Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Insights into COVID-19 vaccines development: Translation from benchside to bedside

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ABSTRACT

Over the past decades, the rapid pace of vaccine development saved 37 million lives, mostly children. The ongoing corona virus disease (COVID-19) pandemic caused the death of more than 4 million worldwide. During 2020, to encounter the pandemic, scientists developed more than 300 vaccines projects against SARS-CoV (severe acute respiratory syndrome coronavirus 2). In 2021, the results emerging from the clinical trials led to the approval and rollout of few vaccines in different countries. To date, at least one dose of a COVID-19 vaccine has been received by more than 3.81 billion people worldwide, equal to about 49.7 percent of the world population. This review was written to the aim of providing a snapshot of COVID-19 disease, highlighting the well-known vaccines, and, finally understanding the effect of mix and match vaccines from different types.

Background: COVID-19 pandemic caused a worldwide lock down. Developing and discovery of vaccines were the best way to encounter the crisis. Many companies developed successful vaccines which reduce the severity of the virus and save life of millions. More information about COVID-19 disease and vaccines are found in this review.

1. Introduction

On November 2002, a new respiratory infectious disease, severe acute respiratory syndrome (SARS), was identified in China and spread to 29 countries causing ~8000 infections and 774 deaths. It was caused by SARS- coronavirus (SARS-CoV) [1]. Ten years later, Middle East respiratory syndrome (MERS), another respiratory illness, caused by Middle East respiratory syndrome coronavirus (MERS-CoV) spread to 27 countries after being discovered in Saudi Arabia [2]. This MERS outbreak caused 2519 infections and 866 deaths [3]. On December 2019, the Corona Virus Disease 2019 (COVID-19) first case was discovered in China and has since become a worldwide pandemic. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, was its causative agent [4]. To date, and according to WHO report, there have been 290,959,019 confirmed cases of COVID-19, including 5446,753 deaths [5].

SARS-CoV-2 shared 79.6% sequence similarity with SARS-CoV and 50% similarity with MERS. They all belonged to Coronaviruses (CoV) family, *Coronaviridae* subfamily. Their genome consisted of positive-sense, single stranded RNA and encoded for structural proteins at its 3′-terminal region, namely spike protein, nucleocapsid protein, membrane protein, and envelope protein which are critical for viral life cycle. Genes responsible for the viral replication are located at 5′ terminal region [6]. More details about human Coronaviruses family (HCoVs) and their classification are found in Table 1 [7–27].

Spike protein (S) plays crucial roles in the interaction between CoV and host cells. Dipeptidyl peptidase 4 (DPP4) for MERS and angiotensin-converting enzyme 2 (ACE2) for SARS-CoV and SARS-CoV-2 were identified as receptors for spike protein [28]. For COVID-19, the vaccine candidates mainly target the spike protein either through the administration of the viral antigens or the Spike sequence gene. This will induce neutralizing antibodies against (S) protein, blocking the interaction between (S) protein and ACE2 receptor and, therefore, preventing the infection [29]. This review aims to give a short glance at the mechanism of infection and transmission of SARS-CoV-2, provide insights on the well-known vaccines that have been issued during the pandemic, and highlight the effects of mix-and-match COVID-19 vaccines.

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Table 1
Classification and Characteristics of HCoVs Family.

Human coronaviruses (HCoVs)	Common HCoVs				SARS-CoV	MERS-CoV	References
Genus	***Genus: Alphacoronavirus***		***Genus: Betacoronavirus***				[7]
Subgenus	***Duvinacovirus***	***Setracovirus***	***Embecoviru***	***Embecoviru***	***Sarbecovirus***	***Merbecovirus***	[53]
Variant of concern name	HCoV-229E	HCoV-NL63	HCoV-OC43	HKU1	SARS-CoV	MERS-CoV	[53]
Earliest documented samples	Africa (1966)	Netherlands (2004)	America (1967)	Hong Kong (2005)	Southern China (2002)	Middle East (2012)	[8,9]
Genome length	27.5 kb	27.5 kb	> 30 kb	> 30 kb	29.7 kb	30.1 kb	[9,10]
Major proteins	S (Spike), E (Envelope), M (Membrane), N (nucleocapsid)		HE (hemagglutinin-esterase), S, E, M, N		S, E, M, N		[7]
Receptor binding	Aminopeptidase N	ACE2	9-O-Ac-Sia receptor	9-O-Ac-Sia receptor	ACE2	Dipeptidyl peptidase4 (DPP4), CD26	[11,12,13,14]
Dominant cell entry	Cathepsin-independent	Clathrin- dependent endocytosis	IFN-induced human IFITM2/3	IFN-induced human IFITM2/3	Clathrin and caveolae-independent	Cell membrane fusion	[13,15,16,17]
Primary mode of transmission	Droplets, aerosol and contact						[9]
Receptor cleavage	TMPRSS11D	Unknown			Cathepsin L/TMPRSS11D	Furin	[10,16,17]
Mutations	additional ORF at the genomic 3′ end (ORF4)	Mutation in ORF3	Additional genes from hosts. Hemagglutinin-esterases (HEs) + deletions in ORF4 + substitution in S proteins.		vary in 3 regions: S protein, ORF8 and ORF3	major variations are located in S Protein, ORF4b and ORF3	[18,19,20]
Epidemiology	Globally peak in winter				2002–2003 (China); Global attack rate:10–60%	2012 (M.E.) 2015 (S. Korea) Endemic in M.E. Attack rate 4–13%	[9,18]
Spread	15–25% per year	4.7% of respiratory illnesses	6.73% per year	1.6% of adult respiratory infections	8098 cases Recorded worldwide	2562 cases globally	[17,21]
Symptoms	Malaise, Headache, Nasal discharge, Sneezing, Sore throat, Fever and cough	Cough, Rhinorrhea Tachypnea, Fever Hypoxia, Croup	Malaise, Headache, Nasal discharge, Sneezing, Sore throat, Fever and cough	Fever, Running nose, Cough, Dyspnea	Fever, Myalgia, Headache, Malaise, Dry cough, Dyspnea Respiratory distress Diarrhea	Fever, Cough, Chills, Sore throat Myalgia, Arthralgia Dyspnea, Pneumonia, Diarrhea vomiting	[8,9]
Candidate genes for disease severity	Lower immunity in infants, young children, elderly, and immunocompromised individuals increase severity.				Interferon induced genes	hDPP4 and ORF5	[9,22,23]
Cells infected	Epithelial respiratory cells (EC) of the upper respiratory tract				T cells, DC, macrophages and respiratory EC	T cells, macrophages, DC and EC	[14,24]
Diagnosis	RT-PCR hybridization				Clinical evaluation, laboratory diagnosis (PCR test, protein-based test, or viral culture), and radiological diagnosis.		[25,26]
Death	life-threatening bronchiolitis and pneumonia but no death recorded				9.6% (774 known)	34.4% (866 deaths recorded)	[9,10,12]
Vaccine	No vaccines are currently available				No effective vaccine despite dozens of attempts to develop them.		[9,27]
Treatment	Chloroquine; Protease inhibitors (lopinavir/ritonavir* and nelfinavir); Ribavirin and indomethacin; Monoclonal antibodies against S protein						[9]
Incubation period	2–5 days	2–4 days	2–5 days	2–4 days	5 days	5 days	[9,12]
probable gene sources	African hipposiderid bats	Bat CoV	Rodents	Rodents	bats	bats	[17,27]
Intermediate host	Camelids?	NA	Cow	NA	Palm civets	Camels	[8] [27],
Prevention	Hand washing, cough etiquette and avoiding close contact with infected persons						[9]

2. Mechanism of infection of SARS-CoV-2

SARS-CoV-2 virus is considered a dangerous virus because it infects the upper respiratory system and can spread easily so infected person are unknowingly spreading the virus days before they begin to experience symptoms [30]. The size of SARS-CoV-2 genome is ranging from 27 to 33 kb [31] and is considered among the largest RNA viruses [32]. The entry of the virus requires an interaction between the S-protein and ACE2 with the help of other receptors and proteases such as TMPRSS2 (Type II transmembrane serine proteases), CD147(cluster of differentiation 147) and ADAM 17 (A disintegrin and metalloprotease 17) proteins [33]. ACE2 receptors are abundantly expressed on the respiratory epithelium cells and are present on other cells types such as bronchial cells, myocardial and the proximal tubular cells of the kidney [34]. Moreover, the S-proteins of SARS-CoV-2 are primed (activated) by proteolysis cleavage which releases 2 subunits S1 and S2. S1 interacts and binds with the host receptor ACE2, for it contains the receptor binding domain (RBD), as well as it has 10 to 20 times more affinity to bind ACE2 [35]. On the other hand, S2 mediates membrane fusion with the host cell to enter to the cytoplasm. After binding, the cell entry is facilitated by priming the spike protein S2 subunit by, TMPRSS2, the host transmembrane serine protease 2 [36]. The next step in coronavirus lifecycle is the translation of its positive sense RNA genome. The nucleocapsid protein that is interacting with the 5′ end and poly A tail facilitates the synthesis of the negative strand. Both replication and transcription occur in convoluted membranes that are adjacent to DMVs, the double membrane vesicles. DMVs are derived from the rough endoplasmic reticulum. Furthermore, accessory and structural proteins will then be translated from the sub genomic mRNAs. Eventually, the obtained enveloped virion will be exported by exocytosis from the cell [37]. During the pandemic, different variants of SARS-CoV-2 evolved. In fact, during replication, genetic mutations occurred and led to the appearance of new variant which in turn caused the continuation of the outbreak. Table 2 detailed the characteristics of different Coronavirus variants [38–53].

3. Mechanism of transmission of SARS-CoV-2

SARS-CoV-2 can be transmitted by airborne transmission via aerosol formation. Aerosols are particles with a small diameter of less than 100 μm, making the direct viral infection easier. Aerosols can be also generated during dental and surgical procedures or formed as droplet nuclei by an infected patient while coughing, sneezing, and talking. In the aerosols, SARS-CoV-2 remains viable for 3 h and for 4–72 h on various surfaces [54]. Additionally, gastrointestinal tract is believed to be another way of transmission. Urine, semen, saliva, and tears are examples of said body fluids that can be mode of virus transmission. During pregnancy and breastfeeding, transmission from mother to infant is rare but it is not entirely absent [12].

4. COVID-19 vaccines technology

The release of the genome sequence of SARS-CoV-2, on January 2020, accelerated the development of vaccine against COVID-19. Protection from severe symptoms, impeding infection in the vaccinated population, ensured long duration of protection (6 months at least) and production on a large scale, an affordable cost and in a limited time are crucial requirements for a potent vaccine [55]. In order to develop their vaccine, research groups used different platforms technology; this includes inactivated viral vaccines which use the attenuated viral particles, viral-vector based vaccines which use an adenovirus to insert the Spike protein gene in the host cell and mRNA vaccines which encapsulated the mRNA of the Spike protein in a lipid nanoparticle vectors. From these technologies, emerge several vaccines authorized or approved for use by the WHO (World Health Organization) [56]. Additional techniques were also used but not yet approved; these include DNA vaccines that use a plasmid DNA to express the antigens of the virus and recombinant protein-based vaccines which use a viral protein combined with an adjuvant [57]. During vaccine development, many steps occur; after the preclinical studies, the vaccine candidate pass by the clinical trials, U.S. Food and Drug Administration (FDA) approval or authorization, manufacturing, and finally, distribution [58]. While the developing of COVID-19 vaccines is considered as fast tracked, every single step had been taken to ensure safety and efficacy. Table 3 summarized the main differences between Sinopharm [59,60], AstraZeneca [61,62], Sputnik V [63,64], Johnson & Johnson [65,66], Pfizer-BioNTech [67,68] and Moderna [69,70] vaccines. Important events occurred during these vaccines' development is also marked in the Fig. 1.

4.1. Inactivated viral vaccines

Except the live genetic material (DNA or RNA) which are destroyed chemically or by heat, this type of vaccine contains the whole virus particles. As a result, the immunogenic elements are intact. Inactivated viral vaccines are safer than live vaccines but they provide a weaker immunity. For that reason, and in order to boost the immune response, adjuvants that stimulate the immune system are added [71]. This development technology has been effectively applied in many well-known vaccines, such as the hepatitis A and rabies vaccine [72]. Fig. 2 detailed the mechanism of action of COVID-19 inactivated vaccine.

4.1.1. Sinopharm vaccine

For the fight against SARS-CoV-2, the Beijing Institute of Biological Products Company and China National Pharmaceutical Group, or Sinopharm, developed an inactivated vaccine, Sinopharm BBIBP-CorV. Three SARS-CoV-2 strains, 19nCoV-CDC-Tan-Strain04 (QD01), 19nCoV-CDC-Tan-Strain03 (CQ01), and 19nCoV-CDC-Tan-HB02 (HB02) were isolated at the Jinyintan Hospital in Wuhan, China, to establish BBIBP-CorV. HB02 strain was then chosen for large-scale virus production and the development of the BBIBP-CorV (Beijing Bio-Institute of biological products Coronavirus vaccine) vaccine due to its high genetic stability. HB02 was replicated in Vero cells. A double douse with beta-propiolactone was done to inactivate the virus and clarify the cell debris. Hence, the viruses were unable to replicate, but spike proteins were unaffected. Inactivated viruses were then combined with aluminum-hydroxide, an adjuvant which stimulates the immune system, before packing them into prefilled syringes [73]. In preclinical studies, it was discovered that immunizing rabbits, rats, mice, non-human primates, and guinea pigs with BBIBP-CorV would result in high levels of neutralizing antibody titers, protecting from SARS-CoV-2. In a Phase 1 trial, the BBIBP-CorV vaccine was found to be safe and well-tolerated in 18–59 years and 60 years groups, where all vaccine recipients had a strong humoral immune response. Moreover, in a Phase 2 trial, the vaccine was also used at 2 μg, 4 μg, and 8 μg in one, two, and three-dose immunization schedules to profile vaccine immunogenicity and safety in adolescents and children, adults, and older people. As a result, 100 percent seroconversion rate in the adult group was faster than the older group. After the first dose, more than 75 percent of vaccine recipients in the adult group seroconverted at day 14. The seroconversion rate of the 4 μg and 8 μg dose recipients reached 100 percent on day 28, and the seroconversion rate of the 2 μg group reached 100 percent on day 42 in the older group. Furthermore, the magnitude of neutralizing antibodies was lower in the older group than in the adult group [74]. A Phase 3 study with 45,000 participants aged > 18 years old was done in Abu Dhabi, Bahrain, Jordan, and Egypt. Treatment of adults with Sinopharm vaccine significantly reduced the risk of symptomatic COVID-19 with an efficacy of more than 72%. Overall, vaccine prevented moderate and severe disease in everyone vaccinated [75].

Table 2
Classification and Characteristics of SARS-CoV-2 Variants.

Human coronaviruses	SARS-CoV2 (Covid-19)											References
Genus	***Genus: Betacoronavirus***											[38]
Subgenus	***Sarbecovirus***											[53]
Variant type	**Variant of concern**					**Variant of interest**						
Variant name	Alpha [B.1.1.7; GRY; 20I(V1)]	Beta [B.1.351; GH/501Y.V2; 20H (V2)]	Gamma [P.1; GR/501Y.V3 20 J (V3)]	Delta [B.1.617.2; G/478 K.V121A, 21I, 21 J]	Omicron [B.1.1.529; GR/484A; 21 K]	Lambda C.37	Eta B.1.525	Iota B.1.526	Kappa B.1.617.1	Mu B.1.621, B.1.621.1	Epsilon B.1.427,B.1.429	[39,40,41]
Earliest documented samples	United Kingdom, Sep-2020	South Africa, Oct-2020	Brazil, Dec-2020	India, Oct-2020	Multiple countries, Nov-2021	Peru, Dec-2020	United Kingdom & Nigeria Dec-2020	New York, Nov-2020	India, Oct-2020	Colombia, Jan-2021	Southern California, May-2020	[39,40,41,42]
Genome length	**~ 29.9 kb**											[10]
Major proteins	S (Spike), E (Envelope), M (Membrane), N (nucleocapsid)											[7]
Receptor binding	**ACE2**											[11]
Dominant cell entry	TMPRSS2 and Cathepsin L dependent											[10]
Primary mode of transmission	**Droplets, aerosol and contact**											[38]
Receptor cleavage	**TMPRSS2/ TMPRSS4**											[10]
Mutations	17 mutations;8 in spike protein (ex N501Y)	10 mutations in spike protein (ex: N501Y; E484K; K417N)	12 mutations in spike protein (ex: N501Y; E484K)	10 mutations in spike protein (ex: L452R; E484Q)	32 out of 50 mutations in spike protein (ex: A67V; Y154D)	Spike protein mutations: G75V, T76I, Δ246–252, L452Q, F490S, D614G, and T859N.	E484K; H69-V70 deletion; Q677H; Other mutations in spike protein A67V, 144del, D614G and F888L	D614G and T951and E484K	7–8 mutations in spike L452R E484Q D614G P681R	E484K and K417N mutations	3 mutations in spike proteins E484K L452R I4205V	[39,40,43,44]
Epidemiology	2019–2020 in China Globally thereafter Ongoing Attack rate											[45]
Spread/Transmissibility	~75%	50% more than Alpha variant	1.7–2.4 times more	50% more than Alpha variant	Spread easier, ~2.5% more	Spread to at least 29 countries	Reported in 68 countries	Spread to at least 43 countries	Spread to at least 52 countries	Spread to at least 39 countries	Spread to at least 30 countries, 18.6–24% more	[42,46,48]

(*continued on next page*)

Table 2 (*continued*)

Human coronaviruses	SARS-CoV2 (Covid-19)										References
Symptoms	Anosmia, loss or change of sense of smell and taste	Loss of appetite, joints pain, loss of sense of smell and taste	Cold-like symptoms with decrease in frequency of hypos-mia/anosmia and dysgeusia.	Sore throat and runny nose	Fatigue and scratchy throat	Cough, loss of sense of smell and taste	No specific symptoms recorded due to the limited number of cases and limited studies done.				[42,45,47,48]
	Common: Fever; Dry cough; Dyspnea; Myalgia; Headache; Diarrhea										
Candidate genes for disease severity	ACE1; TMPRSS2; MX1; HLA/HLA-E; KLRC2,MBL, chromosome 3 cluster (CCR1/2/9…); TLR7 (on X chromosome); INF stimulated genes. The gene and gender affect severity as well.										[22]
Cells infected	T cells, respiratory epithelial cells(EC)										[24]
Diagnosis	Clinical evaluation, laboratory diagnosis (PCR test, protein-based test, or viral culture), and radiological diagnosis.										[49]
Death	mortality hazard ratio:1.64	~1–3% increase in death	more death recorded in some countries	Deaths recorded including fully vaccinated	Not clear BUT no increase in death seems to occur	NO Deaths recorded	12 Deaths recorded	NO Deaths recorded	One Deaths recorded	NO Deaths recorded	[42,48]
Vaccine AstraZeneca (AZ) Pfizer (Pfz) Moderna (Mod)	Prevention70% by AZ; 90% by Pfz; 89% by Mod	Prevention Not effective by AZ; 75% by Pfz; 80% by Mod	Less protective effect of the vaccines used	Prevention 60% by AZ; 88% by Pfz; 80% by Mod	Currently effective against severity and death with less preventive effectivity (34% by AZ; 75% by Pfz)	Resistant to neutralizing antibodies after vaccination	Vaccines neutralizing effect is slightly less robust	Not linked to increased risk for infection after vaccination. Vaccines are protective	Vaccine are not as effective at neutralizing slightly less susceptible to mRNA vaccines	Reduction in the ability of antibodies to neutralize the mu variant	Reduction of neutralizing antibody titers (3–6-fold)	[42,46,48,50]
Treatment	Corticosteroids and IL6 Receptor Blockers; antiviral drug remdesivir (Veklury); casirivimab and imdevimab antibody treatment. (oxygen ventilation is needed in some cases)										[51]
Incubation period	2–14 days										[52]
probable gene sources	Mainly bats										[53]
Intermediate host	Pangolins?										[21]
Prevention	Hand washing, cough etiquette, avoiding close contact with infected persons, avoiding travel to affected areas										[45]

Table 3
Comparison of COVID-19 vaccines.

Vaccine Technology	Inactivated viral vaccines	Viral vector-based vaccine			mRNA based vaccines	
Vaccine type	Sinopharm[59,60]	AstraZeneca[61,62]	Sputnik V[63,64]	Johnson & Johnson[65,66]	Pfizer-BioNTech[67,68]	Moderna[69,70]
Origin	cultured virus particles	ChAdOx1 chimpanzee adenovirus	Adenovirus vectors (Ad26) and (Ad5)	adenovirus 26 (Ad26)	genetically engineered m-RNA	mRNA-1273
Active components	viral solution, aluminum hydroxide	ChAdOx1 chimpanzee adenovirus, S-protein DNA	AD26, AD5, DNA of S-protein	AD26, Spike protein gene	spike protein mRNA	spike protein mRNA
Safety	high safety and immunogenicity	safe	very good safety profile	safe	safe	safe
Administration	intramuscular 3–4 weeks between 2 doses	intramuscular (deltoid muscle) 12 weeks between 2 doses	intramuscular (deltoid muscle) 21 days between 2 doses	intramuscular (deltoid muscle) single dose	intramuscular (deltoid muscle) 2 doses 3 weeks apart	intramuscular 2 doses 28 days apart
Packaging and (Storage)	0.5 ml prefilled syringes (2–8 °C)	0.5 ml prefilled syringes (2–8 °C)	0.5 ml ampoule (−18 °C)	vial of 5 doses (2–8 °C)	0.3 ml dose (−90 to −60 °C). avoid exposure to light	0.5 ml dose (−50° to −15 °C)
Efficacy	50–70% efficacy 14 days after 2nd dose	62–90% efficacy after 2nd dose	91.4% efficiency rate	61–85% (varies in tested countries)	95%	95%
Recommendation	for pregnant and lactating women, and HIV patients	for 18+ individuals, pregnant and lactating women	for 18+ individuals. Not recommended for pregnant & breastfeeding women, and for immunodeficiency patients or drugs addiction	for 18+ individuals, pregnant and lactating women	for 12+ individuals, pregnant and lactating women	for 18+ individuals and pregnant women
Side effects	Flushing, edema, scleroma, rash, itching, fever, weariness, muscle soreness, joint discomfort, difficulty breathing, itchy skin, nausea, cough, and diarrhea	site pain, headache, fatigue, pyrexia, and some nausea, swelling	flu-like diseases, fatigue, headache, and injection site reactions	Swelling, pain, redness, chills, fever, nausea, headache, muscle and tiredness.	fatigue accompanied with headache and fever, chills, joint and muscle pain, swelling, malaise, nausea, lymphadenopathy and allergic reactions	Tiredness, high temperature, headaches, soreness, shivers, nausea, diarrhea, inflammation, pain, redness and itchy rash
Authorization/Approval	WHO	European medicine agency (EMA), WHO as well nation regulators worldwide. Not authorized by FDA	not approved by WHO, FDA or EMA	Authorized by WHO for individuals 18+ but not yet approved by FDA.	Approved by FDA for individuals 16+ and authorized for 5+. Authorized by WHO	Authorized for individuals 18+ but not yet approved by FDA. Authorized by the EMA for 12+ and by WHO

4.2. Viral vector-based vaccine

Viral vector is derived from genetically modified virus. It considered as recombinant virus in which the gene of interest such as S-protein have been cloned. For example, adenovirus or measles virus can produce coronavirus protein. In general, such viral vectors have reduced pathogenicity and cannot cause disease. Replicating and non-replicating viral vector exist; while the first infect the cells and allow the production of new virus particles which in turn can infect new cells the second is not. This means that only initially infected cells can form the vaccine antigen. Both replicating and non-replicating viral vector induce a strong humoral and cellular immune responses [76,77] (Fig. 3).

4.2.1. AstraZeneca COVID-19 vaccine

Oxford-AstraZeneca vaccine uses chimpanzee common cold viral vector (ChAdOx1) to deliver the sequence of SARS-CoV-2 genome responsible for translating the viral spike protein. Oxford University's Jenner Institute developed this vaccine under the name VaxZevria or AZD1222 which was authorized by the European Medicines Agency in February 2021 [78]. The vaccine is generated starting by taking the spike protein of an actual SARS-CoV-2 and then converting it to DNA and insert it in ChAdOx [79]. In addition to that, VaxZevria contains some excipients such as L-histidine and ethanol which are inhibitors of the free-radical oxidation that inactivates the adenovirus, polysorbate 80 a non-ionic surfactant that prevents the adsorption of the adenovirus to the glass surface during storage, sucrose which is a cryoprotectant that prevents freezing and thawing, salts such as sodium chloride, L-histidine hydrochloride monohydrate, disodium edetate dihydrate, and magnesium chloride hexahydrate, and water [80]. Preclinical studies of AZD1222 using animal models showed a high immunogenic profile [81]. On July 20, 2020, a phase 1/2 study showed an acceptable safety profile of the vaccine on 543 volunteers aged between 18 and 55 years [82]. This study enrolled 1077 participants: 543 received the vaccine while 534 received the meningococcal conjugate vaccine (MenACWY) as control. A phase 3 study in adults started on August 28, 2020, to determine the immunogenicity, safety and efficacy of AZD1222 vaccine. 32,451 adults and older adults' participants were enrolled. The study concluded that the vaccine was efficacious and safe in preventing symptomatic and severe COVID-19 in adults and elder [83]. The effect of Vaxzeria on the COVID-19 variants was also tested. The vaccine can provide protection against the Alpha (B.1.1.7), Delta (B.1.617.2), Kappa (B1.617.1), and Gamma variants [84].

4.2.2. Gamaleya – Sputnik V COVID-19 vaccine

The Russian vaccine is termed Sputnik V, which is based on two adenovirus vectors Ad26 (adenovirus Serotype 26 for the first component) and Ad5 (adenovirus serotype 5 for the second), was advanced by the Gamaleya National Center of Epidemiology and Microbiology (Moscow, Russia) and included the spike protein gene of SARS-CoV-2 [85]. Tris-(hydroxymethyl)-aminomethane, Sucrose, Magnesium chlo-

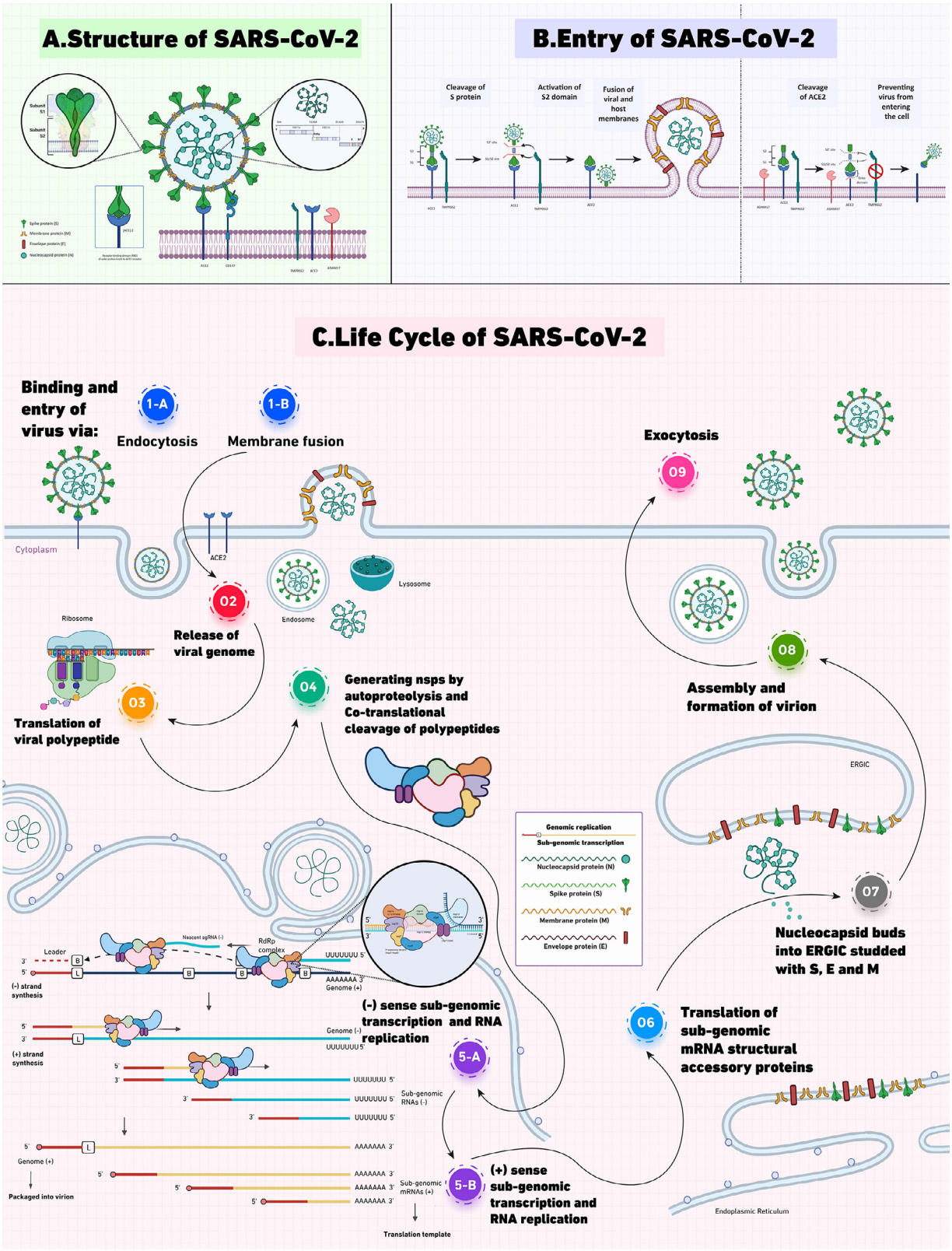

Fig. 1. (A) Structure, (B) Entry and (C) Life cycle of SARS-CoV-2.

ride hexahydrate, Sodium chloride, Disodium EDTA dihydrate, Ethanol, Polysorbate 80, and Water are the other ingredients of this vaccine [86]. Before beginning clinical trials, the vaccine underwent all stages of preclinical testing, including studies on a variety of animals, including two types of primates. On August 1, 2020, phase 1 and 2 clinical trials were completed. In fact, all of the participants are in good health, with no unexpected or undesirable side effects. It is indicated that strong antibody and cellular immunological responses were generated by the vaccination. After receiving the vaccination, none of the participants in the current clinical trials became infected with COVID-19. The vac-

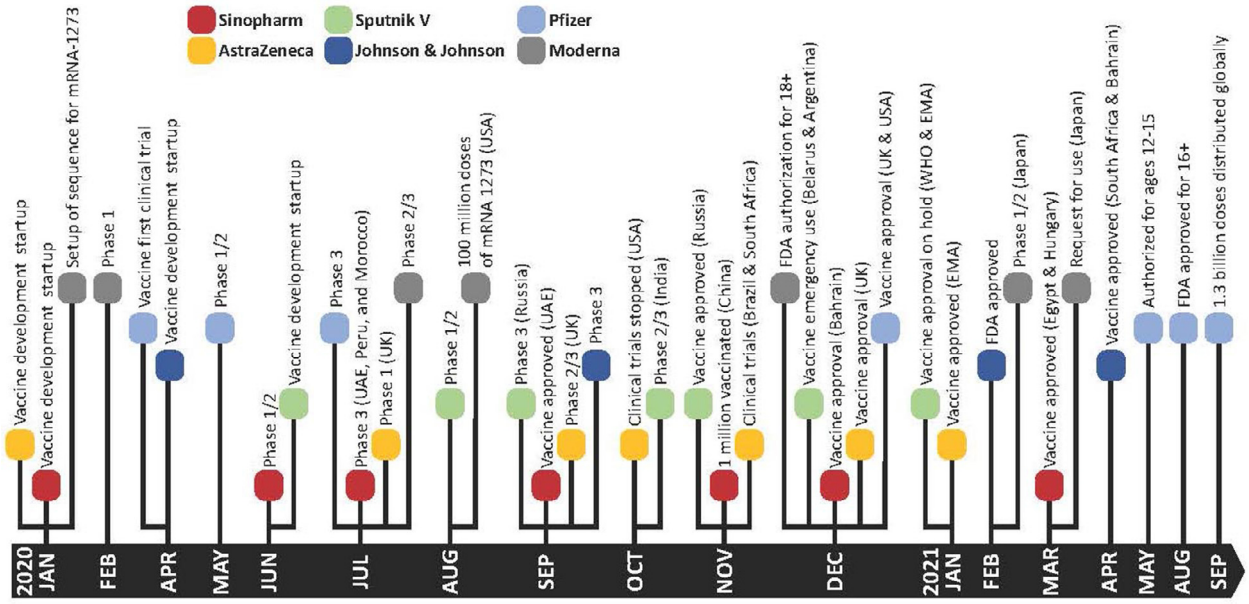

Fig. 2. Vaccines Timeline: Important events during vaccines Development.

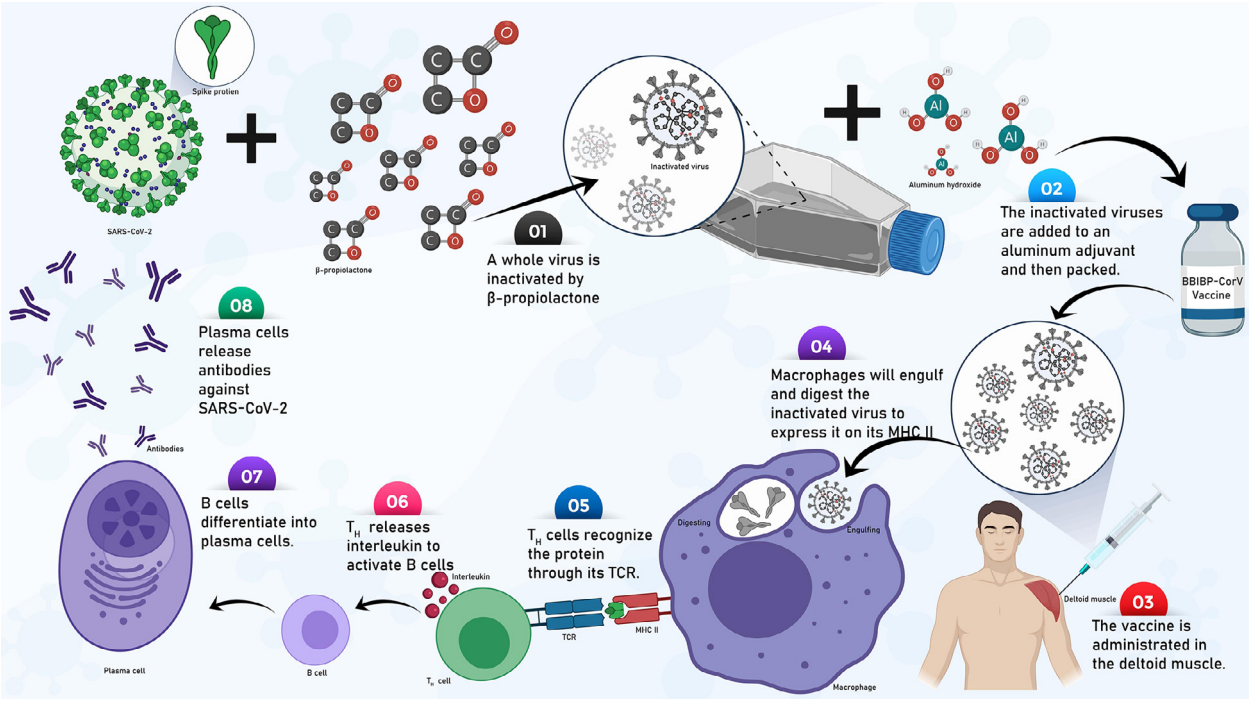

Fig. 3. Mechanism of action of the inactivated viral vaccine.

cine's great efficacy was confirmed by assays with high-precision for antibodies in volunteers' blood serum, as well as the ability of the volunteers' immune cells to be activated in response to the coronavirus's spike S protein, indicating the production of both antibody and cellular immune vaccination responses [87]. Later, on August 25, 2020, post-registration clinical trials involving around 31,000 patients in Russia and Belarus began. It is of quite an importance that a big number of countries, including the United Arab Emirates, India, and Venezuela, participated in the Sputnik V clinical studies on a local level. The Russian Ministry of Health issued the vaccine a registration certificate, on August 11, allowing it to be used to vaccinate the Russian population under emergency rules put in place during the COVID-19 epidemic and to be used by any registered person. Sputnik V has excellent effectiveness, immunogenicity, and safety findings in Phase III clinical trials [63].

4.2.3. Johnson & Johnson (J&J) COVID-19 vaccine

Pharmaceutical Janssen companies start developing a vaccine called the Johnson vaccine which was authorized by the FDA to be used for an emergency in Leiden, USA, and Netherland. J&J vaccine is also known as JNJ78436735 or Ad.26.COV2.S vaccine. It uses the adenovirus 26 (AD26) encoding full-length spike protein. Sugars (polysorbate80, 2-hydroxy-propyl-betacyclodextrin (HBCD) and sodium chloride), acids (citric acid monohydrate), salts (triodium citrate dehydrogenase) and others such as ethanol, polysorbate-80, acetic acid and sucrose are found inside the vaccine. Preclinical studies showed that a

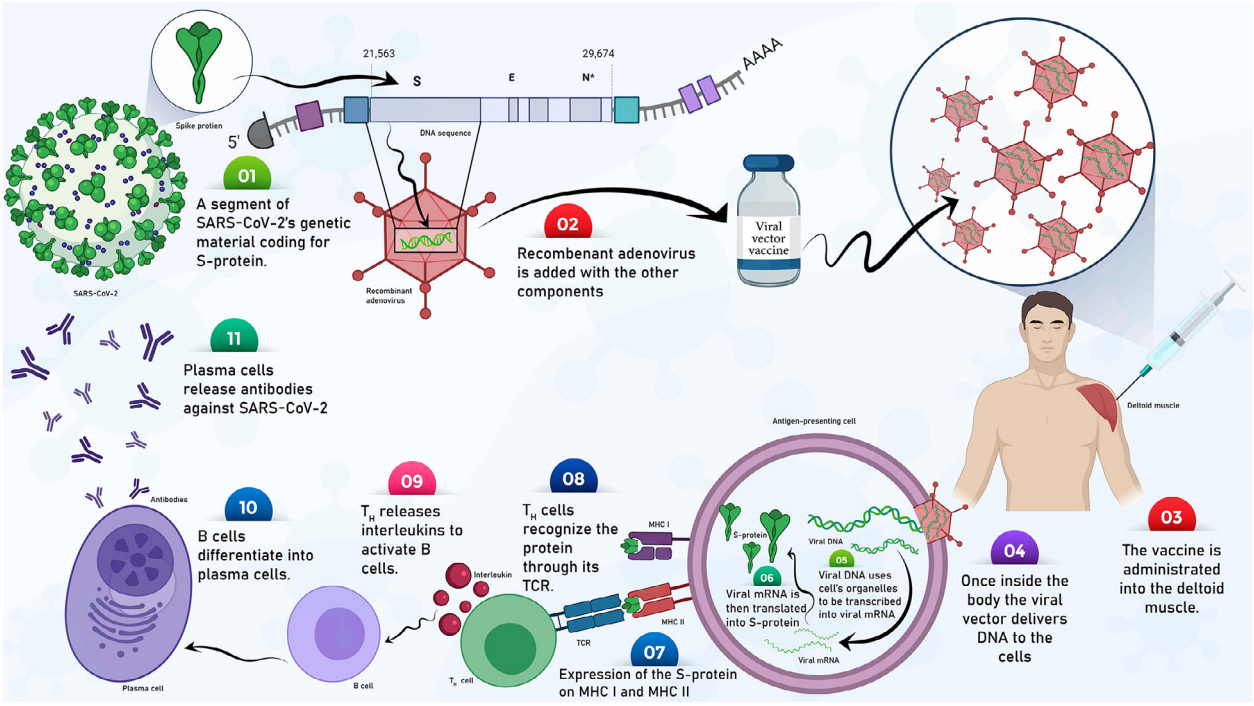

Fig. 4. Mechanism of action of the viral-vector based vaccine.

single-shot vaccine induced a robust immune response in non-human primates [88]. In July 2020, phase 1/2 was done in order to evaluate the vaccine reactogenicity, safety, and immunogenicity. This phase enrolled 1085 participants and has been tested on healthy adults aged from 18 to 55 years and over than 65 years. After 29 days of the vaccination, neutralizing antibodies were detected in 90% or more of participants receiving a single dose of vaccine [89]. A phase 3 study enrolled 44,325 participants: 19,691 who received placebo and 19,630 SARS-CoV-2-negative participants who received Ad26.COV2.S. As a result, single dose of Ad26.COV2.S protected against both symptomatic and asymptomatic SARS-CoV-2 infection [90].

4.3. *mRNA based vaccines*

Engineered messenger RNA strands responsible for the spike protein of SARS-COV-2 are exploited by mRNA vaccines, and then it was wrapped by lipid nanoparticles which are composed of polyethylene glycols, cholesterol, and fats. Researchers aim to preserve and forward the messenger RNA into the cells of the muscle. Consequently, after the injection of the vaccine, the messenger RNA will be released and its genetic code will be directly translated into viral spike proteins. These viral S proteins will be displayed on the cell surface to generate an antiviral immune response after they are degraded into peptides. Furthermore, these proteins will provide the immune system with enough time to generate potent antibodies to counteract and robust Th1-type CD4+ (T helper type 1) and the antigen-specific CD8+ cell responses (Fig. 4).

4.3.1. *Pfizer COVID-19 vaccine*

On April 22, 2020, BioNTech SE, German company, in collaboration with Pfizer Inc., American company, has issued a first clinical trial for Biotech's BNT162 vaccine program to prevent the infection of COVID-19. They have produced, in 2020, 50 million vaccines and more than 1.3 billion doses in 2021 using a novel mRNA technology which allows the easy and rapid manufacturing of the mRNA genetic material. A bioreactor, *in-vitro* transcription, aims to transcribe a DNA template into mRNA then amplify it. BioNTech Pfizer encapsulates its mRNA vaccines within lipid nanoparticles that facilitate the transportation of the RNA and aids in its preservation from degradation. Pfizer-BioNTech COVID-19 Vaccine safety was evaluated by conducting several clinical trials under different conditions and adverse reaction rates in South Africa, United States, Turkey, South America, and Europe. Preclinical studies in mice and macaques revealed that the vaccine was highly immunogenic, induced strong humoral and cellular response against COVID-19, and prevented lung infection in non-human primate [91]. The first study of phase 1/2 trial enrolled 60 participants aged of 18 years and older showed that the vaccine had minimum side effects. A second study was phase 1/2/3 trials and has enrolled 43,998 participants from different nationalities, 12 years of age or older. All these clinical trials have revealed that the vaccine has a 95% efficacy rate in preventing COVID-19 and inducing neutralizing antibodies at high levels. Another study conducted on 2260 adolescents 12 to 15 years confirmed the safety profile and the high efficacy (100%) of the BNT162b2 vaccine against Covid-19 [92]. FDA authorized Pfizer vaccine for children aged between 12 and 15 years old [93]. On September 20, 2021, results from phase 2/3 trial showed robust neutralizing antibody responses with favorable safety profile in children aged between 5 and 11 years old using two-dose of 10 ug administered 3 weeks apart, a smaller dose than 30 ug used for people 12 and older [94]. BNT162b2 vaccine was also tested against the emergent lineages of COVID-19. A recent report, published by Liu et al., showed that samples of serum taken from 24 participants immunized with BNT162b2 vaccine was able to neutralize the SARS-COV-2 with mutated spike protein including those identified in India (B.1.617.1, B.1.617.2 and B.1.618 variants) or B.1.525 variant (first identified in Nigeria) [95] (Fig. 5).

4.3.2. *Moderna COVID-19 vaccine*

Moderna, a Cambridge, Massachusetts-based biotech company, completed the manufacture of their vaccine candidate, mRNA-1273.351, on February 24, 2020 and shipped doses to the NIH (National Institute of Health) for a phase 1 clinical trial that was conducted and funded by NIAID (National Institute of Allergy and Infectious Diseases) [96]. On December, 18, 2020, the Food and Drug Administration (FDA) has granted the Moderna COVID-19 vaccine, a lipid nanoparticle-encapsulated, nucleoside-modified mRNA vaccine encoding the spike

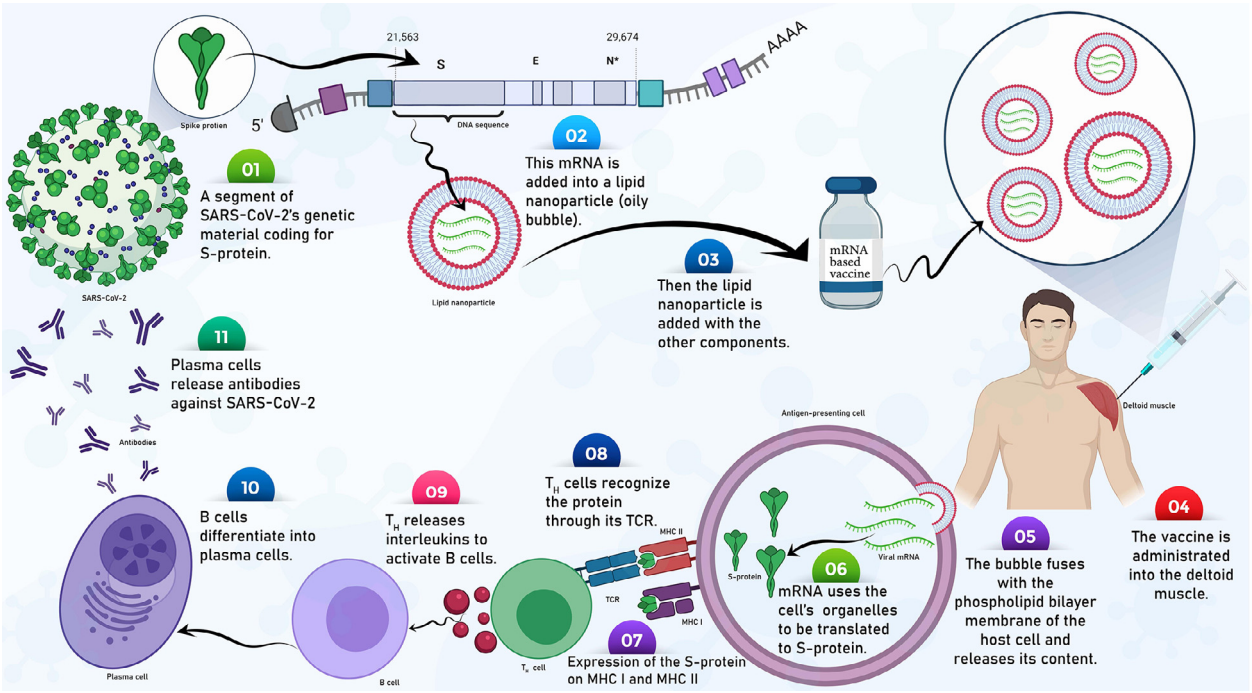

Fig. 5. Mechanism of action of the m-RNA based vaccine.

glycoprotein, an Emergency Use Authorization (EUA). This was the second vaccine approved in the USA under an EUA for the prevention of COVID-19 [97]. Preclinical study in non-human primates showed that mRNA-1273 vaccine protected against a high dose of SARS-CoV-2 infection and led to a significant increase in T cell responses [98]. 600 healthy participants aged 18+ were enrolled in Phase 2 study for the evaluation of the immunogenicity and safety of two vaccinations given 28 days apart [99]. As a result, the immunogenicity and safety profile of the mRNA-1273 was confirmed. A phase 3 study (COVE study) which enrolled 30,415 participants aged 18 years and older showed that the vaccine was able to prevent COVID-19 illness with protection against asymptomatic infection and acceptable safety profile [100]. Moderna vaccine was also tested against COVID-19 emerging variants. The mRNA-1273 vaccine is highly effective against B.1.1.7 (Alpha) and B.1.351 (Beta) infections even after a single dose [101]. A recent report, published in Science, assessed the effect of the antibodies induced by Moderna vaccine, over 7 months, on binding and neutralizing SARS-CoV-2 variants Epsilon, Iota, Alpha, Beta, Gamma, and Delta. All vaccinated individuals had responses to all variants. The lowest antibody recognition was found in Beta variant [102].

5. Mix-and-match COVID-19 vaccines

Combining different vaccines was showed to have benefits. FDA authorized the use of mix and match (or heterologous) booster dose for the available vaccines. A first trial, conducted by researchers in Spain, found that people who received a first dose of the AstraZeneca vaccine followed by second dose of the Pfizer vaccine produced a strong immune response against SARS-CoV-2. Another study in U.K. called Com-COV, showed that people who received the combination of those 2 vaccines showed common vaccine-related side effects at higher rates [103]. Even the use of Mix-and-match vaccines can prevent the roll-outs stalling due to supply issues, some safety concerns remain. Only a few hundred people were enrolled. For this reason and to counteract any undesirable reactions, some large-scale studies still needed, especially each vaccine has its own profile and adverse events [104].

6. Conclusions

The racing between the entire scientific community results in the emerging of many safe and effective vaccines which return life to normal. Even though different technologies were used, all of the vaccine candidates target S protein of SARS-CoV-2 virus and trigger the immune system to activate T-cell responses. Efficacy and durability of these responses differ among specific population groups especially for the group aged >65 years. Finally, even heterologous vaccination seems to have benefits, safety concerns still remain.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Declaration of Competing Interests

The authors declare that they have no competing interests.

Authors' contributions

Marwa Houssein updated, drew table 2 and figure 2, and review-edited all drafts of the manuscript. Aya El Asir Al Hossainy, Jana Al soussi, Jana El Batch, Lana El-Samadi, Sherine El Imam, and Rawan Fakih wrote the first draft of the manuscript. Aya El Asir Al Hossainy

and Jana Al soussi drew figures 1 and 3-5. Hoda Dakdouk drew tables 1 and 2. Mahmoud Khalil supervised, initiated the idea, constructed figure 2, and review-edited all drafts of the manuscript. All authors approved the final version for submission.

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