Review Article

An Immunological Outlook on SARS Coronavirus (SARS-CoV-2) and Its Current Clinical Status

ABSTRACT

The SARS (Severe Acute Respiratory Syndrome) Coronavirus-2 (SARS-CoV-2) originated in China in 2019 and rapidly spread across the globe for which the World Health Organization (WHO) declared it as a pandemic on March 11, 2020. This viral disease is extremely contagious and infectious in nature and the general symptoms include fever, cough and pneumonia followed by a loss of taste, diarrhoea, shortness of breath, acute respiratory distress syndrome and even death. The disease has caused unprecedented risk against the global fitness scenario and therefore have altered the socio-economic-political structure of society. There has been no reported cases of any immunity against the virus, however immune-compromised people are extremely vulnerable to this disease. The diagnosis of the disease is usually done by quantitative Real-time PCR but other methods of detection like serological testing is gaining prominence these days. Approaches are directed towards the development of vaccine candidates and a search is on towards the discovery of potential drugs. Needless to say, the genome architecture of the virus and the viral proteins mounting an immune response play a key role in the development of effective therapeutic strategies. The review article presents an overview of the science behind the pandemic along with the structural chemistry of the pathogen, the prognosis and the vaccine candidates in different stages of development. The review would be beneficial to the scientific fraternity and the common men at large in understanding the central role of the immune system towards the development of successful clinical strategies for diagnosis and therapy to avoid the future encounters by the virus.

Keywords: Keywords: SARS-CoV-2, immunity, genome, pandemic, diagnosis, therapy

1. INTRODUCTION

The ongoing COVID 19 pandemic caused by SARS CoV 2 is pronounced to be one of the foremost pandemics of this millennium. The outbreak of the virus has been reported for the first time in Wuhan, China in December 2019. The virus was remoted from biological samples and changed into diagnosed member of the genus beta-coronavirus placing it alongside SARS coronavirus and MERS virus [1]. The World Health Organization had declared it as a Public Health Emergency of International Concern on 13th January and thereafter an epidemic on 11th March, 2020. The COVID-19 outbreak has posed an international risk to the civilization disrupting the social, political, financial and spiritual sectors completely soon after its advent. The world's top-order economies are at risk of collapse due to the outbreak and it is presumed to be the worst disaster after World War-II.

The impact of this pandemic in India is at disruptive level since it has affected India's economic growth for the financial year 2021 which has been downgraded by the World Bank and credit rating businesses as 1.5 % to 2.8 % [2]. The wet markets in Wuhan, China with huge numbers of wild mammals may have caused the transmission of the present novel coronavirus from animals to humans [3]. The ability of the virus to transfer among humans, the lack of knowledge of infection control in the hospitals and international flight operations have contributed largely to the world wide spread of this viral agent [4]. According to the reports of WHO (Figure 1), the mortality stands highest in case of MARS (outbreak in 2012) followed by SARS (outbreak in 2002-2003), Covid-19 (present outbreak) and pH1N1 influenza (outbreak in 2009). Covid 19 has properties that has never been found in nature and the virus possess the ability to mutate itself leading to the emergence of new strains of the virus. A majority of these strains have been potent in causing viral infections affecting the lower respiratory tract and the virus ravages to the brain and heart form the lungs.

According to Google statistics on 21st September 2020 (Figure 2), the cases resulting from Covid infections are 30.9 million (58%), recovery cases (40%) are 21.2 million and the deaths (2%) is 960K. The reports from google statistics also suggests that India stands second in corona infected cases followed by Brazil, Russia and Peru and U.S. tops the list according to the data. (Figure 3). These figures reveled the seriousness of this pandemic. Till date, no powerful vaccine or drug candidates has been observed to correctly prevent the transmission of the virus or to treat the disease. The immune system of an individual including the cells and organs as well as the changes occurring in the system due to infection play a crucial role in the development of successful immunotherapeutic measures. The present review outlines the guiding immunological principles in conferring immunity against the SARS Coronavirus through a study on its genome organization, prognosis, treatment modules as well as the vaccine candidates available so far against SARS-COV-2. The current clinical status suggests that there are no specific anti -COVID-19 therapies available but the ongoing clinical approaches would surely serve to find better ways to tackle the COVID-19 menace.

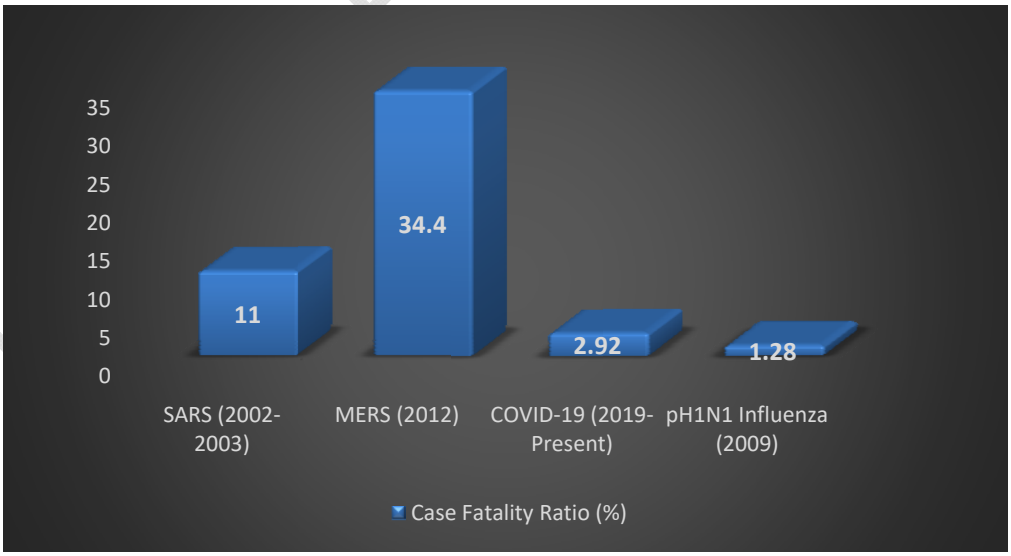


Figure 1. Case fatality ratio of some deadly outbreaks globally (Source - www.who.int)

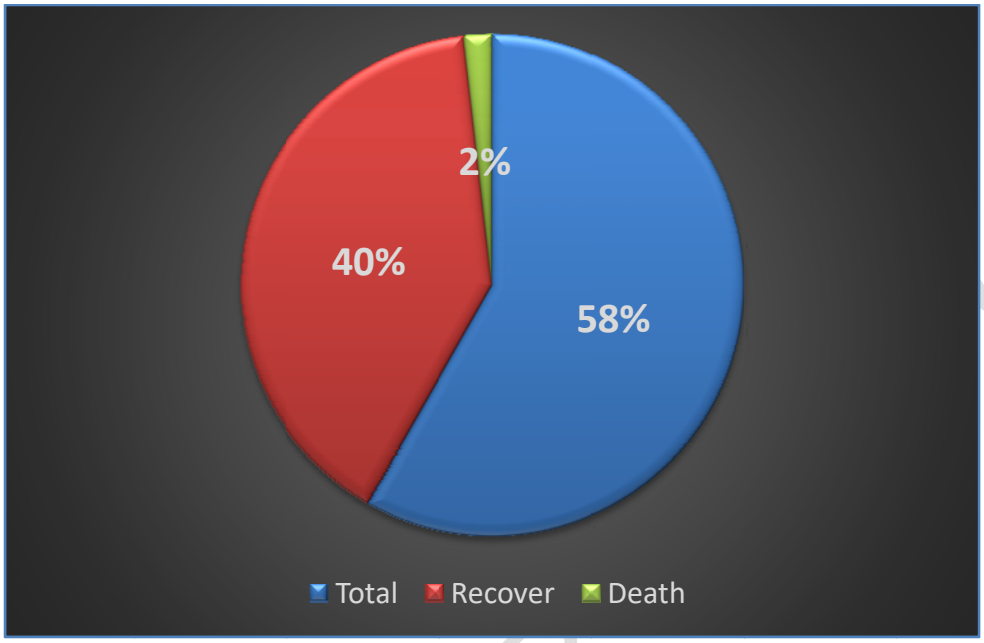
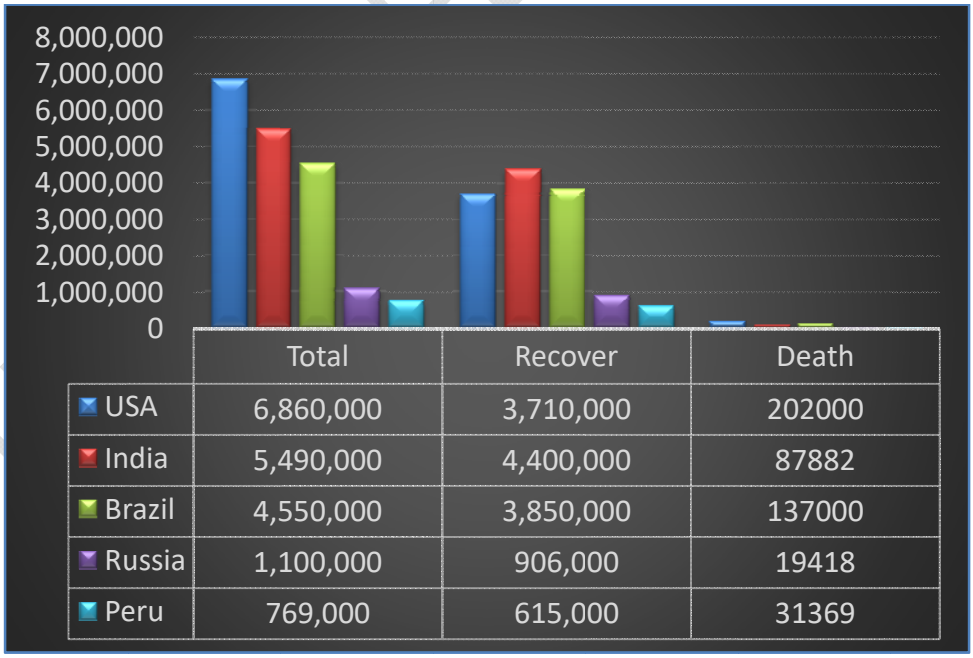


Figure 2. Covid-19 world scenario till 21st September 2020



	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 3. 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 spike glycoproteins on its envelope. The family, Coronaviridae includes a subfamily called Orthocoronavirinae and numerous unclassified coronaviruses. The subfamily, Orthocoronavirinae is classed into four genera, namely, Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), Gammacoronavirus (gammaCoV) and numerous unclassified coronaviruses [4]. 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 60–140 nm. A general model of structure of SARS-CoV-2 virion [5] was proposed in 2020 (Figure 4) (https://asm.org/Articles/2020/January/2019-Novel-Coronavirus-2019-nCoV-Update-Uncoating). 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" [7].

The corona virus 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. Such transmission occurs via direct touch with the infected individuals, near contact via respiratory droplets or by touch with contaminated 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 that averages between 5 to 6 days which may lead to up to 14 days [6].

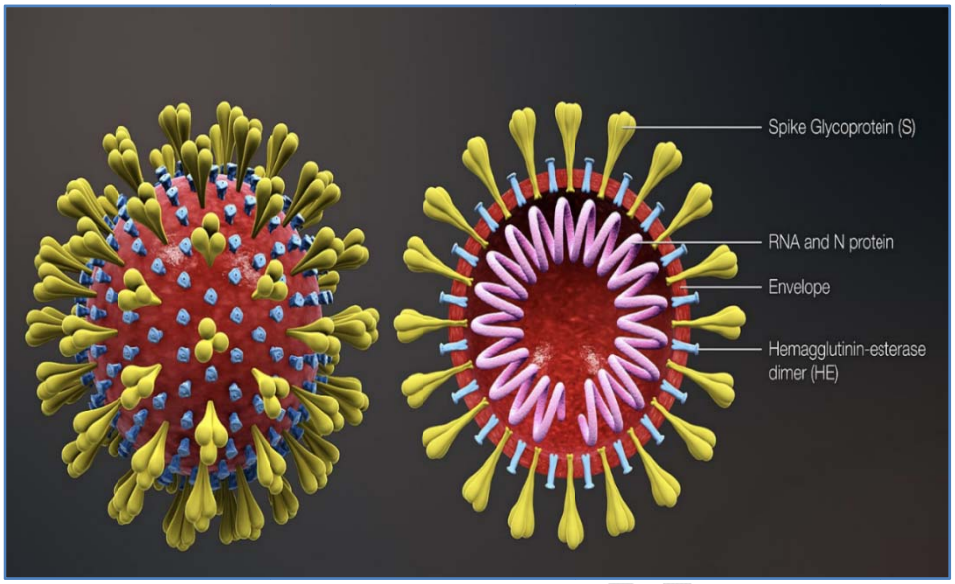


Figure 4. General structure of SARS-CoV-2 virion

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 *ORF*s placed inside the RNA (from 5′ to 3′) is: *ORF-1a/*ab encoding non-structural 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 region (UTR) is 265 nt length and the 3'-UTR is 229 nt length. The *ORF-1a/ab* is approx. 21,300 nt 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. S, *ORF-3a*, E, M and N are approx. three,820, 830, 230, 670 and 1,260 nt in length and 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 5), 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 consist of different enzyme domain names and features as indexed in Figure 4. The four structural proteins, i.e., S, E, M and N 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 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 domain, a transmembrane area and an intracellular area [17]. The S-proteins is heavily N-linked 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 [18]. Also, the S-protein mediates 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].

The M-protein (approx. 25–30 kDa) is the maximum considerable structural protein with 3 transmembrane domain. 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 launching 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. Presence of an N-terminal ectodomain and a C-terminal endodomain with ion channel 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 as an 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 publication 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 or cytoplasm.

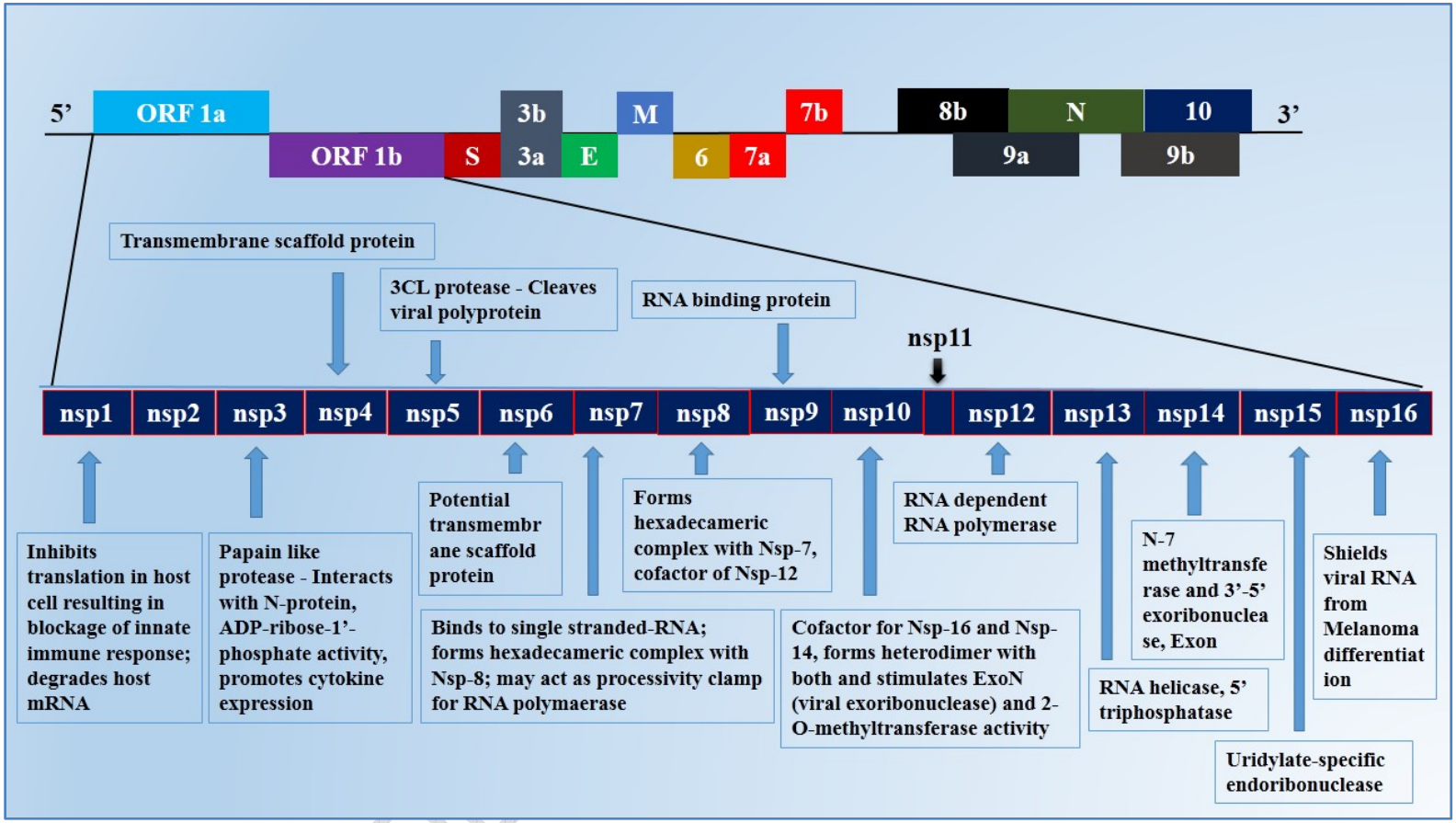


Figure 5. Genome Organization of SARS-CoV-2 and function of major proteins of corona virus

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. 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 6) via vesicles to the periphery and get released by exocytosis.

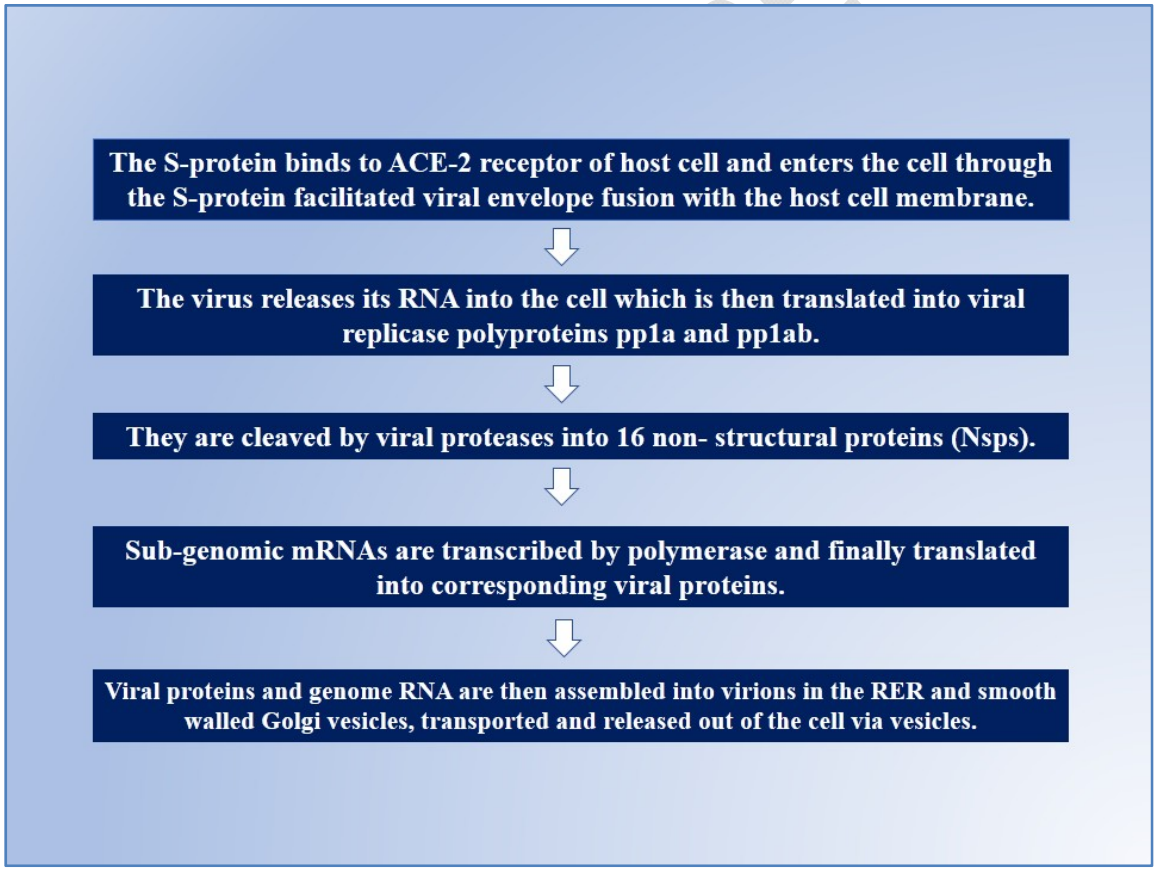


Figure 6. Flowchart of life cycle of SARS Corona Virus

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, D614G 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 lymphocytic 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 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-proteins [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, 33]. The findings of the kinetics of antibody reaction closer to SARS-CoV-2 were logically depicted.

7. CLINICAL DIAGNOSIS STRATEGIES FOR SARS-COV-2

The medical detection of SARS-CoV-2 infection is primarily based 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 in early screening [36]. At times, RT-qPCR might provide defective or false excessive quality or bad effects. In such cases, chest CT test may be of assistance. Recently, reverse transcription-PCR (RT-PCR) based rapid and 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 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- based 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, 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 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. According to a report of the economic times on 7th October 2020, scientists have developed a new method that allows

anyone to easily and quickly detect Covid-19 in just 30 minutes, and is as accurate as the current PCR diagnostic test. The SENSR technology developed by researchers at Pohang University of Science & Technology (POSTECH) in South Korea diagnosis Covid-19 based on the RNA sequence of the virus, reducing the stress on one single testing location and avoiding contact with infected patients as much as possible

8. TREATMENT FOR SARS-COV-2 INFECTION

The improvement of therapeutics for coronaviruses has been going on for SARS-COV-2. 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. The major drugs which are now functional to reduce the effect of Corona virus includes Ramdesivir, Flavipiravir, Lopinavir, Chloroquine, Sarilumab, ASC-09 + ritonavir, Tocilizumab, Lenzilumab, Dapagliflozin etc.

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 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 corona virus is the transmembrane protease, serine-2 (TMPRSS2) which is functional in proteolytic processing of S-protein. Therefore, Camostat mesylate, an inhibitor of TMPRSS2, might gain efficient utility and popularity of scientific use [50]. Trials are also demonstrating at convalescent SARS sufferers to capable of cross-neutralizing SARS-CoV-2 entry. 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 vaccine improvement approaches include vaccine based on viral vector, DNA-vaccine, subunit vaccine, virus like particles (VLPs)-based t vaccine, inactivated complete-virus vaccine and live attenuated vaccine [51] are indexed in Table 2. 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 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 7) and India is now preparing itself to tackle the corona virus pandemic. A subunit vaccine such as a trimerized SARS-CoV-2 S-protein using the patented Trimer-Tag® is being evolved by 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]. Also the siRNA concentrated on ACE-2 mRNA driven by U6 promotor exhibited reduced viral infection in Vero E6cell lines [55].

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

Bharat Biotech's COVAXIN™ (Figure 8), 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. According to an online report on 7th October 2020 by the economics times, the drugs controller general of India (DCGI) has given permission for conducting Phase-1 human clinical trial for an "antisera" that was developed by injecting inactivated SARS-CoV-2 in horses and can be a potential treatment for COVID-19, ICMR officials said on Tuesday. The 'antisera' has been developed by the Indian Council of Medical Research (ICMR) in collaboration with a Hyderabad-based bio-pharmaceutical firm (health.economictimes.indiatimes.com).

Figure 7. Some Indian pharmaceutical companies developing vaccine for coronavirus

Figure 8. 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 9). Under exploratory and preclinical pipeline vaccine development projects, recombinant protein-based vaccine projects are more than other projects (Figure 10). 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 11). Under clinical pipeline vaccine development projects, recombinant protein-based vaccine projects are more followed by non-replicating viral vector, RNA and inactivated virus (Figure 12). Although the leading COVID-19 vaccine candidates have progressed to advanced stages of clinical development at exceptional speed, many uncertainties remain given the lack of robust clinical data so far. Moreover, given the highly unusual circumstances associated with developing a vaccine during the evolution of a novel global pandemic, probability of success benchmarks for traditional vaccine development are likely to underrepresent the risks associated with delivering a licensed vaccine for COVID-19. The most advanced candidates are expected to begin reporting data from pivotal studies over the coming months, which if positive will be used to support accelerated licensure of the first COVID-19 vaccines. Such data will also provide valuable insights for the field and inform ongoing and future development activities aimed not only at controlling the current global pandemic, but also for effective long-term immunization strategies against the disease.

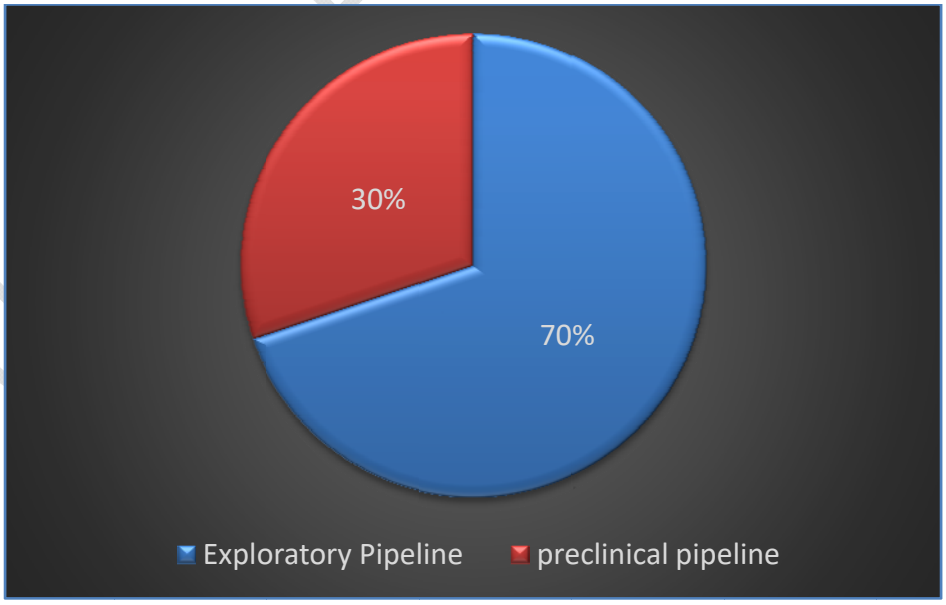


Figure 9. Vaccine development projects under exploratory pipeline and preclinical pipelines

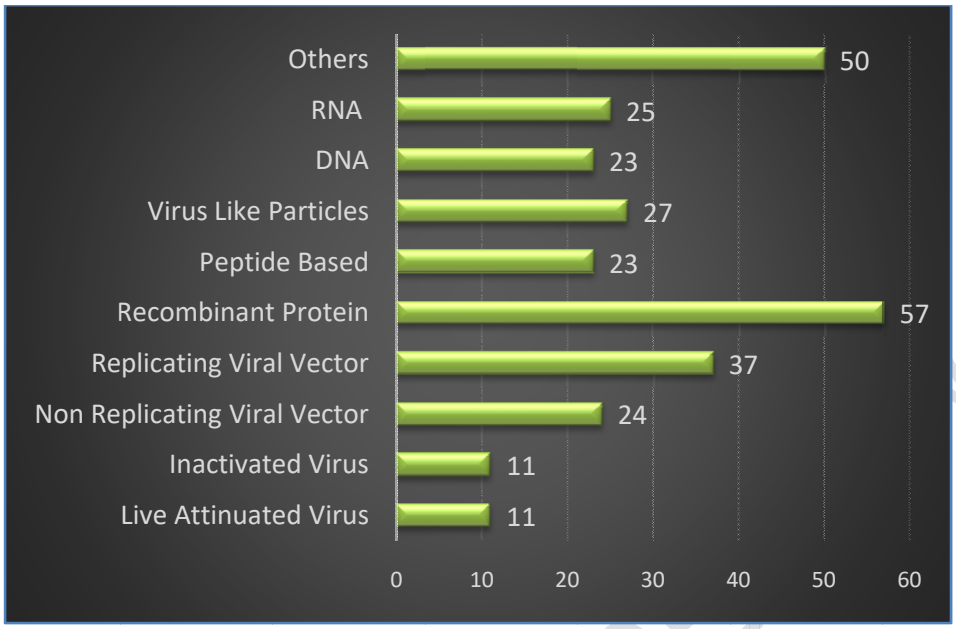


Figure 10. Breakups of vaccine development projects under exploratory pipeline and preclinical pipelines

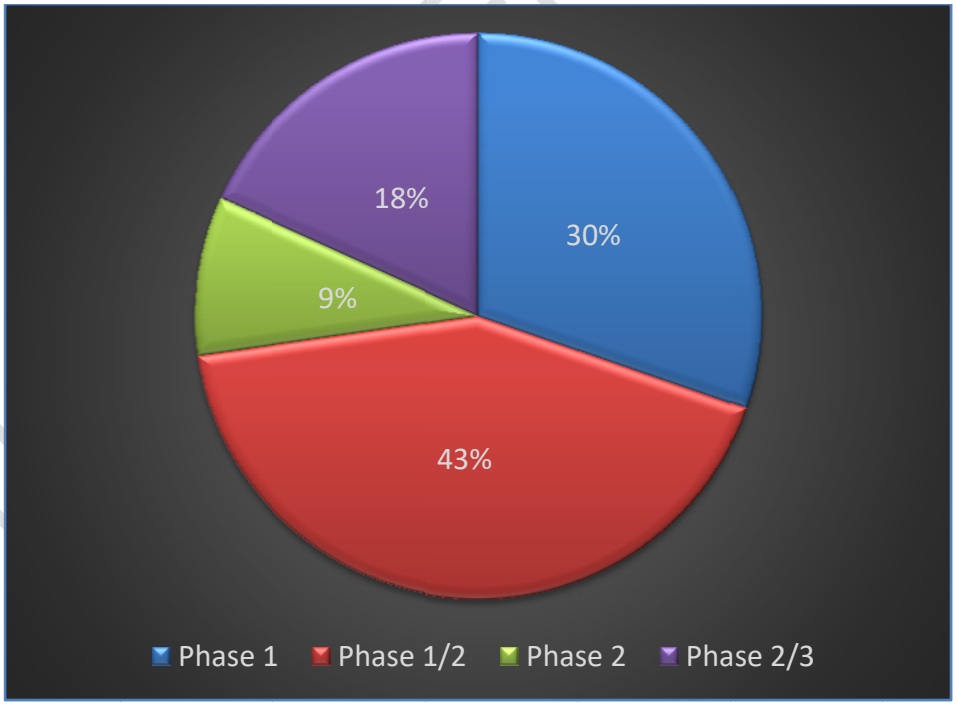


Figure 11. Vaccine development projects under clinical pipelines

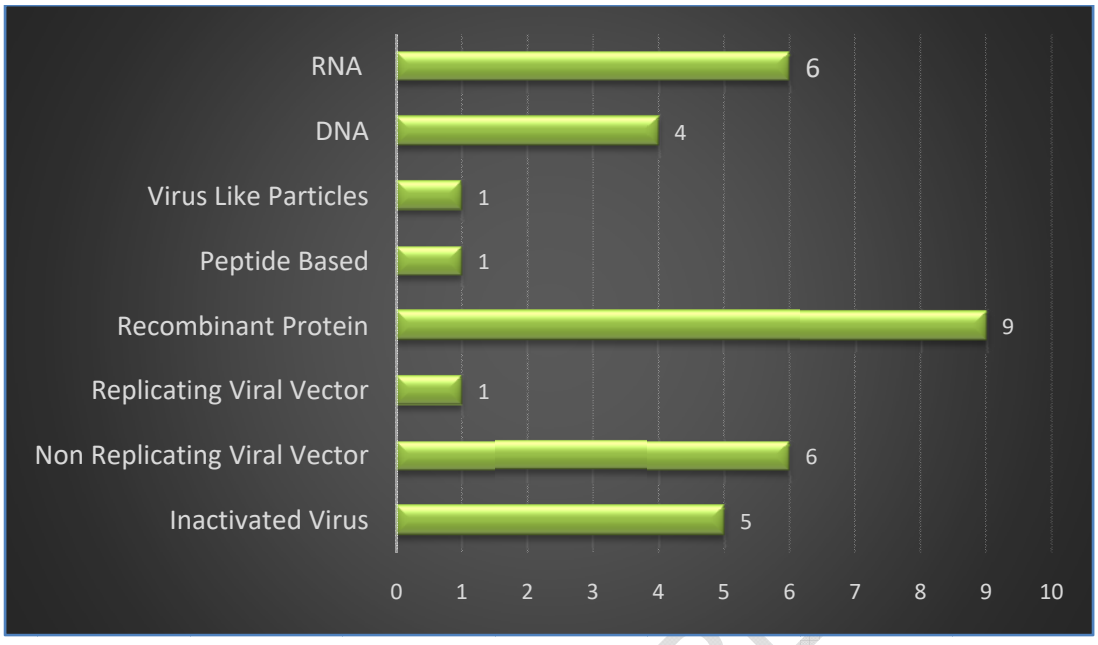


Figure 12. Breakups of vaccine development projects under clinical pipelines

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* [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 candidates to treat COVID19. According to one report (timesnow.com) on 15th May 2020, The AYUSH Ministry, along with CSIR began trials for 4 AYUSH formulations. According to another report on 6th October 2020 (newindianexpress.com), centre releases Ayurveda protocol to combat Covid-19 based on Guduchi, Ashwagandha and AYUSH-64. From sipping hot turmeric milk, *kadha* to performing yoga, and consuming *ashwagandha* and *guduchi* — the Narendra Modi government released the official protocol (Photo 1) of using ayurveda and yoga for Covid-19 prevention and treatment of patients with mild or no symptoms. The Ministry of AYUSH has been promoting ayurveda since the beginning of the pandemic claiming that alternative medicines can help improve immunity against the novel coronavirus. Prime Minister Narendra Modi also promoted the advice by the ministry in his address to the nation in April. Union Health Minister Harsh Vardhan tweeted that the "upgradation of protocols" has been done in sync with the Indian Council of Medical Research and Council of Scientific and Industrial Research (theprint.in). An Ayurvedic medicine developed with Pankajakasthuri Herbal Research Foundation, Kerala, India has been permitted for clinical trials on COVID-19 inflamed adults by 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.

Photo 1. Union Health Minister Harsh Vardhan releases the AYUSH ministry's Covid treatment protocol on 6 October 2020 (@drharshvardhan)

12. CONCLUSION

The world is in desperate need of effective, reliable vaccine strategies for COVID-19. Many labs and businesses have been rushing to produce these vaccines quickly , resulting in more than 160 vaccine candidates, with a handful of clinical trials having reached phase I, II and III within a limited span of 6 months. While COVID-19 and its vaccine specifications are only beginning to be understood, most of the advanced vaccine platforms have been extensively explored for other infections and cancer [61, 62]. While it is important to follow different vaccine strategies in tandem, in order to make well-informed decisions on and strategies to prioritise, it is equally important not to lose sight of this current scientific knowledge.It's already almost seven months since the first report of the SARS-CoV-2 infection has come to limelight and 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.The world is fighting against this pandemic now. The vaccine production is a challenging task and the scientists are working on it. As the proverb says, "prevention is better than cure", we need to protect ourselves and others around us by knowing the facts and taking appropriate precautions (Photo 2). We should actively follow the advice provided by our local health authorities. To prevent the spread of COVID-19, cleaning our hands using soap and water or an alcohol-based hand rub, maintaining safe distance from anyone who is coughing or sneezing, wearing a mask when physical distancing is not possible, covering nose and mouth with one's bent elbow or a tissue when you cough or sneeze, staying home etc. should be practiced to prevent the further spread of this viral infection.

Photo 2. Covid-19 Safety Measures

According to the latest reports of nature briefing on 8th Oct. 2020 (briefing@nature.com), the latest developments in detection of signs of corona virus infection indicated that “Floki” (Photo 3), a springer spaniel, that scientists at the University of Adelaide in Australia are training to detect signs of coronavirus infection in human sweat. The research is part of an international effort to train sniffer dogs to rapidly screen people for COVID-19. The canines are rewarded with positive reinforcement in Floki’s case, being allowed to play with his favourite toy, when they pick a sweat sample from someone with the disease out of a line-up. Preliminary studies show that dogs trained in this way are able to identify people who are infected with the coronavirus before they develop symptoms. A pilot scheme involving 4 sniffer dogs at Helsinki airport indicated that dogs can detect the presence of the virus in less than 10 seconds with nearly 100% accuracy.

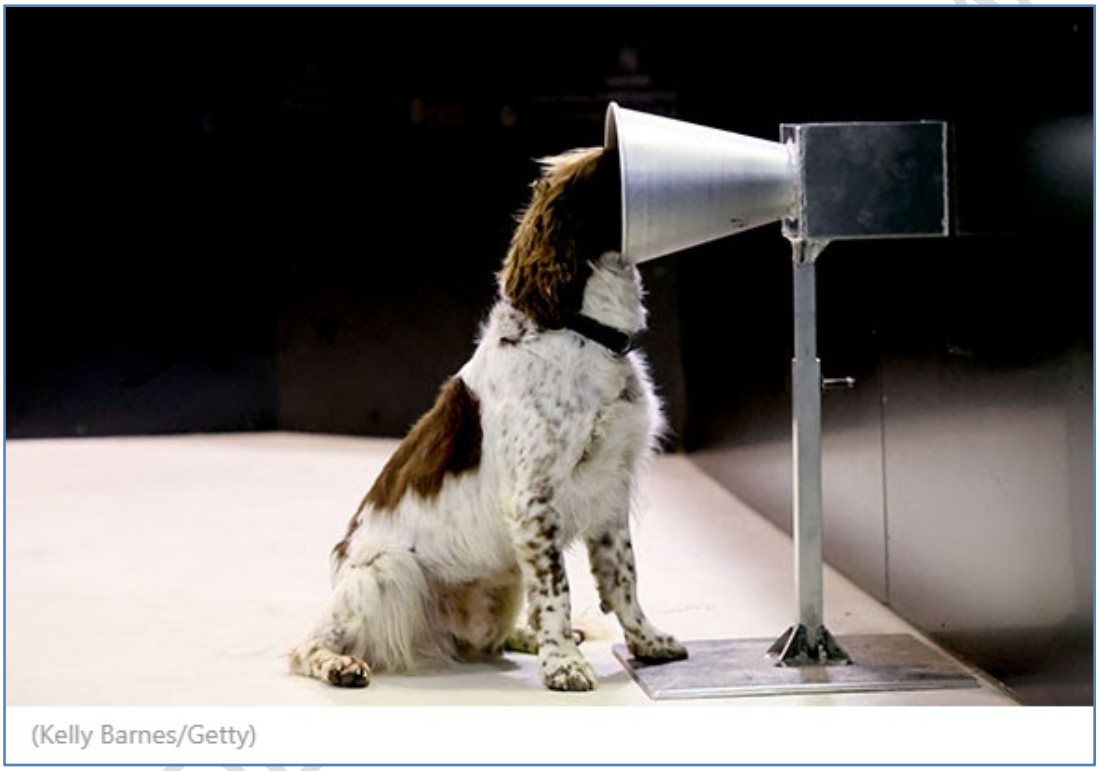


Photo 3. Photograph of Floki, a Springer Spaniel which is being trained to detect signs of coronavirus infection in human sweat (briefing@nature.com)

Given the challenges in resources, manufacturing and issues associated with distribution and regional protectionism. The implementation of vaccination programmes will likely be uneven, asynchronous and variable involving different vaccine platforms and strategies around the globe [63, 64]. In this regard, some resource- rich countries have already secured large numbers of doses of different candidate vaccines without knowing their efficacy. The heated debate has begun globally over who should be at the front of the line when vaccine supply is limited. The founding of the COVID-19 Vaccines Global Access (COVAX) Facility by Gavi, the Coalition for Epidemic Preparedness Innovations (CEPI) and the WHO is an attempt to garner resources and unite higher- and lower- income countries for the coordinated, rapid, transparent and equitable access to COVID-19 vaccines worldwide. According to nature briefing on 9th Oct. 2020, China announced that, it will join

COVAX, the international coalition that aims to fairly distribute COVID-19 vaccines (briefing@nature.com). The effort run by Gavi, the Vaccine Alliance; the Coalition for Epidemic Preparedness Innovations; and the World Health Organization — wants to provide 2 billion vaccine doses to the most-vulnerable people and to health-care workers, especially in poor countries. Some 80 wealthy countries have committed to support the initiative, with the notable exception of the United States. It is not clear yet whether China will commit money or vaccines, and how much. Future research needs to be directed on the following:

a. The identification of coronavirus proteins, their structures and the drug compounds to block them or to develop vaccines to incite the immune system against them and strategies for making enough corona virus drugs.
b. Genome sequencing using the tools of NGS to squash a second wave.
c. Identification of potential strains that thrive in humans and other animals.
d. Circumstances that promote super spreading events.
e. Factors that affect the spread of the virus in different settings.
f. The social, economic, environmental and health effects of the disease.
g. The determination of the age group of people who are more likely to enter hospitals.
h. The ways in which COVID-19 vaccine strategies may evolve over the next few years.

Although China has started its usual financial activities but there have been reports of SARS-CoV-2 high quality cases coming at regular intervals. Same is the case in European countries too. Even though it is broadly perceived that peak infection is over, it is unpredictable what will show up after normalcy restores. In nations like USA, India, Pakistan, the contamination level is gradually increasing. There are some predictions that the situation definitely may worsen at some point of the approaching winter. The healthcare facilities has nearly collapsed in components of 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 unanswered questions about the pandemic which may serve as keys in enriching the sphere of therapeutics. Truly a concerted effort is the need of the hour where nations should divert their resources towards the creation of a strong therapeutic platform to combat the pathogen and to avoid future encounters. The socio-political fraternity, policy makers and the health care personnel's need to play a pivotal role in bridging the gaps regarding the epidemiology of disease, the major predisposing risks, transmission rates, clinical manifestations, phenotypes and treatment options.

The immune response to COVID-19 have shown the following results:

a. Most COVID-19 patients who have recovered from the disease have sufficiently developed antibodies in their blood to the SARS-CoV-2.
b. Most COVID-19 patients develop antibodies about 1-3 weeks after symptoms start and it is the time when many patients start to recover.
c. Patients who have had more severe disease appear to have higher levels of important neutralizing antibodies.
d. Patients who had mild or asymptomatic COVID-19 have low levels of neutralizing antibodies (or even undetectable levels) and it is possible that the innate immune response and the T cell response have cleared the virus.
e. Recent studies have also shown that neutralizing antibodies may disappear after 3 months.

There is a growing body of evidence that a number of investigational agents are being explored for antiviral treatment of COVID-19 and their inclusion in clinical trials. Certain investigational agents have been described in observational studies or are being used anecdotally based on in vitro or extrapolated evidence but it is important to emphasize here that there exists no controlled data supporting the use of any of these agents and their efficacy for COVID-19 still remains unknown. The COVID-19 outbreak is proving to be an unprecedented disaster especially in the most afflicted countries and it is too early to forecast any realistic scenario but for sure it will have a strong impact worldwide. There is a rapidly growing body of literature on this topic and certainly it will help in establishing the best management and treatment strategies.

Disclaimer regarding Consent and Ethical Approval:

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors

COMPETING INTERESTS DISCLAIMER

Authors have declared that no competing interests exist.

AUTHORS' CONTRIBUTIONS

Author 1 and Author 4 contributed equally, designed the study and wrote the first draft of the manuscript. Author 2 and 3 managed the literature searches. Author 7 corrected the manuscript. All authors read and approved the final manuscript.

ACRONYMS

1. ACE-2 receptor - angiotensin-converting enzyme 2 - receptor
2. BSL-3 - Bio-Safety Level 3
3. COVID-19 – Corona virus disease 19
4. CSIR - Council of Scientific and Industrial Research
5. CT test - Computerized tomography test
6. DCGI - Drugs Controller General of India
7. DETECTR - DNA Endonuclease-Targeted CRISPR Trans Reporter
8. DNA – Deoxyribonucleic Acid
9. ELISA - Enzyme-linked immunosorbent assay
10. ERGIC – Endoplasmic Reticulum-Golgi intermediate compartment
11. FDA - Food and Drug Administration
12. Ig – Immunoglobulin
13. IMF - International Monetary Fund
14. MERS - Middle East Respiratory Syndrome
15. Ministry of AYUSH - Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy
16. Nsps - Non-structural proteins
17. ORF – Open reading frame
18. PCR – Polymerase Chain Reaction
19. qRT PCR - Real-Time Quantitative Reverse Transcription PCR
20. RBD - Receptor-binding domain
21. RdRp - RNA-dependent RNA polymerase
22. RNA – Ribonucleic Acid
23. RT-LAMP - Reverse Transcription-Loop Mediated Isothermal Amplification
24. SARS - Severe Acute Respiratory Syndrome)
25. SHERLOCK - Specific High sensitivity Enzymatic Reporter unLOCKing
26. TLRs - Toll-like receptors
27. TMPRSS2 - Transmembrane protease, serine-2
28. USA – United states of America
29. VLPs - Virus like particles
30. WHO – World health organization

REFERENCES

1. Anderson RM, Fraser C, Ghani AC, Donnelly CA, Riley S, Ferguson NM, Leung GM, Lam TH et al. Epidemiology, transmission dynamics and control of SARS: the 2002–2003 epidemic. Philosophical Transactions of the Royal Society of London. Series B: Biol. Sci. 2004;359(1447):1091-105.
2. World Economic Outlook, International Monetary Fund, April 14, 2020.
3. Smith RD. Responding to global infectious disease outbreaks: lessons from SARS on the role of risk perception, communication and management. Soc Sci Med. 2006; 63(12):3113-23.
4. Webster RG. Wet markets - a continuing source of severe acute respiratory syndrome and influenza? The Lancet. 2004;363(9404):234-6.

5. Abduljali, J. M., & Abduljali, B. M. Epidemiology, genome and clinical features of the pandemic SARS-CoV-2: a recent view. New Microbes and New Infections, 2020; 100672.
6. Chen WH, Strych U, Hotez PJ, Bottazzi ME. The SARS-CoV-2 vaccine pipeline: an overview. Curr Trop Med Rep. 2020; 7:61-4.
7. Tyrrell DA, Bynoe ML. Cultivation of viruses from a high proportion of patients with colds. The Lancet. 1966;1(7428):76–7.
8. Yan WX, Chong S, Zhang H, Makarova KS, Koonin EV, Cheng DR, Scott DA. Cas13d is a compact RNA-targeting type VI CRISPR effector positively modulated by a WYL-domain-containing accessory protein. Mol Cell. 2018;70(2):327-39.
9. Fung TS, Liu DX. Human coronavirus: host-pathogen interaction. Annu Rev Microbiol. 2019; 73:529-57.
10. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (CoVID-19) from publicly reported confirmed cases: Estimation and application. Ann Intern Med. 2020;172(9):577–82.
11. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic transmission of SARS-CoV-2-Singapore. Morb Mortal Wkly Rep. 2020;69(14):411–5.
12. Liu YC, Kuo RL, Shih SR. COVID-19: the first documented coronavirus pandemic in history. Biomed J. Press; 2020.1–6.
13. Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, Wang Q, Xu Y et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B. 2020;10(5):766-88.
14. Romano M, Ruggiero A, Squeglia F, Maga G, Berisio R. A structural view of SARS-CoV-2 RNA replication machinery: RNA synthesis, proofreading and final capping. Cells. 2020;9(5):1267.
15. de Wit E, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14(8):523.
16. Yu F, Du L, Ojcius DM, Pan C, Jiang S. Measures for diagnosing and treating infections by a novel coronavirus responsible for a pneumonia outbreak originating in Wuhan, China. Microbes Infect. 2020;22(2):74–9.
17. Wang N, Shi X, Jiang L, Zhang S, Wang D, Tong P, et al. Structure of MERS-CoV spike receptor-binding domain complexed with human receptor DPP4. Cell Res. 2013;23(8):986–93.
18. de Groot RJ, Luytjes W, Horzinek MC, van der Zeijst BA, Spaan WJ, Lenstra JA Evidence for a coiled-coil structure in the spike proteins of coronaviruses. J Mol Biol. 1987;196(4):963-6
19. Glowacka I, Bertram S, Muller MA, Allen P, Soilleux E, Pfefferle S, et al. Evidence that TMPRSS2 Activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J Virol. 2011;85(9):4122–34.
20. Vennema H, Godeke GJ, Rossen JW, Voorhout WF, Horzinek MC, Opstelten DJ, et al. Nucleocapsid-independent assembly of coronavirus-like particles by co-expression of viral envelope protein genes. EMBO J. 1996;15(8):2020–8.
21. Raj VS, Mou H, Smits SL, Dekkers DHW, Müller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature. 2013;495(7440):251–4.

22. Wang K, Chen W, Zhou Y-S, Lian J-Q, Zhang Z, Du P, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. BioRxiv; 2020.
23. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol. 2020;94(7):1–9.
24. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. Mil Med Res. 2020;7(1):1-0.
25. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020;14(2):185–92.
26. Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proc Natl Acad Sci U S A. 2009;106(14):5871–6.
27. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol. 2020;5(4):562–9.
28. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020; 24:91–8.
29. Sawicki SG, Sawicki DL. Coronavirus transcription: a perspective. Curr Top Microbiol Immunol. 2005; 287:31–55.
30. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, Levantovsky R, Malle L, et al. Immunology of COVID-19: current state of the science. Immunity. 2020;52(6):910-41.
31. Cano RL, Lopera HD. Introduction to T and B lymphocytes. In Autoimmunity: From Bench to Bedside. 2013; El Rosario University Press.
32. Sun B, Feng Y, Mo X, Zheng P, Wang Q, Li P, Peng P, Liu X et al. Kinetics of SARS-CoV-2 specific IgM and IgG responses in COVID-19 patients. Emerg Microbes Infect. 2020;9: https://doi.org/10.1080/22221751.2020.1762515.
33. Huang AT, Garcia-Carreras B, Hitchings MD, Yang B, Katzelnick LC, Rattigan SM, Borgert BA, Moreno CA et al. A systematic review of antibody mediated immunity to coronaviruses: antibody kinetics, correlates of protection, and association of antibody responses with severity of disease. medRxiv. 2020; https://doi.org/10.1101/2020.04.14.20065771.
34. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3.
35. To KK, Lu L, Yip CC, Poon RW, Fung AM, Cheng A, Lui DH, Ho DT et al. Additional molecular testing of saliva specimens improves the detection of respiratory viruses. Emerg Microbes Infect. 2017;6(1):1-7.
36. Dai WC, Zhang HW, Yu J, Xu HJ, Chen H, Luo SP, Zhang H, Liang LH et al. CT imaging and differential diagnosis of COVID-19. Can Assoc Radiol J. 2020 ;71(2):195-200.
37. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, Duan G. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses. 2020;12(4):372.

38. Broughton JP, Deng X, Yu G, Fasching CL, Servellita V, Singh J, Miao X, Streithorst JA et al. CRISPR–Cas12-based detection of SARS-CoV-2. Nat Biotechnol. 2020; 16:1-5.
39. https://indianexpress.com/article/explained/coronavirus-vaccine-tracker-september-22-covid-19-latest-news-covax-facility-6605548/
40. Kruse RL. Therapeutic strategies in an outbreak scenario to treat the novel coronavirus originating in Wuhan, China. F1000Research. 2020; 9:72.
41. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, Li Y, Zhu L et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science. 2020; doi: 10.1126/science.abc1932.
42. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. J Am Med Assoc. 2020;323(18):1824-36.
43. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad-spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Series B. 2017;93(7):449-63.
44. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, Kao RY, Poon LL et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004;59(3):252-6.
45. Johnson DE. Biotherapeutics: challenges and opportunities for predictive toxicology of monoclonal antibodies. Int J Mol Sci. 2018;19(11):3685.
46. Vellingiri B, Jayaramayya K, Iyer M, Narayanasamy A, Govindasamy V, Giridharan B, Ganesan S, Venugopal A et al. COVID-19: A promising cure for the global panic. Sci Total Environ. 2020; 725:138277.
47. https://milkeninstitute.org/covid-19-tracker. COVID-19 treatment tracker (updated weekly). Milken Institute. 2020-05-05. Retrieved 2020-05-07. Lay summary.
48. Cure E, Cure MC. Can dapagliflozin have a protective effect against COVID-19 infection? A hypothesis. Diabetes Metab Syndr. 2020;14(4):405.
49. Haagmans BL, Osterhaus AD. Coronaviruses and their therapy. Antivir Res. 2006;71(2-3):397-403.
50. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and Is Blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-280.e8.
51. Enjuanes L, Zuñiga S, Castano-Rodriguez C, Gutierrez-Alvarez J, Canton J, Sola I. Molecular basis of coronavirus virulence and vaccine development. Adv Virus Res.2016;96: 245-286. Academic Press.
52. Jiang S, Bottazzi ME, Du L, Lustigman S, Tseng CT, Curti E, Jones K, Zhan B et al. Roadmap to developing a recombinant coronavirus S protein receptor-binding domain vaccine for severe acute respiratory syndrome. Expert Rev. Vaccines. 2012;11(12):1405-13.
53. Kim D, Lee JY, Yang JS, Kim JW, Kim VN, Chang H. The architecture of SARS-CoV-2 transcriptome. Cell. 2020;181(4):1–8.
54. Loutfy MR, Blatt LM, Siminovitch KA, Ward S, Wolff B, Lho H, Pham DH, Deif H et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. J Am Med Assoc. 2003;290(24):3222-8.
55. Lu CY, Huang HY, Yang TH, Chang LY, Lee CY, Huang LM. siRNA silencing of angiotensin-converting enzyme 2 reduced severe acute respiratory syndrome-

associated coronavirus replications in Vero E6 cells. Eur J Clin Microbiol. 2008;27(8):709-15.
56. Gao ZC. Efficient management of novel coronavirus pneumonia by efficient prevention and control in scientific manner. Zhonghua Jie He He Hu Xi Za Zhi. 2020;43: E001-E001.
57. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020.
58. Pruijssers AJ, Denison MR. Nucleoside analogues for the treatment of coronavirus infections. Curr Opin Virol. 2019; 35:57-62.
59. Abbott TR, Dhamdhere G, Liu Y, Lin X, Goudy L, Zeng L, Chemparathy A, Chmura S et al. Development of CRISPR as an antiviral strategy to combat SARS-CoV-2 and influenza. Cell. 2020;181(4):865-76.
60. Konermann S, Lotfy P, Brideau NJ, Oki J, Shokhirev MN, Hsu PD. Transcriptome engineering with RNA-targeting type VI-D CRISPR effectors. Cell. 2018;173(3):665-76.
61. Afkhami, S., Yao, Y. & Xing, Z. Methods and clinical development of adenovirus-vectored vaccines against mucosal pathogens. *Mol. Ther. Methods Clin. Dev. 2016:* 3.
62. Humphreys, I. R. & Sebastian, S. Novel viral vectors in infectious diseases. Immunology. 2018: 153, 1–9.
63. World Economic Forum. 3 challenges in creating a coronavirus vaccine – and how they are being overcome. World Economic Forum, 2020: https://www. weforum.org/agenda/2020/05/coronavirus- covid-19- vaccine- industry/.
64. Bollyky, T. J., Gostin, L. O. & Hamburg, M. A. The equitable distribution of COVID-19 therapeutics and vaccines. JAMA. 2020: 323, 2462.

USEFUL WEB LINKS

1. **Central Drugs Standard Control Organization**: https://cdsco.gov.in/opencms/opencms/en/Home/
2. **Indian Council of Medical Research**: https://www.icmr.gov.in/
3. **Ministry of Ayush, Government of India**: https://www.ayush.gov.in/
4. **Nature News:** https://www.nature.com/news
5. **Research gate**: https://www.researchgate.net/
6. **World Health Organization**: https://www.who.int/