Review

Immunopathology, host-virus genome interactions, and effective vaccine development in SARS-CoV-2

Desh Deepak Singh [a], Ihn Han [b], Eun-Ha Choi [b,*], Dharmendra Kumar Yadav [c,*]

[a] Amity Institute of Biotechnology, Amity University Rajasthan, Jaipur, India
[b] Plasma Bioscience Research Center, Applied Plasma Medicine Center, Department of Electrical & Biological Physics, Kwangwoon University, Seoul, Republic of Korea
[c] Gachon Institute of Pharmaceutical Science and Department of Pharmacy, College of Pharmacy, Hambakmoeiro 191, Yeonsu-gu, Gachon University, Incheon, Republic of Korea

ARTICLE INFO

ABSTRACT

Coronaviruses are a group of enveloped RNA viruses that are diversely found in humans and now declared a global pandemic by the World Health Organization in March 2020. The population's susceptibility to these highly pathogenic coronaviruses has contributed to large outbreaks, evolved into public health events, and rapidly transmitted globally. Thus, there is an urgent need to develop effective therapies and vaccines against this disease. In the primary stage of severe acute respiratory syndrome coronavirus (SARS-COV-2) infection, the signs and symptoms are nonspecific, and many more cases have been observed than initially expected. Genome sequencing is performed regularly to identify genetic changes to SARS-COV-2, and vaccine development is focused on manufacture, production, and based on specific problems, and very few are available on recent developments in the prevention of outbreaks. The aim of this review article to explore recent updates on SARS-COV-2 in the context of pathogenesis during disease progression, and innate acquired mechanisms of defense, This includes advances in diagnostics, susceptibility, and severity of host-virus genome interactions, modes of transmission, active compounds being used in pre-clinical and clinical trials for the treatment of patients, vaccine developments, and the effectiveness of SARS-COV-2 prevention and control measures. We have summarized the importance of pathophysiology immune response, Diagnostics, vaccine development currently approaches explored for SARS-COV-2.

1. Introduction

The highly contagious and pathogenic novel SARS-CoV-2, causative agent ongoing COVID-19 pandemic, has spread rapidly and posed a health threat of unprecedented magnitude on the global population. This group includes more than 100 viruses commonly found in various animal species, including bats, pangolins, horses, cats, cattle, camels, goats, and humans [1–3]. Coronaviruses are classified in order *Nidovirales,* family *Coronaviridae,* and positive-sense, single-stranded RNA (ssRNA) viruses with a large genome size of approximately 30 kb. There are seven types of coronavirus found in humans, belonging to "alpha and beta" groups, which frequently mutate and show cross-species transmission. Like the other two highly pathogenic coronaviruses SARS-CoV and MERS-CoV, SARS-CoV-2 also caused severe respiratory illness and even

death. The first human coronavirus (alpha-HCoV-229E) was identified in the 1960 s and caused an upper respiratory tract infection, like the common cold [4,5]. Most people are infected with one or more types of viruses. Rarely, coronaviruses infect animals and become new zoonoses, which can infect people and spread in the human population [5]. A new alpha human coronavirus was discovered in 2003, which was associated with pneumonia, rhinorrhea, and laryngotracheobronchitis in children, particularly in immune-compromised individuals. The beta coronaviruses (type 2) are categorized into lineages A, B, C, and D. One member of lineage A (HCoV-OC-43) was discovered in 1967, and a second (HCoV-HKU) was identified in 2005, associated with diarrhea, acute rhinitis, and infection of the lower respiratory tract. From lineage B, SARS-CoV was identified in 2002–03 and its mode of transmission was bat to civet and then, via civet, to humans [2–5]. A second highly transmissible virus from lineage B was discovered in December 2019 in Wuhan, China, and now known as SARS-CoV-2. Another coronavirus of interest belongs to lineage C and caused

* Corresponding authors.
E-mail addresses: choipdp@gmail.com (E.-H. Choi), dharmendra30oct@gmail.com (D.K. Yadav).

an outbreak of Middle East Respiratory Syndrome (MERS) in 2012, from camels to humans [6].

In 2019 in Wuhan, China there were several unusual cases of pneumonia, presenting with a dry cough, dyspnea, fever, and lung tissue damage [3]. The source of many of these cases was recorded as being the Wuhan wild animal and seafood market [7]. On 12th January 2020, China shared the genetic sequence of the infectious agent. China reported virus originated from wild bats and was similar to SARS, hence the infectious agent became known as SARS-CoV-2 at the end of January [8] and declared an emergency a pandemic (global outbreak) of disease [1,9]. SARS-CoV-2 is highly transmissible and 15,296,926 cases and 628,903 deaths from SARS-CoV-2 were recorded in over 200 counties on 24th July 2020. We compared these figures with other coronavirus outbreaks, such as SARS in 2003, where the number of infected persons was approximately 8000, with a 9.5% case fatality rate. MERS in 2012 had approximately 2,500 cases, with a mortality rate of approximately 35% [10,11]. The virus targets the respiratory system and its transmission is by contact, droplets, and fomites from another infected person who may be symptomatic or asymptomatic [12]. The incubation period is around 2 to 14 days [9]. The main symptoms are dry cough, fever, sore throat, and shortness of breath, leading to pneumonia and acute respiratory distress (ARDS), which may require intensive care as shown in Fig. 1 [13]. Overall, the mortality rate is approximately 3%, and increases with age, over 60. The mortality rate is also higher in people with diabetes, heart disease, and kidney disease [14]. In COVID-19 patients, a characteristic feature is a lymphocytopenia and CT chest scans show ground glass-like features, indicative of viral pneumonia [15,16]. Diagnosis of SARS-CoV-2 is made with real-time PCR, by identifying the RNA load via nasal swab (NS) and throat swab (TS), and/or by X-ray and CT scans [15]. The main treatments are supportive, such as antivirals, antimalarials, steroids, and antibiotics [17]. At present, no approved treatments or vaccines are available against SARS-CoV-2 as shown in Fig. 1. However, randomized multicentric clinical trials are under way to look for treatment and vaccine options.

1.1. Pathogenesis during the progression of SARS-COV-2 infection

MERS and SARS share the same mechanism as SARS-CoV-2. Spike protein (S2) binds to the Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM-1) receptor protein, which is expressed in epithelial cells [18]. The virus enters the host cells via receptor-mediated endocytosis and is uncoated, releasing RNA genome into the cytoplasm see human SARS-COV-2 life cycle as shown in Fig. 2 [15]. Spike protein also has another function; binds to ACE2, causing down-regulation, which leads, eventually, to lung injury [19]. The liver produces an inactive form of angiotensin, which circulates in the blood in response to the enzyme renin released by the kidney, and which converts angiotensin to angiotensin-I [13,14]. This circulates in blood in an inactive form and converted to angiotensin-II by an angiotensin-converting enzyme (ACE or ACE1) [20]. This enzyme maintains blood pressure and mediates tissue injury via a series of non-hemodynamic effects [21]. ACE2 would normally cleave angiotensin-II, as part of a negative feedback loop. tTherefore, if ACE2 is downregulated, this would increase blood pressure in SARS-COV-2 patients. Furthermore, angiotensin-II can bind to receptors in the lungs, called type 1a angiotensin-II receptors (AGTR1A), which increases the permeability of the lungs. Here, a problem arises when the downregulation of ACE2 simultaneously upregulates ACE1, due to negative feedback [22–24], and this leads to excessive angiotensin-II. This binds to the AGTR1A receptors, which then causes excessive vascular pulmonary activity, the pathology observed in lung tissue associated with pulmonary destruction [22–24].

1.2. Innate and acquired mechanisms of defense against SARS-CoV-2

The entry of immune cells into the lungs to fight SARS-CoV-2 leads to ARDS [25,26] and it's associated with the upregulation of pro-inflammatory cytokines and chemokines shown in Fig. 3 [27]. In SARS-CoV-2 infected patients, IL-1β, IL-16, CXC chemokines, and ligand 2 (CCL2) levels are high [28]. Individuals recovred from SARS-CoV-2 have shown an early expression of interferons
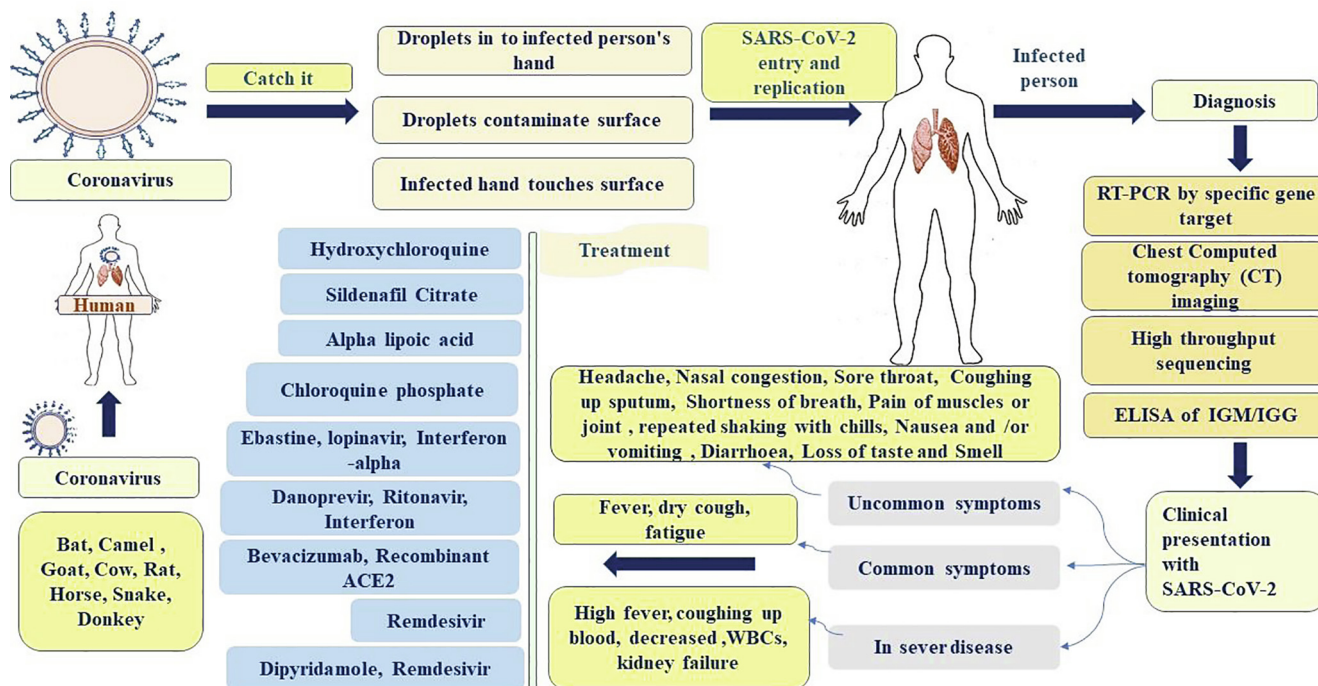

Fig. 1. Flow Diagram of transmission, diagnosis, clinical presentation, and treatment for COVOD-19.
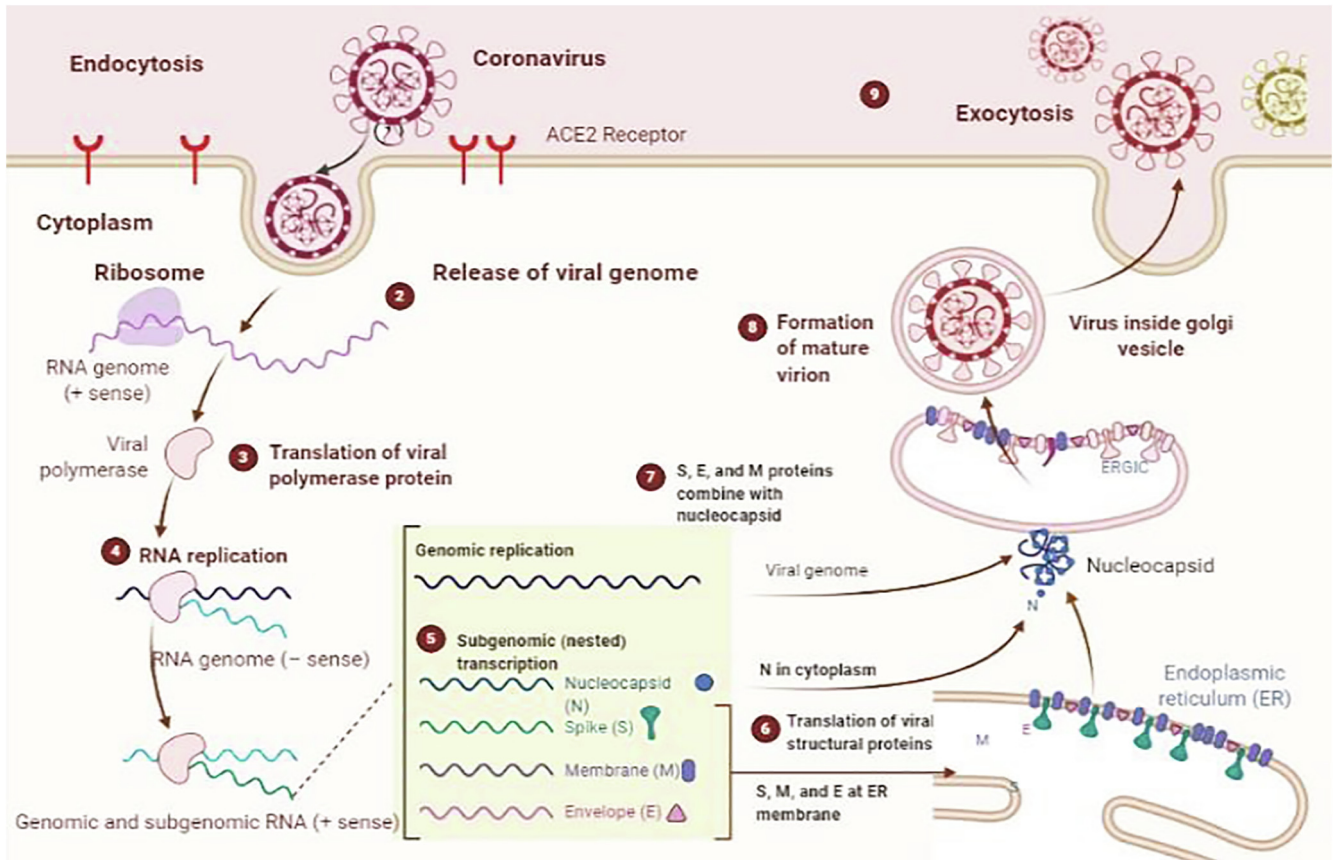
Fig. 2. Life Cycle of Highly Pathogenic Human Coronaviruses. the figure was created using BioRender (https://biorender.com/).
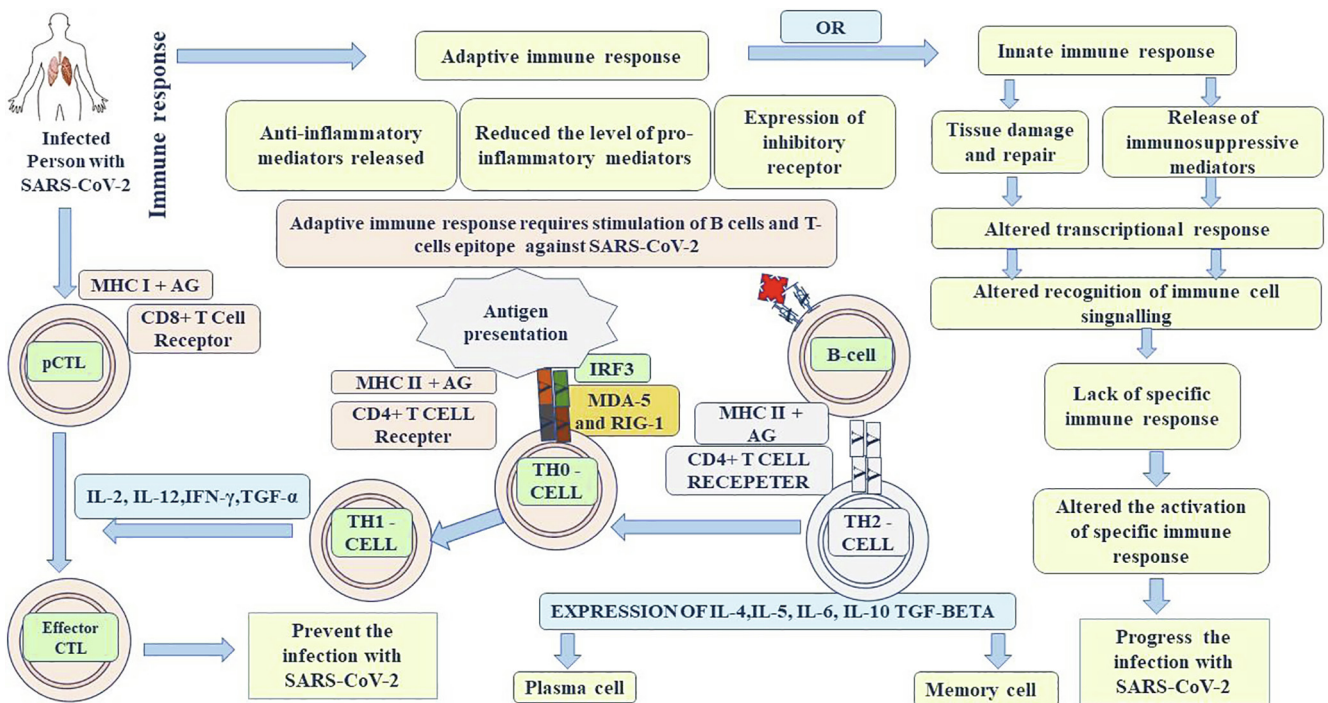
Fig. 3. Immune response the SARS-Co-V2 infection.

IFN-α, IFN-γ, CXCL-10, and CCL2 [29]. IFN-α is an antiviral protein released by infected cells and serves as a signal to produce other anti-viral proteins, so that nearby host cells are more protected.

It activates other immune cells, such as macrophages [29]. IFN-γ is a part of the immune system that destroys particular cells that are infected with SARS-CoV-2 [30]. Chemo attractants such as

CXCL-10 and CCL2 are released to guide other cells to destroy infected cells [31,32]. The adaptive immune response is known to be vital to survival, severe SARS-CoV-2 infection is related to a failure to switch from an innate immune response to an adaptive immune response. Infected people lose their memory cells, effector cells, or enough antibodies to reduce the viral load, unbalancing the host-pathogen interaction [33]. NF-kB an important pro-inflammatory cytokine that regulates some genes encoding other cytokines and chemokines as shown in Fig. 3 [34] that are released by cells and which trigger an immune response against the infection. Nucleocapsid proteins (N-proteins) of SARS-CoV-2 bind to viral RNA, as part of the assembly process, and this may be prevented by host proteins such as MDAS and RIG-1 [35]. These proteins detect viral RNA and trigger cell destruction [36] The EB protein of SARS-CoV-2 inhibited by MAD-5 and RIG-1. If MAD-5 and RIG-1 proteins can function, they activate the mitochondrial surface protein MAVS, and this protein activates E3 ubiquitin ligases, leading to the production of NF-kB, which enters the nucleus and activates pro-inflammatory cytokines [37]. The E3 ubiquitin ligases also activate IRF-3 and IRF-7 transcription factors, which enter the nucleus and upregulate interferon α, γ, and activate immune cells (Fig. 3) [3,38]. However, the M−protein of SARS-CoV-2 inhibits the phosphorylation of IRF-3 and IRF-7 [36]. Therefore, these transcription factors cannot go to the nucleus and cannot up-regulate the interferon at transcription level [3]. The PLPro protein of SARS-CoV-2 is capable of inhibiting the activation of NF-kB, therefore no response in the nucleus and upregulation of pro-inflammatory proteins. In some cases, the production of sufficient cytokines decreases the number of interferons [35,39–41].

1.3. Advances in the diagnosis of SARS-COV-2

The gold standard for diagnosis is RT-PCR, and the Centre for Disease Control and Prevention (CDC) has developed an RT-PCR kit based on a specific target sequence as shown in Fig. 1 [42,43]. Various countries have developed their RT-PCR kits, such as Germany (targeting RdRP, E, and N genes), China (targeting ORF1ab and N), Hong Kong (targeting nsp14 and N genes), Japan (targeting multiple proteins), and Thailand (targeting the N gene). Various diagnostic assays are being developed to detect the virus. Some kits are only able to detect one strain of SARS-CoV-2, and some are sensitive to any SARS agent. The specificity of RT-PCR depends on the expertise of individuals, and samples must be taken from the lower or upper respiratory tract. Moreover, single negative samples do not rule out MERS-CoV infection [15,17]

RT-PCR can often miss the identification together and has some time less sensitivity senstive for acute infection [42]. Tested sample, approximately 3% of those who have negative PCR results have SARS-CoV-2. There could be reasons, for this, perhaps early at the pandemic not enough virus samples for detection and the diagnostic kits were not used correctly [44]. The RT-PCR test may improve over time and suggested, meanwhile, that chest CT is used to identify patients for further testing, which will help to inform isolation and treatment as shown in Fig. 1 [45,46]. CT scan is also good technology to screening for testing but due to poor access to laboratory testing, or in a situation where centralized public health workers are overstretched [47]. In patients with SARS-CoV-2 symptoms, such as fever, cough, and shortness of breath, clinicians often carry out chest X-rays, which are relatively cheap and easy.

The most common abnormal finding that of ground-glass opacities, portions of the lungs show up on X-ray images as a hazy shade of gray, like frosted glass, instead of being black [48,49]. It is important to know that chest X-rays are not very sensitive to SARS-CoV-2. Patients who are highly suspected of having SARS-COV-2 viral pneumonia should probably receive chest CT, even if

their chest X-ray is negative [27,50]. Chest CT provides a more detailed view, with the most common finding, again, being ground-glass opacities scattered throughout the lungs [51,52]. These represent tiny air sacs or alveoli that are filled with fluid and that turn a shade of grey on the CT scan. In severe and advanced infections, more fluid accumulates in the lobes of the lungs, and the appearance progresses to a solid, white consolidation and finally a crazy-paving pattern, with swelling of the interstitial space along the walls of the lung lobules [53,54]. A chest X-ray is informative but not very sensitive or specific to SARS-CoV-2; therefore, individuals should undergo RT-PCR [54,55]. Many countries have been isolating patients with classic CT findings until laboratory tests help to identify the cause of disease. It is also important to evaluate each patient, based on the severity of the disease [55]. Individuals can be asymptomatic or have a very mild form of the disease; the sensitivity of a chest CT falls to about 50% in the first 48 h of symptoms or with individuals with the mild disease [51]. ELISA was used to detect antibodies to MERS-CoV for earlier detection, which is based on the N and S proteins of MERS-Co-V. Micro-neutralization is used to detect specific antibodies in the serum sample, this test is considered more sensitive and specific for the analysis of neutralizing antibodies. The presence of antibodies indicates that the immune response has developed in the infected person, but serology tests are recommended for observation purposes only, not for a diagnosis.

1.4. Case classification and clinical complications with SARS-CoV-2 infection

The new CDC and WHO list of possible SARS-CoV-2 symptoms includes fever, cough, difficulty in breathing, repeated shaking with chills, muscle pain, headache, sore throat, and loss of taste and smell as shown in Fig. 1. In a few cases, patients experience extreme fatigue, diarrhea, and fever 37.8 °C or above [3,9–11,13,56]. Symptoms usually occur 2–14 days after exposure to the virus, but may also be observed for up to 28 days. Not all individuals with SARS-CoV-2 show all symptoms and these range from mild to severe [56]. The test result showed viral nucleic acid declared as a positive SARS-CoV-2 test [14–16]. Suspected cases are those with symptoms who have been exposed to infected cases [13]. Clinically diagnosed cases are those having symptoms, prior exposure, and the presence of a lung imaging feature consisting of coronavirus pneumonia [34,46]. Asymptomatic cases are free from symptoms but test positive for viral nucleic acid. SARS-CoV-2 infection is classified into three categories mild, severe, and critical. Mild cases have either no sign of pneumonia or mild pneumonia [27]. Severe cases show problems of oxygenation, breathing, and characteristic radiological findings on a CT-Scan [57,58]. In severe cases, breathing problems are classified as dyspnea, and patients have a respiratory frequency (RF) > 30/Min [12,14,55,58]. Severity also classified as an oxygen saturation < 93% and PF ratio < 300 [55]. The illness is considered to be severe if lung infiltration or pneumonia occupying more than 50% of their lung field and is seen on a chest radiograph or CT-scan [55,59]. In critical cases, acute respiratory distress syndrome (ARDS) is a major clinical complication of SARS-CoV-2 infection [60]. This syndrome is characterized by hypoxic respiratory failure and bilateral infiltration due to diffuse alveolar damage [61]. This damage can cause respiratory failure, which is associated with V/Q mismatch and pulmonary shunting [62 63]. Large immune-mediated cytokine cascades cause lung alveolar damage, patients are unable to successfully ventilate, and develop respiratory failure [64]. Septic shock causes vasodilation and leads to multiple organ dysfunction, especially in the kidney. Some SARS-CoV-2 patients develop renal failure, in addition to respiratory failure, and may require life support [65]. Patients who develop these complications with

SARS-COV-2 have much higher mortality rates [66]. The overall case fatality rate in the SARS-CoV-2 pandemic near about 3.5%, but in elderly patients, this rises to 14%. Fatality is higher for patients with cardiovascular disease, diabetes , chronic respiratory disease , and cancer [67,68]. Some clinicians have reported the presence of blood clots in young adults (aged < 50 years), which causes serious problems such as heart attack and stroke [69].

1.5. Susceptibility to mutation and severity of host-virus genome interactions

SARS-CoV-2 has mutated into at least 30 different genetic variants. Of these, 19 are novel strains, including six mutations in the spike protein. Different strains have affected different parts of the world. This may lead to potential difficulties in finding a universal method of diagnosis or treatment. Strains from 11 randomly chosen SARS-CoV-2 patients from Hangzhou were isolated and analyzed by deep sequencing [70–72]. Researchers said that the virus has acquired mutations that are capable of substantially changing its pathogenicity. Some of the most pathogenic strains of the virus are more pathogenic than normal strains [73,74]. One mutated strain of SARS-CoV-2 has been more lethal across Europe and New York than in other parts of the United States and other countries [75]. The diversity of viral strains under investigation leads to a consideration of the impact of these mutations on the development of vaccines and drugs. Mutations in the virus genome might cause the disease to be more virulent, more severe, or more transmissible [18,76]. Microbiologists from the Peking School of Life Sciences in Beijing, and the Institute Pasteur of Shanghai, have studied the genome of 103 samples of SARC-CoV-2 [18]. They analyzed the evolutionary relationship between the virus strains and their sequenced genomes. They identified two lineages the milder or less infectious **S** type and the highly infectious, more virulent, and more severe **L** type [77]. The genetic difference between **S** and **L** lineages is in the receptor-binding domain. The L type is more prevalent (70%) in current cases [78,79]. The **L** type was prevalent in the early stages of the outbreak in Wuhan. Later on, the **S** type became prevalent in China because of lockdown control [80]. The Chinese lockdown successfully closed down the spread by isolating people, and this approach seemed to reduce the number of cases of **L** type SARS-CoV-2 in Wuhan after January 2020 [79,80]. If the Chinese lockdown halted the **L** type, the subsequent pandemic may be of the **S** type, which is believed to be less virulent [79–81]. There are also the possibility of infection with both viral types in an individual with SARS-CoV-2. One patient in the US has tested positive for both the **S** and **L** types, so it appears that both lineages are persisting in the pandemic [81,82].

2. Drugs used in pre-clinical and clinical therapy

There is no specific treatment currently available drugs for SARS-CoV-2 [70,71,77]. Some drugs are under investigation and being tested as a potential treatment of SARS-COV-2, as shown in Tables 1 and 2. The antiviral agent famvir has shown efficacy against SARS-CoV-2, and clinical trials have been conducted in 70 patients in Shenzhen, Guangdong province [72,83–87]. Another drug option is remdesevir, an adenosine analog, which is incorporated into the nascent viral RNA chain and results in premature termination. However, the drug is still in a clinical trial [88], a randomized control trial involving 1063 patients, funded by the US, improved recovery from advanced SARS-CoV-2. Preliminary results indicate that patients treated with remdesevir showed a 31% improvement in recovery time over placebo [88]. Chloroquine widely used as an anti-malarial and as a treatment for autoimmune disease, and also reported as having anti-viral activity, blocking virus infection by increasing the endosomal pH required for virus-cell fusion as well as interference with glycosylation of the cellular receptor of SARS-CoV-2 [89]. In addition to its antiviral activity, chloroquine has immune-modulating activity, which may synergistically enhance anti-viral effects *in vivo*. Meanwhile, a clinician from South Korea has reported the use of an anti-HIV drug combination, lopinavir, and ritonavir, to successfully treat SARS-CoV-2 shown in Fig. 1 [90,91]. Researchers in China have reported full recovery from SARS-CoV-2 their blood plasma for possible use as a new treatment of the virus [87,92], an approach is known as hyperimmune globin therapy. Corticosteroids should be avoided

Table 1
List of potential therapeutic option for SARS-COV-2.

S.N.	Drug	Mechanism	Risk	Remark	References
1	Lopinavir	Lopinavir bind to membrane protein and enzyme for coronavirus replication	Cardiac arrhythmias. Carefulness in patients with liver diseases	Preclinical	[16,93]
2	Remdesivir	Inhibit the activity of RNA-dependent RNA polymerases; excise nucleotide analog inhibitors.	Nausea and vomiting	Preclinical	[88]
3	Chloroquine (Antimalarial)	Viral DNA and RNA polymerase, viral protein, glycosylation, ACE2 cellular receptor inhibition, immunomodulation of cytokine release.	Cardiac arrhythmias, retinal damage, especially, G6PD deficiency, Caution in diabetics	Chloroquine has activity against pneumonia patients with SARS-CoV-2 infection; however, specific data are not available.	[89]
4	Antimalarial (Hydroxychloroquine)	*In vitro* activity against SARS-CoV-2, inhibition of viral enzymes or processes such as viral DNA and RNA polymerase; 5ACE2 inhibition.	Diabetics Significant drug interactions	Hydroxychloroquine has activity against SARS-CoV-2.	[93]
5	Azithromycin	Reducing chemotaxis of neutrophils (PMNs) to the lungs by inhibiting cytokines (i.e., IL-8), inhibition	Risk of cardiac arrhythmias	Reduce the excessive cytokine production associated with respiratory viral infections	[93]
6	Azithromycin Macrolide Antibacterial	Downregulate inflammatory responses	Blocking the activation of nuclear transcription factors.	Reduce the excessive cytokine production associated with respiratory viral infections	[93]
7	Tocilizumab	IL-6 Receptor-Inhibiting Monoclonal Antibody	GI perforation, hepatotoxicity	Tocilizumab inhibits IL-6-mediated receptors	[94]
8	SARS-COV-2 Convalescent Plasma	Contain antibodies to SARS-CoV-2	SARS-CoV-2 neutralizing antibody titers may be conducted (optimally greater than 1:320)	FDA approval required	[95]

Table 2
List of probable drug targets against SARS-CoV-2.

Targeted viral components	Mechanism of action	Status	References
Viral spike glycoprotein S			
S1	Monoclonal antibodies against RBD inhibits virus-host cell binding.	Under progress	[97]
S2	HR2P and P1 peptides inhibit fusion of S with a host cell receptor	Under progress	[98]
Oligosaccharides (S)	Griffithsin binds to oligosaccharides on S and inhibits virus-host cell binding	Under progress	[99]
S	siRNA based dsRNA inhibits the replication of SARS-CoV-2.	Under progress	[100]
Viral envelope, membrane, nucleocapsid, and accessory proteins			
E	siRNA based dsRNA inhibits the replication of SARS-CoV-2.	Under progress	[101]
	Hexamethylene amiloride ion act as ion channel inhibitors for SARS-CoV-2.	Under progress	[102]
M	siRNA based dsRNA, inhibits the replication of SARS-CoV-2.	Under progress	[103]
N	siRNA, PJ34, Monoclonal antibodies	Under progress	[104]
Accessory proteins	siRNA – dsRNA act as ORF protein inhibitors, SARS-CoV-2.	Under progress	[17]
Viral enzymes-based inhibiters			
PLpro	GRL0617, Inhibitors of PLpro activity (Optimal activty)	Under progress	[105]
3CLpro	Lopinavir, Inhibitors of 3CLpro activity; Broad spectrum effective in SARS-CoV-2. patients in non-randomized trials	Under progress	[10]
RdRp	Ribavirin, inhibits viral RNA synthesis found effective SARS-CoV-2.; dose need to optimize	Under progress	[106]
BCX4430	Based on analogue to adenosine and inhibit viral RNA polymerase activity; Broad spectrum	Under progress	[107]
RdRp	Analogues of acyclovir inhibit RdRp, effective against MERS–CoV and HCoV-NL63 ● Further investigations required.	Under progress	[108]
Helicase	5-Hydroxychromone derivatives disable the function of helicase	Under progress	[109]
	SSYA10-001 and ADKs, disable the function of helicase Broad spectrum, effective against SARS-CoV-2.	Under progress	[110]
Angiotensin converting enzyme	Benazepril (Lotensin), perindopril (Aceon), quinapril (Accupril), trandolapril (Mavik) Angiotensin -converting enzyme inhibitors and angiotensin-II receptor Blocker	Under progress	[111]

because of their potential in prolonging viral replication, as previously observed in MERS-CoV patients. These are the treatment options currently available, but all are under trial, as part of an effort to test more than 60 types of potential therapeutic drugs, as shown in Table 2.

3. Vaccine development for SARS-CoV-2: hope against hope

Scientists are designing vaccines at various laboratories and institutions around the world as shown in Table 2. Vaccines are made using a highly conserved part of the viral genome, and more than 90 vaccines are under progress against SARS-CoV-2. Some technologies are being used that have never been used before for developing licensed vaccines. Other research groups have begun clinical trials on humans, while others are testing in animal models [96]. Potential vaccines needed to be work for all strains and any mutated variants, and likely to be very challenging to find a single vaccine that works for all [88]. The aim of vaccine development to expose the body to the antigen, without causing the disease. However, antigens will still cause an immune response that can block or kill the virus, if persons become infected later.

One challenge that the antibody response against **S** and **L** is slightly different [112], and L type vaccine induces slightly different antibodies, it is unclear if this will confer cross-immunity to **S** type and vice versa [83]. In the context of the current waves of infection, unclear whether becoming co-infected with both L and S types at the same time leads to more serious illness [113].

SARS-CoV-2 are RNA-based viruses with a 3.4 kbp genome and a couple of changes in the genome of this virus [96,113]. Mutations have been observed in S2 receptors, which are proteins responsible for the infection of host cells. Unfortunately, these viruses are more transmissible and provided challenges to vaccine development, and also need more study in this field [10].

There are several types of SARS-CoV-2 vaccine currently under trial as shown in Table 3, based on genome. Seven research groups are working on inactivated vaccines of SARS-CoV-2 [164]. Twenty-five teams are developing viral vector vaccines, where the virus is genetically altered to induce the body to produce viral proteins. Some viral vector vaccines can destroy replicates inside the host cell, while others prevent replication due to the inactivation of viral genes. Almost 20 groups use the genetic sequences for SARS-CoV-2 proteins, which induce the immune response. Once these genetic instructions (RNA/DNA) are inserted into human cells, the host cells produce viral proteins. The viral spike protein is the main target of RNA/DNA vaccines. Another type of vaccine involves injecting SARS-CoV-2 proteins directly into the body. They can also use small fragments of protein (peptides) or the isolated outer-shell protein of SARS-CoV-2, such proteins can induce an immune response without damaging cells. Germany and the United Kingdom have approved their first two SARS-CoV-2 vaccines. The Paul Ehrlich Institute (PEI) approved for the first clinical trial of RNA-based BNT162b1 vaccine, developed with the use of a lipid nanoparticle, non-viral gene delivery system. The cell then transcribes and translates this genetic information into proteins, which generates an immune response. A team of research scientists

Table 3
List of SARS-CoV-2 Vaccine under clinical trial.

S.N.	Vaccine development	Product category of vaccine	Type of candidate vaccine description	Current status-	Developer	References
1	INO-4800	DNA based	DNA plasmid delivered by electroporation targeted for S1-RBD-protein	Phase-II and III	novio Pharmaceuticals, CEPI, Korea National Institute of Health, International Vaccine Institute (IVI); Thermo Fisher Scientific; Beijing Advaccine Biotechnology; Richter-Helm BioLogic	[114]
2	BNT162 (a1, b1, b2, c2)	RNA Based	S1-RBD-protein targeted	Phase-II and III	(BioNTech, Fosun Pharma,Pfizer); Rentschler ; Biopharma ; Fosun Pharma	[115]
3	SARS-CoV-2/aAPC	lentiviral vector	lentiviral vector, pathogen-specific artificial antigen-presenting dendritic cells targeted spike (S) glycoprotein	Phase I	(Shenzhen Geno-Immune Medical Institute)	[116]
4	LV-SMENP-DC	lentiviral vector	lentiviral minigene vaccine, dendritic cells modified with lentiviral vector and based on multiple viral antigens	Phase I	(Shenzhen Geno-Immune Medical Institute)	[117]
5	bacTRL-Spike	DNA based	DNA; bacTRL-targeted on Spike protein	Phase I	(Symvivo Corporation, University of British Columbia, Dalhousie University)	[118]
6	Ad5-nCoV	Non-replicating viral vector	Recombinant adenovirus type 5 vector targeted on Spike protein	Phase-III	(CanSino Biologics,Institute of Biotechnology of the Academy of Military Medical Sciences); Beijing Institute of Biotechnology; Canada's National Research Council; Petrovax	[43]
7	ChAdOx1 nCoV-19	Adenoviral vector	ChAdOx1 is a replication-deficient simian adenoviral vector derived from isolate Y25 targeted on Spike protein	Phase-III	United Kingdom	[119]
8	mRNA-1273	RNA Vaccine	lipid nanoparticle dispersion containing messenger RNA targeted on Spike protein	Phase I	(Moderna, US National Institute of Allergy and Infectious Diseases)	[120]
9	Ad5-nCoV	Spike protein	recombinant adenovirus type 5 vector	Phase I	(CanSino Biologics, Institute of Biotechnology of the Academy of Military Medical Sciences)	[121]
10	Ad5-nCoV	Non-Replicating	Non-Replicating Viral Vector 2nd Gen E2b-Ad5 Spike, RBD	Phase 2 ChiCTR2000031781 Phase 1 ChiCTR2000030906	Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China; CanSino Biological Inc./Beijing Institute of Biotechnology	[122]
11	DNA plasmid vaccine Electroporation device	DNA	DNA plasmid. Vaccine encoding spike (S) protein delivered by Electroporation	Phase 1 NCT04336410	Inovio Pharmaceuticals	[115]
12	d TBD	Inactivated	Live Attenuated Virus Deoptimized	Preclinical	Osaka University/ BIKEN/ NIBIOHN	[123]
13	Dendritic cell-based vaccine	Non-replicating	Non-replicating viral vector; dendritic cell-based vaccine	Pre-clinical	Vaxart / Emergent BioSolutions	[124]
14	Parainfluenza virus 5	Non-replicating viral vector	parainfluenza virus 5 (PIV5)-based vaccine expressing the spike protein	Pre-clinical	Centro Nacional Biotecnologia (CNB-CSIC), Spain	130)
15	Dendritic cell-based vaccine	Virus-like particle	Virus-like particle-based Dendritic Cell (DC)-targeting vaccine	Pre-clinical	University of Manitoba	[125]
16	GX-19	DNA	DNA Vaccine expressing SARC-CoV-2 S-protein	Pre-Clinical	Genexine Consortium	[126]
17	DNA with electroporation	DNA Vaccine	Adenovirus-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein	Pre-Clinical	Karolinska Institute / Cobra Biologics (OPENCORONA Project)	[127]
18	Recombinant SARS CoV-2 glycoprotein nanoparticle vaccine	Protein Subunit	Recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Phase-I	Novavax	[128]
19	Recombinant deactivated rabies virus containing S1	Protein Subunit	Non-replicating viral vector	Pre-clinical	Bharat Biotech/ Thomas Jefferson University (INDIA)	[129]
20	Adenovirus Type 5 Vector	Replicating viral vector	Ad5-nCoV is a recombinant adenovirus type-5 vector (Ad5) vaccine	Pre-clinical	Zydus Cadila (INDIA)	[130]
21	ChAdOx1-S	Non-Replicating Viral Vector	The immune response generated against the spike protein	Phase-III	University of Oxford/AstraZeneca	[131]
22	LNPencapsulated mRNA	RNA	Lipid nanoparticle-encapsulated mRNA (mRNA-LNP) encoding the receptor-binding domain (RBD)	Phase-I	Moderna/NIAID	[132]
23	Plasmid DNA	DNA	Microneedle array for delivery spike protein based	Pre-Clinical	Immunomic Therapeutics, Inc./EpiVax, Inc./PharmaJet	[133]
24	NasoVAX	Non-Replicating Viral Vector	adenovirus-based NasoVAX expressing SARS2-CoV spike protein	Pre-Clinical	Altimmune	[134]
25	Deoptimized live attenuated vaccines	Live Attenuated Virus	Codon deoptimized live attenuated vaccines	Pre-Clinical	Codagenix/Serum Institute of India	[135]
26	Inactivated + alum	Inactivated viral protein	As viral subunit protein Inactivated	Phase -II	Sinovac	[136]
27	3 LNP-mRNAs	RNA based	mRNA vaccines encode antigens	Phase-III	BioNTech/Fosun Pharma/Pfizer	[137]
28	mRNA	RNA	a vaccine targeting the Spike protein receptor-binding domain	Pre-Clinical	Curevac	[138]

Table 3 (*continued*)

| S.N.	Vaccine development	Product category of vaccine	Type of candidate vaccine description	Current status-	Developer	References
29	Plant-derived VLP	Virus-like particle	QVLP vaccine induced a substantial and sustained increase of hemagglutinin-specific polyfunctional CD4 T cells,	Phase I	Medicago Inc.	[139]
30	VLP	VLP	The target antigen on the surface of the virus like particle	Pre-Clinical	ARTES Biotechnology	[140]
31	Codon deoptimized live attenuated virus	Live attenuated virus	live-attenuated vaccine, it has the potential to stimulate a robust T cell and antibody immune response	Pre-Clinical	Codagenix / Serum Institute of India (INDIA)	[141]
32	Codon deoptimized live attenuated virus	Live attenuated virus	Live Attenuated Covid-19 vaccine based on codon de-optimized technology.	Pre-Clinical	Indian Immunologicals Ltd/ Griffith University (INDIA)	[142]
33	VLA2001, Inactivated	Inactivated	Inactivated + CpG 1018, Spike protein receptor-binding domain	Pre-clinical	Valneva/ Dynavax	[143]
34	Ad5 vector	Non-Replicating Viral Vector	Ad5 adjuvanted Oral Vaccine platform	Pre-Clinical	Vaxart	[144]
35	protein-based adjuvanted	Protein Subunit	Native like Trimeric subunit Spike Protein vaccine	Pre-Clinical	Clover Biopharmaceuticals Inc./GSK/Dynavax	[145]
36	Microneedle arrays S1 subunit	Protein Subunit	MNA-MERS-S1 subunit vaccines	Pre-Clinical	Univ. of Pittsburgh	[146]
37	OMV-based vaccine	Protein subunit	Receptor-binding domain (RBD) in the N-terminal surface subunit (S1), and then employs its C-terminal transmembrane subunit (S2) to fuse with the host cell membrane	Pre-Clinical	BiOMViS Srl/Univ. of Trento	[147]
39	S protein	Protein Subunit	Protein Subunit S protein (baculovirus production), Ii-Key peptide targeted for S protein	Pre-Clinical	Sanofi Pasteur/GSK	[148]
40	gp-96 backbone	Protein Subunit	Activates CD8 T cells, antigen presenting	Pre-Clinical	Heat Biologics/Univ. Of Miami	[149]
41	Peptide vaccine	Protein Subunit	Synthetic Long Peptide Vaccine candidate for S and M proteins	Pre-Clinical	FBRI SRC VB VECTOR,Rospotrebnadzor, Koltsovo	[150]
42	SARS-COV-2 XWG-03 truncated S	Protein subunit	COVID-19 XWG-03 truncated S (spike) proteins.	Pre-Clinical	Innovax/Xiamen Univ./GSK	[151]
43	OMV-based vaccine	Protein subunit	Outer Membrane Vesicle (OMV)-subunit	Pre-Clinical	Quadram Institute Biosciences	[152]
44	Measles Vector	Replicating Viral Vector	Non-Replicating Viral Vector Oral Vaccine platform. (S, N targets)	Pre-Clinical	Institute Pasteur/Themis/Univ. of Pittsburg Center for Vaccine Research/Merck	[153]
45	Replication competent VSV chimeric virus technology (VSVΔG)	Replicating Viral Vector	Replication competent VSV chimeric virus technology (VSVΔG) delivering the SARS-CoV-2 Spike (S) glycoprotein.	Pre-Clinical	IAVI/Merck	[154]
46	M2SR	Replicating Viral Vector	M2-deficient single replication (M2SR) influenza vector	Pre-Clinical	UW-Madison/FluGen/Bharat Biotech	[155]
47	Ii-Key peptide	Protein Subunit	The peptide sequence includes at least one cell-permeable peptide (CPP) domain	Pre-Clinical	Generex/EpiVax	[156]
48	Molecular clamp stabilized Spike protein	Protein Subunit	Molecular clamp stabilized Spike protein iis a COVID-19 protein-based vaccine	Pre-Clinical	University of Queensland/GSK/Dynavax	[157]
49	Oral Ad5 S	Non-Replicating Viral Vector	Adenovirus serotype 5 (Ad5)-based vaccine vectors	Pre-Clinical	Stabilitech Biopharma Ltd	[158]
50	Spike-based	Protein subunit	Protein Subunit RBD-based.	Pre-Clinical	University of Alberta	[159]
51	Measles Virus	RNA	Live attenuated measles virus (S, N targets) is a COVID-19 viral-vector vaccine (S, N targets)	Pre-Clinical	DZIF - German Center for Infection Research	[160]
52	Live viral vectored vaccine based on attenuated influenza virus backbone (intranasal)	Replicating Viral Vector	Live viral vectored vaccine based on attenuated influenza virus backbone (intranasal)	Pre-Clinical	BiOCAD and IEM	[161]
53	Ad26.COV2-S	Non-Replicating Viral Vector	Ad26 (alone or with MVA boost)	Pre-Clinical	Janssen Pharmaceutical Companies	[162]
54	MVA-S encoded	Non-replicating viral vector	Non-replicating viral vector MVA-S encoded SARS-CoV2; MVA-S encoded	Pre-clinical	DZIF – German Center for Infection Research	[163]
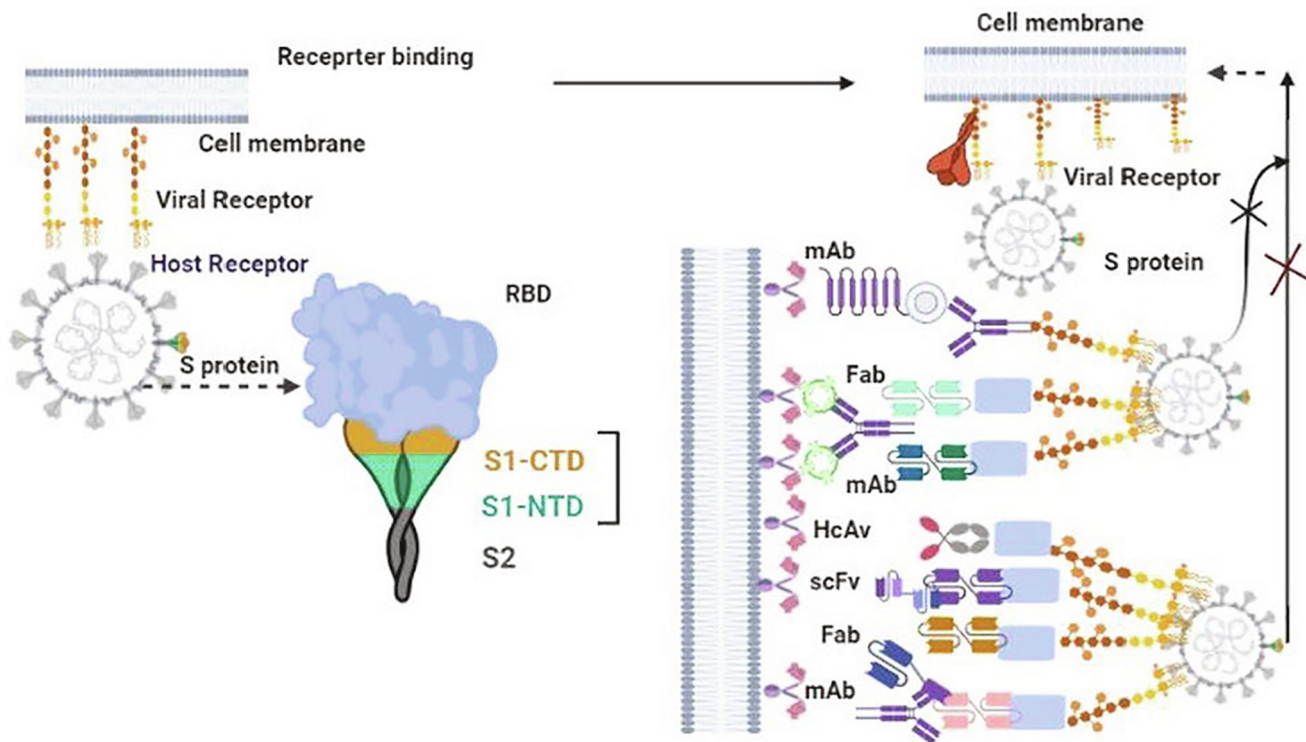
Fig. 4. Potential targets of nAbs against SARS-CoV-2. This figure was created by using BioRender (https://biorender.com/).

working on three other, similar, mRNA vaccines. Similarly, Oxford also launching a trial of the chadOx1 nCoV-19 vaccine, which is based on chimpanzee adenovirus, which includes the spike or **S** protein on the surface of SARS-CoV-2. The mRNA vaccine candidate developed by Imperial College is being tested in an animal model.

4. Neutralizing monoclonal antibodies against SARS-CoV-2

Neutralizing antibodies (Nabs) of coronaviruses tend to target the turmeric spike (S) protein (S1 and S2) and mediate the entry into a host cell. Which is actively involved in the attachment of cell and fusion of the cell membrane via the formation of a six-helix bundle (6-HB) fusion core [164]. The S protein has AA (Amino Acid) that are 77.5% identical and bind to ACE2 on human cells through the S1B domain. S1-RBD and S2 are identified as potential targets for Nabs. To identify antibodies that could potentially neutralize SARS-CoV2. SARS-CoV-2 patents generate immunoglobulin F (IgG) types of antibodies, which is binding to SARS-CoV-2 elements after the onset of disease and blocking SARS-CoV-2 entry of host cells, called neutralizing antibody (NAbs) [164,165]. Possible targets of nAbs on the S protein of SARS-CoV-2as shown in Fig. 4. Monoclonal antibody (mAb), antigen-binding fragment (Fab), single-chain variable region fragment (scFv), or single-domain antibody binds to the RBD, S1 subunit (non-RBD, including NTD), or S2 of the viral S protein, blocking binding between the RBD and the respective receptor (for RBD-targeting nAbs), interfering with the conformational change of S (for S1-targeting nAbs), or hindering S2- mediated membrane fusion (for S2-targeting nAbs), leading to the inhibition of infection with SARS-CoV-2 in the host cells. Several human monoclonal antibodies (mAbs) have been developed from memory B cells [166,167]. A researcher from the field developed 51 cell lines from the humanized mice and evaluate the efficacy and 47D11 were found active and targeted against the S1B receptor binding domain of SARS-CoV-2. Pseudo typed

lentiviral-based neutralization assay was performed to identify the efficacy of Nabs. The potential of pseudo-virus-neutralizing efficacy suggested that the neutralizing capacity of SARS-CoV-2-specific depends on the magnitude and binding affinity of antibodies [165]. Representative SARS-CoV RBD and MERS-CoV RBD-Targeting nAbs are mentioned in table 4.

4.1. Effectiveness of SARS-CoV-2 prevention and control procedures

According to the WHO and CDC, hand washing is the most effective procedure to prevent infection. Asymptomatic spreaders may be present in the community, feeling quite well but still able to pass on the virus [45,72]. It is critical to understand that the asymptomatic spreading of the virus has been shown and that it can be transmitted before symptoms or detection [27]. There are three important concepts: identity, isolation, and information. Once a patient identified, they need to take actions regarding personal hygiene and prevention, such as limiting contact with others as much as possible, staying at home, using available PPE (N-Mask or FFP2-standard masks set by the European Union, gloves, and goggles), and avoid touching the eyes, nose, mouth, and wash hands. Used PPE should be discarded properly to prevent SARS-CoV-2 infection [62]. Hand hygiene should be maintained, such as washing hands for 30 s with an effective soap or hand sanitizer with at least 70% alcohol [181]. High-touch surfaces that may be contaminated with SARS-CoV-2 can also be cleaned, using EPA-approved disinfectants. There is no any disinfectant currently approved by the EPA specifically for SARS-CoV-2, but several disinfectants are available [182]. Current observations suggest that people of all ages are generally susceptible to this new infectious disease. However, those who are in close contact with patients with symptomatic and asymptomatic SARS-CoV-2, including health care workers and other patients in a hospital, are at higher risk of infection [182]. As of February 14, 2020, a total of 1716

Table 4
Representative SARS-CoV RBD- and MERS-CoV RBD-Targeting nAbs.

S.N.	Antibody discovery Neutralizing monoclonal antibodies	Palatiform	Epitope clusters	binding affinities	Protective efficacy	IC50	References
1	3F11	Humanized phage display library	sdAb (a single-domain antibody) llama Animal immunization and sequencing RBD PsV (pseudovirus) neutralization	Blocking RBD–ACE2	Protect mice against the challenge of SARS	IC50 = 0.14 µg/ml.	[165]
2	ab1	B cells of convalescent patients; Single-cell sequencing	Neutralize live SARS-CoV (strain Urbani) infection RBD in the S1.	Blocking RBD–ACE2	Full protection of mice: 0.3 mg of IgG1 ab1.	Reporter Gene neutralization assay: 200 ng/ml; LV neutralization: ND100 < 400 ng/ml	[167]
3	CB6	B cells of convalescent patients	Neutralize live SARS-CoV (strain Urbani) infection RBD in the S1.	Blocking RBD–ACE2	Protection of rhesus macaques: 50 mg/kg.	PsV neutralization: ND50 = 0.036 µg/ml; LV neutralization: ND50 = 0.036 µg/ml;	[168]
4	P2C-1F11	The plasma of convalescing patients	SARS-CoV (strain Urbani) infection RBD	Blocking RBD–ACE2.	Protection of mice.	PsV neutralization: IC50 = 0.03 µg/ml.	[169]
5	rRBD-15	A synthetic human Fab antibody library	SARS-CoV (strain Urbani) infection RBD	Blocking RBD–ACE2.	Protection of mice.	PsV neutralization: IC50 = 12.2 nM.	[170]
6	CC12.1	B cells of convalescent patients	SARS-CoV infection RBD	Blocking RBD–ACE2.	Full protection of Syrian hamsters: Antibody serum concentration of ~ 22 µg/ml.	PsV neutralization: IC50 = 0.019 µg/ml.	[171]
7	COVA1-18	B cells of convalescent patients	SARS-CoV infection RBD	Blocking RBD–ACE2.	Protection of Syrian hamsters: Antibody serum concentration.	PsV neutralization: IC50 = 8 ng/ml	[172]
8	BD-368–2	B cells of convalescent patients; Single cell sequencing	Neutralize live SARS-CoV (strain Urbani) infection RBD in the S1.	Blocking RBD–ACE2 RBD in the S1 domain with high affinity.	B cells of convalescent patients; Single cell sequencing	PsV neutralization: IC50 = 1.2 ng/ml; LV neutralization: IC50 = 15 ng/ml	[166]
9	B38	Peripheral blood of SARS-CoV-2-infected patients	Neutralize live SARS-CoV (strain Urbani) infection RBD	Blocking RBD–ACE2.	Protection of mice: Lung viral load reduced by 32.8% compared with PBS control	LV (live virus) neutralization: IC50 = 0.177 µg/ml;	[173]
10	H4	Peripheral blood of SARS-CoV-2-infected patients	Neutralize live SARS-CoV (strain Urbani) infection RBD	Blocking RBD–ACE2.	Protection of mice: Lung viral load reduced by 26% compared with PBS control.	LV neutralization: IC50 = 0.896 µg/ml;	[173]
11	7B11	Animal immunization; hybridoma technology	Neutralize live SARS-CoV (strain Urbani) infection RBD	Blocking RBD–ACE2.	Protection of mice, Lung viral load reduced by 26% compared with PBS control.	PsV neutralization: IC50 = 10 µg/ml.	[174]
12	CR3022	Gene cloning; Protein expression	SARS-CoV infection RBD.	Blocking RBD–ACE2.		LV neutralization: IC50 = ~ 0.114 µg/ml.	[175]
13	4A8	Peripheral blood of convalescent patients	NTD			PsV neutralization: EC50 = 49 µg/ml	[176]
14	VHH-72-Fc	Animal immunization and sequencing	SARS-CoV (strain Urbani) infection RBD	Blocking RBD–ACE2.	Protection of mice.	PsV neutralization: IC50 ~ 0.2 µg/ml.	[177]
15	311mab–31B5	B cells of convalescent patients	SARS-CoV (strain Urbani) infection RBD	Blocking RBD–ACE2.	Protection of mice.	PsV neutralization: IC50 = 33.8 ng/ml; PsV neutralization: IC50 = 69.8 ng/ml.	[173]
16	H014	Animal immunization and phage display	SARS-CoV infection RBD.	Blocking RBD–ACE2.	Protection of mice: Lung viral load reduced by about 10 ~ 100 folds compared with PBS control.	PsV neutralization: IC50 = 3 nM;	[178]
17	COV2-2196	Peripheral blood of convalescent patients	SARS-CoV infection RBD.	Blocking RBD–ACE2.	Protection of hamsters: Viral RNA copy numbers and infectious virus titers in lung tissues were reduced by 4 logs or more compared with PBS control.	PsV neutralization: IC50 = 0.7 ng/ml	[179]
18	COVA2-15	A synthetic human Fab antibody library	SARS-CoV infection RBD.	Blocking RBD–ACE2.	Protection of mice.	LV neutralization: IC50 = 7 ng/ml.	[172]
19	REGN10989	Transgenic mice; Peripheral blood of SARS-CoV-2-infected patients; Next Generation Sequencing	SARS-CoV infection RBD.	Blocking RBD–ACE2.	Protection of mice.	PsV neutralization: IC50 = 7.23 pM.	[180]

health care workers in China were infected with SARS-CoV-2, comprising 3.8% of all patients nationally, 6 of whom have died [182,183]. A team of research scientists at the Aix-Marseille University, in France, found that some SARS-CoV-2 strains can replicate at 60 °C, and the virus are not completely eliminated until the temperature rises to 90–100 °C.

Peoples with chronic disease may suffer from increased stress due to the coronavirus pandemic because SARS-CoV-2 disease poses higher health risks for them. Stress during the pandemic, including fear, concerns about health and loved ones, changes in routine eating patterns, and difficulty in concentrating, can lead to a worsening of existing health problems, increased use of tobacco, alcohol, and other drugs. Peoples with pre-existing mental health conditions should be aware of worsening caused by the pandemic. Stress can be reduced by taking care of close friends and family, and by helping others to cope, making the community stronger. It will be better to avoid stressful activities that cause anxiety, to keep updated with accurate information, to meditate regularly, try to eat healthy, balanced meals, exercise regularly, sleep more often, and develop an understanding of the actual risk.

5. Conclusion

SARS-CoV-2 continues to increase its death toll as more people become infected. More than 215 countries are reporting new cases, and many struggle to limit their spread. SARS-CoV-2 has origins in mutations to coronavirus strains in animals, such as bats and pangolin. Poorly treated animals are stressed and are responsible for the emergence of new diseases. Wet markets where animals are in close contact with humans are the perfect breeding grounds for new diseases. Coronavirus not only causes respiratory problems, but may also damage the heart, kidneys, liver, and other organs. Half of the SARS-CoV-2 patients have blood or protein in their urine samples, an indication of early kidney damage. SARS-CoV-2 may also cause inflammation of the heart muscles and can cause disturbances in the heart rhythm, ultimately leading to cardiac arrest. The human gastrointestinal tract contains 100 times more ACE2 receptors than the lungs. Research shows that the virus could use these receptors to gain entry into other organs of the body and this might lead to multi-organ failure. The current scenario of the SARS-CoV-2 pandemic proves that the world was not prepared for a disaster on such a scale. In the event of another pandemic in the future, do you believe the world will have learned lessons to prepare for what comes next, such as funding medical research, building better health care systems and infrastructure, and tracking potentially lethal viruses. Researchers are actively working on the characterization of new emerging strains, drug discovery, and the development of SARS-CoV-2 infections. Already, some excellent tools and techniques have been developed for use in the fight against SARS-CoV-2. There are 92 vaccines under development, 45 antibodies, 12 cell-based and, 5 RNA-based therapies, and 52 other therapeutic options are currently being explored to fight the new SARS-CoV-2. Various clinical trials are underway to investigate potential therapies against the SARS-COV-2 pandemic, but no effective treatment is effective available, to date. We hope this work will contribute to protecting and treating people at risk of developing a vaccine for severe SARS-CoV-2 infections.

6. Author's contribution

D.D.S and D.K.Y. conceived and designed the project and collected data from the literature and write the manuscript. I.H. and E.H.C, support editing the Manuscript. All authors contributed to the interpretation and discussion of the results. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] V.M. Cucinotta D, WHO Declares COVID-19 a Pandemic, Acta Bio Med 91(1) (2020) 157-160.
[2] Zheng J. SARS-CoV-2: an emerging coronavirus that causes a global threat. Int J Biol Sci 2020;16(10):1678–85.
[3] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507–13.
[4] Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virol J 2019;16(1).
[5] Poon LLM, Peiris M. Emergence of a novel human coronavirus threatening human health. Nat Med 2020;26(3):317–9.
[6] Omrani AS, Al-Tawfiq JA, Memish ZA. Middle East respiratory syndrome coronavirus (MERS-CoV): animal to human interaction. Pathogens Global Health 2016;109(8):354–62.
[7] Jiang S, Du L, Shi Z. An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies. Emerg Microbes Infect 2020;9(1):275–7.
[8] Mackenzie JS, Smith DW. COVID-19: a novel zoonotic disease caused by a coronavirus from China: what we know and what we don't. Microbiol Australia 2020;41(1).
[9] Zhang J-J, Dong X, Cao Y-Y, Yuan Y-D, Yang Y-B, Yan Y-Q, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75(7):1730–41.
[10] Yang X, Yu Y, Xu J, Shu H, Xia JA, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8 (5):475–81.
[11] Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 2020;323(15).
[12] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020;109.
[13] Raoult D, Zumla A, Locatelli F, Ippolito G, Kroemer G. Coronavirus infections: epidemiological, clinical and immunological features and hypotheses. Cell Stress 2020;4(4):66–75.
[14] Khan G. A novel coronavirus capable of lethal human infections: an emerging picture. Virol J 2013;10(1).
[15] Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DKW, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Eurosurveillance 2020;25(3).
[16] Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol 2020;30 (8):4381–9.
[17] Jean S-S, Lee P-I, Hsueh P-R. Treatment options for COVID-19: the reality and challenges. J Microbiol Immunol Infect 2020;53(3):436–43.
[18] Kim CH. SARS-CoV-2 Evolutionary Adaptation toward Host Entry and Recognition of Receptor O-Acetyl Sialylation in Virus-Host Interaction. Int J Mol Sci 2020;21(12):4549.
[19] Ge X-Y, Li J-L, Yang X-L, Chmura AA, Zhu G, Epstein JH, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 2013;503(7477):535–8.
[20] Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020;12(1).

[21] Demiselle J, Fage N, Radermacher P, Asfar P. Vasopressin and its analogues in shock states: a review. Ann Intensive Care 2020;10(1).

[22] Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, et al. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov 2020;6(1).

[23] Kakodkar P, Kaka N, Baig MN. A comprehensive literature review on the clinical presentation, and management of the pandemic Coronavirus Disease 2019 (COVID-19). Cureus 2020.

[24] Rico-Mesa JS, White A, Anderson AS. Outcomes in patients with COVID-19 infection taking ACEI/ARB. Curr Cardiol Rep 2020;22(5).

[25] Russell B, Moss C, George G, Santaolalla A, Cope A, Papa S, Van Hemelrijck M, Associations between immune-suppressive and stimulating drugs and novel COVID-19—a systematic review of current evidence, ecancermedicalscience 14 (2020).

[26] Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol 2020;215.

[27] Meng H, Xiong R, He R, Lin W, Hao B, Zhang L, et al. CT imaging and clinical course of asymptomatic cases with COVID-19 pneumonia at admission in Wuhan, China. J Infection 2020;81(1):e33–9.

[28] Torres T, Puig L. Managing cutaneous immune-mediated diseases during the COVID-19 pandemic. Am J Clin Dermatol 2020;21(3):307–11.

[29] Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 2020;27(6):992–1000.e3.

[30] de Alwis R, Chen S, Gan ES, Ooi EE. Impact of immune enhancement on Covid-19 polyclonal hyperimmune globulin therapy and vaccine development. EBioMedicine 2020;55.

[31] Choreño-Parra JA, Thirunavukkarasu S, Zúñiga J, Khader SA. The protective and pathogenic roles of CXCL17 in human health and disease: potential in respiratory medicine. Cytokine Growth Factor Rev 2020;53:53–62.

[32] Nikolich-Zugich J, Knox KS, Rios CT, Natt B, Bhattacharya D, Fain MJ. SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. GeroScience 2020;42 (2):505–14.

[33] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033–4.

[34] Rizzo P, Vieceli Dalla Sega F, Fortini F, Marracino L, Rapezzi C, Ferrari R. COVID-19 in the heart and the lungs: could we "Notch" the inflammatory storm?. Basic Res Cardiol 2020;115(3).

[35] Xiong Y, Liu Y, Cao L, Wang D, Guo M, Jiang A, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerging Microbes Infect 2020;9 (1):761–70.

[36] Xia S, Liu M, Wang C, Xu W, Lan Q, Feng S, et al. Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. Cell Res 2020;30(4):343–55.

[37] Choy EH, De Benedetti F, Takeuchi T, Hashizume M, John MR, Kishimoto T. Translating IL-6 biology into effective treatments. Nat Rev Rheumatol 2020;16(6):335–45.

[38] Saghazadeh A, Rezaei N. Immune-epidemiological parameters of the novel coronavirus – a perspective. Expert Rev Clin Immunol 2020;16(5):465–70.

[39] Felsenstein S, Herbert JA, McNamara PS, Hedrich CM. COVID-19: immunology and treatment options. Clin Immunol 2020;215.

[40] Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection–a review of immune changes in patients with viral pneumonia. Emerging Microbes Infect 2020;9(1):727–32.

[41] Zolfaghari Emameh R, Nosrati H, Taheri RA. Combination of biodata mining and computational modelling in identification and characterization of ORF1ab polyprotein of SARS-CoV-2 isolated from oronasopharynx of an Iranian patient. Biol Procedures Online 2020;22(1).

[42] Chan JF-W, Kok K-H, Zhu Z, Chu H, To KK-W, Yuan S, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerging Microbes Infect 2020;9(1):221–36.

[43] C.T.N. NCT04334980, Evaluating the Safety, Tolerability and Immunogenicity of bacTRL-Spike Vaccine for Prevention of COVID-19, ClicinalTrials.gov (2020).

[44] Haveri A, Smura T, Kuivanen S, Österlund P, Hepojoki J, Ikonen N, et al. Serological and molecular findings during SARS-CoV-2 infection: the first case study in Finland, January to February 2020. Eurosurveillance 2020;25(11).

[45] Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19. Pediatric Infectious Dis J 2020;39(5):355–68.

[46] Hu Q, Guan H, Sun Z, Huang L, Chen C, Ai T, et al. Early CT features and temporal lung changes in COVID-19 pneumonia in Wuhan, China. Eur J Radiol 2020;128.

[47] Schweitzer W, Ruder T, Baumeister R, Bolliger S, Thali M, Meixner E, et al. Implications for forensic death investigations from first Swiss post-mortem CT in a case of non-hospital treatment with COVID-19. Forensic Imaging 2020;21.

[48] Butt C, Gill J, Chun D, Babu BA. Deep learning system to screen coronavirus disease 2019 pneumonia. Appl Intelligence 2020:1–7.

[49] Liu Z, Ding L, Chen G, Zhao C, Luo X, Li X, et al. Clinical Time Features and Chest Imaging of 85 Patients With COVID-19 in Zhuhai, China. Front Med 2020;7.

[50] Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, et al. Remdesivir: a review of its discovery and development leading to emergency use authorization for treatment of COVID-19. ACS Cent Sci 2020;6(5):672–83.

[51] Fan L, Li D, Xue H, Zhang L, Liu Z, Zhang B, et al. Progress and prospect on imaging diagnosis of COVID-19. Chin J Acad Radiol 2020;3(1):4–13.

[52] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — preliminary report. N Engl J Med 2020;383(19):1813–26.

[53] Ucar F, Korkmaz D. COVIDiagnosis-Net: deep Bayes-SqueezeNet based diagnosis of the coronavirus disease 2019 (COVID-19) from X-ray images. Med Hypotheses 2020;140.

[54] Bao C, Liu X, Zhang H, Li Y, Liu J. Coronavirus Disease 2019 (COVID-19) CT findings: a systematic review and meta-analysis. J Am College Radiol 2020;17 (6):701–9.

[55] Amanati A, Karimi A, Fahimzad A, Shamshiri AR, Fallah F, Mahdavi A, et al. Incidence of ventilator-associated pneumonia in critically Ill children undergoing mechanical ventilation in pediatric intensive care unit. Children 2017;4(7).

[56] Prevention C.F.D.C.a. Coronavirus (COVID-19),:2020. https://www.cdc.gov/cdc-info/index.html

[57] Addie DD, le Poder S, Burr P, Decaro N, Graham E, Hofmann-Lehmann R, et al. Utility of feline coronavirus antibody tests. J Feline Med Surg 2014;17 (2):152–62.

[58] Bhat R, Hamid A, Kunin JR, Saboo SS, Batra K, Baruah D, et al. Chest imaging in patients hospitalized With COVID-19 infection - a case series. Curr Probl Diagn Radiol 2020;49(4):294–301.

[59] Bor C, Demirag K, Okcu O, Cankayali I, Uyar M. Ventilator-associated pneumonia in critically Ill patients with intensive antibiotic usage. Pakistan J Med Sci 1969;31(6).

[60] Mantuani D, Frazee B, Fahimi J, Nagdev A. Point-of-care multi-organ ultrasound improves diagnostic accuracy in adults presenting to the emergency department with acute dyspnea. Western J Emergency Med 2016;17(1):46–53.

[61] Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated troponin in patients with coronavirus disease 2019: possible mechanisms. J Cardiac Fail 2020;26(6):470–5.

[62] Lai C-C, Liu YH, Wang C-Y, Wang Y-H, Hsueh S-C, Yen M-Y, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. J Microbiol Immunol Infect 2020;53(3):404–12.

[63] Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect Dis 2020.

[64] El Zowalaty ME, Järhult JD. From SARS to COVID-19: a previously unknown SARS- related coronavirus (SARS-CoV-2) of pandemic potential infecting humans – Call for a One Health approach. One Health 2020;9.

[65] Lomoro P, Verde F, Zerboni F, Simonetti I, Borghi C, Fachinetti C, et al. COVID-19 pneumonia manifestations at the admission on chest ultrasound, radiographs, and CT: single-center study and comprehensive radiologic literature review. Eur J Radiol Open 2020;7.

[66] Ghinai I, McPherson TD, Hunter JC, Kirking HL, Christiansen D, Joshi K, et al. First known person-to-person transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the USA. Lancet 2020;395 (10230):1137–44.

[67] Abduljalil JM, Abduljalil BM. Epidemiology, genome, and clinical features of the pandemic SARS-CoV-2: a recent view. New Microb New Infections 2020;35.

[68] Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect 2020.

[69] Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020;395 (10223):514–23.

[70] Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395 (10223):473–5.

[71] Singh DD, Han I, Choi E-H, Yadav DK. Recent advances in pathophysiology, drug development and future perspectives of SARS-CoV-2. Front Cell Dev Biol 2020;8(580202). https://doi.org/10.3389/fcell.2020.580202.

[72] Kumar S, Zhi K, Mukherji A, Gerth K. Repurposing antiviral protease inhibitors using extracellular vesicles for potential therapy of COVID-19. Viruses 2020;12(5).

[73] Lee P-I, Hu Y-L, Chen P-Y, Huang Y-C, Hsueh P-R. Are children less susceptible to COVID-19?. J Microbiol Immunol Infect 2020;53(3):371–2.

[74] Zhu F-C, Li Y-H, Guan X-H, Hou L-H, Wang W-J, Li J-X, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Lancet 2020;395(10240):1845–54.

[75] Dietz L, Horve PF, Coil DA, Fretz M, Eisen JA, Van Den Wymelenberg K, Gilbert JA. 2019 Novel Coronavirus (COVID-19) pandemic: built environment considerations to reduce transmission. mSystems 2020;5(2).

[76] Pachetti M, Marini B, Benedetti F, Giudici F, Mauro E, Storici P, et al. Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase variant. J Transl Med 2020;18(1):179.

[77] Lythgoe MP, Middleton P. Ongoing clinical trials for the management of the COVID-19 pandemic. Trends Pharmacol Sci 2020;41(6):363–82.

[78] Guo Y-R, Cao Q-D, Hong Z-S, Tan Y-Y, Chen S-D, Jin H-J, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Mil Med Res 2020;7(1):11.

[79] Kolifarhood G, Aghaali M, Mozafar Saadati H, Taherpour N, Rahimi S, Izadi N, et al. Epidemiological and Clinical Aspects of COVID-19; a Narrative Review. Arch Acad Emerg Med 2020;8(1):e41.

[80] Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes?. Intensive Care Med 2020;46(6):1099–102.

[81] Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: their roles in pathogenesis. J Microbiol Immunol Infect 2020. https://doi.org/10.1016/j.jmii.2020.03.022.

[82] Rello J, Storti E, Belliato M, Serrano R. Clinical phenotypes of SARS-CoV-2: implications for clinicians and researchers. Eur Respir J 2020;55(5).

[83] Saber-Ayad M, Saleh MA, Abu-Gharbieh E. The rationale for potential pharmacotherapy of COVID-19. Pharmaceuticals 2020;13(5). https://doi.org/10.3390/ph13050096.

[84] Chow N, Fleming-Dutra K, Gierke R, Hall A, Hughes M, Pilishvili T, et al. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 — United States, February 12–March 28, 2020. MMWR Morb Mortal Wkly Rep 2020;69(13):382–6.

[85] Tobaiqy M, Qashqary M, Al-Dahery S, Mujallad A, Hershan AA, Kamal MA, et al. Therapeutic management of patients with COVID-19: a systematic review. Infection Prevention Practice 2020;2(3):100061.

[86] Shen L, Niu J, Wang C, Huang B, Wang W, Zhu N, et al. High-throughput screening and identification of potent broad-spectrum inhibitors of coronaviruses. J Virol 2019;93(12):e00023–19. https://doi.org/10.1128/JVI.00023-19.

[87] Kumar Y, Singh H, Patel CN. In silico prediction of potential inhibitors for the main protease of SARS-CoV-2 using molecular docking and dynamics simulation based drug-repurposing. J Infect Public Health 2020;13(9):1210–23. https://doi.org/10.1016/j.jiph.2020.06.016.

[88] Pawelec G, Weng N-P. Can an effective SARS-CoV-2 vaccine be developed for the older population?. Immunity Ageing 2020;17(1).

[89] N.I.O. Health, NIH clinical trial shows Remdesivir accelerates recovery from advanced COVID-19, 2020.

[90] Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci 2020;117(20):10970–5.

[91] Guo G, Ye L, Pan K, Chen Y, Xing D, Yan K, et al. New Insights of Emerging SARS-CoV-2: epidemiology, etiology, clinical features, clinical treatment, and prevention. Front Cell Dev Biol 2020;8:410.

[92] Rosa SGV, Santos WC. Clinical trials on drug repositioning for COVID-19 treatment. Revista Panamericana de Salud Pública 2020;44:e40.

[93] Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020:105949.

[94] C.T.N. NCT04310228, Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019, ClicinalTrials.gov (2020).

[95] Drug UFA. Recommendations for Investigational COVID-19 Convalescent Plasma. fda.gov 2020.

[96] Gibson WJ, Nafee T, Travis R, Yee M, Kerneis M, Ohman M, et al. Machine learning versus traditional risk stratification methods in acute coronary syndrome: a pooled randomized clinical trial analysis. J Thromb Thrombolysis 2019;49(1):1–9.

[97] Tang XC, Agnihothram SS, Jiao Y, Stanhope J, Graham RL, Peterson EC, et al. Identification of human neutralizing antibodies against MERS-CoV and their role in virus adaptive evolution. Proc Natl Acad Sci 2014;111(19):E2018–26.

[98] Du L, Zhao G, Yang Y, Qiu H, Wang L, Kou Z, et al. A conformation-dependent neutralizing monoclonal antibody specifically targeting receptor-binding domain in Middle East respiratory syndrome coronavirus spike protein. J Virol 2014;88(12):7045–53.

[99] Barton C, Kouokam JC, Lasnik AB, Foreman O, Cambon A, Brock G, et al. Activity of and effect of subcutaneous treatment with the broad-spectrum antiviral lectin griffithsin in two laboratory rodent models. Antimicrob Agents Chemother 2014;58(1):120–7.

[100] O'Keefe BR, Giomarelli B, Barnard DL, Shenoy SR, Chan PKS, McMahon JB, et al. Broad-spectrum in vitro activity and in vivo efficacy of the antiviral protein griffithsin against emerging viruses of the family coronaviridae. J Virol 2010;84(5):2511–21.

[101] Barnard DL, Kumaki Y. Recent developments in anti-severe acute respiratory syndrome coronavirus chemotherapy. Future Virol 2011;6(5):615–31.

[102] Baric RS, Pervushin K, Tan E, Parthasarathy K, Lin X, Jiang FL, et al. Structure and inhibition of the SARS coronavirus envelope protein ion channel. PLoS Pathog 2009;5(7):e1000511. https://doi.org/10.1371/journal.ppat.1000511.

[103] He ML, Zheng BJ, Chen Y, Wong KL, Huang JD, Lin MC, et al. Development of interfering RNA agents to inhibit SARS-associated coronavirus infection and replication. Hong Kong Med J 2009;15(3 Suppl 4):28–31.

[104] Liao H-I, Olson CA, Hwang S, Deng H, Wong E, Baric RS, et al. mRNA display design of fibronectin-based intrabodies that detect and inhibit severe acute respiratory syndrome coronavirus nucleocapsid protein. J Biol Chem 2009;284(26):17512–20.

[105] Báez-Santos YM, St SE, John AD Mesecar. The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds. Antiviral Res 2015;115:21–38.

[106] Mandal RS, Ta A, Sinha R, Theeya N, Ghosh A, Tasneem M, et al. Ribavirin suppresses bacterial virulence by targeting LysR-type transcriptional regulators. Sci Rep 2016;6(1):39454. https://doi.org/10.1038/srep39454.

[107] Taylor R, Kotian P, Warren T, Panchal R, Bavari S, Julander J, et al. BCX4430 – a broad-spectrum antiviral adenosine nucleoside analog under development for the treatment of Ebola virus disease. J Infection Public Health 2016;9(3):220–6.

[108] Pruijssers AJ, Denison MR. Nucleoside analogues for the treatment of coronavirus infections. Curr Opin Virol 2019;35:57–62.

[109] Adedeji AO, Singh K, Calcaterra NE, DeDiego ML, Enjuanes L, Weiss S, et al. Severe acute respiratory syndrome coronavirus replication inhibitor that interferes with the nucleic acid unwinding of the viral helicase. Antimicrob Agents Chemother 2012;56(9):4718–28.

[110] Adedeji AO, Singh K, Kassim A, Coleman CM, Elliott R, Weiss SR, et al. Evaluation of SSYA10-001 as a replication inhibitor of severe acute respiratory syndrome, mouse hepatitis, and middle east respiratory syndrome coronaviruses. Antimicrob Agents Chemother 2014;58(8):4894–8.

[111] Chen YJ, Li LJ, Tang WL, Song JY, Qiu R, Li Q, et al. First-line drugs inhibiting the renin angiotensin system versus other first-line antihypertensive drug classes for hypertension. Cochrane Database Syst Rev 2018:CD008170. https://doi.org/10.1002/14651858.CD008170.pub3.

[112] Hotez PJ, Corry DB, Bottazzi ME. COVID-19 vaccine design: the Janus face of immune enhancement. Nat Rev Immunol 2020;20(6):347–8.

[113] Ojha R, Gupta N, Naik B, Singh S, Verma VK, Prusty D, et al. High throughput and comprehensive approach to develop multiepitope vaccine against minacious COVID-19. Eur J Pharm Sci 2020;151:105375. https://doi.org/10.1016/j.ejps.2020.105375.

[114] C.T.N. NCT04346277, Compassionate Use Open-Label Anti-CD14 Treatment in Patients With SARS-CoV-2 (COVID-19), ClinicalTrials.gov (2020).

[115] NCT04336410 CTN, Safety. Tolerability and Immunogenicity of INO-4800 for COVID-19 in Healthy Volunteers. ClinicalTrials.gov 2020.

[116] NCT04368728 CTN. Study to Describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults. ClinicalTrials.gov 2020.

[117] NCT04299724 CTN. Safety and Immunity of Covid-19 aAPC Vaccine. ClinicalTrials.gov 2020.

[118] NCT04276896 CTN. Immunity and Safety of Covid-19 Synthetic Minigene Vaccin. ClinicalTrials.gov 2020.

[119] NCT04341389 CTN. A Phase II Clinical Trial to Evaluate the Recombinant Novel Coronavirus Vaccine (Adenovirus Vector). ClinicalTrials.gov 2020.

[120] TrialSiteNews. University of Oxford Commences Clinical Trial for Vaccine Candidate (ChAdOx1 nCoV-19) Targeting COVID-19, Clinal trials. Covid-19, University of Oxford, vaccine; 2020.

[121] NCT04283461 CTN. Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) for Prophylaxis SARS CoV-2 Infection. ClinicalTrials.gov 2020.

[122] ChiCTR2000031781, A randomized, double-blinded, placebo-controlled phase II clinical trial for Recombinant Novel Coronavirus (2019-nCOV) Vaccine (Adenovirus Vector), Chinese clinical trial registry (2020).

[123] Innovation NIOB. Laboratory of Vaccine Materials, nibiohn.go.jp 2020.

[124] B. B, Vaxart Announces Additional Positive Pre-Clinical Data for its Oral COVID-19 Vaccine Program, in: I. Vaxart (Ed.) 2020.

[125] C. RUTKOWSKI, UM alumnus on front lines of COVID-19 research in China, news.umanitoba.ca (2020).

[126] L. Han-soo, Genexine, Binex to develop COVID-19 vaccine, koreabiomed.com (2020).

[127] Smith TRF, Patel A, Ramos S, Elwood D, Zhu X, Yan J, et al. Immunogenicity of a DNA vaccine candidate for COVID-19. Nat Commun 2020;11(1):2601. https://doi.org/10.1038/s41467-020-16505-0.

[128] C.T. Arena, Covid-19: China to launch clinical trials for coronavirus vaccine, clinicaltrialsarena.com (2020).

[129] Hamilton E, UW–Madison, FluGen, Bharat Biotech to develop CoroFlu, a coronavirus vaccine, warf.org (2020).

[130] Zydus Cadila launches a fast tracked programme to develop vaccine for the novel coronavirus, 2019-nCoV (COVID-19); 2020.

[131] I. TV, Oxford University's COVID-19 vaccine moves to next stage of human trial, indiatvnews.com (2020).

[132] Novakowski S, Jiang K, Prakash G, Kastrup C. Delivery of mRNA to platelets using lipid nanoparticles. Sci Rep 2019;9(1):552. https://doi.org/10.1038/s41598-018-36910-2.

[133] P. Technology, Covid-19: Entos and Takis to work on separate vaccines, pharmaceutical-technology.com (2020).

[134] COVID-19 Vaccine Candidates assaygenie.com 2020.

[135] C.T. Arena, Serum Institute of India brings Covid-19 vaccine into animal testing, clinicaltrialsarena.com (2020).

[136] C.t.n. NCT01273233, Safety of an Inactivated Enterovirus Type 71 Vaccine in Healthy Adults, clinicaltrials.gov (2013).

[137] P. Inc, BioNTech and Pfizer announce regulatory approval from German authority Paul-Ehrlich-Institut to commence first clinical trial of COVID-19 vaccine candidates, in: B. Media (Ed.) 2020.

[138] CureVac, CureVaćs Optimized mRNA Platform Provides Positive Pre-Clinical Results at Low Dose for Coronavirus Vaccine Candidate, in: curevac.com (Ed.) 2020.

[139] Xu Ruodan, Shi Mingfei, Li Jing, Song Ping. Construction of SARS-CoV-2 Virus-Like Particles by Mammalian Expression System.Front Bioeng. Biotechnol 2020;8:862. https://doi.org/10.3389/fbioe.2020.00862.

[140] Qian C, Liu X, Xu Q, et al. Recent Progress on the Versatility of Virus-Like Particles. Vaccines (Basel) 2020;8(1):139. https://doi.org/10.3390/vaccines8010139.

[141] Syomin BV, Ilyin YV. Virus-Like Particles as an Instrument of Vaccine Production. Molecular Biology 2019;53:323–34.

[142] Jeyanathan M, Afkhami S, Smaill F, et al. Immunological considerations for COVID-19 vaccine strategies. Nat Rev Immunol 2020:615–32. https://doi.org/10.1038/s41577-020-00434-6.

[143] Valneva, Valneva and Dynavax Announce Collaboration to Advance Vaccine Development for COVID-19, in: valneva.com (Ed.) 2020.

[144] Jeyanathan M, Afkhami S, Smaill F, Miller MS, Lichty BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. Nat Rev Immunol 2020;20(10):615–32.

[145] Dynavax, Dynavax and Clover Biopharmaceuticals Announce Research Collaboration to Evaluate Coronavirus (COVID-19) Vaccine Candidate with CpG 1018 Adjuvant, in: D.T. Corporation (Ed.) 2020.

[146] Kim E, Erdos G, Huang S, Kenniston TW, Balmert SC, Carey CD, et al. Microneedle array delivered recombinant coronavirus vaccines: Immunogenicity and rapid translational development. EBioMedicine 2020;55:102743. https://doi.org/10.1016/j.ebiom.2020.102743.

[147] Francesca M, Rossi O, Francesca N, Francesca M. Francesca Micoli. OMV Vaccines and the Role of TLR Agonists in Immune Response. Int J Mol Sci 2020;21(12):4416. https://doi.org/10.3390/ijms21124416.

[148] Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. The spike protein of SARS-CoV–a target for vaccine and therapeutic development. Nat Rev Microbiol 2009 Mar;7(3):226–36. https://doi.org/10.1038/nrmicro2090.

[149] Saha RP, Sharma AR, Singh MK, Samanta S, Bhakta S, Mandal S, et al. Repurposing Drugs, Ongoing Vaccine, and New Therapeutic Development Initiatives Against COVID-19. Front Pharmacol 2020;11:1258. https://doi.org/10.3389/fphar.2020.01258.

[150] Kalita P, Padhi AK, Zhang KYJ, Tripathi T. Design of a peptide-based subunit vaccine against novel coronavirus SARS-CoV-2. Microb Pathog 2020;145.

[151] P. Technology, GSK partners with Innovax Biotech on Covid-19 vaccine, 2020.

[152] Rabaan A.A., Al-Ahmed S.H., Sah R., Al-Tawfiq J.A., Al-Qaaneh A.M., Al-Jamea L.H., Woodman A., Al-Qahtani M., Haque S., Harapan H., Bonilla-Aldana D.K., Kumar P., Dhama K., Rodriguez-Morales A.J.. Recent advances in vaccine and immunotherapy for COVID-19. Human vaccines & immunotherapeutics 2020; 1–12. Advance online publication. https://doi.org/10.1080/21645515.2020.1825896.

[153] Ng WH, Liu X, Mahalingam S. Development of vaccines for SARS-CoV-2. F1000Res. 2020;9:F1000 Faculty Rev-991. https://doi.org/10.12688/f1000research.25998.1

[154] Iavi, Iavi and merck collaborate to develop vaccine against sars cov-2, in: iavi.org (Ed.) 2020.

[155] Eiden J, Volckaert B, Rudenko O, et al. Single Intranasal (IN) Dose of M2SR (M2-Deficient Single Replication) Live Influenza Vaccine Protects Adults Against Subsequent Challenge with a Substantially Drifted H3N2 Strain. Open Forum Infect Dis 2019;6(Suppl 2):S967–8. https://doi.org/10.1093/ofid/ofz360.2425.

[156] GlobeNewswire, Generex Signs Contract with EpiVax to Develop Ii Key Peptide Vaccines to Address the Coronavirus Pandemic, 2020.

[157] Young P.R. Disease X ver1.0: COVID-19. Microbiology Australia 41, 2020;109–112. https://doi.org/10.1071/MA20028

[158] C. R, Adenoviral vectors are the new COVID-19 vaccine front-runners. Can they overcome their checkered past?, 2020.

[159] N. J, University of Alberta researchers in race against time to create COVID-19 vaccine, ualberta.ac (2020).

[160] Dzif, The DZIF focuses on SARS-CoV-2 research, dzif.de (2020).

[161] B. O, Candidats a vaccí contra la Covid-19, segons l'Organització Mundial de la Salut 2020.

[162] TrialSiteNews, CanSino Biological, Moderna, and INOVIO Lead COVID-19 Vaccine Race; 42 Other Candidates in Pre-Clinical Stage, 2020.

[163] Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 Vaccines at Pandemic Speed. The New England Journal of Medicine 2020:1–5. https://doi.org/10.1056/NEJMp2005630.

[164] Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science 2020;369(6499):77–81.

[165] Chi X, Liu X, Wang C, Zhang X, Li X, Hou J, et al. Humanized single domain antibodies neutralize SARS-CoV-2 by targeting the spike receptor binding domain. Nat Commun 2020;11(1).

[166] Cao Y, Su B, Guo X, Sun W, Deng Y, Bao L, et al. Potent neutralizing antibodies against SARS-CoV-2 identified by high-throughput single-cell sequencing of convalescent patients' B cells. Cell 2020;182(1):73–84.e16.

[167] Li W, Drelich A, Martinez DR, Gralinski L, Chen C, Sun Z, et al. Potent neutralization of SARS-CoV-2 in vitro and in an animal model by a human monoclonal antibody. BioRxiv 2020.

[168] Shi R, Shan C, Duan X, Chen Z, Liu P, Song J, et al. A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2. Nature 2020;584(7819):120–4.

[169] Ju B, Zhang Q, Ge J, Wang R, Sun J, Ge X, et al. Human neutralizing antibodies elicited by SARS-CoV-2 infection. Nature 2020;584(7819):115–9.

[170] Liu J, Zhang S, Zhang T, Xiao H, Du J, Zeng S, et al. Isolation of a human monoclonal antibody specific for the receptor binding domain of SARS-CoV-2 using a competitive phage biopanning strategy. Antibody Therapeutics 2020;3(2):95–100.

[171] Rogers TF, Zhao F, Huang D, Beutler N, Burns A, He W-T, et al. Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model. Science 2020.

[172] Brouwer PJM, Caniels TG, van der Straten K, Snitselaar JL, Aldon Y, Bangaru S, et al. Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability. Science 2020;369(6504):643–50.

[173] Chen X, Li R, Pan Z, Qian C, Yang Y, You R, et al. Human monoclonal antibodies block the binding of SARS-CoV-2 spike protein to angiotensin converting enzyme 2 receptor. Cell Mol Immunol 2020;17(6):647–9.

[174] Tai W, Zhang X, He Y, Jiang S, Du L. Identification of SARS-CoV RBD-targeting monoclonal antibodies with cross-reactive or neutralizing activity against SARS-CoV-2. Antiviral Res 2020;179.

[175] Huo J, Zhao Y, Ren J, Zhou D, Duyvesteyn HME, Ginn HM, et al. Neutralization of SARS-CoV-2 by destruction of the prefusion spike. Cell Host Microbe 2020;28(3):445–454.e6.

[176] Chu H, Chan JF-W, Yuen TT-T, Shuai H, Yuan S, Wang Y, et al. Comparative tropism, replication kinetics, and cell damage profiling of SARS-CoV-2 and SARS-CoV with implications for clinical manifestations, transmissibility, and laboratory studies of COVID-19: an observational study. Lancet Microbe 2020;1(1):e14–23.

[177] Wrapp D, De Vlieger D, Corbett KS, Torres GM, Wang N, Van Breedam W, et al. Structural basis for potent neutralization of betacoronaviruses by single-domain camelid antibodies. Cell 2020;181(5):1004–1015.e15.

[178] Lv Z, Deng Y-Q, Ye Q, Cao L, Sun C-Y, Fan C, et al. Structural basis for neutralization of SARS-CoV-2 and SARS-CoV by a potent therapeutic antibody. Science 2020;369(6510):1505–9.

[179] Zost SJ, Gilchuk P, Case JB, Binshtein E, Chen RE, Nkolola JP, et al. Potently neutralizing and protective human antibodies against SARS-CoV-2. Nature 2020;584(7821):443–9.

[180] Hansen J, Baum A, Pascal KE, Russo V, Giordano S, Wloga E, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. Science 2020.

[181] Dhama K, Sharun K, Tiwari R, Dadar M, Malik YS, Singh KP, et al. COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. Hum Vaccines Immunother 2020;16(6):1232–8.

[182] Wang J, Wang Z. Strengths, weaknesses, opportunities and threats (SWOT) analysis of china's prevention and control strategy for the COVID-19 epidemic. Int J Environ Res Public Health 2020;17(7).

[183] Xu C, Jin J, Song J, Yang Y, Yao M, Zhang Y, et al. Application of refined management in prevention and control of the coronavirus disease 2019 epidemic in non-isolated areas of a general hospital. Int J Nursing Sci 2020;7(2):143–7.