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SHORT REVIEW

Conspectus of SARS-CoV-2 - In India

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Abstract

COVID-19 has created much concern among general public, policy makers and especially heath care workers. The reason is not one but varied such as anxiety, fear, compromised health, isolation, economic crisis and social stigma all of which leads to psychological stress. The disease became a global concern due to unmanageable death even in much developed countries. Coronavirus disease 19 (COVID -19) is a newly discovered disease caused by coronavirus which reside both in humans and animals. The article is a detailed review from the origin of the disease, its progression in India and its various other aspects.

Keywords: Covid 19, SARS Cov2, Viral

1. Introduction

COVID-19 has created much concern among the general public, policymakers and especially healthcare workers. The reason is not one but varied such as anxiety, fear, compromised health, isolation, economic crisis and social stigma all of which lead to psychological stress[1]. The disease became a global concern due to its unmanageable death rate, even in developed countries. Coronavirus disease 19 (COVID-19) is a newly discovered disease caused by a coronavirus that resides both in humans and animals[2]. Earlier, WHO recommended an interim name for the virus as 2019-nCoV (novel coronavirus), which was later renamed officially by the International Committee of Taxonomy of Viruses (ICTV) as SARS-CoV[2-4]. Though the disease is claimed to be new, there are similar diseases that were experienced earlier by the human population. Until recently, seven coronaviruses that infect humans have been identified of which a few strains such as 229E, NL63, OC43 and HKU1 cause symptoms associated with the common cold[5]. The earlier diseases that have caused illnesses like the prevailing SARS-CoV-2 include SARS-CoV, (Severe Acute Respiratory Syndrome) and MERS-CoV, (Middle East Respiratory Syndrome)[6]. Across the globe, as of October 2021 about 234,809,103 confirmed cases and 4,800,375 deaths were recorded and about 6,188,903,420 vaccine doses were administered[7].

2. Microbiology

Viruses are an enigma, being less than any living organism, they are an inert collection of organic molecules. SARS-CoV-2 are parasites of about 0.1-0.2 µm in size which contains RNA genome surrounded by a protective coat[8]. The destruction of a virus can happen if the protein coat is dissolved, which can be achieved simply by saponification. Coronaviruses are classified under the family Coronaviridae, which comes under the order Nidovirales and suborder Coronavirineae. These enveloped viruses compose of single-stranded positive-sense RNA as their genetic component. Electron microscopical findings revealed a characteristic fringe of projections, which are mostly round or petal-shaped of about 200A° long on their surface. Later, these fringes were identified as spike proteins. These spikes give the appearance of a solar corona, hence the name coronavirus[9-11]. Coronaviruses are grouped into four genera: alpha, beta, gamma and delta. Alpha and Beta are commonly pathogenic to humans (Table 1), the other two are commonly encountered in birds. Their genomic content is 32 to 43% (G+C)[12]. Next-generation sequencing revealed that the entire length of the genome is 29,881 base pair units, the largest so far identified virus with 5′ capping and 3′ poly-A-tail[13]. These large genomes are fringed by open reading frames (ORF 1a, ORF 1b) at

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the 5′ end. Genes that code for all the important proteins in coronaviruses commonly occur in 5′ to 3′ order thereby coding Spike protein (S), Envelope small membrane protein (E), Membrane protein (M) and Nucleoprotein (N) sequentially[14,15]. Apart from these major structural proteins, other surface and accessory proteins such as Hemagglutinin Esterases (HE), 3a/b protein and 4a/b protein. The surface proteins and their features are tabulated (Table 2). The spike protein existing on the surface of the virus D614 G is dominant and known to mutate causing disease all over the world. SARS-CoV-2 undergoes evolution over a period of time[16,17]. Various sub-types of SARS-CoV-2 include B.1.1.7 detected in the US, P.1 from Japan/Brazil, B.1.351 from South Africa and B.1.427 and B.1.429 from US-California[18] (Figure 1).

2.1 VOC/VOI

Variants of Interest (VOI) is a SARS-CoV-2 variant with predicted genetic changes causing characteristic disease severity, immune modulation and transmissibility. Variants of Concern (VOC) are SARS-CoV-2 variants with an abnormal number or unpredictability of mutations, resulting in unusual clinical presentation, increased transmissibility, and increased virulence.

2.2 Clades of SARS-CoV-2 in India

The national institute of virology declared the existence of the P.1 variant, a Brazilian clade in India that has the capability to spread faster in comparison to other lineages. B.1.351 variant of South Africa has a mutation referred to as N501Y enabling it to be highly transmissible. B.1.1.7 a sub-type predominant in the UK was also isolated in India. The second wave which hit India in March 2021 has a double mutant clade B.1.617 which was identified by INSACOG (the Indian SARS-CoV-2 consortium on genomics) and constitutes a mutation on E484Q and L452R. By April there has been a tremendous increase in infectivity rate and mortality. A triple-mutated variant that has a mutation on E484K which enables them to escape from immune surveillance has been detected, called B.1.618 or Bengal strain. Recently, AY.4.2 lineage a subvariant of the delta strain has been identified (National Institute of virology)[19,20]. By November 2021, a new strain was confirmed by TAG-VE (Technical Advisory Group on SARS-CoV-2 Virus Evolution) from South Africa, B.1.1.529 and named Omicron. This variant has been observed with an increased number of mutations, raising concerns about reinfection. On evaluation, this Omicron variant has been designated as a Variant of Concern

Table 1. Classification of Coronavirus

More Common	Less Common
229E – Alpha	MERS CoV – beta
NL 63 – Alpha	SARS CoV – beta
OC 43 – Beta	SARS CoV
HKU1 – Beta	

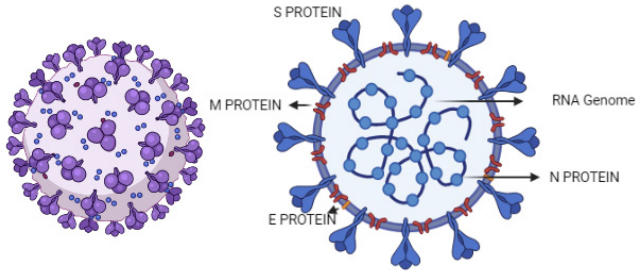

Figure 1. Morphology of coronavirus.

Table 2. Common proteins of SARS CoV and their functions

S. No.	Surface Proteins	Morphology	Function
1	Spike protein	Two subunits S1, and S2. S1- Receptor binding function S2- Fusion activity.	Facilitates the viral attachment to ACE2 receptor
2	Envelope protein	Small hydrophobic integral membrane protein	Functions as Viroporin, essential for viral growth.
3	Nucleocapsid protein	Multivalent RNA binding protein	Holds the RNA genome
4	Membrane glycoprotein	Type III transmembrane protein and most abundant one.	Determines antigenicity
5	Hemagglutinin esterase	Smaller spike protein of betacoronavirus	Helps in viral entry into the host cell

(VOC)[64]. According to the Indian Institute of Sciences, about 10 lineages of coronavirus have evolved from the ancestral Wuhan type. To call a particular evolved subtype a new entity, at least two DNA mutations are expected in the parent RNA form[20].

2.3 Mode of Transmission

SARS-CoV-2 must have conquered the human race possibly by zoonosis since a group of coronavirus is zoonotic. SARS-CoV originated in 2003, for which Civatte cats were found to be the bearers of the virus, whereas for MERS-CoV, which originated in 2012, it was dromedary camels. The original reservoir for this group of coronaviruses was claimed to be bats, while the rest serve as an intermediate host for both diseases. For SARS-CoV-2 (2019), pangolins were considered to be the intermediate host. These are the most sought-after animal for their skin and flesh in Asian countries for their medicinal value. It is a highly poached animal, and numerous studies have concluded the presence of SARS-CoV-2 strains in its lungs[21]. However, much time and deeper analysis are needed to confirm the possibility.

SARS-CoV-2 predominantly spreads through droplets from person to person through direct contact, indirect contact or close contact. The source of infection might be respiratory secretions, saliva or droplets that are produced by sneezing, coughing or talking. Fomite transmission is also highly possible. Transmission of the virus by aerosol-producing medical procedures such as intubation and dental procedures is also possible. Closed spaces with clusters of people may also serve as a source of infection. Other modes of transmission include infection from biological samples such as urine and feces. Maternal transmission during pregnancy and delivery has not been studied in detail. Studies of breast milk revealed no viable viruses. Patients without symptoms can also infect other individuals[21-23].

2.4 Waves

The COVID-19 disease has been modelled to occur in multiple waves. The first wave in India occurred in the year 2020, the second wave occurred in early March 2021, the Third wave in India started in January 2022 and individuals affected had a very short recovery period of five to seven days. A possible pandemic wave scenario is a continuous form of peak and valley, a high peak followed by a fall, a slow burn, and a continuous and moderate transmission status (Figure 2). The Series Interval (SI)

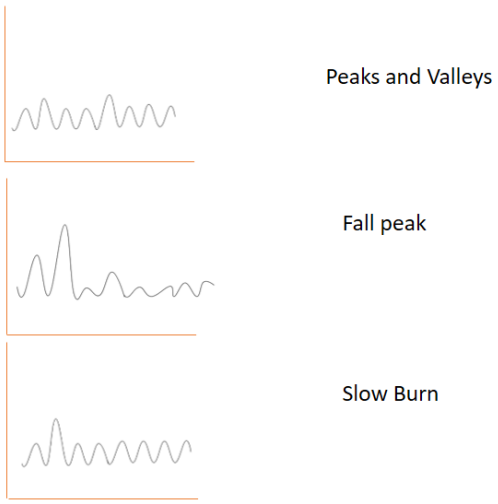

Figure 2. Possible wave scenario of COVID-19.

period from the onset of symptoms in patient 1 to the onset of symptoms in patient 2 is estimated as 4-7.5 days in India. R_0 is the number of people who contracted the disease from one person. The R_0 value for COVID-19 is about 5.7. The case fatality rate of COVID-19 worldwide was less in comparison to MERS and SARS during the early stages. However, in India, the case fatality rate increased from 1.3-3.6% in 2020-2021[24,25].

2.5 Epidemiology

In India, the incidence of disease from January 2020 to April 2021 includes two waves. Cases began to rise in early 2020, with 7 reported cases on January 30th, eventually reaching a peak incidence rate of 97,894 cases by mid-September and falling to 10,000 cases by January 2021. Later it was noted that the cases started splurging in March 2021 and by April 2021 a total of 17,997,267 cases were identified and the total number of death tolled to 201,187. By September 2021 the total number of cases went to 33,264,175 and 442,874 confirmed deaths in accordance to WHO[26]. Evidence-based medicine has reported that most of the pandemics encountered by the global population had two waves. The severity of infection, the population affected, treatment outcome and death are varied for each phase. Modelling studies have portrayed probable outcomes during the second to forthcoming waves. Theories of pandemics are mostly not morally supported. For an instance, Influenza infection has awakened the possibility of cyclical theory with its sudden reappearance. Globally, about 150,000,000 cases had been confirmed by April 2021, and about 3,128,962 deaths had been encountered. Reinfection in the short term has not

been reported yet. However, it has been observed that prior infection reduces the risk of reinfection by 80 to 85 % for about six months[27].

2.6 Pathophysiology

The structure of SARS-CoV-2 plays a major role in pathogenesis. The virus enters the human body through different modes from direct contact to cross-contamination[28]. As the virus enters the body through the respiratory tract it reaches the alveoli and attaches itself to the type II cells of the alveoli. The alveoli of the lungs consist of two types of pneumocytes[29,30]. Type I cells help in gas exchange and type II pneumocytes help in maintaining surface tension. The coronavirus has an affinity to attach to type II pneumocytes through the Spike (S) glycoprotein to the receptor ACE2 (angiotensin-converting enzyme 2)[31]. Apart from ACE2 some cell surface proteases derived from host cells such as TMPRSS2, Cathepsin B and Cathepsin L facilitate the viral entry into the host cell in the form of endosomes[32]. The virus consists of ORF 1a/1b at the 5′ end which encodes for about 15-16 non-structural proteins. Polymerases such as RNA-dependent RNA polymerase, non-structural proteins, and RTC helps in the transcription of the viral genome to form the number of genome copies[33]. These genome copies along with polyproteins result in a number of virions. These viral particles are released by the process of exocytosis.

Once the virions are released into the alveoli, the alveolar macrophages are activated, resulting in inflammation. The body's immune system as a result of inflammation induces the production of IL1, IL6, and TNF-α[34]. These inflammatory mediators in turn result in vasodilation and increase capillary permeability. Increased permeability causes fluid accumulation in the lungs resulting in alveolar edema. As a result of inflammation, cells of the alveoli are disrupted leading to decreased surfactant production and increased surface tension. The alveoli of the lungs collapse which increases the workload of breathing and causes dyspnea-hypoxemia[35].

Continuous inflammation attracts many neutrophils. Neutrophils, as a major corpus in the immune surveillance system, produce reactive oxygen species and proteases to destroy viral particles as well as affect the host's cells, destroying components of the alveolus. Destruction of the alveolar cells and accumulation of debris and fluid all cause consolidation which impairs the gas exchange process and is the causative of productive cough[35,36]. Lowering of partial pressure of the oxygen occurs due to the destruction of the alveolus. To compensate it sympathetic nervous system is activated which causes tachycardia and tachypnea. These inflammatory mediators also activate the hypothalamus, producing prostaglandin, and increasing body temperature. Continuous capillary perfusion, which eventually decreases the blood volume results in septic shock[37]. The continuum of these events causes decreased total vascular resistance, decreased blood pressure, and decreased organ perfusion which causes shut-down of various organs. Inflammatory mediators also increase BUN and creatinine which cause renal damage. Inflamed liver results in increased Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Bilirubin, CRP, Fibrinogen and IL6. The host immune system gets hyper-activated as a result of infection. In the process of trying to eliminate the pathogen "frustrated phagocytosis" occurs leading to the destruction of the host's cell[38] (Figure 3).

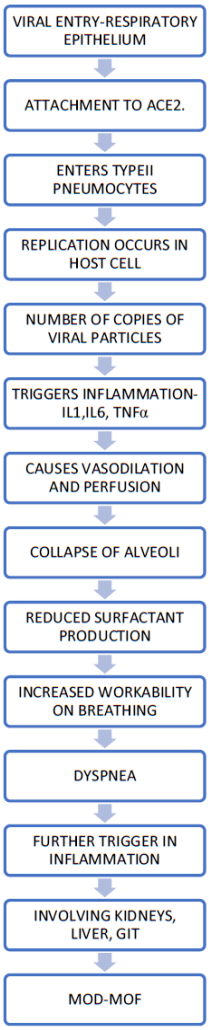

Figure 3. Schematic presentation of Induction of severe disease.

The incubation period for COVID-19 varies widely, an average period of 5.7 days of incubation period was revealed by study findings. The estimated range by the WHO is 1-14 days, although a period of 19 days, as well as 24 days, has also been reported.

2.7 Clinical Presentation

According to the WHO, the most common clinical presentation is fever, dry cough, generalized malaise, sore throat, and body pain with mild pneumonia[39]. Some patients also present symptoms such as diarrhoea, conjunctivitis, headache, hyposmia or anosmia, ageusia or dysgeusia, rashes and headache. The symptoms of corona infection usually occur for 1-2 weeks, yet, patients have been reported to suffer for about 10 weeks also. Aged patients and patients with multiple comorbidities are at higher risk. Those with severe disease may present with serious complications such as dyspnea, pneumonia, acute respiratory distress syndrome, chest pain or stroke, mental illness, neurological disturbances, and kidney damage resulting in acute progressive renal injury (AKI) which acts as a marker for multiple organ involvement, sepsis manifest with symptoms such as severe dyspnea, tachycardia, decreased urine output, altered mental status, hyperbilirubinemia, acidosis, coagulopathy and thrombocytopenia finally multiple organ failure increasing the fatality rate[40] (Figure 4). The second wave in India seems to be more devastating in comparison to the first wave[41].

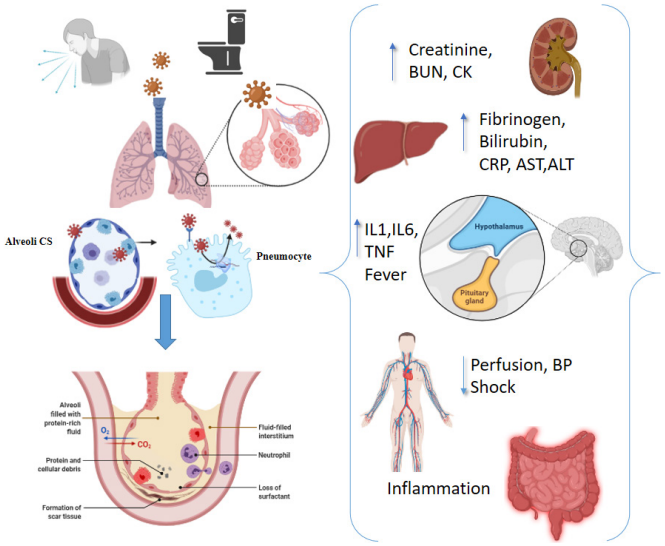

Figure 4. Possible clinical presentation in SARS-CoV-2 infected patients.

Dysgeusia is the first recognized most common oral manifestation of COVID-19, other presentations include erosion, vesicle, bulla, pustules, ulcers, halitosis, erythema, spontaneous bleeding, erythema, hemorrhagic crust, and necrosis. Manifestations on the tongue include depopulation, fissures and COVID tongue - an inflammatory disorder where the production of saliva decreases or ceases resulting in increased bacterial growth, dryness and stickiness. Reports on candidiasis, aphthous stomatitis, and Kawasaki-like lesions were also reported. Many people present with inflammatory diseases of the gastrointestinal tract COVID-19 may also exist with no symptoms to few symptoms[42,43].

3. Diagnostic Investigations

SARS-CoV-2 is diagnosed by either direct identification of the genome by RT-PCR (Real-Time Polymerase Chain Reaction) or indirectly by evaluating the immune response to the infection. RT PCR is considered to be the gold standard in diagnosis[44]. Primers for different regions such as RNA-dependent RNA polymerase genes, and genes encoding proteins E, N and ORF1ab are commonly used. Their sensitivity and specificity are 70% and 95% respectively. Though most laboratory procedures are commonly performed, the possibility of false negative and false positive results is high due to improper specimen collection techniques and handling processes. Day 5- 8 after symptom is considered to be best for RT PCR. A cycle threshold value of more than 35 is considered to be a negative or low viral load.

Serological tests are done to identify IgG, IgA and IgM to evaluate the humoral immune response of the body. These are detected by Enzyme Linked Immuno Sorbent Assay or by Chemiluminescence assay. Tests are conducted to detect antibodies against proteins S and N. their sensitivity and specificity depend on many factors such as disease duration, severity and other handling and processing factors[45].

Other tests such as CRP, ferritin, D-dimer, lactate dehydrogenase, Trop T, prothrombin time, partial thromboplastin time, creatine kinase, creatinine and glutamic pyruvic transaminase may be done if the severity of the disease increases to evaluate the efficiency of the kidney, liver and vascular system. Other blood reports such as a complete blood count will be effectively helpful in the constant evaluation of the cardiovascular system. Immune markers such as IL 1, IL 6, and TNF-α gives

us the inflammatory status of the entire system and the severity of the disease[46].

Apart from molecular and serological assays, X-ray chest, CT chest, and USG can be helpful to study the changes in the lungs and other soft tissue structures. Since most of the patients exhibit COVID-19 pneumonia, these imaging techniques help to understand the disease's progress even in the early stages. Ultrasound not only helps us to evaluate the lungs but also other organs[47].

CO-RADS scores are grading of the disease condition based on Computed Tomography (CT) findings. They are graded from CO-RADS 1-6. CO-RADS 1 indicates normal or non-infectious abnormalities such as congestive heart failure, sarcoid, malignancy, histoplasmosis or fibrosis. CO-RADS 2 indicates no typical signs of COVID-19, infection level is considered to be low. Other infection-associated findings such as bronchiolitis are also evident. CO-RADS 3 is an intermediate finding the CT readings indicate COVID-19, but it need not necessarily be COVID-19. Other infections such as bronchopneumonia, septic emboli and lobar pneumonia. CO-RADS 4 shows a high suspicious infection. CO-RADS 5 is very suspicious, and CO-RADS 6 with positive PCR. Typical CT findings include multifocal ground glass opacities, peripheral and basal distribution, unsharp demarcation, vascular thickening, round crazy paving, consolidations, reversed halo, spider web, cavitations, calcifications, nodular pattern and/or pleural thickening[48]. Yet these findings may overlap with those of other diseases such as H1N1 influenza, viral pneumonia or pneumonitis.

4. Management

The Indian Ministry for Health and Family Welfare, along with the Indian Council of Medical Research (ICMR), has formulated various strategies to effectively manage the current pandemic. Patients with mild symptoms are advised to monitor temperature/oxygen saturation, maintain home quarantine and follow medications for their symptoms. Simple breathing exercises and proning are taught to the patients to combat mild to moderate breathing difficulties. Immunomodulatory drugs such as steroidal therapy and anticoagulant therapy are started prophylactically. Hospital admission is advised when there is a consistent reduction in SpO_2 (92-96%). Patients with severe diseases such as respiratory rate >30/min, dyspnea, and SpO2 < 90% are mandated for ICU admission and artificial respiratory support. Steroidal therapy, anticoagulant therapy, antibiotic therapy to counteract opportunistic bacterial infection, an antiviral drug such as Remdesivir or some physicians prefer antiparasitic drugs. These drug regimens help the immune system fight the infection rather than the treatment protocol. The Food and Drug Administration of the United States has given Emergency Use Authorization (EUA) for drugs such as propofol-liquor 1%, bamlanivimab and etesevimab, regen CoV, baricitinib with remdesivir, COVID-19 convalescent plasma, REGIOCIT, Fresenius Kabi Propoven 2%, Remdesivir and Fresenius Medical, the multi-filtrate PRO system and multiBic/multiPlus solutions[49-50].

5. Vaccines

Vaccines are of great hope in the prevention of severe disease as well as in limiting its spread. Vaccines that obtained EUA from the latest to older include Janssen COVID-19, moderna COVID-19 and Pfizer-BioNtech COVID-19. The Central Drugs Standard Control Organization (CDSCO) of India authorized two drugs, Covishield manufactured by Serum Institute and Covaxin manufactured by Bharat Biotech in India. Both drugs are recommended by the WHO and ICMR. No other infectious diseases, earlier, had so many proposed vaccine candidates. Most of the vaccines are designed to achieve immunity against the virus[53]. The vaccines for COVID-19 are generally of four types. They are:

- Whole Virus
- Protein subunit
- Viral vector
- Nucleic acid

The whole virus is the most conventional type of vaccine. There are two subtypes: a) live attenuated vaccine that has weakened viruses. It can replicate in the host body without causing illness. b) inactivated or killed viruses. COVAXIN is a type of inactivated vaccine developed from dead viruses. They used Whole-Virion Inactivated Vero Cell-derived technology. This type of conventional vaccine is very much safer to be used in all types of patients. This technology does not infect an individual but still teaches the immune system to prepare for an active virus[54].

Viral vector-based vaccines differ from conventional vaccines. They do not possess actual antigenic particles. These antigenic particles are made to be produced by the host itself using vectors. Vectors are modified virus

which delivers the genetic component that code for antigen- Spike proteins of SARS-CoV-2 are generated in this pandemic scenario. A strong immune response from T cells and effective antibody production by B cells were induced. The immunity obtained is similar to the naturally obtained immunity. There are further two types non-replicating vectors and replicating vectors. COVISHIELD uses similar technology, a non-replicating vector, a chimpanzee adenovirus-ChAdOx1 carries the information for the production of S envelope protein. This cold virus is completely incapable of infecting the host yet teaches the immune system to effectively form a defence system[55].

The protein subunit is injecting a purified segment of the virus rather than the entire pathogen. These are also referred to as acellular vaccines. The immune response produced by this type of vaccine is weaker in comparison to others due to the lack of pathogen-associated molecular patterns, which act as a danger signal in an active infection. Thereby proven to be not as effective as other vaccine types[56].

As of April 2021, India has been provided with two vaccines: Covaxin, a vaccine from the Indian Council of Medical Research (ICMR) - National Institute of Virology. It is developed by Bharat Biotech's BSL-3. This vaccine has been approved by the Drug Controller General of India for restricted use during an emergency. It has undergone phase I and phase II clinical trial as well phase I and II Randomized double-blinded multi-centric studies. They have been evaluated for safety, tolerability, immunogenicity and reactogenicity. Phase III human clinical trials are ongoing. Covishield by AstraZeneca which has given authority to Serum Institute of India (SII) to manufacture[57-59]. SII and ICMR are jointly conducting a randomized observer-blind, controlled study. It is carried out to evaluate immunogenicity and safety. Phase II/III human clinical trials have been completed. Both vaccines are double-dosed, spaced apart by 90 days[60]. Other vaccines in India which have been approved by DGCI include ZyCoV D[61], Sputinik[62], Biological E's novel Covid-19 vaccine, BBV154-intranasal vaccine and COVOVAX (ICMR). All these are under human trial.

By November 2021, 1,09,63,59,208 people are vaccinated in India and it was very evident that individuals who are vaccinated with any drug are at lower risk of severe illness[63]. The vaccines proved to be highly effective as there was a very minimal death rate among vaccinated individuals during the most destructive 2nd wave, in India. The vaccine drive program in India has encouraged people of age above 18 years to undergo vaccination, effectively.

6. Conclusion

Amidst raising cases and restricted medical facilities to meet the demand, numerous steps have been implemented by the Indian Health Ministry along with ICMR. The continuous mutation is leading to the emergence of new strains that are not very different from the wild type. Mankind has faced many challenges, like a flood, famine, war and much more. Evolving through a pandemic is neither facile nor strenuous. In a developing country like India, emerging from such situations requires tremendous experiments and interventions. Any novelty which is being delivered out of such a bearing scenario will prove the sustenance of mankind.

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