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REVIEW ARTICLE

A comparison between SARS-CoV-1 and SARS-CoV2: an update on current COVID-19 vaccines

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Abstract

Since the outbreak of the novel coronavirus disease 2019 (COVID-19) in Wuhan, China, many health care systems have been heavily engaged in treating and preventing the disease, and the year 2020 may be called as "historic COVID-19 vaccine breakthrough". Due to the COVID-19 pandemic, many companies have initiated investigations on developing an efficient and safe vaccine against the virus. From Moderna and Pfizer in the United States to PastocoVac in Pasteur Institute of Iran and the University of Oxford in the United Kingdom, different candidates have been introduced to the market. COVID-19 vaccine research has been facilitated based on genome and structural information, bioinformatics predictions, epitope mapping, and data obtained from the previous developments of severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1) and middle east respiratory syndrome coronavirus (MERS-CoV) vaccine candidates. SARS-CoV genome sequence is highly homologous to the one in COVID-19 and both viruses use the same receptor, angiotensin-converting enzyme 2 (ACE2). Moreover, the immune system responds to these viruses, partially in the same way. Considering the ongoing COVID-19 pandemic and previous attempts to manufacture SARS-CoV vaccines, this paper is going to discuss clinical cases as well as vaccine challenges, including those related to infrastructures, transportation, possible adverse reactions, utilized delivery systems (e.g., nanotechnology and electroporation) and probable vaccine-induced mutations.

Keywords Challenges · Coronavirus · COVID-19 · Immunization · SARS-CoV-2 · Vaccine

Introduction

Being considered the newest addition to the Coronaviridae family, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the virus responsible for the coronavirus disease 2019 (COVID-19), which was declared a pandemic on March 11, 2020, by the World Health Organization (WHO) [1]. The term 'Corona' represents crown-like spikes on the outer surface of the coronaviruses, which contain the largest genomes among all the RNA viruses [2, 3]. Up to July 16, 2022, the number of confirmed COVID-19 cases were 566,641,094 including 6,386,256 deaths and 537,853,204 recoveries [4].

Based on the recent WHO updates, the most common symptoms of COVID-19 are fever, cough, tiredness, and loss of taste/smell [5]. The less common ones are sore throat, headache, aches and pains, diarrhea, rashes, or discoloration of fingers or toes, and red or irritated eyes. The disease is assessed into mild, severe, and critical (i.e., respiratory failure, septic shock, multiple organ dysfunction, or failure)

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categories based on the clinical manifestations and severity [6, 7].

Apart from the health-related complications of the disease, its economic burden cannot be ignored. It was reported that global gross domestic product (GDP) dropped about 4.5% in 2020 [8]. Numerous people who have found themselves jobless and lost their insurance have faced a grave situation. The average cost for hospital care for COVID-19 patients ranges from 51,000 to 78,000 USD based on their age [9]. The only similar conditions we have experienced in the twenty-first century are the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome coronavirus (SARS-CoV) outbreaks in 2012 and 2003, respectively. Although SARS-CoV, MERS-CoV, and SARS-CoV-2 belong to the same coronaviruses genus, SARS-CoV-2 is associated with milder infections. This explains why SARS-CoV-2 spreads far easier [10].

Herd immunity occurs when enough of a population is protected against an infection that its transmission ceases, indirectly safeguard those who are not immune. The herd immunity threshold for COVID-19 is at least 60–70% [11]. So far, global vaccination seems to be the only weapon in providing such conditions. In taking advantage of the high genetic similarity between SARS-CoV and SARS-CoV-2 (i.e., 79.6%), various vaccine candidates from nearly all over the world have been introduced throughout the pandemic, with Pfizer's "BNT162b1" and Modena's "mRNA-1273" being the forerunners in acquiring USFDA's authorization for emergency use [12]. From live attenuated or inactivated viruses, viral vectors, and virus-like particles (VLPs) to recombinant proteins and nucleic acids (RNAs and DNAs), diverse platforms have been used in the SARS-CoV-2 vaccine manufacturing process [13, 14]. Each platform has its pros and cons in fields such as storage conditions, price, side effects, efficacy, and safety. It is also affected by multiple factors, one of the most important of which is the issue of mutations.

Considering the importance of proper vaccination and the challenges mentioned above, it is necessary to thoroughly identify all available SARS-CoV-2 vaccines by reviewing their mechanism of action, delivery systems, clinical efficacy, side effects, and possible vaccine-induced mutations. These issues will be comprehensively discussed in the present article, aiming to better the global vaccination process and policymaker decisions.

A comparison between SARS-CoV and SARS-CoV-2

SARS-CoV is a virus responsible for the epidemic that started in 2003 and ended shortly after, resulting in only a few vaccines starting phase 1 clinical trial and other vaccines staying at the pre-clinical phase. Considering this issue, comparing SARS-CoV with SARS-CoV-2 is almost unfeasible; however, lessons regarding SARS-CoV vaccines can be taken to enhance the safety and efficacy of SARS-CoV-2 vaccines. Since a better understanding of SARS-CoV-2 leads to improved vaccine manufacture, this section provides information on this virus and its structure [15].

The phylogenetic tree analysis of SARS-CoV-2 shows that, like SARS-CoV, it belongs to a different clade from MERS-CoV [10]. Based on the genomic sequence comparison, SARS-CoV-2 shares about 79.6% and 50% overall genomic similarity with SARS-CoV and MERS-CoV, respectively [13]. While SARS-CoV and SARS-CoV-2 share their entry receptor, angiotensin-converting enzyme 2 (ACE2), MERS-CoV uses dipeptidyl peptidase (DPP)-4 [16]. Regarding their structural proteins (Fig. 1), spike glycoprotein (S) on the particle's surface consists of two subunits that can bind to the cellular receptors and mediate infection, following which the cell begins replicating in the cytoplasm. Membrane (M) protein increases the membrane curvature, promoting the viral assembly. Envelope (E) protein is involved mainly in numerous functions in the viral replication cycle, such as assembly, release, and pathogenesis. Nucleocapsid (N) protein inhibits interferon (IFN) and plays a significant role in virus transcription and assembly [3, 17, 18]. The results showed 76%, 90.1%, 90.6%, and 94.7% similarities between S, M, N, and E proteins of SARS-CoV and SARS-CoV-2, respectively [19]. Furthermore, some similarities and differences exist between SARS-CoV and SARS-CoV-2 regarding receptor binding domain, host cell entry, and protease activation [20]. SARS-CoV and SARS-CoV-2 bind to the ACE2 receptor of human cells in many tissues, including the lungs, kidneys, heart, and testis, by their receptor-binding domain (RBD) in the S1 subunit [21]. Then, their envelope and the host cell membrane fuse to release the viral nucleocapsid into the target cells [22]. To this end, the S protein should be activated, so the S2 subunit (cleaved from the S1 subunit by host cell proteases) assists the fusion process and transports the virion into the host cells [18].

By comparing the full-length S protein sequences, the most probable alterations were found on the S1 subunit suggesting that the neutralizing antibodies that were once effective against SARS-CoV might not offer protection against SARS-CoV-2. Although cross-reactivity between the antibodies seems to be cross-reactivity, cross-neutralization appears to be relatively rare [10, 23].

SARS-CoV-2 binding affinity is 10–20 times higher than SARS-CoV, causing a more efficient cell entry. SARS-CoV-2 RBD, despite its higher affinity, is possibly less exposed than SARS-CoV RBD. This may be due to the "lying-down" position of its RBD, which can lead to ineffective receptor binding compared to the "standing-up" state

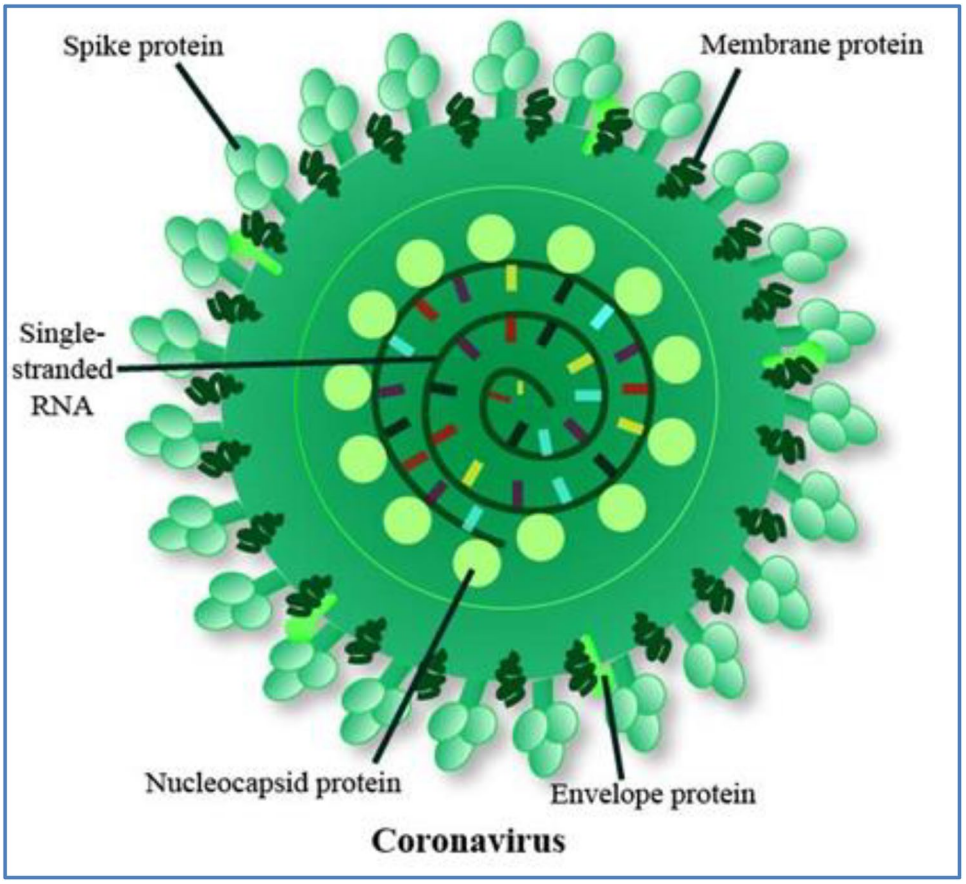

Fig. 1 Schematic presentation of coronavirus virion structure

in SARS-CoV [18]. On the other hand, the immune evasion caused by this position contributes to the conformational masking strategies [18, 20, 23].

A protein sequence alignment analysis was performed to look deeper into the encoded proteins of SARS-CoV-2 and SARS-CoV. Most of them were substantially homologous (95%–100%) and two SARS-CoV-2 proteins (ORF8 and ORF10) had no counterparts in SARS-CoV, making it clinically meaningful to analyze the biological function of these two specific proteins [3].

SARS-CoV and SARS-CoV-2 interactions with the immune system

Pathophysiology of SARS-CoV-2 and SARS-CoV infections closely resemble each other, with aggressive inflammatory responses heavily involved in damage to the airways. Put differently, the viral infection rate and the host response are two contributory factors in this regard [24]. SARS-CoV-2 enters the body through the nasal-oral cavity [25]. Once inhaled, the virus primarily binds to the host cells through its target receptor. Earlier work on SARS-CoV demonstrated that the virus targets cells which express ACE2, such as airway epithelial cells, alveolar epithelial cells, vascular endothelial cells, and macrophages in the lungs. Since SARS-CoV-2 uses the same receptor, these cells are likely to be targeted [24].

SARS-CoV-2, as a cytopathic virus and as part of its replicative cycle, prompts death and injury of virus-infected cells and tissues, which in the airway epithelial cells can lead to elevated levels of virus-linked pyroptosis (a highly inflammatory form of programmed cell death that is frequently seen with cytopathic viruses). This probably triggers an inflammatory response. The released pathogen-associated molecular patterns (PAMPs) such as viral RNA, and damage-associated molecular patterns (DAMPs), including ATP and DNA, are detected by alveolar epithelial cells and alveolar macrophages, which use a variety of pattern-recognition receptors (PRRs). Subsequently, local inflammation occurs following hypersecretion of pro-inflammatory cytokines and chemokines, including interleukin (IL)-6, interferon gamma-induced protein (IP)-10, macrophage inflammatory protein 1α (MIP1α), MIP1β and monocyte chemoattractant protein 1 (MCP1); all of which parallel the observations in SARS-CoV. This results in the recruitment of immune cells, notably monocytes and T lymphocytes but not neutrophils, into the infected location, provoking further inflammation [24, 26].

In a healthy immune response, the primary inflammation caused by either SARS-CoV or SARS-CoV-2 attracts virus-specific T cells to the site of infection to eradicate the

infected cells before the virus spreads and ultimately lead to minimal lung damage, clearance of the virus, and lastly, recovery. However, it has been reported that alveolar dysfunction in two COVID-19 cases led to cytokine storm and failure of multiple organs, including the lungs and heart [27].

In a dysfunctional immune response, the primary inflammation may lead to the gathering of immune cells in the lungs and the overproduction of pro-inflammatory cytokines (also known as a cytokine storm). This causes acute respiratory disease syndrome (ARDS) and eventually lung damage. Patients with severe COVID-19 required intensive care in hospitals displayed higher blood plasma levels of IL-2, IL-7, IL-10, IP-10, MCP1, MIP1α, and tumor necrosis factor (TNF). IL-6 level in these patients continued to increase over time and was higher in non-survivors than survivors. Furthermore, patients with severe disease, compared to patients with a mild infection, showed a significantly higher percentage of CD14 + and CD16 + inflammatory monocytes in peripheral blood. These cells secrete inflammatory cytokines that help the cytokine storm (IP-10, MCP1, and MIP1α) [24, 25]. Subsequently, the cytokine storm might affect other organs, leading to multi-organ damage. For instance, elevated levels of cytokines such as TNF were reported to cause septic shock, myocardial injury, and circulatory failure in some patients, especially those over 60 years of age. Furthermore, non-neutralizing antibodies produced by B cells may boost SARS-CoV-2 infection through antibody-dependent enhancement (ADE), further worsening organ damage [24].

In SARS-CoV-2 infection, production of type I and III interferons decreases, leading to an overall reduction in the transcription of antiviral genes [25]. Research on SARS-CoV found that several viral structural and non-structural proteins can antagonize interferon responses, thus, eluding the immune system. Coronaviruses are implied to possess the ability to escape from immune detection and curb human immune responses, which somewhat explains why they usually have a more extended incubation period [16]. Antagonism happens at different stages of the interferon signaling pathway, including pattern-recognition receptor (PRR) signaling through TNF receptor-associated factor 3 (TRAF3), interferon regulatory factor 3 (IRF3), and other molecules, downstream interferon signaling through STAT1, PRR recognition of viral RNA and host mRNA degradation and host protein translation. Some of these pathways are present in SARS-CoV-2 [24]. SARS-CoV-2 infection can also decrease T cells and enhance the exhaustion of effector T cells, thereby reducing the immune response against the virus. This exhaustion results from a higher expression of inhibitory receptors on the cell's surface, which is influenced by cytokines like IL-6, IL-10, and TNF-α [25, 28–31].

Following the viral clearance of either SARS-CoV or SARS-CoV-2, a group of memory T cells is produced to encounter re-infection. Re-stimulated CD4 + memory T cells activate B cells and other immune cells by cytokine production, while cytotoxic memory T cells assist in eliminating the infected cells during a future infection. In addition to this mechanism, studies on SARS-CoV revealed that produced antibodies were present in the blood for at least six months to two years. According to a study in China, 93.88% of patients after one year and 89.58% after two years tested positive for IgG against SARS-CoV [31]. Whether these results can be extrapolated to all COVID-19 patients worldwide remains unknown and requires further investigations [25].

How antibodies decay is found to vary by individuals, target antigen, antibody isotype, and assay used in studies; anti-N antibodies are the fastest to decrease, followed by anti-RBD and anti-S antibodies [32–34]. The half-life of anti-S antibodies has been estimated to be 126–238 days in different studies [35–37]. Data are showing that SARS-CoV-2-specific IgG was detectable in 90% of seroconversions up to one year post-infection [34, 38].

Factors affecting the severity of the infection

During the current pandemic, numerous studies have addressed the challenges with vaccine efficacy. Some challenges are related to the virus, while others are linked to epidemiological conditions, vaccine platforms, and gender. Most efforts have been focused on stimulating neutralizing antibody production, route of administration, dosage, and injection intervals [39]. The physiological heterogeneity among different individuals plays a critical role in vaccine efficacy [40]. Moreover, factors such as eligibility for all age groups, genetics, gender, ethnicity, history of former infection, and the emergence of new variants of concern (VOC) are considered obstacles to vaccine production [41]. Although results are conflicting regarding the impact of the different factors on the severity of the disease and vaccine responses, a brief explanation of how such issues can affect the overall mortality and morbidity from SARS-CoV and SARS-CoV-2 is provided below.

Genetics

Results from previous studies regarding the effect of host genetic factors on the severity of SARS-CoV are crucial to be used in the SARS-CoV-2 pandemic [42–44], which are discussed as follows.

SARS-CoV

According to an in vivo study, there is a locus on chromosome 3 (including 23 genes and 13 non-coding RNAs), which contributes to SARS-CoV vascular cuffing and inflammation of the lungs [45]. Genetic polymorphism in those genes is

associated with different clinical manifestations in patients. Moreover, human cyclophilin A, a peptidyl-prolyl isomerase, contributes to the viral core sequestration. This protein binds to the N protein of the virus and interacts with the coronavirus proteins and genome. Single nucleotide polymorphism in the cyclophilin A gene contributes to heterogeneity of COVID-19 severity in different individuals [45]. It is also suggested that ACE2 receptor polymorphism brings about varieties within individuals [45, 46]. The severity of the infection and susceptibility to SARS are affected by a particular polymorphism of the CLEC4M gene (in the variable tandem repeats in exon) since L-SIGN, the coded protein of this gene is a receptor for the virus [45, 47]. Diverse quantities in mannose-binding lectin (MBL) may affect protection against SARS. For example, a lower amount of MLB worsened the severity of SARS [46, 47]. It was also reported that Fc gamma RIIA-R/R131 genotype polymorphism, which is in the human Fc gamma receptor IIA gene, was related to the severity of SARS infection [45]. Polymorphism of IFNγ + 874A and RANTES-28G alleles, MIF gene (on influenza), and human leukocyte antigen (HLA) also contributed to SARS' severity and mortality rate. Interactions of all these variables are contentious issues that need further investigation [45–47].

SARS-CoV2

ACE2 ACE2 polymorphisms, such as p.Arg514Gly in the African/African-American population, were linked to cardiovascular and pulmonary disorders by altering the interaction between angiotensinogen and ACE2 receptor [48]. It has been reported that higher expression of ACE2 receptors positively correlated with the severity of the SARS-CoV-2 infection [45]. Since ACE2 is the key receptor for SARS-CoV-2, individuals with diabetes, hypertension, and chronic obstructive pulmonary disease [45] would be more susceptible to SARS-CoV-2 infection. Close contact is essential for recognizing RBD. Changes in ACE2 residues at the binding interface affect affinity, one of the most important determinants of host sensitivity [49]. hACE2 K353 and K31 are the significant areas that form hydrogen bonds with the backbones of N501 and Q493, respectively, in the receptor-binding motif and play a role in the tight binding of the SARS-CoV-2 S protein [50]. The whole-genome sequencing of 1200 individuals and chip genotyping of more than 15,000 participants found two observed missense variants of ACE2, K26R, and S331F, which are responsible for reducing the receptor affinity of the viral Spike protein [51]. It has been discovered that 14 ACE2 polymorphisms with increased susceptibility (I21V, E23K, K26R, N64K, T92I, Q102P, D206G, G211R, R219C, E329G, H378R, V447F, A501T, and N720D) had greater allele frequencies in European (non-Finnish) groups than in East Asian populations. Two resistance-related ACE2 polymorphisms (E35K and F72V) show greater allele frequencies in East Asian groups but are low or absent in European (non-Finnish) populations. These findings are consistent with the pandemic scenario and could help explain why COVID-19 prevalence and fatality rates in Europe and East Asia are so different [49]. Due to these findings, genetic variations in the ACE2 gene among individuals are remarkable factors that affect disease severity [51].

Inflammatory factors Higher amounts of ferritin, D-dimer, C-reactive protein, and increased levels of IL-2, IL-6, IL-10, and TNF-α have been associated with the severity and mortality rates of SARS-CoV-2 infection [45]. Some reports indicated that polymorphisms of rs1800896 in *IL-10*, rs2275913 in *IL-17A*, and rs763780 loci in the *IL-17F* gene were correlated with death rates in different countries [52]. However, in Northwestern Mexico, there was no association between the rs1800871 and rs1800872 polymorphisms and COVID-19 severity and mortality [53]. To find an association between polymorphism of TNF-α gene and COVID-19 severity, a study showed that the presence of TNF-α polymorphism affected people's sensitivity to COVID-19 infection [54].

Transmembrane protease, serine 2 (TMPRSS2) TMPRSS2 is a serine protease in various human tissues and is involved in SARS-CoV-2 infection. Genetic variations on this protein influence virus clearance in the host and predisposition to infection. Generally, polymorphisms at TMPRSS2 RS2070788, RS7364083, and RS9974589 are crucial to consider. Also, the expression of TMPRSS2 is increased with the polymorphism at TMPRSS2 rs8134378 in men and favors the fusion of the virus membrane [45, 46, 55].

HLA loci Numerous studies stated the association between SARS-CoV-2 and HLA gene [47]. One study found that the *HLA-A*24:02* allele influences susceptibility to COVID-19. Moreover, *HLA-B*46:01* affects and enervates the immune system, thus enhancing the severity of the coronavirus infection in the Asian population. Due to some observation, repetition, and conservation of HLA-B*15:03 between various viruses, one can assume that this allele somewhat protects coronaviruses [45]. New outcomes suggest that individuals with *HLA-A*11:01*, *HLA-A*02:06*, or *HLA- B*54:01* are probably preserved from SARS-CoV-2 infection [56]. Other studies on SARS-CoV and MERS-CoV reported that several HLA genotypes are associated with susceptibility or resistance, which include *HLA- B*07:03*, *HLA-B*46:01*, *HLA-C*08:01, HLA-C*15:02*, *HLA-DRB1*03:01*, *HLA-DRB1*11:01*, and *HLA- DRB1*12:02* [57, 58].

Gender

It is demonstrated that men have a higher mortality rate and worse outcomes during the COVID-19 pandemic and SARS

epidemic [57]. It has been shown that vaccines are more efficient in women as they lead to higher antibody responses, though vaccine side effects are more exacerbated within this gender [58, 59]. Several factors, including the immune system, physiological factors, sex hormones, lifestyle, sociocultural behaviors, and prevalence of underlying diseases, are involved in morbidity and mortality [57, 60].

SARS-CoV

Meaningful differences were observed in animal models regarding the level of pro-inflammatory cytokines, IL-6, and specific chemokines. Pro-inflammatory cytokines, IL-6 and C–C motif chemokine ligand 2 (CCL2) and C-X-C motif chemokine ligand 1 (CXCL1) expression were reported to increase in the lungs of male mice. As a result, inflammatory responses in male mice lasted longer, causing higher mortality and lung immunopathology. Moreover, ACE2 expression was lower in females with heart failure than in men [59]. In a group of SARS-CoV cases in Beijing, the infection rate was similar in males and females; however, the studies revealed gender-related differences regarding case fatality rates (CFR), with males experiencing higher CFRs than females [61]. A study on a mouse model of SARS-CoV infection displayed greater susceptibility to the disease in male mice compared to females of the same age [62].

SARS-CoV-2 interaction with different cell types

Estrogens may downregulate the expression of ACE2 receptor genes located on X chromosomes and are associated with interferon expression in previous research [57, 59, 63]. Although some findings reported a relation between ACE2 receptors and mortality rate in men, the exact association is still a mystery. Besides, several studies noted that males have more ACE2 receptors on the endothelium of the lungs [59, 64]. The expression of TMPRSS2 mRNA is not different among males and females in the lung tissue, but it may be regulated by androgens of prostate cells [57, 63]. Moreover, as men express more TMPRSS2 protein in their androgen-sensitive tissues like the prostate and testis, they are more sensitive to the infection [55].

A single X chromosome in men compared to two in women increases inflammation within this gender [64]. Aging significantly reduces immune factors like B cells, T cells, and natural killer cells in males [59]. Sex hormones also regulate the function of the immune system [57, 59, 63]. Higher levels of IL-6 can cause severe disease among males [57]. These differences may eventually lead to a faster clearance of pathogens in females [46].

About early antiviral responses, Toll-like receptor 7 (TLR7) plays a role in innate sensing of the virus and has higher expression in females [57, 59, 64]. IFN-α is also expressed more in adult females than adult males [47]. Altogether, females have more efficient innate immune responses and a higher level of inflammatory cytokine production than males [58, 65]. Viral detection takes longer in males [63]. Macrophage and neutrophil activity and pattern recognition receptors are also said to differ among these two genders but have not been completely clarified [58].

In adaptive immune responses, antibody levels are higher in females since estrogens lead to escalation of the somatic hypermutations, gender dissimilarities in germinal center formation, fewer stringent selection against autoreactive B cells, and the epigenetic obtainability of B cell loci [63, 64]. T cells are also affected by gender. Overall, T-cell responses are more robust in females than males [58]. It has been shown that ACE2 genes are expressed in the testicles at high levels, and that is why viral clearance takes longer for males compared to female counterparts [59].

Age

During the time of the COVID-19 pandemic, the elderly population became more susceptible to the disease, and they were at increased risk of death; therefore, it is crucial to compare mortality and morbidity variations between individuals of different ages, since these factors can lead to diverse responses to viruses as well as vaccines [66–68]. The relation between ACE2 expression and aging is still in investigation. ACE2 expression was lower in the heart, but its activity was raised in aged animals [69]. In the lungs, ACE2 mRNA expression was higher in adult females, whereas protein levels and activity were reduced in the aged females compared to males. In the kidneys, ACE2 activity is sex-dependent rather than age-dependent, with an elevation in males [70]. Estrogens and androgens level is also reduced as people get older, which may impact ACE2 expression.

Moreover, higher levels of ACE2 in children probably lead to a protective effect against SARS-CoV-2 [71]. This is most likely due to children's unique ACE plasma profile that can be identified from birth. A rise in urine and plasma levels of ACE2, as well as an increase in local placental production and activity of ACE2, was recognized during mid to late pregnancy as a result of estradiol, known as the modulator of the ACE/ACE2. ACE can cross the placenta, allowing the mother to pass on her immunity and other protective soluble elements to the infant [72–74]. The number of lymphocytes significantly decreases at the early stages of the disease in adults, while children have normal white blood cells and lymphocytes count [67]. It is also mentioned that "trained immunity" in children can lead to a milder disease [71]. Breastmilk containing some antiviral proteins such as Lactoferrin and Casein,

Table 1 List of vaccine candidates, which all have at least passed clinical trial phase II/III

SARS-CoV-2 vaccine and developer [85, 86]	Vaccine platform/ Immunization attribution	Doses information/ Route of administration	Preclinical data	Features	Clinical data limitations and disadvantages	Registration code
GRAd COV2/ReiThera (LEUKOCARE/Univercells) [85, 87, 88]	- Non-replicating viral vector - Replication-defective gorilla adenovirus (GRAd) encoding S protein - Injection of this vaccine leads to encoding of full-length S protein	- Single-dose - 5×10^{10} VP, 1×10^{11} VP or 2×10^{11} VP - IM	- A good safety profile in preclinical studies	- Inducing strong immune responses according to low pre-existing immunity to the vector in human beings - The technology is based on proprietary replication-defective gorilla adenoviral vector, inducing a strong humoral and cellular immune response - The vector is similar to human species C adenovirus virus - The company emphasis on a stable liquid formulation - Required temperature: 2–8 °C (refrigerator)	- Occurrence of solicited systemic AE signs and symptoms	Phase I: NCT04528641 Phase II/III: NCT04791423
AG0301 (AnGes + Takara Bio + Osaka University) [89, 90]	- DNA-based vaccine - No published data is available yet	- Double-dose (day 0, 14) - Low dose: 1 mg, twice at 2-week intervals - High dose: 2 mg, twice at 2-week intervals - IM	- Using alum adjuvant AG0301-COVID19 leads to elevated levels of neutralizing antibodies and T cell responses in the rats, while solving the problem of organ toxicity	- Available for 18 to 65 years - Short time required from the design to clinical trials - After the second immunization, serum neutralizing activity was detected - Short-term storage in refrigerator (2–8 °C) or room temperature (20–30 °C)	- Imparts low immunogenic responses in humans and larger animals compared to small animal immune systems	Phase I/II: NCT04463472 NCT04527081 jRCT2051200085 Phase II/III: NCT04655625

Table 1 (continued)

SARS-CoV-2 vaccine and developer [85, 86]	Vaccine platform/ Immunization attribution	Doses information/ Route of administration	Preclinical data	Features	Clinical data limitations and disadvantages	Registration code
SCB-2019 (Clover Biopharmaceuticals Inc, GSK) Dynavax) [83, 91]	- Protein subunit, SCB-2019 with AS03 or Cp,G 1018 adjuvant plus alum adjuvant (Native like trimeric subunit spike protein vaccine) - Expressing S protein: the trimeric S protein of SARS-CoV-2 binds to host cell surface receptor ACE2 leading to virus entry	- Double-dose (day 0, 21) - IM	- Induction of a strong neutralizing immune response in animals - Protecting non-human primates from SARS-CoV-2 challenges	- Elicited high seroconversion rates of binding and neutralizing antibodies as well as Th1-based CD4 + T-cell responses in candidates -Using more established vaccine technologies -Required temperature: 2–8 °C (refrigerator)	- Local adverse events within youth aged 18–54 years and adults aged 55–75 years was 35% and 34%, respectively However, systemic adverse events were reported 30% in old adults and 34% in young adults after the second injection	Phase I: NCT04405908 Phase II/III: NCT04672395

The information contained in this table is up to December 11, 2021. Data has no obligation to be updated as the result of new information or future events of developments

Abbreviations: AE: Adverse event; ID: Intradermal; IM: Intramuscular; S protein: Spike protein; VP: Virus particle

along with maternal antibodies, are other factors protecting infants against infection [66].

In 2021, after global vaccination, several studies were done to evaluate age as one of the factors for vaccine immune responses. Xia et al. claimed that people aged 60 and above who received the Sinopharm inactivated vaccine showed fewer neutralizing antibodies than those aged 18–59. In another study, Müller et al. concluded that 31.3% of people aged 80 and older given the BNT162b2 vaccine display no neutralizing antibodies after the second injection, compared to 2.2% of those younger than 60 [39]. Therefore the diversity in the responses among age categories was enumerated as a challenge for vaccine production.

Ethnicity and geographical differences

African-American race is considered to have a greater mortality rate [75]. A study showed that ACE2 expression was high in East Asian females [76]. TMPRSS2 allele frequency is also different among populations as it is a lower frequency in East Asians [55]. Thus, differences in gene expression, immune system, or even genetic background play a role in diverse responses to SARS-CoV-2 [76]. Furthermore, some national variations such as their access to health care, quality of nutrition, substance abuse, social distancing policies, social behavior, the incidence of obesity, diabetes, being over 65 years old, access to health care, and socioeconomic development level should be considered to explain why mortality rates vary from place to place [75, 77, 78].

Infection history

At the beginning of the global vaccination, the debatable issue was whether previously infected patients with COVID-19 were required to receive the same full range of vaccination regimens as those who were not experienced. Hence, the rate of specific anti-SARS-CoV-2 neutralizing antibodies in the serum samples was examined. Among vaccine regimens using the BNT-162b2nAb, titers were considerably lower in uninfected people receiving both doses than in previously infected patients receiving only one dose. Thereby, to maximize the herd [79] of the entire regimens, it is recommended to vaccinate previously infected patients with only a single dose [39, 80–82].

SARS-CoV and SARS- CoV-2 vaccines

COVID-19 vaccine producers have taken the previous investigations on SARS vaccines (in 2003) into account. During the SARS outbreak, it took almost four months to develop a range of usable antigens for the animal, and cell culture trials before the genome sequence of the coronavirus became available. The first human trial on the SARS

Table 2 List of vaccines which have received approval from at least one regulatory body

SARS-CoV-2 vaccine and developer	Vaccine platform/ Immunization attribution	Doses information/ Route of administration	Preclinical data	Features	Challenges and clinical limitations
mRNA-1273 (Moderna, National Institute of Allergy and Infectious Diseases) [92–95]	- Lipid nanoparticle encapsulated messenger RNA (mRNA), coding virus spike protein - Expressing S protein	- Double-dose (Day 0 and 28) - Costs about $32-37 per dose, while many developed countries are injecting for free - IM	- Producing neutralizing antibodies and CD8+ T cells in mice. - Two doses of mRNA-1273 vaccine prevented the infection in the lungs and nasal mucosa of non-human primates after SARS-CoV-2 exposure	- Target population: aged 18 and over - Majority of receivers in clinical studies were at the risk of virus exposure in the workplace - Rapid production as it is mRNA vaccine - After the first injection, huge antibody responses to both full-length S-2P and receptor-binding domain in all receivers were reported - No onsite dilution is necessary - This vaccine got an emergency use authorization on Dec 18, 2020. - Shows 91.4% efficacy among those who receive two doses of vaccine with no background of COVID-19 - Efficacy: 94.5% -Seroconversion rate: 100% after the second dose - Provides immunogenicity at least 119 days after the first injection and 90 days after the second one - New form of the virus in the UK and the Republic of South Africa has no impact on mRNA-1273 vaccine function - Multiple vials should be kept in -25º and -15ºC. Storage possible for up to 30 days at normal refrigerator temperature	- Difficult transportation in low-income countries and warmer climates - Common side effects: allergic symptoms, injection site pain, tenderness, lymph nodes and facial swelling, headache fatigue, myalgia, chills, vomiting and nausea, fever - Side effects were more severe after the second injection, disappearing within a few days - Anaphylaxis reaction occurred in 2.5 per million injected doses - Neutralizing titer levels to the South African version were reduced six times
Sputnik V (Gam-COVID- Vac Lyo Gamaleya Research Institute) [95–99]	- Non-replicating viral vector (adeno-based) (adenovirus 26 and adenovirus 5(- Expressing S protein	- Double-dose (Day 0, 21) - The cost of one dose is less than $10 - IM	- Desired antibody level, preventing adhesion of the virus to the receptor and T-cell response was acquired	- Studies reveal that the safety of heterologous vaccine based on rAd26-S and rAd5-S is enough - Both formulations (frozen and liquid) indicated good immunogenicity - All receivers produced antibodies against SARS-CoV-2 glycoprotein - IgG responses were higher in comparison to those recovered from SARS-COV2 - Provides immunogenicity within 18 days after the first injection - Due to the unique platform, it takes a short time to be manufactured - Seroconversion rates: 100% -Efficacy: 91.6% (100% efficacy in severe cases) -The liquid form of the vaccine can be stored at 2-8°C - Supply chain shipping condition for liquid form: around -18°C	- 94% of side effects were mild across all participants age group - Common side effects: pain at the injection area, hyperthermia headache, asthenia, and muscle and joint pain - Short duration of follow-up (42 days) - Drawback of adeno-based vaccine is that large doses are needed, around 10^{10} or 10^{11} particles - Contrary to its function against the South Africa variant (B.1.351), Sputnik exhibits impressive function against the UK variant (B.1.1.7)

Table 2 (continued)

SARS-CoV-2 vaccine and developer	Vaccine platform/ Immunization attribution	Doses information/ Route of administration	Preclinical data	Features	Challenges and clinical limitations
CoronaVac (Sinovac Research and Development) [83, 95, 100–103]	- Inactivated SARS-CoV-2 - Manifold viral antigens	- Double-dose (Days 0, 14) - IM	- Data showed good immunogenicity in the non-human primate model - Antibody titers from macaque were admitted as complete protection against SARS-CoV-2 - Weak cellular responses - T cell cytokine production did not improve significantly, thus it does not have pathogenicity for the lung, heart, spleen, liver, kidney, and brain tissues	Phase I/II: - Neutralizing antibody titers were variable as 8-24 - Infrequent re-infection reports - Endpoint: 28 days Phase III: - Primary efficacy endpoint: two weeks after the second vaccination - The incidence of solicited and unsolicited local and systemic adverse effects one week after vaccination is the key protection endpoint - Study was based on only healthy adults and those who have a condition that is under control on a therapeutic level - In older people, there was a slight decrease in titer - Seroconversion rates: 92% in adults below 60 and 98% in adults above 60 in the 3 µg dose - Efficacy: 50% Brazil, 65% Indonesia, 67% Chile, 84% Turkey -Required temperature: 2-8°C (refrigerator)	- T cell responses in phase II were not determined and were low in the participants - Reactions mediated by CD8+ cells were not considered - People younger than 18 were not concluded - Vaccine-enhanced disease risk - A live virus is needed, as well as the ability to produce large quantities of it
Ad5- nCoV (CanSino Biological Inc. Beijing Institute of Biotechnology) [83, 95, 103, 104]	- Non-replicating viral vector. Adenovirus type 5 vector, recombinant vaccine - Expressing S protein	- Single-dose - 5×10^{10} VP - IM	- Was safe and provided robust immunogenic response in animal models	- There is no need to cultivate a live virus - Generation is fast - IFN-γ ELISPOT responses have been discovered in both phase I and II - Adverse effects are less common in people who already have anti-Ad5 antibodies - Published data showed antibody level is negatively associated with pre-existing anti-vector immunity and age (>55 years) - Humoral responses to SARS-CoV-2 peaked on day 28 and were followed by a fast specific T-cell response beginning in week two - Seroconversion was 44-61% after one dose and 97-100% after two doses Neutralization was 28-42% after one injection and 50-75% after two doses - Phase II: Seroconversion (neutralization) was 59-61% after two doses - Efficacy: 74.8 % - Required temperature: 2-8°C (refrigerator)	- Phase I: mild or moderate local reactions (in 54% of volunteers) / mild-severe systemic adverse events (in 46% of volunteers) - Phase II: side effects in 72% of volunteers, especially in high dose group. More severe symptoms were also detected (9%), including fever and injection site pain - Anti-vector immunity exists - May be unsuitable for immunocompromised patients

Table 2 (continued)

SARS-CoV-2 vaccine and developer	Vaccine platform/ Immunization attribution	Doses information/ Route of administration	Preclinical data	Features	Challenges and clinical limitations
EpiVacCorona (FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo) [105]	- Protein subunit - Synthesized peptides of SARS-CoV-2 antigens	- Double-dose (Days 0, 21) - IM	- High immunogenicity detected - After two injections, 100% of the participants had neutralizing antibody titers of 1:20 to 1:160, with a GMT of 1:68 on day 35 after the first dose	- Safe - Low reactogenicity detected (mild and transient local reactions, no systemic adverse reactions) - Well-tolerated - Due to the virus mutations, most conserved regions of S protein were used in the vaccine epitopes - Decent mode of storage and transportation - Antibody production in 100% of participants due to vaccination (mostly 42 days after receiving the second dose) - Required temperature: 2-8°C (refrigerator)	- Pain at the injection site was the most reported adverse reaction. - High body temperature in one of the volunteers 12 hours after the first injection (not contributed to vaccination) - Acute respiratory viral infection reported in three cases (two placebo volunteers and one in phase I trial)
BNT162b2 (Pfizer, BioNTech, Fosun Pharma) [83, 92, 106–110]	- Lipid nanoparticle containing mRNA - Encodes a P2 mutant spike protein (PS 2)	- Double dose (Day 0 and 21) - A dosage of 30 µg at a cost of $19.50 - IM	- Elicited high neutralizing antibody titers in mice after a single injection - Robust T helper 1 (TH1) and T follicular helper (TFH) type CD4+ responses as well as a robust IFN-γ, IL-2, CD8+ T-cell response - In rhesus macaques, the TH1-based CD4+ T-cell response and IFN-γ, CD8+ T-cell response mirrored that of the cellular immunogenicity profile reported in mice - Seven days after a second dose of two-dose series, 50% virus neutralization titer of antibodies reached 18-times more than in a human SARS-CoV-2 convalescent serum panel	- First vaccine that acquired USFDA approval for emergency use (recommended for 16-year-olds and above) - Has been approved by more than 80 countries - Rapid production - BNT162b2 caused lower incidence and severity of systemic reactions than BNT162b1, particularly in older adults - The vaccine remained effective against B.1.1.7 (the UK variant) with a slight but significant decrease in neutralization that was more apparent in participants under 55 years of age - Provides immunogenicity for at least 119 days after the first dose -52% after the first shot and 95% beginning one week after the second injection (over 94% in adults older than 65 years) - Challenging storage and transportation conditions. Ideal condition includes special freezer filled with dry ice at a temperature of 70 °C±10 °C - When stored under 2-8 °C conditions, the vials cannot be re-frozen or stored under frozen condition - Could be stored for five days at refrigerated (2-8°C) conditions - Could be stored for 15 days (10 + 5) by refilling with dry ice - Efficacy: 95% (≥16 years old) 100% (12–15 years old) 91.3% (six months after the second dose)	- Common reported adverse reactions in participants (≥16): pain at the injection site, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling and redness, nausea, malaise, and lymphadenopathy, with a mean duration of 2-3 days - Severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions, diarrhea, vomiting, and pain in extremity (arm) have been reported following the Pfizer-BioNTech COVID-19 vaccine during mass vaccination outside of clinical trials

Table 2 (continued)

SARS-CoV-2 vaccine and developer	Vaccine platform/ Immunization attribution	Doses information/ Route of administration	Preclinical data	Features	Challenges and clinical limitations
BBIBP-CorV (Sinopharm, China National Biotec Group Co, Beijing Institute of Biological Products) [83, 111–114]	- Inactivated SARS-CoV-2 virus - Multiple viral antigens	- Double-dose (Day 0 and 21 or day 0 and 28) - The 4μg dose seems to be more effective - Sinopharm intended to charge the government roughly $30/dose (may vary from $19-$36) - IM	- Provoke high levels of neutralizing antibodies titers in mice, rats, guinea pigs, rabbits, and nonhuman primates (cynomolgus monkeys and rhesus macaques) - Two-dose immunizations using 2 μg/dose provided highly efficient protection against SARS-CoV-2 intratracheal challenge in rhesus macaques, without detectable antibody-dependent enhancement of infection	- Induces humoral response against SARS-CoV-2 - The first inactivated SARS-CoV-2 vaccine tested on human - Its first dose was 79% effective in terms of preventing symptomatic SARS-CoV-2, which is lower than the 86% efficacy reported earlier the same month by the United Arab Emirates (Latest efficacy is reported to be 79.34%) - Efficacy: 78.1% - Has been approved in at least 35 countries - All adverse reactions were mild or moderate in severity - Safe and well tolerated in people aged 18 and above. - Required temperature: 2-8°C (refrigerator)	- Due to the lack of transparency surrounding Chinese made vaccines, vaccine hesitancy appears to be a problem - A lower efficacy than Pfizer's or Moderna's. - The most common adverse reaction was fever. -Less effective against the B.1.351 variant (the South African variant)
ChAdOx1 nCoV-19 (AZD-1222) University of Oxford AstraZeneca [115]	-Non-replicating viral vector ChAdOx1-S -Expressing S protein	- Double dose (Day 0 and 28 Or) 1 dose - 5×10^{10} VP (nominal ± 1.5 $\times 10^{10}$ VP) - IM	- Prevention of pneumonia was shown without transmission in the non-human primates (in rhesus macaque)	- Safety and immunogenicity is similar across ages - mRNA vaccine caused lower reactogenicity in older adults, in comparison to younger adults - Containing a wider range of receivers, including adults aged 70 years and older - Efficacy against death, seroconversion against non-spike proteins - No severe local symptoms or hospitalization were reported by participants received ChAdOx1 SARS-COV2 vaccine - Induced spike-specific CD4 T-cell cytokine responses with a predominantly Th1 profile - Could be kept in normal refrigerators up to 6 months - Efficacy: about 79% - Cheaper than Moderna and Pfizer vaccinew (costs only a few dollars)	- Common side effects: rare blood coagulation disorder (Despite this, some countries have decided to continue using the vaccine in their immunization programs), injection site tenderness (>60 %), injection site pain, headache, fatigue (>50%), chills, pyrexia (>30%), malaise (>40%), arthralgia, nausea (>20%)

Table 2 (continued)

SARS-CoV-2 vaccine and developer	Vaccine platform/ Immunization attribution	Doses information/ Route of administration	Preclinical data	Features	Challenges and clinical limitations
Ad26.COV2-S (Johnson & Johnson) [83, 91, 116]	- Ad26-vectored, non-replicating - Inducing S protein synthesis	- Single-dose (Also, the company is testing 2 shots vaccine with an interval of eight weeks) - Each vial contains 5*10^10 vp - IM	- By neutralizing antibodies, this vaccine provided approximately complete immunity against SARS-CoV-2 in lung	- Target population: aged 18 and older - Involved participants infected with a new variant of virus called B.1.351 - The first single dose SARS-COV2 vaccine - No hospitalizations and mortality were reported among participants - Protective against multiple variants - Could be stored for at least 3 months in a normal refrigerator. It has constant structure for 2 years at -20°C - Shipping through normal cold chain technology - Capable of easy long-term storage and administration in comparison to mRNA vaccines - Efficacy: Totally, 66.9% protection against moderate cases 28 days after vaccination. - Showing 85% safety in severe situations.	- No longer available outside the clinical trials -Clinical trial phase III side effects: blood clots in combination with low platelets, injection site pain, fever (9%), fatigue, abdominal pain, shortness of breath, severe headache, myalgia (leg pain) - Younger people experience more side effects due to the stronger immune system
ZF2001 (RBD-Dimer) (Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences) [83, 114, 117]	- Protein subunit adjuvant recombinant protein - Dimeric RBD	- Double-dose (Day 0 and 28) or triple dose (Day 0, 28 and 56) - 25-50 μg/dose (25 μg triple-dose is preferable) -IM	- 93–100% seroconversion rate of neutralizing antibodies while induced Th1 and Th2 cytokines response	- Chinese 5th vaccine candidate to enter late-stage human testing - Study group: aged 18-59 years - Generally safe - Risks of producing live pathogens are eliminated - No vaccine-related serious adverse events - Most of the local or systemic adverse events were mild or moderate and resolved within 3-4 days - Compared to other SARS-CoV-2 vaccine candidates, it had lower occurrence of fatigue and fever - Efficacy: 81.76% - Low-cost temperature requirements (2-8 ℃)	- Requires specific adjuvants to boost the immune response - The reports belong to local adverse events were injection-site pain, redness, induration and itch. - The most common systemic adverse effects were cough, fever, fatigue and headache. - Less effective against the UK variant
Sinopharm (China National Biotec Group Co + Wuhan Institute of Biological Products BBIBP-CorV) [111, 112, 118, 119]	- Inactivated SARS-CoV-2 vaccine - Manifold viral antigens	- Double dose (Day 0 and 21) - 3 μg/0.5 mL - $30 per dose - IM	- Data showed good immunogenicity in the non-human primate model - Antibody titers from macaque were admitted as complete protection against SARS-CoV-2	- Safety and immunogenicity of a booster dose - Infrequent re-infection reports - PiCoVacc` got approval for emergency use in China because of inducing humoral responses, good safety and immunogenicity - Phase I of trials for the vaccine candidate has demonstrated a good safety profile -Seroconversion rates: over 90% - Efficacy: 79.34% - Primary safety endpoint: 28 days - Required temperature: 2-8°C (refrigerator)	- T cell responses in phase II trial were not determined and were low in the participants - Reactions mediated by CD8+ cells were not considered - Study was based on only healthy adults. - Adverse reactions: pain, redness, headache, swelling, fatigue

Table 2 (continued)

SARS-CoV-2 vaccine and developer	Vaccine platform/ Immunization attribution	Doses information/ Route of administration	Preclinical data	Features	Challenges and clinical limitations
COVIran Barakat (Shifa Pharmed Industrial Co.) [120]	- Inactivated SARS-CoV-2 virus + alum - Multiple viral antigens	- Double-dose (Day 0 and 14) - IM	- Two different doses (3 µg or 5 µg per dose) evoke a high level of SARS-CoV-2 specific neutralizing antibodies in mice, rabbits, guinea pig, monkeys, and Rhesus macaques on day 21 and day 42 after the first dose	- Required temperature: 2-8°C (refrigerator)	- Common side effects: injection site pain and itch
NVX-CoV2373 (Novavax) [83, 101, 103, 121, 122]	- Protein subunit full-length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvant with matrix M1 - Recombinant S protein	-Double-dose (Day 0 and 21) - SARS-CoV-2rS (5 µg) + matrix-M1 adjuvant (50 µg) (co-formulated) - IM	- High levels of S-specific neutralizing (anti-spike IgG antibodies), antibodies prevent the upper respiratory tract infections - It also caused the spleen to produce CD4+ and CD8+ multifunctional T cells, CD4+ follicular T helper cells, and antigen-specific germline B cells	Phase I-II: - Safe - Inducing T helper 1 response - After a second dose of NVX-CoV2373, 100% of participants developed neutralization titers - There was no variation in antibody reaction between 25 µg and 5 µg levels - Two shots had a boosting effect - Required temperature: 2-8°C (refrigerator) - It is a ready-to-use liquid formulation - Efficacy: 95.6% 89.3% (UK), 60.1% (in HIV negative subjects, South Africa) - 60% effective against variant B.1.351 and 85.6% effective against variant B.1.1.7.	- No serious adverse events were observed except mild fever for a day in one receiver - No or mild local adverse events - Efficacy in UK was 89% but it was only 49% in South Africa
QazCovid-in®-vaccine (Research Institute for Biological Safety Problems) [123]	- Inactivated SARS-CoV-2 virus	- Double-dose (Day 0 and 21) - IM	- No published data is available yet	- Immune response is directed against spike protein and many other SARS-CoV-2 antigens - Easy handling - Less expensive - More stable than live attenuated vaccines - Required temperature: 2- 8°C (refrigerator) - 100% Efficacy in phase I - 96% Efficacy in phase II	- Short duration of immune memory (unpublished work) - Common side effects: injection site pain and itch, hyperemia (unpublished work)
ZyCoV-D (Cadila Healthcare Limited) [83, 87]	- DNA plasmid (Using non-replicating and a non-integrating plasmid carrying the gene) - Translation of plasmid DNA into viral protein	- Triple-dose (Day 0, 28 and 56) - ID	- Immune response is provoked in multiple animal species like mice, rats, guinea pigs and rabbits - Wild-type virus is completely neutralized via the antibodies produced from the vaccine injection - Safe, well tolerated and immunogenic in rabbits	- Non-infectious - No potential toxicity from viral vectors - Minimum to no risk of vaccine enhanced the other diseases - Stimulate both neutralizing antibodies titers and Th1 response - Minimal risk of anti-vector immunity (effective) - Speedy development - Enhanced vaccine stability and lower cold chain requirements - Efficacy: 67% - Required temperature: 2-8°C (refrigerator)	- While no death reports among candidates, at least one severe side effect happened to ¼ of them.

Table 2 (continued)

SARS-CoV-2 vaccine and developer	Vaccine platform/ Immunization attribution	Doses information/ Route of administration	Preclinical data	Features	Challenges and clinical limitations
CIGB-66 (RBD+ aluminum hydroxide) Center for Genetic Engineering and Biotechnology [124–127]	- Protein subunit - RBD dimer	- Triple-dose (Day 0, 24 and 28 or day 0, 28 and 56) - IM	- The sera from mice, rats and NHP immunized with C-RBD-H6 PP protein inhibited the RBD-ACE2 receptor binding and neutralize the SARS-CoV-2 in microneutralization tests	- Required temperature: 2-8°C (refrigerator) - Available for 19 to 80 years of age - Abdala vaccine exhibited high antibody titers, enhanced antigen presentation and T-cell activation properties upon interaction with receptors in antigen presenting cells - Larger immune responses induced by the 0-28-56 days vaccination schedule than those induced by the 0-14-28 days vaccination schedule, regardless of the dose. However, quick antibody responses could be induced within a relatively short period of time by using a 0-14-28 days schedule.	- 92.8% efficacy against symptomatic disease - 100% efficacy in preventing severe systemic disease and death of vaccinated people -90% effectiveness in critically ill people - Minimal and mild adverse reactions, mostly from the site of injection with most common symptom being injection site pain - Better immunological performance in 19-54 age group

The information stated in this article includes data up until December 11, 2021

Abbreviations: GMT: Geometric mean titer; IM: Intramuscular; RBD: Receptor-binding domain; S protein: Spike protein; UK: United Kingdom; VP: Virus particle

vaccine was conducted in Beijing (December 2004) after the epidemic had ended. Therefore, studies stopped at the preclinical stage, and still, there are no available vaccines against SARS-CoV and MERS-CoV [83, 84] (Table 3). The lack of SARS-CoV and MERS-CoV vaccines could be related to insufficient funding and a poor understanding of the viruses' biology [84].

The mechanism of action of SARS-CoV and SARS-CoV-2 vaccines significantly resemble each other. Scientists attempt to find ways to expose the immune system to the spike protein on the virus membrane to stimulate virus identification during further exposure and induce antibody responses (Tables 1, 2 and 3). To this end, the same vaccine platforms were used to develop vaccines against SARS-CoV and SAR-CoV-2, which are discussed as follows. SARS-CoV, SAR-CoV-2, and MERS vaccine evolution is briefly summarized in Fig. 2.

Vaccine platforms

Virus-based vaccines

Virus-based vaccines are the platform most commonly used for other diseases, either as an inactivated (killed) or live attenuated virus that contains most of the virus antigens [14]. In killed vaccines, the virus is inactivated by radiation, heat, or formaldehyde. This platform offers a broad antigenic profile while being safe (i.e., the incapability to replicate) and less expensive than DNA/RNA vaccines. In live attenuated vaccines, serial passage of the virus leads to a reduction in its virulence. Hence, this platform produces strong and long-lasting humoral and cellular immune responses and offers a broad antigenic profile. Meanwhile, virus-based vaccines are associated with safety concerns due to their higher risk of virus replication, and thus, they are rarely used in immunocompromised patients [140–142].

Protein-based vaccines

Instead of using the whole virus, many researchers choose protein subunit vaccines and use antigens with strong immunogenicity, for example, the S protein or only the RBD [14]. The recombinant RBD vaccines compose of several conformational neutralizing epitopes, stimulating effective neutralizing antibodies against SARS-CoV [143]. Another protein-based vaccine strategy includes virus-like particles (VLP), offering a broad antigenic profile via imitating the SARS-CoV-2 structure on the surface of a non-replicative empty virus shell without genetic material [14, 140]. This platform is considered safer with lower cost than conventional vaccine platforms [141, 142].

Table 3 Summary of SARS-CoV and MERS-CoV vaccines after the preclinical stage

Vaccine developer	Vaccine platform	Type of candidate vaccine	Non-coronavirus candidates	SARS-CoV/ MERS-CoV
Institute Pasteur France [128, 129]	- MV-SARS recombinant measles virus vaccine expressing SARS-CoV antigen	- Replicating viral vector	Wnv, Chik, Ebola, Lassa, and Zika	SARS (Has never been tried on humans)
Vaxine Pty Ltd, Australia Chinese Center for Disease Control and Prevention [121]	- Protein subunit	- SARS recombinant S protein with delta inulin as an adjuvant	It boosts immunogenicity against a broad range of viral and bacterial antigens like Ebola, Zika, Influenza, and Hip B	SARS
Novavax [130]	- Virus-like particle	- SARS VLPs S protein and influenza matrix M1 protein (with the help of S protein, M1 creates VLPs) - Containing 0.8 µg S protein without an adjuvant reduces lung virus titer	RSV, Flu	SARS
National Institute of Allergy and Infectious Diseases (NIAID) [131]	- DNA	- 3-dose DNA vaccine - VRC-SRSDNA015-00-VP	Ebola, HIV, and Wnv	SARS
Sanofi [132]	- Inactivated virus with aluminum hydroxide adjuvant	- Whole virus, monovalent, licensed product	Influenza and others	SARS
Sinovac Biotech Ltd (Beijing Kexing Bioproduct), Chinese Centre for Disease Control and Prevention; Chinese Academy of Medical Sciences [133]	- Inactivated virus	- Double-dose inactivated virus	NA	SARS
King Abdullah International Medical Research Center (KAIMRC) / University of Oxford's Jenner Institute [134]	- ChAdOx1 and MVA based	- Replication-deficient adenovirus vector-based vaccine expressing MERS-CoV S protein - A single dose induces immune responses against MERS-CoV	NA	MERS
INO-4700(GLS-5300), Inovio Pharmaceuticals and GeneOne Life Science Inc. [135]	- DNA plasmid	- Expressing the MERS-CoV S glycoprotein - Dosage: 0.67 mg, 2 dases at 0 and 8 weeks, or 3 doses at 0, 4, 12 weeks	Lassa, Nipah, HIV, Filovirus, HPV, Zika, Hip B	MERS
IDT Biologika GmbH [136, 137]	- Non-replicating viral vector	- Double-dose recombinant MVA-MERS-S	Chik, Ebola, Lassa, Nipah, Marburg, Zika, influenza	MERS
University of Oxford [138, 139]	- Non-replicating viral vector	- Single-dose ChAdOx1 MERS vaccine, expressing S protein	Malaria, Influenza, Chik, RABV, Rvfv	MERS

Abbreviations: CHIKV: Chikungunya virus; CoV: Corona virus; Hip B: Hepatitis B; HIV: Human immunodeficiency viruses; HPV: Human papillomavirus; MV: Measles vaccine; MVA: Modified vaccinia Ankara; NA: Not available; RABV: Rabies virus; RVFV: Rift valley fever virus; RSV: Respiratory syncytial virus; S protein: Spike protein; VLP: Virus-like particle; WNV: West Nile virus

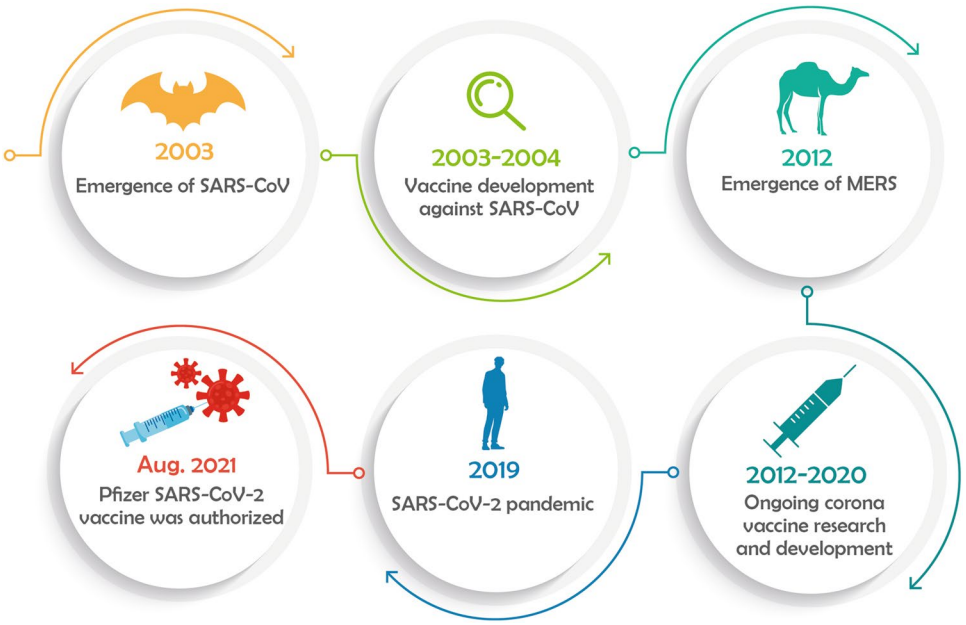

Fig. 2 The rise and fall of coronaviruses in the past two decades

Viral vector-based vaccines

Several viruses, e.g., vesicular stomatitis virus (VSV), influenza, measles, and adenovirus, could also be engineered as replicative or non-replicative recombinant vectors which express coronavirus S protein [14]. Vaccines produced by this platform are categorized as replicating and non-replicating vectors. In non-replicating kinds, virus replication is prevented by removing a gene responsible for encoding a structural protein. As the name suggests, replicating vectors can replicate in the cells and, therefore, require a smaller dosage. However, there are some safety concerns regarding their administration in immunocompromised patients [141, 142].

Nucleic acid-based vaccines

DNA-based vaccines DNA vaccines are usually created using plasmid DNA containing eukaryotic expression elements to encode one or more antigens. DNA vaccines are stable, generally administered through intramuscular and intradermal injection, and activate both humoral and cellular immune responses. One obstacle is that they shall cross two cellular membranes before entering the nucleus. Another is that no DNA vaccine has previously been approved for human administration [14, 142].

RNA-based vaccines The mRNA, encapsulated in lipid nanoparticles, enters the cytoplasm as a template to be translated, making multiple copies of the antigen. It may code the full-length S protein or a fraction [14, 141]. Like vector and DNA-based vaccines, mRNA vaccines can induce both humoral and cellular immunity. mRNA vaccines are considered to be safe, fast, and efficient. The only setback is the low temperature needed for transportation and storage [141, 142].

DNA/ RNA as vaccine delivery system for COVID-19

The key challenge in developing DNA/RNA vaccines is the host cells' probability of being picked up. There are two standard methods of introducing the DNA/RNA into the host immune cells [14]: first, using viral vectors; and second, using a delivery system to carry the DNA/RNA across the cell membrane to boost the synthesis of S protein.

Electroporation

This method temporarily applies a high-voltage electric pulse to the living cells. Consequently, DNA can pass through the membrane with more permeability. INOVIO pharmaceutical uses this technology (CELLECTRA®) to produce the COVID-19 vaccine [144].

Oligonucleotides (DNA/RNA) delivery

Oligonucleotides are macromolecules that present high therapeutic indexes remarkably when the formulation is tailored to reach specific tissues and sites of action. In the process of oligonucleotide delivery, nanoparticles need to encapsulate adequate amounts of nucleic acid and have specific tissue targeting properties. Thus, combining LNPs (Lipid-Based Nanoparticles) and immune-modulatory oligonucleotide adjuvants induces synergistic effects for immunologic responses [145, 146].

Table 4 Case reports of reinfection

Reported	Country	Age/ Gender	Time gap	Explanation	Recovered	References
Nov. 21	South Korea	21/Female	10 days	- Symptoms: 1st case: mild; 2nd case: mild - The genetic sequencing results belonged to a different strain of SARS-CoV-2	Yes	[179]
Aug. 28	United States	25/Male	31 days	- Symptoms: 1st case: mild; 2nd case: severe - First, a very high dose of virus might have led to the second instance of infection and a more severe disease. Second, it is possible that reinfection was caused by a more virulent version of the virus, whether generally or specifically in this person. Third, a mechanism of ADE might be the cause. It is possible that a case of continuous infection entailing deactivation was reported	Yes	[180]
Sep. 29	Qatar	20 s/Male	45 days	NA; nearly all of the suspected cases were men and young adults	Yes	[181]
Aug. 30	Ecuador	46/Male	47 days	- Symptoms: 1st case: mild; 2nd case: moderate - High levels of IgG antibodies were found after the second infection	Yes	[182]
Sep. 23	United States	42/Male	51 days	- Symptoms: 1st case: mild; 2nd case: severe	Yes	[183]
Sep. 15	India	25/Male	100 days	- Symptoms: 1st case: asymptomatic 2nd case: asymptomatic - Second infection was asymptomatic but had a higher viral load	Yes	[184, 185]
Sep. 15	India	28/Female	101 days	- Symptoms: 1st case: asymptomatic 2nd case: asymptomatic - Second infection was asymptomatic but had a higher viral load	Yes	[184, 185]
Sep. 26	United States	60/NA	118 days	- Symptoms: 1st case: severe; 2nd case: mild	Yes	[184]
Oct. 16	Sweden	53/Female	120 days	- Symptoms: 1st case: mild; 2nd case: milder - Low levels of antibodies were found after the second infection with a low viral load in the nasopharynx	Yes	[184]
Aug. 24	Hong Kong	33/Male	123 days	- Symptoms: 1st case: mild; 2nd case asymptomatic	Yes	[186]

The randomized data gathered is until January 2021, though, in recent months more cases have been confirmed

Abbreviations: ADE: Antibody-dependent enhancement; NA: Not available

Adeno-associated virus (AAV) and lentivirus-based vaccines

Seven front runners (in clinical stages) of COVID-19 vaccine candidates mainly use nucleic acid vaccines which contain non-replicating viral vectors such as adeno-associated virus or lentivirus for vaccine delivery [146]. AAV encodes different antigens, stimulating a robust immune response in vaccinated individuals via various delivery methods. With these promising qualities, rAAV vectors are widely used for vaccine development (e.g., AAV-2 serotype as a vector for delivery of SARS-CoV immunogen) [147–149].

Lipid nanoparticle (LNP) systems

Viruses and nanoparticles are similar in size. Nano-materials are also ideal for antigen delivery as adjuvants and copies of viral structures, allowing nanotechnology to assist vaccine development [150]. Nanotechnology aids novel vaccine design, especially in the case of COVID-19. The first vaccine candidate launched into clinical trials is an mRNA vaccine delivered via lipid nanoparticles [146]. The announcement of the Pfizer and Moderna vaccines breakthrough in November 2020 has gained the attention of scientists and manufacturers. Practically, a vital part of these vaccines' success is based on their drug delivery particle, the lipid nanoparticle carrier. This system solves the delivery challenges by transporting the vaccine to the proper cellular populations and subcellular locations [92].

Moreover, LNPs can fulfill the basic conditions of an RNA/DNA delivery system. They can also preserve nucleic acids from digestion when they move to the target cell. Last, LNPs can be produced by catatonic outer membranes to allow cell entry [151–153].

LNPs improve the stability of mRNA-based vaccines such as mRNA-1273 Moderna. Nanocarriers present these payloads (DNA-RNA) to antigen-presenting cells (APCs). These carriers can provide innate adjuvant behavior and synchronize delivery of both antigen and adjuvant to target immune cells [154, 155].

Silica nanoparticle for DNA and RNA delivery

This method has been proven to be safe. It is an alternative to the LNP method to cover LNP deficiencies (i.e.,

insufficient delivery of nucleic acids into the cells). Another crucial advantage is that the mesoporous silica-nanoparticles (MSNs) have excellent biocompatibility and chemical stability attaching to oligonucleotides, including DNA, RNA, and siRNA [146, 150].

COVID-19 vaccine challenges

Probably, the best way to limit infections is vaccination. It has two outstanding usages; first, decreasing the number of infected people and hence lessening virus spreading; second, preventing multi-infection, and if not, reducing post-recovery syndromes [15]. The manufacturers have been facing some challenges during the development of the COVID-19 vaccine, as outlined below.

Animal models

The virus's ability to infect a particular cell or tissue (viral tropism) may lead to the suspension of the vaccine development at the preclinical phase and is the rationale behind animal testing [156]. This big challenge must be addressed before the clinical phases [15]. Another challenge is that the vaccine candidate may trigger an immune response in animal models, which may not be replicated in humans. This is because animals may not produce biological characteristics akin to the human model, which makes the mortality and efficacy rates unreliable [157]. Nevertheless, pigs make good models since they are susceptible to SARS-CoV-2 and have a human-like nature [158]. In vitro experiments on animal models do not necessarily assure a similar efficacy for humans.

Viral vector-based vaccines

The viral vector's challenge lies in the production of the vaccine. This incomplete process results in the defective vector turning into some plasmids. Viral vector-based vaccine production has an impact on the cost and recovery yield. Enhancing the downstream process reduces the price and increases the recovery yield [150].

S protein

Vaccines block the interaction between ACE2 receptors on the host cells and S proteins [159]. While not much biological data exists on the whole mechanism [158]. If there is enough concentration of S protein in the body, its bioavailability causes the infection to spread [159]. Moreover, the ratio of the titer of antibody IgG to nucleotides and virion depends on the S protein. The formation of S protein complexes decreases the IgG efficacy [159]. Vaccine developers focus more on S protein as a functional site of the virus due to its ability to attach to the receptor. Vaccines can block this and make virus-neutralizing antibodies in the lung cells [158]. Mutation of S protein, although it may lead to stronger binding between S protein and receptor by affecting the function, might not affect viral pathogenicity [159].

Humoral immune responses

Recombinant protein vaccines cause humoral immune responses, which cannot provide decent immunogenicity for the body [150]. These proteins may have higher efficacy if adjuvants are added to their formulations; for instance, Novavax, adjuvanted with matrix M1, uses the noted strategy [83]. Recently, Sanofi adjuvanted recombinant protein SARS-CoV-2 vaccine candidate in collaboration with the US Biomedical Advanced Research and Development Authority (BARDA) and GSK is under major examination focusing on original D.614 virus as well as B.1.351 variant among 18 and older, in diverse regions [160]. This platform is suitable for middle- and low-income countries since it is inexpensive and safer than other platforms [161].

Glycosylation

Glycosylation of the vaccine upon administration in humans is a big challenge. Through glycosylation, the vaccine camouflages itself so the immunogenic antigens cannot be visible to the immune system leading to evasion from the host immune system. This phenomenon may negatively impact the effectiveness of the vaccine [159].

mRNA vaccines

mRNA is a platform that has been much used in designing the new vaccines for SARS-CoV-2. It limits the spreading of infections; however, drawbacks, including safety and immunogenicity, are among the challenges hindering vaccine development. Moreover, RNA is destroyed quickly, another con of this platform [159]. The risk of infection still exists in vaccine platforms that use weakened or killed viruses. However, they are more reliable and safer than others. These vaccines have some non-specific effects like activating memory cells, i.e., antibodies produced by mRNA vaccines target S protein (skipping the glycosylation), unlike vaccines containing killed or weakened viruses [159]. Consequently, vaccines that only contain specific antigens, such as Pfizer/BioNTech (BNT162b2) or Moderna/NIAID (mRNA-1273), are better able to launch an adaptive immune attack against the virus. By introducing these latter antigens, the immune

system is distracted without being able to target the virus effectively with induced antibodies or T cells [162].

Mutations' effect on vaccine efficacy

A mutation is an expected change in genome sequencing that makes organisms different. So far, many mutations have been reported, but most do not affect transmission and pathogenicity. Usually, due to the ability of proofreading during replication, the rate of mutations is less than other RNA viruses. However, it has been suggested that a G614 mutation in the virus spike glycoprotein (compared to the previous variant of D614) could increase the transmission and infectivity of the virus but did not affect disease severity [163]. Moreover, studies have shown that certain medicines could affect the rate of coronavirus mutation. Coronavirus mutation rates increased when β-D-N4-hydroxycytidine-5'-isopropyl ester (NHC) exerted antiviral activity. This compound inhibited the replication of highly pathogenic human coronaviruses. EIDD-2801, an antiviral drug known as molnupiravir, is more effective at combating MERS-CoV infection when mutation rates are higher [164].

These are variants with various mutations in their genome sequences which may cause further challenges in vaccine efficacy:

- Variant B.1.1.7 (also known as 20I / 501Y.V1 and VOC 202,012/01): this variant was discovered for the first time in the United Kingdom. Significant mutations in the deletion processes are found in strains N5014, P681H, H69-V70, and Y144/145 of B.1.1.7. These mutations of N501Y increased the affinity to the receptor binding, explaining the rapid spread of B.1.1.7 [165]. One of the mutations in the B.1.1.7 variant is a mutation in the N501Y receptor binding domain that has increased the virus transmission rate [158]. A study of variant B.1.1.7 of SARS-CoV-2 showed that its mortality rate was 30 percent higher than other previous variants [165].
- Variant B.1.351 (also known as 20H / 501Y.V2): this variant was found in South Africa. The N501Y and E484K mutations have also been found within this variant, the latter is said to affect neutralization by polyclonal and monoclonal antibodies. There has been no evidence that this variant is associated with the disease severity [158]. Numerous mutations have been identified in NTD, three in RBD, and one at the furin cleavage site. Due to the emergence of new variants, the efficacy of current monoclonal antibodies (mAb) therapies and vaccines is at risk. In conclusion, many mutations occur, either in the antigenic supersite (NTD16,17) or in the ACE2-binding site (which is a major target of antiviral antibodies) [165, 166].
- Variant B.1.1.28 (with the new name P.1 that was discovered in the four Brazilian passengers in Tokyo, Japan): The P.1 variant also has 17 mutations and three deletions, as well as the E484K and N501Y mutations. The possibility exists that certain mutations within this variant could impair the ability of antibodies produced by infection or vaccination to neutralize or detect the virus [158]. Viruses with co-mutations with the P.1 variant carry an increased risk of spreading the disease. It is a fact that the common mutation in the variant permitted contamination similar to that in the South African variant, as well as creating new risk factors [165, 166].
- Variant B.1.617.2 (also known as Delta) was first detected in Maharashtra in October 2020. It has spread nationwide since then. Compared to the wild-type Wuhan-1 bearing D614G, B.1.617.2 is sixfold less sensitive to neutralizing serum antibodies from recovered individuals and eightfold more sensitive to antibodies induced by vaccination. A lower level of neutralizing antibody against B.1.617.2 was found in ChAdOx1 vaccinates than in BNT162b2 [167].
- South Africa first reported the variant B.1.1.529 (named Omicron) to WHO on November 24, 2021. A recent epidemiological report on South Africa showed three distinct peaks in reported cases. In the spike, Omicron has 26–32 mutations, which make it highly divergent. There is a possibility that some of these mutations involve immune escape potential and higher transmission; however, existing data are conflicting [166].

Problems with vaccination strategies

Cold chain

Currently, companies are dealing with conserving the vaccines in the cold chain since biological compounds have better stability in liquid form. They invest 80% of their production expenses [150]. Converting liquid from vaccine to dry powder (currently available for intranasal vaccines) makes transportation more accessible, reduces vaccine cost, and makes it more heat-resistant [150]. Lyophilized spike protein was fully functional when incubated at 60 °C during the experiment. On the other hand, the integrity of the liquid formulations was compromised on day 7 at 40 °C. However, the liquid formulation of Spike protein failed after less than one day at 60 °C [168].

Antibody-dependent enhancement (ADE)

ADE is a dangerous condition that may aggravate the inflammation in vaccinated individuals upon exposure to the SARS-CoV-19. The mechanism behind this phenomenon is yet to be discovered. However, one possibility is that the non-neutralizing anti-S antibodies may expedite

uptake by macrophages. This leads to macrophage stimulation, production of pro-inflammatory cytokines (IL-6, IL-8, and MCP1), and loss of tissue-repaired cytokine (TGFβ), causing the virus to enter the host cell and spread the infection [169]. A neutralizing antibody acts as a viral receptor. It binds to the surface spike proteins of coronaviruses, causing a conformational alteration in the spike and intermediating viral access to IgG Fc receptor-expressing cells. This immunopathological event has been reported in other viral infections. Previously, it has been shown that if the target cells were reinfected by another serotype of dengue virus (i.e., secondary infection), the pre-existing antibodies could not thoroughly neutralize the virus and led to ADE. Thus, human trials should carefully evaluate vaccine safety and potentially harmful immune responses [159]. One action plan to reduce the chance of ADE is using the S1 or RBD antigen of SARS-CoV-2 instead of the complete full-length S protein. Moreover, selecting Th1-skewed adjuvants rather than alum adjuvants may avoid the inflammatory, immunepathological, and ADE effects [159].

Side effects

During the process of SARS and MERS vaccine manufacturing, trials failed due to significant and potentially lethal side effects. For instance, a whole-virus (inactivated) vaccine was tested in ferrets and non-human primates, and a virus-like particle vaccine was tested in mice. The vaccines provided protection; however, the lungs of mice were infected with the virus [158]. One of the common immunopathological complications related to SARS-CoV and MERS-CoV vaccines was ADE [170]. In addition, elevated temperature (range 1–2.5 °C peaked on the second day), nasal discharge, and sneezing were observed in ferrets during the SARS-CoV whole killed and adenovirus vector-based vaccine study [171]. According to the above-mentioned adverse effects, development processes end at the preclinical phase.

Nonetheless, everything has changed when it comes to the current COVID-19 pandemic. One year has passed since the first wave of the pandemic, and still, we are facing this virus' mutations. Despite all the expected adverse effects, vaccine manufacturers should try their best not to eradicate but at least alleviate vaccines' side effects necessarily. Most SARS-CoV-2 vaccines use only small portions of the virus or the virus' RNA as a platform. This may sidestep the problems with SARS-CoV vaccines containing more virus parts. Therefore, many different methods for vaccines are being tested by global laboratories to reduce these side effects [172].

Despite estimated side effects, approved vaccines worth the risk of not contracting COVID-19. The first dose and second dose of vaccination have unpleasant but not serious side effects, except in pregnant women and children [172]. These adverse effects are similar in different COVID-19 vaccines that reached the third clinical trial phase. These effects are also classified based on their duration and intensity [172].

According to the studies on SARS-CoV and MERS-CoV vaccine development process, there is a concern about the use of coronavirus S-based vaccines since inflammatory and pathological immune effects such as pulmonary eosinophilic infiltration and ADE may occur. Earlier studies on SARS and MERS vaccine candidates have pointed to the risk of ADE; however, there is no clear evidence for SARS-CoV-2 [95, 173].

Since side effects of COVID-19 vaccines are mild and transient, they are usually out of concern. There may be pain, redness, or swelling at the injection site. Tiredness, headache, muscle pain, chills, fever, and nausea are common side effects in the rest of the body [174]. These symptoms may be signs of immune system response in the activation of T-cells and B-cells. However, our attention was drawn to an issue, society's uncertainty about being vaccinated. Therefore, we cannot assure vaccines are safe unless most of society has taken a shot [24, 175].

Reinfections

When a virus variant in circulation causes a second infection, which was not known to be present at the first infection, it is probably considered reinfection. Some SARS-CoV-2 reinfections (primarily mild) have been documented in several studies [176]. Kojima and Klausner reviewed several clinical and epidemiological studies. They found that the risk of reinfection with SARS-CoV-2 decreased by 80.5–100 percent among those who had had COVID-19 [176]. Vaccination efficacy against SARS-CoV-2 may vary in cases with a history of previous COVID-19 infection. Some studies compared the risk of reinfection between previously infected individuals who had never been vaccinated and those who had received vaccination after infection. A case–control study from May–June 2021 in Kentucky found that previously infected individuals who were unvaccinated had 2.3 times greater odds of reinfection than previously infected but vaccinated individuals. Delta was not the dominant variant in the United States at the time of the study [177]. A series of matched-cohort studies involving 1,531,736 individuals vaccinated with mRNA vaccines between December 21, 2020, and September 19 found that prior SARS-CoV-2 infection was associated with a significantly lower risk for breakthrough infection among vaccine receivers [178]. Such findings provide evidence for the claim that post-infection immunity plus post-vaccination immunity may result in antibody responses bigger than post-infection immunity (hybrid immunity). However, a severe SARS-CoV-2 has been reported after recovery from breakthrough infection

by an alpha variant is fully vaccinated (COVISHIELD®) health workers [177]. Whole genome sequencing confirmed that reinfection had happened with the Delta variant.

After vaccination, the ratio of reinfection has decreased. Besides, Omicron may have an increased risk for reinfection than other variants of concern (e.g., those who have previously had COVID-19 are more likely to become infected with Omicron), but the information is limited [166]. The immunological black box of COVID-19 has not been fully decoded, and more cohort and retrospective studies are required to improve our understanding of vaccine efficacy upon emergence of new variants (Table 4).

Conclusion

During the SARS-CoV outbreak in 2002–2003, although 44 vaccines were launched in preclinical stages, only six vaccines got into clinical trials. In contrast to SARS-CoV-2, the prevalence of SARS-CoV was not that high, and the epidemic ended after a while. Therefore, the development of all SARS vaccines was left incomplete. Consequently, at the beginning of the COVID-19 outbreak, scientists used previous SARS-CoV data to extend COVID-19 vaccines. While published data on COVID-19 vaccines showed considerable efficacy and immunogenicity, future studies will provide more accurate information on probable vaccination impacts on receivers considering age, gender, and ethnicity, providing an opportunity to prevent people from transmitting the virus. COVID-19 vaccine developers are currently facing many challenges, including cold supply chain, vaccine stability duration, transportation difficulties, complications concerning booster doses, short time follow-up duration, not enough data about immunization and vaccines' long-term effects, the probability of asymptomatic infections after vaccination, interaction of vaccines with other medicines and more notably, limited number of receivers.

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Declarations

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