Review Article

An Immunological Outlook on SARS Coronavirus and Its Current Clinical Status

ABSTRACT

The SARS (Severe Acute Respiratory Syndrome) Coronavirus-2 originated in China in 2019 has created a huge pandemic outbreak as a result of the virus named as COVID-19 by World Health Organization. It has been seemed as an unprecedented risk against the global fitness scenario, as well as the arena of socio-economic-political structure. The viral disease is extremely contagious and infectious in nature. In human, the receptor of the virus, angiotensin converting enzyme-2, is present inside the cellular membranes of multiple vital organs. The virus has specific durability in special infected surfaces which are the important modes of its transmission. No immunity has been reported against the virus however, immune-compromised people are extremely vulnerable to this disease. For its diagnosis, reverse transcription-based test is currently being used as the serological diagnosis is still not an ordinary practice due to several reasons. In this direction, multiple public and personal sector companies are working towards vaccine development and research for antiviral pills and drug-repurposing is also underway. Several candidate vaccines and pills are now in various levels of scientific trials. In the present review, we summarize the science behind the pandemic, its prognosis, treatment and efforts towards therapeutic development. The review would be beneficial to the scientific fraternity to understand the future, emerging and re-rising of this pandemic.

Keywords: SARS-CoV-2, COVID-19, Diagnosis, Treatment, Coronavirus, Pandemic

1. INTRODUCTION

The ongoing coronavirus pandemic, because of severe acute respiration syndrome coronavirus 2 (SARS CoV 2) is pronounced to be one of the foremost pandemics of this millennium. The virus outbreak has been reported to be first pronounced in Wuhan, China in December 2019. The virus was remoted from biological samples and changed into diagnosed member of the Genus, beta-coronavirus, putting it alongside Severe Acute Respiratory Syndrome (SARS) coronavirus and Middle East Respiratory Syndrome (MERS) virus [1]. It was declared as a Public Health Emergency of International Concern via the World Health Organization on 13th January thereafter as an epidemic on 11th March, 2020. Lasting for greater than 12 months, it inflamed round 500 million human beings worldwide that lead to death of around 100 million human beings.

The COVID-19 outbreak has posed as an international risk to the civilization. The financial, political, social and spiritual structures of the sector are disturbed because of the pandemic. The world's top-order economies which include the US, China, Japan, UK, Germany, France, Italy etc., are at the risk of collapse due to the outbreak. It is presumed to be the worst disaster after World War-II. Under such circumstances, the International Monetary Fund (IMF) predicts that the US financial system itself may additionally decline by means of 5.9 %, which is about two times the decline fee faced in the course of the monetary disaster in 2009 [2].

The monetary impact of this pandemic in India is at disruptive level. India's economic growth for the financial year 2021 has been downgraded by the World Bank and credit rating businesses as 1.5 % to 2.8 % [2]. The SARS-CoV identified first in November 2002 in the Guangdong province of Southern China [3]. As in case of the latest SARS-CoV-2 outbreak, the SARS-CoV changed and believed to have been transmitted from animal hosts to human from the open markets in China (Anderson et al., 2004). As the findings suggest [4], the wet markets in Wuhan, China with huge numbers and forms of wild recreation mammals may have caused the transmission of the present novel coronavirus from animals to human.

This virus possesses the capacity to propagate at an alarming rate, thereby ensuing in disorder clusters from an unmarried index patient [4]. The capacity for human-to-human transmission, the lack of know-how of the infection control of the virus in the hospital and international air journey opened the manner for international spread of this agent [4]. Covid 19 has properties that has never been found in nature. According to google statistics on 21st September 2020 (Figure 1), word wide the total Covid cases are 30.9 million (58%), the recovery cases (40%) are 21.2 million and the deaths (2%) due to Covid is 960K.

According to the same report from google statistics, India stands second position in corona cases followed by Brazil, Russia and Peru and the 1st position is occupied by USA (Figure 2). These figures reveled the seriousness of this pandemic. Till date, no powerful vaccine or healing has been observed to correctly prevent the transmission of the virus or treat the disease. This review is aimed to recognize the genetics of coronavirus, numerous diagnostic techniques adopted for detection of the virus and the substantial variety of remedy that has potential to be carried out for the treatment and prevention of the disorder.

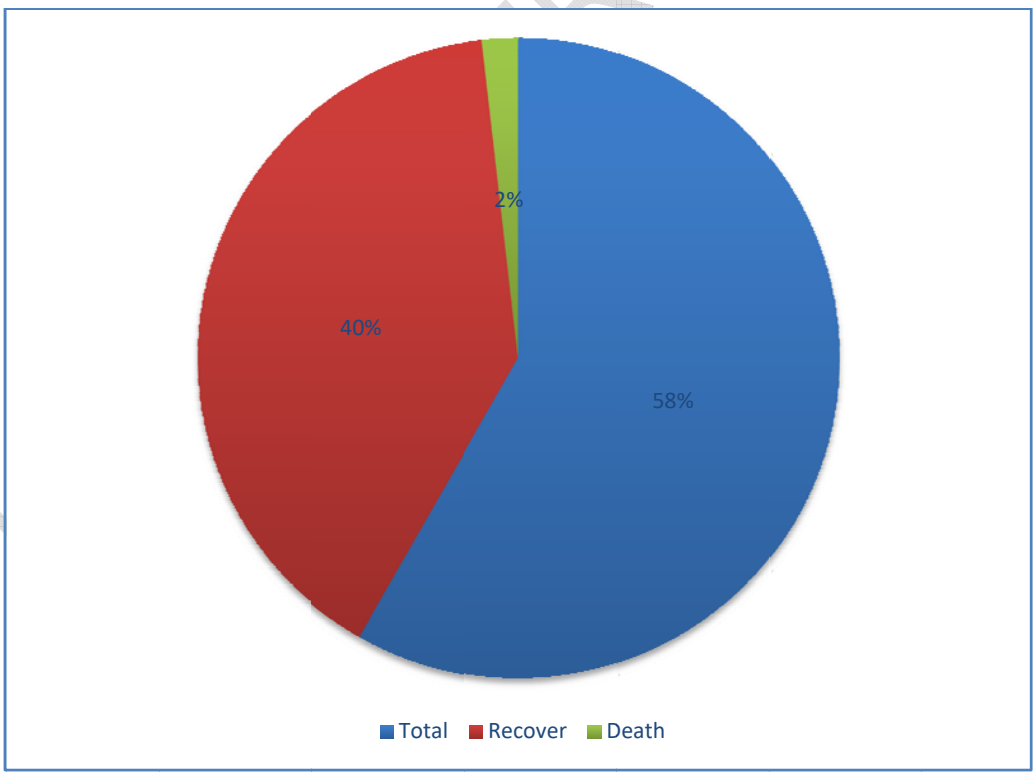
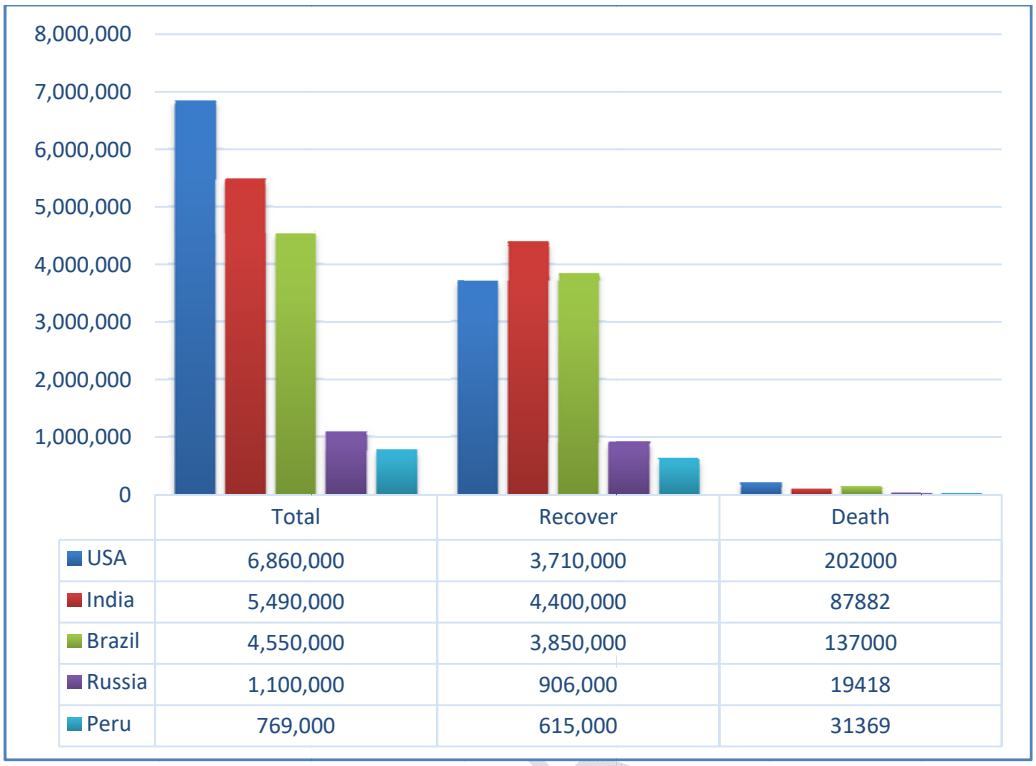


Figure 1. Covid-19 world scenario till 21st September 2020



	Total	Recover	Death
USA	6,860,000	3,710,000	202000
India	5,490,000	4,400,000	87882
Brazil	4,550,000	3,850,000	137000
Russia	1,100,000	906,000	19418
Peru	769,000	615,000	31369

Figure 2. Covid-19 cases of top five countries till 21st September 2020

2. SARS CORONA VIRUS 2 – AN OVERVIEW

The Coronaviridae, to which the CoVs belong, is a large family of positive-stranded RNA viruses. When viewed beneath electron microscopes, they exhibit a crown-like shape (coronam is the Latin means 'crown') because of the nearness of spike glycoproteins on its envelope. The family, Coronaviridae (order Nidovirales) includes a subfamily called Orthocoronavirinae and numerous unclassified coronaviruses. The subfamily, Orthocoronavirinae is classed into four genera, namely, Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV), and numerous unclassified coronaviruses (Cascella et al., 2020). Studies had indicated that bats and rodents are presumably the carriers of alphaCoVs and betaCoVs; in all likelihood carriers of deltaCoVs and gammaCoVs are avian species. SARS-CoV-2 is a betaCoV; it has spherical or elliptical and regularly pleomorphic structure with a diameter of approximately 60–a hundred and forty nm. A general model of structure of SARS-CoV-2 virion [5] was proposed in 2020.

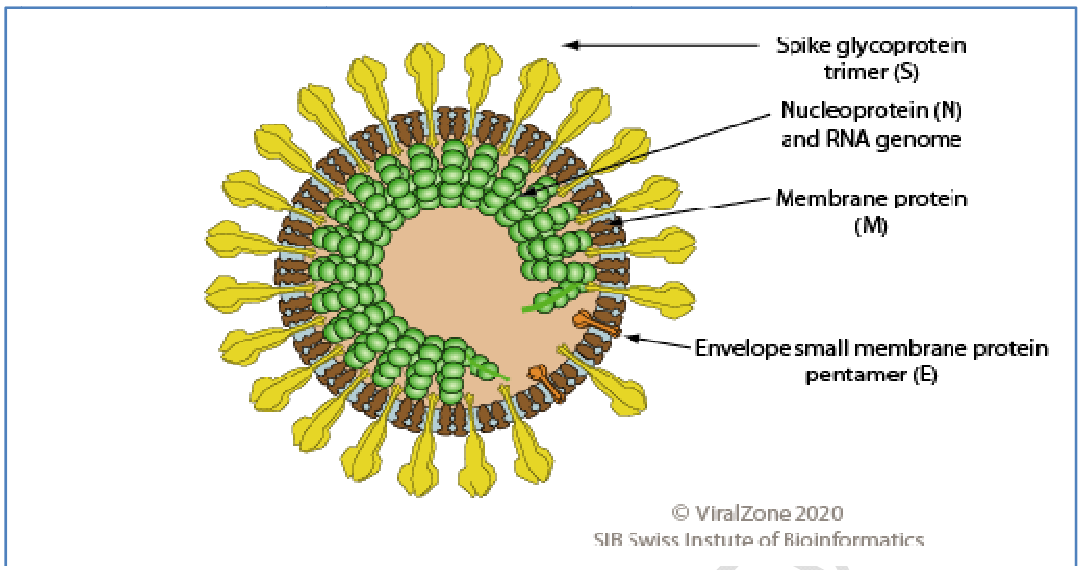


Figure 3. General structure of SARS-CoV-2 virion

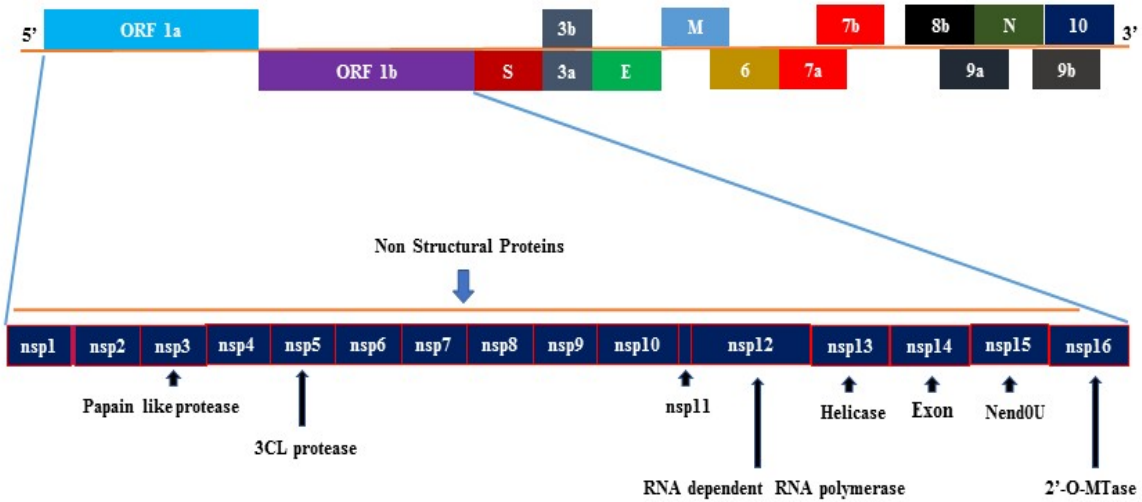
Although the origin of SARS-CoV-2 is not clear, genomic analysis shows that SARS-CoV-2 possibly developed from a strain discovered in bats primarily because it shares 89% nucleotide identification with a bat coronavirus (SARS-like-CoVZXC21) and 82% nucleotide identification with the sooner acknowledged SARS-CoV [6]. The first human coronaviruses were characterized and named “B814” inside the Sixties through Tyrrell and Bynoe [7]. it turned into liable for higher respiratory tract infections in people including kids in UK. Since then, seven human-infecting coronaviruses had been identified. Among them, alphaCoVs together with HCoV (Human coronavirus)-229E and HCoV-NL63, and betaCoVs such as HCoV-HKU1 and HCoV-OC43 has low pathogenicity and slight respiration signs [8]. The other three recognized betaCoVs, SARS-CoV, MERS-CoV and SARS-CoV-2 has excessive pathogenicity and transmissibility. The suggested mortality prices of SARS-CoV and MERS-CoV changed into approx. 10 % and approx. 35 % respectively [6]. The primary mode of transmission of SARS-CoV-2 is from symptomatic person vendors. Such transmission occurs via direct touch with the infected individuals, near contact via respiratory droplets or by touch with contaminated gadgets and surfaces [9].

Recent studies have indicated that viral shedding is maximum in the higher breathing tract from the initial 3 days from starting of the signs [10]. Other modes of transmission encompass pre-symptomatic and asymptomatic transmission. Pre-symptomatic transmission alludes to transmission occurring no longer earlier than symptoms appear after contamination. Such transmission takes place usually one to three days earlier than the infected man or woman end up symptomatic [11]. Asymptomatic transmission alludes to transmission at some stage in the incubation time body that averages between 5 to 6 days which may lead to up to 14 days [6]. Nevertheless, there has been no documented asymptomatic transmission of SARS-CoV-2.

3. STRUCTURE, GENOME ORGANISATION AND FUNCTION OF MAJOR PROTEINS OF SARS-COV-2

The ssRNA genome of SARS-CoV-2 consists of approx. 30,000 nucleotides and is modified with a 5'-cap structure and a 3'-poly-A tail; it has the biggest recognized RNA genome. The order of ORFs placed inside the RNA (from 5′ to three′) is: ORF-1a/ab encoding nonstructural proteins (Nsps) for replication, spike (S), envelope (E), membrane (M) and nucleocapsid (N); several accessory proteins which include ORF-3b, 6, 7a/b, and 8b, 9a/b, 10 [12]. Its 5′ untranslated area (UTR) is 265 nt lengthy and the 3'-UTR is 229 nt lengthy. The ORF-1a/ab is approx. 21,300 nt in period and encode replicase polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab), respectively. Both of those polyproteins are proteolytically cleaved into 16 putative Nsps encoding for non-structural proteins (Nsp-1 to Nsp-sixteen), which shape the complex replication machinery. The genes that encode the components of the mature virus, i. E., S, ORF-3a, E, M and N are approx. three,820, 830, 230, 670 and 1,260 nt in length; they play critical roles in viral structure integrity or as in the case of the spike-protein [13], for viral entry in the host (Figure 4), where ORFs are open reading frames, 1a and 1b are non-structural proteins genes (Nsps), S is the structural protein gene, E is the envelope protein gene, M is the membrane protein gene, N is the nucleocapsid genes and 3a,3b,7a,7b, 8b, 9a, 9b and 10 are the accessory protein genes. The figure clears the concept of structure and genome organization of corona virus. An important and essential characteristic of Nsps is rearranging the membranes derived from the rough endoplasmic reticulum into double-membrane vesicles which serves as floor for viral replication and transcription [12]. Nsp-12, is the key enzyme (RNA-dependent RNA polymerase, RdRp) controlling the synthesis of all viral RNA molecules [14].

Another unique Nsp is Nsp-14; being an exoribonuclease, it has the proofreading capability important to protect the huge RNA genome from detrimental mutations [15]. Nsp-3 and Nsp-five code for two viral proteases, papain like protease and chymotrypsin-like protease (3CLpro), respectively. The Nsps likewise consists of different enzyme domain names and features as indexed in Figure 4. The four structural proteins, i.e., S, E, M and N, play number one roles within the structure of the virus particle; they are also additionally engaged in different factors of the replication cycle. The S-protein (approx. 200 kDa) of the virus adheres to the host cell floor receptors bringing about fusion and viral entry in the Host. It makes a homotrimer making the awesome spike-like shape, and serves as a full-size target [16] of neutralizing antibodies. At the N-terminal area of S-protein, a globular S1-domain is present that is trailed by way of membrane-proximal S2-area, a transmembrane area and an intracellular area [17]. The S-proteins is heavily N-connected glycosylated and it gains access into the endoplasmic reticulum thru an N-terminal sign sequence. The S1-area is the receptor-binding domain (RBD) of the S-protein and the S2-area paperwork the stalk of the spike [18]. Also, the S-protein mediates cell-cellular fusion among inflamed and adjacent uninfected cells forming multinucleated large cells, resulting in direct viral unfold among cells even as warding off virus neutralising antibodies [19].



Nsp-1	Inhibits translation in host cell resulting in blockage of innate immune response; degrades host mRNA.
Nsp-3	Interacts with N-protein, ADP-ribose-1'-phosphate activity, promotes cytokine expression.
Nsp-4	Transmembrane scaffold protein (for structure of double-membrane vesicles)
Nsp-5	Cleaves viral polyprotein
Nsp-6	Potential transmembrane scaffold protein
Nsp-7	Binds to single stranded-RNA; forms hexadecameric complex with Nsp-8; may act as processivity clamp for RNA polymaerase
Nsp-8	Forms hexadecameric complex with Nsp-7; may act as processivity clamp for RNA polymerase; cofactor of Nsp-12.

Nsp-9	RNA binding protein.
Nsp-10	Cofactor for Nsp-16 and Nsp-14, forms heterodimer with both and stimulates ExoN (viral exoribonuclease) and 2-O-methyltransferase activity.
Nsp-12	RNA-dependent RNA polymerase.
Nsp-13	RNA helicase, 5' triphosphatase.
Nsp-14	N-7 methyltransferase and 3'-5' exoribonuclease, ExoN (important for proofreading of viral genome)
Nsp-15	Uridylate-specific viral endoribonuclease
Nsp-16	Shields viral RNA from Melanoma differentiation associated protein-5 recognition and 2'-O-ribose methyltransferase.

Nsp-2 and Nsp-8 has unknown function

Figure 4. Genome Organization of SARS-CoV-2 and function of major proteins of corona virus

The M-protein (approx. 25–30 kDa) is the maximum considerable structural protein with 3 transmembrane domain names. It defines the form of the viral envelope by playing a central role in virus assembly. The M- and E-proteins represent the viral membrane and their interplay results in the manufacturing and launch of virus-like particles [20]. The transmembrane protein, E (approx. 8–12 kDa), is the smallest amongst all the structural proteins. It plays vital roles in viral assembly/budding. Presence of an N-terminal ectodomain and a C-terminal endodomain with ion channel hobby has been reported in this protein. The most effective protein of CoV that binds to its RNA genome is the N- protein (nucleocapsid; approx. 46kDa). The crucial role of N-protein is genome encapsidation, i.e., to bundle the viral genome into lengthy, flexible, helical ribonucleoprotein complexes referred to as nucleocapsids.

4. REPLICATION CYCLE OF THE CORONAVIRUS

4.1 STEP 1. ENTRY OF CORONAVIRUS

SARS-CoV-2 enters into the host cellular system via the interaction between the S-protein and ACE-2 receptor of the host [21]. Recently, another viable human receptor, CD147, has been distinguished as a possible path of viral intrusion which is likewise mediated with the aid of the identical protein [22]. A glutamine residue (Q493) inside the RBD of SARS-CoV-2 and a Lysine (K31) of the human ACE-2 receptor has been worked out to engage for the S-protein-receptor binding [23]. A recent file suggests that ACE-2-binding performance with S-protein of SARS-CoV-2 is 10–20 fold better than that of SARS-CoV which additionally can be a reason of the particularly infectious nature of SARS-CoV-2 [24]. This S-protein-ACE-2 receptor interplay serves as the number one determinant of contamination which also defines the tissue tropism or quick unfold of the virus in the host. Recently, single-cellular RNA sequencing (scRNA-seq) was performed and observed the samples from massive human physiological structures like respiratory, cardiovascular, digestive, and urinary systems [25]. After attachment, proteolytic cleavage occurs by the host protease at two sites within the S2 subunit of the S-protein resulting in its activation [26]. This conformation change in the S-protein is observed by the fusion of viral envelope with the host mobile membrane through endocytosis. Thereafter, the virus releases its genomic RNA into the host mobile cytosol/cytoplasm.

4.2 STEP 2. REPLICATION AND TRANSCRIPTION OF THE GENETIC MATERIAL

Once inside the cell, the *ORF-1a* and *ORF-1ab* of the virion RNA is translated by host ribosomes to produce the viral replicative enzymes, polyprotein 1a/1ab (pp1a/pp1ab). A frame-shift between *ORF-1a* and *ORF-1b* initiates the production of both pp1a and pp1ab polypeptides which are processed by proteolysis for producing 16 Nsps. Assembly of these Nsps leads to formation of the replicase-transcriptase complex in the double-membrane vesicle to make an environment suitable for RNA synthesis [27]. Viral RNA synthesis generates both genomic and sub-genomic RNAs through negative-strand intermediates by discontinuous transcription [28]. Sub-genomic RNAs fill in as mRNAs for translation of the structural and accessory genes present downstream of the replicase polyprotein.

4.3 STEP 3. ASSEMBLY AND RELEASE OF VIRAL PROTEINS

The S, E and M proteins enter the endoplasmic reticulum and Golgi apparatus assembly while the N-protein is remaining attached with the genomic RNA. New virus particles are enveloped in the ERGIC (ER-Golgi intermediate compartment). After assembly, the virus particles get transported (Figure 5) via vesicles to the periphery and get released by exocytosis

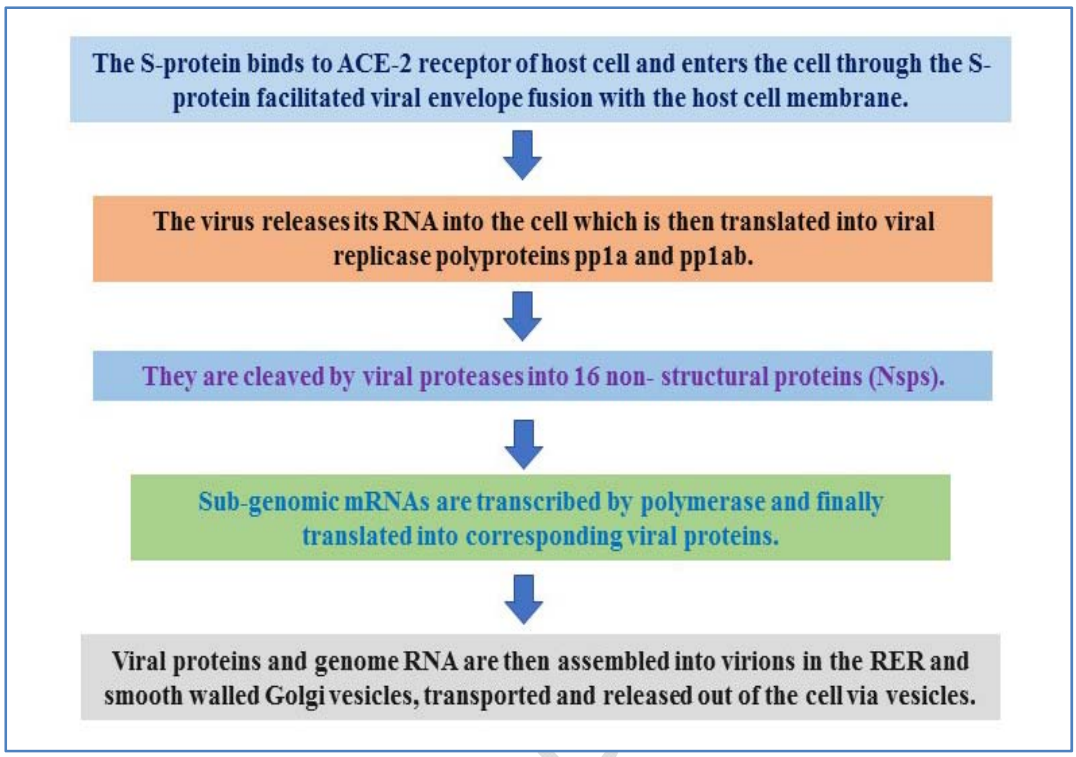


Figure 5. Flowchart of life cycle of SARS Corona Virus

5. MUTATIONS IN CORONA VIRUS – A CASE STUDY

Different SARS-CoV-2 strains do not yet have a significant effect on the trajectory of the pandemic, but they can in the future, according to a report published in the nature briefing on 8 Sept. 2020. As it spreads, SARS-CoV-2 is evolving much more slowly compared to HIV. But for Korber, one mutation stood out. It was in the spike protein encoding gene, which helps to enter cells with virus particles. In tests from people with COVID-19, Korber saw the mutation occurring again and again. The amino acid aspartate was frequently replaced by glycine at the 614th amino-acid position of the spike protein because of a copying fault that altered a single nucleotide in the 29,903-letter RNA code of the virus. Virologists have named it a mutation of D614G. Lineage has been found in nearly all sequenced SARS-CoV-2 samples, according to the same article. This stability has been highlighted by other genome data-more than 90,000 isolates were sequenced and made public (www.gisaid.org).

Of 29,903, a computer geneticist at University College London, who monitors the variations for signs that they confer an evolutionary advantage, two SARS-CoV-2 viruses obtained from anywhere in the world vary by an average of just 10 RNA letters. Despite the slow mutation rate of the virus, researchers have catalogued more than 12,000 SARS-CoV-2 genome mutations. In viruses collected in China and Germany at the end of January, D614 G was first spotted; most of the scientists believe that the mutation originated in China. Three mutations in other parts of the SARS-CoV-2 genome are now almost always accompanied, potential evidence that most D614 G viruses have a common ancestor. The majority of available evidence indicates that D614 G does not avoid the detection of SARS-CoV-2 by the immune system's neutralizing antibodies. But evidence is emerging that other mutations may help protect some antibodies from the virus.

6. IMMUNITY AGAINST CORONA VIRUS INFECTION

SARS-CoV-2 infection can result in the malfunction of lungs that displays pneumonia-like symptoms. The two main immunity mechanisms *viz*. innate and adaptive immunity, can act in reaction to the viral infection [29]. Innate immunity act as a number one antiviral defense mechanism vital to combat in opposition to natural contamination but the perception of the specific innate immune response to SARS-CoV-2 is acutely narrow [30]. The T and B cells are lymphocytes forming a major part of the adaptive immune response in human. While the T-cells are liable for the cell mediated immunity, the B-cells are responsible for humoral immunity [31]. The body's humoral and innate immunity is stimulated via the presence of the antigens, which, in turn, is mediated by using virus-precise B- and T-cells [9]. Cytotoxic T-cells play important roles in mobile immunity in the course of viral contamination through the method of apoptosis. The CD4 T-cells permits the B-cells for generating antibodies and strategize the comments of different immune cells, while CD8 T-cells wreck the inflamed cells to lessen the viral drift. But down-regulated T-cellular responses may be an effect of immunopathology [30]. For CoV infections, it is vital to manipulate the immune reaction, because an impaired immune reaction may result in immunopathological condition [9]. The severity of the disease is probably dependent on the robustness of those T-cellular responses.

When the virus makes an entry into the cellular system, the antigen received is supplied to the antigen-presentation cells, which happens to be the core part of the anti-viral immunity [9]. B-cell reaction is an essential memory reaction which can avoid reinfection. Nevertheless, SARS-CoV-2 draws out energetic B-mobile response found out by using the fast and near-everyday detection of virus precise IgM, IgG, IgA and neutralizing IgG antibodies in the days following contamination [30]. The SARS-precise IgG antibodies are commonly S-protein and N-protein unique [15]. The N-protein and S-protein precise IgM and IgG are evolved fairly after the symptom outbreak which can be used for the prognosis of viral contamination, greater precisely via studying the dynamics of S-precise IgG [32]. The findings of the kinetics of antibody reaction closer to SARS-CoV-2 were logically depicted [33]. Evidence of antibody remarks toward the SARS-CoV-2 infection revealed that individuals recovered from contamination broaden antibodies against the virus.

7. CLINICAL DIAGNOSIS STRATEGIES FOR SARS-COV-2

The medical detection of SARS-CoV-2 infection is primarily based mostly on auxiliary research which consist of nucleic acid-based quantitative polymerase chain reaction (RT-qPCR) and high throughput sequencing, serological assays like enzyme related immunosorbent assay, immune identity generation of IgM/IgG, automatic tomography-check etc. [9]. RT-qPCR is one among the powerful diagnostic approach for the detection of SARS-CoV-2 within the respiratory tract [34], that can be performed using the samples like sputum pattern or nasopharyngeal swab and on saliva. The top breathing tract, nasopharyngeal and oropharyngeal swabs are typically amassed as specimen and sputum is considered as a non-invasive decrease breathing tract specimen [35]. Saliva serves as a more effective specimen thinking about the ease of pattern collection, that may reduce the hazard of hospital received contamination. Due to the sudden outburst of COVID-19 cases, numerous non-public sector corporations have begun to rapidly produce RT-qPCR for medical examination [9]. Besides, scientific imaging like CT scans especially, chest CT, may show lesions in lung tissues of the infected people arising because of the infection and extremely good fee in early screening [36]. At times, RT-qPCR might provide defective or false excessive quality/bad effects. In such cases, chest CT test may be of assistance. Recently, opposite transcription-PCR (RT-PCR) based totally rapid quick check kits have been used for the diagnosis of SARS-CoV-2 contamination, but that may also lead to false detection.

For example, in Meghalaya, India, five suspected individuals examined awful of their RT-PCR effects whose samples had been first tested splendid with fast checking out kits (www.shillongtimes.com). Since COVID-19 is a respiratory disease, CT scan may be beneficial in spotting distinguishable capabilities in sufferers or people having a regular immune reaction [9]. Certain serological exams are still underneath improvement for the evaluation of COVID-19. As such, the applicability of the N-protein based IgG ELISA (detection achievement fee 94.7 %) of SARS-CoV became significantly higher than that of the S-protein based IgG ELISA (detection achievement price 58.9 %). However, similar comparison has no longer been made in SARS-CoV-2. In contemporary times, CRISPR/Cas13-based totally definitely SHERLOCK (Specific High sensitivity Enzymatic Reporter unLOCKing) platform has been used for the prognosis SARS-CoV-2 [37]. Scientists [37,38] recently attempted a CRISPR/Cas12-primarily based totally assay for detection of SARS-CoV-2 from extracted RNA samples from patients. They referred to as the approach SARS-CoV-2 DNA Endonuclease-Targeted CRISPR Trans Reporter (DETECTR). DETECTR showed blessings over qRT–PCR including speedy reversal time, unmarried nucleotide goal specificity, isothermal amplification (via Reverse Transcription-Loop Mediated Isothermal Amplification, RT-LAMP), ease of use and no necessity for complex infrastructure [38]. In this technique, primers had been first designed by means of selecting the envelope and nucleoprotein genes of SARS-CoV-2 which have become altered to fulfil the condition for LAMP. In order to decide the SARS-CoV-2 like coronaviruses, Cas12 gRNA modified into exactly designed from the nucleoprotein gene. Under maximum suitable conditions, the DETECTR assay grew to become into completed on the E and N gene, inclusive of an RT–LAMP response at 62°C for 20–30 min and Cas12 detection reaction at 37°C for 10 min. The Tata Group has recently been noted for the launch of the first commercial launch of India's Clustered Regularly Interspaced Short Palindromic (CRISPR) Covid-19 test. The work initiated by CSIR under the sickle cell mission for genome diagnostics and therapeutics led to new knowledge that could be harnessed to quickly create a new SARS-CoV-2 diagnostic tool, Anurag Agrawal, Director, CSIR-IGIB, said. This test is driven by the Feluda [39] Institute of Genomics and Integrative Biology (CSIR-IGIB) of the Council of Science and Industrial Research, which is an acronym for the FNCAS9 Editor-Limited Uniform Detection Assay.

8. TREATMENT FOR SARS-COV-2 INFECTION

The improvement of therapeutics for coronaviruses has been going on for the reason that SARS-CoV outbreak in 2002-2003. Vaccines had been advanced that had been discovered powerful in inducing synthesis of antibody and in providing safety against SARS-CoV. However, these vaccines had been found to set off hypersensitive reaction to SARS-CoV components, posing risk for its application [38]. Till date, there are no antiviral tablets or vaccines as the remedy of SARS-CoV-2. The current outbreak of COVID-19 has reemphasized the urgent need for treatment and preventive vaccine. Usually, for remedy of coronaviruses, three strategies are employed [9] : (i) Efficacy checking of maximum of the prevailing antiviral tablets for drug repurposing, (ii) Screening existing compounds listed in chemical libraries containing and (iii) Discovery and improvement of recent drugs unique to the present infection primarily based at the genome and biophysical knowledge of SARS-CoV-2 [40]. Besides those, quite a few therapeutic strategies have been followed which include monoclonal antibodies, angiotensin receptor blockers, nucleic acid-based therapy, epitope-based peptide vaccines etc. The therapeutics underneath trial is targeted for inhibition of entry, inhibition of viral fusion to the host cellular membrane, inhibition of replication of viral genome by using interferons, RNA interference mediated inhibition of replication, focused on viral proteases for inhibiting replication, and inhibition of replication by means of different compounds (Table 1) entitled the candidate drugs in use or in trial for SARCoV-2 infection.

Table 1. Candidate drugs in use or in trial for treatment of SARS-CoV-2 infection

Candidate drug	Description	Mode of action of the drug
Remdesivir [41]	Antiviral	Inhibiting RNA synthesis by adenosine nucleotide analogue in coronaviruses
Chloroquine [42]	Antiparasitic and antirheumatic	Interferes with glycosylation of SARS-CoV cellular receptors
Favipiravir [43]	Antiviral used against influenza	Inhibits the RNA-dependent RNA polymerase of RNA viruses
Lopinavir [44]	Antiviral, immune suppression	A protease inhibitor; inhibits RNA replication and release of virus from host cell. Also inhibits the action of 3CL-protease
Sarilumab [45]	Human monoclonal antibody against interleukin-6 receptor	Slows down the process of cytokine release, thus preventing organ damage
ASC-09 + ritonavir [46]	Antiviral	A protease inhibitor, inhibits RNA replication
Tocilizumab [42]	Human monoclonal antibody against interleukin-6 receptor	Slows down the process of cytokine release, thus preventing organ damage
Lenzilumab [47]	Humanized monoclonal antibody for relieving pneumonia	Acts against cytokine release syndrome
Dapagliflozin [48,49]	Sodium-glucose cotransporter 2 inhibitor	Prevents the lowering of cytosolic pH and reduces viral load
CD24Fc [47]	Antiviral immunomodulator against-inflammatory response	Strengthens innate immune system against excessive inflammation

9. VACCINE CANDIDATES AVAILABLE FOR SARS-COV-2 TREATMENT

A recombinant protein received via fusion of the extracellular area of human ACE-2 and the Fc-area of the human immunoglobulin IgG1 turned into lately shown to exert inhibitory activities against SARS-CoV-2 through binding to the RBD of SARS-CoV and SARS-COV-2. In addition, another feasible target to dam CoV access is the transmembrane protease, serine-2 (TMPRSS2) which is worried in proteolytic processing of S-protein. Therefore,

Camostat mesylate, an inhibitor of TMPRSS2, might gain efficient utility and popularity of scientific use [50]. Trials demonstrating sera from convalescent SARS sufferers also are stated to capable of cross-neutralizing SARS-CoV-2 entry, this also consists of a few promises in treating SARS-CoV-2 infection [50]. Till now, the binding S-protein has been the principle antigenic aspect to set off host immune responses. Vaccine improvement for coronaviruses began critically after the SARS and MERS outbreaks. A number of vaccine applicants are already being developed but most are still inside the pre-scientific clinical testing level. The capacity vaccine improvement approaches (Table 2) include vaccine primarily based on viral vector, DNA-vaccine, subunit vaccine, virus like particles (VLPs)-based totally vaccine, inactivated complete-virus vaccine and live attenuated vaccine [51].

Ability to stimulate toll-like receptors (TLRs) along with TLR-3, TLR-7/8, and TLR-9 and having an inherent immunogenicity is an added advantage of the use of complete virus vaccines [51]. An immunogenic virus-like nanoparticle, NVX CoV2373, based totally on expression of a recombinant S-protein, was developed by means of Novavax, a US based company (www.natureasia.com). Their proprietary Matrix-MTM, an adjuvant stimulates excessive tiers of neutralizing antibodies that enhances immune responses. Some Indian pharmaceutical companies are in a race to develop vaccine for deadly coronavirus (Figure 6) and India is now preparing itself to tackle the corona virus pandemic.

Figure 6. Some Indian pharmaceutical companies developing vaccine for coronavirus

A subunit vaccine such as a trimerized SARS-CoV-2 S-protein using the patented Trimer-Tag® is being evolved by means of Clover Biopharmaceuticals Technology (China). Meanwhile, at Baylor College of Medicine, a subunit vaccine comprised of simplest the RBD of the SARS-CoV S-protein was developed by a consortium led with the aid of Texas Children's Hospital Center for Vaccine Development. This vaccine formulated on alum was stated to have an advantage of having ability to limit host immunopotentiation [52]. Recombinant adenovirus-based vaccine expressing MERS-CoV S-protein precipitated systemic immune responses providing long-lasting immunity to the virus upon intranasal management in mice, which shows that this vaccine can be a superior candidate for clinical trial towards SARS-CoV-2 [53]. Interferons (IFNs) can inhibit viral replication and infection by means of inducing both innate and adaptive immune response.

Clinical trials with recombinant IFN-α have been mentioned to be powerful for the remedy of SARS-patients [54]. In another approach, siRNA concentrated on ACE-2 mRNA driven by U6 promotor exhibited reduced viral infection in Vero E6cell lines [55]. Bharat Biotech's COVAXIN™ (Figure 7), India 's indigenous COVID-19 vaccine, was developed in collaboration with the National Institute of Virology (NIV) of the Indian Council of Medical Research (ICMR). The indigenous, inactivated vaccine is produced and manufactured in the high containment facility of Bharat Biotech's BSL-3 (Bio-Safety Level 3). The vaccine has received approval from DCGI (Drugs Controller General of India) for Phase I & II Human Clinical Trials and trials will begin in July 2020 across India. The results of these studies were positive and demonstrated comprehensive protection and successful immune responses, he added. In addition to Bharat Biotech, at least five other Indian firms are working on the deadly coronavirus vaccine.

Table 2. Status of some important COVID19 Vaccines globally under clinical trial

Vaccine Name	**Company**	**Country**	**Vaccine Platform**
mRNA-1273	Modern Inc	USA	RNA
AZD1222	Oxford University	UK	Non replicating Virus
COVAXIN™ (Figure 7)	Bharat Biotech	India	Inactivated Virus
Ad5-nCoV	CanSino Biologics	China	Non replicating Virus
Unnamed Russuan Vaccine	Gamaleya Institute of Epidemiology and Microbiology	Russia	Isolated strain
Second Russian Vaccine	Siberian Vector Institute	Russia	Using a platform first developed for Ebola
Bnt162	Pizer-BioNTech	USA/Germany	RNA
ZyCov-D	Zydus Cadila	India	DNA, Recombinant Measels Virus
Self-amplifying RNA Vaccine	Imperial College of London	UK	RNA
BCG Vaccine	Murdoch Children's Research Institute	Australia	Live attenuated Virus
Plant Based Vaccine	Medicago GSK, Dynavax	Canada	Virus like Particle
rADV-S	International Vaccin Instiurte (IVI)	South Korea	Non-replicating viral vector
Recombinant measles virus Spike protein	University Health Network, Center for Disease Control and Prevention (CDC)	Canada	Replicating Viral Vector
SARS VLPs S protein and influenza M1 protein	Novavax	USA	Virus-like Particle
VRC SRSDNA015-00-VP	National Institute of Allergy and Infectious Diseases (NIAID)	USA	DNA
SARS recombinant spike protein plus delta inulin	Vaxine Pty. Ltd.	Australia	Protein subunit

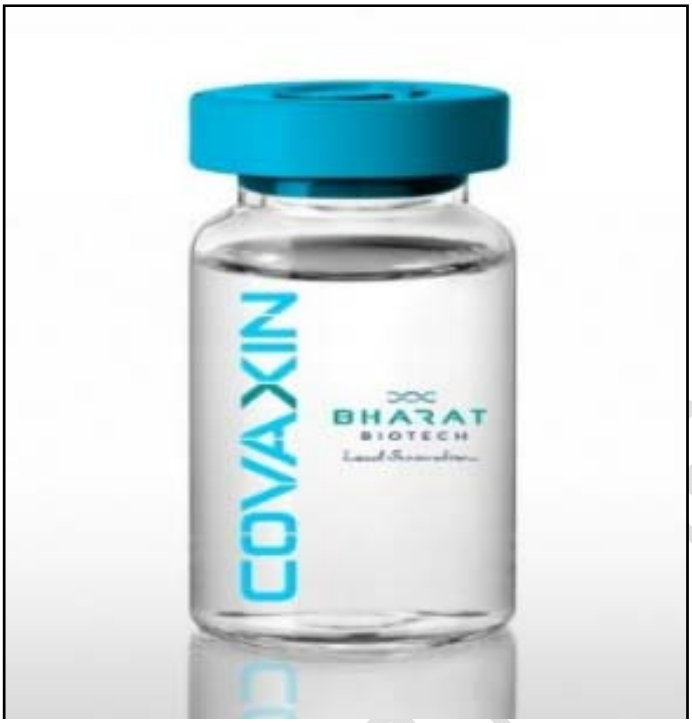


Figure 7. Covaxin - Indian 1st Covid-19 vaccine, successfully enters human trials

10. EVOLUTION OF GLOBAL COVID19 VACCINE DEVELOPMENT

The COVID19 vaccine production pipeline is divided into exploratory and preclinical pipelines on 7 September 2020 (https:/www.nature.com/articles/d41573-020-00151-8), according to a nature review report on drug discovery on 7 September 2020 (https:/www.nature.com/articles/d41573-020-00151-8), and the clinical pipeline, including traditional approaches, includes live attenuated and inactivated; novel approaches include viral vector, RNA, DNA, recombinant protein, p As of September 3, 2020, the global COVID-19 R&D vaccine landscape includes 321 vaccine candidates, according to this study, of which 33 vaccine candidates are in clinical trials.

The number of projects under exploratory pipeline is 201 comprising 70% of the total projects conducted worldwide and as compared to these 87 projects (30%) are under preclinical pipeline (Figure 8). Under exploratory and preclinical pipeline vaccine development projects, recombinant protein-based vaccine projects are more than other projects (Figure 9). Under the same report of nature reviews drug discovery on 7th September 2020, as of 3rd September 2020, the number of projects under clinical pipeline is 33 comprising 30% (10 projects) in phase 1, 43% (10 projects) phase 1/2, 9% (3 projects) in phase 2 and 18% (6 projects) in phase 2/3 (Figure 10). Under clinical pipeline vaccine development projects, recombinant protein-based vaccine projects are more followed by non-replicating viral vector, RNA and inactivated virus (Figure 11).

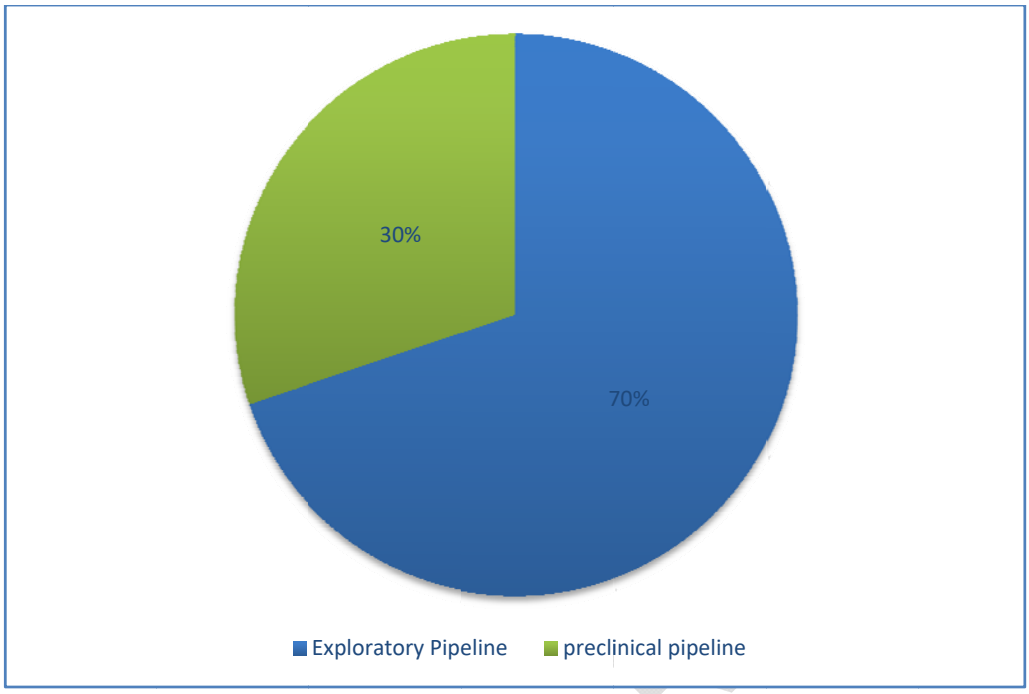


Figure 8. Vaccine development projects under exploratory pipeline and preclinical pipelines

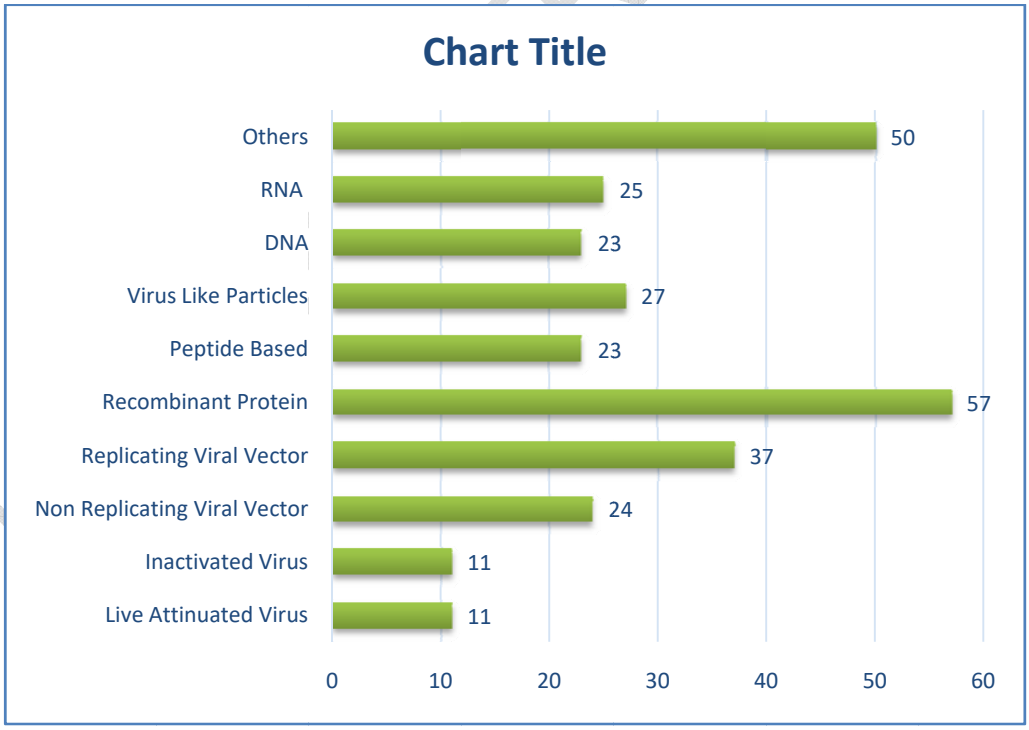


Figure 9. Breakups of vaccine development projects under exploratory pipeline and preclinical pipelines

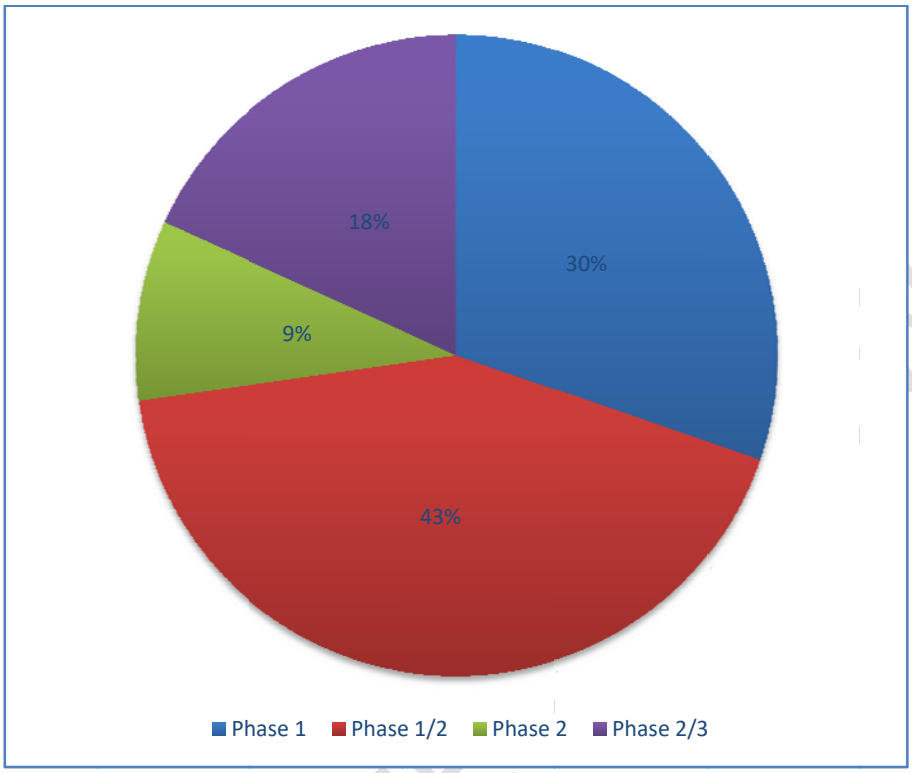


Figure 10. Vaccine development projects under clinical pipelines

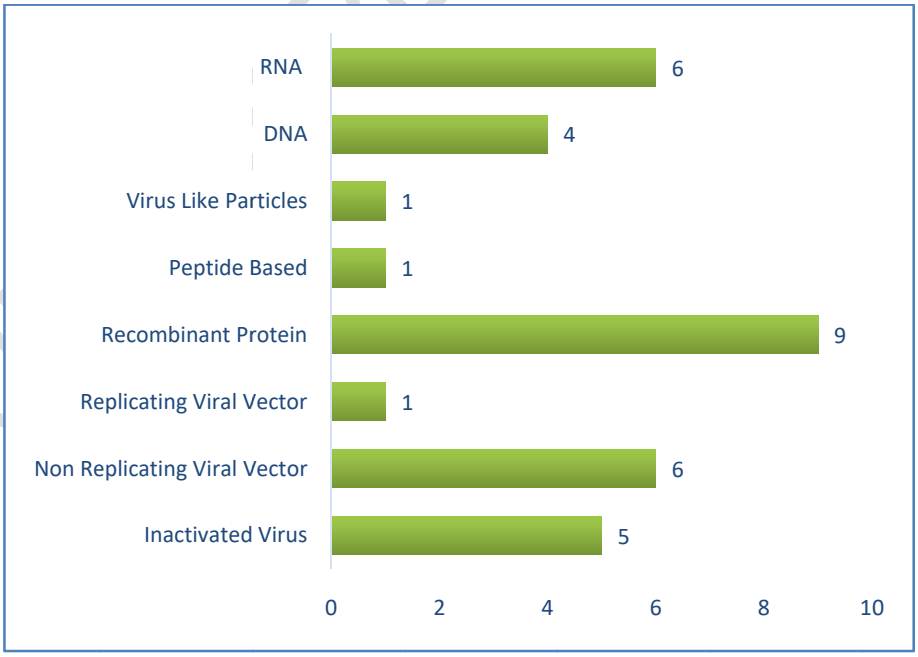


Figure 11. Breakups of vaccine development projects under clinical pipelines

11. OTHER REMEDIAL STRATEGIES FOR COVID-19 SUFFERERS

Initially, a combination of lopinavir and ritonavir used with other antiretroviral agents to provide durable virus suppression and improved immune response. It is found that the coronavirus RdRp may be a crucial goal for viral inhibitors as it plays a critical position in viral RNA synthesis [56]. Remdesivir, an adenosine triphosphate analog, terminates viral RNA replication via inhibiting RdRp, thereby stopping extension of the new RNA strand. Therefore, remdesivir has been pronounced as a promising antiviral drug against RNA viruse [57]. It has been the most extensively used drug against COVID-19 so far. The preliminary facts of management of remdesivir on hospitalized patients with excessive signs and symptoms showed a faster recovery. Recently, scientists additionally discovered that remdesivir is a powerful control of SARS-CoV-2 in *in vitro* and many are to be functionally explored [22]. Therefore, it received emergency use authorization from the FDA (Food and Drug Administration) on May 1, 2020.

Meanwhile, chloroquine became additionally mentioned to have immunomodulatory activity [22] and to inhibit SARS-CoV-2 efficaciously *in vitro*. The viruses enter the cells through endo-lysosomal pathway, the autophagosome and lysosomal fusion may be blocked via chloroquine and hydroxychloroquine, thereby inhibiting viral access. The pills also inhibit the viral genome replication main to its effective manage in clinically managed trials [42]. In addition, cellular experiment with arbidol, a small indole by-product molecule, also observed to reveal antiviral impact on SARS-CoV [22]; it can considerably bring down the incidence of extreme cases with a unique mechanism of concentrated on the interaction of S-protein/ACE-2 and for that reason, inhibiting membrane fusion of the viral envelope [42]. Meanwhile, using nucleoside analogues as antivirals can be any other technique for treatment towards SARS-CoV-19 [58], diverse instructions of nucleoside analogues have been validated in Vero cells towards SARS-CoV [44].

Meanwhile, an antineoplastic drug, carmafur, is pronounced to inhibit the 3CLpro of SARS-CoV-2 inhibiting viral perpetuation in cells. Thus, this drug proved to be an able antiviral treatment for COVID-19 [37]. Favilavir, any other anti-viral drug, were said to be successfully treating SARS-CoV-2 contamination with lesser side effects. Furthermore, these days a CRISPR-based system that recognizes and degrades the viral genome in the host's mobile had been proposed for COVID-19 remedy [59]. The gadget employs a currently discovered RNA-guided RNA endonuclease, a category 2 kind VI-D CRISPR-Cas13d system [60], derived from *Ruminococcus flavefaciens* XPD3002 and was also stated previously for use to inhibit the entry of RNA virus in human cells [8]. Cas13d has an excessive catalytic activity in human cells which could provide a capacity mechanism for focused on SARS-CoV-2 genome [59].

There are also several trials of Indian traditional ayurvedic herbs for COVID-19. Ashwagandha, Yashtimadhu (Mulethi), Guduchi Pippali (Giloy) and a polyherbal Ayurvedic formulation, known as AYUSH-64, have been identified as the 4 candidates to treat COVID19. An Ayurvedic medicine developed with the aid of Pankajakasthuri Herbal Research Foundation, Kerala, India has been permitted for clinical trials on COVID-19 inflamed adults by way of Clinical Trials Registry of India. It has been pronounced that it has proved to be a success within the clinical trials in reducing COVID-19 symptoms. There are still some of clinical trials going on in Indian and other nations for locating a hit therapy/drug against the SARS-CoV-2 disease.

12. CONCLUSION

It's already almost six months since the first report of the SARS-CoV-2 infection. The COVID-19 pandemic has made the planet stuck in an unprepared situation and the disorder is yet to come beneath entire control of the present healthcare machine. Although China has started nearly all usual financial activities, there had been reports of SARS-CoV-2 high quality cases coming in regular intervals. Same is the case in Europe. Even though it is broadly perceived that peak infection is over, it is unpredictable what will show up after normalcy returns. In nations like USA, India, Pakistan etc., the contamination level is gradually increasing. There are some predictions that the situation definitely may get worse at some point of the approaching winter. The healthcare device has nearly collapsed in components of our united states and as of now, the main emphasis is on flattening the curve. There is nearly no provision at this factor to fill the gaps of the epidemiology of the sickness and the mechanism of evolution and mode of infection of the virus. There are several questions, last unanswered about the pandemic which can be keys in improvement of the vaccine and therapeutics. Individual nations mobilizing ample investment for the needed studies on this line is a challenge. Therefore, a concerted effort must be the purpose of the clinical community trials. However, latest socio-political trends are obstructing the creation of such willful and dependable consortium. We believe, the judgment of right and wrong of the sector leaders and policymakers will ultimately collate and humankind will be successful over the virus.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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