of anticoagulation factors such as antithrombin and protein C, the net effect of plasma is prothrombotic. Immunoglobulin therapy, derived from whole plasma, is subjected to a US Food and Drug Administration warning about the risks of thrombosis, particularly in older vulnerable patients, particularly for those with predisposing cardiovascular risk factors, and hypercoagulable conditions [108]. It has been established that COVID-19 is a life-threatening thrombotic disorder and an excellent recent pathophysiology synthesis has concluded that SARS-CoV-2 does not only produces an inflammatory and hypercoagulable condition, but can also cause a hypo-fibrinolytic state not regularly observed with most other types of

coagulopathy [108]. Most recently, plasma from convalescent COVID-19 patients has been shown to directly for *in vitro* studies, cause endothelial cell damage [115].

12.1 Principles of targeting cells' 'trash compactor' as a potential lead to a new antiviral to fight COVID-19 infection and management

COVID-19 is an emerging and rapidly evolving pandemic in which the National Institute of Health (NIH) group of scientists have discovered a key pathway in lysosomes that coronaviruses are capable of exploiting to exit the cells. The principles of Targeting cells' 'trash compactor' could possibly lead to a potential new antiviral to fight COVID-19 infection and management [29,32,112]. A biological pathway has been studied that the novel coronavirus is capable of using to integrate in order to exit cells as it spreads through the body. A better understanding of this important pathway may provide an insight into the possibility of blocking the transmission of the SARS-CoV-2 virus, the causal agent of COVID-19 disease [88,112].

In cell studies, it has been reported for the first time by group of researchers that the coronavirus can exit infected cells through the lysosome, which is an organelle known as the cells' *"trash compactor."* The lysosome normally plays a role of destroying viruses and other pathogens before they leave the cells. However, it has been discovered that the coronavirus deactivates the lysosome's disease-fighting mechanism, thus permitting the virus to freely spread throughout the body [14,39,107]. Strategy to target this lysosomal pathway could lead to the development of a new and more effective antiviral therapies to fight COVID-19. This finding is a new hope and come at a time when new coronavirus cases are surging worldwide, with related U.S. deaths nearing 225,000 [41,113].

Scientists have so far understood that viruses enter and infect cells and then use the cell's protein-making machinery to make multiple copies of themselves before exiting the cell. However, researchers have only a limited understanding of how viruses specifically exit the cells. An illustration on how the virus exit the cells through lysosomes is shown in Fig. 3.

This illustration shows components of the lysosome exocytosis pathway, which coronaviruses can use to exit cells. Also shown are components of the normal biosynthetic secretory pathway.

It is general understood that most viruses including influenza, hepatitis C, and West Nile viruses exit cells through the so-called biosynthetic secretory pathway [9, 114]. That is the central pathway that cells use to transport hormones, growth factors, and other materials to their surrounding environment. Studies have demonstrated that coronaviruses also use this pathway. In a pivotal experiment, it has been reported that something different that exposes coronavirus-infected cells (specifically, mouse hepatitis virus) to certain chemical inhibitors known to block the biosynthetic pathway [15]. It is interesting to note that the coronaviruses can get out of the cells intact and this has given the first clue that maybe coronaviruses are using another pathway to exit cells. In order to understand the pathway, some scientist have designed additional experiments using microscopic imaging and virus-specific markers involving human cells. They have discovered that coronaviruses somehow target the lysosomes, which are highly acidic, and congregate there [44, 112]. This finding has raised yet another question that if the coronaviruses are accumulating in lysosomes and lysosomes are acidic, why are the coronaviruses not destroyed before exiting?

In a series of advanced studies, it has been demonstrated that lysosomes get de-acidified in coronavirus-infected cells, significantly weakening the activity of their destructive enzymes. Consequently, the viruses remain intact and ready to infect other cells when they exit [28, 60, 106]. This has demonstrated that the coronavirus is well adapted to using these lysosomes to get out, but they are also disrupting the lysosome to carry out its normal function. Studies have also shown that the disruption of the normal lysosome function appears to harm the cells' immunological machinery. This very fundamental cell biology finding could help explain some of the issues that are observed in the clinic regarding immune system abnormalities in COVID patients like the cytokine storms, in which an excess of certain pro-inflammatory proteins in the blood of COVID patients invades the immune system and cause high death rates [11,96,115].

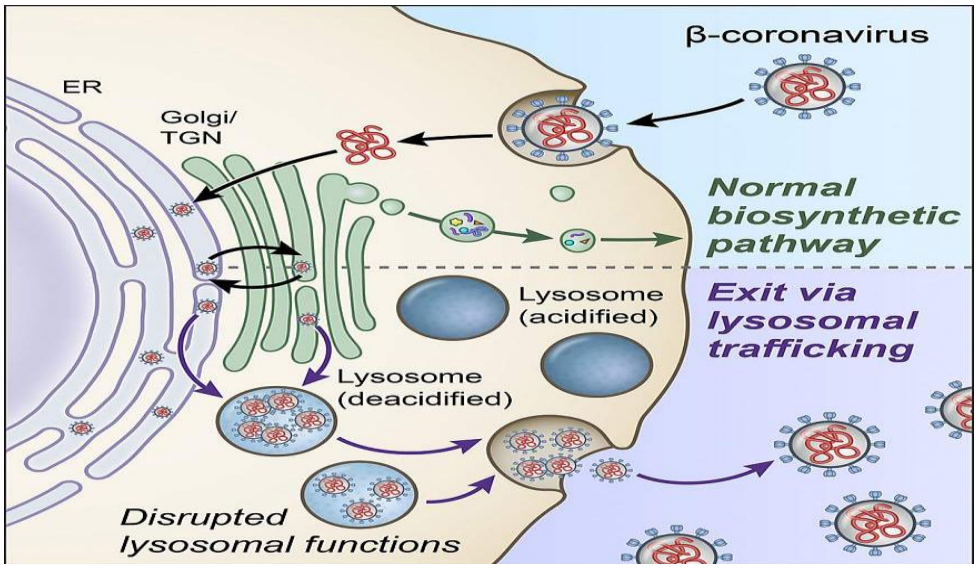

Fig. 3. Exit of viruses through the Biosynthetic secretary pathways [113]

With the identification of this mechanism, researchers may be able to find ways to disrupt this pathway and prevent lysosomes from delivering viruses to the outside of the cell; or re-acidify lysosomes in order to restore their normal functions in coronavirus-infected cells so they can fight COVID-19 infections [88]. One experimental enzyme inhibitor has already been identified that can potentially block coronaviruses from getting out of the cell. The lysosome pathway offers a whole different way of thinking about targeted therapeutics and further studies are needed to determine if such interventions can be effective and whether existing drugs can help block this pathway [41,112].

13. CONCLUSION

Many important questions on effectiveness of COVID-19 vaccines are still to be answered within the context of the current pandemic outbreaks. Further studies need to be conducted on post-introduction vaccine efficacy for particular countries in order to address these questions. COVID-19 vaccination has the ability to confer immune protection of the population from COVID-19 infection. The elderly and pediatric population are the vulnerable groups that are predisposed to have some more adverse effects from the vaccine, which are considered as normal signs that the body has developed a defense or protection against the virus. These side effects have the potential to significantly affect patients from performing their normal daily activities, although the effects may subside in a few days. Some subjects may not show observable side effects, and allergic reactions may be rare. Serious adverse effects (SAE) that could cause a long-term health problem are often unlikely following any COVID-19 vaccination. Vaccine monitoring generally has shown that side effects may happen within six weeks of exposure to a vaccine dose. The benefits of COVID-19 vaccination outweigh the known and potential risks.

It is reported that with the increasing vaccine hesitancy especially in limited resources countries couple with the limited access to vaccine, there is an increasing need for capacity building in order to sensitize actors and stake holders for a better understanding of potential vaccine side effects. There is also the possibility to explore the effectiveness of herd immunity protection from vaccinated population and those acquired from unvaccinated population. More studies on the toxicity of COVID-19 vaccines and other therapeutics drugs are still in need of potential exploitation, to further a continuous development and improvement on new therapeutic indications.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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