Review Article

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AN OVERVIEW OF COVID-19 VACCINES AND THE CHALLENGES OF THE PHARMACEUTICAL INDUSTRY

ABSTRACT

The coronavirus (COVID-19) took the world by storm and triggered intensive research mobilization and action towards vaccines and drug repurposing. This led to more vaccine development followed by regulatory approval for use to enhance 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 therapy approach in the management of the global COVID-19 pandemic has been reviewed.

Key words, coronavirus, COVID-19, vaccine, SARS-COV-2, immunity, China,

INTRODUCTION.

It was on 10th of January 2020 that the world was informed on the SARS-CoV-2 genetic sequence availability through the genomic platform of the Global Initiative on Sharing Avian Influenza Data (GISAID), and by the 19th of March 2020, the global pharmaceutical industry declared a major commitment to find therapeutic solution for COVID-19 management [1, 2]. So far, many COVID-19 vaccines have proven to be 95% effective in preventing symptomatic COVID-19 infections at the clinical trials phase III studies [3]. Since March 2021, more than a dozen vaccines have successfully gained regulatory approval for public use, most especially 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].

Other vaccines that have made progress in the market include; the four viral vector vaccines (Sputnik V, the Oxford-AstraZeneca vaccine, Convidicea and the Johnson and Johnson vaccine), in addition to two protein subunit vaccines (EpiVacCorona and RBD-Dimer) [4-6]. It is worth noting that since March 2021, approximately 308 vaccine candidates have been at different stages of development, with 73 in clinical research, in addition to 24 in phase 1 trials, 33 in phase I-II trials, and 16 in Phase III development [6-9]. The COVID-19 vaccines after approval have been introduced and marketed in many countries round the world. Some of the regulatory guidelines for consideration to determine a good vaccine prior to 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 review of the evidence of proof of efficacy (POE) and proof of safety (POS) is mandatory for each vaccine candidate, which include regulatory review and approval in the country where the vaccine is manufactured, before WHO can recommend the vaccine candidate for prequalification approval. Part of this review and approval process involves the Global Advisory Committee on Vaccine Safety (GACVS) [11-13].
- In addition to the review of the vaccine data for regulatory requirements, the evidence of quality must also be reviewed for the purpose of policy recommendations on setting the guide on how the vaccines should be used.
- An external team of experts constituted by WHO, called the Strategic Advisory Group of Experts on Immunization (SAGE), must analyzes the vaccine clinical trials results, alongside the evidence on the disease, affected age groups, the disease risk factors, rationale use, and other relevant information. SAGE then further recommends when and how the vaccines should be used in disease interventions.
- Public Health Officials within their national regulatory policy in different countries could decide whether to approve the vaccines for national use and develop policies for how to use the vaccines in their country based on the WHO recommendations.
- The vaccines must be manufactured in large quantities, that is scale up production is required, which has been a major challenging process so far, and cold chain management in low medium income countries.
- The final step, requires that all approved vaccines need quality distribution through a complex logistical process, with rigorous stock management and temperature control in the cold chain regulatory quality process) [14].

Many countries so far, have put in place the implementation of phased distribution plans that prioritize those at highest risk of complications, such as the elderly, and those at high risk of exposure and transmission, such as healthcare workers [15-17]. Since the 15th of March 2021, 381.34 million doses of COVID-19 vaccine have been administered worldwide based on official reports from National Health Agencies (NHA) [7,18]. AstraZeneca-Oxford has anticipated producing 3 billion doses by 2021, Pfizer-BioNTech 1.3 billion doses, and Sputnik V, Sinopharm, Sinovac, and Johnson & Johnson 1 billion doses each. Moderna production targets of 600 million doses and Convidicea 500 million doses in 2021 [18-22]. By December 2020, more than 10 billion vaccine doses were preordered by many countries globally [23], with about half of the doses purchased by developed countries which comprises just 14% of the world's population [9, 24].

Before the onset of COVID-19, a vaccine for an infectious disease had never been produced in less than 10 years [25], and no vaccine is in existence yet for preventing a coronavirus infection in humans [26]. However, vaccines have been developed against many pathogens caused by coronaviruses, including, the infectious bronchitis virus in avian, canine coronavirus, and the feline coronavirus [2, 27-29]. Earlier studies to develop vaccines for viruses in the family Coronaviridae that affect humans have been aimed at severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) [6, 30]. Vaccines against SARS [31] and MERS [32] have been tested in non-human animals in preclinical studies [33].

Studies reported in 2005 and 2006, showed that the identification and development of novel vaccines and drugs for the treatment and management of SARS was a priority for governments and state institutions, public health sectors globally at that time [9, 34-36]. Since 2020, there was no cure or protective vaccine proven to be safe and effective against SARS in humans [3, 37]. There was no proven existence of vaccine against MERS [38]. It is worth noting that when MERS was prevalent, it was assumed and postulated that the existing SARS research may provide a useful template for developing vaccines and therapeutic solution against a MERS-CoV infection [39-41]. Since March 2020, there was just one (DNA based) MERS vaccine that has gone through the Phase I clinical trials in humans [42], and three others in progress, all belonging to the viral-vectored vaccines: two adenoviral-vectored (ChAdOx1-MERS, BVRS-GamVac) and one MVA- vectored (MVA-MERS-S) [43].

Background history of the coronavirus vaccine:

After the coronavirus was isolated in December 2019 [22], its genetic sequence was published on 11th of January 2020, unlocking an emergency international response to prepare for an outbreak and speed up development of a preventive COVID-19 vaccine [3, 17, 33]. As from the early months of 2020, vaccine development was expedited via unprecedented collaboration within the multinational pharmaceutical industry and between governments [20]. In June 2020, tens of billions of dollars were available for investment by corporations, governments, international health organizations, and university research groups to develop many vaccine candidates and prepare for global vaccination programs for immunization against COVID-19 infection [15, 27, 44]. Following the Coalition for Epidemic Preparedness Innovations (CEPI), the geographic distribution of COVID-19 vaccine development place North American entities having about 40% of the activity compared to 30% in Asia and Australia, 26% in Europe, and a few projects in South America and Africa [3, 28, 41].

In February 2020, the WHO declared they did not expect a vaccine against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative virus, to become available in less than 18 months [9]. The rapidly growing infection rate of COVID-19 worldwide during early part of 2020 then called for international alliances and government efforts to urgently organize resources to make multiple vaccines a priority on shortened timelines [25], with four vaccine candidates entering clinical trials evaluation in March 2020. National regulatory authorities granted emergency use authorizations for twelve vaccines. Six of those were approved for emergency or full use by at least one WHO-recognized stringent regulatory authorities.

On 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]. On 11 August 2020, Russia declare the approval of her Sputnik V vaccine for emergency use, though one month later only small amounts of the vaccine were distributed for use outside of the phase 3 trial [9, 46]. The Pfizer–BioNTech partnership submitted an Emergency Use Authorization (EUA) request to the FDA for the mRNA vaccine BNT162b2 (active ingredient lozinameran) on 20 November 2020 [33, 47]. On 2 December 2020, the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) gave a temporary regulatory approval for the Pfizer-Biotech vaccine [48, 49], becoming the first country to approve this vaccine and the first country in the Western world to approve the use of any COVID-19 vaccine [50]. As of 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 an EUA for mRNA-1273, the Moderna vaccine [53].

Potential evaluation of Vaccine efficacy:

The efficacy of a new vaccine is defined by its effectiveness during clinical trials process [14]. The efficacy is the risk of getting the disease by vaccinated participants in the trial compared with the risk of getting the disease by unvaccinated participants [13]. An efficacy of 0% means that the vaccine does not work (identical to placebo). An efficacy of 50% means that there are half as many cases of infection as in unvaccinated individuals [35]. It is not a clear evidence to compare the efficacies of the different vaccines due to the fact that the trials were run with different populations, geographic locations, and variants of the virus [23, 36]. In the case of COVID-19, a vaccine efficacy of 67% may be enough to slow the pandemic, but this take into consideration that the vaccine confers sterilizing immunity which is necessary to prevent transmission [16].

Vaccine efficacy is an indication of disease prevention, and a poor indicator of transmissibility of SARS-CoV-2 since asymptomatic patients can be highly infectious [7, 13]. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) established a cutoff of 50% as the efficacy required for approval for a COVID-19 vaccine [1, 17] and aiming for a realistic population vaccination coverage rate of 75%, while depending on the actual basic reproduction number. The necessary effectiveness of a COVID-19 vaccine is expected to be at least 70% in order to prevent an epidemic and at least 80% to eradicate it without further barrier-imposed measures, such as social distancing [30]. In calculating efficacy, symptomatic COVID-19 is generally defined as having both a positive PCR test and at least one or two of defined lists of COVID-19 symptoms, even though there is variability in exact specification between trials [3]. The trial location can affect the reported efficacy as different countries have different incidence and prevalence of SARS-COV-2 variants.

Types of COVID-19 Variants:

The emergence of a SARS-CoV-2 variant that is moderately or fully resistant to the antibody response expressed by the current generation of COVID-19 vaccines may require modification of the vaccines [36]. Clinical trials have shown that many vaccines developed for the initial strain have lower efficacy for some variants against symptomatic COVID-19 [5]. Since February 2021, the FDA considered that all FDA authorized vaccines were effective in protecting against circulating strains of SARS-CoV-2 [34].

SARS-COV-2 variant B.1.1.7:

In December 2020, a new SARS-CoV variant B.1.1.7, was identified in the UK [4, 19] and early results of study suggested there was protection to the UK variant by the Pfizer and Moderna vaccines [11, 21, 35]. One study indicated that the Oxford-AstraZeneca vaccine had an efficacy of 42–89% against the B.1.1.7 variant, versus 71–91% against non-B.1.1.7 variants [9, 45]. Preliminary data from a clinical trial on NovaVax vaccine indicated that the vaccine was about 96% effective 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]

The 501.V2 variant:

Moderna launched a clinical trial of a new vaccine to tackle the South African 501.V2 also known as B.1.351 [14, 37]. On 17 February 2021, Pfizer announced neutralization activity was able to reduce by two-thirds for the 501.V2 variant, while stating no claims about the efficacy of the vaccine in preventing illness for this variant could yet be made [42]. In January 2021, Johnson & Johnson, conducted trials for its Ad26.COV2. S vaccine in South Africa, and reported that the level of protection against moderate to severe COVID-19 infection was 72% in the United States and 57% in South Africa [41]. On 6 February 2021, the Financial Times reported that provisional trial data from a study undertaken by South Africa's University of the Witwatersrand in conjunction with the Oxford University demonstrated reduced efficacy of the Oxford-AstraZeneca COVID-19 vaccine against the 501.V2 variant [23, 40]. The study showed that with a sample size of 2,000 volunteers participating in the study, the AZD1222 vaccine indicated only "minimal protection" in all but the most severe cases of COVID-19 [2, 7]. On 7 February 2021, the Minister for Health for South Africa suspended the planned deployment of around 1 million doses of the vaccine whilst they examine the data and awaited advice on how to proceed [9].

Vaccine formulation

As of September 2020, eleven of the vaccine candidates in clinical development use adjuvants to enhance immunogenicity [12]. An immunological adjuvant is a substance formulated with a vaccine to elevate the immune response to an antigen [42], such as the COVID-19 virus or influenza virus [8]. Specifically, an adjuvant may be used in formulating a COVID-19 vaccine candidate to boost its immunogenicity and efficacy to reduce or prevent COVID-19 infection in vaccinated volunteers [45]. Adjuvants used in COVID-19 vaccine formulation may be particularly effective for technologies using the inactivated COVID-19 virus and recombinant protein-based or vector-based vaccines [19]. In some cases, aluminum salts, known as "alum", were the first adjuvant used for licensed vaccines, and are the adjuvant of choice in some 80% of adjuvant vaccines [37]. The alum adjuvant initiates diverse molecular and cellular mechanisms to enhance immunogenicity, including release of proinflammatory cytokines [42]

Planning and development of vaccines.

Since early 2020, vaccine development has been expedited via unprecedented collaboration in the multinational pharmaceutical industry and the governments in some cases [45]. By the statement of the Coalition for Epidemic Preparedness Innovations (CEPI), the geographical distribution of COVID-19 vaccine development gives the North American entities having about 40% of the activity when compared to 30% in Asia and Australia, 26% in Europe, and a few projects in South America and Africa [46-48]. Multiple regulatory procedures along the complete vaccine development path are evaluated, and considers the following for evaluation [13, 49]

- the safety that looks at the level of acceptable toxicity of the vaccine.,
- the vulnerability of the populations as main targets,
- priority given for vaccine efficacy breakthroughs,
- emphasis must be given to the duration of vaccination protection,
- A special develop delivery systems must be considered (such as oral or nasal, rather than by injection),
- There must be dose regimen implementation,
- Consideration on the importance of vaccine stability and storage characteristics (cold chain quality assurance),
- The need for emphasis on emergency use authorization before formal licensing is granted,
- Develop a platform for optimal manufacturing for scale up production of billions of doses, and
- the need for the dissemination and rapid distribution access of the licensed vaccine.
- The dosing trials must run simultaneously over months, and potentially compromising safety and quality assurance [6, 53, 54].

Case study of Chinese Vaccine development in LMIC

Considering the Chinese vaccine as a case study within the regulatory point of view for a low middle income country (LMIC) it was observed that the Chinese vaccine developers and the government through the Chinese Centre for Disease Control and Prevention began their mobilization research in January 2020 [55], and by March 2020 there was mobilized follow up of many vaccine candidates on short timelines, with the objective to showcase Chine state of the art technology strength over the developed countries [57]. The intention of the Chinese vaccine developers was to reassure the Chinese population about the potential quality of the vaccine and to reassure the Chinese people about the quality of vaccines produced in China [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]. Furthermore, 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 has to progress through several phases of clinical trials to evaluate for safety, immunogenicity, efficacy, dose range and drug interactions, adverse effects [11, 17, 63]. Vaccine developers have obligation to invest much resources internationally to source out enough participants for Phase II–III clinical trials when the virus has been proven to be a ‘moving target’ of changing transmission rate across and within countries, now forcing companies to compete for trial participants [64-66].

The Clinical trial organizers have other challenges of having people in the population unwilling to be vaccinated due to *vaccine hesitancy* and not wanting to be *guinea pigs*, a vaccine very new in the market with no long history of safety yet [19, 68] or disbelieving the science of the vaccine technology and its ability to prevent infection [3, 69]. Even though, new vaccines are developed during the COVID-19 pandemic, licensure of COVID-19 vaccine candidates still require submission of a full dossier of information on the discovery, development and manufacturing quality and this has been a major challenge especially for resource limited countries [23, 70-71].

Vaccine development Challenges:

There have been several potential challenges with the development of COVID-19 vaccine. The urgent need to develop a vaccine for COVID-19 has led to fast tracking schedules that shortened the standard vaccine development timeline, and in many cases combining clinical trial process over months, a process that normally takes over 10 years in a typically conducted sequential 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 efficacy, safety and quality results.

COVID-19 Vaccine Organizations

Internationally, the access to COVID-19 tools accelerator is a G20 and World Health Organization (WHO) initiative that was declared in April 2020 [46, 72]. It is constituted of a multidisciplinary support structure to facilitate partners to share resources and knowledge. This comprises 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 documented a large international, multi-site, individually randomized controlled clinical trial that allows 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 is to prioritize which vaccines should go into Phase II and III clinical trials, and put in place the harmonization of Phase III protocols for all vaccines that have gone through the pivotal development stage [45, 75].

National governments developed countries have also been involved in vaccine development. For example, Canada announced funding for 96 research vaccine projects at Canadian companies and universities, with plans to develop a "vaccine bank" that could be used for future coronavirus outbreaks [46, 76], and to encourage clinical trials, develop manufacturing and supply chains for vaccines [3, 47, 76].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].

Great Britain formed a COVID-19 vaccine task force in the month of April 2020 to stimulate local efforts for accelerated development of a vaccine through collaborations of industry, universities, and government agencies [14, 78]. It integrated every phase of development from research to manufacturing [49]. In the United States also, the Biomedical Advanced Research and Development Authority (BARDA), a federal agency funding disease-fighting technology, announced funding mobilization investments to support

American COVID-19 vaccine development and manufacture of the most promising candidates [27, 79]. Most pharmaceutical companies with track record of experience in vaccine development at large scale such as Johnson & Johnson, AstraZeneca, and GlaxoSmithKline (GSK), have formed alliances with biotech companies, governments, and universities to accelerate progression in developing an effective vaccine [41, 80].

MAIN TYPES OF COVID-19 VACCINE:

There are four 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 works by trying to smuggle the antigen into the body, others use the body's own cells to make the viral antigen.

Whole Virus:

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

Protein subunit:

The subunit vaccines are developed to use fragments of the pathogen like protein fragments in order to trigger an immune response and by so doing minimizing the risk of adverse effects, but may weaken the immune response [12, 85] and therefore will require adjuvants, to boost the immune response. A named example of the protein subunit vaccine is the hepatitis B vaccine.

Nucleic acid:

Nucleic acid vaccines are developed to use genetic material of either RNA or DNA in providing cells with the instructions to make the antigen. In the case of COVID-19, the target is usually the viral spike protein [29]. Once this genetic material gets into human cells, and uses the cells' protein factories to make the antigen that can trigger an immune response [86]. The advantages of the nucleic acid vaccine are the fact that they are cheap and easy to use. Since the antigen is produced inside our own cells and in large quantities, the immune reaction is likely to be strong. A disadvantage of nucleic acid vaccine is that so far, no DNA or RNA vaccines have been licensed for human use, which may cause more hurdles with regulatory approval. In addition, RNA vaccines need to be kept at ultra-cold temperatures, -70 ºC or lower, which can be challenging for countries that do not have specialized cold storage equipment, particularly low resource countries.

Viral vector:

Viral vector vaccines also work by giving cells genetic instructions to produce antigens. But they differ from nucleic acid vaccines in that they use a harmless virus, different from the one the vaccine is targeting, to deliver these instructions into the cell [27]. One type of virus that has often been used as a vector is adenovirus, which causes the common cold. Unlike with nucleic acid vaccines in which our own cellular machinery is hijacked to produce the antigen from those instructions, in order to trigger an immune response, viral vector vaccines can mimic natural viral infection and should therefore trigger a strong immune response. However, since there are possibilities that many people may have already been exposed to the viruses being used as vectors, some may be immune to it, making the vaccine less effective [70]. The three types of response: (1) RNA vaccine, (2) subunit vaccine, (3) viral vector vaccine are illustrated in figure 1.

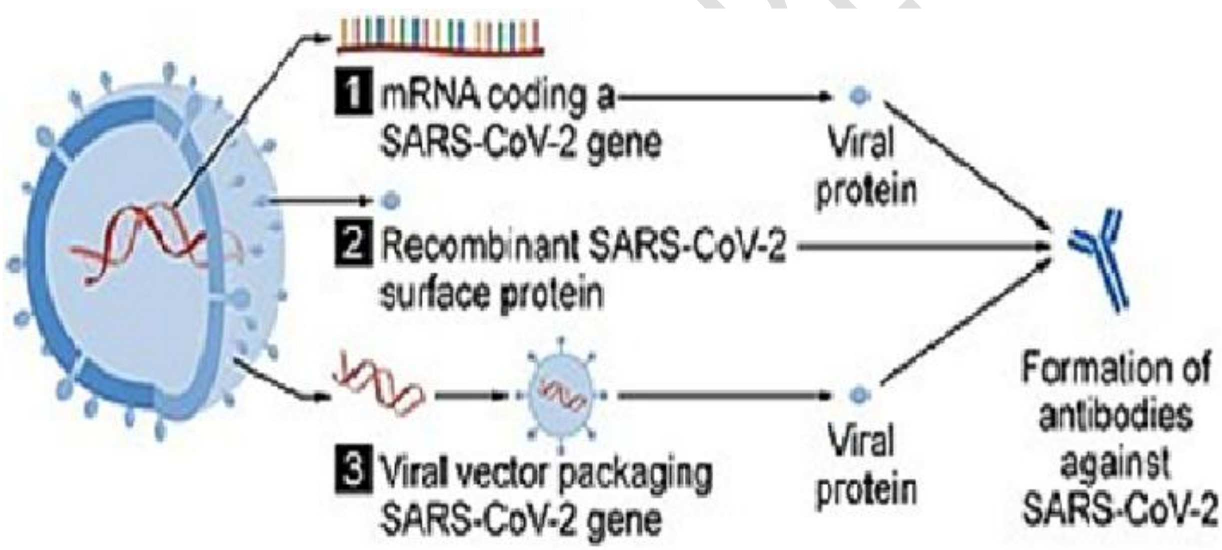

Figure 1: Diagram showing three vaccine types for forming SARS-CoV-2 proteins to prompt an immune response: (1) RNA vaccine (2) subunit vaccine, (3) viral vector vaccine [17].

As of January 2021, nine different technology platforms, with the technology of numerous candidates remaining undefined are under research and development to develop an effective vaccine against COVID-19 [30]. Most of the platforms of vaccine candidates in clinical trials were focused on the coronavirus spike protein and its variants as the primary antigen of COVID-19 infection [60, 82]. Platforms being 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].

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

RNA vaccines

An RNA vaccine contains RNA which when introduced into a tissue, acts as messenger RNA (mRNA) to cause the cells to build the foreign protein and stimulate an adaptive immune response which teaches the body how to identify and destroy the corresponding pathogen or cancer cells [49]. RNA vaccines often, but not always, use nucleoside-modified messenger RNA. The delivery of mRNA is achieved by a coformulation of the molecule into lipid nanoparticles which protect the RNA strands and help their absorption into the cells [88]. RNA vaccines were the first COVID-19 vaccines to be authorized in the United States and the European Union [23, 86]. As of January 2021, authorized vaccines of this type are the Pfizer-BioNtech COVID-19 [90] and the Moderna COVID 19 vaccine [91]. As of February 2021, the CVnCoV RNA vaccine from CureVac was awaiting authorization in the EU [91, 92]. The illustration of the RNA vaccine Messenger RNA is demonstrated in Figure 2.

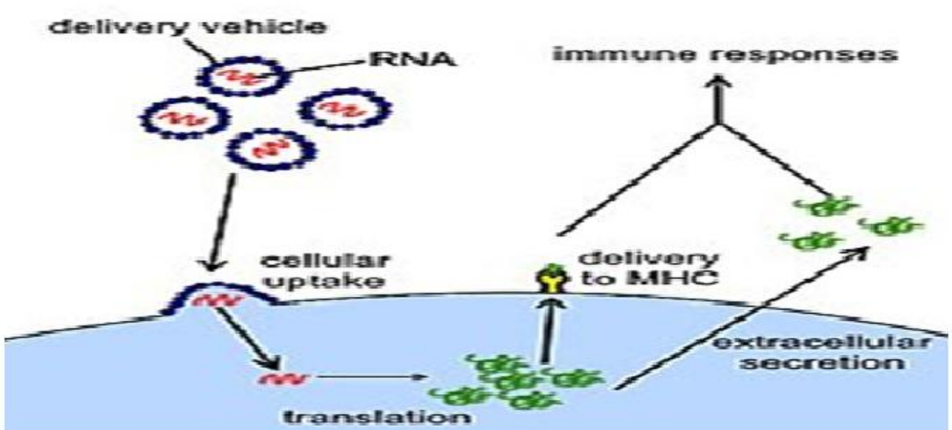

Figure 2: Schematic illustration of the operation of an RNA vaccine. Messenger RNA contained in the vaccine enters cells and is translated into foreign proteins, which trigger an immune response [27].

Adenovirus vector vaccines

These vaccines are examples of non-replicating viral vectors, using an adenovirus shell containing DNA that encodes a SARS-CoV-2 protein [35, 93]. The viral vector-based vaccines against COVID-19 are non-replicating, which means that they do not make new virus particles, but rather produce only the antigen which elicits a systemic immune response [17, 93]. As of January 2021, authorized vaccines of this type are the British Oxfors-AsraZeneca COVID-19 vaccine 94], Russian Sputnik V [95], Chinese Convidicea, and the Johnson & Johnson COVID-19 vaccine [90, 96]. Convidicia and Johnson and Johnson vaccine are both one-shot vaccines which offer less complicated logistics; and can be stored under ordinary refrigeration for several months [97]. Sputnik V, uses Ad26 for the first dose the same as Johnson & Johnson vaccine and Ad5 for the 2nd dose the same as Convidicea with similar single dose effectiveness and full trial taking place on single dose effectiveness.

Inactivated virus vaccines:

Inactivated vaccine consist of virus particles that have been grown in culture and then are killed using a method such as heat or formaldehyde to lose disease producing capacity, while still stimulating an immune response [25]. As of January 2021, the authorized vaccines of this type were the Chinese CoronaVac [97], BBIBP-CorV, [98] and the Indian Covaxin, as well as CoviVac [99]. Vaccines in clinical trials include the Valneva COVID-19 vaccine [78, 100].

Subunit vaccines:

Subunit vaccine present one or more antigens without introducing whole pathogen particles. The antigens involved are often protein subunits, but can be any molecule that is a fragment of the pathogen [101]. As of January 2021, the only authorized vaccine of this type was the peptide vaccine EpiVacCorona [23, 102]. Vaccines in clinical trials include the Navavax COVID-19 vaccine [12, 44] and RBD-Dimer [3, 103]. The V451 vaccine was previously in clinical trials, which were terminated because it was found that the vaccine could potentially cause incorrect results for subsequent HIV testing [67, 85]

Other types

Additional types of vaccines that are in clinical trials include multiple DNA plasmid vaccine [94, 98] at least two lentivirus vector vaccines [98] a conjugate vaccine, and a vesicular stomatitis displaying the SARS-CoV-2 spike protein [99]. Scientists investigated whether existing vaccines for unrelated conditions could prime 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 there no evidence that this vaccine is effective against COVID-19 [29].

Overview of the Vaccine approach for the management of COVID19 pandemic:

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 rare types of blood clotting events 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 subsequently 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 "considered plausible" that there was a causal relationship between the vaccination and the occurrence of thrombosis in combination with thrombocytopenia and that, "although such adverse reactions are 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]

Signs and symptoms:

Thrombosis

The thrombosis events associated with the COVID-19 vaccine may occur 5-28 days after its administration to patients Several unusual types of thrombosis have been routinely reported to in patients [109]: There has been cerebral venous sinus thrombosis and thrombosis of the splanchnic veins. Cerebral venous sinus thrombosis may also 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, may occur and arterial thrombosis has been reported [108]. The low platelet count 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 reported as part of the syndrome [109]. DIC may cause a range of symptoms, including abnormal bleeding, breathlessness, chest pain, neurological symptoms, low blood pressure, or swelling [21, 110]. COVID-19 vaccines have shown some adverse effects that are listed as common in the two- or three-days following vaccination which are usually mild and temporary [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 found together after COVID-19 vaccination, an antibody against platelet factor has been identified [22, 112]. This phenomenon is mostly encountered in cases of 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 who had not been exposed to heparin [19, 57, 113].

One striking feature of thrombocytopenia in the presence of anti-PF4 antibodies is the ability of some to develop thrombosis, a phenomenon called heparin-induced thrombocytopenia if heparin is involved [30, 114]. Thrombocytopenia is generally a common symptom after many viral infections [9] and it has been regularly reported after administration of adenoviral gene transfer vectors [11, 66, 115], even though the mechanisms are not yet known. There is no confirmed causal link to the syndrome and any COVID-19 vaccination [45]. However, EMA is conducting 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 sometimes in patients treated with heparin, that is heparin induced thrombocytopenia (HIT) [109].

CONVALESCENCE PLASMA THERAPY APPROACH:

Convalescent plasma generated great enthusiasm in the earliest days of the coronavirus disease 2019 (covid-19) pandemic because of a plausible mechanism of action, its 100-year history of use in the treatment of other infectious diseases, and rapid availability from voluntary donors [111,113]. In the linked PLACID Trial, Agarwal and colleagues evaluated convalescent plasma for the treatment of moderate covid-19 in patients admitted to hospital in India [107, 112]. Strengths of the study included a primary hard outcome meaningful to patients, proper patient enrollment with no exclusions for comorbidities, careful attention to 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 contained detectable titers of antibodies to severe acute respiratory coronavirus 2 (SARS-CoV-2), the virus responsible for covid-19 [32, 115].

In prespecified, intention-to-treat analyses, the PLACID Trial investigators found no net benefit associated with convalescent plasma in patients admitted to 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]. Restriction 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 through direct antiviral action of neutralizing antibodies on SARS-CoV-2 RNA [105, 115] In the PLACID Trial, a statistically significant 20% higher rate of conversion to a negative result for SARS-CoV-2 RNA occurred 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, which is derived from whole plasma, is subject to a US Food and Drug Administration warning about the risks of thrombosis, particularly in older patients, particularly those with cardiovascular risk factors, and hypercoagulable conditions [108]. It now understood 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 state, but also a hypo-fibrinolytic state not usually observed with most other types of coagulopathy [108]. Of recent, plasma from convalescent covid-19 patients has been shown to directly in in vitro studies, cause endothelial cell damage. 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. This publication has motivated more interest in future and ongoing clinical trials [115].

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

COVID-19 is an emerging, rapidly evolving situation and the National Institute of Health (NIH) group of scientists have discovered a key pathway in lysosomes that coronaviruses are capable of exploiting to exit cells. The principles of Targeting cells' 'trash compactor' could possibly result to a new potential antiviral approach 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 hijack and exit cells as it spreads through the body. A better understanding of this important pathway may provide an insight into the possibility to stop the transmission of the SARS-CoV-2 virus the causal agent of COVID-19 disease [88, 112].

In cell studies, the researchers reported for the first time that the coronavirus can exit infected cells through the lysosome, which is an organelle known as the cells' "trash compactor." Normally, the lysosome plays a role of destroying viruses and other pathogens before they leave the cells. However, the researchers discovered that the coronavirus deactivates the lysosome's disease-fighting mechanism, permitting the virus to freely spread throughout the body [14, 39, 107]. Strategy to target this lysosomal pathway could lead to the development of new and more effective antiviral therapies to fight COVID-19. The 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 understood for some time 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 figure 3.
This illustration shows components of the lysosome exocytosis pathway, which coronaviruses use to exit cells. Also shown are components of the normal biosynthetic secretory pathway.

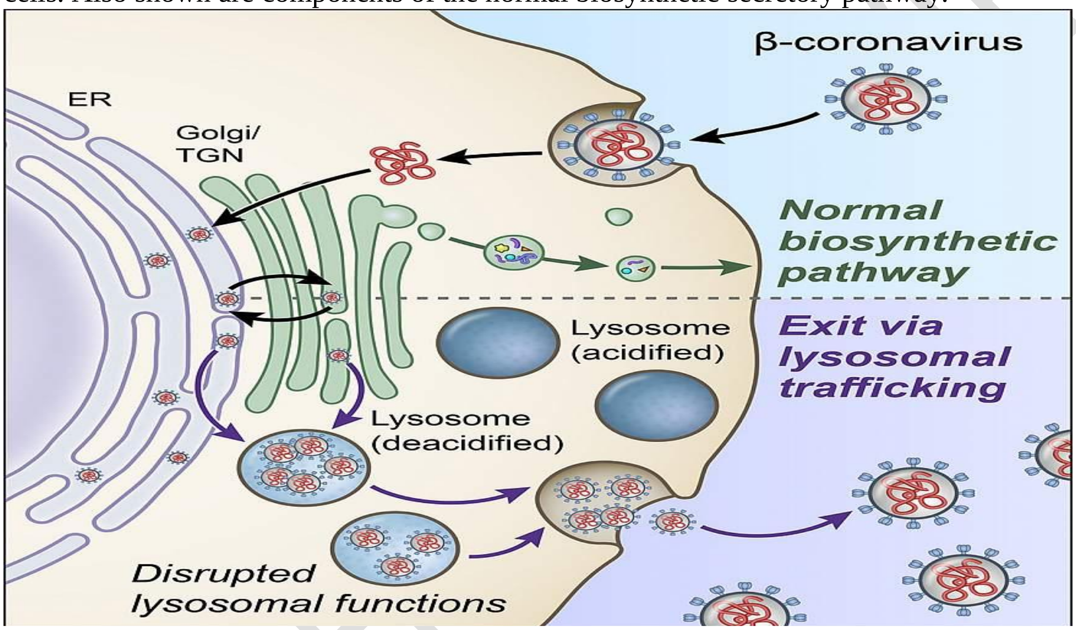

Figure 3. Exit of viruses through the Biosynthetic secretary pathways [113]

It is widely known 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 just fine and this has given the first clue that maybe coronaviruses are using another pathway to exit cells. In order to understand the pathway, the scientists 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 experiments, 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 overwhelm the immune system and cause high death rates [11, 96, 115].

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]. The authors have already identified one experimental enzyme inhibitor 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].

CONCLUSION

There are many unanswered important questions on effectiveness of COVID-19 vaccines within the framework of the current pandemic settings. There is a need to conduct post-introduction vaccine efficacy studies within selected countries to address these questions. COVID-19 vaccination has the potential to enhance protection of the population from COVID-19 infection. Adults and pediatric population are predisposed to have some more effects from the vaccine, which are 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 noticeable side effects, and allergic reactions may be rare. Serious adverse effects (SAE) that could cause a long-term health problem are extremely unlikely following any COVID-19 vaccination. Vaccine monitoring generally has shown that side effects may happen within six weeks of receiving a vaccine dose. The benefits of COVID-19 vaccination outweigh the known and potential risks.

With the increasing vaccine hesitancy especially in limited resources countries compounded by the limited access to vaccine, there is an increasing need for capacity building to sensitize actors and stake holders for a better understanding of potential side effects. There is also the possibility to explore the efficiency 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 needs to be in constant exploitation, for continuous development and improvement on new therapeutic indications.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests, non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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