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An Overview of Adenovirus Vector-based Vaccines against SARS-CoV-2

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ABSTRACT

Adenovirus vectors have been employed to develop a vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for curtailing the Covid-19 pandemic spreading. Many different viral vectors have been mainly targeting the SARS-CoV-2 spike (S) protein as an antigen. Spike (S) protein is comprised of S1 and S2 subunits, in which the receptor-binding domain (RBD) of S1 is responsible for recognizing and engaging with its host cellular receptor protein angiotensin-converting enzyme 2 (ACE2), S2 accounts for membrane fusion of virus and host cell. Chimpanzee adenovirus was also used as a vector vaccine for SARS-CoV-2 (ChAdSARS-CoV-2-S) by intramuscular injection, and intranasal administration has been tested. Adenovirus vector-based vaccines are the most advanced, with several vaccines receiving Emergency Use Authorization (EUA). It was shown that rhesus macaques were protected from SARS-CoV-2 challenge after a month of being vaccinated with ChAd-SARS-CoV-2-S. A single intranasal or two intramuscular ChAd-SARSCoV-2-S vaccines could induce humoral antibodies and T cell responses to protect the upper and lower respiratory tract against SARS-CoV-2. As the effectiveness was demonstrated in non-human primates, ChAd-SARS-CoV-2-Sa potential option for preventing SARS-CoV-2 infection in humans. However, detecting novel more transmissible and pathogenic SARS-CoV-2 variants added concerns about the vaccine efficacy and needs monitoring. Moreover, the cause of recently documented rare cases of vaccine indicated immune thrombotic thrombocytopenia. This review article provided details for the adenovirus vector vaccine for SARS-CoV-2 in humans and tried to provide solutions to the adenovirus vector hemagglutinin issue.

Keywords: ACE2, Adenovirus, Immune response, SARS-CoV-2, Spike protein, Vaccine**,** Viral vectors.

INTRODUCTION

Coronaviruses (family Coronaviridae) are common pathogens of humans and animals. Four coronaviruses are endemic in humans (human coronavirus NL63 (HCoV-NL63), HCoV-229E, HCoV-OC43, and HCoV-HKU1) and typically infect the upper respiratory tract, causing common-cold symptoms (Drosten et al., 2003). In the past two decades, three zoonotic coronaviruses (severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2) have infected humans after spilling over from animal reservoirs. Severe acute respiratory syndrome coronavirus originated in China and caused an epidemic in 2003, whereas MERS-CoV is currently causing intermittent outbreaks in the Middle East; SARS-CoV-2 emerged in late 2019 (Peiris et al., 2003; Zaki et al., 2012; Lamers and Haagmans, 2022). They cause a global pandemic of acute respiratory disease, coronavirus disease 2019 (Covid-19), which threatens human public health and safety (Redondo et al., 2021). Approximately 636 million people have been infected with SARS-CoV-2, and about 6.5 million died due to Covid-19 by September 2022 (Lamers and Haagmans, 2022). Coronaviruses enveloped, positive sense single-stranded (+ ss) RNAbelongs to the beta coronaviruses family (Wong and Perlman, 2022). This virus encodes a set of structural proteins (membrane protein, nucleocapsid protein, envelope protein, and spike glycoprotein), non-structural proteins (of which most compose the viral replication and transcription complex), and accessory proteins (Lamers and Haagmans, 2022). The structural proteins and a lipid bilayer derived from the host form an enveloped virion (or virus particle), delivering viral genomic RNA into the cell (Hoffmann et al., 2020). The spike protein is a connection with the target cell receptors (including

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angiotensin-converting enzyme 2 (ACE2), which is involved in the entrance of the SARS-CoV-2 into the host cells (Kirchdoerfer et al., 2018). The SARS-CoV-2 spike(S) protein has been the focus of vaccine research and therapeutic antibodies since its interaction with the cell surface receptor angiotensin-converting enzyme 2 (ACE2) is so essential for coronavirus entry into human cells (Sharma et al., 2020). The Spike (S) protein of SARS-CoV-2 comprises two subunits, S1 and S2, which are subsequently processed to produce a smaller S2 protein (Hassan et al., 2021). In contrast, membrane fusion is promoted by the S2 protein, which contains the receptor-binding domain (RBD) that potently neutralizes monoclonal antibodies (Chhikara et al., 2020). To combat SARS-CoV-2, several academic virology institutes and universities are working together with major pharmaceutical industrial groups to innovate and develop vaccines targeting various platforms, such as the SARS-CoV-2 inactivated virus and subunit vaccines, as well as viral-vectored (Kyriakidiset al., 2021). Emergency use authorization vaccines (Pfizer/BioNTech BNT162b2, Moderna 1273 mRNA, Johnson and Johnson Ad26.COV2, and AstraZeneca ChAdOx1 nCoV-19) were administered by intramuscular injection, which resulted in uncertain mucosal immunity, while other vaccines were in advanced clinical trials in humans to evaluate the safety and efficacy (Prakash 2022). In non-human primates, numerous intramuscular vaccinations protected against pneumonia caused by SARS-CoV-2, but they varied in their abilities to prevent upper respiratory tract infection and transmission (Bingbing et al., 2019; Sternberg and Naujokat, 2020).

An increasing number of preclinical and clinical investigations are now using adenovirus vectors to deliver vaccine antigens, including influenza, measles, hepatitis B, rabies, anthrax, Ebola, severe acute respiratory syndrome (SARS), the human immunodeficiency virus type 1 (HIV-1), malaria, and tuberculosis (Mirzaei et al., 2020). Because they do not integrate into the cells' genome and can provide large titers of recombinant viruses and high levels of gene expression when used in both dividing and non-dividing cells (Tu et al., 2020). Additionally, it was proposed to use an adjuvant to deliver DNA encoding the SARS-CoV-2 S-protein in an oral tablet vaccine based on a non-replicative recombinant adenovirus vector vaccine (Appaiahgari and Vrati, 2015). SARS-CoV-2 vaccines based on a chimpanzee adenovirus (simian Ad-36) and chimpanzee Ad-23 have been approved for use in humans as single intranasal doses and intramuscular injections in most countries, respectively (Tu et al., 2020). The ChAd-SARS-CoV-2-S intranasal dosage produced neutralizing antibodies and T cell responses, restricting or preventing upper and lower respiratory tract infection following the SARS-CoV-2 challenge. SARS-CoV-2 infection and human transmission might be minimized by administering this single intranasal dosage vaccine to non-human primates (Lee et al., 2017; Vrba et al., 2020).

Viral vector-based vaccines for SARS-CoV-2

There are two types of viral vector-based vaccines; replicating and non-replicating. Non-replicating viral vector-based vaccines use replication-deficient viral vectors to deliver genetic material of a particular antigen to the host cell to induce immunity against the desired antigen; there are seven viral vector-based vaccines in use, two of which are Ebola vaccines and five are COVID-19 vaccines (Vanaparthy et al., 2021). Replicating vector vaccines produces new viral particles in the cells they enter, which then enter more new cells and will also make the vaccine antigen (it expresses two types of genes; early genes and late genes (Figure 1). Early genes are responsible for viral replication, while late genes are responsible for virion release (Bulcha et al., 2021). They are used as vaccine vectors against numerous infections like human immunodeficiency virus (HIV), malaria, and tumor-associated antigens (Vanaparthy et al., 2021).

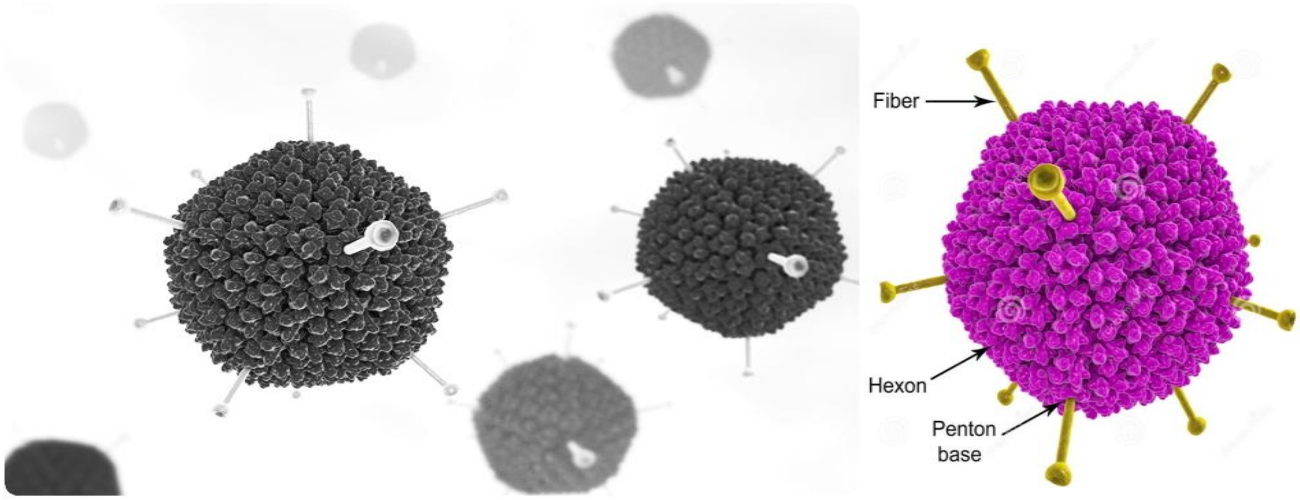

Figure 1. Molecular model of an adenovirus (Image retrieved from https://www.dreamstime.com/stock-illustration)

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Advantages and disadvantages of viral vector

Advantages of viral vectors

Viral vectors have the unique property of acting as vaccine vectors and inducing innate and adaptive immune responses in mammalian hosts (Zaiss et al., 2005). The concept of viral vector vaccines differs from that of subunit vaccines, as the latter help prevent infectious diseases by eliciting a humoral response (Sasso et al., 2020). Recombinant viral vectors are potentially therapeutic because they enable intracellular antigen expression and induce a robust cytotoxic T lymphocyte (CTL) response, eliminating virus-infected cells. Despite their efficacy, viral vectors present unavoidable problems that need to be addressed. In the near future, viral vector-based vaccines may be increasingly used to fight major diseases (Zaiss et al., 2005).

Disadvantages of viral vectors

Some viral vector integration of their genome into the host genome can lead to cancer. Another obstacle to the clinical use of viral vectors presents pre-existing immunity against the vector due to previous exposure to the virus and the production of neutralizing antibodies that reduce vaccine efficacy (Wang et al., 2019). The development of viral vectors requires a high biological safety level to gain public acceptance, non- (or low) pathogenic viruses are often selected (Verdera et al., 2020). In most cases, viruses are genetically engineered to reduce or eliminate pathogenicity. Additionally, most viral vectors are replication-defective. For example, in adenovirus-based vectors, the E1A and E1B encoding regions needed for replication in infected cells are deleted and replaced with the target gene (Custers et al., 2021). If adenovirus is used as a vaccine vector, it may be difficult or impossible to provide future booster doses because the human body develops tolerance to the vector. People with immunity to adenoviruses may find that vector distribution is ineffective in certain situations (Wang et al., 2019; Afshar et al., 2022).

Although only a few hundred cases have been reported among the more than several million vaccinated people worldwide, the problem should be solved promptly. After the first detected cases in individuals vaccinated with the ChAdOx1 nCoV-2 vaccine, persons were vaccinated with the Ad26. CoV2.S vaccine also developed vaccine-induced immune thrombotic thrombocytopenia (Chen et al., 2021). Adenovirus gene transfer was previously associated with vaccine-induced immune thrombotic thrombocytopenia and has been induced by adenovirus vaccine administration (Poland, et al., 2020). One of the common factors for all vaccines causing vaccine-induced immune thrombotic thrombocytopenia is using the SARS-CoV-2 S protein as the antigen. It was postulated that the generated soluble S protein variants are responsible for severe side effects by binding to ACE2-expressing endothelial cells in blood vessels leading to thromboembolic events (DeFrancesco, 2020; Nappi et al., 2021). The vaccine-induced immune thrombotic thrombocytopenia disease mechanism includes the interaction of the SARS-CoV-2 S protein with C-type lectin receptors, heparin sulfate proteoglycans and the CD receptor, and interaction of the adenovirus vector with the CD receptor or platelet factor antibodies (Desheva, 2018). Although some ideas and hypotheses have been presented, the reasons for causing vaccine-induced immune thrombotic thrombocytopenia are still unresolved and require further investigations (Chung et al., 2020). As initially established by Rosén in 1958, HA by human adenoviruses (A through F) exhibits various HA characteristics. Subgenus D adenoviruses may be divided into three clusters: cluster DI adenoviruses agglutinate both rat and human erythrocytes, cluster DII adenoviruses agglutinate only rat erythrocytes, and cluster DIII adenoviruses agglutinate only rat erythrocytes (Amanat et al., 2021). Erythrocyte agglutination is fiber-mediated, and particular receptors on the erythrocyte membrane appear to be involved. Intact virions can build a bridge between erythrocytes, resulting in HA, since they contain multiple fibers. Fibers alone cannot induce HA since they are just one valent. The polymers that may agglutinate erythrocytes are derived from fibers derived from tissue cultures and recombinant fibers. A study of the amino acid sequences on the fiber knob showed unique domains that may be involved in rat and human erythrocyte agglutination (Pring-Åkerblom et al., 1998). The 27 chimeric and mutant Ad9 (subgenus DI), Ad17 (subgenus DII), Ad28 (subgenus DIII), and Ad3 (subgenus B) fiber proteins produced in Escherichia coli were used to identify and describe these domains (Lee et al., 2017; Rhodes, 2021). The simian adenovirus vector ChAdOx1 was utilized in one approach to avoid any pre-existing adenovirus immunity in humans. As shown in tables 1 and 2, The ChAdOx1 nCoV-19 vaccine candidate showed protection in immunized rhesus macaques (Vrba et al., 2020; Wang et al., 2021a).

Adenovirus and adeno-associated virus vector-based vaccines

Adenovirus vectors have a long tradition as gene transfer and vaccine vectors, particularly the second and third-generation adenovirus vectors, have demonstrated high safety levels and good delivery efficacy (Dormond et al., 2009). The codon-optimized SARS-CoV-2 S protein has been utilized as the common antigen although different strategies related to vector engineering have been applied, as shown in figures 2 and 3. COVID-19 vaccines derived from viral vectors have been produced using adenoviruses (Ad5) serves as vector' for the SARS-CoV2 surface protein gene in four prospective COVID-19 vaccines that expression of the spike glycoprotein from SARS-CoV-as shown in figures 2 and 3 (Ku et al., 2021; Berndt et al., 2021). The efficacy of Ad5-nCoV was assessed in mice and ferrets, in which SARS-COV-2 replication occurs in the upper respiratory tract but not in the lungs (Wu et al., 2020). Both intranasal and

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intramuscular administration routes were tested, and IN resulted in complete protection against SARS-CoV-2 in the upper and lower respiratory tracts in mice (Table 1). However, concerns regarding issues with IN administration in people with asthma led to IM being chosen for Ad5-nCoV vaccination in the first human clinical trials (Zhu et al., 2020).

Human adenovirus serotype 26 vaccines

Janssen/Johnson and Johnson (Ad26.COV2-S)

The Ad26.COV2-S vaccine developed by Janssen Vaccines and Prevention BV (Johnson and Johnson) uses a first-generation Ad26 vector (E1/E3 deleted) to deliver the pre-fusion stabilized SARS-CoV-2 spike protein. This protein has been stabilized through a mutation in a furin cleavage site, and a proline substitution. Details of these modifications are reviewed in (Bos et al., 2020). A single-dose vector administration protected the animals against severe SARS-CoV-2 pneumonia and mortality. In a non-human primate model, the vaccine elicited strong neutralizing antibody production after a single dose intramuscular administration and conferred protection against the SARS-CoV-2 challenge. The authors noted that additional studies are needed to assess this vector's mucosal delivery and evaluate the durability of the established near-complete protection against SARS-CoV-2 infection (Berndt et al., 2021). Ad26.COV2-S was used as a single-shot vaccine in people aged 18 and ups in the United States and 40 other countries (Kurup and Schnell, 2021). However, in mid-April, US regulators temporarily paused Ad26.COV2-S vaccine administration to investigate 15 reported cases of severe thrombosis with thrombocytopenia, out of 7.98 million doses administered. Similar results have been reported in individuals receiving the ChAdOx1-nCov19 vaccine outside the US (Table 1). Following an FDA/CDC review and a risk/benefit analysis, vaccine administration was resumed - the risk of developing the rare vaccine-induced condition, termed thrombosis with thrombocytopenia syndrome (TTS, Kowarz et al., 2022).

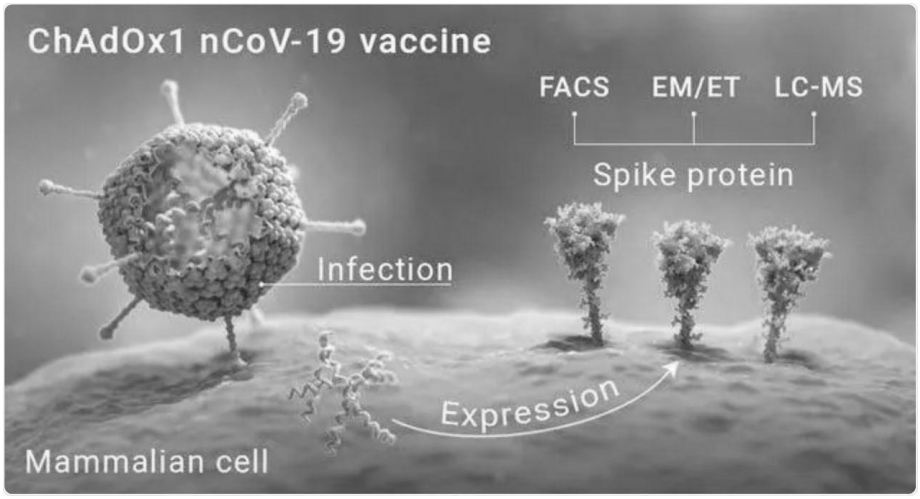

Figure 2. The protein spikes form on the surface of cells presented with the vaccine (Watanabe et al., 2021).

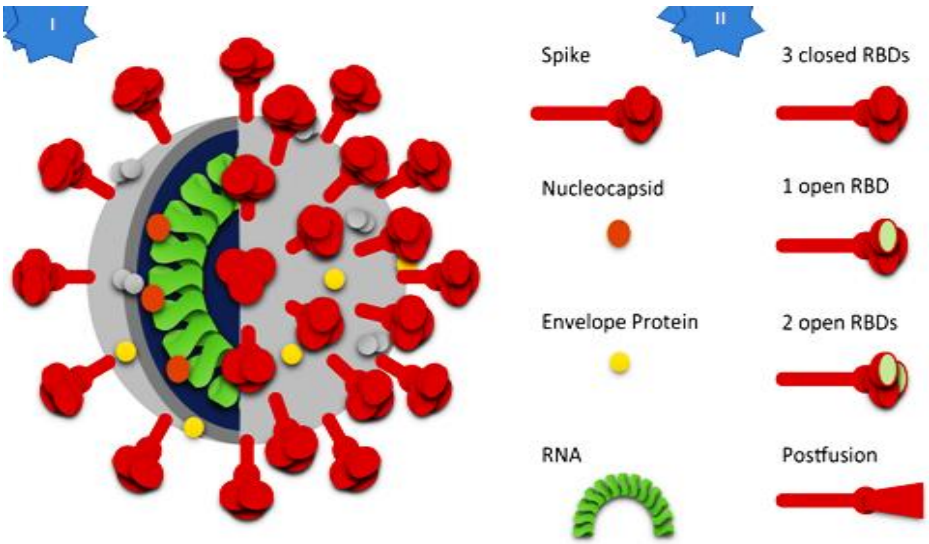

Figure 3. Coronavirus structure and relevant aspects for vaccine development. I: Current vaccines are capitalizing on epitopes in the SARS-CoV-2 proteins to elicit immune responses. The major proteins used for vaccine development are the nucleocapsid, and the spike protein, essential for cell entry. II: Spike protein can have conformation modifications protease-mediated. The stabilization of the protein in its prefusion form improves protein expression as well as immunogenicity (Mendonça et al., 2021).

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Table 1. List of SARS-CoV-2 vaccines for their characteristics, efficacy, and effectiveness against SARS-CoV-2

Type of vaccine / Manufacturer	Dose/ Injection dose interval in the phase III trial	Condition of use/storage	Composition	Reference
RNA-based BNT16b2 Pfizer/BioNtech	30 µg 5–7-dose vial 0.3 mL per dose Intramuscularly 2 doses 21 days apart	Frozen vials prior to use can be stored before dilution fom -80°C to -60°C up to the end of their expiry date or from-25°C to -15°C for up to 2 weeks	A synthetic messenger ribonucleic acid (mRNA) encoding the spike protein of SARS-CoV-2, lipids, Pbs, and sucrose	World Health Organization (2021)
mRNA-1273/ Moderna	100 µg 11 or 15-dose vial 0.5 mL per dose/ Intramuscularly 2 doses 28 days apart	Supplied as a frozen suspension stored between -50°C and-15°C Unopened vial: +2°C to +8°C for up to 30 days +8°C to +25°C for up to 24 hours After opening: +2°C to +25°C and discarded after 12 hours	A synthetic messenger ribonucleic acid (mRNA) encoding the spike protein of SARS-CoV-2. The	
RNA-based / CVnCoV	12 µg/ Intramuscularly 2 doses 28 days apart	Concentrated CVnCoV will be stored frozen at -60°C (in the clinical trial) CVnCoV must be diluted Unopened vial: 3 months at +2°C to +8°C Room temperature for 24 hours	NA	
AstraZeneca/University of Oxford / AZD ChAdOx1 nCoV-19 vaccine Non-replicating viral vector	5×10^{10} viral particles (standard dose) 8 doses or 10 doses of 0.5 mL per vial/ Intramuscularly 2 doses 4–12 weeks apart	Do not freeze Unopened vial: 6 months (+2°C to +8°C) After opening: no more than 48 hours in a refrigerator (+2°C to +8°C) Used at temperature up to +30°C for a single period of up to 6 hours	Chimpanzee Adenovirus encoding the SARS-CoV-2 spike glycoprotein (ChAdOx1-S), not less than 2.5×10^{8} infectious units (Inf.U)	
Ad26.COV2.S/ Johnson and Johnson Non-replicating viral vector	5×10^{10} viral particles 10 doses of 0.5 mL per vial/ Intramuscularly A single dose	Should be protected from light Supplied as a liquid suspension Unopened vial can be stored at +2°C to +8°C until the expiration date or at +9°C to +25°C for up to 12 hours	Replication-incompetent recombinant adenovirus type 26 vector expressing the SARS-CoV-2 spike protein in a stabilized conformation. (5×10^{10} vp)	
Gam-COVID-Vax Sputnik V/ Gamaleya Research Institute/ Non-replicating viral vector	10^{11} viral particles per dose for each recombinant adenovirus 0.5 mL/dose/ Intramuscularly 2 doses 21 days apart	Transport: two forms: lyophilized or frozen Storage: +2°C to +8°C	Two vector components, rAd26-S and rAd5-S	
NVX-CoV2373/ Novavax/ Protein-based	5 µg protein and 50 µg Matrix-M adjuvant/ Intramuscularly 2 doses 21 days apart	Liquid formulation Storage: +2°C to +8°C	SARS-CoV-2 rS with matrix-M1 adjuvant (5 µg antigen and 50 µg adjuvant)	
CoronaVac/ Sinovac Biotech/ Inactivated virus	3 µg 0.5 mL per dose/ Intramuscularly 2 doses 28 days apart	Supplied as a vial or syringe of 0.5 mL Do not freeze Protect from light Storage and transport between +2°C and +8°C Shake well before use Shelf-life: 12 months	Inactivated CN02 strain of SARS-CoV-2 created with Vero cells Aluminum hydroxide, disodium hydrogen phosphate dodecahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride	
BBIBP-COrV	4 µg 0.5 mL per dose/ Intramuscularly 2 doses 21–28 days apart	Supplied as a pre-filled syringe or vial Cannot be frozen Protect from light Store and transport refrigerated (+2°C to +8°C)	Inactivated virus 19nCoV-CDC-Tan-HB02 Excipients: disodium hydrogen phosphate, sodium chloride, sodium dihydrogen phosphate, aluminum hydroxide adjuvant	
Covaxin	6 µg Single dose: 0.5 mL 10-dose or 20-dose vial/ Intramuscularly 2 doses 28 days apart	Supplied as a single dose or multidose vial Do not freeze Stored at +2°C to +8°C	6 µg whole-virion inactivated SARS-CoV-2 antigen (strain: NIV-2020-770), and other inactive ingredients such as aluminum hydroxide gel (250 µg), TLR 7/8 agonist (imidazoquinolinone) 15 µg, 2-phenoxyethanol 2.5 mg, and phosphate buffer saline® up to 0.5 m	

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Table 2. Based on observation, adverse reactions to vaccinations were observed in several cases during Coronavirus Disease 2019

Vaccine	Serious adverse events	Cases per million doses administered	Country	Age	Number of participants or doses studied	References
RNA-based BNT16b2 Pfizer/BioNtech	Anaphylaxis	4.8/million	USA	≥12 years	11.8 million doses administered (57% BNT162b2) to 6.2 million individuals	(Klein et al., 2021)
	Anaphylaxis + anaphylactoid reactions	476 cases among 40 million doses	UK	≥16 years	40 million doses (1 and 2)	
	Myocarditis Lymphadenopathy Appendicitis Herpes zoster infection	2.7/100 000 78.4/100 000 5/100 000 15.8/100 000	Palestine	≥16 years	1 736 832 participants (884 828 vaccinated)	
	Bell's palsy Myocarditis/Pericarditis Transverse myelitis	2.6/100 000 0.86/100 000 0.01/100 000	Hongkong	≥12 years	4 776 700 doses	
	Myocarditis Pericarditis	6/million 4.9/million	UK	≥16 years	40 million doses (1 and 2)	
mRNA-based / CVnCoV	Anaphylaxis	5.1/million	USA	≥12 years	11.8 million doses administered (43% mRNA-1273) to 6.2 million individuals	(Klein et al. 2021)
		2.5/million	USA	≥16 years	4 041 396 doses	(CDC, 2021)
	Myocarditis Pericarditis	20.4/million 14.8/million	UK	≥18 years	2.3 million doses (1 and 2)	
AstraZeneca/University of Oxford / AZD ChAdOx1 nCoV-19 vaccine Non-replicating viral vector	Thromboembolic events	0.61/million	India	≥18 years	Retrospective survey of 75 random subjects	
	Thrombosis with thrombocytopenia syndrome Capillary Leak Syndrome Myocarditis Pericarditis Anaphylaxis or anaphylactoid reactions	14.9/million 20.5/million 12 cases among 48,9 million doses 2.1/million 3.3/million 816 cases among 48.9 million doses	UK	≥18 years 18–49 ≥18 years	48.9 million doses (1 and 2)	
	Guillain-Barré syndrome	833 cases among 592 million doses	Worldwide	≥18 years	592 million doses	(EMA, 2021)
	Thrombosis with thrombocytopenia syndrome	1503 cases among 592 million doses	Worldwide	≥18 years	592 million doses	
Ad26.COV2.S/ Johnson and Johnson Non-replicating viral vector	Thrombosis with thrombocytopenia syndrome Guillain–Barré syndrome	45 cases for 14.3 million doses (3/million) 185 cases for 14.3 million	USA	≥18 years	14.3 million doses	
Sputnik V	Expected local and systemic reactions The most frequent symptoms were local pain, asthenia, headache, and joint pain	2.1% of participants suffered severe reactions in San Marino's population	Republic of San Marino	18–89 years	Cohort of 2558 participants	(Montalti et al., 2021)
CoronaVac	Bell's palsy Encephalopathy	3.8/100 000 0.01/100 000	Hong Kong	≥12 years	n = 2 811 500 doses	
	Anaphylaxis Thromboembolic events Bell's palsy Guillain–Barré syndrome	2/million 1.15/million 8.73/million 0.29/million	Chile	≥16 years	n = 13 862 155 doses	
BBIBP-COrV	No serious side effects were reported	—	Jordan	Mean age: 35–40 years	No date specified	
	No severe side effects were reported.	—	Iraq	≥18 years		

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Sputnik V (gam-COVID-vac)

Sputnik V is a vaccine candidate developed by the Gamaleya Research Institute in Russia. The vaccination protocol consists of a two-dose regimen utilizing two human Ads: Ad26 as prime and Ad5 as a boost. Heterologous Ad vector prime-boost immunization protocols, where a different type of virus is applied at each dose, are used to circumvent immune responses against the viral vector. To assess the efficacy of Sputnik V, two phases with three clinical trials were carried out (NCT04530396, NCT04564716). In an interim report of the NCT04530396 trial, involving 21,977 adults, the vaccine candidate with a prime-boost regimen showed 91.6% efficacy against COVID-19 (Table 1). Regarding safety, the reported adverse events were mostly graded 1, and none of the reported serious adverse events could be associated with the vaccination. As of April 2021, Sputnik V was approved for emergency use in Russia and several other countries (Mendonça et al., 2021).

Non-human adenovirus vaccines

Oxford/AstraZeneca (ChAdOX1-nCoV)

During the 2012 Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak, the Oxford group developed a vaccine using their ChAd (chimpanzee Ad) technology, which circumvents pre-existing immunity to Ad5 (Ewer et al., 2017. The vector was developed from an Ad isolated from a chimpanzee fecal sample and vectorized by deletion of E1/E3 and modifications in E4 (E4Orf4, Orf6, and Orf6/7 swapped with human Ad5). The Oxford AstraZeneca COVID-19 vaccine uses a replication-deficient chimpanzee adenovirus vaccine vector (ChAdOx1) that has been authorized for usage, recombinant adenovirus type 26 (Ad26) in the Johnson and Johnson COVID-19 vaccineAd5-nCoV and UQ-CSL V451 both employ recombinant adenovirus type-5 (Ad5), Gam-COVID-Vac (also known as Sputnik-V) vaccine uses an Ad26-based vaccination as shown in figures 2 and 3 (Zhu et al., 2020). The fiber protein is responsible for the virion's attachment to specific cell surface receptors (Giacca and Zacchigna, 2012). An N-terminal tail, a variable-length shaft, and a globular C-terminal knob make up the fiber protein that protrudes from the 12 vertices of the capsid (Holterman et al., 2004). Molecular recognition and nuclear localization signals are both located at the conserved N terminus (Wang et al., 2019). Adenovirus fibers' receptor binding selectivity may be adjusted by swapping knob domains, as evidenced by studies demonstrating the Ad5 knob's ability to prevent viral infection. Adenoviruses of subgenus C and Ad9 (of subgenus D) share a fiber receptor, but subgenus C and B adenovirus serotypes recognize different receptors. A 46-kDa HeLa cell surface protein has recently been shown to function as a shared receptor for adenoviruses of subgenus C and coxsackie B viruses (Tatsis and Ertl, 2004). Furthermore, it has been found that the class I major histocompatibility complex can also act as an adenovirus receptor (Appaiahgari and Vrati, 2015). The fiber knob also carries the type-specific antigen, which defines, together with the hexon's antigen, the adenovirus's serotype specificity. The determinant consists of at least 17 amino acids that are not confined to a specific area on the fiber knob (Ricobaraza et al., 2020). The positive findings from preclinical studies in rodents and non-human primates supported the transfer to clinical trials with the ChAdOx1 nCoV-19 vaccine candidate (Lombardi et al., 2021). High safety and both humoral and cellular immune responses were obtained in phase I/II clinical trials, as shown in figures 2 and 3 (Lu et al., 2020; Lombardi et al., 2021). Additionally, phase III clinical evaluation of more than 30,000 volunteers has been conducted (Bricker et al., 2021). Interim phase III results from the UK, Brazil, and South Africa showed good vaccination safety and 62.1% vaccine efficacy after two vaccinations with 5×10^{10} ChAdOx1 nCoV-19 particles and up to 90% in individuals receiving a prime dose of 2.2×10^{10} particles and a boost of 5.5×10^{10} particles as shown in Table 1 and 2(Douglas, 2007; Basheeruddin Asdaq et al., 2022).

The ChAdOx1 nCoV-19 vaccine received a EUA in the UK in December 2020 (Cederwall and Påhlman, 2019; Kashte et al., 2021). In contrast to the ChAdOx1 nCoV-19 vaccine, the Ad26.COV2.S vaccine is based on the human Ad26 serotype expressing the prefusion-stabilized SARS-CoV-2 S protein, and requires only one immunization (Cederwall and Påhlman, 2019). This was confirmed in hamsters, where a single injection of Ad26.COV2.S elicited neutralizing antibodies and protected the animals from SARS-CoV-2-associated pneumonia and death (Biserni, et al., 2021). Moreover, a single immunization of macaques elicited strong neutralizing antibody responses and protected against SARS-CoV-2 challenges (Baron et al., 2018). In the context of clinical trials, a single administration of Ad26.COV2.S elicited rapid binding, neutralization antibody responses, and cellular immune responses in a phase I study in 25 healthy volunteers (Ricobaraza et al., 2020). Moreover, 1,045 healthy volunteers were vaccinated with a single dose of 1×10^{10} or 5×10^{10} Ad26.COV2.S particles in phase I/II study showed good safety and strong immune responses (Spunde et al., 2022).

The Ad26.COV2.S vaccine has been subjected to large phase III clinical trials with 60,000 participants (Coughlan, 2020, Bibby et al., 2022). As mentioned earlier, simian adenovirus vectors have been used for SARS-CoV-2 vaccine development to address any potential pre-existing immunity against human adenoviruses in the population (Folegatti et al., 2022).

However, the current adenovirus-based vaccines, except for Ad26.COV2.S requires a prime-boost regimen (Almuqrin et al., 2021). Neutralizing antibodies against adenoviruses might reduce the efficacy of a second or a third

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immunization with the same adenovirus serotype. For this reason, a strategy of prime vaccination with an Ad26 serotype vector expressing the SARS-CoV-2 S protein followed by a booster vaccination with another adenovirus serotype, the Ad5 expressing the SARS-CoV-2 S protein, was evaluated (Pei et al., 2019). In preclinical studies, the rAd26-S/rAd5-S vaccine candidate showed 100% protection in transgenic mice, hamsters, and primates (Punga et al., 2020). Moreover, good safety, mild adverse events, and robust immune responses were observed in phase I/II clinical trials (Soudet and Stutz, 2019). Phase III study with the rAd26-S/rAd5-S vaccine showed tolerability and 91.6% vaccine efficacy (Poland et al., 2020). The rAd26-S/rAd5-S (Sputnik V) vaccine received a EUA in Russia in July 2020, although only preliminary vaccine evaluation had been conducted in 76 volunteers (DeFrancesco, 2020).

A third-generation Ad5 serotype vector expressing the SARS-CoV-2 S protein (Ad5-S-nb2) was intramuscularly administered into mice and ferrets, which resulted in protection against challenges with SARS-CoV-2 (Desheva, 2018). Moreover, the Ad5-S-nb2 vaccine provided projection against SARS-CoV-2 in rhesus macaques (Chung et al., 2020). In the case of clinical trials, a single dose of Ad5-S-nb2 induced both binding and neutralizing antibodies in healthy volunteers (Zhu et al., 2020). However, the level of response depended on pre-existing Ad5 antibodies and the age of the vaccinated person (Giacca and Zacchigna, 2012). Interim results from a phase III trial indicated that a single dose of the Ad5-S-nb2 vaccine showed an overall efficacy of 65.3% in preventing all symptomatic COVID-19 disease 28 days post-vaccination (Wang et al., 2019). Moreover, Ad5-S-nb2 showed a 90.1% efficacy in preventing severe COVID-19 disease 28 days post-immunization. The Ad5-S-nb2 received a EUA in February 2021 in China (Holterman et al., 2004). The gorilla adenovirus GRAd has been used to express the perfusion-stabilized SARS-CoV-2 S protein (Appaiahgari and Vrati, 2015). The GRAd-COV2 vaccine candidate elicited robust immunogenicity in both mice and macaques. The functional antibodies neutralized SARS-CoV-2 infection blocked SARS-CoV-2 S protein binding to angiotensin-converting enzyme 2 (ACE2) and generated robust Thelper 1(Th1)-dominated cellular responses. The GRAd-COV2 vaccine candidate is undergoing phase I evaluation (Ricobaraza et al., 2020). In another vaccine approach, the chimpanzee adenovirus serotype 68 (ChAdV68; Rhodes, 2021) was combined in a prime-boost regimen with a SAM expressing the SARS-CoV-2 S protein and T-cell epitopes from the SARS-CoV-2 N protein. A dose-escalation phase I clinical trial with a ChAdV68 prime vaccination and SAM boost vaccination is in progress (Lu et al., 2020). The AAV vector-based vaccine candidate AAVCOVID-1 was recently introduced (Wang et al., 2021b). The SARS-CoV-2 S gene was expressed from an AAV2 inverted terminal repeat (ITR) with an AAVrh32.33 capsid, showing potent immunogenicity in mice and non-human primates. Moreover, a single immunization provided complete protection in macaques challenged with SARS-CoV-2. Neutralizing antibodies were sustained for a year. Neither pre-existing immunity against AAVCOVID-1 in humans nor cross-reactivity to common AAV vectors used in gene therapy were detected. Single-dose administration, high-yield manufacturing, and one-month stability at room temperature make the AAV-based approach attractive for potential global use once efficacy has been confirmed in clinical trials (Zabaleta et al., 2021).

Immunogenicity, safety results of current adenovirus vaccines

Evaluation of vaccine immune response

A reliable assessment of a vaccine capacity to generate T-cell responses might be made using quantitative approaches, such as intracellular cytokine testing (Zeedan et al., 2014; Zeedan et al., 2019). It is impossible to verify the effectiveness of vaccination using such quantitative approaches as titration or challenge with a virus that produces severe injury or death in experimental animals (Wang et al., 2021, Zabaleta et al., 2021). Due to their capacity to stimulate innate immune system cells, induce the maturation of immature dendritic cells into antigen-presenting cells, and express significant levels of transgene products in the majority of vectors, deleted AdHu5 vectors have a high level of immunogenicity (Zhou and Ertl, 2006; Horton et al., 2007, McLean, 2018).

ChAdOx1 nCoV-19 was safe, tolerated, and immunogenic, while reactogenicity was reduced with paracetamol. A single dose elicited both humoral and cellular responses against SARS-CoV-2, with a booster immunization augmenting neutralizing antibody titers (Das et al., 2022). The preliminary results of this first-in-human clinical trial supported clinical development progression into ongoing phase 2 and 3 trials. Older age groups with comorbidities, health-care workers, and those with higher risk for SARS-CoV-2 exposure are being recruited and assessed for efficacy, safety, and immunogenicity of ChAdOx1 nCoV-19 given as a single-dose or two-dose administration regimen in further trials conducted in the UK and overseas. Evaluation of the vaccine in children once sufficient safety data have been accumulated in adult studies. Phase 3 trials are now underway in Brazil, South Africa, and the UK and will evaluate vaccine efficacy in diverse populations, as shown in tables 1 and 2 (Folegatti et al., 2020).

SARS-CoV-2 variants and vaccine efficacy

Despite the success achieved in developing vaccines against COVID-19, the detection of novel SARS-CoV-2 lineages has raised concern about vaccine efficacy. For instance, the B.1.1.7 variant (alpha) was initially claimed to possess higher transmission rates and was found to spread rapidly in the UK (Dhawan et al., 2022). The alpha variant

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carrying the N510Y mutation and deletion of amino acids 69 and 70 in the RBD of the SARS-CoV-2 S protein was determined to be 75% more transmissible than the wild-type strain with the 501N sequence. It was recently demonstrated that individuals who tested positive for the alpha variant showed a mean log10 viral load 1.05 higher than non-alpha variant subjects (Jones et al., 2021). In addition to the alpha variant, the South African B.1.351 (beta, Mwenda et al., 2021), the Brazilian B.1.1.28.1 (gamma), and the Indian B.1.617 (Cantón et al., 2021) variants have been identified. Related to vaccine efficacy, adenovirus vector-, RNA-, and protein subunit-based vaccines have been tested. A small but significant reduction in neutralizing antibody activity against the N501A and the K417N-E484K-N501Y mutations in the SARS-CoV-2 S protein was detected for the two approved RNA-based vaccines (Wang et al., 2021). In another study, 20 volunteers vaccinated with the BNT162b2 RNA vaccine showed similar neutralizing titers to SARS-CoV-2 with either N501 or Y501 in the S protein, nanoparticle encapsulated SARS-CoV-2 S protein subunit vaccine NVX-CoV22373 the efficacy against the alpha variant was 86%, and against the beta, the variant was 60% (Xie et al., 2021). In the case of adenovirus-based vaccines, variability related to protection efficacy has been discovered. For instance, in a phase II/III trial, similar vaccine efficacy against the alpha variant and other lineages was obtained (Chi et al., 2022). However, reduced neutralization activity was measured against the alpha variant compared to non-alpha variants in vitro after ChAfdOx1 nCoV-19 vaccine administration (Mahase, 2021). Despite that, the vaccine protected against the alpha variant. However, in another study, the ChAdOx1 nCoV-19 failed to provide protection against mild-to-moderated COVID-19 caused by the beta variant (Madhi et al., 2021).

In contrast, Ad26.COV2.S vaccine showed clinical efficacy against symptomatic COVID-19 and also against the beta variant despite its partial resistance to neutralizing antibodies (Alter et al., 2021). Moreover, humoral and cellular responses against the original SARS-CoV-2 strain and the beta variant were observed. However, the median pseudovirus-neutralizing antibody titers were 5-fold lower than the original SARS-CoV-2 strain. Overall, the detected and potentially emerging new variants demand a thorough follow-up on vaccine efficacy and the readiness to re-engineer available vaccines to ensure the efficacy of vaccine protection (Alter et al., 2021).

Properties of adenoviruses

Double-stranded DNA adenoviruses have genomes between 34 and 43 kb, making them easier to manipulate for reprogramming. Figure 1 shows how alternative splicing and poly(A) sites in different polypeptide strands helped the virus adapt to its small genome. Adenoviruses were the first respiratory viruses to be identified in tissue culture. The capacity of diverse human and animal organ and tissue cells to develop in vitro on synthetic medium, as well as the ability of viruses to replicate on sensitive cells, resulting in cytopathic effects. The Adenoviridae family includes at least 120 viruses that may infect mammals, birds, reptiles, amphibians, and fish (Bricker et al., 2021; Lombardi et al., 2021). There are 51adenovirus serotypes from humans and 27 serotypes from simians, including seven chimpanzee serotypes that are isolated from other mammalian species and cause infections ranging from mild respiratory infections to life-threatening multi-organ diseases. The six most studied human serotypes (A-F; B1, and B2) were split into B1 and B2 based on sequence homology and their capacity to agglutinate red blood cells (Tatsis and Ertl, 2004; Douglas et al., 2007). Adenovirus types are presently included in Rosen's hemagglutination Group I, although they are generally considered typical members. Three types indicated three important points included hemagglutination titers which were consistently higher with a rat than with rhesus or African green monkey erythrocytes; hemagglutination inhibition titers might be readily demonstrated with rats but not with rhesus erythrocytes. Standardized hemagglutination and hemagglutination inhibition procedures were described and statistically evaluated for all (Cederwall and Påhlman, 2019; Zeedan et al., 2020).

Adenovirus infections

Adenoviruses can cause both acute and long-term symptoms. Adenovirus of the human serotypes (AdHu), including AdHu1, AdHu2, and AdHu5 (subgenus C), frequently infect people and cause various symptoms, such as mild upper respiratory infections in children. Pneumonia (AdHu4) and meningoencephalitis (AdHu7, 12, and 32) can result from adenoviruses, especially in immunocompromised persons and children (Baron et al., 2018). The signs and symptoms of adenoviruses in chimpanzees, which are being studied for vaccine development, are yet unclear. Several human adenovirus serotypes were widely distributed and infected the majority of infants and young children in the early stages of their lives (Ricobaraza et al., 2020). According to several studies, 45% to 80% of persons had antibodies that neutralized AdHu5 viruses (Spunde et al., 2022). Depending on the location where they live, 5-15% of adults had virus-neutralizing antibodies to AdHu 35. Chimpanzee viruses were typically utilized in preclinical vaccination testing (Biserni et al., 2021).

Tropism

The capacity of adenoviruses to bind to host cell receptors is known as tropism (Baron et al., 2018; Spunde et al., 2022). The distal knob domain of the fiber initially binds to the coxsackie adenovirus receptor (CAR), which is

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expressed on many cell types, including hepatocytes, the basolateral surface of epithelial cells, endothelial cells, myoblasts, and heart muscle cells. Even though lymphoid cells lack the ability to produce CAR, they serve as a reservoir for viral infections that utilize CAR (Baron et al., 2018).

Hemagglutination

Adenoviruses, rubeola, and myxoviruses have a standardized hemagglutination (HA) test reproducibility of 84 to 96 percent, whereas reoviruses have a standardized hemagglutination-inhibition test reproducibility of 78 to 93 percent (Ricobaraza et al., 2020). Since Roséninitially demonstrated HA by human adenoviruses in 1958, serotypes of six subgenera(A-F) exhibit various characteristics. Subgenus D adenoviruses may be divided into three clusters. Cluster DI adenoviruses agglutinate both rat and human erythrocytes, and cluster DII adenoviruses agglutinate only rat erythrocytes (Coughlan, 2020). The adenovirus fiber mediates the agglutination of erythrocytes. Based on differential hemagglutinating properties, subgenus D adenoviruses can be subdivided into clusters DI, DII, and DIII. While subgenus DI adenoviruses agglutinate rat and human erythrocytes, DII adenoviruses simply agglutinate rat erythrocytes and DIII adenoviruses display no or only weak rat erythrocyte agglutination (Spunde et al., 2022). Amino acid sequence comparisons revealed distinct domains on the fiber knob, which could be involved in hemagglutination. To localize and characterize the domains responsible for the interaction with rat and human erythrocytes, potential hemagglutination domains of the adenovirus type 9 (Ad9, subgenus DI) fiber knob was introduced into Ad17 (subgenus DII) and Ad28 (subgenus DIII) fiber knobs by primer-directed mutagenesis (Bibby et al., 2022). Furthermore, rat erythrocyte hemagglutination domains were also introduced into the Ad3 (subgenus B) fiber knob, which only agglutinated monkey erythrocytes (Folegatti e al., 2022). The recombinant proteins were tested in HA tests. All eight subgroups I strains were related to prototype C-1 chimpanzee adenovirus and human adenovirus type 16. Six strains of subgroup II were closely antigenically related to each other, and human adenovirus type 5 by hemagglutination inhibition (HI). Four additional strains were partially cross-reactive in HI tests with human adenovirus type 2 and highly cross-reactive with one another. The remaining two strains of subgroup II represented previously unreported serotypes that were not related to known adenoviruses or to each other, as demonstrated by HI techniques (Bibby et al., 2022). The linear genome flanked by two origins for DNA replication (ITRs) has eight units for RNA polymerase II-mediated transcription (Pei et al., 2019; Punga et al., 2020).

Chimpanzee adenoviruses

Twenty-seven serotypes from simians, including seven from chimpanzees, each containing adenovirus complement-fixing antigen, are divided into three main subgroups according to their hemagglutinating properties. Subgroup I is composed of eight strains that cause hemagglutination of rhesus or vervet monkey erythrocytes; subgroup II consists of 12 strains that agglutinate selected rat erythrocytes in the presence of heterotypic immune serum to members of the Rosen subgroup III of human adenoviruses. Finally, chimpanzee subgroup III is composed of two strains that fail to agglutinate monkey, rat, guinea pig, or human-type O erythrocytes (Soudet and Stutz, 2019; DeFrancesco 2020; Chung et al., 2020; Poland et al., 2020).

CONCLUSION

The SARS-CoV-2 pandemic has shown that Ad vectors are strong vaccine candidates. Clinical trials with Ad vaccines have demonstrated they are safe in humans, with no serious adverse events observed in most individuals. Ad vaccines produced protective humoral and cellular immune responses, even after a single dose in some cases. Adenovirus studies have allowed researchers to circumvent the problem by using blood clotting in a vaccinated person and show promise as carriers for antigen delivery of vaccines currently in development. Numerous adenovirus-based vaccines have approved the use of viral vectors in the creation of COVID-19. They have been widely utilized in mass immunizations. Despite having slightly lower vaccine efficacy than RNA-based vaccines, they have been frequently used in bulk vaccinations. However, comparing the effectiveness of several COVID-19 vaccines is difficult due to the various phases to determine their safety, dosage schedule, and level of protection to evaluate vaccines on an individual basis, not in comparison to one another and broad range of protection from 80 to 95% efficacy for Pfizer and BioNTech, to approximately 60 to 70% revealed by a vaccine made by AstraZeneca of Oxford. Although phase III clinical trials involve a significant number of people who have been vaccinated, the vaccines are often tested in different geographical locations and at different stages of the pandemic rather than being compared in the same way. In this context, the adenovirus-based ChAdOx1 nCoV-19 and mRNA-based BNT162b2 and mRNA-1273 vaccines showed prior to the emergence of the SARS-CoV-2 alpha, beta, gamma, and delta variants, which does not make the vaccines any less effective. Finally, a deep understanding of the structural features of S will facilitate the design and development of successful vaccines against coronavirus SARS-CoV-2 for large populations.

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Authors' contribution

All authors equally contributed Research ideas planned the study design and performed data. All authors checked and approved the final version of the manuscript for publication in the present journal.

Competing interests

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Ethical considerations

All ethical issues have been checked by the authors, including plagiarism, double submission and data originality.

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