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Current Prevention and Clinical Management of COVID-19 in India

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Abstract:

The COVID-19 pandemic has clasped the world by furore storm. India has been the epicenter of the surge in COVID cases since March 2021 which is being considered as the second wave. With every passing week, new guidelines were being implemented by various states as well as the central government to control the situation. Hospitals were running out of beds, oxygen, and medicinal supply with patients with comorbidities suffering the most. A handful of drugs have been approved for direct or emergency use to counter the situation. However, over time some of these drugs have faced strong backlash for being ineffective and hence are no longer in use. In this review, we shall study various vaccines that have been approved in India and abroad and, also various drugs which were approved for treating the COVID-19 patients.

Keywords*:* COVID-19, Pandemic, Comorbidities, Vaccines

1. Introduction

The SARS-CoV-2 coronavirus pandemic has affected every country throughout the world. Previous outbreaks of the coronavirus include severe acute respiratory syndrome or (SARS)-CoV and the Middle East respiratory Syndrome or (MERS)-CoV [1]. In December 2019, all news networks were inundated with news of the outbreak of the disease in Wuhan, Hubei province of China. Since its first public reporting, thousands have lost their lives to this virus. Countries with strong health infrastructure, like Germany and Italy, were brought down to their knees by the sheer devastation caused by the virus. Developing nations like India have had to take a hard blow not only because of its population but also because of its poor healthcare infrastructure. However, with respect to its population scale and presumably because of the timely imposing of nationwide lockdowns, India did not suffer much in the first wave [2]. However, the number of cases skyrocketed by the time second wave struck the nation in March 2021. As of 29th of July 2021, since the outbreak a total of 3.15Cr cases have been reported in India. After the peak of the second wave, by the month of May a gradual decrease in the number of cases was observed. While the cases are coming down, a new

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variant of the virus called "the Delta Plus variant" has been detected in numerous states. This variant has been found to be more transmissible than the previous variants. Some have questioned the efficacy of the vaccines against the Delta Plus variant. The experts have, however, clarified that the approved vaccines are efficacious against the new variant.
As we discuss this topic, experts are warning us of a possible third wave which may strike us in the near future. The extent of severity is being speculated but we must be prepared. The government is reportedly preparing itself to avoid any scarcity similar to what the nation had to face during the second wave of the COVID-19 pandemic.

Fortunately, a number of vaccines have been approved by various regulatory bodies all over the world. It must be understood that the vaccines do not guarantee that the recipient will not have the disease. It may, however, decrease the severity of the disease and give us a fighting chance [3]. Some other drugs have also been approved for management of the disease in mild, moderate & severely affected patients [4].

2. The Viral Mutation

Nations are taking extensive measures to accelerate the vaccination drive and implementing strict guidelines to control the pandemic. However, the SARS-CoV-2 virus has been mutating which is making it, highly contagious [5]. The UK variant, B.1.1.7, was detected in the month of November of 2020 and was found to be 40-80% more transmissible than the base variant. Other variants such as the ones from South Africa (B.1.351), Brazil (P.1) and India (B.1.617) have also been found to be significantly contagious than the previous base variants of the year 2020. Not much has been understood regarding the severity of the disease when caused by these variants, but a clear increase in transmissibility has been observed [6, 7]. However, at present as the cases rise in India, scientists have expressed the concern about the two mutations in B.1.617 (E484K and L452R) which have been termed as "double mutant". It is speculated that these mutations may have led to the decrease in the sensitivity of the virus to the antibodies causing an increase in the number of infections [8]

3. Current Management Strategies Against Covid-19

3.1. Vaccines Against COVID

Globally Approved Vaccines:

Table 1: The table informs us about the various vaccines that have been approved in various countries throughout the world (Regulatory Affairs Professionals Society, 2021).

Sl. No.	Name	Primary Developers	Origin	Vaccine Type
1.	Comirnaty (BNT162b2)	Pfizer, BioNTech; FosunPharma	Multinational	mRNA-based vaccine
2.	Moderna COVID-19 Vaccine (mRNA-1273)	Moderna, BARDA, NIAID	US	mRNA-based vaccine
3.	COVID-19 Vaccine AstraZeneca (AZD1222); also known as Covishield and Vaxzevria	BARDA, OWS	UK	Adenovirus vaccine
4.	SputnikV	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia	Recombinant adenovirus vaccine (rAd26 and rAd5)
5.	COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)	Janssen Vaccines (Johnson & Johnson)	Netherlands, US	Non-replicating viral vector

6.	CoronaVac	Sinovac	China	Inactivated vaccine (formalin with alum adjuvant)
7.	BBIBP-CorV	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	Inactivated vaccine
8.	EpiVacCorona	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Russia	Peptide vaccine
9.	Convidicea (Ad5-nCoV)	CanSino Biologics	China	Recombinant vaccine (adenovirustype 5 vector)
10.	Covaxin (BBV152)	Bharat Biotech, ICMR;Ocugen	India	Inactivated vaccine
11.	WIBP-CorV	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	Inactivated vaccine
12.	CoviVac	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products	Russia	Inactivated vaccine
13.	ZF2001	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	China, Uzbekistan	Recombinant vaccine
14.	QazVac (QazCovid-in)	Research Institute for Biological Safety Problems	Kazakhstan	Inactivated vaccine

Till date a number of vaccines have been granted approvals for conducting human trials by various regulatory authorities across the globe as can be seen in the table above. Pharma giants like J&J, Pfizer and Moderna along with multiple other pharmaceutical companies have developed highly promising vaccines with great efficacy percentages [9]. As of this date, three vaccines have been approved for use in India and we may see an increase in this number soon as cases surge in the subcontinent. Three vaccines which have been approved are:

3.1.2. COVAXIN (BBV152)

Covaxin was instigated by an Indian Pharmaceutical company called as Bharat Biotech. India's top drug regulatory body, CDSCO (Central Drugs and Standards Committee Organization), had issued an emergency approval for the vaccine on 3rd January 2021. Covaxin is similar to China's Sinovac as it utilizes a completely ineffective SARS-CoV-2 viral particle which consists of RNA encapsulated by a protein shell in a manner such that it is unable to replicate. The vaccine comes as a two-dose regimen of 28 days gap in between. The results of phase I trials on the safety of the vaccine have been reported [10]. The results of phase II trials are yet to be published. Till date, the data that has been received indicates enhanced immune response and tolerability to the vaccine. On 3rd March 2021, Bharat Biotech released an interim efficacy data of its on-going phase III trials which showed a clinical efficacy of 81% [8].

3.1.3. COVISHIELD (AZD1222)

Covishield is a vaccine developed by Oxford University-AstraZeneca collaboration. Its large-scale production was performed by Serum Institute of India (SII), Pune. Covishield is an adenovirus vector-based vaccine AZD1222. To compare the efficacy of the original Oxford-

ChAdOx1 and Covishield, SII and Indian Council of Medical Research (ICMR) jointly conducted a Phase II/III observer-blind, randomized, controlled study in healthy adults at 14 centers in India. 1600 eligible participants of age 18 or above were selected for the study. Four hundred of them were randomly assigned to receive either Covishield or Oxford-ChAdOx1. The remaining 1200 were given Covishield or Placebo. The safety and immunogenicity data revealed that the results were similar and comparable to the data from previously conducted trials abroad which had shown efficacy of about 70.42% [11]. Recently, the SII requested the Drug Controller General of India (DCGI) to grant permission to conduct clinical trials of Conovax (NVX-CoV2373). Conovax was developed in partnership with Novavax, claiming an efficacy of 89.3% in its UK trial [12]. Currently, the gap between the first and the second dose has been increased from 6-8 weeks to 12-16 weeks.

3.1.4 SPUTNIK V

During August 2020, Russia announced that they had developed a vaccine to fight SARS-CoV-2 and had become one of the first nations to achieve this feat. In their vaccine prototype, the researchers used common cold viruses. They opted for two adenovirus vectors (rAd26 and rAd5) which were dosed separately as a two-day regimen, 21 days apart (The Scientist, 2020). To make the final vaccine, the researchers combined the adenoviruses and the SARS-CoV-2 spike protein which forces the body to make an immune response. Phase I and II results were published on September 2, 2020 and the reports claimed that all of the participants developed SARS-CoV-2 antibodies. No serious effects were detected, and the adverse effects if developed were mild in nature. Interim Phase III results indicated that the vaccine was 91.6% effective in preventing symptomatic infection. Four deaths were recorded during the study and all four were not vaccine related. As India has been facing a tough time because of the second wave, in the second week of April 2021, the regulatory bodies have given a nod to the Russian vaccine for emergency use. This makes it the third vaccine made available to the people after COVISHIELD and COVAXIN [13,14].

3.2. Drugs Recommended Against COVID-19

3.2.1. Chloroquine (CQ) & Hydroxychloroquine (HCQ)

Chloroquine (CQ) and hydroxychloroquine (HCQ) are aminoquinolines that have been used widely for the treatment of malaria, and autoimmune diseases. These two medications, in addition to their antimalarial properties, have immunomodulatory properties, enabling them to be used to treat autoimmune diseases including systemic lupus erythematosus and rheumatoid arthritis. Chloroquine and hydroxychloroquine are known to accumulate in lysosomes (lysosomotropic) and block their function. Toll-like receptor (TLR) signaling can also be disrupted by HCQ and CQ. Chloroquine or hydroxychloroquine may also bind to nucleic acids directly, potentially inhibiting TLR–ligand interactions, and thereby blocking TLR9 signaling at the intracellular levels [15]. CQ/HCQ have been found to possess the potential to block SARS-CoV-2 blinding to ACE2 receptors by interfering with its glycosylation process. CQ and HCQ could prevent the virus from binding to cell membranes and subsequently preventing its cell entry. They also inhibit viral replication and their release from host cells [16]. However, the drugs were not found to be very effective against COVID-19 and hence faced immense backlash [17].

3.2.2. Favipiravir (Avigan)

Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is an antiviral agent that obstructs RNA viruses' RNA-dependent RNA polymerase (RdRp) intensively, potently, selectively, and aggressively. Favipiravir-RTP inhibits influenza virus with an IC_{50} of 0.022 g/mL but has no effects on human DNA polymerases α, β, γ subunits at concentrations up to 100 g/ml. Favipiravir inhibits a wide variety of RNA viruses, including arena, bunya, flavi

and filoviruses that cause hemorrhagic fevers, in addition to the influenza virus [18]. The COVID-19 virus was described as a single-stranded RNA beta-coronavirus with the RdRp gene identical to that of SARS-CoV and MERS-CoV after genome sequencing. Clinical trials have suggested that Favipiravir was found to increase ALT, ALP, AST and total bilirubin levels in patients and hence, are suggested not to be given to patients with liver complications. The antiviral agent was also found out to be teratogenic in nature and so must not be prescribed to pregnant women [19, 20].

3.2.3. Remdesivir (RDV)

RDV is an adenosine analogue that inhibits RdRp (RNA-dependent RNA polymerase). It was developed by Gilead Sciences and was first used to treat Ebola virus disease [21]. It is a broad-spectrum antiviral drug that has been shown *in vitro* and *in vivo* to inhibit SARS-CoV-2. United States Food and Drug Administration (USFDA) recently approved RDV for use in patients aged 12 and up who weigh at least 40 kg for the treatment of COVID-19 and require hospitalization. In a recent double-blind, randomized, placebo-controlled trial of intravenous RDV in patients hospitalized with COVID-19 and evidence of lower respiratory tract infection, RDV was found to be effective. In adults hospitalized with COVID-19, the efficacy of RDV was superior to placebo in reducing the time of recovery [17].

3.2.4. Nitazoxanide (Alinia)

Nitazoxanide is a broad-spectrum antiviral agent that is currently being used in clinical trials for the treatment of influenza and other viral respiratory infections. Nitazoxanide inhibits the expression of the viral N protein in the Middle East respiratory syndrome coronavirus (MERS-CoV) and other coronaviruses *in vitro* [22]. The mechanism of action was thought to be based on its interference with host-regulated pathways involved in viral replication rather than virus-specific pathways, which explains the broad-spectrum antiviral activity. Nitazoxanide is being currently studied in clinical trials, including randomized controlled trials, for the investigation, treatment and therapeutics of influenza and other acute respiratory infections due to its broad-spectrum antiviral activity. Even though preliminary findings are not promising, it's *in vitro* activity against SARS-CoV-2 is promising. However, further evidence is required to evaluate its function in COVID-19 management *in vivo* [23].

3.2.5. Molnupiravir (MK-4482)

Molnupiravir, also known as EIDD-2801/MK-4482, is a prodrug of b-D-N4-hydroxycytidine which has proven its potential against various RNA viruses, highly pathogenic coronaviruses, influenza viruses and encephalitic viruses[24]. Molnupiravir upon incorporation into the viral RNA chain, it induces an error which causes the virus to mutate in an uncontrollable manner such that it crosses its own biologically tolerable threshold, this results in the impairment of its viral fitness and leading to its death[25]. Molnupiravir has shown effectiveness in *in vitro* studies against SARS-CoV-2 in human airway epithelial cells. It also showed effectiveness in mice infected with SARS-CoV and MERS-CoV and improved pulmonary function. Reports of the first human Phase I trials which were conducted in a randomized (3:1), double-blind and placebo-controlled study showed that the drug expressed good pharmacokinetics and was well tolerated [26].

3.2.6. Monoclonal Antibody

3.2.6.1 Tocilizumab

Tocilizumab is a monoclonal antibody that blocks IL-6 signaling by inhibiting its binding to receptors [27, 28]. In a randomized trial involving 389 hospitalized COVID-19 patients, out of which 249 were treated with tocilizumab while 128 were administered placebo, it was

found out that tocilizumab reportedly reduced the progression of the disease in COVID-19 patients with pneumonia. However, no significant improvement in survival was noted [29].

3.2.7. Convalescent Plasma (CP)

It was proposed that plasma from patients who have recovered from COVID-19 could be used as a novel therapy [30]. Although the risks of antibody enhancement and transfusion related reactions still remain unknown, this method is otherwise considered to be safe. The FDA had granted CP therapy Emergency Use Authorization (EUA) in the month of August 2020 for hospitalized COVID-19 patients. The data received in the earlier stages indicated that CP was a promising course for the management of critically ill patients. However, in recent times this method is discouraged because of ineffectiveness and mutation related problems [31] .

3.2.8. Anticoagulants

Critically ill COVID-19 patients are at a higher risk of developing venous thromboembolism (VTE). It was reported in a recent meta-analysis that VTE occurred in 22.7% of the ICU patients. Patients who were not admitted in the ICU were also in the risk of developing VTE [32]. Data suggests that immuno-thrombosis is supposedly a lot more prominent in COVID-19 patients than previously expected [33]. The current general guidelines suggest the standard dose of anticoagulants to be given to COVID-19 patients for thromboprophylaxis. Patients who are at a risk of VTEs such as thrombophilia, obesity, etc. were administered with VTE prophylaxis post discharge [34].

3.3. Demerits

In the last few months, as we have learned a lot about the virus, as well as how some of the drugs which were being widely used for the treatment or management or COVID-19, are actually ineffective. WHO has recommended strictly against the use of Remdesivir as it provides no efficacy against the virus (World health Organization, 2020). In the days to come the drug may be opted out completely for the treatment of COVID-19. Another drug called Ivermectin, an antiparasitic drug, has also been called off by various officials after proved to be ineffective in the treatment of COVID-19 (US National Library of Medicine, 2020). Drugs like CQ, HCQ, Favipiravir have also been facing huge criticisms for not living up to the expectations. An article published earlier this year argues how convalescent plasma therapy is ineffective and may pose a reason behind the mutations being observed in the virus [31].

3.4. New Drugs Approved in India

3.4.1. 2-deoxy-D-glucose (2-DG)

The drug Controller General of India had recently granted permission for emergency use of 2-deoxy-D-glucose (2-DG) which was developed by Nuclear Medicine and Allied Sciences (INMAS), a lab of Defense Research and Development Organization (DRDO), in alliance with Dr. Reddy's Laboratories (DRL), Hyderabad. As we know, viruses tend to alter the host cell metabolism processes to make an optimal environment for its rapid spread. This involves enhanced uptake of glucose for metabolic signaling. Sustained hyperglycemia may impose increased glucose metabolism which may eventually enhance SARS-CoV-2's activity in the body. Thus, this drug aims at disrupting this glucose mechanism which presents a strong strategy to control the SARS-CoV-2 pathogenesis [35].

3.4.2. Casirivimab and Imdevimab Cocktail

In the month of November 2020, the FDA had authorized Casirivimab and Imdevimab cocktail for emergency use. After having reviewed the reports from the phase I and phase II data it was concluded that this combination can be used to treat mid to moderate cases, pediatric patients and even severe cases [36]. On the first week of May 2021, Roche India announced that they had received emergency use approval for their antiviral cocktail preparation by the Central Drugs Standards Control Organization (CDSCO) for COVID-19

treatment and recently, in a collaboration with Cipla, Roche India has issued a statement stating that the second batch of the COVID-19 drug will be available by mid-June.

4. The Fungal Infection Crisis

We were fortunate to observe a decrease in terms of case-positivity rate in the second wave. However, along with the second wave came the wave of opportunistic fungal infections. Fungal infections such as Aspergillosis, Candida and Mucormycosis have been reported as some of the main fungal pathogens co-infecting patients with COVID-19.

Mucormycosis is uncommon but is fatal for patients with compromised or suppressed immune system. It is caused by mold fungi of genus *Rhizopus*, *Rhizomucor*, *Mucor*, *Cunninghamella* and *Absidia* of order *"Mucorales"* and class *"Zygomycetes"* [37]. Over the past few weeks, the cases of mucormycosis have been increasing rapidly in the world, mostly in India. COVID-19 patients, whether recovered or not, provide an ideal environment for Mucorales spored to germinate (low oxygen, high glucose because of diabetes or steroid intake, high iron levels, etc.). Diabetes Mellitus is very common is India and with DM being the most common link associated with mucormycosis, the situation is only worsening with time. DM associated mucormycosis has reported an overall mortality of 46% globally [38]. COVID-19 patients with comorbidities like DM, who were under long term treatment with corticosteroids, have been found to be highly susceptible to fungal infections such as aspergillosis and mucormycosis [39].

With newer case reports of *Mucor septicus*, (also known as yellow fungus disease) surfacing on the headlines, the situation is turning grim. The figures are escalating at an alarming and startling rate. Drugs such as Amphotericin B are running out of stock in various parts of the country. However, as per the Government of India, this issue will soon be resolved.

5. COVID-19 and Neurological Disorders

Human corona viruses are capable of inducing short- and long-term neurological disorders and are found in the human CNS, the route of transmission being trans-neuronal or hematogenous which may further lead to consequences in long term. Such possible covid associated neurological disorders include Encephalitis, acute flaccid paralysis, Guillain-Barré syndrome or ADEM [40-43]. Early-stage symptoms of these neurological disorders include hypogeusia and hyposmia rhinitis, anosmia [44]. Some cerebrovascular disorders are also linked with COVID-19 infection such as ischemic stroke, intracerebral hemorrhage, and cerebral venous sinus thrombosis. These cerebrovascular disorders may worsen the infection by multi-organ dysfunction [45-52]. Interferon alpha-2a, Lopinvair or ritonavir are the possible causative drugs for the several neuropathies in covid patients [53-55]. So, it is high time to search for an alternative medicine to treat neuropathies induced in COVID-19 patients. The ACE2-R is the key molecule through which covid-19 mediates its action in the brain. ACE2-R, angiotensin converting enzyme 2 receptor is present in the glial cells and neurons. Once COVID-19 binds with ACE2-R in the brain, the viral cycle is initiated [45, 46]. Further screening of antiviral compounds from herbs or plants and exploring the respective docking models may lead to more elaborate understanding of the covid associated neuropathies.

6. Triple Mutations in SARs Cov2 in India

Whole viral genomes, 598 in number, were analyzed and 47 G lineages were traced. The most common mutation being B.1.617. Within that four clusters are associated to specific spike protein mutations. Those are as follows:

(i) In December 2020, H1101D and T95I, a small proportion of these sequences showed the B.1.1.7 variant.

(ii) In the receptor binding domain (RBD) the mutations such as L452R and E484Q of the spike protein, a G142D and P681R outside the RBD (Increased from January 2021)
(iii) E484Q was not included in one of the mutation clusters but had T19R and D950N mutations in the spike protein.
(iv) D111D was not found in the cluster in the absence of the E484Q mutation, but it did occur in conjunction alongside the RBD mutations L452R and E484Q.

Reports revealed a rise in the frequency of nonsynonymous mutations (those that change protein sequences) since February 2021 [57].

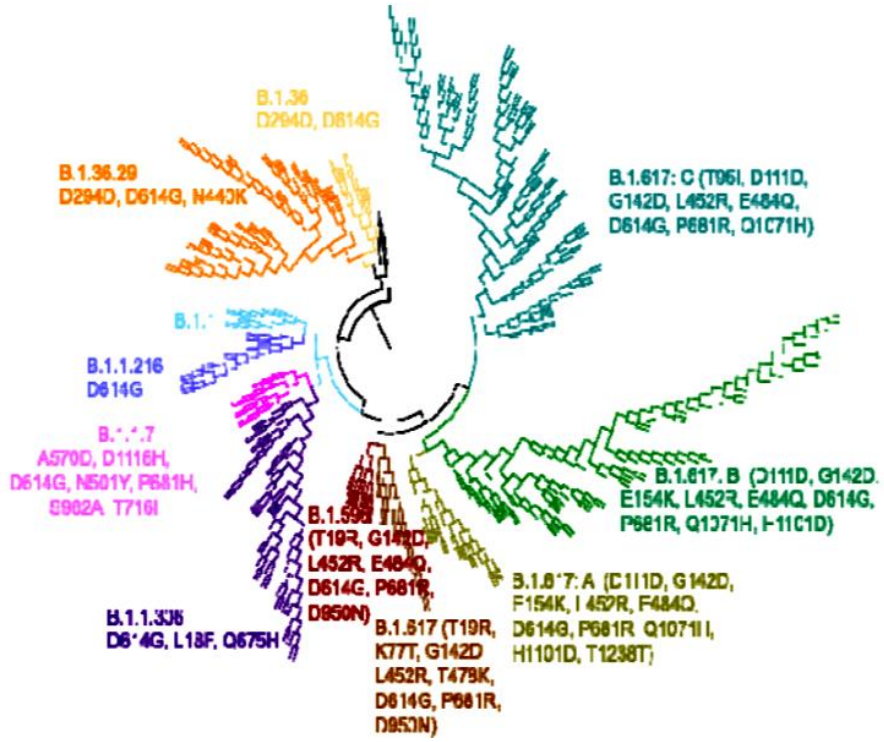

Figure 1: PangoLIN lineages of SARS-CoV-2 genomes revealing the maximum likelihood and the co-occurring mutations in the spike protein in the sub-clusters of lineage B.1.617.

6.1. Key Roles of Mutants

- The role of L452R mutation is to remove the hydrophobic interactions with other nearer residues. The stability of the complex is increased by the shift of L452 to hydrophilic 452R.
- The E484Q mutation hinders an electrostatic bond in the RBD.
- Increased membrane fusion is facilitated by the P681R mutation present in the furin cleavage site.

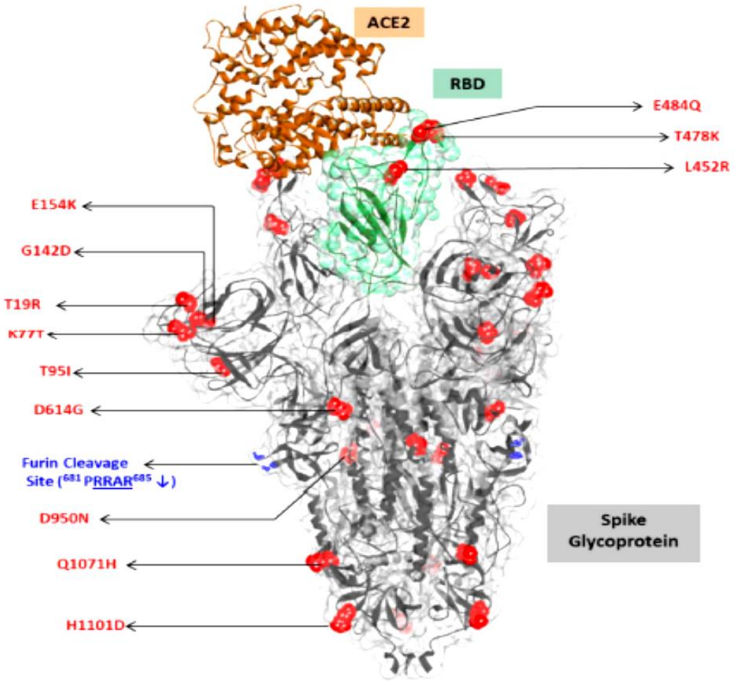

Figure 2: Furin-cleaved crystal structure of SARS-CoV-2 spike glycoprotein (grey surface viewpoint) in complex and combination with ACE2 (brown solid ribbon structure) with key mutations. RBD region shown in green [57].

6.2. Delta Plus Variant of COVID-19:

The origin of delta variant was first recorded in India and accounts for about 90% cases in UK, 36 cases were observed, out of which 11 were travel associated. The delta plus variant has a K417N mutation and it is the sub-lineage of the delta variant (which originated from India). The K417N mutation is in the spike protein (the coronavirus mushroom-shaped extension and projection on the surface which permits it to enter human cells). This K417N mutation has also been found in Beta variant (B.1.351 lineage). Beta variant has immune evading properties. 11 Countries have recorded 197 cases in total, as of June 16,2021 Britain (36), Canada (1), India (8), Japan (15), Nepal (3), Poland (9), Portugal (22), Russia (1), Switzerland (18), Turkey (1), the United States (83). The delta plus variant has been considered as "Variant of concern" as it has antibody neutralizing properties [58].

7. Emerging Variants and Vaccines Introduced Against the Variants:

Table 2: Milestones in vaccine development as communicated by Jia and Gong, 2021

Reporting Institution	Mode of Action	Effect on the Mutations/Variant
bioRxiv	Neutralizing capacity of sera from human subjects or non-human primates that received the mRNA-1273 vaccine and demonstrated that compared with vesicular stomatitis virus (VSV) pseudo virus,	VSV pseudo viruses with S protein comprising K417N-E484K-N501Y-D614G resulted in a 2.7-fold higher geometric mean titer reduction.
Moderna (mRNA-1273) or Pfizer-BioNTech (BNT162b2)	Antibody and memory B cell responses	The neutralization activity induced by both vaccines decreased slightly, but

vaccines.		nevertheless, significantly, against SARS-CoV-2 variants encoding E484K or N501Y, or the K417N-E484K-N501Y combination.
bioRxiv	Reduced the possibility of immune escape by the mutant virus	Covaxin, the COVID-19 vaccine developed by Bharat Biotech, effectively neutralized the UK variant of SARS-CoV-2,

It is also reported that efficacy of ChAdOx1 nCoV-19 against the B.1.1.7 variant (74.6%) was similar to that of the vaccine against other lineages (84%) whereas the neutralizing activity of the ChAdOx1 nCoV-19 vaccine was 9-fold less potent against the B.1.1.7 variant than against the non-B.1.1.7 lineage [59]. Multiplexed-chimeric spikes have been shown in studies to mitigate and prevent SARS-like zoonotic coronavirus infections as a consequence to the pandemic. Chimeric spike mRNA vaccines are capable of neutralizing D614G, mink cluster five and the UK B.1.1.7., and South African B.1.351 which are considered as "variants of concern" [60].

In another recent study, the ChAd–BNT dosing strategy was compared with homologous ChAd– ChAd dosing. It was inferred with higher immunoglobulin G (IgG) and IgA immune responses to the SARS-CoV-2 spike protein, was of significance and 20- to >60-fold greater titers of neutralizing antibody against the Alpha (B.1.1.7), Beta (B.1.351) and Gamma (P.1) SARS-CoV-2 variants of concern. Homologous ChAd–ChAd vaccination showed fewer titers of IgG antibodies than ChAd–mRNA (either BNT162b2 or mRNA-1273) or mRNA–mRNA vaccination and higher CD8+ T cell responses were observed in the ChAd–mRNA group [61]. In addition to these facts another report also states that the heterologous ChAd–mRNA vaccine approach has an advantage over the homologous type as it induces comparatively high IgG and neutralizing-antibody response [62]. Complementary stimulation of different immune pathways can be contributed by the combination of two vaccine strategies. This mix-and match- approach can maximize the immune responses which will facilitate in decreasing the infection of emerging variants [63].

ICMR study included 18 participants who were given Covaxin after their first dose of Covishield in Uttar Pradesh. The safety and immunogenicity profiles of people treated with Covaxin and Covishield were compared and found that immunization with a combination of an adenovirus vector platform-based vaccine followed the use of an inactivated entire virus vaccine was not only safe, but also boosted immunogenicity. The IgG antibody and neutralizing antibody response of the participants was significantly higher among those who were given the mixed-up doses compared to those who were not given this. The reaction of 18 people who received the combination of doses was compared with 40 people who received Covishield and 40 people who received Covaxin [64].

8. Omicron variant (2022):

B.1.1.529 (Omicron) was the mutated form of corona in the year 2022. As a result, the WHO has created a definition of variations of concern for molecular surveillance [65]. Extensive research and vaccine development is presently being done to stop the pandemic and stop illness outbreaks that might cripple healthcare systems worldwide [66, 67]. There are various types of vaccine based on the type of nucleic acid, proteins used for the production of vaccines. They are:

1.Inactivated Virus Vaccines
- CoronaVac
- WIBP-CorV
- BBIBP-CorV
- BBV152

2.Protein Subunit Vaccines
- NVX-CoV2373
- FINLAY-FR-2

3.Viral Vector (non-replicating) Vaccines
- ChAdOx1
- Ad26.COV2.S
- Gam-COVID-Vac

4.Nucleic Acid-based (RNA) Vaccines
- BNT162b2
- mRNA-1273
- CVnCoV

For the prevention of SARS-CoV2 infection, symptomatic COVID-19, and severe or critical COVID-19, a number of COVID-19 vaccinations are extremely effective or probably highly effective. Evidence supporting the majority of vaccination candidates increasing the risk of systemic reactogenicity events (such as fever) ranges from moderate to strong. Any negative event's supporting evidence was largely speculative. There is evidence that suggests that there is probably no difference in the likelihood of significant adverse events between mRNA-1273, CVnCoV, ChAdOx1, Ad26.COV2.S, GamCOVIDVac, WIBPCorV, and BBIBPCorV and placebo. Additionally, all reports relate to the short-term effects of the vaccine because the majority of RCTs only tracked individuals for 2 months following full immunization. More research is required to determine the extent of extra protection because results cannot be simply generalized to pregnant women and people with immune system compromises [68].

Conclusion

The second wave of the pandemic struck India with a brutal force. The healthcare sector underwent a lot of stress. The number of cases has been declining but the death rate was worse this time. As scientists work hard towards developing a stronger treatment alternative, thousands are dying every single day in the country. In terms of treatment options, we are in a better position than where we were at the beginning of the pandemic. We have several strong drugs that are playing an important role in managing the situation. The government had also announced that citizens of age ≥ 18 to be eligible for vaccination from the 1^{st} of May 2021which was an important step because majority of the Indian population are the young adults. Although there are many drugs available for COVID-19 there are notable side effects for some of these drugs, also, due to some limitations in the clinical setup it is tough to conduct follow-up studies for all the patients after post recovery. To minimize and diminish the side effects the target compounds (e.g., a single compound used to treat covid -19 induced neuropathy as well as diabetes) from various plants should be screened and taken for future docking studies and clinical trials to reduce the deaths due to co-morbidities and side effects. Single compound curating multiple disorders is the need of the hour, in this the docking studies can act as a preliminary and necessity base for clinical trials. Researchers from around the globe are conducting multiple trials with potential molecules to fight COVID-19 which raises a hope for newer options in the treatment and management of COVID-19 patients. Rapid detection of variants of Covid-19 has been updated till date to screen the mutants evolving in each country and its clinical impact, chimeric spike mRNA vaccines have been developed but still efficacy of the vaccines against the new delta plus variant is on current testing. Another solution at the earliest possible for treating the COVID-19 is the mix- and

match- vaccine approach which helps to enhance the ability of the immune system to fight against the new variants. Therefore, the health authorities at the international level should focus on being prepared for the new viral mutations and vaccines.

Abbreviations

(SARS)-CoV: Severe Acute Respiratory Syndrome Coronavirus, (MERS)-CoV: Middle East Respiratory Syndrome Coronavirus, COVID-19: Coronavirus Disease 2019, CDSCO: Central Drugs and Standards Committee Organization, ICMR: Indian Council of Medical Research, DCGI: Drug Controller General of India, CQ: Chloroquine, HCQ: Hydroxychloroquine, TLR: Toll-Like Receptor, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, AST: Aspartate Aminotransferase, RDV: Remdesivir, USFDA: United States Food and Drug Administration, EUA: Emergency Use Authorization, CP: Convalescent Plasma, VTE: Venous Thromboembolism, DRL: Dr. Reddy's Laboratories.

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