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The scientific community in COVID-19 global pandemic: A systematic update on recent progress and challenges

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ABSTRACT

The novel coronavirus, which emerged in China in late December 2019, is officially named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The rapid spread of the virus across the continent has disrupted human life in every aspect leading to health and economic crises. The World Health Organization (WHO) declared the novel coronavirus outbreak as a global pandemic on March 11, 2020. In spite of complete lockdown and quarantine efforts in many countries, the occurrence of infections continues to rise, with more than 88 million laboratory-confirmed cases and over 1.9 million deaths worldwide as on January 10, 2021. Since the beginning of the outbreak, lot of intriguing studies about the phylogenetic evolution, epidemiology, pathogenesis, transmission, clinical characteristics, and possible treatment of Corona Virus Disease 2019 (COVID-19) have been published. This review aims to provide an insight into the progress in this regard and provides a reference for future studies including general awareness. We have discussed the origin, transmission, and infection mechanism of coronaviruses in host cells as well as available treatment options with relevant case studies. Furthermore, the stages of vaccine development, types of vaccines, and candidate vaccines with their phases of clinical trial are also incorporated. In a nutshell, the article is an attempt to retrieve the latest information available on virus behavior, efficacy of the available drugs, and development of candidate vaccines on SARS-CoV-2.

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1. Introduction

Viral diseases have always been dreadful to humans and new viral infections are being reported frequently [1]. Coronavirus comprises a group of viruses that cause infections in birds and mammals. A novel and highly contagious viral disease, first reported in Wuhan (China) in December 2019, is named 'Corona Virus Disease 2019 which is caused by a new strain of SARS-CoV (severe acute respiratory syndrome coronavirus) called as SARS-CoV-2 [2]. Taxonomically, the SARS-CoV-2 virus belongs to family Coronaviridae, and order Nidovirales (Figure 1). This is the seventh virus in the family of coronavirus and attacks mainly human respiratory systems. WHO declared COVID-19 as worldwide pandemic in March 2020 [3]. After SARS (Severe Acute Respiratory Syndrome) in 2003 and MERS (Middle East Respiratory Syndrome) in 2012, this is the third large-scale pandemic virus in Corona family. The mortality rate of SARS-CoV-2 in humans (2.9%) is not very high in comparison to the previously reported SARS-CoV (10%) and MERS-CoV (30%) pandemics [4]. But the number of infected people in and outside China just after two months of its emergence, there were more than 3500, indicating a very high transmission rate and rapid spread of the virus across the continent.

2. Epidemiology

After the emergence of COVID-19 in China, the virus rapidly spread to Spain, France, Italy and America. At present, the entire globe (except Antarctica) from west to the east is infected with it. As per WHO report, globally more than 88 million confirmed cases along with 1.9 million deaths have been reported tillJanuary10, 2021. Majority of the deaths have been reported from America (55%), Europe (27%) and South-East Asia (12%). Epidemiological data also indicates that the number of death cases is profoundly high in Central Europe as compared to South-East Asia. The possible reason can be the geographical, social, cultural, and genetic differences, and different viral strains between the populations of the two regions [5,6]. Currently, the virus is predominant in the regions of America, Europe, and South-East Asia. The highest occurrence of cases has been reported from United States of America (37,538,493), India (10,395,278), Brazil (7,8,10,400) Russia (3,332,142), and France (2,660,740) [7].

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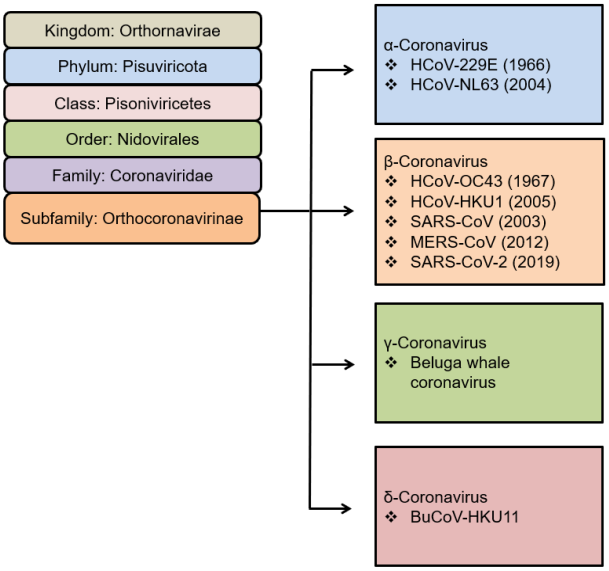

Figure 1. Classification of coronaviruses.

3. Methodology

A systematic literature search was performed using PubMed, Google Scholar, and Web of Science to access the articles published from December 2019 to December 2020. The search terms/key words included 'novel coronavirus', 'SARS-CoV-2', 'COVID-19', 'Pandemic-2019', 'transmission', 'symptoms', 'treatment', 'Vaccine development', and 'Clinical management. The appropriate literature reports, 260 in numbers, which included most of the searched keywords, were imported to Endnote. The exclusion and inclusion criteria were based on PRISMA guideline (Figure 2) [8].

4. Results

Duplicate articles, non-focused articles, articles showing only abstract, and articles published in non-English languages were screened out. Finally, 30 studies were chosen for quantitative analysis. Information available at the WHO website [7] and studies which came up during the reference cross check were also used in this study. All data were last updated on December 2020 before the submission.

5. The 2019 pandemic virus

Coronaviruses are single-stranded RNA virus ranging from 27-34 kb in length, 80-120 nm in diameter, and encircled with a nucleocapsid. Four known types of coronaviruses are α-coronavirus, β-coronavirus, δ-coronavirus, and γ-coronavirus [9]. SARS-CoV-2, which is similar to SARS-CoV and MERS-CoV, is also a β-coronavirus comprising of positive sense single-stranded RNA of 29.9 kb length [10]. The genome sequence similarity of SARS-CoV-2 and SARS-CoV is almost 79% [11]. Study revealed that the spike glycoprotein of the SARS-CoV-2is the combination of bat SARS-CoV and a mysterious Beta-CoV, thus suggesting zoonotic origin of the virus [12]. Two species of snakes have been recognized as an intermediate host of SARS-CoV-2; however, no authoritative evidence has emerged so far to support this view [13].

Like typical coronaviruses, the structural entity of SARS-CoV-2 also contains spike glycoprotein (S), membrane glycoproteins (M), envelope glycoprotein (E), and nucleocapsid protein (N) along with other non-structural and accessory proteins [10]. S, E and M proteins jointly form the viral envelope and the N protein contains RNA genome [14]. The S protein is a transmembrane protein, forms homotrimers, and enables viral binding and entry into the host cell. The M protein imparts shape to the virus and is responsible for membrane flexibility and curvature. The E protein participates in the assembly and release of the virus and assists in viral pathogenesis [15]. Nonstructural proteins are involved in viral replication and host cell infection by attenuating the host defense mechanism [16].

5.1. Genomic divergence of viruses (Difference in existing and original strains)

SARS-CoV-2 genome possesses 14 different ORF (open reading frame) encoding 27 proteins (Figure 3) [11]. First, ORF at the 5' terminus covers two-thirds of the whole genome and codes for two polypeptides, i.e., pp1ab and pp1a, which collectively translate 15 non-structural proteins. Different ORFs at 3' terminus code for the four structural proteins (S, M, E, and N) and eight accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b and orf14) [11].

A single mutation (N501T) in spike protein of SARS-CoV-2 significantly boosted its binding affinity with host cell angiotensin-converting enzyme 2 (ACE-2) as compared with SARS-CoV indicating that the genomic variation affected the functionality of the virus [17]. A genomic divergence study published in March 2020 reported a few notable variations in the proteins of SARS-CoV and SARS-CoV-2, including the absence of 8a protein and fluctuation in the number of amino acids in 8b and 3c proteins in SARS-CoV-2. But, the effect of these genomic differences in viral behavior and function is not explained [11].

In early 2020, researchers identified two deletions *ORF7b* and *ORF8* in SARS-CoV-2 genome and it was noted that people infected with these viruses did not need supplemental oxygen whereas, people infected with normal viruses needed supplemental oxygen, suggesting that this might be an important adaption to infecting humans [18]. The virus undergoes mutation during its overseas journey and at present, there are at least six available strains of the SARS-CoV-2[19]. The original L strain appeared in Wuhan in December 2019; its first mutated S strain appeared at the beginning of 2020 and was followed by V and G strains by mid-January 2020.

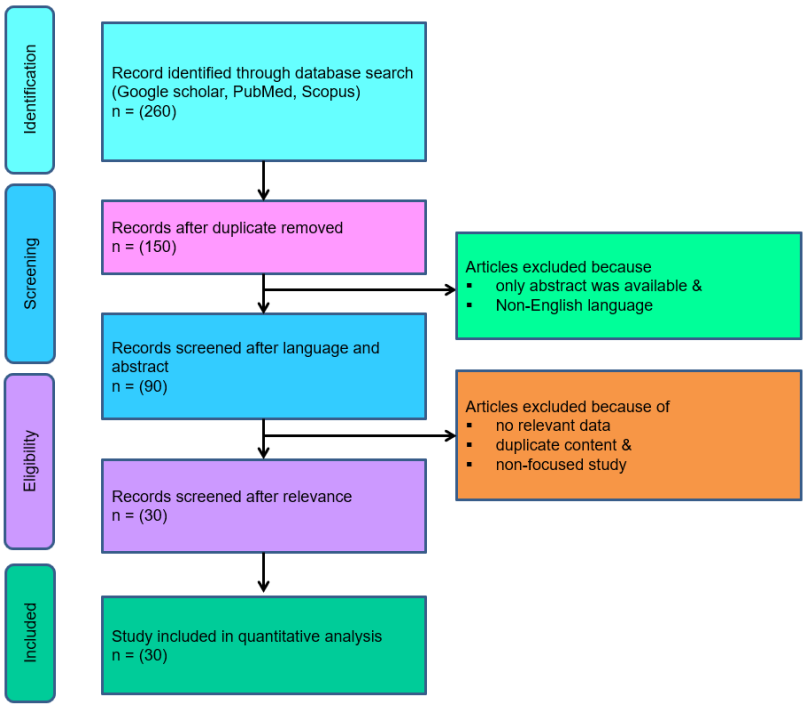

Figure 2. PRISMA flow chart of literature survey and screening process.

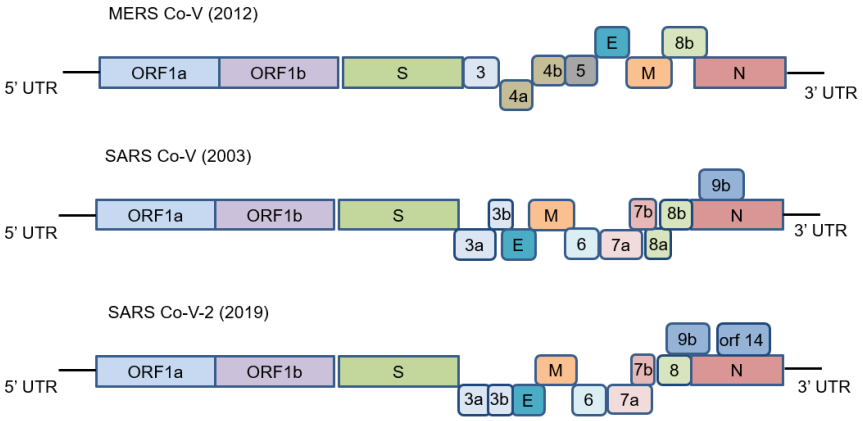

Figure 3. Genomic structure of human coronaviruses; SARS-CoV, MERS-CoV and SARS-CoV-2.

Strain G was further mutated to strains GR and GH at the end of February 2020. Mercatelli *et al*. reported that strain G and its related strains GR and GH are the most dominant, representing 74% of all gene sequences analyzed till date [19]. Fortunately, the virus shows limited diversity in spite of its mutations. Two widespread mutations, P4715L in ORF1ab and D614G in Spike, have already become consensus [20]. How this widespread D614G mutation affects the virus or human is not clear yet. D614G mutation is in the interface between the individual spike protomers and is therefore unlikely to have a major impact on the efficacy of vaccines currently underway for restricted use in the world. The receptor binding domain (RBD) of spike protein is crucial in vaccine development as some of which exclusively target the RBD [21]. The Spike glycoprotein receptor-binding domain (RBD) of SARS-CoV-2 mediates the viral particle's binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of human cells. Recently, a new strain of the Sars-CoV-2 virus known as VUI - 202012/01 or the lineage B.1.1.7. has been identified in the COVID-19 Genomics UK Consortium dataset (under investigation in December 2020), which features an amino acid substitution in the Spike RBD (N501Y mutation). The new strain, B.1.1.7, is not so dead but is 70% more transmissible and contagious compared to the previous mutated versions. This new phylogenetic group of SARS-CoV-2 variant has undergone 23 non-synonymous mutations and deletions. Findings showed that the increased infectivity of SARS-CoV-2 lineage B.1.1.7 is associated with the increase in the interaction force affinity between the Spike RBD Y501 mutant residue with the ACE2 receptor [22]. The genomic characterization of an emergent SARS-CoV-2 lineage underwent an unexpectedly large number of genetic changes including in the receptor-binding domain and associated with the furin cleavage site [23,24].

5.2. Infection mechanism of virus

SARS-CoV-2 also uses ACE-2 receptor for the entry to the host epithelial cell to cause infection, similar to SARS-CoV (Figure 4) [25,26]. S protein present on the external surface of SARS-CoV-2 is comprised of two functional domains S1 and S2.

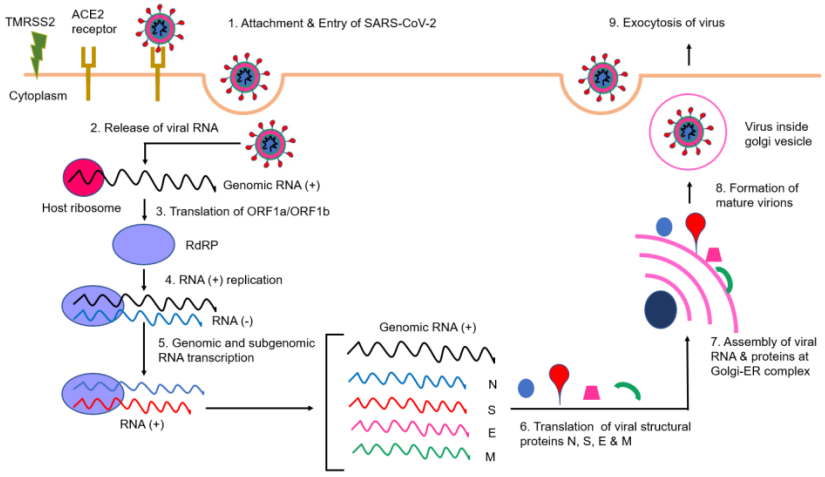

Figure 4. Infection and life cycle of SARS-CoV-2 into human epithelial cell. The virus enters into the nasal cavity during inhalation and the RBD region of S protein binds with ACE-2 receptor present on the epithelial cell. S protein of S/ACE-2 complex is cleaved at S1/S2 cleavage site by TMPRSS2. The S2 domain interacts with host cell membrane to facilitate endocytosis, followed by the entry of viral RNA in to the host cell. The viral RNA translates into two large polypeptide chains, which later cleaved into nonstructural proteins. Meanwhile, a replicase-transcriptase-complex of viral and host proteins is formed which enables the synthesis of RNA and structural proteins of the virus. The newly formed viral RNA and structural proteins accumulate at the ER-Golgi system and assembled to form new viruses, which are then exported from the host cell through exocytosis.

The RBD is present in the S1subunit of S protein and contains a 3-D structure to maintain the Vander Waals forces [27]. The virus enters into the nasal cavity during inhalation and the RBD region of S protein binds to ACE-2 receptors present on the epithelial cells of the nasal cavity. The glutamine-394 residue in the RBD region of SARS-CoV-2 interacts with the critical lysine-31 residue of ACE-2 receptor present on the human cell surface and enables the entry of virus to the host cell [17]. RBD region is loosely attached among the virus that encourages the virus to infect multiple hosts [28]. S protein of S/ACE-2 complex is cleaved at S1/S2 cleavage site by the serine protease TMPRSS2, cathepsin L, and furin to permit the entry of virus in to host cells [29]. Subsequently, the S2 domain interacts with the host cell membrane to facilitate endocytosis, followed by the entry of viral RNA in to the host cell. The exact endocytosis pathway used by the virus is still not clear and depends on the nature of the cell [16]. Once the viral RNA enters into the host cytoplasm, it hijacks the host translational machinery to synthesize different proteins needed for its own replication. The viral RNA translates into two large polypeptide chains, which later cleaved into NSPs. Meanwhile, a replicase-transcriptase-complex of viral and host proteins is formed which enables the synthesis of RNA and structural proteins of the virus. The newly formed viral RNA and structural proteins accumulate at the ER-Golgi system and assemble to form new viruses, which are then exported from the host cell through exocytosis [16].

The expression of ACE-2 is abundant in the respiratory tract including nasal, bronchial, and alveolar cells of the lungs and also in the epithelial cells of the gastrointestinal (GI) tract. TMPRSS2 is present in alveolar cells and GI tract. The co-existence of ACE-2 and TMPRSS2 in the respiratory tract as well as its direct participation in the inhalation accounts for the predominant role of the respiratory system in COVID-19 [30].

5.3. Pathogenicity of virus

Virus initiates replication and moves downward in to the alveolar cells after successful entry into the host cell. Simultaneously, it also tries to escape encounter from the host immune response, but macrophages and dendritic cells detect the virus particle and trigger a strong immune response (Figure 5). To overcome the rapidly increasing virus progeny in the lungs, the immune cells get hyper activated and an imbalance occurs in immune regulation leading to excess inflammatory secretion termed as cytokine storm [31]. The storm includes inflammatory cytokines viz. IL-6, IL-12, IL-18, CRP, and D-dimer which causes acute respiratory distress syndrome (ARDS) in the lungs leading to respiratory failure and is presumably the primary cause of death in SARS-CoV-2 infections [32]. The cytokines and chemokine storm mainly occur in lung but due to the systematic inflammation cardiovascular system is also affected and leads to cardiac arrhythmias, intravascular thrombosis, heart failure and finally death [33]. Coagulopathy is also a common comorbid and often found in hospitalized COVID-19 patients. The increased cytokine production and prothrombotic factors play a prominent role in increasing the severity of coagulopathy. The markers of coagulopathy include increased D-dimer levels, disseminated intravascular coagulation, and thrombocytopenia [34].

Striking evidence exhibited that in COVID-19, the virus also affects the central nervous system (CNS), cerebrovascular events (CVEs) and intracranial hemorrhage [35]. Furthermore, SARS-CoV-2 can enter in to the CNS either by blood stream or by retrograde neuronal transport and can cause neurological abnormalities [36]. The expression of ACE-2 in the CNS encourages viral entry to the brain [37]. The direct pathology of neuro-invasion has not yet been identified for SARS-CoV-2, but virus particles have been detected in brain autopsy samples [38]. In a clinical study based on 214 COVID-19 patients, 78 (36.4%) cases of neurological disorders revealed a high prevalence of neurological symptoms in COVID-19 patients [39].

5.4. How does the immune system respond to the virus?

The cellular immune response involves activation of $CD4^+$ and $CD8^+$ T-cells. The functions of $CD4^+$ T-cells include the production of antibodies (Abs) (IgM, IgA & IgG) against S, RBD, and N proteins of the virus and $CD8^+$ T-cells clear the infected cells of the host [40]. The formation of antibodies against viral proteins confers the development of many vaccines under clinical trials. Moreover, the presence of Abs in the serum sample of SARS-CoV-2 infected patients was considered beneficial for the formation of protective immunity.

The available data suggested that in most cases of SARS-CoV-2 infection, the immune response was displayed during 7-10 days after infection.

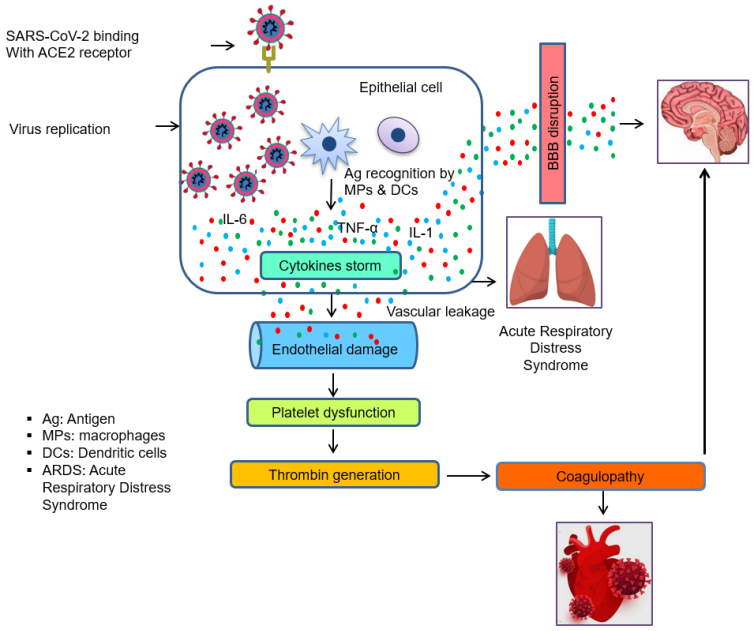

Figure 5. Schematic presentation of pathogenicity caused by SARS-CoV-2 infection. The rapidly proliferating viral population leads to cytokine production inside the epithelial cell. The cytokine storm includes IL-6, IL-12, IL-18, CRP, and D-dimer which causes acute respiratory distress syndrome (ARDS) in lungs leading to respiratory failure and death. The cytokine storm also affects the cardiovascular system and CNS by systematic inflammation and leads to cardiac arrhythmias, intravascular thrombosis, intracranial hemorrhage, heart failure and death.

The presence of IgM and IgA was detected in 5-7 days and IgG was detected in between 7-10 days of onset of disease [41]. The longevity of Abs is also not ascertained in SARS-CoV-2 infection, but seasonal coronaviruses impart protection for short duration. In earlier SARS infections, Ab was found to diminish by 12-52 weeks of onset of symptoms. Similarly, in SARS-CoV-2 infection, a decline in serum IgM and IgA titers was found after 4 weeks of onset of symptoms, whereas the IgG remained at peak for at least 7 weeks [42]. A group of 122 people on an US fishing boat were tested for SARS-CoV-2 and its antibodies before and after viral exposure. It was reported that 104 members tested COVID-19 positive, but 3 people who showed antibodies before exposure escaped the infection. The study, therefore, provided statistically significant data to support the hypothesis of acquired immunity in case of SARS-CoV-2 infection [43]. However, gradually, cases from many countries have been reported claiming the reinfection of SARS-CoV-2 [44]. The duration of protection of host cells by antibodies against reinfection is still uncertain. All available reports on the formation of protective immunity due to SARS-CoV-2 infection include data analysis of short duration. Therefore, longer duration data analysis is needed to understand the longevity of memory and host cell protection.

6. Viral infection into global pandemic

The first case of SARS-CoV-2 transfer from bat to human was reported at Wuhan seafood market in China, where live animals are sold regularly. Since the first incident, the number of infected people has gone up exponentially. Although, several victims did not have direct contact with the market thus suggesting local human-to--to-human transmission and even more dangerous community transmission which led to the pandemic status [45]. The virus reportedly stays in the air for a prolonged time and can survive for hours on contaminated metal surfaces, latex surgical gloves, and sterile sponges. Transmission occurs by coming in close contact with an infected person (within 1 m), either by inhalation of respiratory droplets (>10 μm) or skin-to-skin contact and by touching the contaminated surface [46]. Furthermore, reports suggest that SARS-CoV can survive in stool samples up to 4 days [47]. The presence of SARS-CoV-2 has also been spotted in fecal samples of infected patients, so the fecal route of transmission should not be ruled out [48]. The presence of stool, from an infected patient in wastewater may generate a further route of transmission via the generation of virus-laden aerosols during wastewater treatment as reported in Hong Kong in 2003 during SARS-CoV outbreak [49]. The presence of coronaviruses has been reported in water, sewage, and pure or pasteurized settled sewage, and the viruses can remain infectious for 3 days to 3 weeks [50]. Therefore, the contaminated sewage-borne aerosols also pose a possible source of SARS-CoV-2 transmission and needs further study.

Earlier, the transmission of infectious diseases was linked to the presence of microorganisms in airborne particulate matter (PM)/airborne dust [51]. Air pollution is common in many countries and surface adsorption of SARS-CoV-2 on airborne PM or dust may contribute the long - range transmission of viral infections. Inhalation of virus-laden fine PM could transport the virus into deep alveolar tissues, tracheobronchial regions and increase the chance of infection [46]. Further investigation on the survival of SARS-CoV-2 in airborne PM/dust will explain their role in transmission.

6.1. Virus and demography: who are at risk?

Although, SARS-CoV-2 can infect persons of any age, but middle and old age people are generally more susceptible; most of the COVID-19 patients are in between 48 to 58 years. [52]. The Chinese Center for Disease Control and Prevention (CCDC) case report of 44,500 confirmed cases of SARS-CoV-2 infections, 87% of patients were in the age group of 30-79 years. In 70-80 years age group, the SARS-CoV-2 infection comes in comorbidity with some previous disease which increases the chances of death (8–15%) in this age group [53].

The prevalence of SARS-CoV-2 infection was found to be same in both males and females, but a gender-based difference in the mortality rate was observed.

Table 1. List of available drugs to manage COVID-19 symptoms with the result of clinical trials. Table Abbreviation: FPV: Favipiravir; ARB: Arbidol; IFN: Interferon; LPV/RTV: Lopinavir and ritonavir; RBV: Ribavirin; HCQ: Hydroxychloroquine; AZT: Azithromycin; CP: Convalescent plasma.

No	Drug	Clinical trial	Sample size	Groups	Result
1	Favipiravir (FPV)	Multicenter, controlled, open-label, randomized superiority trial	240	Grp1. FPV (120) Grp 2. ARB (120)	Symptom improvement was markedly low in FPV group as compared with ARB group (ChiCTR200030254) [111]
2	Remdesivir	Randomized, double-blind, placebo-controlled, multicenter trial	237	Grp 1. Remdesivir (158) Grp 2. Placebo (79)	Rapid improvement in remdesivir injected group [112]
		Double-blinded, randomized, placebo-controlled trial	1063	Grp 1. Remdesivir (538) Grp 2. placebo (521)	Recovery time was reduced in remdesivir group (11 days) than placebo (15 days) and the mortality rate were also reduced (NCT04280705) [68]
3	(FPV)/LPV+RTV	open-label, non-randomized, before-after controlled study	80	Grp 1 (35) FPV (oral)+IFN-α (aerosol inhalation) Grp 2. Control (45) (LPV/RTV+ IFN-α)	FPV treatment was useful and exhibited notable improvement (91.43%) in chest imaging compared with the control (62.22%) treatment [65]
4	LPV/RTV+ IFNβ-1b	Multicenter, prospective, open-label, randomized, phase 2 trial	127	Grp 1(86) LPV+RTV+RBV+ IFNβ-1b Grp 2. (41)Control (LPV/RTV) for 14 days	The combined treatment (Grp 1) was better and safe in improving the symptoms and attenuating viral load in the nasopharynx NCT04276688 [71]
5	IFN-α2b	An uncontrolled, exploratory case study	77	Grp 1. IFN-α2b (7) Grp 2. ARB (24) Grp 3. IFN-α2b + ARB (46)	IFN-α2 b alone or with ARB reduced the duration of detectable virus in nasopharynx and also the duration of inflammatory response [75]
6	HCQ	Open labeled non-randomized clinical trial	42	Grp 1. HCQ (20) Grp 2. HCQ+AZT (6) Grp 3. Control (16)	Significant reduction of viral load in patients with HCQ treatment; effect was augmented by AZT [113]
		Uncontrolled, non-comparative, observational study	80	79 HCQ+AZT	Significant clinical recovery and rapid reduction of viral congestion in nasopharynx except two deaths [79]
7	Tocilizumab	Retrospective, observational, multicenter cohort study	764 ICU patients	Grp 1. (210) Tocilizumab Grp 2. (554) No tocilizumab	Tocilizumab treatment reduces mortality in hospitalized patients requiring ICU support [114]
8	CPT	Retrospective, randomized blinded, single center clinical trial	1568	Grp1. (1430) standard treatment Grp 2. (168) (ABO-compatible CP)	50% reduction in death and intensive care unit (ICU) admission rates as compared with standard treatment [92]
		Retrospective, propensity score–matched case–control study	195	Grp1. Plasma treatment (39) Grp 2. Control (156)	CP recipients needs less supplemental oxygen than control group by 14th day of post-transfusion [115]

Study conducted on a very large sample from 9 countries including 194,349,591 men and 201,715,364 women reported the men to women mortality ratio of 1.4: 1 per 100,000 population [54]. Life style and chromosomal differences were considered the most suitable explanation for the death due to gender difference, the author added. Initially during the spread of the virus, age was considered as one of the prominent risk factors, but with the progression of pandemic, both sex and age are considered as prominent risk factors.

Pregnant women are at higher risk for respiratory pathogens and acute pneumonia infections therefore it is important to understand the mother to neonatal transfer of SARS-CoV-2. Recently, a small study was conducted on COVID-19 positive pregnant women to see the neonatal transfer of SARS-CoV-2 and the results exhibited that all babies were born healthy indicating a zero case of neonatal transfer [55]. All the observations in this study were from the caesarean delivery. To decide the pregnancy and COVID-19 associated risks, a systematic review by retrieving 49 studies found that 8 out of 292 (2.7%) women who delivered their babies vaginally had COVID-19 confirmed babies and 20 out of 364 (5.3%) women who had caesarean baby had COVID-19 confirmed baby. Therefore, the study concluded that neonatal transmission of COVID-19 is infrequent and the infection rate is independent of the delivery route [56]. Further, most of the infected newborns were asymptomatic or exhibited mild symptoms [57].

Till now, very few cases of SARS-CoV-2 infection have been found in children (age 0-17 years) compared with adults, therefore, the potential of viral infection and transmission in children is not much clear [58]. The viral loads in the nasopharynx and the efficacy of viral transmission in children are almost the same as in adults [59]. The comparison of the incidence of infection in children before and after opening of schools and other activities can provide additional insight into the pediatric infection.

6.2. Strive of the scientific community against pandemic viruses

The cases of COVID-19 infections are continuously increasing, unfortunately no medicine/ vaccine has been officially approved to treat COVID-19 patients until earlier in the last year 2020. Therefore, at that time, clinical management involves protective and control measures along with supplemental oxygen and ventilation to prevent the rapid spread of the virus and to manage the disease symptoms. Therefore, there is a pressure on the scientific community to find some alternative medicine to tackle/combat the virus effectively. To overcome this issue, scientists are trying the repurposing of the available drugs. WHO has announced a number of drugs that showed efficacy against SARS-CoV-2 infection. Until now, antivirals have found the most effective use against the virus, which lowers the ability of the viruses to invade the cells and arrest their multiplication process. We have discussed the usage and clinical trial reports (Table 1) of the drugs currently being used to manage SARS-CoV-2 infection in the following section.

Vaccines typically require years of research and testing before reaching the clinic, and although scientists have been working tirelessly for vaccine development in 2020. It is now certain that the vaccine appears at the earliest as scientists embarked on a race to produce safe and effective corona virus vaccines in record time. Researchers are currently testing 64 vaccines in clinical trials on humans, and 20 have reached the final stages of testing. At least 85 preclinical vaccines are under active investigation in animals.

Table 2. List of all vaccines that have been approved and set for emergency use in certain countries.

No	Vaccine developer	Type	Phase	Status
1	Pfizer-BioNTech	mRNA	2, 3	Approved in Canada, other countries. Emergency use in U.S., other countries.
2	Moderna	mRNA	3	Approved in Canada. Emergency use in U.S.
3	Gamaleya	Adenovirus	3	Early use in Russia. Emergency use in Belarus, Argentina.
4	Oxford-AstraZeneca	Adenovirus	2, 3	Emergency use in Britain, India, Argentina.
5	CanSino	Adenovirus	3	Limited use in China.
6	Johnson & Johnson	Adenovirus	3	-
7	Vector Institute	Protein	3	Early use in Russia.
8	Novavax	Protein	3	-
9	Sinopharm	Inactivated	3	Approved in China, U.A.E., Bahrain. Emergency use in Egypt.
10	Sinovac	Inactivated	3	Limited use in China.
11	Sinopharm-Wuhan	Inactivated	3	Limited use in China, U.A.E.
12	Bharat Biotech	Inactivated	3	Emergency use in India.

The Food and Drug Administration (FDA's) authorization for emergency use of the first COVID-19 vaccine is a significant milestone in battling this devastating pandemic that has affected so many families in the United States and around the world. The FDA granted the first emergency use authorization (EUA) to a coronavirus vaccine on Dec. 11, developed by New York-based Pfizer and the German company BioNTech and is over 90 percent effective. The Oxford-AstraZeneca vaccine has been approved for emergency use in the UK on 30 December. In India, The Drugs Controller General of India (DCGI) on 3rd January 2021 formally announced the approval of India's 1st Covid-19 vaccine, Bharat Biotech's Covaxin and the Serum Institute of India's Covishield for 'restricted use' in the country [60]. Table 2 is a list of all vaccines that have been approved and set for emergency use in certain countries.

6.2.1. Antivirals in the treatment of COVID-19

Favipiravir (FPV) was approved in 2014 against influenza virus in Japan. It inhibits the replication enzyme, RNA dependent RNA polymerase (RdRp), and arrests the replication process of the virus. It has been permitted in many countries to treat COVID-19 [61]. However, FPV has not yet been approved by the U.S. FDA [62] but EUA has been allowed in many countries based on statistically significant positive results [63,64]. The idea of combined treatment of FPV with interferon-α(IFN- α) was found effective[65].

Remdesivir (GS-5734) is a widely known antiviral drug formerly designed to target Ebola virus. It also inhibits viral replication by attenuation of RNA transcription, which arrests the virus's ability to multiply [66]. The first case of SARS-CoV-2 infection in Washington State was reported on January 19, 2020 in a 35-year-old man who successfully recovered after remdesivir treatment [67]. However, the efficacy and safety of remdesivir in patients with SARS-COV-2 infection still needs to be established by clinical studies. Ongoing studies with larger sample sizes will continue to update our understanding of the effect of remdesivir on COVID-19[68]. In continuation to the further studies on remdesivir, a phase 3 randomized, open label trial is under progress to evaluate the safety and antiviral activity of the drug (GS-5734™) in 1113 participants with moderate SARS-COV-2 infection compared to standard care treatment (NCT04292730) [69].

Lopinavir and ritonavir (LPV/RTV) are protease inhibitors which are used against HIV infection and inhibit viral replication. A study published in March 2020 in the New England Journal of Medicine concluded that treating COVID-19 patients with LPV/RTV added no clinical advantage in comparison with standard supportive care [70]. However satisfactory results were reported when LPV/RTV were given in combination with IFNs [71]. A double-blind, randomized, placebo-controlled phase II clinical trial of LPV/RTV is under progress in COVID-19 patients with cancer and immune suppression [72]

Type 1 IFNs are a large subgroup of IFNs including IFN-α and IFN-β. IFN-α is a broad-spectrum antiviral drug commonly used to treat hepatitis, whereas IFN-β is usually given in multiple sclerosis. WHO has recommended the use of IFN-αagainst SARS-CoV-2 infection [73]. A review published in Nature [74] claimed that severe COVID-19 patients showed strong response to type I IFN, which was contradictory to previous reports [71,75]. This study further suggested that understanding the dynamics of type I IFN at different stages of infection might help in understanding the therapeutic use in COVID-19 patients [74].

6.2.2. Anti-malarial in the treatment of COVID-19: expectations and reality

Chloroquine (CQ) and Hydroxychloroquine (HCQ) are anti-malarial drugs and are also used in the treatment of inflammation. These drugs alter the working environment of the virus by altering the optimum pH inside the cells to arrest the viral activity. Clinical trials of both drugs against COVID-19 have been approved by FDA [73] as both drugs reduced the transmission of SARS-CoV and SARS-CoV-2*in vitro* experiments [76]. Based on these findings, CQ and HCQ were suggested to treat hospitalized COVID-19 patients in several countries. Studies conducted on COVID-19 patients to evaluate the efficacy of CQ reported a significant reduction in disease symptoms and in viral congestion in lungs much earlier than controls [77,78]. Gautret, *et al.* found that the combined treatment of HCQ and azithromycin could be more effective against SARS-CoV-2 infection [79]. Based on the results of these studies, the USFDA issued an EUA on March 28, 2020, to permit the use of CQ and HCQ for the treatment of COVID-19 hospitalized patients.

6.2.3. Hydroxychloroquine in treatment of COVID-19

A number of large clinical trials were initiated to assess the effectiveness of HCQ, as well as other potent drugs against COVID-19 worldwide. The Solidarity trial, to compare four treatments including HCQ against standard care, was started by WHO in March 2020. It recruited over 3500 patients from 400 hospitals in 35 countries ("Solidarity" clinical trial for COVID-19 treatment [80]. A similar trial was started at the University of Oxford, the RECOVERY trial, and recruited more than 11,000 patients from 175 NHS hospitals to evaluate six different therapies including HCQ [81].

On May 22,2020, *Lancet* published a case study involving more than 96,000 patients from six continents. The study conducted during December 2019 to April 2020 reported a high risk of ventricular arrhythmia/heart disease and death in CQ or HCQ treated SARS-CoV-2 patients than control group [82]. After this study, WHO paused the HCQ arm of its Solidarity trial, but later the paper was retracted due to objections raised by the scientific community and the Solidarity trial was restarted on June 4, 2020. Meanwhile, the team leading the RECOVERY trial claimed that HCQ had no clinical advantage for patients with COVID-19and closed HCQ arm activity [83]. Finally, on June 17, 2020, WHO also announced to stop the HCQ arm of the Solidarity trial. Strategies are being developed continuously to

make HCQ potent and, NIH has begun a phase 2b clinical trial of HCQ together with azithromycin to evaluate their efficacy in hospitalization and death in SARS-CoV-2 infected patients [84]. However, the prophylactic use of CQ and HCQ is discouraged now because of their acute side effects (worsening vision, nausea, digestive disorders and heart failure). A case study in Arizona reported the death of a husband and critical condition of wife after taking CQ to protect themselves from SARS-CoV-2 infection [85].

6.2.4. Tocilizumab mystery in COVID-19

Tocilizumab is a recombinant humanized monoclonal antibody of IgG1 class, which is directed against both soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor [86]. It is an immunosuppressive drug available under the name Actemra and has been used for the treatment of rheumatoid arthritis and to reduce inflammation. An initial clinical trial of tocilizumab on 20 acute COVID-19 patients reported 95% recovery within two weeks [1]. FDA approved a phase 3 trial of Actemrain severe SARS-CoV-2infections. Further, Roche announced that in the phase3 COVACTA trial, Actemra®/RoActemra® (tocilizumab) did not improve the clinical status of the patients and death occurred in hospitalized adult patients with severe COVID-19 associated pneumonia [87]. In another attempt to establish the efficacy of the drug, all available data from 13 published, 15 pre-print clinical studies and 5776 patients were further evaluated. The study concluded that there were insufficient data regarding the safety and efficacy of the drug, as only a few trials were multicenter, the sample size receiving tocilizumab was not large and most studies were without control [88]. WHO has recommended the use of tocilizumab only in severe clinical conditions [89].

6.2.5. Potential role of Convalescent plasma therapy in COVID-19

Convalescent plasma (CP) therapy is a classic adaptive immunotherapy and is widely used for the control and treatment of many infectious diseases since a long time. FDA has approved the use of blood plasma from recovered COVID-19 patients having high neutralizing antibody titer and also use of such people as a potent donor source of CP [90]. FDA approved a multicenter, open label trial on a hospitalized COVID-19 patient using CP and preliminary data analysis of the first 20,000 patients established the safety and benefit of CP treatment [91]. CP therapy could be more effective if it is administered to COVID-19 patients before the severe lung infections. [92].

7. Vaccines in infectious diseases

Vaccines are the utmost reasonable and effectual measures to prevent and control infectious diseases [93]. It is dire need to develop an effective vaccine against SARS-CoV-2 infection. The identification of SARS-CoV-2 was achieved within 3 months of its spread. The studies on its other biological characteristics are undergoing vigorously to facilitate the rapid development of vaccine. Globally, confirmed COVID-19 cases are still increasing at an alarming rate and it may become a flu-like seasonal disease and remain in coexistence with human beings for a long time [94]. Thus, vaccine development is necessary even if it is occurring at a slower pace than the spreading of COVID-19 pandemic. To date, nearly forty pharmaceutical firms and academic institutions have launched their vaccine development programs against SARS-CoV-2 infection globally. However, the course of vaccine production has to follow the strict rules set by various regulatory agencies and is not an overnight task. Broadly the vaccine production process can be classified as: (a) the vaccine designing process, (b) its safety and efficacy in animal studies followed by (c) clinical trials (phases 1, 2, and 3), and (d) regulatory approval. Generally, it takes a decade or two for a new vaccine to go from the design to approval stage [95]. However, the process of vaccine development against COVID-19 has briskly reached the phase 3 clinical trial (Table 3) at various places worldwide and it is expected to be the fastest vaccine ever produced in human history. Viral diversity has challenged vaccine development efforts for other viruses such as HIV-1, influenza, or Dengue, as these viruses constitute a more diverse population than SARS-CoV-2 virus. Currently, circulating SARS-CoV-2 constitutes a comparatively homogeneous population and there is indication of purifying selection but little sign of diversifying selection [96]. Therefore, we can be cautiously optimistic that viral diversity should not be an obstacle for the development of a SARS-CoV-2 broad spectrum vaccine. The various vaccines that are being currently developed (Table 3) should elicit reactive responses against circulating variants of SARS-CoV-2.

7.1. Types of vaccines

Whole-cell killed or live-attenuated vaccines possess multiple epitopes to the host and therefore, can potentially induce a robust immunologic response against pathogen [97]. They are traditionally developed vaccines with advanced technology and may become the leading candidates to put into a clinical trial against SARS-CoV-2 infection.

Subunit vaccines contain one or more antigens with strong immunogenicity capable of efficiently activating the host immune system. Usually, these require the addition of adjuvants to elicit a prompt and strong immune response. The earlier research on coronavirus indicated that N, E, and M proteins are not suitable antigens for vaccine development because of the highly conserved region in the coronavirus and the weak immune response produced by N, E and M. Furthermore, it was established that out of the two subunits of S protein, S2 is 99% conserved and the variation resides in the RBD region of S1 subunit which is used in ACE-2 interaction and virus entry into host cell [17]. Therefore, inhibiting virus entry is a prime strategy to prevent viral infection. So far, a number of SARS-CoV-2 subunit vaccines are under the process of development and the majority of them uses the S protein as antigen.

With the advancements in mRNA synthesis, modification, and delivery technology, the development of mRNA vaccines has regained attention in the recent past. Furthermore, mRNA vaccines could be a better alternative to traditional vaccines; they are highly potent, can be easily produced, cost-effective, and safe [98]. The mRNA vaccine production includes antigen selection, sequence optimization, altered nucleotide screening, delivery system optimization, immune response and safety evaluation [99]. One of the plausible short coming of mRNA-based vaccine could be the storage and transportation in developing and under-developed countries due the stability of mRNA vaccine in deep freezer at -70 to 80 °C. On November 9, Pfizer and BioNTech announced the successful completion of a phase 3 clinical trial of their mRNA vaccine candidate BNT162b2, and reported that the vaccine was found more than 90 percent effective after first dose and three weeks later after the second dose and 95% effective irrespective of age, gender, race and demographics [100]. Just a week later, Moderna has announced 94.5% efficacy of its vaccine candidate mRNA-1273 against COVID-19 infection [101]. On December 9, 2020 Pfizer/BioNTech vaccine got approval from FDA [102]. Later on December 30, the Oxford-AstraZeneca vaccine has been approved for emergency use in the UK [103]

DNA vaccines are usually comprised of plasmid DNA molecules encoding one or more antigens. They are considered better than mRNA vaccines in terms of stability and delivery efficiency. However, DNA vaccines have an associated risk of vector integration and mutations in the host genome [104].

Table 3. List of candidate vaccine (under progress) with the description of type, developer and phases of clinical trials.

Details of the Vaccine				Clinical trial status			
No	**Candidate Name**	**Type of vaccine**	**Developer**	**Phase**	**Doses (days)**	**Sample size & age**	**Description**
1	BBV152	Whole-Virion Inactivated	*Bharat* Biotech	Phase 2 Completed	2 (0, 28)	755 P, ≥ 18 years	Adaptive Randomized, Double-blind, Multicenter [116]
2	CoronaVac	Whole-Virion Inactivated	Sinovac	Phase 3	2 (0, 14)	13060 P, 18-59 ≥ 60 years	Randomized, Double-blind, placebo controlled [117]
3	Inactivated SARS-CoV-2 Vaccine (Vero cell)	Whole-Virion Inactivated	Beijing Institute of Biological Products/Sinopharm	Phase 3	2 (0, 21)	45000 P, ≥ 18 years	Multicenter, Randomized, Double Blind, Parallel Placebo Controlled [118]
4	AZD1222	Non-replicating viral vector (ChAdOx1-S)	University of Oxford/AstraZeneca	Phase 3 Completed	2 (0, 28)	40,000 P, ≥ 18 years	Randomized, Double-blind, placebo controlled, multicenter [119]
5	Ad5-nCoV	Non-replicating viral vector (Adenovirus Type 5)	CanSino Biological Inc	Phase 3	1	40,000P, ≥ 18 years	Randomized, Double-blind, Placebo-controlled [120]
6	Ad26.COV2.S	Non-Replicating Viral Vector	Janssen Pharmaceutical Companies	Phase 3	2 (0, 21)	30,000 P, (18-55) years	Randomized, Double-blind, Placebo-controlled [121]
7	TMV-083	Replicating viral vector	Institute Pasteur	Phase 1	2 (0, 28)	90 P, ≥ 18 years	Randomized, two center, Placebo-controlled Trial [122]
8	Gam-COVID-VacLyo (Sputnik V)	Non-replicating viral vector	Gamaleya Research Institute	Phase 3	2 (0, 21)	40,000 P, ≥ 18 years	Open-label, Non-Randomized, Parallel Assignment, two-stage study [123]
9	m-RNA 1273	LNP-encapsulated m-RNA	Moderna/NIAID	Phase 3	2 (0, 28)	30000 P, ≥ 18 years	Randomized, observer blind, placebo-controlled [124]
10	BNT162b1 BNT162b2	LNP m-RNAs	BioNTech/ Pfizer	Phase 3 Completed	2 (0, 28)	43998 P, 18-85 years	Randomized, observer blind, placebo-controlled study [125]
11	CVnCoV	mRNA	Curevac	Phase 2a	2 (0, 28)	691 P, 18-60) years	Randomized, Observer-blind, Multicenter, Controlled, [126]
12	ARCT-021	mRNA	Arcturus/Duke-NUS	Phase 1/2	1	92 P, 21- 55 & 56-80 years	A Randomised, Double Blinded, Placebo Controlled, participants in two age group [127]
13	LNP-nCoVsaRNA	RNA	Imperial College London	Phase 1	1	320 P, 18-45 & 18-75 years	Open label, non-randomized, phase participants, two age group [128]
14	nCov Vaccine	DNA plasmid vaccine	Cadila Healthcare Limited	Phase 1/2	3 (0, 28, 56)	1048 P, 18-55 years	Prospective, randomized, adaptive, clinical study [129]
15	GX-19	DNA Vaccine	Genexine Consortium	Phase 1/2a	2 (0, 28)	210 P, ≥ 18 years	Multi-center, Randomized, Double-blind, Placebo-controlled Study participants in healthy adult [130]
16	INO-4800	DNA plasmid vaccine with electroporation	Inovio Pharmaceuticals	Phase 1/2a	2 (0, 28)	160 P, 19-64 years	randomized, open label and double-blind study [131]
17	AG0301-COVID19	DNA plasmid vaccine + Adjuvant	Osaka University/ AnGes/ Takara Bio	Phase 1/2	2 (0, 14)	30 P, 20-65 years	Non-randomized, Open-label, Non-controlled [132]
18	SARS-CoV-2 rS	Protein Subunit (Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Novavax	Phase 1/2	2 (0, 21)	1419 P, 18-59 years	Randomized, Observer-Blinded [133]
19	KBP-COVID-19	Protein Subunit (RBD based)	Kentucky Bioprocessing, Inc	Phase 1/2	2 (0, 21)	180 P, 18-49 & 50-70 years	First-in-human, Observer-blinded, Randomized, Placebo-controlled, Parallel Group Study in two Age group, [134]
20	Recombinant new corona vaccine	Protein subunit (Adjuvanted recombinant protein (RBD-Dimer)	Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences	Phase 3	3 (0, 30, 60)	29000 P, 18-59 years	Randomized, Blinded, Placebo-controlled [135]
21	COVAX-19	Recombinant spike protein with Advax™ adjuvant	Vaxine Pty Ltd/Medytox	Phase 1	1	40 P, 18-65 years	Randomized, Controlled study [136]
22	Coronavirus-Like Particle COVID-19 Vaccine	Plant-derived VLP adjuvanted with CpG 1018 or AS03	Medicago Inc.	Phase 2/3	2 (0, 21)	30612 P, 18-55 years	Randomized, Partially-Blinded, Dose-Ranging Study in [137]

Live vector vaccines are live viruses (the vector) that possess miscellaneous antigen(s). The vaccines show strong immunogenicity and safety like live attenuated vaccines and subunit vaccines respectively and are widely used to induce cellular immunity.

Synthetic Peptide/Epitope Vaccines carry only certain shreds of intact antigens and are generally prepared by chemical synthesis technique. Although the preparation and quality control processes are simple, vaccines impart low immunogenicity due to the low molecular weight and structural complexity. Therefore, structural alterations, delivery systems, and adjuvants are prerequisite in their formulation [105].

David Curiel and their colleagues created a chimpanzee adenovirus vectored vaccine encoding a prefusion stabilized spike protein (ChAd-SARS-CoV-2-S) and evaluated the efficacy in SARS-CoV-2 infected bioengineered mice expressing the human ACE-2 receptor [106]. The study reported that intranasal administration of ChAd-SARS-CoV-2-S induced a strong and better immune response to those receiving intramuscular injection. Furthermore, no remnants of the virus were found in nasopharyngeal tracts in intranasal dosing, whereas traces of viral RNA were present in the lungs of mice in intramuscular dosing [96]. In parallel, another team reported the genesis of a candidate vaccine having a replication-incompetent recombinant serotype 5 adenovirus, Ad5-S-nb2, carrying a codon-optimized gene encoding Spike protein (S) and evaluated the potency in mice and rhesus macaques. The team considered the time interval as an important factor and reported that a single dose intramuscular or intranasal administration of the vaccine produced immunity against SARS-CoV-2 after 30 days of the first vaccination [107].

Plant based biomolecules were found successful in boosting the immune response and giving tolerance to viral infections. However, the use of plants for the development of vaccines, and antiviral agents are of limited use [108].

On a different track from traditional vaccine development methods of using killed or attenuated viruses, Medicago proposed a plant-based vaccine. Although, the details are confidential, the basic idea is to develop a virus-like particle (VLP) that mimics the appearance and conformation of SARS-CoV-2, and its subsequent expression in tobacco plant to form subunit proteins. For large scale production of vaccine doses, the company also plans to use adjuvant with VLP [109]

A recent study by Rajapaksha *et. al.* showed that the phytochemicals (taepeenin J and Nortaepeenin B) found in existing Ayurveda drugs have the ability to inhibit the Interleukin 6 (IL-6R) and Interleukin 1 (IL-1R) receptors and are the potential candidates for further in vitro studies for the development of medicine against cytokine storm on behalf of SARS-COV-2 infected patients. The study was proved through computational investigation of possible allosteric inhibitory actions on IL-6R and IL-1R using selected phytochemicals [110].

8. Conclusion

COVID-19 is not only a massive health crisis but also a threat to human life and development globally. The pandemic is moving like a wave leaving in deaths, damaging immune systems, and weakening economies globally. Though, the virus went with some mutations and its severity is weakening, the transmission is still very high. Currently, the world is re-opening but the healing is uncertain as the incidence of new cases is constantly increasing and some countries are going on lockdown again. To treat a viral disease, vaccination and use of antivirals are the available way outs. The vaccine development is a tedious and lengthy process and some of the approved vaccines for emergency use arrived very recently came in the year 2020-21. Therefore, taking the second option of using antivirals, scientists started the repurposing of existing drugs to treat COVID-19 patients. However, in various clinical trials, the drugs did not show efficacy and in some cases produced many side effects. To overcome the limitations, combination of drugs/multidrug is being evaluated and positive results have come forth in few studies. The nature of virus is very unpredictable, specifically, its new variants due to the mutations in the spike RBD region, but novel information is continuously being added about the nature and mechanism of viral action. Therefore, the longevity of any existing drug could not be ascertained. Moreover, looking at the past pandemics, the arrival of another pandemic era cannot be ruled out. New approaches to treat/manage coronaviruses infections are the need of the hour considering the overall global scenario.

Plant based products are being used since ancient times against infectious diseases. Plant based vaccines have also passed the phase 1 clinical trial and have entered in phase 2/3. Phytochemicals like alkaloids, flavonoids, saponins, terpenoids, and essential oils possess strong antioxidant properties and could give promising results in developing antivirals and managing the severity of disease. Structural modifications in existing drugs by reducing the toxicity and improving efficacy may also be useful in disease control.

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References

[1]. Zhang, Q.; Wang, Y.; Qi, C.; Shen, L.; Li, J. *J. Med. Virol.* **2020**, *92* (6), 540–545.
[2]. Lai, C.-C.; Shih, T.-P.; Ko, W.-C.; Tang, H.-J.; Hsueh, P.-R. *Int. J. Antimicrob. Agents* **2020**, *55* (3), 105924.
[3]. Zhang, C.; Zheng, W.; Huang, X.; Bell, E. W.; Zhou, X.; Zhang, Y. *J. Proteome Res.* **2020**, *19* (4), 1351–1360.
[4]. Rohde, R., Novel Coronavirus (2019-nCoV) Update: Uncoating the Virus https://asm.org/Articles/2020/January/2019-Novel-Coronavirus-2019-nCoV-Update-Uncoating (accessed December 9, 2020).
[5]. Yamamoto, N.; Bauer, G. *Med. Hypotheses* **2020**, *144* (110160), 110160.
[6]. Toyoshima, Y.; Nemoto, K.; Matsumoto, S.; Nakamura, Y.; Kiyotani, K. *J. Hum. Genet.* **2020**, *65* (12), 1075–1082.
[7]. WHO Coronavirus (COVID-19) Dashboard https://covid19.who.int/ (accessed December 9, 2020).
[8]. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D. G. *PLoS Med.* **2009**, *6* (7), e1000097.
[9]. Chan, J. F.-W.; To, K. K.-W.; Tse, H.; Jin, D.-Y.; Yuen, K.-Y. *Trends Microbiol.* **2013**, *21* (10), 544–555.
[10]. Wu, F.; Zhao, S.; Yu, B.; Chen, Y.-M.; Wang, W.; Song, Z.-G.; Hu, Y.; Tao, Z.-W.; Tian, J.-H.; Pei, Y.-Y.; Yuan, M.-L.; Zhang, Y.-L.; Dai, F.-H.; Liu, Y.;

Wang, Q.-M.; Zheng, J.-J.; Xu, L.; Holmes, E. C.; Zhang, Y.-Z. *Nature* **2020**, *579* (7798), 265–269.
[11]. Wu, A.; Peng, Y.; Huang, B.; Ding, X.; Wang, X.; Niu, P.; Meng, J.; Zhu, Z.; Zhang, Z.; Wang, J.; Sheng, J.; Quan, L.; Xia, Z.; Tan, W.; Cheng, G.; Jiang, T. *Cell Host Microbe* **2020**, *27* (3), 325–328.
[12]. Li, B.; Si, H.-R.; Zhu, Y.; Yang, X.-L.; Anderson, D. E.; Shi, Z.-L.; Wang, L.-F.; Zhou, P. D. *mSphere* **2020**, *5* (1). https://doi.org/10.1128/msphere.00807-19.
[13]. Rothan, H. A.; Byrareddy, S. N. *J. Autoimmun.* **2020**, *109* (102433), 102433.
[14]. Wu, C.; Liu, Y.; Yang, Y.; Zhang, P.; Zhong, W.; Wang, Y.; Wang, Q.; Xu, Y.; Li, M.; Li, X.; Zheng, M.; Chen, L.; Li, H. *Acta Pharm. Sin. B.* **2020**, *10* (5), 766–788.
[15]. Chen, Y.; Liu, Q.; Guo, D. *J. Med. Virol.* **2020**, *92* (4), 418–423.
[16]. Marian, A. J. *Cardiovasc. Pathol.* **2021**, *50* (107278), 107278.
[17]. Wan, Y.; Shang, J.; Graham, R.; Baric, R. S.; Li, F. *J. Virol.* **2020**, *94* (7). https://doi.org/10.1128/jvi.00127-20.
[18]. Young, B. E.; Fong, S.-W.; Chan, Y.-H.; Mak, T.-M.; Ang, L. W.; Anderson, D. E.; Lee, C. Y.-P.; Amrun, S. N.; Lee, B.; Goh, Y. S.; Su, Y. C. F.; Wei, W. E.; Kalimuddin, S.; Chai, L. Y. A.; Pada, S.; Tan, S. Y.; Sun, L.; Parthasarathy, P.; Chen, Y. Y. C.; Barkham, T.; Lin, R. T. P.; Maurer-Stroh, S.; Leo, Y.-S.; Wang, L.-F.; Renia, L.; Lee, V. J.; Smith, G. J. D.; Lye, D. C.; Ng, L. F. P. *Lancet* **2020**, *396* (10251), 603–611.
[19]. Mercatelli, D.; Giorgi, F. M. *Front. Microbiol.* **2020**, *11*. https://doi.org/10.3389/fmicb.2020.01800.
[20]. Dearlove, B.; Lewitus, E.; Bai, H.; Li, Y.; Reeves, D. B.; Joyce, M. G.; Scott, P. T.; Amare, M. F.; Vasan, S.; Michael, N. L.; Modjarrad, K.; Rolland, M. *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117* (38), 23652–23662.
[21]. Grubaugh, N. D.; Hanage, W. P.; Rasmussen, A. L. *Cell* **2020**, *182* (4), 794–795.
[22]. Starr, T. N.; Greaney, A. J.; Hilton, S. K.; Ellis, D.; Crawford, K. H. D.; Dingens, A. S.; Navarro, M. J.; Bowen, J. E.; Tortorici, M. A.; Walls, A. C.; King, N. P.; Veesler, D.; Bloom, J. D. *Cell* **2020**, *182* (5), 1295-1310.e20.
[23]. Rambaut, A.; Loman, N.; Pybus, O.; Barclay, W.; Barrett,J.; Carabelli,A.; Connor, T.; Peacock,T.; Robertson,D. L.; Volz, E. Preliminary genomic characterization of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563 (accessed December 9, 2020).
[24]. Santos, J. C.; Passos, G. A. *bioRxiv*, 2021. https://doi.org/10.1101/2020.12.29.424708.
[25]. Hoffmann, M.; Kleine-Weber, H.; Krüger, N.; Müller, M.; Drosten, C.; Pöhlmann, S. *bioRxiv*, 2020. https://doi.org/10.1101/2020.01.31.929042.
[26]. Gralinski, L. E.; Menachery, V. D. *Viruses* **2020**, *12* (2), 135.
[27]. Xu, X.; Chen, P.; Wang, J.; Feng, J.; Zhou, H.; Li, X.; Zhong, W.; Hao, P. *Sci. China Life Sci.* **2020**, *63* (3), 457–460.
[28]. Raj, V. S.; Mou, H.; Smits, S. L.; Dekkers, D. H. W.; Müller, M. A.; Dijkman, R.; Muth, D.; Demmers, J. A. A.; Zaki, A.; Fouchier, R. A. M.; Thiel, V.; Drosten, C.; Rottier, P. J. M.; Osterhaus, A. D. M. E.; Bosch, B. J.; Haagmans, B. L. *Nature* **2013**, *495* (7440), 251–254.
[29]. Jaimes, J. A.; Millet, J. K.; Whittaker, G. R. *iScience* **2020**, *23* (6), 101212.
[30]. Lukassen, S.; Chua, R. L.; Trefzer, T.; Kahn, N. C.; Schneider, M. A.; Muley, T.; Winter, H.; Meister, M.; Veith, C.; Boots, A. W.; Hennig, B. P.; Kreuter, M.; Conrad, C.; Eils, R. *EMBO J.* **2020**, *39* (10), e105114.
[31]. Melenotte, C.; Silvin, A.; Goubet, A.-G.; Lahmar, I.; Dubuisson, A.; Zumla, A.; Raoult, D.; Merad, M.; Gachot, B.; Hénon, C.; Solary, E.; Fontenay, M.; André, F.; Maeurer, M.; Ippolito, G.; Piacentini, M.; Wang, F.-S.; Ginhoux, F.; Marabelle, A.; Kroemer, G.; Derosa, L.; Zitvogel, L. *Oncoimmunology* **2020**, *9* (1), 1807836.
[32]. Mehta, P.; McAuley, D. F.; Brown, M.; Sanchez, E.; Tattersall, R. S.; Manson, J. J. *Lancet* **2020**, *395* (10229), 1033–1034.
[33]. Akhmerov, A.; Marbán, E. *Circ. Res.* **2020**, *126* (10), 1443–1455.
[34]. Martín-Rojas, R. M.; Pérez-Rus, G.; Delgado-Pinos, V. E.; Domingo-González, A.; Regalado-Artamendi, I.; Alba-Urdiales, N.; Demelo-Rodríguez, P.; Monsalvo, S.; Rodríguez-Macías, G.; Ballesteros, M.; Osorio-Prendes, S.; Díez-Martín, J. L.; Pascual Izquierdo, C. *Eur. J. Haematol.* **2020**, *105* (6), 741–750.
[35]. Reddy, S. T.; Garg, T.; Shah, C.; Nascimento, F. A.; Imran, R.; Kan, P.; Bowry, R.; Gonzales, N.; Barreto, A.; Kumar, A.; Volpi, J.; Misra, V.; Chiu, D.; Gadhia, R.; Savitz, S. I. *Case Rep. Neurol.* **2020**, *12* (2), 199–209.
[36]. Baig, A. M.; Khaleeq, A.; Ali, U.; Syeda, H. *ACS Chem. Neurosci.* **2020**, *11* (7), 995–998.
[37]. Bittmann, S.; Weissenstein, A.; Villalon, G.; Moschuring-Alieva, E.; Luchter, E. *J. Clin. Med. Res.* **2020**, *12* (5), 320–322.
[38]. Solomon, I. H.; Normandin, E.; Bhattacharyya, S.; Mukerji, S. S.; Keller, K.; Ali, A. S.; Adams, G.; Hornick, J. L.; Padera, R. F., Jr; Sabeti, P. *N. Engl. J. Med.* **2020**, *383* (10), 989–992.
[39]. Mao, L.; Jin, H.; Wang, M.; Hu, Y.; Chen, S.; He, Q.; Chang, J.; Hong, C.; Zhou, Y.; Wang, D.; Miao, X.; Li, Y.; Hu, B. *JAMA Neurol.* **2020**, *77* (6), 683–690.
[40]. Poland, G. A.; Ovsyannikova, I. G.; Kennedy, R. B. *Lancet* **2020**, *396* (10262), 1595–1606.
[41]. Stephens, D. S.; McElrath, M. J. *JAMA* **2020**, *324* (13), 1279–1281.
[42]. Zeng, H.; Xu, C.; Fan, J.; Tang, Y.; Deng, Q.; Zhang, W.; Long, X. *JAMA* **2020**, *323* (18), 1848–1849.
[43]. Addetia, A.; Crawford, K. H. D.; Dingens, A.; Zhu, H.; Roychoudhury, P.; Huang, M.-L.; Jerome, K. R.; Bloom, J. D.; Greninger, A. L. *J. Clin. Microbiol.* **2020**, *58* (11). https://doi.org/10.1128/JCM.02107-20.
[44]. Iwasaki, A. *Lancet Infect. Dis.* **2021**, *21* (1), 3–5.
[45]. Organization, W. H. *Coronavirus Disease 2019 (COVID-19) Situation Report–51*; World Health Organization: Geneva, Switzerland, 2020.
[46]. Qu, G.; Li, X.; Hu, L.; Jiang, G. *Environ. Sci. Technol.* **2020**, *54* (7), 3730–3732.
[47]. Weber, D. J.; Rutala, W. A.; Fischer, W. A.; Kanamori, H.; Sickbert-Bennett, E. E. *Am. J. Infect. Control* **2016**, *44* (5), e91–e100.
[48]. Wang, W.; Xu, Y.; Gao, R.; Lu, R.; Han, K.; Wu, G.; Tan, W. *JAMA* **2020**, *323* (18), 1843–1844.
[49]. Peiris, J. S. M.; Chu, C. M.; Cheng, V. C. C.; Chan, K. S.; Hung, I. F. N.; Poon, L. L. M.; Law, K. I.; Tang, B. S. F.; Hon, T. Y. W.; Chan, C. S.; Chan, K. H.; Ng, J. S. C.; Zheng, B. J.; Ng, W. L.; Lai, R. W. M.; Guan, Y.; Yuen, K. Y. *Lancet* **2003**, *361* (9371), 1767–1772.
[50]. Casanova, L.; Rutala, W. A.; Weber, D. J.; Sobsey, M. D. *Water Res.* **2009**, *43* (7), 1893–1898.
[51]. Yu, I. T. S.; Li, Y.; Wong, T. W.; Tam, W.; Chan, A. T.; Lee, J. H. W.; Leung, D. Y. C.; Ho, T. *N. Engl. J. Med.* **2004**, *350* (17), 1731–1739.
[52]. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; Cheng, Z.; Yu, T.; Xia, J.; Wei, Y.; Wu, W.; Xie, X.; Yin, W.; Li, H.; Liu, M.; Xiao, Y.; Gao, H.; Guo, L.; Xie, J.; Wang, G.; Jiang, R.; Gao, Z.; Jin, Q.; Wang, J.; Cao, B. *Lancet* **2020**, *395* (10223), 497–506.
[53]. Wu, Z.; McGoogan, J. M. *JAMA* **2020**, *323* (13), 1239–1242.
[54]. Bhopal, S. S.; Bhopal, R. *Lancet* **2020**, *396* (10250), 532–533.
[55]. Chen, H.; Guo, J.; Wang, C.; Luo, F.; Yu, X.; Zhang, W.; Li, J.; Zhao, D.; Xu, D.; Gong, Q.; Liao, J.; Yang, H.; Hou, W.; Zhang, Y. *Lancet* **2020**, *395* (10226), 809–815.
[56]. Walker, K. F.; O'Donoghue, K.; Grace, N.; Dorling, J.; Comeau, J. L.; Li, W.; Thornton, J. G. *BJOG* **2020**, *127* (11), 1324–1336.
[57]. Trevisanuto, D.; Cavallin, F.; Cavicchiolo, M. E.; Borellini, M.; Calgaro, S.; Baraldi, E. *Arch. Dis. Child. Fetal Neonatal Ed.* **2020**, fetalneonatal-2020-319837.
[58]. Stokes, E. K.; Zambrano, L. D.; Anderson, K. N.; Marder, E. P.; Raz, K. M.; El Burai Felix, S.; Tie, Y.; Fullerton, K. E. *MMWR Morb. Mortal. Wkly. Rep.* **2020**, *69* (24), 759–765.
[59]. Heald-Sargent, T.; Muller, W. J.; Zheng, X.; Rippe, J.; Patel, A. B.; Kociolek, L. K. *JAMA Pediatr.* **2020**, *174* (9), 902–903.
[60]. Zimmer, C.; Corum, J.; Wee, S.-L. Coronavirus Vaccine Tracker. *The New York times*. The New York Times April 1, 2021, https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html (accessed April 1, 2021).
[61]. Elfiky, A. A. *Life Sci.* **2020**, *248* (117477), 117477.
[62]. Li, G.; De Clercq, E. *Nat. Rev. Drug Discov.* **2020**, *19* (3), 149–150.
[63]. Radhakrishnan, A.; Arunachalam, R.; Elango, A. *SSRN Electron. J.* **2020**. https://doi.org/10.2139/ssrn.3636958.
[64]. Agrawal, U.; Raju, R.; Udwadia, Z. F. *Med J. Armed Forces India* **2020**, *76* (4), 370–376.
[65]. Cai, Q.; Yang, M.; Liu, D.; Chen, J.; Shu, D.; Xia, J.; Liao, X.; Gu, Y.; Cai, Q.; Yang, Y.; Shen, C.; Li, X.; Peng, L.; Huang, D.; Zhang, J.; Zhang, S.; Wang, F.; Liu, J.; Chen, L.; Chen, S.; Wang, Z.; Zhang, Z.; Cao, R.; Zhong, W.; Liu, Y.; Liu, L. *Engineering (Beijing)* **2020**, *6* (10), 1192–1198.
[66]. Li H.; Wang Y. M.; Xu J. Y.; Cao B. *Zhonghua Jie He He Hu Xi Za Zhi* **2020**, *43* (0), E002.
[67]. Holshue, M. L.; DeBolt, C.; Lindquist, S.; Lofy, K. H.; Wiesman, J.; Bruce, H.; Spitters, C.; Ericson, K.; Wilkerson, S.; Tural, A.; Diaz, G.; Cohn, A.; Fox, L.; Patel, A.; Gerber, S. I.; Kim, L.; Tong, S.; Lu, X.; Lindstrom, S.; Pallansch, M. A.; Weldon, W. C.; Biggs, H. M.; Uyeki, T. M.; Pillai, S. K. *N. Engl. J. Med.* **2020**, *382* (10), 929–936.
[68]. Beigel, J. H.; Tomashek, K. M.; Dodd, L. E.; Mehta, A. K.; Zingman, B. S.; Kalil, A. C.; Hohmann, E.; Chu, H. Y.; Luetkemeyer, A.; Kline, S.; Lopez de Castilla, D.; Finberg, R. W.; Dierberg, K.; Tapson, V.; Hsieh, L.; Patterson, T. F.; Paredes, R.; Sweeney, D. A.; Short, W. R.; Touloumi, G.; Lye, D. C.; Ohmagari, N.; Oh, M.-D.; Ruiz-Palacios, G. M.; Benfield, T.; Fätkenheuer, G.; Kortepeter, M. G.; Atmar, R. L.; Creech, C. B.; Lundgren, J.; Babiker, A. G.; Pett, S.; Neaton, J. D.; Burgess, T. H.; Bonnett, T.; Green, M.; Makowski, M.; Osinusi, A.; Nayak, S.; Lane, H. C. *N. Engl. J. Med.* **2020**, *383* (19), 1813–1826.
[69]. Case Medical Research. *Case Medical Research* **2020**. https://doi.org/10.31525/ct1-nct04292730 (accessed December 9, 2020).
[70]. Cao, B.; Wang, Y.; Wen, D.; Liu, W.; Wang, J.; Fan, G.; Ruan, L.; Song, B.; Cai, Y.; Wei, M.; Li, X.; Xia, J.; Chen, N.; Xiang, J.; Yu, T.; Bai, T.; Xie, X.; Zhang, L.; Li, C.; Yuan, Y.; Chen, H.; Li, H.; Huang, H.; Tu, S.; Gong, F.; Liu, Y.; Wei, Y.; Dong, C.; Zhou, F.; Gu, X.; Xu, J.; Liu, Z.; Zhang, Y.; Li, H.; Shang, L.; Wang, K.; Li, K.; Zhou, X.; Dong, X.; Qu, Z.; Lu, S.; Hu, X.; Ruan, S.; Luo, S.; Wu, J.; Peng, L.; Cheng, F.; Pan, L.; Zou, J.; Jia, C.; Wang, J.; Liu, X.; Wang, S.; Wu, X.; Ge, Q.; He, J.; Zhan, H.; Qiu, F.; Guo, L.; Huang, C.; Jaki, T.; Hayden, F. G.; Horby, P. W.; Zhang, D.; Wang, C. *N. Engl. J. Med.* **2020**, *382* (19), 1787–1799.
[71]. Hung, I. F.-N.; Lung, K.-C.; Tso, E. Y.-K.; Liu, R.; Chung, T. W.-H.; Chu, M.-Y.; Ng, Y.-Y.; Lo, J.; Chan, J.; Tam, A. R.; Shum, H.-P.; Chan, V.; Wu, A. K.-L.; Sin, K.-M.; Leung, W.-S.; Law, W.-L.; Lung, D. C.; Sin, S.; Yeung, P.; Yip,

C. C.-Y.; Zhang, R. R.; Fung, A. Y.-F.; Yan, E. Y.-W.; Leung, K.-H.; Ip, J. D.; Chu, A. W.-H.; Chan, W.-M.; Ng, A. C.-K.; Lee, R.; Fung, K.; Yeung, A.; Wu, T.-C.; Chan, J. W.-M.; Yan, W.-W.; Chan, W.-M.; Chan, J. F.-W.; Lie, A. K.-W.; Tsang, O. T.-Y.; Cheng, V. C.-C.; Que, T.-L.; Lau, C.-S.; Chan, K.-H.; To, K. K.-W.; Yuen, K.-Y. *Lancet* **2020**, *395* (10238), 1695–1704.

[72]. Lopinavir/Ritonavir for the Treatment of COVID-19 Positive Patients With Cancer and Immune Suppression in the Last Year https://clinicaltrials.gov/ct2/show/NCT04455958 (accessed December 9, 2020).

[73]. Dong, L.; Hu, S.; Gao, J. *Drug Discov. Ther.* **2020**, *14* (1), 58–60.

[74]. Lee, J. S.; Shin, E.-C. *Nat. Rev. Immunol.* **2020**, *20* (10), 585–586.

[75]. Zhou, Q.; Chen, V.; Shannon, C. P.; Wei, X.-S.; Xiang, X.; Wang, X.; Wang, Z.-H.; Tebbutt, S. J.; Kollmann, T. R.; Fish, E. N. *Front. Immunol.* **2020**, *11*, 1061.

[76]. Colson, P.; Rolain, J.-M.; Lagier, J.-C.; Brouqui, P.; Raoult, D. *Int. J. Antimicrob. Agents* **2020**, *55* (4), 105932.

[77]. Jie, Z.; He, H.; Xi, H.; Zhi, Z. *Zhonghua Jie He He Hu Xi Za Zhi* **2020**, *43* (3), 185–188.

[78]. Gao, J.; Tian, Z.; Yang, X. *Biosci. Trends* **2020**, *14* (1), 72–73.

[79]. Gautret, P.; Lagier, J.-C.; Parola, P.; Hoang, V. T.; Meddeb, L.; Sevestre, J.; Mailhe, M.; Doudier, B.; Aubry, C.; Amrane, S.; Seng, P.; Hocquart, M.; Eldin, C.; Finance, J.; Vieira, V. E.; Tissot-Dupont, H. T.; Honoré, S.; Stein, A.; Million, M.; Colson, P.; La Scola, B.; Veit, V.; Jacquier, A.; Deharo, J.-C.; Drancourt, M.; Fournier, P. E.; Rolain, J.-M.; Brouqui, P.; Raoult, D. *Travel Med. Infect. Dis.* **2020**, *34* (101663), 101663.

[80]. "Solidarity" clinical trial for COVID-19 treatments https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments (accessed December 9, 2020).

[81]. Randomised Evaluation of COVID-19 Therapy - Full Text View - ClinicalTrials.Gov https://clinicaltrials.gov/ct2/show/ (accessed December 9, 2020).

[82]. Mehra, M. R.; Ruschitzka, F.; Patel, A. N. *Lancet* **2020**, *395* (10240), 1820.

[83]. Torjesen, I. *BMJ* **2020**, *369*, m2263.

[84]. Evaluating the Efficacy of Hydroxychloroquine and Azithromycin to Prevent Hospitalization or Death in Persons With COVID-19 https://clinicaltrials.gov/ct2/show/NCT04358068 (accessed December 9, 2020).

[85]. Waldrop, T.; Alsup, D.; McLaughlin, E. C. Here's What You Need to Know about Chloroquine. *CNN*. March 24, 2020. https://edition.cnn.com/2020/03/23/health/arizona-coronavirus-chloroquine-death/index.html (accessed December 9, 2020).

[86]. Consortium. *Lancet* **2012**, *379* (9822), 1214–1224.

[87]. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia https://www.roche.com/investors/updates/inv-update-2020-07-29.htm (accessed December 9, 2020).

[88]. Cortegiani, A.; Ippolito, M.; Greco, M.; Granone, V.; Protti, A.; Gregoretti, C.; Giarratano, A.; Einav, S.; Cecconi, M. *Pulmonology* **2021**, *27* (1), 52–66.

[89]. Organization, W. H. Clinical Management of COVID-19: Interim Guidance. *World Health Organization* **2020**.

[90]. Chen, L.; Xiong, J.; Bao, L.; Shi, Y. Convalescent Plasma as a Potential Therapy for COVID-19. *Lancet Infect. Dis.* **2020**, *20* (4), 398–400.

[91]. Joyner, M. J.; Bruno, K. A.; Klassen, S. A.; Kunze, K. L.; Johnson, P. W.; Lesser, E. R.; Wiggins, C. C.; Senefeld, J. W.; Klompas, A. M.; Hodge, D. O.; Shepherd, J. R. A.; Rea, R. F.; Whelan, E. R.; Clayburn, A. J.; Spiegel, M. R.; Baker, S. E.; Larson, K. F.; Ripoll, J. G.; Andersen, K. J.; Buras, M. R.; Vogt, M. N. P.; Herasevich, V.; Dennis, J. J.; Regimbal, R. J.; Bauer, P. R.; Blair, J. E.; van Buskirk, C. M.; Winters, J. L.; Stubbs, J. R.; van Helmond, N.; Butterfield, B. P.; Sexton, M. A.; Diaz Soto, J. C.; Paneth, N. S.; Verdun, N. C.; Marks, P.; Casadevall, A.; Fairweather, D.; Carter, R. E.; Wright, R. S. *Mayo Clin. Proc.* **2020**, *95* (9), 1888–1897.

[92]. Xia, X.; Li, K.; Wu, L.; Wang, Z.; Zhu, M.; Huang, B.; Li, J.; Wang, Z.; Wu, W.; Wu, M.; Li, W.; Li, L.; Cai, Y.; Bosco, B.; Zhong, A.; Liu, X.; Lv, T.; Gan, Z.; Chen, G.; Pan, Y.; Liu, C.; Zhang, K.; Xu, X.; Wang, C.; Wang, Q. *Blood* **2020**, *136* (6), 755–759.

[93]. Remy, V.; Largeron, N.; Quilici, S.; Carroll, S. *Value Health* **2014**, *17* (7), A450.

[94]. Neher, R. A.; Dyrdak, R.; Druelle, V.; Hodcroft, E. B.; Albert, J. *Swiss Med. Wkly* **2020**, *150*, w20224.

[95]. Zhang, J.; Zeng, H.; Gu, J.; Li, H.; Zheng, L.; Zou, Q. *Vaccines (Basel)* **2020**, *8* (2), 153.

[96]. Singh, D.; Yi, S. V. *Exp. Mol. Med.* **2021**. https://doi.org/10.1038/s12276-021-00604-z

[97]. Sharma, A.; Krause, A.; Worgall, S. *Hum. Vaccin.* **2011**, *7* (10), 999–1011.

[98]. Pardi, N.; Hogan, M. J.; Porter, F. W.; Weissman, D. *Nat. Rev. Drug Discov.* **2018**, *17* (4), 261–279.

[99]. Jahanafrooz, Z.; Baradaran, B.; Mosafer, J.; Hashemzaei, M.; Rezaei, T.; Mokhtarzadeh, A.; Hamblin, M. R. *Drug Discov. Today* **2020**, *25* (3), 552–560.

[100]. Adnal, M. Pfizer concludes phase 3 study of COVID-19 vaccine candidate, says it's 95% effective https://www.oneindia.com/international/pfizer-concludes-phase-3-study-of-covid-19-vaccine-candidate-says-it-s-95-effective-3178319.html (accessed December 9, 2020).

[101]. Herper, M.; Branswell, H.; McFarling, U. L.; Florko, N.; St. Fleur, N. Moderna's Covid-19 vaccine is strongly effective, early look at data show https://www.statnews.com/2020/11/16/modernas-covid-19-vaccine-is-strongly-effective-early-look-at-data-show/ (accessed December 9, 2020).

[102]. Burton, T. M.; Hopkins, J. S. FDA Set to Release Analyses of the Pfizer-BioNTech Covid-19 Vaccine. *Wall Street journal (Eastern ed.)*. wsj.com December 8, 2020. https://www.wsj.com/articles/fda-set-to-release-analyses-of-the-pfizer-biontech-covid-19-vaccine-11607423403 (accessed December 9, 2020).

[103]. Triggle, J. G. A. Covid-19: Oxford-AstraZeneca Vaccine Approved for Use in UK. *BBC*. December 30, 2020. https://www.bbc.com/news/health-55280671 (accessed December 9, 2020).

[104]. Liu, M. A. *Vaccines (Basel)* **2019**, *7* (2), 37.

[105]. Azmi, F.; Ahmad Fuaad, A. A. H.; Skwarczynski, M.; Toth, I. *Hum. Vaccin. Immunother.* **2014**, *10* (3), 778–796.

[106]. Hassan, A. O.; Kafai, N. M.; Dmitriev, I. P.; Fox, J. M.; Smith, B. K.; Harvey, I. B.; Chen, R. E.; Winkler, E. S.; Wessel, A. W.; Case, J. B.; Kashentseva, E.; McCune, B. T.; Bailey, A. L.; Zhao, H.; VanBlargan, L. A.; Dai, Y.-N.; Ma, M.; Adams, L. J.; Shrihari, S.; Danis, J. E.; Gralinski, L. E.; Hou, Y. J.; Schäfer, A.; Kim, A. S.; Keeler, S. P.; Weiskopf, D.; Baric, R. S.; Holtzman, M. J.; Fremont, D. H.; Curiel, D. T.; Diamond, M. S. *Cell* **2020**, *183* (1), 169-184.e13.

[107]. Feng, L.; Wang, Q.; Shan, C.; Yang, C.; Feng, Y.; Wu, J.; Liu, X.; Zhou, Y.; Jiang, R.; Hu, P.; Liu, X.; Zhang, F.; Li, P.; Niu, X.; Liu, Y.; Zheng, X.; Luo, J.; Sun, J.; Gu, Y.; Liu, B.; Xu, Y.; Li, C.; Pan, W.; Zhao, J.; Ke, C.; Chen, X.; Xu, T.; Zhong, N.; Guan, S.; Yuan, Z.; Chen, L. *Nat. Commun.* **2020**, *11* (1), 4207.

[108]. Prasad, A.; Muthamilarasan, M.; Prasad, M. *Plant Cell Rep.* **2020**, *39* (9), 1109–1114.

[109]. Silverman, E. Medicago strikes Covid-19 vaccine deals with GSK, Dynavax https://www.statnews.com/pharmalot/2020/07/09/covid19-coronavirus-pandemic-vaccines-medicago-glaxo-dynavax/ (accessed December 9, 2020).

[110]. Rajapaksha, H.; Perera, B. T.; Meepage, J.; Perera, R. T.; Dissanayake, C. *Eur. J. Chem.* **2020**, *11* (4), 351–363.

[111]. Chen, C.; Zhang, Y.; Huang, J.; Yin, P.; Cheng, Z.; Wu, J.; Chen, S.; Zhang, Y.; Chen, B.; Lu, M.; Luo, Y.; Ju, L.; Zhang, J.; Wang, X. *bioRxiv*, **2020**. https://doi.org/10.1101/2020.03.17.20037432

[112]. Wang, Y.; Zhang, D.; Du, G.; Du, R.; Zhao, J.; Jin, Y.; Fu, S.; Gao, L.; Cheng, Z.; Lu, Q.; Hu, Y.; Luo, G.; Wang, K.; Lu, Y.; Li, H.; Wang, S.; Ruan, S.; Yang, C.; Mei, C.; Wang, Y.; Ding, D.; Wu, F.; Tang, X.; Ye, X.; Ye, Y.; Liu, B.; Yang, J.; Yin, W.; Wang, A.; Fan, G.; Zhou, F.; Liu, Z.; Gu, X.; Xu, J.; Shang, L.; Zhang, Y.; Cao, L.; Guo, T.; Wan, Y.; Qin, H.; Jiang, Y.; Jaki, T.; Hayden, F. G.; Horby, P. W.; Cao, B.; Wang, C. *Lancet* **2020**, *395* (10236), 1569–1578.

[113]. Gautret, P.; Lagier, J.-C.; Parola, P.; Hoang, V. T.; Meddeb, L.; Mailhe, M.; Doudier, B.; Courjon, J.; Giordanengo, V.; Vieira, V. E.; Tissot Dupont, H.; Honoré, S.; Colson, P.; Chabrière, E.; La Scola, B.; Rolain, J.-M.; Brouqui, P.; Raoult, D. *Int. J. Antimicrob. Agents* **2020**, *56* (1), 105949.

[114]. Guaraldi, G.; Meschiari, M.; Cozzi-Lepri, A.; Milic, J.; Tonelli, R.; Menozzi, M.; Franceschini, E.; Cuomo, G.; Orlando, G.; Borghi, V.; Santoro, A.; Di Gaetano, M.; Puzzolante, C.; Carli, F.; Bedini, A.; Corradi, L.; Fantini, R.; Castaniere, I.; Tabbì, L.; Girardis, M.; Tedeschi, S.; Giannella, M.; Bartoletti, M.; Pascale, R.; Dolci, G.; Brugioni, L.; Pietrangelo, A.; Cossarizza, A.; Pea, F.; Clini, E.; Salvarani, C.; Massari, M.; Viale, P. L.; Mussini, C. *Lancet Rheumatol* **2020**, *2* (8), e474–e484.

[115]. Liu, S. T. H.; Lin, H.-M.; Baine, I.; Wajnberg, A.; Gumprecht, J. P.; Rahman, F.; Rodriguez, D.; Tandon, P.; Bassily-Marcus, A.; Bander, J.; Sanky, C.; Dupper, A.; Zheng, A.; Nguyen, F. T.; Amanat, F.; Stadlbauer, D.; Altman, D. R.; Chen, B. K.; Krammer, F.; Mendu, D. R.; Firpo-Betancourt, A.; Levin, M. A.; Bagiella, E.; Casadevall, A.; Cordon-Cardo, C.; Jhang, J. S.; Arinsburg, S. A.; Reich, D. L.; Aberg, J. A.; Bouvier, N. M. *Nat. Med.* **2020**, *26* (11), 1708–1713.

[116]. Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) for COVID-19 in Healthy Volunteers - Full Text View - ClinicalTrials.Gov https://clinicaltrials.gov/ct2/show/NCT04471519 (accessed December 9, 2020).

[117]. Clinical Trial of Efficacy and Safety of Sinovac's Adsorbed COVID-19 (Inactivated) Vaccine in Healthcare Professionals - Full Text View - ClinicalTrials.Gov https://clinicaltrials.gov/ct2/show/NCT04456595 (accessed December 9, 2020).

[118]. A Study to Evaluate The Efficacy, Safety and Immunogenicity of Inactivated SARS-CoV-2 Vaccines (Vero Cell) in Healthy Population Aged 18 Years Old and Above - Full Text View - ClinicalTrials.Gov https://clinicaltrials.gov/ct2/show/NCT04510207 (accessed December 9, 2020).

[119]. Phase III Double-blind, Placebo-controlled Study of AZD1222 for the Prevention of COVID-19 in Adults https://clinicaltrials.gov/ct2/show/NCT04516746 (accessed December 9, 2020).

[120]. Phase III Trial of A COVID-19 Vaccine of Adenovirus Vector in Adults 18 Years Old and Above https://clinicaltrials.gov/ ct2/show/NCT04526990 (accessed December 9, 2020).
[121]. A Study of Ad26.COV2.S in Adults (COVID-19) https://clinicaltrials.gov/ct2/show/NCT04436276 (accessed December 9, 2020).
[122]. Clinical Trial to Evaluate the Safety and Immunogenicity of the COVID-19 Vaccine - Full Text View - ClinicalTrials.Gov https://clinicaltrials.gov/ct2/show/NCT04497298 (accessed December 9, 2020).
[123]. Clinical Trial of Efficacy, Safety, and Immunogenicity of Gam-COVID-Vac Vaccine Against COVID-19 - Full Text View - ClinicalTrials.Gov https://clinicaltrials.gov/ct2/show/NCT04530396 (accessed December 9, 2020).
[124]. A Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 Vaccine in Adolescents 12 to <18 Years Old to Prevent COVID-19 - Full Text View - ClinicalTrials.Gov https://clinicaltrials.gov/ct2/show/NCT04649151 (accessed December 9, 2020).
[125]. Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals https://www.clinicaltrials.gov/ct2/show/NCT04368728 (accessed December 9, 2020).
[126]. A Dose-Confirmation Study to Evaluate the Safety, Reactogenicity and Immunogenicity of Vaccine CVnCoV in Healthy Adults for COVID-19 https://clinicaltrials.gov/ct2/show/NCT04515147 (accessed December 9, 2020).
[127]. Ascending Dose Study of Investigational SARS-CoV-2 Vaccine ARCT-021 in Healthy Adult Subjects https://clinicaltrials.gov/ct2/show/NCT04480957 (accessed December 9, 2020).
[128]. Ward, D.; McCormack, S. Clinical Trial to Assess the Safety of a Coronavirus Vaccine in Healthy Men and Women 2020. https://doi.org/10.1186/ISRCTN17072692 (accessed December 9, 2020).
[129]. CTRI http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=45306&EncHid=&userName=vaccine (accessed December 9, 2020).
[130]. Safety and Immunogenicity Study of GX-19, a COVID-19 Preventive DNA Vaccine in Healthy Adults https://clinicaltrials.gov/ct2/show/NCT04445389 (accessed December 9, 2020).
[131]. Safety, Tolerability and Immunogenicity of INO-4800 Followed by Electroporation in Healthy Volunteers for COVID19 https://clinicaltrials.gov/ct2/show/NCT04447781 (accessed December 9, 2020).
[132]. Study of COVID-19 DNA Vaccine (AG0301-COVID19) https://clinicaltrials.gov/ct2/show/NCT04463472 (accessed December 9, 2020).
[133]. Evaluation of the Safety and Immunogenicity of a SARS-CoV-2 rS Nanoparticle Vaccine With/Without Matrix-M Adjuvant https://clinicaltrials.gov/ct2/show/NCT04368988 (accessed December 9, 2020).
[134]. KBP-201 COVID-19 Vaccine Trial in Healthy Volunteers https://clinicaltrials.gov/ct2/show/NCT04473690 (accessed December 9, 2020).
[135]. A Phase III Clinical Trial to Determine the Safety and Efficacy of ZF2001 for Prevention of COVID-19 https://clinicaltrials.gov/ct2/show/NCT04646590 (accessed December 9, 2020).
[136]. Monovalent Recombinant COVID19 Vaccine - Full Text View - ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT04453852 (accessed December 9, 2020).
[137]. Study of a Recombinant Coronavirus-Like Particle COVID-19 Vaccine in Adults https://clinicaltrials.gov/ct2/show/NCT04636697 (accessed December 9, 2020).