other emerging viral diseases. Several therapeutic and preventive strategies, including vaccines, immunotherapeutics, and antiviral drugs, have been exploited against the previous CoV outbreaks (SARS-CoV and MERS-CoV) (8, 104, 164–167). These valuable options have already been evaluated for their potency, efficacy, and safety, along with several other types of current research that will fuel our search for ideal therapeutic agents against COVID-19 (7, 9, 19, 21, 36). The primary cause of the unavailability of approved and commercial vaccines, drugs, and therapeutics to counter the earlier SARS-CoV and MERS-CoV seems to owe to the lesser attention of the biomedicine and pharmaceutical companies, as these two CoVs did not cause much havoc, global threat, and panic like those posed by the SARS-CoV-2 pandemic (19). Moreover, for such outbreak situations, the requirement for vaccines and therapeutics/drugs exists only for a limited period, until the outbreak is controlled. The proportion of the human population infected with SARS-CoV and MERS-CoV was also much lower across the globe, failing to attract drug and vaccine manufacturers and producers. Therefore, by the time an effective drug or vaccine is designed against such disease outbreaks, the virus would have been controlled by adopting appropriate and strict

proteins without the presence of S protein would not confer any noticeable protection, with the absence of detectable serum SARS-CoV-neutralizing antibodies (170). Antigenic determinant sites present over S and N structural proteins of SARS-CoV-2 can be explored as suitable vaccine candidates (294). In the Asian population, S, E, M, and N proteins of SARS-CoV-2 are being targeted for developing subunit vaccines against COVID-19 (295).

The identification of the immunodominant region among the subunits and domains of S protein is critical for developing an effective vaccine against the coronavirus. The C-terminal domain of the S1 subunit is considered the immunodominant region of the porcine deltacoronavirus S protein (171). Similarly, further investigations are needed to determine the immunodominant regions of SARS-CoV-2 for facilitating vaccine development.

However, our previous attempts to develop a universal vaccine that is effective for both SARS-CoV and MERS-CoV based on T-cell epitope similarity pointed out the possibility of cross-reactivity among coronaviruses (172). That can be made possible by selected potential vaccine targets that are common to both viruses. SARS-CoV-2 has been reported to be closely related to SARS-CoV (173, 174). Hence, knowledge and understanding of

might be lower. Further genetic analysis is required between SARS-CoV-2 and different strains of SARS-CoV and SARS-like (SL) CoVs to evaluate the possibility of repurposed vaccines against COVID-19. This strategy will be helpful in the scenario of an outbreak, since much time can be saved, because preliminary evaluation, including *in vitro* studies, already would be completed for such vaccine candidates.

Multiepitope subunit vaccines can be considered a promising preventive strategy against the ongoing COVID-19 pandemic. *In silico* and advanced immunoinformatic tools can be used to develop multiepitope subunit vaccines. The vaccines that are engineered by this technique can be further evaluated using docking studies and, if found effective, then can be further evaluated in animal models (365). Identifying epitopes that have the potential to become a vaccine candidate is critical to developing an effective vaccine against COVID-19. The immunoinformatics approach has been used for recognizing essential epitopes of cytotoxic T lymphocytes and B cells from the surface glycoprotein of SARS-CoV-2. Recently, a few epitopes have been recognized from the SARS-CoV-2 surface glycoprotein. The selected epitopes explored targeting molecular dynamic simulations,

(173, 174). Hence, knowledge and understanding of S protein-based vaccine development in SARS-CoV will help to identify potential S protein vaccine candidates in SARS-CoV-2. Therefore, vaccine strategies based on the whole S protein, S protein subunits, or specific potential epitopes of S protein appear to be the most promising vaccine candidates against coronaviruses. The RBD of the S1 subunit of S protein has a superior capacity to induce neutralizing antibodies. This property of the RBD can be utilized for designing potential SARS-CoV vaccines either by using RBD-containing recombinant proteins or recombinant vectors that encode RBD (175). Hence, the superior genetic similarity existing between SARS-CoV-2 and SARS-CoV can be utilized to repurpose vaccines that have proven *in vitro* efficacy against SARS-CoV to be utilized for SARS-CoV-2. The possibility of cross-protection in COVID-19 was evaluated by comparing the S protein sequences of SARS-CoV-2 with that of SARS-CoV. The comparative analysis confirmed that the variable residues were found concentrated on the S1 subunit of S protein, an important vaccine target of the virus (150). Hence, the possibility of SARS-CoV-specific neutralizing antibodies providing cross-protection to COVID-19 might be lower. Further genetic analysis is required

(181). CEPI has also funded Moderna to develop a vaccine for COVID-19 in partnership with the Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH) (182). By employing mRNA vaccine platform technology, a vaccine candidate expressing SARS-CoV-2 spike protein is likely to go through clinical testing in the coming months (180). On 16 March 2020, Jennifer Haller became the first person outside China to receive an experimental vaccine, developed by Moderna, against this pandemic virus. Moderna, along with China's CanSino Biologics, became the first research group to launch small clinical trials of vaccines against COVID-19. Their study is evaluating the vaccine's safety and ability to trigger immune responses (296).

Scientists from all over the world are trying hard to develop working vaccines with robust protective immunity against COVID-19. Vaccine candidates, like mRNA-1273 SARS-CoV-2 vaccine, INO-4800 DNA coronavirus vaccine, and adenovirus type 5 vector vaccine candidate (Ad5-nCoV), are a few examples under phase I clinical trials, while self-amplifying RNA vaccine, oral recombinant COVID-19 vaccine, BNT162, plant-based COVID-19 vaccine, and Ii-Key peptide COVID-19 vaccine are

vaccine that can produce cross-reactive antibodies. However, the success of such a vaccine relies greatly on its ability to provide protection not only against present versions of the virus but also the ones that are likely to emerge in the future. This can be achieved by identifying antibodies that can recognize relatively conserved epitopes that are maintained as such even after the occurrence of considerable variations (362). Even though several vaccine clinical trials are being conducted around the world, pregnant women have been completely excluded from these studies. Pregnant women are highly vulnerable to emerging diseases such as COVID-19 due to alterations in the immune system and other physiological systems that are associated with pregnancy. Therefore, in the event of successful vaccine development, pregnant women will not get access to the vaccines (361). Hence, it is recommended that pregnant women be included in the ongoing vaccine trials, since successful vaccination in pregnancy will protect the mother, fetus, and newborn.

The heterologous immune effects induced by Bacillus Calmette Guérin (BCG) vaccination is a promising strategy for controlling the COVID-19 pandemic and requires further investigations. BCG is a widely used vaccine against tuberculosis in high-

From experience with several outbreaks associated with known emerging viruses, higher pathogenicity of a virus is often associated with lower transmissibility. Compared to emerging viruses like Ebola virus, avian H7N9, SARS-CoV, and MERS-CoV, SARS-CoV-2 has relatively lower pathogenicity and moderate transmissibility (15). The risk of death among individuals infected with COVID-19 was calculated using the infection fatality risk (IFR). The IFR was found to be in the range of 0.3% to 0.6%, which is comparable to that of a previous Asian influenza pandemic (1957 to 1958) (73, 277).

Notably, the reanalysis of the COVID-19 pandemic curve from the initial cluster of cases pointed to considerable human-to-human transmission. It is opined that the exposure history of SARS-CoV-2 at the Wuhan seafood market originated from human-to-human transmission rather than animal-to-human transmission (74); however, in light of the zoonotic spillover in COVID-19, is too early to fully endorse this idea (1). Following the initial infection, human-to-human transmission has been observed with a preliminary reproduction number (R_0) estimate of 1.4 to 2.5 (70, 75), and recently it is estimated to be 2.24 to 3.58 (76). In another study, the average reproductive number of

and SARS, along with adopting and strengthening a few precautionary measures owing to the unknown nature of this novel virus (36, 189). Presently, the main course of treatment for severely affected SARS-CoV-2 patients admitted to hospitals includes mechanical ventilation, intensive care unit (ICU) admittance, and symptomatic and supportive therapies. Additionally, RNA synthesis inhibitors (lamivudine and tenofovir disoproxil fumarate), remdesivir, neuraminidase inhibitors, peptide (EK1), anti-inflammatory drugs, abidol, and Chinese traditional medicine (Lianhuaqingwen and ShuFengJieDu capsules) could aid in COVID-19 treatment. However, further clinical trials are being carried out concerning their safety and efficacy (7). It might require months to a year(s) to design and develop effective drugs, therapeutics, and vaccines against COVID-19, with adequate evaluation and approval from regulatory bodies and moving to the bulk production of many millions of doses at commercial levels to meet the timely demand of mass populations across the globe (9). Continuous efforts are also warranted to identify and assess viable drugs and immunotherapeutic regimens that revealed proven potency in combating other viral agents similar to SARS-CoV-2.

COVID-19 patients showing severe signs are

pieces of evidence are available that link NSAID uses with the occurrence of respiratory and cardiovascular adverse effects. Hence, as a cautionary approach, it is better to recommend the use of NSAIDs as the first-line option for managing COVID-19 symptoms (302). The use of corticosteroids in COVID-19 patients is still a matter of controversy and requires further systematic clinical studies. The guidelines that were put forward to manage critically ill adults suggest the use of systemic corticosteroids in mechanically ventilated adults with ARDS (303). The generalized use of corticosteroids is not indicated in COVID-19, since there are some concerns associated with the use of corticosteroids in viral pneumonia. Stem cell therapy using mesenchymal stem cells (MSCs) is another hopeful strategy that can be used in clinical cases of COVID-19 owing to its potential immunomodulatory capacity. It may have a beneficial role in attenuating the cytokine storm that is observed in severe cases of SARS-CoV-2 infection, thereby reducing mortality. Among the different types of MSCs, expanded umbilical cord MSCs can be considered a potential therapeutic agent that requires further validation for managing critically ill COVID-19 patients (304).

Repurposed broad-spectrum antiviral drugs

risk regions. It is derived from a live attenuated strain of Mycobacterium bovis. At present, three new clinical trials have been registered to evaluate the protective role of BCG vaccination against SARS-CoV-2 (363). Recently, a cohort study was conducted to evaluate the impact of childhood BCG vaccination in COVID-19 PCR positivity rates. However, childhood BCG vaccination was found to be associated with a rate of COVID-19-positive test results similar to that of the nonvaccinated group (364). Further studies are required to analyze whether BCG vaccination in childhood can induce protective effects against COVID-19 in adulthood. Population genetic studies conducted on 103 genomes identified that the SARS-CoV-2 virus has evolved into two major types, L and S. Among the two types, L type is expected to be the most prevalent (~70%), followed by the S type (~30%) (366). This finding has a significant impact on our race to develop an ideal vaccine, since the vaccine candidate has to target both strains to be considered effective. At present, the genetic differences between the L and S types are very small and may not affect the immune response. However, we can expect further genetic variations in the coming days that could lead to the emergence of new strains (367).

vaccine, and Ii-Key peptide COVID-19 vaccine are under preclinical trials (297). Similarly, the WHO, on its official website, has mentioned a detailed list of COVID-19 vaccine agents that are under consideration. Different phases of trials are ongoing for live attenuated virus vaccines, formaldehyde alum inactivated vaccine, adenovirus type 5 vector vaccine, LNP-encapsulated mRNA vaccine, DNA plasmid vaccine, and S protein, S-trimer, and Ii-Key peptide as a subunit protein vaccine, among others (298). The process of vaccine development usually takes approximately ten years, in the case of inactivated or live attenuated vaccines, since it involves the generation of long-term efficacy data. However, this was brought down to 5 years during the Ebola emergency for viral vector vaccines. In the urgency associated with the COVID-19 outbreaks, we expect a vaccine by the end of this year (343). The development of an effective vaccine against COVID-19 with high speed and precision is the combined result of advancements in computational biology, gene synthesis, protein engineering, and the invention of advanced manufacturing platforms (342).

The recurring nature of the coronavirus outbreaks calls for the development of a pan-coronavirus vaccine that can produce cross-reactive antibodies.

species' barrier. As a result, the whole world is suffering from novel SARS-CoV-2, with more than 4,170,424 cases and 287,399 deaths across the globe. There is an urgent need for a rational international campaign against the unhealthy food practices of China to encourage the sellers to increase hygienic food practices or close the crude live-dead animal wet markets. There is a need to modify food policies at national and international levels to avoid further life threats and economic consequences from any emerging or reemerging pandemic due to close animal-human interaction (285).

Even though individuals of all ages and sexes are susceptible to COVID-19, older people with an underlying chronic disease are more likely to become severely infected (80). Recently, individuals with asymptomatic infection were also found to act as a source of infection to susceptible individuals (81). Both the asymptomatic and symptomatic patients secrete similar viral loads, which indicates that the transmission capacity of asymptomatic or minimally symptomatic patients is very high. Thus, SARS-CoV-2 transmission can happen early in the course of infection (82). Atypical clinical manifestations have also been reported in COVID-19 in which the only reporting symptom was fatigue. Such patients may lack respiratory signs, such as fever, cough, and sputum (83). Hence, the clinicians

require sedatives, analgesics, and even muscle relaxation drugs to prevent ventilator-related lung injury associated with human-machine incoordination (122). The result obtained from a clinical study of four patients infected with COVID-19 claimed that combination therapy using lopinavir/ritonavir, arbidol, and Shufeng Jiedu capsules (traditional Chinese medicine) was found to be effective in managing COVID-19 pneumonia (193). It is difficult to evaluate the therapeutic potential of a drug or a combination of drugs for managing a disease based on such a limited sample size. Before choosing the ideal therapeutic agent for the management of COVID-19, randomized clinical control studies should be performed with a sufficient study population.

Antiviral Drugs

Several classes of routinely used antiviral drugs, like oseltamivir (neuraminidase inhibitor), acyclovir, ganciclovir, and ribavirin, do not have any effect on COVID-19 and, hence, are not recommended (187). Oseltamivir, a neuraminidase inhibitor, has been explored in Chinese hospitals for treating suspected COVID-19 cases, although proven efficacy against SARS-CoV-2 is still lacking for this drug (7). The *in vitro* antiviral potential of FAD-approved drugs, *viz.*,

vitro antiviral potential of FAD-approved drugs, *viz.*, ribavirin, penciclovir, nitazoxanide, nafamostat, and chloroquine, tested in comparison to remdesivir and favipiravir (broad-spectrum antiviral drugs) revealed remdesivir and chloroquine to be highly effective against SARS-CoV-2 infection *in vitro* (194). Ribavirin, penciclovir, and favipiravir might not possess noteworthy *in vivo* antiviral actions for SARS-CoV-2, since higher concentrations of these nucleoside analogs are needed *in vitro* to lessen the viral infection. Both remdesivir and chloroquine are being used in humans to treat other diseases, and such safer drugs can be explored for assessing their effectiveness in COVID-19 patients.

Several therapeutic agents, such as lopinavir/ritonavir, chloroquine, and hydroxychloroquine, have been proposed for the clinical management of COVID-19 (299). A molecular docking study, conducted in the RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 using different commercially available antipolymerase drugs, identified that drugs such as ribavirin, remdesivir, galidesivir, tenofovir, and sofosbuvir bind RdRp tightly, indicating their vast potential to be used against COVID-19 (305). A broad-spectrum antiviral drug that was developed in the United States, tilorone dihydrochloride (tilorone),

considerable protection in mice against a MERS-CoV lethal challenge. Such antibodies may play a crucial role in enhancing protective humoral responses against the emerging CoVs by aiming appropriate epitopes and functions of the S protein. The cross-neutralization ability of SARS-CoV RBD-specific neutralizing MAbs considerably relies on the resemblance between their RBDs; therefore, SARS-CoV RBD-specific antibodies could cross-neutralized SL CoVs, i.e., bat-SL-CoV strain WIV1 (RBD with eight amino acid differences from SARS-CoV) but not bat-SL-CoV strain SHC014 (24 amino acid differences) (200).

Appropriate RBD-specific MAbs can be recognized by a relative analysis of RBD of SARS-CoV-2 to that of SARS-CoV, and cross-neutralizing SARS-CoV RBD-specific MAbs could be explored for their effectiveness against COVID-19 and further need to be assessed clinically. The U.S. biotechnology company Regeneron is attempting to recognize potent and specific MAbs to combat COVID-19. An ideal therapeutic option suggested for SARS-CoV-2 (COVID-19) is the combination therapy comprised of MAbs and the drug remdesivir (COVID-19) (201). The SARS-CoV-specific human MAb CR3022 is found to bind with SARS-CoV-2 RBD, indicating its potential as a therapeutic agent

recovered patients and used for plasma transfusion twice in a volume of 200 to 250 ml on the day of collection (310). At present, treatment for sepsis and ARDS mainly involves antimicrobial therapy, source control, and supportive care. Hence, the use of therapeutic plasma exchange can be considered an option in managing such severe conditions. Further randomized trials can be designed to investigate its efficacy (311).

Potential Therapeutic Agents

Potent therapeutics to combat SARS-CoV-2 infection include virus binding molecules, molecules or inhibitors targeting particular enzymes implicated in replication and transcription process of the virus, helicase inhibitors, vital viral proteases and proteins, protease inhibitors of host cells, endocytosis inhibitors, short interfering RNA (siRNA), neutralizing antibodies, MAbs against the host receptor, MAbs interfering with the S1 RBD, antiviral peptide aimed at S2, and natural drugs/medicines (7, 166, 186). The S protein acts as the critical target for developing CoV antivirals, like inhibitors of S protein and S cleavage, neutralizing antibodies, RBD-ACE2 blockers, siRNAs, blockers of the fusion core, and proteases (168).

All of these therapeutic approaches have revealed

host innate immune systems could enlighten our understanding of the lung inflammation associated with this infection (24).

SARS is a viral respiratory disease caused by a formerly unrecognized animal CoV that originated from the wet markets in southern China after adapting to the human host, thereby enabling transmission between humans (90). The SARS outbreak reported in 2002 to 2003 had 8,098 confirmed cases with 774 total deaths (9.6%) (93). The outbreak severely affected the Asia Pacific region, especially mainland China (94). Even though the case fatality rate (CFR) of SARS-CoV-2 (COVID-19) is lower than that of SARS-CoV, there exists a severe concern linked to this outbreak due to its epidemiological similarity to influenza viruses (95, 279). This can fail the public health system, resulting in a pandemic (96).

MERS is another respiratory disease that was first reported in Saudi Arabia during the year 2012. The disease was found to have a CFR of around 35% (97). The analysis of available data sets suggests that the incubation period of SARS-CoV-2, SARS-CoV, and MERS-CoV is in almost the same range. The longest predicted incubation time of SARS-CoV-2 is 14 days. Hence, suspected individuals are isolated for 14 days to avoid the risk of further spread (98). Even though a high similarity has been reported

The exploration of fully human antibodies (human single-chain antibodies; HuscFvs) or humanized nanobodies (single-domain antibodies; sdAb, VH/VHH) could aid in blocking virus replication, as these agents can traverse the virus-infected cell membranes (transbodies) and can interfere with the biological characteristics of the replicating virus proteins. Such examples include transbodies to the influenza virus, hepatitis C virus, Ebola virus, and dengue virus (206). Producing similar transbodies against intracellular proteins of coronaviruses, such as papain-like proteases (PLpro), cysteine-like protease (3CLpro), or other nsps, which are essential for replication and transcription of the virus, might formulate a practical move forward for a safer and potent passive immunization approach for virus-exposed persons and rendering therapy to infected patients.

In a case study on five grimly sick patients having symptoms of severe pneumonia due to COVID-19, convalescent plasma administration was found to be helpful in patients recovering successfully. The convalescent plasma containing a SARS-CoV-2-specific ELISA (serum) antibody titer higher than 1:1,000 and neutralizing antibody titer more significant than 40 was collected from the recovered patients and used for plasma transfusion

the United States, tilorone dihydrochloride (tilorone), was previously found to possess potent antiviral activity against MERS, Marburg, Ebola, and Chikungunya viruses (306). Even though it had broad-spectrum activity, it was neglected for an extended period. Tilorone is another antiviral drug that might have activity against SARS-CoV-2.

Remdesivir, a novel nucleotide analog prodrug, was developed for treating Ebola virus disease (EVD), and it was also found to inhibit the replication of SARS-CoV and MERS-CoV in primary human airway epithelial cell culture systems (195). Recently, *in vitro* study has proven that remdesivir has better antiviral activity than lopinavir and ritonavir. Further, *in vivo* studies conducted in mice also identified that treatment with remdesivir improved pulmonary function and reduced viral loads and lung pathology both in prophylactic and therapeutic regimens compared to lopinavir/ritonavir-IFN-γ treatment in MERS-CoV infection (8). Remdesivir also inhibits a diverse range of coronaviruses, including circulating human CoV, zoonotic bat CoV, and prepandemic zoonotic CoV (195). Remdesivir is also considered the only therapeutic drug that significantly reduces pulmonary pathology (8). All these findings indicate that remdesivir has to be further evaluated for its

Repurposed broad-spectrum antiviral drugs having proven uses against other viral pathogens can be employed for SARS-CoV-2-infected patients. These possess benefits of easy accessibility and recognized pharmacokinetic and pharmacodynamic activities, stability, doses, and side effects (9). Repurposed drugs have been studied for treating CoV infections, like lopinavir/ritonavir, and interferon-1β revealed *in vitro* anti-MERS-CoV action. The *in vivo* experiment carried out in the nonhuman primate model of common marmosets treated with lopinavir/ritonavir and interferon beta showed superior protective results in treated animals than in the untreated ones (190). A combination of these drugs is being evaluated to treat MERS in humans (MIRACLE trial) (191). These two protease inhibitors (lopinavir and ritonavir), in combination with ribavirin, gave encouraging clinical outcomes in SARS patients, suggesting their therapeutic values (165). However, in the current scenario, due to the lack of specific therapeutic agents against SARS-CoV-2, hospitalized patients confirmed for the disease are given supportive care, like oxygen and fluid therapy, along with antibiotic therapy for managing secondary bacterial infections (192). Patients with novel coronavirus or COVID-19 pneumonia who are mechanically ventilated often require sedatives, analgesics, and even muscle

that remdesivir has to be further evaluated for its efficacy in the treatment of COVID-19 infection in humans. The broad-spectrum activity exhibited by remdesivir will help control the spread of disease in the event of a new coronavirus outbreak.

Chloroquine is an antimalarial drug known to possess antiviral activity due to its ability to block virus-cell fusion by raising the endosomal pH necessary for fusion. It also interferes with virus-receptor binding by interfering with the terminal glycosylation of SARS-CoV cellular receptors, such as ACE2 (196). In a recent multicenter clinical trial that was conducted in China, chloroquine phosphate was found to exhibit both efficacy and safety in the therapeutic management of SARS-CoV-2-associated pneumonia (197). This drug is already included in the treatment guidelines issued by the National Health Commission of the People's Republic of China. The preliminary clinical trials using hydroxychloroquine, another aminoquinoline drug, gave promising results. The COVID-19 patients received 600 mg of hydroxychloroquine daily along with azithromycin as a single-arm protocol. This protocol was found to be associated with a noteworthy reduction in viral load. Finally, it resulted in a complete cure (271); however, the study comprised a small population and, hence, the

specifically in the respiratory tract will help to reduce virus-triggered immune pathologies in COVID-19 (209). The later stages of coronavirus-induced inflammatory cascades are characterized by the release of proinflammatory interleukin-1 (IL-1) family members, such as IL-1 and IL-33. Hence, there exists a possibility that the inflammation associated with coronavirus can be inhibited by utilizing anti-inflammatory cytokines that belong to the IL-1 family (92). It has also been suggested that the actin protein is the host factor that is involved in cell entry and pathogenesis of SARS-CoV-2. Hence, those drugs that modulate the biological activity of this protein, like ibuprofen, might have some therapeutic application in managing the disease (174). The plasma angiotensin 2 level was found to be markedly elevated in COVID-19 infection and was correlated with viral load and lung injury. Hence, drugs that block angiotensin receptors may have potential for treating COVID-19 infection (121). A scientist from Germany, named Rolf Hilgenfeld, has been working on the identification of drugs for the treatment of coronaviral infection since the time of the first SARS outbreak (19).

The SARS-CoV S2 subunit has a significant function in mediating virus fusion that provides entry into the host cell. Heptad repeat 1 (HR1) and heptad

virological, radiological, and pathological observations indicated that the monkeys with reexposure had no recurrence of COVID-19, like the SARS-CoV-2-infected monkeys without rechallenge. These findings suggest that primary infection with SARS-CoV-2 could protect from later exposures to the virus, which could help in defining disease prognosis and crucial inferences for designing and developing potent vaccines against COVID-19 (274).

PREVENTION, CONTROL, AND MANAGEMENT

In contrast to their response to the 2002 SARS outbreak, China has shown immense political openness in reporting the COVID-19 outbreak promptly. They have also performed rapid sequencing of COVID-19 at multiple levels and shared the findings globally within days of identifying the novel virus (225). The move made by China opened a new chapter in global health security and diplomacy. Even though complete lockdown was declared following the COVID-19 outbreak in Wuhan, the large-scale movement of people has resulted in a radiating spread of infections in the surrounding provinces as well as to several other countries. Large-scale screening programs might

into the host cell. Heptad repeat 1 (HR1) and heptad repeat 2 (HR2) can interact and form a six-helix bundle that brings the viral and cellular membranes in close proximity, facilitating its fusion. The sequence alignment study conducted between COVID-19 and SARS-CoV identified that the S2 subunits are highly conserved in these CoVs. The HR1 and HR2 domains showed 92.6% and 100% overall identity, respectively (210). From these findings, we can confirm the significance of COVID-19 HR1 and HR2 and their vital role in host cell entry. Hence, fusion inhibitors target the HR1 domain of S protein, thereby preventing viral fusion and entry into the host cell. This is another potential therapeutic strategy that can be used in the management of COVID-19. Other than the specific therapy directed against COVID-19, general treatments play a vital role in the enhancement of host immune responses against the viral agent. Inadequate nutrition is linked to the weakening of the host immune response, making the individual more susceptible. The role played by nutrition in disease susceptibility should be measured by evaluating the nutritional status of patients with COVID-19 (205).

Animal Models and Cell Cultures

For evaluating the potential of vaccines and therapeutics against CoVs, including SARS-CoV, MERS-CoVs, and the presently emerging SARS-CoV-2, suitable animal models that can mimic the clinical disease are needed (211, 212). Various animal models were assessed for SARS- and MERS-CoVs, such as mice, guinea pigs, golden Syrian hamsters, ferrets, rabbits, nonhuman primates like rhesus macaques and marmosets, and cats (185, 213–218). The specificity of the virus to hACE2 (receptor of SARS-CoV) was found to be a significant barrier in developing animal models. Consequently, a SARS-CoV transgenic mouse model has been developed by inserting the hACE2 gene into the mouse genome (219). The inability of MERS-CoV to replicate in the respiratory tracts of animals (mice, hamsters, and ferrets) is another limiting factor. However, with genetic engineering, a 288-330$^{+/+}$ MERS-CoV genetically modified mouse model was developed and now is in use for the assessment of novel drugs and vaccines against MERS-CoV (220). In the past, small animals (mice or hamsters) have been targeted for being closer to a humanized structure, such as mouse DPP4 altered with human DPP4 (hDPP4), hDPP4-transduced mice, and hDPP4-Tg mice (transgenic for expressing

mice, and hDPP4-Tg mice (transgenic for expressing hDPP4) for MERS-CoV infection (221). The CRISPR-Cas9 gene-editing tool has been used for inserting genomic alterations in mice, making them susceptible to MERS-CoV infection (222). Efforts are under way to recognize suitable animal models for SARS-CoV2/COVID-19, identify the receptor affinity of this virus, study pathology in experimental animal models, and explore virus-specific immune responses and protection studies, which together would increase the pace of efforts being made for developing potent vaccines and drugs to counter this emerging virus. Cell lines, such as monkey epithelial cell lines (LLC-MK2 and Vero-B4), goat lung cells, alpaca kidney cells, dromedary umbilical cord cells, and advanced *ex vivo* three-dimensional tracheobronchial tissue, have been explored to study human CoVs (MERS-CoV) (223, 224). Vero and Huh-7 cells (human liver cancer cells) have been used for isolating SARS-CoV-2 (194).

Recently, an experimental study with rhesus monkeys as animal models revealed the absence of any viral loads in nasopharyngeal and anal swabs, and no viral replication was recorded in the primary tissues at a time interval of 5 days post-reinfection in reexposed monkeys (274). The subsequent virological, radiological, and pathological

animal species is necessary to prevent the possibility of virus spread and initiation of an outbreak due to zoonotic spillover (1).

Personal protective equipment (PPE), like face masks, will help to prevent the spread of respiratory infections like COVID-19. Face masks not only protect from infectious aerosols but also prevent the transmission of disease to other susceptible individuals while traveling through public transport systems (313). Another critical practice that can reduce the transmission of respiratory diseases is the maintenance of hand hygiene. However, the efficacy of this practice in reducing the transmission of respiratory viruses like SARS-CoV-2 is much dependent upon the size of droplets produced. Hand hygiene will reduce disease transmission only if the virus is transmitted through the formation of large droplets (314). Hence, it is better not to overemphasize that hand hygiene will prevent the transmission of SARS-CoV-2, since it may produce a false sense of safety among the general public that further contributes to the spread of COVID-19. Even though airborne spread has not been reported in SARS-CoV-2 infection, transmission can occur through droplets and fomites, especially when there is close, unprotected contact between infected and susceptible individuals. Hence, hand hygiene is

there, there is an increase in the outbreak of this virus through human-to-human transmission, with the fact that it has become widespread around the globe. This confirms the fact similar to the previous epidemics, including SARS and MERS, that this coronavirus exhibited potential human-to-human transmission, as it was recently declared a pandemic by WHO.[26]

Respiratory droplets are the major carrier for coronavirus transmission. Such droplets can either stay in the nose or mouth or enter the lungs via the inhaled air. Currently, it is known that COVID-19's transmission from one person to another also occurs through touching either an infected surface or even an object. With the current scant awareness of the transmission systems however, airborne safety measures with a high-risk procedure have been proposed in many countries. Transmission levels, or the rates from one person to another, reported differ by both location and interaction with involvement in infection control. It is stated that even asymptomatic individuals or those individuals in their incubation period can act as carrier of SARS-CoV2.[27, 28] With the data and evidence provided by the CDC, the usual incubation period is probably 3 to 7 days, sometimes being prolonged up to even 2 weeks, and the typical symptom occurrence

variant group. The receptor-binding gene region appears to be very similar to that of the SARS-CoV and it is believed that the same receptor would be used for cell entry.[17]

4.1 Virion structure and its genome

Coronaviruses are structurally enveloped, belonging to the positive-strand RNA viruses category that has the largest known genomes of RNA. The structures of the coronavirus are more spherical in shape, but their structure has the potential to modify their morphology in response to environmental conditions, being pleomorphic. The capsular membrane which represents the outer envelope usually has glycoprotein projection and covers the nucleus, comprising a matrix protein containing a positive-strand RNA. Since the structure possesses 5'-capped and 3'-polyadenylated ends, it remains identical to the cellular mRNAs.[18] The structure is comprised of hemagglutinin esterase (HE) (present only in some beta-coronaviruses), spike (S), small membrane (E), membrane (M) and nucleocapsid (N), as shown (Figure 1). The envelope containing glycoprotein is responsible for attachment to the host cell, which possesses the primary anti-genic epitopes mainly those

consolidation. It is also abnormal in asymptomatic patients/ patients with no clinical evidence of lower respiratory tract involvement. In fact, abnormal CT scans have been used to diagnose COVID-19 in suspect cases with negative molecular diagnosis; many of these patients had positive molecular tests on repeat testing [22].

Differential Diagnosis [21]

The differential diagnosis includes all types of respiratory viral infections [influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, human metapneumovirus, non COVID-19 coronavirus], atypical organisms (mycoplasma, chlamydia) and bacterial infections. It is not possible to differentiate COVID-19 from these infections clinically or through routine lab tests. Therefore travel history becomes important. However, as the epidemic spreads, the travel history

exponentially in other countries including South Korea, Italy and Iran. Of those infected, 20% are in critical condition, 25% have recovered, and 3310 (3013 in China and 297 in other countries) have died [2]. India, which had reported only 3 cases till 2/3/2020, has also seen a sudden spurt in cases. By 5/3/2020, 29 cases had been reported; mostly in Delhi, Jaipur and Agra in Italian tourists and their contacts. One case was reported in an Indian who traveled back from Vienna and exposed a large number of school children in a birthday party at a city hotel. Many of the contacts of these cases have been quarantined.

These numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing. Though the SARS-CoV-2 originated from bats, the intermediary

weeks, and the typical symptom occurrence from incubation period to infection takes an average of 12.5 days.[29]

6 CLINICAL DIAGNOSIS

The symptoms of COVID-19 remain very similar to those of the other respiratory epidemics in the past, which include SARS and MERS, but here the range of symptoms includes mild rhinitis to septic shock. Some intestinal disturbances were reported with the other epidemics, but COVID-19 was devoid of such symptoms. When examined, unilateral or bilateral involvement compatible with viral pneumonia is observed in the patients, and bilateral multiple lobular and sub-segmental consolidation areas were observed in patients hospitalised in the intensive care unit. Comorbid patients showed a more severe clinical course than predicted from previous epidemics. Diagnosis of COVID-19 includes the complete history of travel and touch, with laboratory testing. It is more preferable to choose serological screening, which can help to analyse even the asymptomatic infections; several serological tests are in progress for SARS-CoV-2.[14, 30]

4.2 Viral replication

Usually replication of coronavirus occurs within the cytoplasm and is closely associated with endoplasmic reticulum and other cellular membrane organelles. Human coronaviruses are thought to invade cells, primarily through different receptors. For 229E and OC43, amino peptidase-N (AP-N) and a sialic acid containing receptor, respectively, were known to function in this role. After the virus enters the host cell and uncoating process occurs, the genome is transcribed, and then, translated. A characteristic feature of replication is that all mRNAs form an enclosed group of typical 3′ ends; only the special portions of the 5′ ends are translated. In total, about 7 mRNAs are produced. The shortest mRNA codes and the others can express the synthesis of another genome segment for nucleoprotein. At the cell membrane, these proteins are collected and genomic RNA is initiated as a mature particle type by burgeoning from internal cell membranes.[22, 23]

5 PATHOGENESIS

Coronaviruses are tremendously precise and mature in most of the airway epithelial cells as observed through both in vivo and in vitro

exponentially in other countries including South Korea, Italy and Iran. Of those infected, 20% are in critical condition, 25% have recovered, and 3310 (3013 in China and 297 in other countries) have died [2]. India, which had reported only 3 cases till 2/3/2020, has also seen a sudden spurt in cases. By 5/3/2020, 29 cases had been reported; mostly in Delhi, Jaipur and Agra in Italian tourists and their contacts. One case was reported in an Indian who traveled back from Vienna and exposed a large number of school children in a birthday party at a city hotel. Many of the contacts of these cases have been quarantined.

These numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing. Though the SARS-CoV-2 originated from bats, the intermediary

droplets can spread 1–2 m and deposit on surfaces. The virus can remain viable on surfaces for days in favourable atmospheric conditions but are destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide etc. [13]. Infection is acquired either by inhalation of these droplets or touching surfaces contaminated by them and then touching the nose, mouth and eyes. The virus is also present in the stool and contamination of the water supply and subsequent transmission via aerosolization/feco oral route is also hypothesized [6]. As per current information, transplacental transmission from pregnant women to their fetus has not been described [14]. However, neonatal disease due to post natal transmission is described [14]. The incubation period varies from 2 to 14 d [median 5 d]. Studies have identified angiotensin receptor 2 (ACE-) as the receptor through which

Epidemiology and Pathogenesis [10, 11]

All ages are susceptible. Infection is transmitted through large droplets generated during coughing and sneezing by symptomatic patients but can also occur from asymptomatic people and before onset of symptoms [9]. Studies have shown higher viral loads in the nasal cavity as compared to the throat with no difference in viral burden between symptomatic and asymptomatic people [12]. Patients can be infectious for as long as the symptoms last and even on clinical recovery. Some people may act as super spreaders; a UK citizen who attended a conference in Singapore infected 11 other people while staying in a resort in the French Alps and upon return to the UK [6]. These infected droplets can spread 1–2 m and deposit

was linked to a family member and 26 children had history of travel/residence to Hubei province in China. All the patients were either asymptomatic (9%) or had mild disease. No severe or critical cases were seen. The most common symptoms were fever (50%) and cough (38%). All patients recovered with symptomatic therapy and there were no deaths. One case of severe pneumonia and multiorgan dysfunction in a child has also been reported [19]. Similarly the neonatal cases that have been reported have been mild [20].

Diagnosis [21]

A suspect case is defined as one with fever, sore throat and cough who has history of travel to China or other areas of persistent local transmission or contact with patients with similar travel history or those with confirmed

identified angiotensin receptor 2 (ACE_2) as the receptor through which the virus enters the respiratory mucosa [11].

The basic case reproduction rate (BCR) is estimated to range from 2 to 6.47 in various modelling studies [11]. In comparison, the BCR of SARS was 2 and 1.3 for pandemic flu H1N1 2009 [2].

Clinical Features [8, 15–18]

The clinical features of COVID-19 are varied, ranging from asymptomatic state to acute respiratory distress syndrome and multi organ dysfunction. The common clinical features include fever (not in all), cough, sore throat, headache, fatigue, headache, myalgia and breathlessness. Conjunctivitis has also been described. Thus, they are indistinguishable from other respiratory infections. In a subset

Interestingly, disease in patients outside Hubei province has been reported to be milder than those from Wuhan [17]. Similarly, the severity and case fatality rate in patients outside China has been reported to be milder [6]. This may either be due to selection bias wherein the cases reporting from Wuhan included only the severe cases or due to predisposition of the Asian population to the virus due to higher expression of ACE_2 receptors on the respiratory mucosa [11].

Disease in neonates, infants and children has been also reported to be significantly milder than their adult counterparts. In a series of 34 children admitted to a hospital in Shenzhen, China between January 19th and February 7th, there were 14 males and 20 females. The median age was 8 y 11 mo and in 28 children the infection was linked to a family member and 26

themselves while examining such patients and practice hand hygiene frequently.

- Suspected cases should be referred to government designated centres for isolation and testing (in Mumbai, at this time, it is Kasturba hospital). Commercial kits for testing are not yet available in India.

- Patients admitted with severe pneumonia and acute respiratory distress syndrome should be evaluated for travel history and placed under contact and droplet isolation. Regular decontamination of surfaces should be done. They should be tested for etiology using multiplex PCR panels if logistics permit and if no pathogen is identified, refer the samples for testing for SARS-CoV-2.

glass opacities and sub segmental consolidation. It is also abnormal in asymptomatic patients/ patients with no clinical evidence of lower respiratory tract involvement. In fact, abnormal CT scans have been used to diagnose COVID-19 in suspect cases with negative molecular diagnosis; many of these patients had positive molecular tests on repeat testing [22].

Differential Diagnosis [21]

The differential diagnosis includes all types of respiratory viral infections [influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, human metapneumovirus, non COVID-19 coronavirus], atypical organisms (mycoplasma, chlamydia) and bacterial infections. It is not possible to differentiate COVID-19 from these infections clinically or through routine

been used based on the experience with SARS and MERS. In a historical control study in patients with SARS, patients treated with lopinavir-ritonavir with ribavirin had better outcomes as compared to those given ribavirin alone [15].

In the case series of 99 hospitalized patients with COVID-19 infection from Wuhan, oxygen was given to 76%, non-invasive ventilation in 13%, mechanical ventilation in 4%, extracorporeal membrane oxygenation (ECMO) in 3%, continuous renal replacement therapy (CRRT) in 9%, antibiotics in 71%, antifungals in 15%, glucocorticoids in 19% and intravenous immunoglobulin therapy in 27% [15]. Antiviral therapy consisting of oseltamivir, ganciclovir and lopinavir-ritonavir was given to 75% of the patients. The duration of non-invasive ventilation was 4–22 d [median 9 d]

infections clinically or through routine lab tests. Therefore travel history becomes important. However, as the epidemic spreads, the travel history will become irrelevant.

Treatment [21, 23]

Treatment is essentially supportive and symptomatic.

The first step is to ensure adequate isolation (discussed later) to prevent transmission to other contacts, patients and healthcare workers. Mild illness should be managed at home with counseling about danger signs. The usual principles are maintaining hydration and nutrition and controlling fever and cough. Routine use of antibiotics and antivirals such as oseltamivir should be avoided in confirmed cases. In hypoxic patients, provision of oxygen through nasal prongs, face mask, high flow nasal

mask and practice cough hygiene. Caregivers should be asked to wear a surgical mask when in the same room as patient and use hand hygiene every 15–20 min.

The greatest risk in COVID-19 is transmission to healthcare workers. In the SARS outbreak of 2002, 21% of those affected were healthcare workers [31]. Till date, almost 1500 healthcare workers in China have been infected with 6 deaths. The doctor who first warned about the virus has died too. It is important to protect healthcare workers to ensure continuity of care and to prevent transmission of infection to other patients. While COVID-19 transmits as a droplet pathogen and is placed in Category B of infectious agents (highly pathogenic H5N1 and SARS), by the China National Health Commission, infection control measures recommended are those for

[median 17 d]. In the case series of children discussed earlier, all children recovered with basic treatment and did not need intensive care [17].

There is anecdotal experience with use of remdeswir, a broad spectrum anti RNA drug developed for Ebola in management of COVID-19 [27]. More evidence is needed before these drugs are recommended. Other drugs proposed for therapy are arbidol (an antiviral drug available in Russia and China), intravenous immunoglobulin, interferons, chloroquine and plasma of patients recovered from COVID-19 [21, 28, 29]. Additionally, recommendations about using traditional Chinese herbs find place in the Chinese guidelines [21].

Prevention [21, 30]

category A agents (cholera, plague). Patients should be placed in separate rooms or cohorted together. Negative pressure rooms are not generally needed. The rooms and surfaces and equipment should undergo regular decontamination preferably with sodium hypochlorite. Healthcare workers should be provided with fit tested N95 respirators and protective suits and goggles. Airborne transmission precautions should be taken during aerosol generating procedures such as intubation, suction and tracheostomies. All contacts including healthcare workers should be monitored for development of symptoms of COVID-19. Patients can be discharged from isolation once they are afebrile for atleast 3 d and have two consecutive negative molecular tests at 1 d sampling interval. This recommendation is different from pandemic flu where patients were

4 VIROLOGY

Coronaviruses, a family of viruses within the nidoviruses superfamily, are further classified according to their genera, alpha-, beta-, gamma- and deltacoronaviruses (α-, β-, γ- and δ-). Among those, alpha and beta species are capable of contaminating only mammals, whereas the other two genera can infect birds and could also infect mammals.[13, 14] Two of these genera belong to human coronaviruses (HCoVs): α-coronaviruses, which comprise human coronavirus 229E (hcov229E) and human coronavirus NL63 (hcovNL63), and β-coronaviruses, which are human coronavirus HKU1, human coronavirus OC43, MERS-COV (known as Middle East respiratory syndrome coronavirus) and SARS-CoV (referred to as severe acute respiratory syndrome coronavirus).[15]

The severe acute respiratory syndrome CoV-2 (SARS-CoV-2) is now named novel COVID-19 (coronavirus disease 2019).[16] Genome sequencing and phylogenetic research revealed that the COVID-19-causing coronavirus is a beta-coronavirus that belongs to the same subtypes as SARS virus, but still exists in a variant group. The receptor-binding gene region

(entertainment parks etc). China is also considering introducing legislation to prohibit selling and trading of wild animals [32].

The international response has been dramatic. Initially, there were massive travel restrictions to China and people returning from China/ evacuated from China are being evaluated for clinical symptoms, isolated and tested for COVID-19 for 2 wks even if asymptomatic. However, now with rapid world wide spread of the virus these travel restrictions have extended to other countries. Whether these efforts will lead to slowing of viral spread is not known.

A candidate vaccine is under development.

Practice Points from an Indian Perspective

high commercial value, since they are used in traditional Chinese medicine (TCM). Therefore, the handling of bats for trading purposes poses a considerable risk of transmitting zoonotic CoV epidemics (139).

Due to the possible role played by farm and wild animals in SARS-CoV-2 infection, the WHO, in their novel coronavirus (COVID-19) situation report, recommended the avoidance of unprotected contact with both farm and wild animals (25). The live-animal markets, like the one in Guangdong, China, provides a setting for animal coronaviruses to amplify and to be transmitted to new hosts, like humans (78). Such markets can be considered a critical place for the origin of novel zoonotic diseases and have enormous public health significance in the event of an outbreak. Bats are the reservoirs for several viruses; hence, the role of bats in the present outbreak cannot be ruled out (140). In a qualitative study conducted for evaluating the zoonotic risk factors among rural communities of southern China, the frequent human-animal interactions along with the low levels of environmental biosecurity were identified as significant risks for the emergence of zoonotic disease in local communities (141, 142).

The comprehensive sequence analysis of the

observed through both in vivo and in vitro experiments. There is an enhanced nasal secretion observed along with local oedema because of the damage of the host cell, which further stimulates the synthesis of inflammatory mediators. In addition, these reactions can induce sneezing, difficulty breathing by causing airway inhibition and elevate mucosal temperature. These viruses, when released, chiefly affect the lower respiratory tract, with the signs and symptoms existing clinically. Also, the virus further affects the intestinal lymphocytes, renal cells, liver cells and T-lymphocytes. Furthermore, the virus induces T-cell apoptosis, causing the reaction of the T-cell to be erratic, resulting in the immune system's complete collapse.[24, 25]

5.1 Mode of transmission

In fact it was accepted that the original transmission originated from a seafood market, which had a tradition of selling live animals, where the majority of the patients had either worked or visited, although up to now the understanding of the COVID-19 transmission risk remains incomplete.[16] In addition, while the newer patients had no exposure to the market and still got the virus from the humans present there, there is an increase in the outbreak of