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Review article

Systematic Review on COVID-19 Vaccines: Comparative Study of AstraZeneca, Pfizer-BioNTech, Sputnik V, Johnson & Johnson, Moderna and Corona Vac.

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Abstract

The novel Coronavirus (SARS-CoV-2) has spread all over the world and the disease, COVID-19, is still wreaking a lot of havoc. Vaccination seems to be the best solution to overcome this pandemic. Several vaccines have been proposed around the world and some of them are already being dispensed, such as AstraZeneca, Pfizer-BioNTech, Sputnik V, Johnson & Johnson, Moderna and CoronaVac. Population around the World have expressed many doubts about these vaccines and resistance to vaccination has been observed. This, for lack of reliable information on these vaccines. The purpose of this systematic review is to provide a comparison of these homologated vaccines and reliable information on them. Online databases were investigated to search publications on these vaccines and the bibliography was created using Endnote 7.0. Investigations concerned antigenic targets, vaccine types, number and timing of doses, neutralizing antibodies, cellular immunity and safety concerns. The main target protein in COVID-19 vaccines is the spike protein (S). Whereas AstraZeneca, Sputnik V and Johnson & Johnson vaccines are adenoviral vector vaccines, Pfizer-BioNTech and Moderna are mRNA vaccines while CoronaVac is a viral attenuated vaccine. Except for Johnson & Johnson which requires one dose, the other vaccines require two doses. All of them induced cellular and humoral immune responses. This review has allowed us to provide to the scientific community and population reliable information about the vaccines and their safety concern.

Keywords: ***COVID-19, Vaccines and SARS-CoV-2***

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a highly transmissible and pathogenic coronavirus that causes an acute respiratory disease known as "Coronavirus 2019 Disease" (COVID-19) [1]. COVID-19 was firstly reported in Wuhan, the capital of China's Hubei province, in December 2019, and has since spread worldwide, causing an unusual viral pneumonia outbreak [2]. A year later, the disease has progressed, making the United States of America (USA) the most affected country with a high mortality rate, but the progression remains low in Africa [3]. As of 2nd March, 2021, 6:09pm CET, 114,140,104 confirmed cases of COVID-19, including 2,535,520 deaths worldwide, have been reported to the World Health Organization (WHO) [4]. Human coronaviruses genetics and virulence factors, and also the pathophysiology and epidemiology of human coronaviruses diseases have been described SARS-CoV-2 affects everyone, regardless of age or sex, but affects children less severely than adults [5]. The only preventive approach suggested by researchers is the development of vaccines against SARS-CoV-2. In order to develop a safe and effective vaccine, it is essential that preclinical and clinical trials are conducted with vigilance to avoid serious adverse effects [6]. At the time we are writing this paper, the emergence of SARS-CoV-2 has currently led to 4,931 studies on COVID-19 and 226 vaccine studies listed in the National Institute of Health's database aimed at finding a solution to this pandemic [7]. Researchers have developed several potential candidate vaccines that have shown promise in phase II and III trials [8]. As of March 2nd, 2021, 182 candidate vaccines were in preclinical evaluation and 62 vaccines in clinical evaluation [9]. The WHO granted an Emergency Use Exemption under the Emergency Use Listing (EUL) protocol to Pfizer's COVID-19 vaccine (BNT162b2)

on December 31st, 2020. On February 15th, 2021, WHO granted another emergency use authorization, for two versions of the AstraZeneca/Oxford COVID-19 vaccine manufactured by the Serum Institute of India and SKBio [10]. To date, Pfizer-BioNTech, Moderna and AstraZeneca are the three vaccines licensed in Europe, Sputnik V in Russia, Johnson & Johnson in USA, CoronaVac in China. In just one year, scientists have accomplished the feat of developing a vaccine to try to stop the COVID-19 pandemic [11]. Population around the World have expressed many doubts about these vaccines and resistance to vaccination has been observed. This, for lack of reliable information on these vaccines. The purpose of this review is to make a systematic comparison of these vaccines in order to provide to the scientific community and population reliable information about the vaccines and their safety concern.

Methods

The study was carried out on March 2021. Online databases (PubMed, Elsevier, Google scholar, and also WHO) were investigated, to search publications on properties of six COVID-19 vaccines, notably AstraZeneca, Pfizer-BioNTech, Sputnik V, Johnson & Johnson, Moderna and CoronaVac. We were curious about antigenic targets of the vaccines, types of vaccines, number and timing of doses, neutralizing antibodies against SARS-CoV-2, cellular immunity against SARS-CoV-2 and safety concerns. All the literature found were discussed by the editorial team of this paper (**Figure 1**).

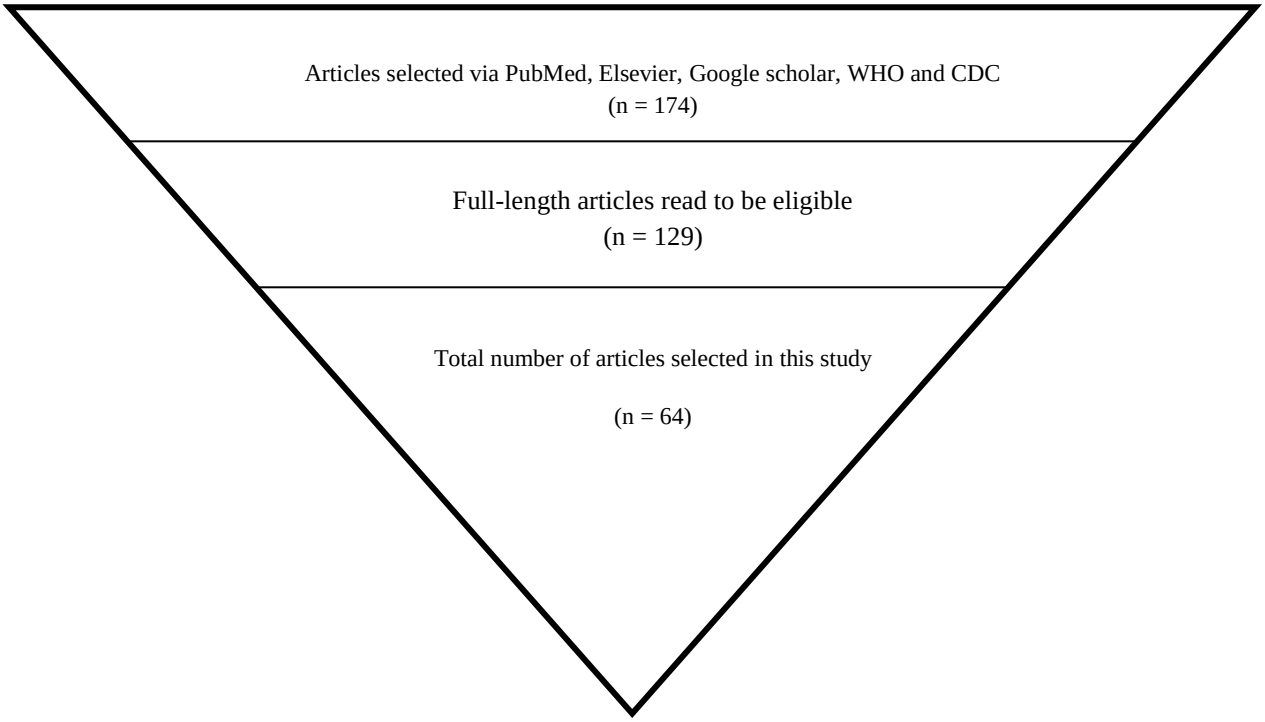

Figure 1: Process of literature review. The pyramid represents the literature review steps. A total of 174 articles were identified and selected on PubMed, Elsevier, Google scholar, and WHO. After that, 129 were used based on their relevance to the topic. Finally, 64 were served for this review, given the impact factor and the level of journals in which they were published.

Antigenic targets of vaccines

The international scientific community believes that vaccination is now the best way to limit the spread of SARS-CoV-2 disease. Thus, vaccines are an urgent countermeasure medical for this public health crisis. Numerous approaches to the DNA-based synthetic vaccine have led to the emergence of several vaccines. Therefore, it would be important to understand the protective principle of the new vaccines against SARS- CoV-2. Regarding the immune actors and the mechanisms involved, it has recently been observed that both humoral and cellular immunity play an important role in the protective immunity against SARS-CoV-2 infection [12].

T-cell depletion in mice has been shown to impair viral clearance in SARS- CoV-2 infections, suggesting that T cells play an important role in controlling of SARS-CoV-2 infection. Various data indicate that in patients with SARS-CoV-2, CD4+ and CD8+ T cell responses are associated with moderate disease, which also demonstrates their involvement in the immunity against COVID-19 [13]. However, an ideal vaccine should induce both humoral and cellular immune responses. The quality of the vaccine depends in part on the structure of the viral particle and the immunogenicity of its antigens. Due to the reciprocity between the SARS-CoV and the SARS-CoV-2, the ultra-structure of the COVID-19 virus was quickly revealed by a number of authors for vaccine implementation [14]. Thus, it was revealed that SARS- CoV-2 carries important structural proteins: S (Spike), M (membrane) and E (envelope), and N protein (nucleocapsid) which is found in the ribonucleoprotein core along the viral RNA genome (**Figure 2**). SARS-CoV-2 contains 8 accessory proteins and 15 non-structural proteins (nsp1-16) [15,16].

The primary target protein for COVID-19 vaccines is the spike protein (S) [17]. The S protein comprises an S1 subunit and an S2 subunit and exists in the virus envelope as a homotrimer. The S1 subunit determines receptor recognition via its receptor binding domain (RBD), whereas the S2 subunit is responsible for membrane fusion, which is necessary for the entry of the virus [18]. Indeed, structurally, SARS-CoV-2 comprises three transmembrane proteins which are incorporated into the viral lipid envelope and maintain the viral RNA into the virion: spike protein (S) and two

smaller proteins, membrane protein (M) and envelope protein (E). The S protein trimer in its pre-fusion conformation show that the S protein comprises two subunits: S1 and S2. S1 subunit includes the N-terminal domain (NTD) and the receptor-binding domain (RBD while the S2 subunit contain fusion peptide (FP), connecting region (CR), heptad repeat 1 (HR1), heptad repeat 2 (HR2) and central helix (CH). The human angiotensin-converting enzyme 2 (hACE2) is the host receptor for SARS-CoV-2 S protein. It binds to its host receptor through the RBD and dissociates the S1 subunits. Cleavage at both S1-S2 and S2' sites result in structural rearrangement of the S2 subunit required for virus-host membrane fusion. Hence, the RBD is an important target for the SARS-CoV-2 vaccine. In addition, each vaccine protein has its specificity, target and specific immune response (**Figure 2**).

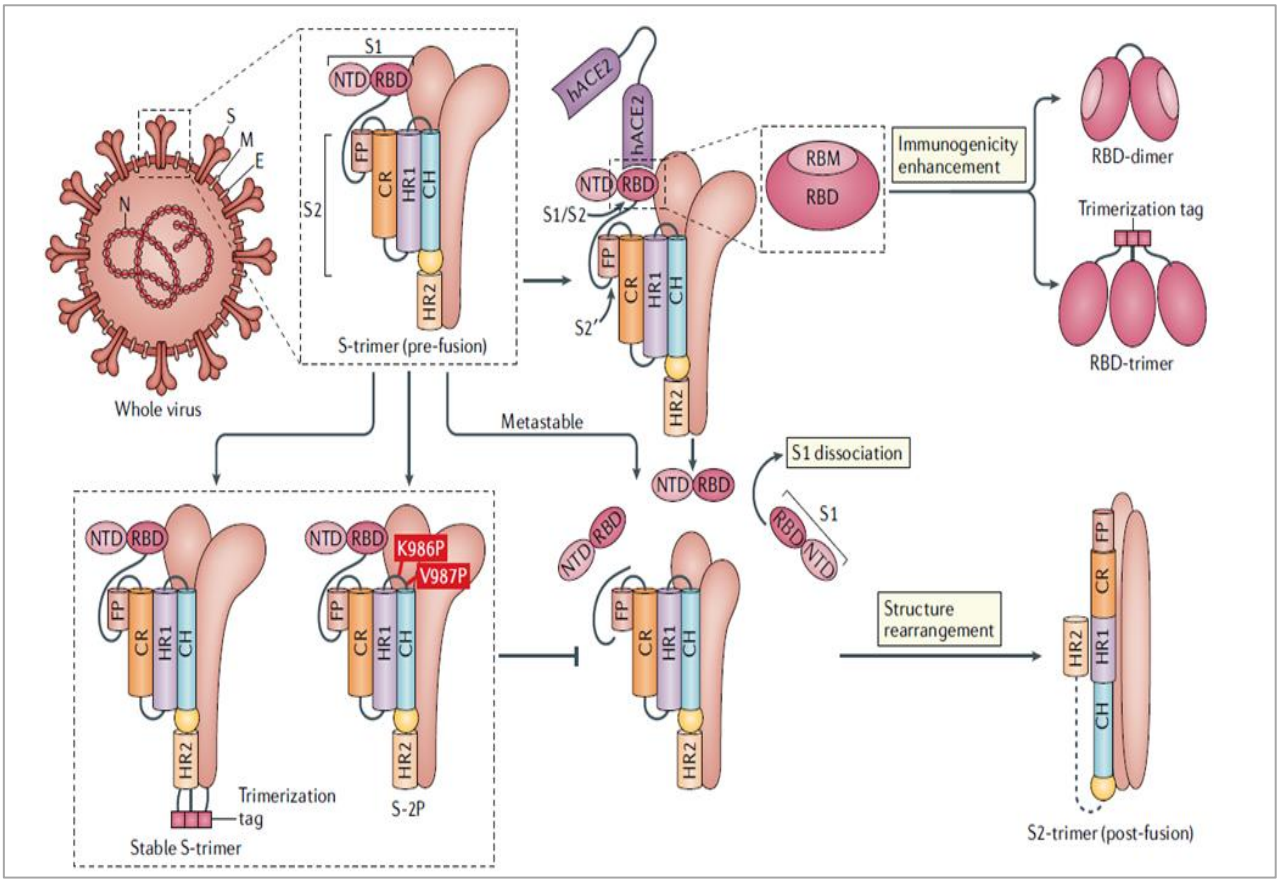

Figure 2: Antigen targets used in COVID-19 vaccine (Adapted from [17]).

Types of COVID-19 vaccines

To date, several COVID-19 vaccines are already available in many countries including AstraZeneca, Pfizer-BioNTech, Sputnik V, Johnson & Johnson, Moderna and CoronaVac.

Table 1 shows a comparative study of the 6 vaccines studied in this review, including their various targets, the dosage required, the timing within each dose as well as the specific immune response associated with each vaccine. AstraZeneca is a chimpanzee adenovirus vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein developed by the University of Oxford in UK and AstraZeneca in Cambridge; two (2) doses of vaccine 2-4 weeks apart are required for strong immunization against SARS CoV-2 [19]. The strong CD4+ and CD8+ responses, even in the absence of an adjuvant, make AstraZeneca a suitable vaccine vector for pathogenic viruses that elicit a strong cellular immune response [20,21,22]. Sputnik V (Gam-Covid-Vac) is a Russian vaccine using adenovirus 5 (Ad5) and adenovirus 26 (Ad26) as vectors for the expression of SARS-CoV-2 spike protein. It induces neutralizing antibodies and CD4+ and CD8+ T cells responses immune responses after 2 doses of vaccine between 3 weeks per dose. The rAd26-S and rAd5-S, carry the SARS-CoV-2 full spike glycoprotein [23]. Johnson & Johnson's COVID-19 vaccine uses adenovirus technology. A single dose of this vaccine is effective in inducing neutralizing antibodies. The adenovirus DNA has been modified to produce an essential part of the SARS-CoV-2 virus particle against which the body then develops an immune response. The entire length of the spike protein is expressed by the Ad26 and is stabilized by furin cleavage site mutations and two consecutive proline stabilizing mutations in the hinge region [24]. The Adenovirus delivering the SARS-CoV-2 DNA particle is not infectious (no proliferation). This system is based on DNA molecules that are stable and that do not require ultra-cold storage, which facilitates its distribution [25]. Pfizer-BioNTech and Moderna, compared to the above-mentioned vaccines, are mRNA vaccines. While Moderna's target is simply the spike protein, Pfizer-BioNTech's target is more specific, the RBD of the SARS-CoV-2 spike protein. Two doses of Pfizer-BioNTech vaccine administrated between two weeks apart induce a specific Th1 immune response. For the Moderna vaccine, two doses of vaccine administered 2 weeks apart induce neutralizing antibodies and T-cell responses. The latest approved SARS-CoV-2 vaccine mentioned here is CoronaVac developed by Sinovac Life Sciences in China. Unlike the other vaccines mentioned above, CoronaVac is an inactivated SARS-CoV-2 virus and uses aluminium hydroxide as an adjuvant that has shown good immunogenicity in mice, rats, and non-human primates [26,27]. In inactivated SARS CoV-2 vaccines, the viruses are physically or chemically inactivated but preserve the integrity of the virus particle, which serves as the immunogen. Due to its richness, the whole virus particle serves as an antigenic target for vaccines and contains all structural proteins namely S, N, M and E proteins

[28,17]. Live-attenuated virus vaccines can also generate non-structural and accessory proteins in vivo [29]. It has been reported that, CoronaVac vaccines can induce broader antibody and T-cell responses than the above-mentioned vaccines, which are based on a single protein or protein fragments [26,30].

Table 1: Description of six COVID-19 vaccines already available in the public health program

Vaccines	Institution (Country)	Technology	Target	Number of doses	Duration between 2 doses	Type of response	References
AstraZeneca (AZD1222)	University Oxford/Astra Zeneca (UK)	Chimpanzee Adenovirus vector	Spike protein.	2 doses	4 - 12 weeks	Induction of CD4+ and CD8+ cells responses in pigs and mice (First dose). Increased virus neutralizing antibodies titers in pigs (Second dose)	**[25,31]**
Johnson & Johnson	Janssen /Johnson Johnson (Netherland/US)	Human Adenovirus vector, Ad26	Spike protein	1 dose	-	Induction of neutralizing antibodies and reduce the occurrence of COVID-19 in hamsters and rhesus macaques (Single dose)	**[32,24,33]**
Pfizer-BioNTech	Pfizer, Inc; (Philadelphia, Pennsylvania)	mRNA	Spike protein	2 doses	3 weeks	Induction of Th1, deviation of T cells responses with RBD-specific CD8+ and CD4+ T cell expansion	**[34,35,36]**
SputnikV (Gam-Covid-Vac)	Gamaleya National Center of Epidemiology and Microbiology (Russia)	Human Adenovirus vectors, Ad26 and Ad5	Spike protein	2 doses	3 weeks	Induction and binding of neutralizing antibodies and the T-cell responses (CD4+ and CD8+ cells).	**[37]**
Moderna Vaccine	US company Moderna (US)	mRNA-1273	Spike protein (RBD)	2 doses	4 weeks	Induction of potent antibodies and CD8+ responses, neutralizing antibodies.	**[38,39,40]**
CoronaVac	Sinovac, Life Sciences, Beijing (China)	Inactivated SARS CoV-2	Inactivated Whole virus	2 doses	2weeks	Induction of S- specific, RBD-specific and N- specific IgG, and nAbs in mice, rats and NHPs; no induction of either Th1 or Th2 cell responses in NHPs; induction of RBD-specific IgG and NAbs in humans; no obvious vaccine-induced T cell responses in humans	**[26,41]**

To each type of vaccine, corresponds a specific technology used. While some are based on the use of viral vectors: the adenovirus; which carries the genes of the coronavirus and replicates slowly in the host cells, others are mRNA vaccines or consist of attenuated or inactivated viruses. Figure 3 shows the main types of technology used for the SARS-CoV-2 vaccine. For DNA vaccines, the viral antigen(s) encoded by a recombinant DNA plasmid are produced in host cells via a sequential process of transcription and translation whereas mRNA vaccines are synthesized by in vitro transcription. They produce the viral antigen(s) in the cytoplasm through direct protein synthesis in vivo. Inactivated vaccines consist of physical or chemical inactivation of viruses but preserve the integrity of the viral particle, which serves as the immunogen. Antigens are produced by the transduced host cells after immunization. In live attenuated virus technology, the virus is attenuated by in vitro or in vivo passage or by reverse-genetic mutagenesis. The resulting virus becomes non-pathogenic or weakly pathogenic but maintains immunogenicity by mimicking live virus infection. The “protein subunit” vaccine strategy uses only viral proteins or key peptides that can be made in vitro in bacteria, yeast, insects or mammalian cells. Most vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are based on this strategy. The “virus-like particle” vaccine strategy relies on the co-expression of structural viral proteins to form non-infectious particles that serve as the immunogen for the vaccine.

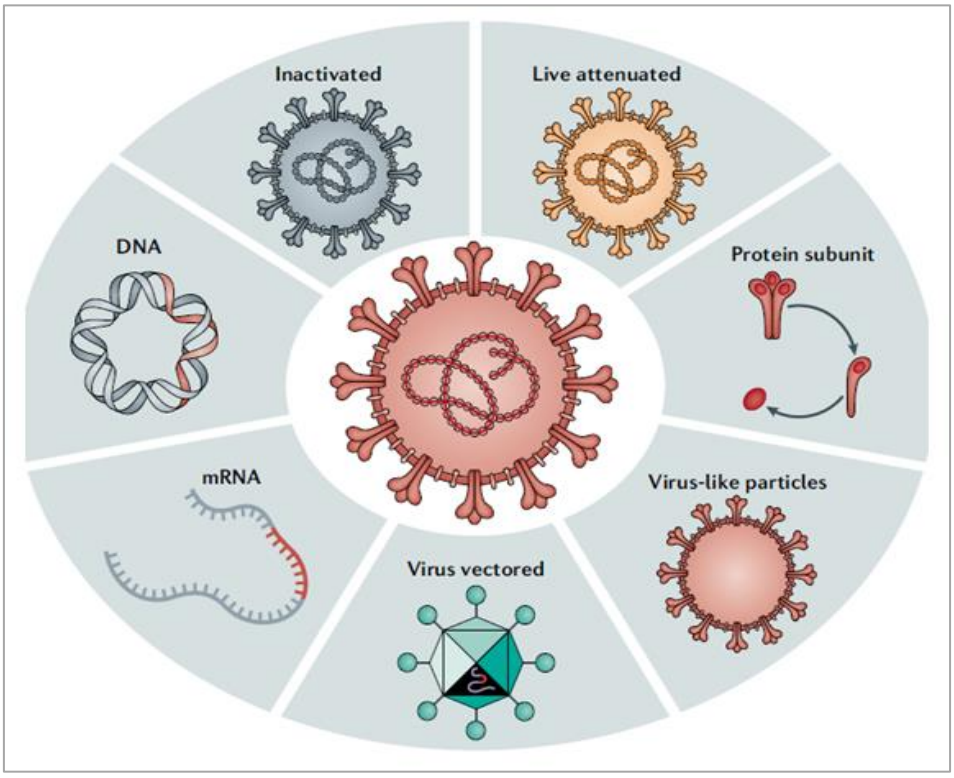

Figure 3: The main types of technology used for the SARS-CoV -2 vaccine (Adapted from [17])

Number and timing of doses

The WHO COVID-19 Vaccine Tracker and Landscape compiles detailed information on each COVID-19 vaccine candidate in development by closely tracking their progress through the pipeline. To date, 76 vaccines candidates are in clinical phase, with 32% (n=24) of vaccines listed on the PS (Protein subunit) platform, representing the largest number of vaccines in clinical phase, followed by VVnr (Viral Vector non-replicating) with 14% (n=11), DNA 14% (n=11); IV (Inactivated Virus) 13% (n=10); RNA 12% (n=09); VVr (Viral Vector replicating) 5% (n=4); VLP (Virus Like Particle) 4% (n=3), VVr + APC (VVr + Antigen Presenting Cell) 3% (n=2), LAV (Live Attenuated Virus) 1% (n=1) and VVnr + APC (VVnr + Antigen Presenting Cell) 1% (n=1) accounting for the smallest number of vaccines in the clinical phase (**Table 2**).

Table 2: Candidates in clinical phase as of 2nd March, 2021 [10]

Platform	Number of vaccines in clinical trials n (%)
PS (Protein subunit)	24 (32%)
VVnr (Viral Vector non-replicating)	11 (14%)
DNA (Desoxyribonucleic Acid)	11 (14%)
IV (Inactivated Virus)	10 (13%)
RNA (Ribonucleic Acid)	9 (12%)
VVr (Viral Vector replicating)	4 (5%)
VLP (Virus Like Particle)	3 (4%)
VVr + APC (Virus Like Particle + Antigen Presenting Cell)	2 (3%)
LAV (Live Attenuated Virus)	1 (1%)
VVnr + APC (Viral Vector non-replicating + Antigen Presenting Cell)	1 (1%)
Total number of vaccines	**76 (100%)**

Table 3 provides data on the number of doses, schedule, and routes of administration of the vaccines in clinical trials. As of 2nd of March 2021, 63% of the vaccines (n=48) are administered in two (2) doses, 16% (n=12) in one dose and 20% (15) are undocumented. 84% (64) of the vaccines are injectable with 78% (n=59) administered intramuscularly, 3% (n=2) orally, and 13% (n=10) have no data. These data are represented graphically in **Figure 4**.

Table 3: Number of doses, schedule and route of administration of candidates in clinical phase as of 2nd March, 2021 [10]

Number of doses & schedule	Number of vaccines in clinical trials n (%)
1 dose	**12 (16%)**
Day 0	12
2 doses	**48 (63%)**
Day 0 + Day 14	6
Day 0 + Day 21	17
Day 0 + Day 28	25

3 doses	**1 (1%)**
Day 0 + Day 28 + Day 56	1
TBD / No Data (ND)	**15 (20%)**
Total number	**76 (100%)**
Route of administration	
Oral	**2 (3%)**
Injectable	**64 (84%)**
Sub cutaneous (SC)	2 (3%)
Intra dermal (ID)	3 (4%)
Intra muscular (IM)	59 (78%)
TBD / No Data (ND)	**10 (13%)**

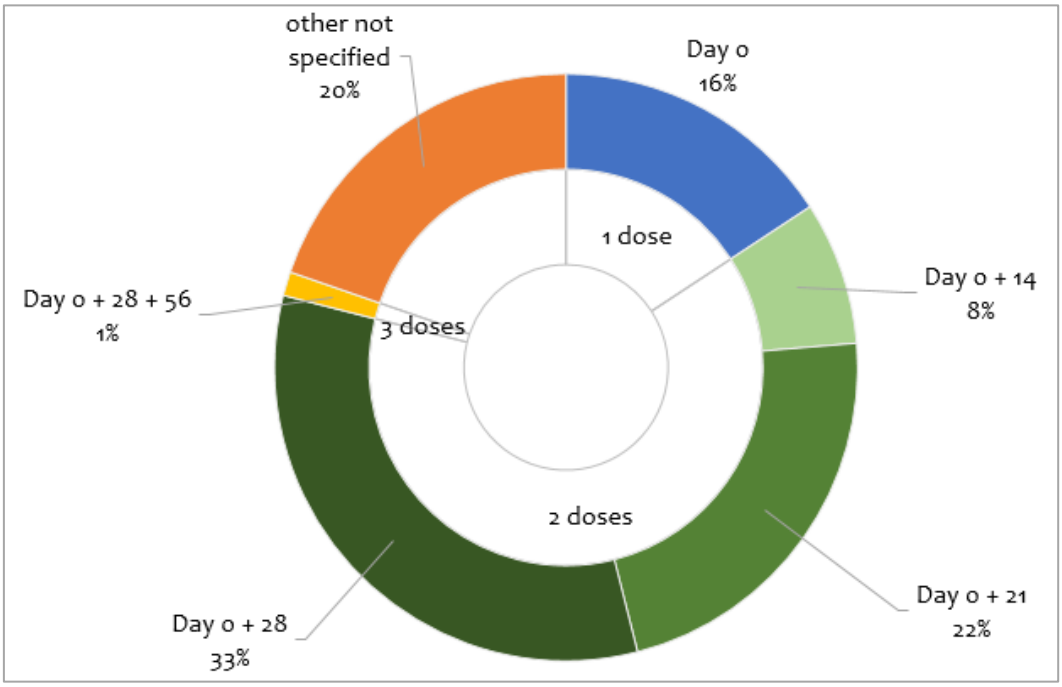

Figure 4: Number and timing of doses of vaccines against SARS-CoV-2

AstraZeneca vaccine (ChAdOx1 nCoV-19)

AstraZeneca (ChAdOx1 nCoV-19) is a chimpanzee adenoviral vector-based vaccine with a full-length SARS-CoV-2 spike insert developed at the Oxford University (Oxford, UK). Its Immunogenicity and safety have been evaluated in four (04) randomized controlled trials in the United Kingdom, Brazil and South Africa, and results on cohorts of healthy adults aged 70 years or older have been published [42-45]. The ChAdOx1 nCoV-19 vaccine was approved for emergency use by the UK regulatory authority, the Medicines and Health Products Regulatory Agency, on a dosing regimen of two standard doses administered 4 -12 weeks apart for adults aged 18 years and older, and has since been licensed for use in many other countries [46].

Pfizer-BioNTech vaccine

Pfizer-BioNTech COVID-19 vaccine (BNT162b2) is a lipid nanoparticle-based modified RNA vaccine. The RNA of the vaccine encodes a stabilized, full-length, pre-fused, membrane-anchored, SARS-CoV-2 spike protein. Immunization with Pfizer-BioNTech COVID-19 vaccine consists of 2 doses (30 µg, 0.3 mL each) administered intramuscularly, 3 weeks apart. This dose conferred 95% protection against COVID-19 in individuals of 16 years of age and older. Safety on a median of 2 months was similar to that of other viral vaccines. On December 11th, 2020, the Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for this vaccine [47,34].

Sputnik V vaccine

The Sputnik V vaccine uses human adenovirus 26 (Ad26) and adenovirus 5 (Ad5) as expressing vectors of the SARS-CoV-2 spike protein [48]. In the Phase III clinical trial of this vaccine, 0.5 mL/dose was administered intramuscularly in an initial booster schedule: twenty-one day between dose 1 (rAd26) and dose 2 (rAd5), with both vectors carrying SARS-CoV-2 glycoprotein S gene, and showed 91.6% efficacy against COVID-19 [23].

Moderna vaccine (mRNA-1273)

In December 2020, FDA (Food and Drug Administration) issued an Emergency Use Exemption (EUA) for Moderna COVID-19 vaccine (mRNA-1273; ModernaTX, Inc, Cambridge, Massachusetts), an encapsulated lipid nanoparticle and modified nucleoside mRNA vaccine encoding the stabilized SARS-CoV-2 spike glycoprotein. This vaccine consists of two doses (100 µg, 0.5 mL each) administered intramuscularly, four weeks apart in people of 18 years of age or older [34]. The vaccine showed 94.1% efficacy in preventing COVID-19 disease, including severe disease, in the Phase III clinical trial [49].

Johnson & Johnson vaccine (Ad26.COV2.S)

Ad26.COV2.S, a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encodes a full-length and stabilized SARS-CoV-2 spike protein. Administered intramuscularly in people of 18 years and older, it consists of a single dose of 0.5 mL each [50].

CoronaVac vaccine

CoronaVac (Sinovac Life Sciences, Beijing, China) is an inactivated COVID-19 vaccine candidate that has shown good immunogenicity in mice, rats, and non-human primates with vaccine-induced neutralizing antibodies to SARS-CoV-2, which could neutralize ten representative strains of SARS-CoV-2 [26]. CoronaVac vaccine consists of 3 μg in 0.5 mL of aluminium hydroxide diluent per dose, administered intramuscularly at day 0 and day 28, in adults aged 18-59. Phase-three trials, which were conducted on health-care workers in Brazil, yielded an efficacy rate of only 50.7% (with a 95% confidence interval of 35.7% to 62.2%), just slightly above the WHO threshold of 50% for COVID-19 vaccines [41].

Neutralizing antibodies against SARS-CoV-2

A neutralizing antibody (NAb) is considered a type of antibody that is capable of preventing an infectious agent (e.g., virus) from infecting a cell by inhibiting its biological effect [51]. Such an antibody is very often protective for the host, as it interferes with the binding of the virus to its receptors on the target cell [52].

It is known that in COVID-19, SARS-CoV-2 enters the targeted host cells through its envelope spike protein (S protein) which binds to the angiotensin converting enzyme-2 (ACE2) on the host cell [53]. Indeed, the S protein is a type I trimeric fusion protein composed of two functional subunits: S1 (receptor-binding domain RBD and N-terminal domain NTD) that mediates attachment of the virus to host cells and S2 (C-terminal) for its membrane fusion [54]. Thus, antibodies capable of binding to the S protein of SARS-CoV-2's should have the potential role of neutralizing the virus entry in cells and protecting the host from developing COVID-19 symptoms.

Considerable efforts have been done to isolate and characterize NAbs produced by convalescent COVID-19 patients that, not only target the S protein but also have a high potency to neutralize the virus [55]. Most of them were found to bind the RBD of S1 subunit and also to the nucleocapsid protein (NP) of the virus [56]. Neutralizing antibodies against SARS-CoV-2 were also predominantly IgG1 isotypes (anti-S-RBD and anti-NP) [57].

Cellular immunity against SARS-CoV-2

Immune response to a viral infection involves not only a humoral response but also a cellular response for complete protection. In the case of COVID-19, CD4+ T cells have evidently, a central role in the cellular response and also in inducing antibodies production, by collaborating with B cells [53]. An effective response against SARS-CoV-2 should also involve cytotoxic or killer CD8+ T cells that directly kill infected cells [58].

Immunization against SARS-CoV-2

The cellular and humoral immune responses induced by AstraZeneca, Johnson & Johnson, Sputnik V, Moderna, Pfizer-BioNTech and CoronaVac vaccines are summarized in **Table 4**. The AstraZeneca vaccine also named ChAdOx1nCoV-19, has been shown to a induce cellular immune response involving NK cells for innate immunity and CD8+ T cells, IFNγ+ T cells and IgG+ B cells that increase from day 7 to day 28 for adaptative immunity after one dose. Early antibodies such as anti-IgM and anti-IgA were detected as early as day 14 after vaccination, whereas anti-IgG1 and IgG3 were released after 28 days [59]. Sputnik V demonstrated induction of specific anti-RBD- neutralizing IgGs 14 days post-dose and production of antigen-specific CD4+ and CD8+ T cells that correlated with high IFNγ levels after 28 days [23]. The Moderna vaccine induced a Th1 cell response with minimal Th2 cells response with specific anti-RBD IgGs, 29 days after one dose [60]. A booster vaccination (second dose) helped to increase CD8+ T cells [61]. With the Pfizer-BioNTech vaccine, an expansion of IFNγ CD4+ and CD8+ T cells was generally noted, while neutralizing anti-RBD IgGs were detected at day 21 after one vaccination [62,36]. Similarly, interim results of Johnson & Johnson vaccine showed a rising of CD4+ T cells at day 14 after a vaccination dose, followed by the production of neutralizing antibodies by 29 days [50]. Finally, phases 1 and 2 trials of CoronaVac vaccine showed immunization of participants in 28 days after each dose of vaccine but IFNγ level, indicating T cells response was low **[22]** (**Table 4**).

Table 4: Immune response induced by COVID-19 different vaccines

Type of vaccine	Cellular immunity	Neutralizing antibodies
AstraZeneca (ChAdOx1 nCoV-19)	NK cell ; $CD8^+$ T cells ; $IFNg^+$ T cells ; IgG^+ B cells rising by day 7-28 after one vaccination	Anti-IgM and anti-IgA increased at day 14 after vaccination; anti-IgG1, anti-IgG3 increased at day 28 after one vaccination
Sputnik V (Gam-COVID-Vac)	Antigen-specific $CD4^+$ and $CD8^+$ T cells with high levels of IFNg at day 28 after one vaccination	SARS-CoV-2 RBD-specific IgGs detected at day 14 after one vaccination
Moderna (mRNA-1273)	Th1 with minimal Th2 cells response after one vaccination; $CD8^+$ T cells response after the second vaccination	Pick of anti-RBD IgGs at day 29 after one vaccination
Pfizer-BioNTech (BNT162b1)	Expansion of IFNg $CD4^+$ cells and $CD8^+$ T cells	Anti-RBD neutralizing IgGs rising at day 21 after one vaccination
Johnson & Johnson (Ad26.COV2.S)	At day 14 after one vaccination, rising of $CD4^+$ T cells, with low $CD8^+$ T cells response	Neutralizing antibodies detected at day 29 after one vaccination
CoronaVac	Low $IFNg^+$T cells response	Neutralizing antibodies responses to live SARS-CoV-2 28 days after each dose

This table shows the cellular immunity and neutralizing antibodies of AstraZeneca, Sputnik V, Moderna, Pfizer-BioNTech, Johnson & Johnson and CoronaVac vaccines.

Delays of vaccines neutralizing antibodies appearance

Figure 5 shows neutralizing antibodies appearance of each candidate vaccine. We note that the Sputnik V vaccine induces neutralizing antibodies earlier than others (14 days after vaccination). It is followed by Pfizer-BioNTech vaccine with neutralizing antibodies detected at day 21 and both, AstraZeneca and CoronaVac vaccines that induce neutralizing antibodies 28 days after vaccination. The Moderna and Johnson & Johnson vaccines come later with neutralizing antibodies released at day 29 post-vaccination (**Figure 5**).

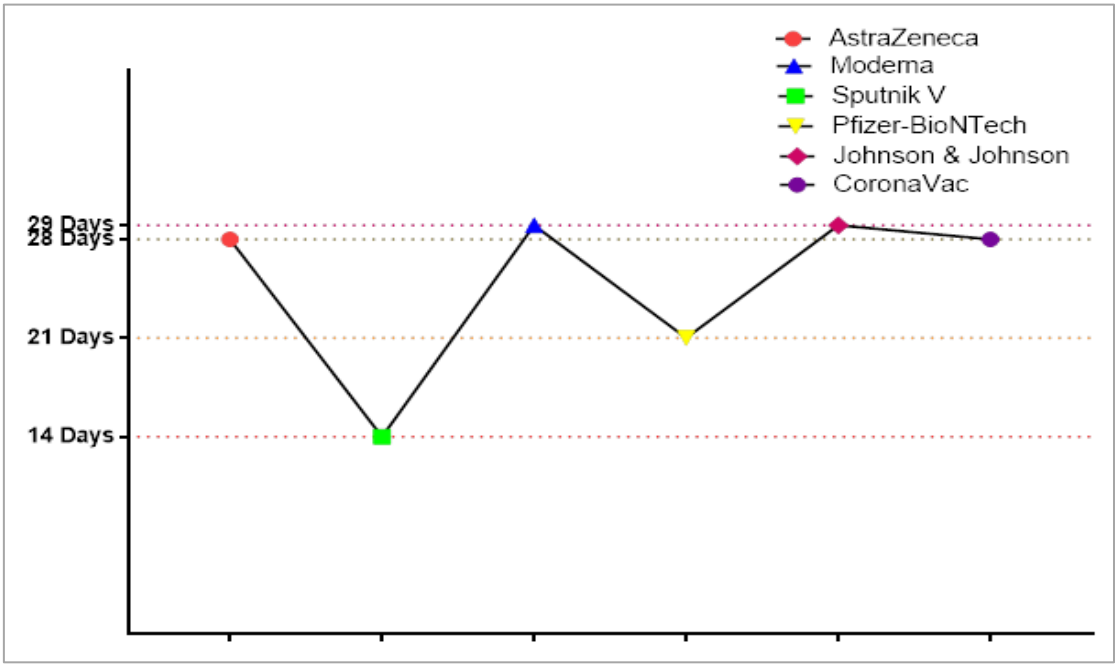

Figure 5: Delays of antibodies appearance. Y axis shows the number of days after one dose of vaccination. X axis shows the different types of vaccines as mentioned in the legend.

Safety concerns

Vaccination, a major advance in infectious diseases prevention, reduces the risk of complications and mortality following exposure to infectious agents. Vaccination induces protection against a pathogen by mimicking its natural interaction with the human immune system [63].

Vaccination is not without consequences. In fact, some people have a background of allergic reactions to a specific food, medicine, or vaccine. Hence, people all over the world have great concerns about the safety of the authorized vaccines against SARS-CoV-2.

The current available literature has revealed some side effects of Pfizer-BioNTech, AstraZeneca, Sputnik V, Moderna, Johnson & Johnson and CoronaVac vaccines although their beneficial role.

Pfizer-BioNTech

Polack *et al* observed in persons of 16 years of age or older that BNT162b2 was 95% effective in preventing COVID-19 (95% credible interval, 90.3 to 97.6). The vaccine efficacy was observed regardless of factors such as age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. The short-term side effects of the vaccine were mild-to-moderate pain at the injection site, fatigue, and headache. In addition, the safety of the vaccine over a median period of 2 months was similar to that of other viral vaccines [47].

AstraZeneca

In participants who received two standard doses (5 × 1010 viral particles), vaccine efficacy was 62.1% and in participants who received a low dose (2.2 × 1010 viral particles) followed by a standard dose, efficacy was 90.0%; overall vaccine efficacy across both groups was 70.4%. In a cohort, Voysey *et al* had in total of 74 341 person-months of safety follow-up (median 3.4 months, IQR 1•3-4.8): 175 severe adverse events occurred in 168 participants, 84 events in the ChAdOx1 nCoV-19 group and 91 in the control group. Three events were classified as possibly related to a vaccine: one in the ChAdOx1 nCoV-19 group, one in the control group, and one in a participant who remains masked to group allocation. As a result of their work, Voysey *et al* concluded that ChAdOx1 nCoV-19 had an acceptable safety profile [42].

Sputnik V

The vaccine had an efficacy of 91.6%. Most reported adverse events were grade 1. 0.3% participants in the vaccine group and 0.4% participants in the placebo group had serious adverse events; none were considered vaccine-associated, with confirmation from the independent data monitoring committee. Four deaths were reported during the study (<0.1% of 16 427 participants in the vaccine group and <0.1% in the placebo group), none of which were considered vaccine-related. The authors of this interim analysis concluded that Sputnik V (Gam-COVID-Vac) was well tolerated in a large cohort [37].

Moderna

The demonstrated vaccine efficacy with mRNA-1273 was 94.1%. Reactogenicity was transient and moderate; rare adverse events were observed and the incidence of vaccination was similar in the mRNA-1273 and the placebo groups. Overall, no safety concerns were identified [49].

Johnson & Johnson

Sadoff *et al* detected neutralizing-antibodies titers against wild-type SARS-CoV-2 in 90% or more of all participants on day 29 after the first vaccine dose, independently of vaccine dose or age group, and reached 100% by day 57 with a further increase in titers in one of their cohorts. Titers remained stable until at least day 71. At the second dose of the vaccine, the titer increased by a factor of 2.6 to 2.9. Fatigue, headache, myalgia, injection-site pain and fever were noted after the first dose of the vaccine, but after the second dose, the occurrence of adverse effects was lower [64].

CoronaVac

Trials were conducted in two groups of subjects, aged 18 to 59 years and 60 years and older. Overall, the incidence of adverse reactions ranged from 8 to 33% depending on the dose of vaccine administered and the timing of sampling. The severity of adverse reactions observed was mild or moderate; the most frequently reported reaction was injection-site pain [41,22]. As of now, it remains a phase 3 trial. For this purpose, 3 µg is the propose dose of CoronaVac for efficacy assessment.

Conclusion

This review aimed to compare six COVID-19 vaccines: AstraZeneca, Pfizer-BioNTech, Sputnik V, Johnson & Johnson, Moderna and CoronaVac. Investigation allowed us to know that around 76 candidate vaccines are being assayed but only the six listed here are homologated. These vaccines which are already being administered are Adenovirus vectored vaccines (AstraZeneca, Sputnik V, Johnson & Johnson), mRNA vaccines (Pfizer-BioNTech and Moderna) and inactivated SARS-CoV-2 (CoronaVac) which mimic SARS-CoV-2 infection, so that immune response produces neutralizing antibodies and memory cells to counteract an eventual infection. Clinical trials have shown that all six COVID-19 vaccines studied are beneficial for immunity although some side effects have been noticed.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' contribution

GK, CNT, PET, CHS, EHK, MOA and DFB performed literature review
GK, CNT, PET, CHS and HEK edited the manuscript
MOA and DFB reviewed the manuscript
GK, YA and SK approved the manuscript for publishing

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