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Review Article

An overview of SARS-COV-2 epidemiology, mutant variants, vaccines, and management strategies

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ABSTRACT

Background: Over the last two decades, humanity has observed the extraordinary anomaly caused by novel, weird coronavirus strains, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). As the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus has made its entry into the world, it has dramatically affected life in every domain by continuously producing new variants. The vaccine development is an ongoing process, although some vaccines got marketed. The big challenge is now whether the vaccine candidates can provide long-lasting protection or prevention against mutant variants.

Methods: The information was gathered from various journals, electronic searches via Internet-based information such as PubMed, Google Scholar, Science Direct, online electronic journals, WHO landscape, world meters, WHO website, and News.

Results: This review will present and discuss some coronavirus disease 19 (COVID-19) related aspects including: the pathophysiology, epidemiology, mutant variants vaccine candidates, vaccine efficacy, and

Abbreviations: ACE2, angiotensin-converting enzyme-2; ADRP, ADP ribose-1′-phosphatase; ARTES, Germany: based biotechnology company specialized in recombinant protein production and process development from microbial expression systems; BIOCAD, BIO computer aided design RNA; CanVirex AG, Swiss Biotech Association; CARDS, Covid 19 acute respiratory distress syndrome; CBC, complete blood count; CCHFV, Crimean-Congo hemorrhagic fever virus; CDC, center for disease control and prevention; CEA, carcinoembryonic antigen; CHIKV, chikungunya virus; CMV, cytomegalovirus; CNBG, China National Biotec Group; CNRS, centre national de la recherche scientifique; COPD, chronic obstructive pulmonary disease; COVID-19, corona virus disease 2019; CPAP, continuous positive airway pressure; CRP, C-reactive protein; DMVs, double-membrane vesicles; DWRAIR, Diseases/Walter Reed Army Institute of Research; DZIF, German Center for Infection Research; EBOV, Ebola virus; ECDC, European Centre for Disease Prevention and Control; ERGIC, endoplasmic reticulum- golgi intermediate compartment; ExoN, exoribonuclease; FiO_2, fraction of inspired oxygen; GCIR, German Center for Infection Research; GMV, glycine mosaic virus; GLA, glucopyranosyl Lipid A; GPO, Government Pharmaceutical Organization; HeV, hepatitis virus E; HBV, hepatitis B virus; HFNC, high-flow nasal cannula; HLC, high lung compliance; IAVI, international AIDS vaccine initiative; IDIBAPS, Pi i Sunyer Biomedical Research Institute; IEM, Institute For Engineering in Medicine; InfA, influenza virus-A; INRAE, National Research Institute for Agriculture, Food and Environment; IPV, inactivated polio virus; IMV, Instruments de Médecine Vétérinaire; LASSA, lassa virus; LASV, lassa mammarenavirus; LinKinVax, French biotechnology startup that focuses on speeding up vaccine; LiteVax BV, spike-based (epitope screening); LLC, low lung compliance; LVVV, live viral vectored vaccine; MARV, Marburg virus; MDA5, melanoma differentiation associated protein; MERS-CoV, Middle East Respiratory Syndrome coronavirus; MIGAL, Galilee Research Institute Ltd; MMR, measles mumps rubella; MVA, modified vaccinia virus Ankara; NERVTAG, new and emerging respiratory virus Threats advisory group; NiV, Nippa virus; NIV, non-invasive ventilation; NLC, nanostructured Lipid Carriers; NORV, norovirus; NSCLC, non-small cell lung cancer; NSP, non-Structural proteins; O-MT, *O*-methyl transferase-2; OMV, outer membrane vesicle; ORFs, open reading frames; Osivax, clinical stage biotechnology company; P.C., preclinical; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; PEEP, positive end-expiratory pressure; PPI, proton pump inhibitors; RBD, receptor-binding domain; RVF, Rift Valley fever; RdRp, RNA dependent RNA polymerase; RTC, replication transcription complex; RTI, respiratory tract infections; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SIG, SARS-COV-2 Interagency Group; SpO_2, oxygen saturation; SRC VB VECTOR, State Research Centre of Virology and Biotechnology; TMPRSS2, transmembrane protein serine 2; TRSs, transcriptional regulatory sequences; USAMRIID/WARIAR, United States Army Medical Research Institute of Infectious; VEE, Venezuelan equine encephalitis; VLP, virus like particle; VOC, variant of concern; VOHC, variant of high consequences; VOI, variant of interest; VRI, Vaccine Research Institute; VSV, vesicular stomatitis virus.

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management strategies. Due to the high death rate, continuous spread, an inadequate workforce, lack of required therapeutics, and incomplete understanding of the viral strain, it becomes crucial to build the knowledge of its biological characteristics and make available the rapid diagnostic and vital therapeutic machinery for the combat and management of an infection.

Conclusion: The data summarizes current research on the COVID 19 infection and therapeutic interventions, which will direct future decision-making on the effort-worthy phases of the COVID 19 and the development of critical therapeutics. The only possible solution is the vaccine development targeting against all variant strains to halt its progress; the identified theoretical and practical knowledge can eliminate the gaps to improve a better understanding of the novel coronavirus structure and its design of a vaccine. In addition, to that the long-lasting protection is another challenging objective that need to be looked into.

Contents

Introduction

Andrews and Gledhill in 1951 screened a hepatitis virus from mice which are now known as a single-stranded RNA coronavirus. Its diseases and cause have been recognized in animals and humans for over 50 years. 229E and OC43 were the first coronaviruses to cause very mild infections like common colds in humans. Later on, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) emerged from civet cats, camels, bats [1]. The family of coronavirus is called as Coronaviridae which comprises of two subfamilies, Coronaviridae and Letovirinae [2,3]. Pneumonia's initial diagnosis and unknown cause made the cluster of patients in China admitted into hospitals in December 2019. The reports confirmed the potential coronavirus outbreak, of coronavirus disease 19 (COVID-19), and WHO gave it a name on February 11, 2020 [4]. In response to the outbreak, the center for disease control and prevention (CDC) conducted epidemiological and etiological investigations via Wuhan city's Health authorities. Nearly 1 billion cases per year and economic losses of hundreds of billions of dollars occur due to this zoonotic illness, demonstrating the importance of developing vaccine design strategies for virus families with pools of causing extensive zoonotic diseases. The transcriptional regulatory sequences (TRSs) mediates discontinuous transcription and transcribes sub genomic RNAs, which make up the structure of a virus particle [5,6]. Advances in understanding viral machinery, the role of various viral proteins, their genetic structure, host immune responses, and the ability to confer protection switch its way to developing a vaccine successfully. An additional challenge is conducting clinical trials in this pandemic loss by utilizing the current evidence and critical knowledge gaps to better understand the virus strategy to safeguard public health. This review, has focused and emphasized points on the COVID 19 pathophysiology, epidemi-

ology, mutant variants, vaccine candidates, vaccine efficacy and strategies for disease management.

Pathophysiology

Coronavirus spike glycoprotein (S) with the expression of their subunits S1 and S2 binds to the host cell receptor's surface. S1 determines the cellular tropism and host range and helps attach the virus to the target cell. In contrast, the S2 subunit helps infusion with the host cells (mainly alveolar epithelial cells and small intestine enterocytes) with the aid of Angiotensin-Converting Enzyme-2 (ACE2) claw-like structure of the receptor by endocytosis [7,8]. When this S protein binds to the ACE-2 receptor, the transmembrane protein serine 2 (TMPRSS2), which is associated with the cell surface, mediates cleavage of S protein trimer, and the fusion mechanism is activated via endosomal acid proteases (cathepsin L) [9–11]. ACE2 is an 805 amino acid containing integral membrane protein consists of 3 domains that are a domain at the transmembrane side, a domain at the extracellular side and a domain at the cytoplasmic side, and the N-terminal peptide. The enzyme sheddase helps release soluble protein into the bloodstream by cleavage of the active carboxypeptidase domain from the transmembrane domain [12]. When there is a lysosome-mediated drop in pH, the endosome membrane fuses with the virus's envelope and releases a nucleocapsid in the cytoplasm. The cellular proteases degrade the capsid, and the positive sense RNA viral genome ranges between 27−32 kbp is left free. This viral genomic RNA consists of at least 6 open reading frames (ORFs). ORF1a and ORF1b are present at the 5′end, constitute a common fraction of the whole genome length RNAs, and are translated into pp1a and pp1ab proteins. Protease helps in cleavage of those proteins in to 16 non-structural proteins (NSP1 –NSP16) [13–15]. Some of these NSPs, like NSP3, encode for papain-like proteases (PLP) and NSP5 codes for 3CL-proteases. Both of these proteins form a polypeptide "Replication transcription complex" (RTC) and helps in innate immune response blockage via genomic transcription and translation process. NSP15 encodes for RNA helicase, whereas NSP12 for RNA dependent RNA polymerase (RdRp) and synthesis of subgenomic RNAs (sgRNAs) stand genomic RNAs occurs [16] (Fig. 1).

Other NSPs protein functions are listed below in Table 1

Four Structural proteins are coded by ORFs located on 3′ end:

1) Membrane (M) shape the virions [17].
2) Spike (S) recognizes the ACE2 receptor on the host cell surface [18].
3) Envelope (E) helps in assembly and release of virions [19].
4) Nucleocapsid (N) packages the genome in the virions, provides pathogenicity.

There are many other structural and accessory proteins that are specific to the different species. Membrane exocytosis helps budding of completed assembled SARS-COV-2 particles via endoplasmic reticulum in the endoplasmic reticulum-golgi intermediate compartment (ERGIC). It is currently known that interaction of mainly M protein with different structural proteins of virus E, S aids in the generation of the virion scaffold promoting assembly, budding, and release of mature virus particle by exocytosis. After the final phase of maturation, all the components of the virus fit together, the particle is infectious and ready to begin a new cycle [20–23].

Epidemiology

Coronaviruses which mainly infect birds and mammals, comprise a large family (Coronaviridae) of giant enveloped positive-strand RNA viruses, which can be a cause of upper and lower respiratory tract infections (RTI) manifest as pneumonia, bronchitis, MERS, SARS, COVID 19. These three new coronaviruses caused respiratory disease outbreaks with their unique features, but SARS and MERS are less infectious and have significantly higher fatality rates than SARS-COV-2. The following Table 2 demonstrates the fundamental difference between the three of them [57–59].

Origin

Disease spread globally over eight million after the emergence of many pneumonia-like cases in Wuhan, Hubei province China (Early December 2019).

Topological dispersal

On December 31, 2019, the Chinese government first confess the numerous cases of pneumonia of an unknown cause presumed to be a zoonotic illness that would later be called COVID 19. The first case of death was reported on January 11. The Wuhan city was locked down with over 11 million populations on January 23. A week later, thousands of cases were reported, and WHO immediately declared a global health emergency [60]. With the start of July 2020, there were approximately 8.6 million cases and 450,000 deaths due to COVID 19 [61].

Global response

Italy

Italy was the following unfortunate country after China experienced a significant outbreak and resulted in the highest death rate, 7.2%. Milan, the most dynamic city alone, represents 10% of the Italian economy, "The country's economic engine" was drastically slowed after Italy experienced a surge in coronavirus cases. Italy went from discovering the first official COVID 19 case to the prohibition of all movements and non-essential business activities in a matter of weeks (February 21- March 22). Around 3,949,517 cases and 119,021 deaths took place until 25th of April 2021 [61].

France and Germany

The "quick and dirty Sunday morning" analysis confirmed the trend of viral proliferation in France and Germany exceeds more than in Italy, South Korea, and Japan with a similar temperature. The study also suggests that intense containment measures as in Italy, South Korea, and Japan may help to slowdown proliferation [62]. France is 4th country affected and around 5,473,579 cases and 102,713 deaths took place until 25th of April 2021. Germany 10th leading country in COVID 19 cases and around 3,277,661 cases and 82,117 deaths took place until 25th of April 2021 [61].

Japan

Japan, though with a more significant percentage of the population, experienced a low mortality rate compared to Italy mainly because of their cluster-based testing approach and adoption of the "**3C**" method (avoidance of closed spaces, crowded spaces, close contact) (Bloomberg, 2020). Around 556,999 cases and 9854 deaths were reported in Japan until 25th of April 2021 [61].

United States

U.S reached the highest count of reported cases worldwide from the first known patient in late January to August 28th where there are 6 million cases and nearly 2 lakh deaths. About 32,766,119 cases

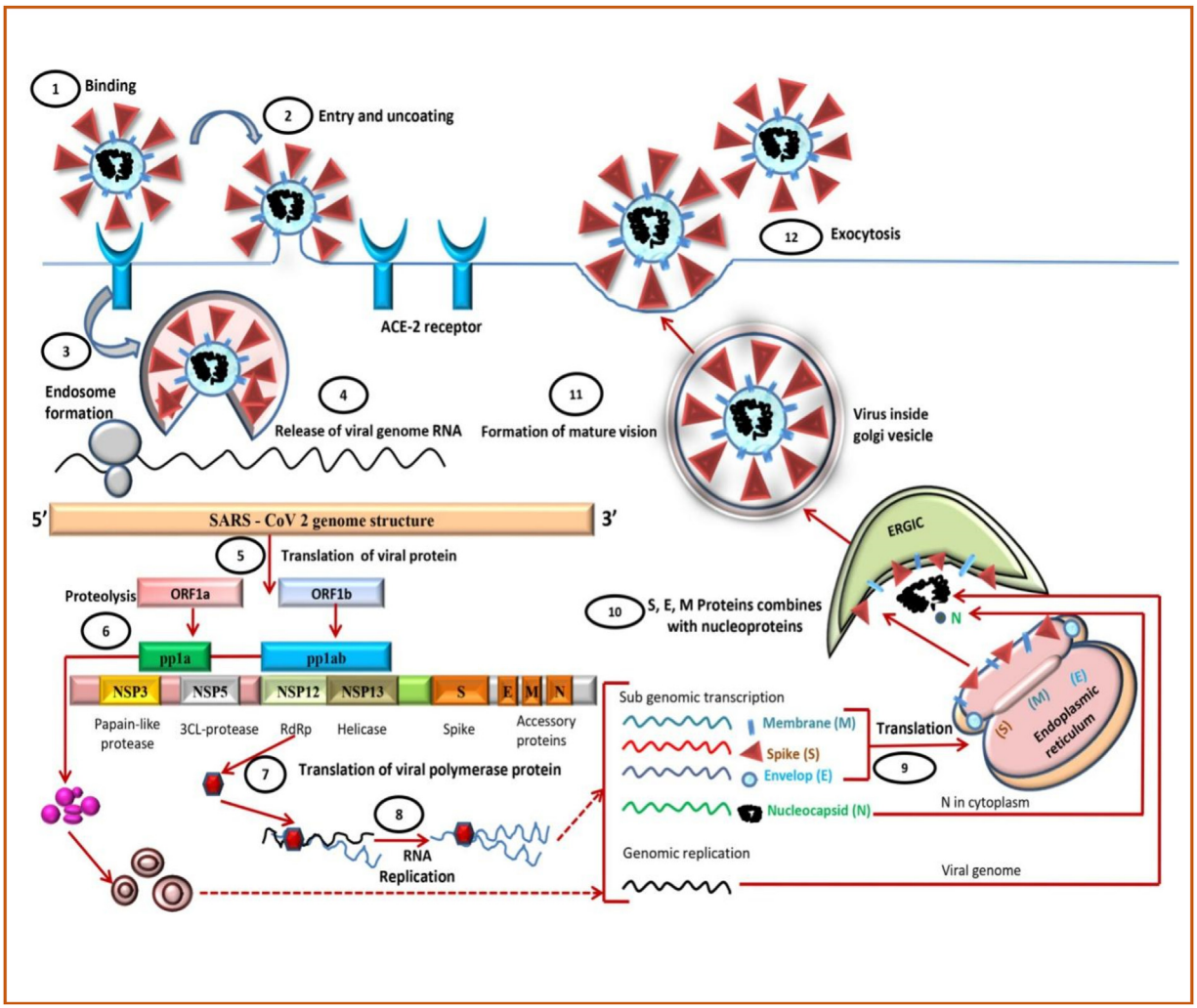

Fig. 1. The life cycle of SARS-CoV-2 in the host cells.

Table 1
Functions of non-structural proteins (NSP1-16).

Nonstructural Proteins	Function	Reference
NSP1	Innate immune response blockage by promotion of mRNA degradation	[24–27]
NSP2	Unknown function, binds to prohibiting proteins	[28,29]
NSP3	Papain lyase, cytokine expression promotion, blocking host innate immune response, activity of ADRP	[30–35]
NSP4	Potential transmembrane scaffold protein, maintains DMVs proper structure	[36,37]
NSP5	Main protease (Mpro), viral polyprotein cleavage	[38]
NSP6	Potential transmembrane scaffold protein	[39]
NSP7	NSP7 forms a hexadecameric complex with NSP8. For RNA polymerase, it acts as a processivity clamp	[40]
NSP8	For RNA polymerase, it acts as a processivity clamp and also plays a role as a primase	[41,42]
NSP9	Binding protein for RNA	[43]
NSP10	It acts as a cofactor for NSP14 and 16 by forming a heterodimer with both of them and stimulating the activity of N viral exoribonuclease (ExoN) and *O*-methyl transferase	[44,45]
NSP12	RdRp)	[46]
NSP13	RNA Helicase, 5′ Triphosphatase	[47,48]
NSP14	Shows ExoNactivity which is important for viral genome proofreading, addition of 5′ cap to viral RNAs by MTase.	[49–52]
NSP15	Endoribonuclease of virus	[53,54]
NSP16	*O*-methyl transferase (2′-O-MT); viral RNA shielding from MDA5 recognition	[55,56]

have been reported and 585,449 deaths had took place on 25th of April 2021 and US is at the forefront [61].

Brazil

The second highest number of cases is found in Brazil, especially the Amazon state country's northwest, which has the highest mortality rate. Manaus, the state capital, and the bustling city make the potential hotspots for transmitting the virus (CDC, 2020).). Brazil is third affected country and around 14,238,110 cases and 386,623 deaths took place until 25th of April [61].

Russia

Russia was centered in Moscow's city, accounted for the highest number of cases measuring 257.7 thousand, followed by Moscow

Table 2
Differences of SARS-COV, MERS CoV, SARS-COV-2.

	SARS-CoV	MERS-CoV	SARS-CoV-2
First notified	November 2002 in China's Guangdong province	September 2012, in Saudi Arabia	December 2019 in Wuhan, China
Mode of transmission	Infected civets, droplets produced by sneezing, coughing, breathing, talking	Droplets from person to person (unclear from camels to humans)	Droplets by coughing, sneezing, talking
Mean incubation period	4–5 days	6–7 days	1–14 days
Key symptoms	Dry cough at first, fever, malaise, body aches and pains, diarrhea (in the first or second week)	Fever, cough, shortness of breath, nausea/vomiting, diarrhea	Fever, dry cough, shortness of breath, fatigue
Treatment	No specific treatment	No specific treatment	No specific treatment
Mortality rate	11%	34%	3–4%
Vaccine	No vaccine	No vaccine	No vaccine

Table 3
Variants of concern (VOC).

Additional mutations and lineage	First detected	Substitutions on spike protein	Impact on immunity evidence
B.1.1.7 (20I/501Y.V1)	United Kingdom (Sept 2020)	Δ69/70, Δ144, (E484K*), (S494P*), N501Y, A570D, D614G, P681H, T716I, S982A, D1118H (K1191N*)	Unclear [2]
B.1.1.7 + E484K	United Kingdom (Dec 2020)	E484K, N501Y, D614G	Neutralisation (v) [2,5]
B.1.351 (20H/501.V2)	South Africa (Sep 2020)	D80A, D215G, Δ241/242/243, K417N, E484K, N501Y, D614G, A701V	Escape (v) [7,8]
B.1.427 (20C/S:452R)	U.S.A (California)	L452R, D614G	Neutralisation (v)
B.1.429 (20C/S:452R)	U.S.A (California)	S13I, W152C, L452R, D614G	Neutralisation (v)
P.1 (20J/501Y.V3)	Japan/Brazil	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	Neutralisation (v) [11]

* = Aminoacid substitution on the variants.

Oblast with 67 thousand cases by August 24, 2020. It has registered ten folds of low mortality than Spain, Britain, Italy, and France despite having many cases. The country's well-funded healthcare system is to be appreciated for managing better than those in the U.S and Western European countries. Mass testing (has nearly 6 million tests carried out so far) helps people identify and isolate more people affected by the virus. They quickly convert hospitals and clinics to virus treatment centers. Russia is also at top leading in COVID 19 cases. Around 4,753,789 cases and 107,900 deaths took place until 25th of April 2021 [61].

India

India, among all other countries, has the lowest fatality rate (2.41%) as of July 23 in the World even though it stands third after the United States and Brazil for having a large number of cases in Asia. The first case of COVID 19 was reported in Kerala on January 30. By mid of May 2020, 6 major cities like Delhi, Mumbai, Kolkata, Chennai, Pune, and Ahmedabad accounted for around 50% of all cases reported in the country [65]. In India, there is progressive rise of COVID 19 and about 16,951,621 cases and 192,309 deaths are reported till 25th of April 2021 [61].

Etiology in different groups

The virus is transmitted via major routes such as droplets, contact, and aerosols. It has also been detected in the faecal samples of patients in the United States and China. Major risk factors include people more than 60 years of age, and even people underlying non-communicable diseases (NCDs): diabetes, hypertension, chronic lung disease, cerebrovascular disease, cardiac disease, chronic kidney failure, immune-suppression and cancer patient. Due to immunosuppressive state and many other physiological adaptive changes pregnant women are more susceptible to RTI but currently evidence of SARS-CoV-2 transmission through the placenta to the new-born has not been observed. In one of the studies, the samples of amniotic fluid, blood obtained from the umbilical cord, throat swab of neonates, and maternal milk were collected from newborn babies whose mothers were SARS-CoV-2 positive. Still, none of the neonates were found to be positive [66].

Mutations and severity of infection

Before SARS-CoV-2 other viruses also mutate themselves. There are different mutant variants of SARS-CoV-2 that have reported and increased the severity of infections. In UK, new and emerging respiratory virus threats advisory group (NERVTAG) published a paper with the result outcome from many preliminary analyses of B.1.1.7 [67]. One of the variants was detected in England and was highly transmissible and got dispersed to several other countries. This variant contains seventeen mutations in the genome in which 8 are on S protein which is main antigenic target of 3 SARS-CoV-2 vaccines that have been licensed in England [67]. The NERVTAG proposed that infections by B.1.1.7 have high chances of death, as compared to parent virus. The other highly infectious variant P.1 in Brazil was reported in the mid-2020. This variant has increased the rate of infections, severity of the disease and the Manaus city, in Brazil where the health department is totally in a collapsed position. Today Brazil is third leading country in the SARS-CoV-2 infection globally because of these variants [67].

The B.1.351 variant was first identified in South Africa in 2020. The vaccines manufactured by Moderna claimed on Jan 25, 2021 that our vaccine is effective against both B.1.1.7 and B.1.351 variants. However, the claim was based on an *in vitro* study. In addition to that, a South African variant was having decreased levels of neutralizing antibody titers. The company Pfizer has claimed that our vaccine will work against B.1.1.7 variant because of their investigations in laboratory, although these studies have not been peer reviewed [67]. As long as the variants emerged, the more havoc it will create, vaccines will not work and the severity of the disease will be more. In India, more than three hundred thousand cases hit each day as on 25th of April 2021 because of the double and triple mutant variants [61]. There should be big focus on the drug development against SARS-COV-2 rather than whole focus

Table 4
Variants of interest (VOI) [2].

Additional mutations and lineage	First detected	Substitutions on spike protein	Impact on immunity evidence
B.1.525	Nigeria (Dec 2020)	E484K, D614G, Q677H	Neutralisation
B.1.427/B.1.429	United States (Sep 2020)	L452R, D614G	Neutralisation
P.3	The Philippines (Jan 2021)	E484K, N501Y, D614G	Neutralisation
B.1.616	France (Feb 2021)	V483A, D614G, H655Y, G669S	
B.1.617 (20A)	India (Feb 2020)	L452R, E484Q, D614G	
B.1.617.1 (20A/S:154K)	India (Dec 2020)	(T95I), G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	Neutralisation
B.1.617.2 (20A/S:478K)	India (Dec 2020)	T19R, (G142D), Δ156, Δ157, R158G, L452R, T478K, D614G, P681R, D950N	Neutralisation
B.1.617.3 (20A)	India (Oct 2020)/(Feb 2021)	T19R, G142D, L452R, E484Q, D614G, P681R, D950N	Neutralisation
B.1.620	Place not clear (Feb 2021)	S477N, E484K, D614G	Neutralisation
B.1.621	Colombia (Jan 2020)	R346K, E484K, N501Y, D614G	Neutralisation

Table 5
Variants of monitoring.

Additional mutations and lineage	First detected	Substitutions on spike protein	Impact on immunity evidence
B.1.214.2	Place not clear (Dec 2020)	Q414K, N450K, ins214TDR, D614G	
A.23.1 + E484K	United Kingdom (Dec 2020)	E484K, Q613H	Neutralisation
A.27	Place not clear (Dec 2020)	L452R, N501Y, H655Y	Neutralisation
A.28	Place not clear (Dec 2020)	E484K, N501T, H655Y	Neutralisation
C.16	Place not clear (Oct 2020)	L452R, D614G	Neutralisation
C.37	Peru (Dec 2020)	L452Q, F490S, D614G	
B.1.351 + P384L	South Africa (Dec 2020)	P384L, K417N, E484K, N501Y, D614G	Escape
B.1.351 + E516Q	Place not clear (Jan 2021)	K417N, E484K, N501Y, E516Q, D614G	Escape
B.1.1.7 + L452R	United Kingdom (Jan 2021)	L452R, N501Y, D614G	Neutralisation
B.1.1.7 + S494P	United Kingdom (Jan 2021)	S494P, N501Y, D614G	Neutralisation
C.36 + L452R	Egypt (Dec 2020)	L452R, D614G	Neutralisation
AT.1	Russia (Jan 2021)	E484K, D614G	Neutralisation
B.1.526 (20C/S:484K)	United States New York (Nov/Dec 2020)	(L5F*), T95I, D253G, (S477N*), (E484K*), D614G, (A701V*)	Neutralisation
B.1.526.1 (20C)	United States New York (Oct/Nov 2020)	D80G, Δ144, F157S, L452R, D614G, (T791I*), (T859N*), D950H	Neutralisation
B.1.526.2	United States (Dec 2020)	S477N, D614G	
B.1.1.318	Place not clear (Jan 2021)	E484K, D614G	Neutralisation
P.2	Brazil (Jan 2021)	E484K, D614G	Neutralisation

* Detected in few sequences but not all.

on the vaccines. Such as in cases of other viral diseases which have been controlled by drugs not by vaccines like HIV. Vaccines may be effective against a single variant but drugs might work against many variants as is evidenced by many antiviral drugs. There are three CDC established classifications for multiple variants of the virus in collaboration with SIG. They are: variant of concern (VOC), variant of interest (VOI), and variant of high consequences (VOHC).

VOHC's

These variants have clear evidence that medical counter measures (MCMs) or measures for prevention reduced the effectiveness significantly compared to the previous variants. Fortunately, there are no SARS-CoV-2 variants observed so far at this high level of consequences [68].

VOC's

There is a clear evidence of transmissibility, severity, and immunity which require efforts to control the virus spread, CDC reporting, health actions of public, test and research to evaluate the vaccine effectiveness [68]. List of variants are given in Table 3.

VOI's

These variants have genetic markers which are specific which changes the binding of receptor, treatment efficacy reduction, has a clear evidence of transmissibility, severity, neutralization reduction by previously generated infection or vaccination. These variants require health actions of public, increased laboratory characterization, assessing how quickly the virus spreads by epidemiological investigations. B.1.617 and B.1.617.2 are classified as VOC by WHO and UK on 7th May 2021 respectively [2]. List of variants of interest are given in Table 4.

Table 6
Effect and management of corona in different phenotypes.

L-Phenotype	H-Phenotype
Low elastance (HLC)	High elastance (LLC)
Low ventilation perfusion ratio	High shunt from right to left
The low weight of lung	The high weight of lung
Low recruitability	High recruitability
PaO_2/FiO_2 = 95 mmHg	PaO_2/FiO_2 = 84 mmHg
Non-intubated patients	Severe ARDS treated patients
-HFNC, CPAP, NIV	-PEEP is higher,
Intubated patients:	-Prone position lying
-Volumes greater than 6 mg/kg (up to 8–9 mg/kg) can be ventilated for hypercapnic patients	-Extracorporeal support
-PEEP reduced 8–10 cm H_2O	
-Prone positioning only as a rescue maneuver	

Variants under monitoring

Through genomic variant rules-based screening, preliminary scientific evidence, epidemic intelligence these variants are detected as signals. There is a weak evidence which is not been assessed by European centre for disease prevention and control (ECDC) that they show similar properties as of VOC (Table 5).

Biomarkers helpful in assessing the clinical trend are HFNC (high-flow nasal cannula), CPAP (continuous positive airway pres-

Table 7
Overview of efficacy of various marketed COVID 19 vaccine in human subjects.

	Dose regimen	Formulation	Effective against (Phase III trails)	Post implementation effectiveness	Response in humans for antibodies	Response in humans for T cells	References
mRNA Pfizer/BioNtech (BNT162b2)	30 g Mrna, 2 doses, 21 days apart	To lock protein in the pre – fusion state "S" subunit is modified by two mutations of proline by forming lipid nanoparticle	After 2 doses – 95% After 1 dose – 52% Data review suggestion 14 days after 1st dose – 93% 6 months post 2nd dose – 91%	Symptomatic infection - 1 dose – 94–96%2 doses – 46 –80% Asymptomatic infection : 1 dose – 79% 2 doses 90% Hospitalization: 1 dose – 71–85% 2 doses - 87% Any infection: 1 dose – 46–72% 2 doses 86–92%	After 2nd dose S1-binding antibody increases. Nab was present in significant amount after 2nd dose	After 2nd dose increase in antigen-specific IFNγ^+ CD4$^+$ and CD8$^+$ T cells, more IFNγ and IL-2 secretion than IL- 4, T_H1 cell polarization	[80]
Moderna (Mrna – 1273)	100 g Mrna, 2 doses, 28 days apart	To lock protein in the pre – fusion state "S" subunit is modified by two mutations of proline by forming lipid nanoparticle	After 1 dose – 95% After 2 doses – 92%	Symptomatic infection - 1 dose – 80% 2 doses – 90%	After 14 days S - binding antibody detected and its levels increases slightly by 28 days and marked increase after 2nd dose. Nab levels are minimum after 1st dose reaches at peak after 2nd dose 14 days	After 1st dose small increases in TNF and IL-2-secreting cells. After 2nd dose Significant increases in CD4$^+$ T cells secreting T_H1 type cytokines (TNF > IL-2 > IFNγ). Minimum change in T_H2 cell, CD8$^+$ responses	
Viral vector Oxford University/Astra-Zeneca (ChAdOx1 nCoV-19)	2.5–5 $\times$ 10^{10} viral particles, 2 doses, $\geq$28 days apart	Simian adenovirus vector recombinant replication – deficient full – length S protein with a Tpa leader sequence	After 1 dose – 76% After 2 doses – 62–67% Low dose followed by high dose – 90% $\geq$12-week interval, (81%), <6-week interval (55%)	Hospitalization : After 1st dose 80–94%	After 14 days S - binding antibody detected and its levels increases slightly by 28 days and marked increase after 2nd dose 14 days. More IgG3 and IgG1. Nab detected after 1st dose and increases after 14 days of 2nd dose. After 28–56 days of single dose and peak IgM and IgA responses at day 14 or 28	After 1st dose 14 days Peak T cell responses which is higher after 28 days 2nd dose. At 14 day there is increase in TNF and IFNγ production by CD4$^+$ T cells	
Gamaleya Research Institute (Gam-COVID-Vac)	10^{11} viral particles, 2 doses, 21 days apart	Dose 1 human adenovirus 26 replication-deficient, recombinant	After dose 1 74% After dose 2 91%	–	After 14 days of 1st dose - NAb (61)% S – binding antibody (85–89%) are detected. After 14 days of 2nd dose- binding antibody (98%) and neutralizing antibody (95%)	After 1st dose 14 days CD4$^+$ and CD8$^+$ T cells are observed. After 2nd dose 7 days S-specific IFNγ responses are observed	
Janssen (Ad26.COV2.S)	5 $\times$ 10^{10} viral particles, 1 dose	S protein two amino acid changes at S1/S2 junction that remove cleavage of furin and 2 proline substitutions for replication-deficient recombinant Human adenovirus 26	After 1st dose 67%	-	After 28 days of vaccination S-binding and neutralizing antibody are present and their levels remain after 84 days of post vaccination.	At 14 and 28 days of post vaccination CD4$^+$ and CD8$^+$ T cells are present IFNγ and/or IL-2 secretion suggesting T_H1 cell	
CanSino Biologics (Ad5-nCoV)	1 dose 5 $\times$ 10^{10} viral particles	Simian adenovirus vector recombinant replication – deficient full – length S protein with a Tpa leader sequence	After 1st dose 66% Decreases to 50% at 5–6 months	After 1st dose Hospitalization (80–94%)	RBD binding antibodies are observed after 14 days of vaccination (44%). Anti RBD binding antibodies after 28 days of vaccination, Nab's (47–50%)	After 28 days 78–88% had T cell response based on IFNγ ELIspot After 14 day peak T cell responses were observed	

Table 7 (*Continued*)

	Dose regimen	Formulation	Effective against (Phase III trails)	Post implementation effectiveness	Response in humans for antibodies	Response in humans for T cells	References
Protein subunit Novavax (NVX – CoV2373	(5 μg protein, 2 doses, 21 days apart	Full-length S protein with mutations at S1/S2 cleavage	After 2nd dose 7 days 90%		After 1st dose 21 days S-binding antibody and Nab is detected After 2nd dose- 7 days significant increase is observed	After 2nd dose 7 days $CD4^+$ T cell responses are observed. Based on IL-2 and TNF production T_H1 cell phenotype; minimal T_H2 cell responses are measured	
Whole - cellinactivated virus Bharatth Biotech (BBV152)	6 μg protein, 2 doses, 28 days apart	Grow SARS – CoV-2 in Vero cells adsorbed on to aluminium hydroxide and imidazoquinoline molecule after inactivation with β-propiolactone	After 2 doses 78%		After 1st dose anti – S binding antibodies are observerd (65%), NAbs (48%) After 2nd dose 14 day (98%) and 97% respectively	Strong bias towards T_H1 cell phenotype (IFNγ and TNF), with minimal T_H2 cell responses After 2nd dose 76 day $CD4^+CD45RO^+$ memory T cells increases	

sure), NIV (noninvasive ventilation), PEEP (positive end-expiratory pressure), FiO2 (fraction of inspired oxygen), PaO2 (partial pressure of arterial blood), ARDS (acute respiratory distress syndrome), HLC (High Lung Compliance), LLC (Low lung Compliance) [68].

Management of COVID 19

Breathing movement: oxygen support: 5–15% of patients with COVID 19 require intensive care and ventilatory support as it pri-

Table 8
Draft of COVID 19 vaccine candidates- WHO landscape 2020.

Description of vaccine	Type of vaccine candidate	The target for coronavirus	Non-corona virus candidate's same platform	Developers
A vaccine based on DNA	Vaccine inserts compatible with multiple delivery systems are engineered	SARS-CoV-2 and Sarbeco-CoV		University of Cambridge + DIOSynVax Ltd
	DNA Vaccine	SARS-CoV2		University of Ege
	Plasmid DNA vaccine N and RBD			Nottingham/Nottingham Trent University/Scancell
	DNA with electroporation			Cobra Biologics/Karolinska Institute
	DNA with electroporation			Vaccine Research Center Chula
	DNA			Evvivax/Applied DNA Sciences/Takis
	Needle-free delivery for DNA with plasmid		SARS	PharmaJet/Immunomic Therapeutics, Inc./EpiVax, Inc.
	S, S1, S2, RBD and N, DNA plasmid vaccine			Egypt, National Research Centre
	DNA vaccine			BioNet Asia
	ms DNA vaccine			Waterloo University/MediphageBioceuticals
	DNA Vaccine			Santos Pharmaceuticals
	S-gene containing DNA plasmids			Biosun Pharmed
	Plasmid vaccine with DNA			Bangladesh, Globe Biotech Limited
	Nanostructured RBD with plasmid DNA			Slovenia, National Institute of Chemistry
	Vaccine encoding RBD with plasmid DNA			Norway, Vaccibody, Oslo Research Park
	Immunostimulatory DNA sequences			Inserm
Inactivated virus (IV)	CpG 1018 + Inactivated, egg-based, Membrane expressing whole Chimeric Newcastle Disease Virus (NDV) - SARS - CoV- 2, S protein (Lexapro) anchored Pre-fusion-stabilized trimeric			PATH/Dynavax/Institute of Vaccines and Medical Biologicals (IVAC; Vietnam)
	CpG 1018 + Inactivated, egg-based, Membrane expressing whole Chimeric Newcastle Disease Virus (NDV) - SARS - CoV- 2, S protein (Lexapro) anchored Pre-fusion-stabilized trimeric			PATH/Dynavax/GPO; Thailand)
	CpG 1018 + Inactivated, egg-based, Membrane expressing whole Chimeric Newcastle Disease Virus (NDV) - SARS - CoV- 2, S protein (Lexapro) anchored Pre-fusion-stabilized trimeric			PATH/Dynavax/Institute Butantan (Brazil)
	Alum + Inactivated		J.E., ZIKA	KM Biologics
	Inactivated			University of Selcuk
				NIBIOHN/BIKEN/University of Osaka
	CpG 1018 + Inactivated			Dynavax/Sinovac
	CpG 1018 + Inactivated			Dynavax/Valneva

Table 8 (*Continued*)

Description of vaccine	Type of vaccine candidate	The target for coronavirus	Non-corona virus candidate's same platform	Developers
	The whole virus Inactivated			Egypt, National Research Centre
	Inactivated			Kocak Farma Ilac ve Kimya San. A. S
	Alum + Inactivated			Shifa Pharmed
	Inactivated		MMR, IPV	Milad Pharmaceutics Co.
	Inactivated		MMR, IPV	Zista Kian Azuma Co.
Live attenuated virus (LAV)	Live attenuated vaccines, which are codon deoptimized			AcıbademLabmed Health Services A.S./Mehmet Ali Aydinlar University
	Live attenuated vaccines, which are codon deoptimized			University of Griffith/Indian Immunologicals Ltd
Live attenuated bacterial vector (LABV)	Live attenuated vaccine bacterial (pertussis)			Institut Pasteur Lille
	Live attenuated bacterial vector			TheRex, ALtraBio
Viral vector (non-replicating)	Sendai virus vector			I.D. Pharma
	Adenovirus-based			University of Ankara
	(AAV SARS-COV-2) Adeno-associated virus vector			AveXis/Massachusetts General Hospital/Massachusetts Eye and Ear
	VLP encoded by MVA		MARV, HIV, EBOV, LASV	BravoVax/GeoVax
	MVA-S encoded		Multiple candidates	IDT Biologika GmbH/GCIR-DZIF
	MVA-S			Spain, IDIBAPS-Hospital Clinic
	Adeno5-based			University of Erciyes
	(GREVAX™ platform) Ad5 S		MERS	Greffex
	Oral Ad5 S		HSV-2, VZV, Zika and Norovirus	Stabilitech Biopharma Ltd
	HLA-matched peptides + adenovirus-based	Pan-Corona		Valo Therapeutics Ltd
	Structural proteins expressing MVA	SARS-CoV2	Multiple candidates	Spain, Centro Nacional Biotecnología
	Spike protein expressing vaccine Parainfluenza virus 5 (PIV5)-based		MERS	Lowa University/Georgia University
	S1 containing Recombinant deactivated rabies virus		CCHFV, LASSA, EBOV, MERS, NiV, HeV	Thomas Jefferson University/Bharat Biotech
	H1N1 vector H1N1 vector			Egypt, National Research Centre
	S expressing Newcastle disease virus			Mount Sinai, Icahn School of Medicine
	Lentiviral Vector			Institut Pasteur -Theravectys
	Lentiviral Vector			AIOVA
	Retro-VLP Particles Lentiviral Vector			University of Sorbonne
	intranasal administration Ad 5 vector			Eastern Finland University and Helsinki University
	TBD		VEE, HBV, RVF, EBOV, LASV, CHIKV, NORV, InfA	Vaxart
Protein subunit (P.S.)	Mannose-conjugated chitosan nanoparticle delivered via RBD protein			University of Kazakh National Agrarian/University of Ohio State
	Essai O/W 1,849,101 adjuvant with recombinant spike protein			University of Kazakh National Agrarian
	Peptides			Neo7Logic
	Essai O/W 1,849,101 adjuvant with recombinant spike protein			National Scientific Center for Especially Dangerous Infections/Kazakhstan, University of Kazakh National Agrarian
	Recombinant spike protein			Colloids and Interfaces Max-Planck-Institute
	FAR-Squalene adjuvant + RBD protein (baculovirus production)			Universidad Peruana Cayetano Heredia (UPCH)/FarmacológicosVeterinarios SAC (FARVET SAC)
	Protein Subunit			Rep of Kazakhstan, Research Institute for Biological Safety Problems
	RBD-protein			Mynvax
	Recombinant S protein			Biomedicine and Genome Center Izmir
	Novel adjuvant + Peptide		HIV, Malaria, Zika, NSCLC	University of Bogazici
	3M052 adjs./S subunit intranasal liposomal formulation with GLA			University of Virginia
	Adjuvant, E coli-based Expression + S-Protein (Subunit)			Nigeria, Oyo State, Ogbomoso, Trinity Immonoefficient and Ogbomoso Laboratory, Helix Biogen Consult
	S, N, M and S1 protein subunit			Egypt, National Research Centre
	Protein Subunit			Argentina, San Martin and CONICET University
	Adj. + RBD protein fused with Fc of IgG			Thailand, GPO/University of Chulalongkorn
	Capsid-like Particle			AdaptVac (PREVENT - n CoV consortium)
	VLPs Drosophila S2 insect cell expression system			ExpreS2ion
	LNP formulated peptide antigens			IMV Inc
	S Protein			USAMRIID/WRAIR

Table 8 (*Continued*)

Description of vaccine	Type of vaccine candidate	The target for coronavirus	Non-corona virus candidate's same platform	Developers
	Adjuvant + Sprotein		Influenza	UMN Pharma/Shionogi/National Institute of Infectious Disease, Japan
	Adjuvant + VLP-recombinant protein			BIKEN/University of Osaka/National Institutes of Biomedical Innovation, Japan
	S1 subunit microneedle arrays		MERS	Pittsburgh University
	Peptide			Vaxil Bio
	Adjuvanted protein subunit (RBD)			Biological E Ltd
	Peptide		Breast CA vaccine, HPV therapeutic vaccine, ZIKA, Ebola, Marburg, HIV, Influenza	Flow Pharma Inc
	S protein			A.J. Vaccines
	Ii-Key peptide		SARS-CoV, Influenza, HIV	EpiVax/Generex
	S protein		H7N9	Georgia University/EpiVax
	EPV-CoV-19 protein subunit			EpiVax
	gp-96 backbone		HIV, Malaria, Zika, NSCLC	Miami University/Heat Biologics
	vaccine subunit			Koltsovo, Rospotrebnadzor, FBRI SRC VB VECTOR
	RBD protein or S1		SARS	Baylor College of Medicine
	Plant produced protein subunit			CC-Pharming/iBio
	Nanoparticles (based on S-protein and other epitopes), recombinant protein			Saint-Petersburg scientific reseacrh institute of vaccines
	Truncated S (spike) proteins SARS-COV-2 XWG-03		HPV	GSK/University of Xiamen/Innovax
	Microsphere adjuvanted peptide			VIDO-Intervac, Saskatchewan University
	S and M proteins synthetic Long Peptide Vaccine candidate			OncoGen
	S and N proteins Oral *E. coli*-based protein expression system			MIGAL Galilee Research Institute
	Nanoparticle vaccine			Lake Pharma, Inc.
	(RBD-Fc + Adjuvant) plant-based vaccine			Chula Vaccine Research Center/BaiyaPhytopharm
	vaccine based on OMV		Flu A, Plague	Quadram Institute Biosciences
	vaccine based on OMV			Trento University/BiOMViSSrI
	tobacco mosaic virus (TMV) structurally modified spherical particles		Rotavirus, Rubella	University of Lomonosov Moscow State
	Spike-based		Hepatitis C	Alberta University
	S1-Fc fusion recombinant protein			AnyGo Technology
	Recombinant protein			Yisheng Biopharma
	(Insect cell line baculovirus expression system)			Bristol University U.K. and Vietnam, Vabiotech
	Recombinant S protein in IC-BEVS			Applied Biotechnology Institute, Inc.
	Heat stable, orally delivered subunit			Axon Neuroscience S.E.
	Spike protein peptides			G.C. Pharma, MOGAM Institute for Biomedical Research
	Protein Subunit			Tel Aviv University/Neovii
	RBD-based			Epivax/Intravacc
	OMVsubunit			LiteVax BV ImmunoPrecise
	(Epitope screening) Spike-based			University of Ankara, Middle East Technical University, Nanografi Nano Technology
	Spike-based			Iran
	Adjuvant with a recombinant spike			University of Tampere
	BEVS produced recombinant S protein			INRAE, CEA, Vaxinano
	Nanoformulated protein subunit			CNRS, CEA
	Adenoviral Carrier protein subunit			VRI, LinkinVax
	DC-targeted epitopes			Universidad Peruana Cayetano Heredia (UPCH)/FarmacológicosVeterinarios SAC (FARVET SAC)
Bacterial vector replicating	Protein expression system of RBD based on Oral Salmonella enteritidis (3934Vac)			K.U. Leuven
Viral vector Replicating	YF17D Vector			Cadila Healthcare Limited
	Measles Vector			Koltsovo, Rospotrebnadzor, FBRI SRC VB VECTOR
	Measles Vector			CanVirex AG/DZIF - German Center for Infection Research
	S, N targets measles virus		CHIKV, H7N9, Zika	Southern Research/Tonix Pharma
	S protein expressing horsepox vector		Monkeypox, Smallpox	IEM and BIOCAD
	(Intranasal) Atenuated influenza virus backbone LVVV		Influenza	Koltsovo, Rospotrebnadzor, FBRI SRC VB VECTOR
	(Intranasal) Influenza A virus, recombinant vaccine		Influenza	

Table 8 (*Continued*)

Description of vaccine	Type of vaccine candidate	The target for coronavirus	Non-corona virus candidate's same platform	Developers
	Expressing antigenic portion of the Spike protein attenuated influenza		Influenza	Fundação Oswaldo Cruz and Instituto Buntantan
	RBD expressing influenza vector			Hong Kong University
	SARS-CoV-2 Spike (S) glycoprotein delivered by Replication-competent VSV chimeric virus technology (VSVΔG)		Lassa, Marburg, Ebola	Merck/IAVI
	DC-targeting replicating VSV vector			Manitoba University
	VSV-S		MERS, HIV	Western Ontario University
	VSV-S			Aurobindo
	VSV vector			FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo
	Influenza vector M2-deficient single replication (M2SR)		Influenza	Bharat Biotech/FluGen/UW-Madison
	(NDV-SARS-CoV-2/Spike) Newcastle disease virus vector			Utrecht University/Intravacc/Wageningen Bio veterinary Research
	(APMV) Avian paramyxovirus vector	SARS-CoV3		University of Lancaster, UK
	RBD expressing Intranasal Newcastle disease virus vector (rNDV-FARVET)			Universidad Peruana Cayetano Heredia (UPCH)/FarmacológicosVeterinarios SAC (FARVET SAC)
Vaccine based on RNA	NLC saRNA formulated	SARS-CoV2		Amyris, Inc. Infectious Disease Research Institute
	S encoding LNP-encapsulated Mrna			Max-Planck-Institute of Colloids and Interfaces
	Self-amplifying RNA			Gennova
	mRNA		Live, attenuated virus (LAV)	University of Selcuk
	LNP-mRNA			Sanofi Pasteur/Translate Bio
	LNP-mRNA			Precision Nanosystems/CanSino Biologics
	Cocktail encoding VLP LNP-encapsulated Mrna		Live, attenuated bacterial vector (LABV)	RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University
	RBD encoding LNP-encapsulated mRNA			RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University
	SARS-CoV-2 derived replicating Defective RNAs			Centro Nacional Biotecnologia (CNB-CSIC), Spain
	mRNA encapsulated LNP		MERS	Daiichi-Sankyo/Tokyo University
	mRNA encapsulated Liposome			BIOCAD
	mRNA candidates			RNAimmune, Inc.
	mRNA			Koltsovo, Rospotrebnadzor, FBRI SRC VB VECTOR
	mRNA			Stermina/University of Tongji/China CDC
	Intranasal delivery system mRNA			eTheRNA
	mRNA			Greenlight Biosciences
	mRNA			IDIBAPS-Hospital Clinic, Spain
	mRNA			Providence Therapeutics
	mRNA			Cell Tech Pharmed
	mRNA			ReNAP Co
	LNP-encapsulated mRNA D614G variant			Globe Biotech Ltd
	Encapsulated mRNA			CEA
Protein subunit	SARS-CoV-2 S, M, N and NSPs targets to induce T cell responses (CD8)			OSE immunotherapeutics
sVirus like particle	VLP			Max Planck Institute for Dynamics of Complex Technical Systems
	Virus-like particle-based Dendritic Cell (D.C.)-targeting vaccine			Manitoba University
	VLP			University of BezmialemVakif
	VLP			Middle East Technical University
	(eVLP) Enveloped Virus-Like Particle	SARS-CoV-2, SARS-CoV, & MERS-CoV	CMV, GBM, Zika	VBI Vaccines Inc.
	HIV VLPs integrated by S protein	SARS-CoV2		Grifols/Barcelona Supercomputing/IRTA–CReSA/IrsiCaixa AIDS Research
	Adjuvant + VLP			GPO/Siriraj Hospital/University of Mahidol
	Baculovirus vehicles, Virus-like particles and lentivirus		Malaria	Oncoimmunology group, Navarrabiomed
	RBD displayed on virus-like particles			Saiba GmbH
	Multiepitope display ADDomerTM			Bristol University's Max Planck Centre and Imophoron Ltd
	Unknown			Doherty Institute
	VLP	SARS-CoV1, SARS-CoV2		OSIVAX

Table 8 (*Continued*)

Description of vaccine	Type of vaccine candidate	The target for coronavirus	Non-corona virus candidate's same platform	Developers
	eVLP	SARS-CoV2	Malaria	ARTES BiotechnologARTESBiotechnolog
	Whole virus/VLPs peptides			Sao Paulo University
	VLPs produced in BEVS			University of Tampere
	VLP derived by plant			University of Shiraz

marily injures the vascular endothelium as it is a systemic disease, and a patient with COVID 19 ARDS that is covid 19 acute respiratory distress syndrome (CARDS) can develop multiorgan failure if not managed expertly. There are two types of SARS-COV-2 phenotypes for Respiratory support management. Target SpO2: 92–96% (82–92% in COPD patients), PaO2 $\geq$ 8 kPa = 60 mm Hg, PaCO2 < 6 kPa or pH > 7.3, FiO2 $\leq$ 0.4, Morphine sulphate, Midazolam, Benzodiazepine is given as per the severity of disease. Awake proning, monitoring C- reactive protein (CRP), CBC examination, chest x-ray [69]. Table 6, shown, demonstrates the differences between different phenotypes [70,71].

Cough management

Sixty percent of COVID 19 positive cases report dry cough with zero phlegm production due to inflammation or irritation in your respiratory tract, which can get better with steam, humidifiers, honey consumption, cough suppressants, saltwater gargle, codeine phosphate, morphine sulfate as per the severity of infection [72,73].

Fever management

Fever after five days of infection is the most common in 99% of cases as your body's normal immune response tries to kill a virus. Advising the patients to consume a large number of fluids and to take paracetamol or ibuprofen can help to manage fever. Still, the use of ibuprofen use has marked a question of concern as the adaptive immune response will interfere with the release of prostaglandins, suppressing the fever response also leads to an increase in activity of lymphocyte, hyperemic response, and organ tissues oxygenation, causing failure of multiple organs [74,75].

GI disturbances

Pain in the abdomen (3.6%), looseness of the bowels (10.1%), Emesis (3.6%) is joint in COVID 19 patients due to its ACE2 receptor, which is expressed highly in gastrointestinal intestinal epithelial cells. Also, its viral RNA has been found in stool specimens of patients. A cohort endoscopy study of 95 COVID 19 patients reported six additional cases and identified viral RNA in the stomach, esophagus, intestinal duodenum, and rectum from 2 severe cases. Treatment relies on supportive care, antiemetics, proton pump inhibitors (PPI), antidiarrheals, promethazine, ondansetron, metoclopramide, adequate hydration, fresh ginger boiled in water added with honey can also treat nausea and weakness can reduce vomiting. If loose motions persist, stop the diet and consume coconut water (John Wiley, 2020), (Lipi Roy, 2020).

Vaccines

Acute viral infections remain a leading cause of morbidity andmortality. This novel coronavirus pandemic has triggered unprecedented global health researchers and scientists to find a safe, effective vaccine against this virus. Extensive research can be done by gaining the knowledge from SARS and MERS vaccines development strategies and knowing the key targets such as receptor-binding domain (RBD) of spike protein, nucleotide identification, immunization route, suitable animal model utilization, production facility scalability, are some of the essential parameters to be considered [78]. There are seven COVID 19 vaccines in the third phase of clinical trials. Out of which four are from China, two of the candidates are from China National Biotec Group (CNBG) [79]. On August 27, Sputnik V advanced Russia vaccine trials of Sputnik V announced COVID 19 vaccine trials for over six months in forty thousand volunteers (Table 8).

COVID 19 vaccine efficacy

The vaccines were marketed in short span of time after the deadly pandemic. The most important thing was whether these vaccines have good efficacy in neutralising the SARS-CoV-2 virus or there is long term protection by generating memory B-cells and T-cells. In Table 7 we have discussed various marketed vaccines and their efficacy like the dosage regimen, antibody response, T cell response, and effectiveness. There are many vaccines which have received emergency approval in many countries. As of April 2021, 28 vaccines which have entered phase III clinical trials, and other 5 reported showed efficacy in the submitted reports to the peer-reviewed regulatory authorities for their emergency use through literature and/or through detailed publicly reports are available. For minimal protection 2 doses of vaccines are required for most of the them. Only 2 mRNA vaccines have shown efficacy at first dose after the detection of moderate TH1 cells and non neutralizing antibodies (Nabs). Induction of antibody dependent effector mechanisms, T-cell response, virus neutralization suggests that T cells, innate immune mechanisms, NAbs low levels and other immune effector mechanisms are involved which helps in easy identification of protection mechanism and further understanding of immune system involvement for further development of vaccines.

Conclusion

SARC-CoV-2 is a novel strain of coronavirus that is liable for causing the global pandemic. This has challenged all the crucial factors like the global economy, medical infrastructure, and public work life, particularly the variant strains are causing havoc. The impact of this pandemic is so severe that it has shaken most countries' economies. Since the tremendous advancement has been achieved in understanding the condition, shortly there seems a strong possibility of some of the therapeutic interventions to combat the SARS-COV-2 pandemic; till then, the only trusted intervention which is currently viable and proven to control is the following of strict quarantine measures, but to reach that intervention to all the affected groups there is a need of a more extensive set of randomized trials and fast testing of the condition to combat the disease effectively. However, this comprehensive review can provide some of the references for the follow-up medical studies. The spread of coronavirus trajectory across the World is difficult to predict as one country's problems will become global. The only possible solution is the vaccine development targeting against all variant strains to halt its progress, the identified theoretical and practical knowledge, current evidence, international alliances, ini-

tiatives, and ideas based on the values of cooperation, inclusiveness, and equity can eliminate the gaps to improve better understanding of the novel coronavirus structure and its design of a vaccine.

Author's contribution

TF and JAM contributed equally in data collection and drafting the article. AHM, TA and KA contributed in data analysis and interpretation, and drafting the article. SA supervision and critical revision. All authors approved the final version of the article.

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Competing interests

None declared.

Ethical approval

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