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SARS-CoV-2 Genetic Variations, Immunity, and Efficacy of Vaccines: The Current Perspectives and Future Implications

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Abstract From the time since its discovery, the novel SARS-CoV-2 had spread throughout the world and has been a challenge for the healthcare system to control its spread and manage the infected patients. Although the mortality rates varied around the globe, what was common was the impact of COVID-19 on the societal, cultural, political, and economic aspects. With no specific anti-viral drug available, the initial days of the pandemic were even more stressful and resulted in increased morbidity and mortality. Gradually, by the observations, and studies of clinicians and scientists, we could improve our knowledge regarding the nature of the virus, its potential origins, pathogenic mechanisms, methods of diagnosis, treatment, and effective strategies for the management of COVID-19 patients. Interestingly, the virus had been found mutating, and therefore, even after more than a year into the pandemic, we still are putting up a fight against the novel virus. Availability of the vaccine, despite hesitancy, has been the high point in the current pandemic. Molecular studies have revealed thousands of SARS-CoV-2 variants spread throughout the world. Several countries have been experiencing waves of infection forcing restricted people movements and lockdowns. The variability in the infection rates and intensities influenced by age, gender, and other factors remain to be completely understood. Efficacy of the vaccines, their safety, immune responses against SARS-CoV-2 infections has been at the forefront of the research studies. In this review, we discuss the molecular and immunological aspects of SARS-CoV-2 infection with a note on the current perspectives and future implications of the virus and vaccine research.

Keywords: *SARS-CoV-2, COVID-19, molecular studies, immunological aspects, vaccine research*

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1. Introduction

It has been more than a year into the Coronavirus disease-19 (COVID-19) pandemic, and it still is a tug of the war-like situation between the virus and humankind [1,2]. The COVID-19 is caused by a novel virus named severe acute respiratory syndrome Coronavirus -2 (SARS-CoV-2) that has emerged from the Hunan market in the Hubei province of China. The virus has spread throughout the world, causing pandemics, affecting millions of people, and causing extensive morbidity and mortality [3,4,5]. The microbial emergences and re-emergences are not uncommon to humans as evidenced by the occurrences of novel microbes like the Human Immunodeficiency Virus (HIV), Ebola virus, Zika virus, the Influenza virus, and most recently the SARS-CoV, and Middle East Respiratory Syndrome Coronavirus (MERS).

The SARS-CoV-2 has been reported to have increased transmission rates as compared to the SARS-CoV, MERS-CoV, and Influenza virus. The transmission rate of viruses is indicated numerically by R_0 (R naught). The R_0 is a mathematical representation of the ability of a microbe to transmit the infection. The R_0 defines the transmissibility of viral infection from an infected person to another person/persons. If a virus has an R_0 equal to 1, it means that an infected person may transmit the infection to one person. The R_0 in turn will influence the doubling time of the infected population. The SARS-CoV-2 has an R_0 ~5 and maybe more, as compared to its predecessors SARS-CoV (R_0~1), and MERS-CoV (R_0~1). The R_0 of previous pandemics that include the 1918 Spanish flu (R_0~1 and up to 2.4) and the 2009 Influenza virus (R_0~2 and up to 16) were reflecting their increased transmissibility rates [3,4].

Unlike the most recent CoV pandemics including the SARS-CoV, and MERS-CoV, the current SARS-CoV-2 had spread to almost every corner of the world. The mortality rates were higher in both the previous pandemics (SARS-CoV (10%), MERS-CoV (35%)) as compared to the current one (around 2%) [5].

2. Historical Aspects of Human and Microbe Encounters

Human beings have been dealing with the threat of infectious diseases for centuries. People never knew that the microorganisms were responsible for causing infections until the discovery of the "germ theory of disease" by Louis Pasteur. Infectious diseases like syphilis, plague, smallpox, rabies, leprosy, and others were responsible for increased morbidity and mortality in the preceding centuries. The reason being the lack of knowledge of the microorganisms, protective measures, and antimicrobial agents.

The Smallpox viral infection was responsible for the death of millions of human beings. During the Smallpox pandemic, Edward Jenner had noted that the people with proximity to cattle (milkmaids, farmers) were either not suffering from infection or only developing mild Smallpox infection. Later, Jenner got an idea/probable solution to the problem. He injected the extracts of the lesions which were present on the hands of the milkmaids into the people who had smallpox infection [6]. Interestingly, it worked, and people were protected against the Smallpox infection.

Simultaneously, Louis Pasteur tried to save chicken that were dying of diarrhoeal disease (chicken cholera). He injected the dried and boiled fecal extracts of the diseased chicken into the healthy chicken and found that they were protected against deadly diarrhea [7].

Later, Louis Pasteur also used the same method to discover vaccines against rabies. He extracted the infected animal's brain tissue and injected it into the rabbit's spinal cord. This resulted in the death of the rabbit. He then collected the spinal cord extract and injected the same into a healthy animal [8]. He repeated this process, and in due course of time, he realized that the infection-causing ability of the Rabies virus was lost. This Rabies virus, which lost its virulence, was used to protect other organisms. This process was later understood as attenuation, a method of relieving the infection-causing ability of the microorganism used to develop vaccines.

In all those instances, it was noted that the immune system may have been able to recognize the microorganism, a similar/related microorganism in case of smallpox, and an organism with lost virulence in case of chicken cholera and rabies. Louis Pasteur, later coined the term vaccine (Vacca means cow), and the process of injecting a similar microorganism or the attenuated/killed microorganism to protect against infection was called vaccination [9].

In the later years, it was understood that the humans have an in-built mechanism to counter infections, and it was attributed to the production of the cells, called antibodies, and other immune cells which fight the infection-causing microorganisms or extraneous agents, which were later termed as antigens [10].

Immunological responses to SARS-CoV-2 were noted to be complex. This is evident from the varied clinical course observed among the infected people, which were influenced by age, gender, and several other factors like the presence of co-morbidities [11,12,13].

3. The Emergence of SARS-CoV-2, Bat Colonization, and Immunity

The novel SARS-CoV-2 is continuing to cause extensive morbidity and mortality throughout the globe. It has severely affected humans on the health, education, social, and economic front. Most studies have pointed the emergence of the novel SARS-CoV-2 to bats, and some believed that pangolins and snakes could have acted as reservoirs and carriers for further viral transmissions.

Since bats have been reported to colonize human habitats, there is a possibility of exposure of humans to bat feces and other body secretions. Also, humans have the habit of visiting ancient caves, constructions, and deep forests that could potentially inhabit bats and facilitate exposure to bat feces and body secretions. There are some places in the world where bats are considered a food delicacy. Such a habit of humans is probably one of the main reasons why the microbes can spill over or jump from animals to humans. This is evident from the emergence of SARS-CoV-2 from a wet market where different types of wild/exotic animals were being handled and sold.

A previous study from Korea reported the prevalence of coronaviruses among the bat feces, which were genetically similar to the SARS-CoV-2, and MERS-CoV [14]. The areas screened include caves and abandoned mines. The study also found an 'H' strain Rotavirus which was previously reported in humans and pigs. This report suggests that bats have the potential to acquire viruses from the environment including humans and animals.

The coronaviruses detected in this study were previously reported from China. This points to the fact that the viruses could be transmitted among bats, and when they travel, could relocate the virus in different geographical regions. The study also identified viruses belonging to the mammals, plants, insects, fungi, and bacteriophages colonized in bats.

Bats act as reservoirs of more than 200 viruses, more particularly the RNA viruses due to their unique genetic composition and to be able to undergo genetic variations [15].

Not only viruses but bats were also noted to carry bacteria and fungi in their kidneys as evident by a study from West Indies [16].

4. SARS-CoV-2 Genetic Variations

Microbes are intrinsically prone to mutations and genetic variations probably due to their speed of multiplication. In terms of genetic variations and mutations, it seems that the size of microorganisms also correlates with the occurrence of mutations. Viruses undergo the highest number of genetic variations followed by bacteria, fungi, protozoa, and animals including humans. Moreover, among viruses, RNA viruses have been noted to undergo high rates of genetic variations. This is evident from the behavior of HIV, HCV, Influenza, Dengue, among others which have been infecting humans both seasonally (Influenza, Dengue), as well as pandemics

(HIV), and we still do not have a validated vaccine for any of the infections caused by these viruses.

The Coronaviruses also belong to the RNA group of viruses possessing abilities to undergo genetic variations and mutations. There are different types of CoVs among which the Beta CoVs have been noted to infect humans. And interestingly, both the previous CoV outbreaks and the current pandemic virus belong to the same group.

From the time since its discovery, SARS-CoV-2 underwent several genetic variations and resulted in the emergence of strains that have been noted to possess features like increased transmission rates, and resistance to monoclonal antibodies. A few of these viral strains were declared as variants of concern by the World Health Organization (WHO). The characteristics of variants are depicted in Table 1.

A network has been established to track the genomic changes, transmission patterns, and epidemiology of the novel SARS-CoV-2 [25]. The study of SARS-CoV-2 lineages showed 'A' lineage as the root from where the rest have evolved [26,27,28]. It was noted that the US, the UK, and the European regions revealed maximum numbers of circulating lineages. Also, some lineages were confined to a specific country and several others were observed to be mixed lineages that were scattered across more than one country or geographic region. The SARS-CoV-2 lineages and their origins are depicted in Table 2.

Table 1. The characteristics of some SARS-CoV-2 variants

Name of the mutant	Type of mutation	Nature of mutation	Effect
D614G (March 2020) Probably the first variant and noted in several lineages	Spike protein substitutions	D614G, Aspartic acid is replaced by Glycine	Increased transmission both In vivo, and Ex vivo, no impact on the monoclonal antibody therapy and convalescent/post-vaccination sera [17,18,19]
Y453F in B.1.1.298 Denmark, Mink strain	Receptor binding domain (RBD) of spike protein	Y453F, tyrosine is replaced by phenylalanine	Increased transmissibility and four-fold affinity to ACE-2 receptors [20]
B.1.1.7/N501Y.V1/Alpha UK	Spike glycoprotein, and RBD of spike protein	69del, 70del, 144del, E484K, S494P, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H K1191N	Variant of concern ~50% increased transmission, No impact on monoclonal antibody therapy and minimal impact on convalescent and post-vaccination sera [23,24]
B.1.351/Beta South Africa	Spike protein substitutions	D80A, D215G, 241del, 242del, 243del, K417N, E484K, N501Y, D614G, A701V	Variant of concern ~50% increased transmission, significantly reduced susceptibility to monoclonal antibodies, reduced protection with convalescent and post-vaccination sera [23,24]
P.1/Gamma Brazil, Japan	Spike protein substitutions	K417T, E484K, and N501Y, and several others	Variant of concern, significantly reduced susceptibility to monoclonal antibodies, reduced protection with convalescent and post-vaccination sera [23,24]
B.1.617.2/Delta India	Spike protein substitutions	P681R, L452R, and several others	Variant of Concern Increased transmissibility, reduced susceptibility to monoclonal antibodies, reduced protection with convalescent and post-vaccination sera [23,24]
B.1.617.3/Delta India	Spike protein substitutions	T19R, G142D, L452R, E484Q, D614G, P681R, D950N	Variant of concern Reduced susceptibility to monoclonal antibodies, reduced protection with convalescent and post-vaccination sera [23]
B.1.617.1/Kappa India	Spike protein substitutions	T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	Resistant to monoclonal antibodies, reduced protection after vaccination [23]
B.1.525/Eta UK/Nigeria	Spike protein substitutions, and deletions	A67V, 69del, 70del, 144del, E484K, D614G, Q677H, F888L	Variant of note, resistant to monoclonal antibodies, reduced protection after vaccination [23,24]
P.2 /Zeta Brazil	Spike protein substitutions	E484K, F565L, D614G, V1176F	Reduced susceptibility to monoclonal antibodies, reduced protection with post-vaccination/convalescent sera [23]
B.1.526/Iota USA	Spike protein substitutions	L5F, D80G, T95I, Y144-, F157S, D253G, L452R, S477N, E484K, D614G, A701V, T859N, D950H, Q957R	Reduced susceptibility to monoclonal antibodies, reduced protection with post-vaccination/convalescent sera [23]
B.1.427/Epsilon USA-California	Spike protein substitutions	L452R, D614G	~20% increased transmission, reduced susceptibility to monoclonal antibodies, reduced protection with post-vaccination/convalescent sera [23]
B.1.429/Epsilon-lineage USA-California	Spike protein substitutions	S13I, W152C, L452R, D614G	~20% increased transmission, reduced susceptibility to monoclonal antibodies, reduced protection with post-vaccination/convalescent sera [23]
A.23.1 Uganda	Spike protein substitutions, deletions, and eliminations	F157L, V367F, Q613H and P681R, P681H	Preliminary reports suggest no impact on the monoclonal antibody therapy and convalescent/post-vaccination sera [22,24]

Table 2. SARS-CoV-2 genetic lineages and the countries of origin

A (Chinese lineage), A.1, A.2.5, A.3, B.1.1.26, B.1.1.61, B.1.1.72, B.1.1.77, B.1.1.93, B.1.1.98, B.1.1.113, B.1.1.116, B.1.1.118, B.1.1.128, B.1.1.132, B.1.1.135, B.1.1.139, B.1.1.148, B.1.1.158, B.1.1.169, B.1.1.172, B.1.1.174, B.1.1.177, B.1.1.180, B.1.1.182, B.1.1.186, B.1.1.192, B.1.1.205, B.1.1.207, B.1.1.210, B.1.1.222, B.1.1.225-226, B.1.1.231, B.1.1.239, B.1.1.258(USA lineage), A.2 (Spanish lineage), A.2.2, B.1.1.136, B.1.1.142 (Australian lineage), A.2.3, B.1.1.14, B.1.1.43 (Scottish lineage), A.2.4 (Panama lineage), A.2.5.1 (Costa Rica lineage), A.2.5.2, B.1.1.202 (Italian lineage), A.5 (Mixed lineage), A.6 (Thai lineage), A.7, B.1.1.46, B.1.1.101,B.1.1.216, (Indian lineage), A.11 (Ghana/Senegal lineage), A.12 (Sierra Leone lineage), A.15, B.1.1.90 (Sweden/Denmark lineage) A.16, B.1.1.48, B.1.1.214 (Japanese lineage), A.17 (French lineage), A.18, A.19 (Cote D'Ivoire lineage), A.21 (Mali/Burkina Faso lineage), A. 22, B.1.1.133 (UAE/Europe), (UAE lineage), A.23, A.25 (Ugandan lineage), A.23.1 (International/mixed lineage), A.24 (South Korean lineage), A.26 (UK lineage), A.27, A.28, B.1.1.153, B.1.1.159 (European/mixed lineage), A.29 (International lineage), A.30 (International/Tanzania lineage), B (First discovered lineage), B.1, B.1.1.5, B.1.1.10, B.1.1.58, B.1.1.70, B.1.1.189, B.1.1.218B.1.1.241, B.1.1.243, (European lineage), B.1.1, B.1.1.1, B.1.1.3-4, B.1.1.7-8, B.1.1.12-13, B.1.1.15, B.1.1.37, B.1.1.41, B.1.1.45, B.1.1.51, B.1.1.55, B.1.1.59, B.1.1.86, B.1.1.89, B.1.1.92, B.1.1.95, B.1.1.97, B.1.1.107, B.1.1.109, B.1.1.115, B.1.1.123, B.1.1.125, B.1.1.130, B.1.1.134, B.1.1.137-138, B.1.1.145, B.1.1.147, B.1.1.149, B.1.1.154-155, B.1.1.164, B.1.1.165, B.1.1.168, B.1.1.171, B.1.1.178, B.1.1.193-194, B.1.1.196-198, B.1.1.200, B.1.1.203 (Ecuador), B.1.1.204, B.1.1.208, B.1.1.213, B.1.1.217, B.1.1.220B.1.1.223, B.1.236, B.1.1.240, B.1.1.253, B.1.1.255-256(UK/England lineage), B.1.1.16, B.1.1.29, B.1.1.38, B.1.1.82, B.1.1.114, B.1.1.190, B.1.1.237(Wales), B.1.1.249(Wales) (Wales with European base lineage), B.1.1.17 (Icelandic lineage), B.1.1.25, B.1.1.175 (Bangladesh lineage), B.1.1.27 (Oman lineage), B.1.1.28, B.1.1.33 (Brazilian lineage), B.1.1.30 (Lithuanian lineage), B.1.1.31, B.1.1.127, B.1.1.129, B.1.1.152, B.1.1.163, B.1.1.184 (Russian lineage), B.1.1.34, B.1.1.40, B.1.1.52, B.1.1.53, B.1.1.54, B.1.1.56, B.1.1.57, B.1.1.62, B.1.1.84, B.1.1.99, B.1.1.117, B.1.1.254 (South African lineage), B.1.1.39, B.1.1.47, B.1.1.144 (Switzerland and mixed lineage), B.1.1.50 (Israel and Palestine lineage), B.1.1.63 (HongKong lineage), B.1.1.67 (England and South Africa lineage), B.1.1.71 (Dutch and Central Europe lineage), B.1.1.74, B.1.1.83, B.1.1.119, B.1.1.160 (North Irish and Ireland lineage), B.1.1.75, B.1.1.221 (Belgian lineage), B.1.1.87 (Hungarian lineage), B.1.1.88 (Portugal lineage), B.1.1.91 (Sweden lineage), B.1.1.100, B.1.1.191(Denmark lineage), B.1.1.110 (Peru lineage), B.1.1.111 (African lineage Zambia/Zimbabwe), B.1.1.112, B.1.1.122 , B.1.1.185, B.1.1.209(Netherlands lineage), B.1.1.121, B.1.1.157, B.1.1.176 (Canadian lineage), B.1.1.141 (Russian, Latvian, Netherlands), B.1.1.161 (Saudi lineage),B.1.1.162 (England Russia, Latvia), B.1.1.170 (UK/Denmark), B.1.1.181 (Mostly Turkey/Canadian), B.1.1.187(UK/Italy), B.1.1.201 (India, Singapore, Texas), B.1.1.219 (UK, Denmark, Norway, Sweden), B.1.1.224 (Denmark, Germany), B.1.1.232, B.1.1.234 (Mixed Europe), B.1.1.242 (Gambia, Switzerland), B.1.1.251 (UK, USA),B-D, G, K-N, P, R, S, U-W, Y-Z, AA-AH, AJ-AN, AP, AQ, AS-AW, AY, XA A.2.1, A.8, A.10, A.13, A.14, A.20, B.1.1.2, B.1.1.6, B.1.1.20, B.1.1.32, B.1.1.33, B.1.1.35, B.1.1.60, B.1.1.64-66, B.1.1.73, B.1.1.76, B.1.1.78-81, B.1.1.85, B.1.1.94, B.1.1.96, B.1.1.102-106, B.1.1.108, B.1.1.124, B.1.1.126, B.1.1.131, B.1.1.140, B.1.1.143, B.1.1.146, B.1.1.150-151, B.1.1.156, B.1.1.167, B.1.1.173, B.1.1.179, B.1.1.183, B.1.1.195, B.1.1.199, B.1.1.206, B.1.1.211-212, B.1.1.215, B.1.1.223, B.1.1.233, B.1.1.235, B.1.1.238, B.1.1.245-248, B.1.1.250, B.1.1.252, B.1.1.259-260, B.1.1.264, B.1.1.276, B.1.1.278, B.1.1.281, B.1.1.287, B.1.1.292-293, B.1.1.295, B.1.1.313-314, B.1.1.439, B.1.3.1-4, B.1.5, B.1.5.2, B.1.5.5-6, B.1.11-13, B.1.5.15-19, B.1.5.21, B.1.5.25-36, B.1.8.2, B.1.9.6, B.1.11, B.1.19, B.1.21, B.1.25-26, B.1.34, B.1.36.3-6, B.1.36.11, B.1.36.13-15, B.1.36.17.1, B.1.74-75, B.1.79-80, B.1.82, B.1.88-90, B.1.95, B.1.98, B.1.102, B.1.107, B.1.109, B.1.114, B.1.133, B.1.135-136, B.1.138, B.1.141, B.1.144, B.1.150, B.1.152, B.1.154, B.1.156, B.1.160.1-6, B.1.177. 1, B.1.177. 13, B.1.177. 22, B.1.183, B.1.185-186, B.1.191, B.1.193, B.1.196, B.1.197, B.1.200, B.1.202, B.1.204, B.1.207, B.1.209, B.1.216-217, B.1.226, B.1.228, B.1.230, B.1.244, B.1.246, B.1.253, B.1.255, B.1.257, B.1.258.8, B.1.258.13, B.1.259, B.1.261-62, B.1.266, B.1.269, B.1.271-72, B.1.275, B.1.278, B.1.283, B.1.286, B.1.288, B.1.290, B.1.295, among several others

5. The Effects of SARS-CoV-2 Infection on Immunity and Vaccination

The complexities associated with SARS-CoV-2 infection are evident from the available literature. The infected patients respond differently with most remaining completely asymptomatic and clear the virus without needing any intervention, some suffer from mild and self-limiting infection, and few others develop severe infection leading to complications, severe morbidity, and death. Therefore, the underlying immune mechanism among the infected patients needs to be completely understood.

In a recent study that assessed the immunological responses among SARS-CoV-2 infected patients, efficient cell-mediated immune responses were observed among the patients infected in the last six months [29]. However, the study noted heterogeneity in the immune responses and the causes for which are not completely understood suggesting further studies in this regard.

A study among the mildly infected patients showed that both the humoral and cell-mediated immune responses were elicited wherein the neutralizing antibodies and T cells were demonstrated. Also noted were the memory cells that lasted for a significantly longer period ensuring protection against future antigenic exposures [30].

Antibody (IgM, and IgG) responses among SARS-CoV-2 infected patients were assessed within 2-3 weeks after the onset of symptoms and later at 4-7 weeks after the recovery. This study had revealed that although robust antibody responses were elicited initially, there was a 50% reduction in the levels of antibodies raising questions about long-term immunity following natural infection [31].

An assessment of antibody response (IgM, and IgG) among patients diagnosed as mild to moderate, severe, and critical illness following infection with SARS-CoV-2 revealed that the time required to reach threshold IgM among critical patients (23 days) was higher than that of the severely infected patients (16 days). Interestingly, this study had revealed that the IgG (11 days) seroconversion was earlier than IgM (14 days) [32].

Adequate quantities of anti-spike protein IgG antibodies were demonstrable even after six months of SARS-CoV-2 infection and sufficient amounts of memory B-cells, CD4+T cells, and CD8+T cells were observed. This study emphasizes the potential long-time protection after infection and supports the benefits of vaccination [33].

Despite mounting almost sterilizing immune responses where the virus is completely cleared from the infected people, and evidence of adequate antibody and T cell responses with proof of memory B, and T cells, there are several reports of SARS-CoV-2 re-infections. Also noted were reinfections with a different genetic variant of SARS-CoV-2 [34]. This suggests the importance of molecular epidemiology of the novel virus, continuous booster doses, and investigating newer and more effective vaccine strategies.

The vaccine against SARS-CoV-2 had been manufactured using a novel, and insufficiently proven technology that uses mRNA coding for the desired antigen of the microorganism. The mRNA is delivered through a vector virus like the human Adenovirus, Chimpanzee Adenovirus, among others. Therefore, there is a great bit of hesitancy among people throughout the world concerning the safety, efficacy, and immunogenicity of vaccines.

Nevertheless, there are more than ten vaccines currently being approved nationally and internationally, with some being under clinical trials against SARS-CoV-2 [35]. It is, therefore, necessary to make public the data on the safety, efficacy, immunogenicity, and the results of pre-clinical, clinical, and post-marketing studies to minimize the vaccine hesitancy and improve its coverage [36].

Interestingly, the vaccines approved against SARS-CoV-2 have been only for emergency use, and most vaccines are yet to complete the phase III trials. Also, some of the vaccine candidates in the human clinical trials did not have pre-clinical data. However, the World Health Organization (WHO) is actively studying the vaccines and listing them for emergency use [37]. The vaccines currently under clinical trials along with those approved for emergency use are shown in Table 3.

Table 3. SARS-CoV-2 vaccines, developers, vaccine type, dosage, route of administration, regulatory approvals

Name of vaccine/Strain used	Manufacturer/Developer	Type of vaccine	Route of administration, dose: Single/Booster	Pre-clinical trial data	Current status
BBIBP-CorV/19nCoV-CDC-Tan-HB02 (HB02) strain	Beijing Institute of Biological Products/Sinopharm, China	Whole cell inactivated vaccine	Intramuscular, Booster	Available	Phase III clinical trial, WHO Emergency Use Listing
WIV04 strain	Wuhan Institute of Biological Products/Sinopharm, China	Whole cell inactivated vaccine	Intramuscular, Booster	Not available	Phase III clinical trial
CoronaVac/PiCoVacc	Sinovac, China	Whole cell inactivated vaccine	Intramuscular, Booster	Available	Phase III clinical trial, emergency use approved in China, WHO Emergency Use Listing
Ad5-nCoV	CanSino Biological inc./Beijing institute of biotechnology, China	Virus vector: a non-replicating, adenovirus type 5 (Ad5)-vector	Intramuscular, Single	Not available	Phase III clinical trial
Ad26.COV2·S	Janssen pharmaceutical, USA	Virus vector: a non-replicating, adenovirus type 26 (Ad26)-vector	Intramuscular, Single	Available	Phase III clinical trial, WHO Emergency Use Listing
AZD1222/ChAdOx1nCoV-19/Covishield	Oxford University and AstraZeneca, UK/Serum Institute of India	Virus vector: non-replicating simian adenovirus vector ChAdOx1	Intramuscular, Single, Booster	Available	Phase III clinical trial, UK,MHRA, and CDSCO, India had approved for its emergency use. WHO Emergency Use Listing
Sputnik V	Gamaleya research institute, Russia	Virus vector: non-replicating viral vectors, adenovirus type 5 (rAd5) and adenovirus type 26 (rAd26)	Intramuscular, Booster	Not available	Phase III clinical trial, CDSCO, India had approved its emergency use
mRNA-1273/Moderna	Moderna/NIAID, USA	mRNA encoding a stabilized S protein encapsulated in lipid nanoparticles	Intramuscular, Booster	Available	Phase III clinical trial, CDSCO, India approved for its emergency use, WHO Emergency Use Listing
BNT162b2	Pfizer/BioNTech/Fosun, USA	Nucleoside-modified mRNA encapsulated in lipid nanoparticles	Intramuscular, Booster	Available	Phase III clinical trial, authorized for use under an EUA by the FDA, WHO Emergency Use Listing
NVX-CoV2373	Novavax, USA	Trimeric SARS-CoV-2 S protein nanoparticle plus Matrix-M1 adjuvant	Intramuscular, Booster	Available	Phase III clinical trial
Covaxin/BBV152	Bharath Biotech in collaboration with the Indian Council Medical research (ICMR), and National Institute of Virology (NIV), India	Whole cell inactivated vaccine	Intramuscular, Booster	Available	Phase III clinical trial, CDSCO, India had approved its emergency use
CovaxinBBV154 Intranasal (vaccine candidate)	Bharath Biotech, India	Adenovirus vector with ChAD-SARS-CoV-2-S strain	Intranasal	Available	Pre-clinical trials

Table 4. SARS-CoV-2 vaccine candidates and platforms being tested at various clinical trial phases

Vaccine Platform	Number of candidate vaccines in phase 1 clinical trials (n%)	Number of candidate vaccines in phase 2 clinical trials (n%)	Number of candidate vaccines in phase 3 clinical trials (n%)	Number of candidate vaccines in phase 4 clinical trials (n%)
PS (Protein subunit)	9 (25%)	6 (60%)	8 (42%)	0 (0%)
VVnr (Viral Vector (non-replicating))	7 (19%)	0 (0%)	1 (5%)	3 (38%)
DNA	4 (11%)	0 (0%)	1 (5%)	0 (0%)
IV (Inactivated Virus)	4 (11%)	0 (0%)	7 (37%)	2 (25%)
RNA	8 (22%)	2 (10)	2 (11%)	3 (38%)
VVr (Viral Vector (replicating))	0 (0%)	1 (10%)	0 (0%)	0 (0%)
VLP (Virus Like Particle)	1 (3%)	1 (10%)	0 (0%)	0 (0%)
VVr + APC (VVr + Antigen Presenting Cell)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
LAV (Live Attenuated Virus)	2 (6%)	0 (0%)	0 (0%)	0 (0%)
VVnr + APC (VVnr + Antigen Presenting Cell)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

According to the WHO data, there are currently 108 vaccines under clinical development and almost double the number (184) of vaccine candidates are under pre-clinical studies [37]. The vaccines that were approved for emergency use are now undergoing phase 4 trials. SARS-CoV-2 vaccine candidates modelled using different vaccine platforms that are currently under different phases of clinical trials are listed in Table 4.

The primary endpoints that are of increased importance in vaccine development are to assess their ability to resist infection, disease, and death. Evaluating the vaccines for primary endpoints is too early because several approved vaccines are still in their phase 3 clinical studies [39]. Moreover, the current vaccine development strategies (mRNA, viral vectors) that are used to develop/manufacture SARS-CoV-2 vaccines are novel, and therefore long-term safety and efficacy of vaccines become particularly important [40]. Although vaccines are now available for people in many countries, the side effects of vaccination and vaccine-related adverse events are currently being reported. A recent study had noted that Gillian Barré Syndrome (GBS), an autoimmune condition that was previously associated with infectious diseases could be seen in people after vaccination [41]. Nevertheless, it is argued that the benefits of vaccination must not be ignored for any reason during the current pandemic situation.

The safety of vaccination among patients suffering from immunological diseases including Irritable Bowel Disease (IBD), and multiple sclerosis, among others were recently assessed. Patients suffering from such conditions are generally prescribed immune-modulatory drugs which may impact their immune responses. It was therefore recommended that in such patients the dosage and timings of the immunosuppressive drugs must be carefully planned before being vaccinated [42,43].

6. Current Perspectives

The current pandemic looks extremely devastating because of the increased population in the present times as compared to the previous centuries. This has led to the under-preparedness of health infrastructures to handle large numbers of patients. Also contributing to the seriousness of the disease was the presence of a greater number of people above the age of 60 years, and people with co-morbidities like diabetes mellitus, cardiovascular diseases, and other debilitating diseases including chronic kidney diseases. Moreover, transmission through the respiratory aerosols had facilitated the virus to spread extensively and select susceptible populations.

As per the available literature, and emerging pieces of evidence, it is imperative that the similarity of the novel SARS-CoV-2 with the prevalent Bat CoV's to which humans may have been previously exposed, could be a possible reason for the current mortality rates. Also, it must be noted that the mortality rates in the early phases of the pandemic were higher owing to the lack of knowledge concerning the virus, and its modes of transmission, and potential patient management strategies that included treatment for hypoxia, where the infected patients suffer from reduced blood oxygen saturation.

A robust immune response is essential for the elimination of viruses from the human body, which is not the case in people with immunodeficiencies, co-morbidities, and other debilitating disorders. This is evident by the reports of increased mortality rates among the aged population and people with other co-morbidities and asymptomatic to mild infections among young and healthy individuals.

Laboratory research including SARS-CoV-2 specific cell lines, organoids, and animal models was recently reviewed. It was noted that SARS-CoV-2 can be cultured in primary human lung epithelial cells, intestinal epithelial cells, Vero cells, CaCo-2 cells, HEK-293, H1299, Calu-3 cell lines, human iPSC-derived lung, small intestine, and blood vessel organoids, and transgenic hACE-2, adenovirus, hACE-2 mouse models, hamster, ferrets, and non-human primates like African green monkeys, rhesus macaques, and cynomolgus macaques. These were being used to improve the understanding of the virus's growth rates, biology, treatment outcomes, and investigate the potential targets against which drugs can be manufactured [44,45,46,47].

Understanding ACE-2 polymorphism and its relation to the binding affinities of the variants of SARS-CoV-2

could contribute to the development of therapeutic drugs [48]. Recently, the nanomedicine-based platform was suggested for the future development of COVID-19 vaccines. The benefit of nano-based vaccines included easy manipulations to the vaccine that can effectively work against the emerging mutant types, and cost-effectiveness [49].

Application of fixed-bed bioreactor-based production of recombinant vesicular stomatitis virus (rVSV), for the manufacture of viral vector vaccines was suggested. This methodology was found suitable for the vaccine preparations against HIV, Ebola virus, and SARS-CoV-2, among others [50].

7. Conclusions and Future Areas of Research

The SARS-CoV-2, which is responsible for COVID-19 appears to possess a complex pathological mechanism that facilitates it to choose susceptible populations. The COVID-19 showed the influence on age, gender, and other co-morbidities as evidenced by varied clinical outcomes. Increasing mutations are intrinsic to the Coronaviruses, and therefore SARS-CoV-2 needs to be closely observed/monitored for the emergence of variants of concerns.

Future studies must concentrate on the impact of variants on the efficacy of vaccines. Also, important is to gather as much data as possible concerning the long-term safety, and efficacy of the vaccines. Considering bats are now proven to be potential reservoirs of microbes, extensive research is needed to find out the microbial species harboured in bats at various geographical regions across the globe. Laboratory research must look for the potential mutations that a microbe may undergo while present in the current host and after jumping to another host, and thereafter. With improved scientific, technological, and infrastructural capabilities we should try to identify the reasons for bats being able to survive even while carrying several microbial species and not getting affected by them.

Although we are currently in the second year of the pandemic, there is still a lot left to understand about the behaviour of novel SARS-CoV-2 in terms of the infection rates and the rates of morbidity and mortalities among the rural and urban population who might be differently exposed to bats carrying coronaviruses. Extensive large-scale screening of the people for the presence of anti-SARS-CoV-2 antibodies could contribute to improved understanding of the immune responses to exposures, infections, and vaccinations.

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