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Review Article

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

Tahmeena Farooqi1,1, Jonaid Ahmad Malikb,c,1, Almas Hanif Mullan, Turki Al Hagbanc, Khaled Almansourd, Mohammed Abrar Ubaidf, Saleh Alghamdi1, Sirajudeen Anwarh,∗

1 Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research, Hyderabad, Telangana, India
2 Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research, Guwahati, India
3 Department of Biomedical Engineering, Indian Institute of Technology (IIT), Roorkee, Punjab, India
4 Department of Pharmacology, Coa College of Pharmacy, Goa, India
5 Department of Pharmacaceutics, RG College of Pharmacy, Dosti, Tamil Nadu, India
6 Department of Clinical Pharmacy, Faculty of Clinical Pharmacy, Alba University, Alba, Saudi Arabia
7 Department of Pharmacology and Toxicology, College of Pharmacy, University of Hail, Hail, Saudi Arabia

ARTICLE INFO

Article history:
Received 24 May 2021
Received in revised form 7 August 2021
Accepted 10 August 2021

Keywords:
SARS-COV-2 Epidemiology Variant strains Vaccine candidates WHO landscape

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 meteors, 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; CanVixes 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, coronavirus 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; FiO2, fraction of inspired oxygen; GCGR, German Center for Infection Research; GMV, glycine virus; GLA, glucopyranosyl Lipid A; GPO, Government Pharmaceutical Organization; HeV, hepatitis E virus; HBV, hepatitis B virus; HFNc, high-flow nasal cannula; HIC, high lung compliance; IAVI, international AIDS vaccine initiative; IDIAPS, Pi I Sunyer Biomedical Research Institute; IEM, Institute For Engineering in Medicine; Infla, 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 marmannarens virus; LinKinVax, French biotechnology startup that focuses on speeding up vaccine; LiteVax BV, spike-based (epitope screening); LLV, 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; NERVTAQ, new and emerging respiratory virus Threats advisory group; NIV, Nipah virus; NIV, non-invasive ventilation; NLC, nanolstructured Lipid Carriers; NORV, norovirus; NSCLC, non-small cell lung cancer; NSF, non-Structural proteins; O-MT, O-methyl transferase-2; OMV, outer membrane vesicle; ORFs, open reading frames; Ovisax, clinical stage biotechnology company; PC, preclinical; PaCO2, partial pressure of carbon dioxide; PaO2, partial pressure of oxygen; PEEP, positive end-expiratory pressure; PIP, proton pump inhibitors; RR, receptor-binding domain; RFV, Rift Valley fever; RdRp, RNA dependent RNA polymerase; RT, replication transcription complex; RTP, respiratory tract infections; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SIG, SARS-COV-2 Interagency Group; SpO2, oxygen saturation; SRC VB VECTOR, State Research Centre of Virology and Biotechnology; TPMRSS2, transmembrane protein serine 2; TRS, transcriptional regulatory sequences; USAMRIID/WRARI, United States Army Medical Research Institute of Infectious; VEE, Venezuelan equine encephalitis; VIP, virus like particle; VOC, variant of concern; VONC, variant of high consequences; VOI, variant of interest; VRI, Vaccine Research Institute; VSV, vesicular stomatitis virus.

∗ Corresponding author.
E-mail address: si.anwar@uoh.edu.sa (S. Anwar).
1 These authors have equal contribution.

https://doi.org/10.1016/j.jiph.2021.08.014
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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.

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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, Coronavirinae 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 (TRRs) 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 infection 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 polyepitope “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
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) | ΔΔ69/70, ΔΔ144, (E484K*), (S494P*), N501Y, A570D, D614G, P681H, T716I, S982A, D1118H (K1191N*), | Unclear [2] |
| B.1.1.7 + E484K | United Kingdom (Dec 2020) | E484K, N501Y, D614G | Escape [v] [7,8] |
| B.1.1.7 + E484K | United Kingdom (Dec 2020) | D614G, Δ241/242/243, K417N, E484K, N501Y, D614G, A701V | Neutralisation [v] [2,5] |
| B.1.427 (20C/S:452R) | U.S.A (California) | L452R, D614G | Neutralisation [v] |
| B.1.429 (20C/S:452R) | U.S.A (California) | S13L, W152C, L452R, D614G | Neutralisation [v] |
| P.1 (20J/501Y.V3) | Japan/Brazil | L18F, T20K, F26S, D318Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I | Neutralisation [v] [11] |

* = Aminoacid substitution of variant.

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 new-born 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.
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.

**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-**
| Dose regimen | Formulation | Effective against (Phase III trials) | 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 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, Th1 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 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 Th1 type cytokines (TNF > IL-2 > IFNγ). Minimum change in Th2 cell, CD8+ responses | |
| Viral vector Oxford University/AstraZeneca (ChAdOx1 nCoV-19) | 2.5–5 × 10^10 viral particles, 2 doses, ≥28 days apart | Simian adenovirus vector recombinant replication – deficient full – length S protein with a Tpa leader sequence | After 1 dose ~ 76% | Hospitalization: After 1st dose 80–94% | After 1st dose 14 days Peak T cell responses which is higher after 28 days 2nd dose. At 14 day there is in 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 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 × 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 Th1 cell polarization | |
| CanSino Biologics (Ad5-nCoV) | 1 dose 5 × 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%) | |

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

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

| 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 DNA Vaccine Plasmid DNA vaccine N and RBD DNA with electroporation DNA with electroporation DNA Needle-free delivery for DNA with plasmid S, S1, S2, RBD and N, DNA plasmid vaccine DNA vaccine mS DNA vaccine DNA Vaccine S-gene containing DNA plasmids Plasmid vaccine with DNA Nanostructured RBD with plasmid DNA Vaccine encoding RBD with plasmid DNA Immunostimulatory DNA sequences CpG 1018 = Inactivated, egg-based, Membrane expressing whole Chimeric Newcastle Disease Virus (NDV) - SARS-CoV-2, S protein (Lexapro) anchored Pre-fusion-stabilized trimeric CpG 1018 = Inactivated, egg-based, Membrane expressing whole Chimeric Newcastle Disease Virus (NDV) - SARS-CoV-2, S protein (Lexapro) anchored Pre-fusion-stabilized trimeric CpG 1018 = Inactivated, egg-based, Membrane expressing whole Chimeric Newcastle Disease Virus (NDV) - SARS-CoV-2, S protein (Lexapro) anchored Pre-fusion-stabilized trimeric Alum + Inactivated Inactivated CpG 1018 = Inactivated CpG 1018 = Inactivated | SARS-CoV-2 and Sarbeco-CoV SARS-CoV2 | SARS | University of Cambridge + DIOSynVax Ltd University of Ege Nottingham/Nottingham Trent University/Scancell Cobra Biologics/Karolinska Institute Vaccine Research Center Chula Evivax/Applied DNA Sciences/Takis Pharmajet/Immunomic Therapeutics, Inc./EpiVax, Inc. Egypt, National Research Centre Biornet Asia Waterloo University/MediPhageBiocuticals Santos Pharmaceuticals Biosun Pharmaed Bangladesh, Globe Biotech Limited Slovenia, National Institute of Chemistry Norway, Vaccibody, Oslo Research Park Inserm PATH/Dynavax/Institute of Vaccines and Medical Biologicals (IVAC; Vietnam) | PATH/Dynavax/GPO; Thailand PATH/Dynavax/Institute Butantan (Brazil) |
| Description of vaccine | Type of vaccine candidate | The target for coronavirus | Non-corona virus candidate’s same platform | Developers |
|------------------------|---------------------------|---------------------------|------------------------------------------|-------------|
| Live attenuated virus (LAV) | The whole virus Inactivated | Inactivated | MMR, IPV | Egypt, National Research Centre |
|                         | Inactivated | Alum + Inactivated | IPV | Kocak Farma \(ve\) Kimya San. A. S |
|                         | Inactivated | Live attenuated vaccines, which are codon deoptimized | IPV | Shifa Pharmmed |
|                         | Live attenuated vaccines, which are codon deoptimized | | | Milad Pharmaceutics Co. |
| Live attenuated bacterial vector (LABV) | Adenovirus-based | VLP encoded by MVA | | Zista Kian Azuma Co. |
| (non-replicating) | (AAV SARS-COV-2) Adeno-associated virus vector | | | AcibademLabmed Health Services |
|                         | MAV-S encoded | | | A.S./Mehmet Ali Aydinalar University |
|                         | MAV-S Adenos6-based | | | Immunologicals Ltd |
|                         | (CBEVAX™ platform) Ad5 S | | | Institut Pasteur Lille |
|                         | Oral Ad5 S | | | TheRex, Altrabio |
|                         | HLA-matched peptides + adenovirus-based structural proteins expressing MVA Spike protein expressing vaccine Paramyxovirus virus 5 (PIV5)-based | Pan-Corona SARS-Cov2 | | University of Ankara |
|                         | S containing Recombinant deactivated rabies virus H1N1 vector H1N1 vector | | | AveXis/Massachusetts General Hospital/Massachusetts Eye and Ear |
|                         | S expressing Newcastle disease virus Lentiviral Vector | | | BravoVax/GeoVax |
|                         | Lentiviral Vector | | | |
|                         | Retro-VLP Particles Lentiviral Vector intranasal administration Ad 5 vector | | | |
|                         | TBD | | | |
| Protein subunit (P.S.) | Mannose-conjugated chitosan nanoparticle delivered via RBD protein | | | Thomas Jefferson University/Blarat Biotech |
|                         | MVA-O/W 1,849,101 adjuvant with recombinant spike protein | | | Egypt, National Research Centre |
|                         | Peptides | | | Mount Sinai, Icahn School of Medicine |
|                         | Essai O/W 1,849,101 adjuvant with recombinant spike protein | | | Institut Pasteur - Theravectys |
|                         | Recombinant spike protein | | | AIOVA |
|                         | FAR-Squalene adjuvant + RBD protein (baculovirus production) | | | University of Sorbonne |
|                         | Protein Subunit | | | Eastern Finland University and Helsinki University |
|                         | RBD-protein | | | Vaxart |
|                         | Recombinant S protein | | | University of Kazakhstan National Agrarian/University of Ohio State |
|                         | Novel adjuvant + Peptide | | | University of Kazakhstan National Agrarian |
|                         | 3M052 ads./S subunit intranasal liposomal formulation with GLA | | | Neo7Logic |
|                         | Adjuvant, E coli-based Expression + S-Protein (Subunit) | | | National Scientific Center for Especially Dangerous Infections/Kazakhstan |
|                         | S, N, M and S1 protein subunit Protein Subunit | | | University of Kazakhstan National Agrarian |
|                         | Adj. + RBD protein fused with Fc of IgG Capsid-like Particle | | | Colloids and Interfaces |
|                         | VLPs Drosophila S2 insect cell expression system LNP formulated peptide antigens S Protein | | | Max-Planck-Institute |
|                         | HIV, Malaria, Zika, NSCLC | | | Universidad Peruana Cayetano Heredia (UPCH)/FarmacologicosVeterinarios |
|                         | | | | SAC (PARET SAC) |
|                         | | | | Reg of Kazakhstan, Research Institute for Biological Safety Problems |
|                         | | | | Mynvax |
|                         | | | | Biomedicine and Genome Center Izmir University of Bogazici |
|                         | | | | University of Virginia |
|                         | | | | Nigeria, Oyo State, Ogbomoso, Trinity Immunonefficient and Ogbomo |
|                         | | | | Laboratory, Helix Biogen Consult |
|                         | | | | Egypt, National Research Centre |
|                         | | | | Argentina, San Martin and CONICET University |
|                         | | | | Thailand, GP0/University of Chulalongkorn |
|                         | | | | AdaptVac (PREVENT - n CoV consortium) |
|                         | | | | Expres2ion |
|                         | | | | IMV Inc |
|                         | | | | USAMRIID/WRAIR |
| Description of vaccine | Type of vaccine candidate | The target for coronavirus | Non-corona virus candidate’s same platform | Developers |
|------------------------|---------------------------|---------------------------|------------------------------------------|------------|
| S protein              | S protein                 | Influenza                 | UMN Pharma/SHionogi/National Institutes of Infectious Disease, Japan BIKEN/University of Osaka/National Institutes of Biomedical Innovation, Japan Pittsburg University Vaxil Bio Biological E Ltd Flow Pharma Inc |
|                       | S protein                 | MERS                      |  |  |
|                       | gp-96 backbone            | HIV                       |  |  |
|                       | S protein                 | HIV, Malaria, Zika, NSCLC |  |  |
|                       | Tobacco mosaic virus (TMV) |  |  |  |
|                       | Spike-based               | Flu A, Plague             |  |  |
|                       | Spike-based               | Rotavirus, Rubella        |  |  |
|                       | Protein Subunit           |  |  |  |
|                       | RBD-based                 |  |  |  |
|                       | OMV subunit               |  |  |  |
|                       | (Epitope screening)       |  |  |  |
|                       | Spike-based               |  |  |  |
|                       | S1-Fc fusion recombinant protein |  |  |  |
|                       | Recombinant protein       |  |  |  |
|                       | Recombinant 5 protein in IC-BEVS |  |  |  |
|                       | Heat stable, orally delivered subunit |  |  |  |
|                       | Spike protein peptides    |  |  |  |
|                       | Protein Subunit           |  |  |  |
|                       | RBD-based                 |  |  |  |
|                       | OMV subunit               |  |  |  |
|                       | (Epitope screening)       |  |  |  |
|                       | Spike-based               |  |  |  |
|                       | Adjuvant with a recombinant spike |  |  |  |
|                       | BEVS produced recombinant 5 protein |  |  |  |
|                       | Nanoformulated protein subunit |  |  |  |
|                       | Adenoviral Carrier protein subunit |  |  |  |
|                       | DC-targeted epitopes      |  |  |  |
|                       | Protein expression system of RBD based on Oral Salmonella enteritidis (3934Vac) |  |  |  |
|                       | Bacterial vector replicating |  |  |  |
|                       | Viral vector Replicating  |  |  |  |
|                       | YF17D Vector              |  |  |  |
|                       | Measles Vector            |  |  |  |
|                       | Measles Vector            |  |  |  |
|                       | S, N targets measles virus |  |  |  |
|                       | S protein expressing horsepox vector |  |  |  |
|                       | (Intranasal)              |  |  |  |
|                       | Attenuated influenza virus backbone |  |  |  |
|                       | (Intranasal)              |  |  |  |
|                       | Influenza A virus, recombinant vaccine |  |  |  |
### 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 | LNP-mRNA, LNP-mRNA | Influenza | | Sanofi Pasteur/Translate Bio Precision Nanosystems/Cansino Biologics |
| SARS-CoV-2 Spike (S) glycoprotein delivered by Replication-competent VSV chimeric virus technology (VSV ΔG) | LNP-mRNA, LNP-mRNA | Live, attenuated virus (LAV) | | University of Lancaster, UK |
| DC-targeting replicating VSV vector | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| VSV-S | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| VSV-S | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| VSV vector | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| Influenza vector M2-deficient single replication (M2SR) (NDV-SARS-CoV-2/Spike) Newcastle disease virus vector | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| (APMV) Avian paramyxovirus vector | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| RBD expressing Intranasal Newcastle disease virus vector (rNDV-FARVET) | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| Vaccine based on RNA | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| SARS-CoV2 formulated | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| S encoding LNP-encapsulated Mrna | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| Self-amplifying RNA mRNA | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| LNP-mRNA | LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| Cocktail encoding VLP LNP-encapsulated Mrna | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| RBD encoding LNP-encapsulated mRNA | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| SARS-CoV-2 derived replicating Defective RNAs | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| mRNA | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| mRNA | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| mRNA | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| mRNA | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| mRNA | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| mRNA | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| LNP-encapsulated mRNA D614G variant | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| Encapsulated mRNA | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| Protein subunit | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| SARS-CoV-2 S, M, N and NSPs targets to induce T cell responses (CD8) | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| sVirus like particle | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| VLP | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| Virus-like particle-based Dendritic Cell (D.C.)-targeting vaccine | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| VLP | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| (eVLP) Enveloped Virus-Like Particle | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| HIV VLPs integrated by S protein | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| Adjuvant + VLP | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| Baculovirus vehicles, Virus-like particles and lentivirus | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| RBD displayed on virus-like particles | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| Multi epitope display ADDoNetTM | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
| Unknown | LNP-mRNA, LNP-mRNA | RNA cure Biopharma/Shanghai Jiao Tong University/Fudan University | | University of Tongji/China CDC |
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 (ARDS) 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 ≥ 8 kPa = 60 mm Hg, PaCO2 < 6 kPa or pH > 7.3, FiO2 ≤ 0.4, Morphone sulphate, Midazolam, Benzodiazepine is given as per the severity of infection. 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 and mortality. 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-
ties, 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.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Not required.

Acknowledgement

The authors would like to thank National Institute of Pharmaceutical Education and Research (NIPER), Guwahati and Hyderabad for fellowships.

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