MINI REVIEW

Global scenario, public health concerns and mitigation strategies to counter current ongoing SARS-CoV-2 / COVID-19 pandemic

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ABSTRACT
Severe acute respiratory syndrome Coronavirus- 2 (SARS-CoV-2), the etiological agent of the novel coronavirus disease (COVID-19), has posed a great public health threat to the global community as a pandemic. The origin of the virus has been linked to animals, through a yet-to-be-identified intermediate host. The disease is transmitted to humans mainly through inhalation or contact with infected droplets. The variable clinical presentation of COVID-19 includes fever, cough, sore throat, breathlessness, fatigue and malaise; however, cutaneous, ocular, neurological, and gastrointestinal manifestations have also been reported. There is an urgent need to strengthen One Health surveillance, intervention, and management strategies to understand the ecology of coronaviruses and to prevent epidemics in the future. Global attention toward the development of treatments, immunotherapies, vaccines, and control options to combat the COVID-19 pandemic has been on an increasing trend. Here, we review the current epidemiological status, public health concerns, and mitigation strategies for COVID-19.

Introduction

Ever since 2000 A.D., at least one new event of an emerging disease has occurred from time to time, including Nipah, severe acute respiratory syndrome (SARS), Ebola, Middle East respiratory syndrome (MERS) and Zika. The ongoing episode of the coronavirus disease (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus- 2 (SARS-CoV-2) has posed a great public health threat as a pandemic. Therefore, the question of how these pathogens evolve and cause severe or mild infections arises. A spillover of viruses from wild birds, bats, and monkeys to humans has been reported. Human activities including deforestation, illegal wildlife trade, and hunting of bush meat may be responsible for the spillover effect linked to animal-human interplay. Besides, altered ecosystems, intensive animal rearing, and large-scale distribution of uncontrolled foods of animal origin may also contribute to such species jump.

The dread and terror brought about by the COVID-19 pandemic has repeated the history of zoonotic diseases over time. SARS-CoV-2, emerged in 2019 at Wuhan, China, is the third highly pathogenic coronavirus (CoV) to infect humans. The enduring emergence of CoVs at regular intervals poses a significant threat to the public health and global economy. The pandemic has been suggested to have a zoonotic origin as the early case-patients reported had a history of visiting the Huanan Seafood Wholesale Market, where the wildlife merchandise were reported. Upon its pandemicity, the World Health Organization (WHO) has declared COVID-19 as a public health emergency of international concern (PHEIC). The COVID-19 pandemic has taken the lives of more than 100,000s people out of more than few millions confirmed human cases and has affected the society, environment, and global economy, as a whole.

The symptoms of COVID-19 usually include fever, cough, sore throat, breathlessness, fatigue, and malaise. In most cases, the disease is mild; however, in the elderly and those with comorbidities, it may progress to pneumonia, acute respiratory distress syndrome, and multi-organ dysfunction.

Paradoxically, even after a decade of research on CoVs, there are still no licensed vaccines or therapeutic agents to treat CoV infections, thus highlighting an urgent need to develop effective vaccines or post-exposure prophylaxis to prevent future epidemics. Although potential vaccine candidates have been identified and are undergoing various phases of clinical trials, a successful outcome has not yet been established. Several similarities exist between the clinical, genetic, and epidemiological features of SARS-CoV-2 and those of SARS-CoV infections. Therefore, research advancements on SARS treatment might help the scientific community quickly understand the pathogenesis of COVID-19 and develop effective therapeutic/prophylactic agents to treat and prevent this infection. Monoclonal antibodies represent the major class of bio-therapeutics for passive immunotherapy to fight against viral infections. The therapeutic potential of monoclonal antibodies has been well recognized in the treatment of many diseases. A number of review articles on the current status of COVID-19 epidemiology, pathogenesis, and vaccine development are available. In this mini-review, we discuss the epidemiological aspects of COVID-19, the...
associated clinical features, public health concerns, vaccine developments underway, and immunotherapy approaches.

Epidemiology

Coronavirus (CoV) belongs to the subfamily Orthocoronavirinae of Coronavirusidae family under the Order Nidovirales, whose members are named after their crown-like appearance under the electron microscope. CoVs are reported to manifest respiratory, enteric, hepatic and neurologic diseases. Based on the genotypic and serotypic characteristics, subfamily Orthocoronavirinae has four genera namely, alpha-corona virus (α-CoV), beta-corona virus (β-CoV), gamma-corona virus (γ-CoV) and delta-corona virus (δ-CoV). Mammals are frequently infected with α- and β-CoV, while, birds with γ- and δ-CoV. Human pathogenic coronaviruses include SARS-CoV, the Middle Eastern respiratory syndrome coronavirus (MERS-CoV), and the presently recoded SARS-CoV-2, which are all betacoronaviruses.

Virology

Coronaviruses (CoVs) have the largest genome among known RNA viruses. CoVs are enveloped and consists of a positive-sense, single-stranded RNA with the size varying between 26 and 32 kb. The genome of SARS-CoV-2 virion is about 29.9 kb with a nucleocapsid buried inside the phospholipid bilayer covered by two different types of spike proteins, namely, the spike glycoprotein trimer (S) with membrane (M) protein and envelope (E) protein. The spike proteins are found in all CoVs, whereas hemagglutinin-esterase (HE) is found only in certain CoVs. The phylogenetic analysis revealed that SARS-CoV-2 shares 79.50% and 50% sequence identity with SARS-CoV and MERS-CoV, respectively. Nevertheless, the sequence identity between the conserved replicase domains in ORF1ab of SARS-CoV-2 and SARS-CoV (94.60%) and between those in SARS-CoV-2 and other β-CoVs (less than 90%) clearly indicates that SARS-CoV-2 belongs to the lineage B (Sarbecovirus) of β-CoVs. The phylogenomic diversity of COVID-19 viruses from the coronavirus pandemic is given in Figure 1, while the features of COVID-19 genome are given in Figure 2.

Origin and hosts

The origin of SARS-CoV-2 remains obscure. SARS-CoV-2 has shown high genome sequence identities (87.6%–87.8%) to SARSr-Rp-BatCoV-ZXC21/ZC45 detected in Rhinolophus pusillus bats in 2015 and to SARSr-Ra-BatCoV-RaTG13 (96.1% genome identity with SARS-CoV-2) detected in Rhinolophus affinis bats in 2013. Subsequently, the two viral strains exhibiting 85.3% and 89.7% genome identities to SARS-CoV-2 were detected in smuggled pangolins in 2017. However, none of the existing SARSr-CoVs represent its immediate ancestor, despite the close relatedness of SARS-CoV-2 to strains isolated from bat and pangolin. The SARS-CoV-2 strains are closely related. It has been suggested that the Wuhan outbreak might have originated from a point source with subsequent human-to-human transmission.

Whereas, identification of potential recombination sites around the receptor-binding domain (RBD) region suggested that SARS-CoV-2 might be a recombinant virus, with the evolution of its genome backbone from the Yunnan bat virus–like SARSr-CoVs and acquisition of its RBD region from the pangolin virus–like SARSr-CoVs. It could also be possible that the pangolin SARSr-CoVs originated from bat viruses as a result of animal mixing.

The RBD is considered as a hot spot for the construction of recombinant CoVs for receptor and viral replication studies. Therefore, the suspicion of an artificial recombinant virus has been raised owing to the presence of evolutionarily distinct SARS-CoV-2 RBD and the unique insertion of S1/S2 cleavage site among Sarbecovirus species. However, currently, no evidence exists to prove that SARS-CoV-2 is an artificial recombinant virus. Further surveillance studies to identify the possible source and evolutionary path of SARS-CoV-2 in bats are warranted.

COVID-19 is postulated to have emerged from animals, although its exact source is not clear. SARS-CoV-2 has been shown to replicate poorly in dogs, pigs, chickens, and ducks; however, ferrets and cats were permissive to the infection. Experimentally, cats were found to be susceptible to airborne infection, providing important insights into the animal models for SARS-CoV-2. Further, Shi et al. explained that the ferrets are widely used as animal models for investigating human respiratory viruses. Ferrets infected with SARS-CoV-2...
exhibited elevated body temperatures and virus replication, and shed virus in nasal washes, saliva, urine, and feces up to 8 days post-infection.\textsuperscript{20} All naive direct contact ferrets were positive for SARS-CoV-2 at 2 days post-contact and a few naive indirect contact ferrets were positive for viral RNA, suggesting its air-borne transmission. The detection of viral antigens was reported in the nasal turbinate, trachea, lungs, and intestine with acute bronchiolitis present in infected lungs.\textsuperscript{20}

Transmission of the virions from humans to dogs, domestic cats, tigers, and lions has also been recently reported.\textsuperscript{21} Pigs, cats, ferrets, and primates have been identified as good candidates for susceptibility to SARS-CoV-2. The potential implications indicate the need for One Health surveillance, intervention, and management strategies to mitigate the effects on animal populations and prevent a second preparedness failure during this health emergency.

Interestingly, all human CoVs may be potentially zoonotic, thus making bats the most likely natural hosts for the known CoVs.\textsuperscript{1,2,22} For instance, during the SARS pandemic of 2002–2003, the preliminary observations pointed to a zoonotic origin RS-CoV, with civets as the foci of human infection.\textsuperscript{23} However, the roosting sites of bats were located away from the human activity areas; hence, the virus could have been probably transmitted to humans from another animal host after mutation or recombination in animal hosts. For instance, in SARS-CoV and MERS-CoV, civets and dromedary camels served as the animal hosts, prior to the human transmission. In SARS-CoV-2, 99\% identity has been identified between pangolin origin CoV and SARS-CoV-2, which could be inferred that SARS-CoV-2 might have originated from pangolins.\textsuperscript{24}

The screening of serum samples (n = 1914) from 35 animal species for SARS-CoV-2-specific antibodies using double-antigen sandwich ELISA could not reveal the presence of SARS-CoV-2-specific antibodies in the tested samples, which excluded the possibility of 35 animal species as the intermediate host for SARS-CoV-2.\textsuperscript{25} The samples included those from companion animals, including pet dogs and cats, street dogs, and cats, which dispelled public concerns about pets being the carriers of SARS-CoV-2.

Recently, respiratory disease outbreaks caused by SARS-CoV-2 with increased mortality were reported in mink farms in the Netherlands.\textsuperscript{26,27} An acute interstitial pneumonia with acute alveolar damage was found in the minks died at the peak of the outbreaks. The viral RNA was detected in throat swabs and by immunohistochemical detection of viral antigen in nasal conchae, trachea, and lung (Molenaar et al., 2020). The probable source of the initial infection to minks was pointed at humans based on sequence analysis of mink-derived viruses. In Denmark, three mink farms were confirmed to be positive for SARS-CoV-2. Similar mutations in the viral genome of infected minks and infected farmers were found with the possibility that the virus was transmitted to minks via infected humans.\textsuperscript{28} The possible exposure of farm workers to virus excreted by minks has been postulated due to the presence of viral RNA in inhalable dust collected from the farms.\textsuperscript{27}

**Receptor insights**

The virus utilizes angiotensin-converting enzyme 2 (ACE2), a functional receptor in humans, for its entry into cells, as in the case of SARS-CoV.\textsuperscript{17} ACE2 receptors, expressed in the lungs, heart, kidneys, and intestine,\textsuperscript{29} bind directly to the S proteins of CoVs and undergo structural rearrangement so as to enable the fusion of viral membrane with the host cell membrane.\textsuperscript{11,15} Upon its entry into alveolar epithelial cells, SARS-CoV-2 replicates rapidly, which results in cytokine storm syndrome (hypercytokinemia) and damage the pulmonary tissue. The cytokine storm syndrome is a group of disorders characterized by the uncontrolled production of pro-inflammatory cytokines, which culminates in acute respiratory distress syndrome (ARDS) and multiple organ failure.\textsuperscript{12}

The preliminary research has shown that SARS-CoV-2 can use ACE2 from bats, civet cats, swine, cats, ferrets, non-human primates (NHPs), and humans as a receptor.\textsuperscript{13,30,31} Infection in a pet dog in Hong Kong suggested that the canine ACE2 could also be recognized by SARS-CoV-2. Pangolins have been proposed as potential amplifying host in some studies.\textsuperscript{18,32}

**Transmission**

It is currently believed that this deadly CoV strain originated from wild animals in the Huanan market of Wuhan, a city in the Hubei province, China. Bats, snakes, and pangolins have been cited as potential carriers of the virus, based on the sequence homology between the nucleic acids of CoV isolated from these animals and the viral nucleic acid isolated from SARS-CoV-2-infected patients.\textsuperscript{33}

The most common symptoms at the onset of illness caused by SARS-CoV-2 are given in Table 1. The major routes of transmission in humans include respiratory droplets and contact. It has been recently reported that SARS-CoV-2 could be detected in the urine and feces of laboratory-confirmed individuals; which indicates the potential of faeco-oral route as yet another possible route of virus transmission.\textsuperscript{44} Nonetheless, it is uncertain whether the virus could be transmitted through the consumption of contaminated foods, aerosols, or in utero. For now, patients with COVID-19 are considered as the prime sources of infection; asymptomatic persons and patients in incubatory stage of infection have been proved to shed infectious virions and could serve as potential sources of infection.\textsuperscript{45}

The transmission efficiency of any respiratory virus has significant implications on its mitigation. The basic

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**Table 1. The most common as well as non-common symptoms at the onset of illness, SARS-CoV-2.**

| Symptoms                                                                 | References |
|--------------------------------------------------------------------------|------------|
| Fever, cough, fatigue, pneumonia and myalgia                             | 34,35      |
| Gastrointestinal symptoms, including anorexia, nausea, vomiting and diarrhea | 36,37      |
| Gastrointestinal symptoms without respiratory symptoms or fever          | 38         |
| Hypercoagulable state with increased risk of venous thromboembolism     | 39         |
| Neurological manifestations, including headache, dizziness, altered consciousness, ischemic and hemorrhagic strokes, muscle injury | 40         |
| Taste or olfactory disorders including anosmia, Skin and ocular manifestations | 41         |
| Cutaneous manifestations                                                 | 42         |
| Ocular manifestations consistent with conjunctivitis                    | 43         |
reproductive number (R0) of SARS-CoV-2, in its initial evaluation, was estimated to be 2.20 (1.40–3.90), which implies that on an average, each infected person could spread the infection to another two individuals.46 However, the high viral titers observed in the oropharynx during the course of early infection aroused serious concern regarding the enhanced infectivity of the virus when the disease symptoms are minimal. The R0 of SARS-CoV and MERS-CoV in the absence of intervention was found to be 2.30–3.70; however, after the mitigation strategies were employed, the R0 dropped to less than 1.0,47 explaining the basis of controlling the outbreaks. It could be worth mentioning that the R0 estimates may vary based on numerous exogenous factors (biological, socio-behavioural, and environmental) and should be cautiously interpreted.

It has been speculated that SARS-CoV-2 might have emerged as a recombinant virus between the bat coronavirus and a coronavirus of origin-unknown48 which might have occurred within the viral spike glycoprotein. Additionally, it has been suggested that the genome of SARS-CoV-2 is most similar to that of bat coronavirus and its codon usage bias is most similar to that of snake. In summary, homologous recombination may have contributed to the cross-species transmission of the virus.48

The case fatality rate (CFR) of SARS-CoV-2 has been reported to be age-dependent, with higher rate in the elderly population, especially men, and with an overall interim CFR of approximately 1%–3%. The number of asymptomatic individuals could be much higher than the official case number.59 Persons of all ages are susceptible to COVID-19. Large droplets generated by symptomatic patients, including those generated before the onset of symptoms, as well as asymptomatic people during coughing and sneezing can transmit the infection.30 The viral loads were found to be higher in the nasal cavity than in the throat with no difference in viral burden between symptomatic and asymptomatic people.51 The virus can remain viable on the inanimate surfaces for days under favorable atmospheric conditions. It can be destroyed in less than a minute using common disinfectants such as sodium hypochlorite, hydrogen peroxide etc.52 The virus may be present in the stools and contaminated water supply and it has been hypothesized that it may be subsequently transmitted via aerosolization or faeco-oral route.53

Infection source, transmission route, and susceptible population are the three vital elements for the emergence of an infectious disease.54 In the current COVID-19 pandemic, infected patients are the main source of infection and they produce a huge quantity of virus in the upper respiratory tract during the prodromal period.51 As the patients exhibit mild clinical symptoms during the incubation period, their mobility leads to the spread of infection. Asymptomatic carriers can also be a source of infection.56 The incubation period of the disease varies from 1–14 days and could reach up to 24 days, making it difficult to screen for infections. Additionally, the disease is mainly spread through respiratory droplets and contact, with the possibility of aerosol transmission in a closed environment.55

Infections among health workers confirmed the high infectivity of the disease.56 Nosocomial transmission has also been reported. Infections among health workers has accounted for 3.83% of the total infections.38 Personal protective equipments (PPE), including fluid-resistant gown, gloves, eye protection, full face shield, and fit-tested N95 respirators, is necessary to ensure the safety of healthcare workers who need to be in contact with critically ill patients with confirmed or suspected SARS-CoV-2 infection.57 The factors influencing the zoonotic events need to be properly understood in an attempt to limit future outbreaks.

A retrospective cohort study was conducted on 201 patients admitted to Wuhan Jinyintan Hospital with confirmed COVID-19 pneumonia.58 The median age of the patients was 51 years, and 128 (63.7%) patients were men. Of the 201 patients, 84 patients (41.8%) developed ARDS, and of these 84 patients, 44 patients (52.4%) succumbed and had co-morbidities such as hypertension in 27.4% patients and in 13.7% patients and diabetes in 19.0% patients and 5.1% patients, with and without ARDS, respectively. The risk factors associated with the development of ARDS and with progression from ARDS to death included older age (hazard ratio (HR), 3.26; 95% CI, 2.08–5.11; and HR, 6.17; 95% CI, 3.26–11.67, respectively), neutrophilia (HR, 1.14; 95% CI, 1.09–1.19; and HR, 1.08; 95% CI, 1.01–1.17, respectively), and organ and coagulation dysfunction (e.g., higher lactate dehydrogenase (HR, 1.61; 95% CI, 1.44–1.79; and HR, 1.30; 95% CI, 1.11–1.52, respectively). High fever (≥39°C) was also associated with higher likelihood of development of ARDS and lower likelihood of death. Older age was associated with greater risk of development of ARDS and death likely owing to less rigorous immune response. Although high fever was associated with the development of ARDS, it was also associated with better outcomes among patients with ARDS.58

Travel-related cases were the main source of COVID-19 cases during the early stages of the current epidemic in Italy,59 however, later it became dominated by local transmission. The CFRs in China and Italy were identical at 2.30.

**Status of vaccine development**

Given the severity of COVID-19, vaccines and therapeutics are urgently needed to tackle this novel virus. Currently, no human CoV vaccine has been approved. In addition, the safety of many technologies used (production platforms, vectors, and so on) need to be tested thoroughly; 23 candidate vaccines are under clinical evaluation, while 140 are under pre-clinical evaluation stage. Moreover, as of now, 75 countries have expressed their partnering interests to protect the populations through joining the COVAX - a unique facility to guarantee fair and rapid access to COVID vaccines globally. The target for the vaccine, the S protein, has been identified. This is usually followed by two important steps typically needed before bringing a vaccine into clinical trials. The vaccine needs to be tested in appropriate animal models to study its protection ability. However, animal models for SARS-CoV-2 might be complex to develop. The virus did not grow in wild-type mice, and it has been found to induce mild disease in transgenic animals expressing human angiotensin-converting enzyme 2 (ACE2).60 Pathogenicity studies are ongoing in ferrets and non-human primates. In the absence of a suitable animal model, serum from vaccinated animals can be tested in *in vitro* neutralization assays. Secondly, the toxicity of vaccines needs to be tested in animals, e.g., in rabbits. This testing has to
be performed in research facilities; however, good laboratory practice compliance may take 3–6 months to complete.

The results obtained from the trials of SARS-CoV vaccines, performed with an inactivated virus vaccine and a spike-based DNA vaccine were safe and induced neutralizing antibody (NAb) titers. Some neutralizing monoclonal antibodies (nMabs) isolated against SARS-CoV, like CR3022, can cross-react to the RBD of SARS-CoV-2 suggesting that SARS-CoV-1 vaccines might cross-protect against SARS-CoV-2.

The sequence identity of the RBD is reported to be 73.5% between SARS-CoV-1 and SARS-CoV-2. However, only 47.8% identity has been reported in the most variable region of RBD, viz., receptor-binding motif irrespective of the similar receptor-binding mechanism of SARS-CoV-2 and SARS-CoV. However, the conserved amino acid sequences between the RBDs of SARS-CoV-2 and SARS-CoV suggest that these RBDs may produce cross-reactive antibodies; but the production of antibodies with cross-reactive potential is unknown to date. In addition, the RBD of SARS-CoV-2 is considered as a potential antigen with the probability of inducing abundant Nabs against SARS-CoV-2; hence, may be used as a crucial candidate for subunit vaccine development. Moreover, RBM-specific nMabs prevent SARS-CoV-2 infection by blocking ACE2 receptor interactions, potentially making it a promising passive antibody-based agent in the absence of a COVID-19 vaccine.

The SARS-CoV-2 vaccines underway

A recombinant subunit vaccine based on the trimeric S protein (S-Trimer) of SARS-CoV-2 is under pre-clinical testing. Subunit vaccines using the “molecular clamp” (a polypeptide that stabilizes a surface protein and improves recognition of the correct antigen) are being developed at The University of Queensland. Furthermore, a DNA plasmid-based vaccine, viz., INO-4800, encoding the S protein is being developed by Inovio Pharmaceuticals. Moreover, the INO-4800 vaccine is delivered in healthy individuals by two intradermal injections followed by electroporation of the vaccine. Pre-clinical trials for the DNA vaccine (INO-4800) against COVID-19, which induces activation of T cells by delivering DNA plasmids that express the SARS-CoV-2 spike, have been started by Inovio Pharmaceuticals in collaboration with Beijing Advaccine Biotechnology with the advantages to produce therapeutic antibodies and activate immune cells via intradermal administration into the patient. In addition, Inovio pharmaceuticals enrolled 40 healthy individuals for the Phase 1 clinical trial of the INO-4800 vaccine. Furthermore, after attaining immunogenicity data along with safety evaluation from Phase 1 trial, Inovio pharmaceuticals is planning to advance the INO-4800 vaccine to Phase 2 trial as soon as possible along with the production of one million doses by the end of the year 2020 for emergency use and additional trials if required (INO-4800 DNA Coronavirus Vaccine, 2020). Another mRNA vaccine mRNA-1273, encoding viral spike (S) protein of SARS-CoV-2 has entered Phase 1 clinical trials. This has been designed in silico, which would enable rapid development and evaluation of vaccine efficacy. A COVID-19 vaccine using the Hyleukin-7 platform technology, which enhances immune responses by the fusion of interleukin-7 (IL-7) to hycFc is being developed.

An mRNA-based vaccine (mRNA1273-COVID-19 vaccine) expressing target antigen in vivo in the vaccine after injection of mRNA encapsulated in lipid nanoparticles is currently under Phase 1 clinical trial (ClinicalTrials.gov: NCT04283461). Moreover, the mRNA1273-COVID-19 vaccine encodes a full surface, prefusion stabilized S protein, and reached directly to a clinical trial in record 69 days without any pre-clinical testing due to its highly safe nature. Additional approaches in the pre-clinical stage include recombinant-protein-based vaccines (focused on the S protein), viral-vector-based vaccines (focused on the S protein), DNA vaccines (focused on the S protein), live-attenuated vaccines, and inactivated virus vaccines. All these platforms have advantages and disadvantages, and it is not possible to predict which strategy will be faster or more successful.

In addition, a Chimpanzee Adenovirus Vector (ChAdOx1) based vaccine developed against SARS-CoV-2 by Oxford’s Jenner Institute has progressed to Phase 3 clinical trials. However, the trials mainly aimed to study its reactogenicity, tolerability, and safety along with immunogenicity in 510 volunteers but the vaccine is also being evaluated for its efficacy to prevent SARS-CoV-2 infection (NCT04324606). Moreover, the ChAdOx1 is a non-replicating virus with one or a few encoded antigens and the vaccine may generate a strong immune response even after one dose hence it can be safely used in older individuals, children, and people with co-morbidities. As per reports, another adenovirus vector-based vaccine, viz., Ad5-nCoV is being developed by CanSino Biologics of China, which is a genetically engineered vaccine candidate and uses a replication-defective adenovirus type 5 (Ad5) as a vector to deliver the S protein gene of SARS-CoV-2. Moreover, the Ad5-nCoV is reported to be the most advanced DNA vaccine candidate at present and has already completed the Phase 2 trial. Furthermore, the company has started enrolling healthy volunteers of more than 18 years of age for the next phase, randomized, double-blinded, and placebo-controlled clinical trials. However, the Ad5-nCoV vaccine has been declared a top contender for SARS-CoV-2 vaccine by the WHO but the scientists are worried about the immunity among the people against the Ad5 vector attributed to the possibility of vaccine failure along with associated harmful effects as observed earlier in a trial conducted by Merck for an Ad5-based HIV vaccine.

An inactivated-adsorbed COVID vaccine manufactured by Sinovac in healthcare professionals (Profiscov) are under Phase 3 clinical trials (NCT04456595). The study will be estimated to be conducted over 8870 participants as a double-blind trial with randomly allocated participants to placebo as well as vaccine groups (1:1). The vaccine candidate will be tested for its efficacy, safety and immunogenicity.

Immunotherapy

Immunotherapy is regarded as an effective method for the clinical treatment of infectious diseases. Various attempts to develop immunotherapy for COVID-19 have included plasma therapy, polypeptide hormone for the maturation of T cells,
immunoglobulins, ACE2 immunoadhesin, and a monoclonal antibody against interleukin-6. Several approaches (Table 2) have been suggested to control infections of SARS-CoV-2, including vaccines, viral-vectors, nanoparticles, inactivated whole virus, DNA as vaccines, monoclonal antibodies, oligonucleotides, peptides, interferon, and small molecule drugs. The humoral immune response is crucial for preventing viral infections.

Passive immunotherapy is important in the short-term protection and prevention of viral infections. Many drawbacks associated with serum therapy and intravenous immunoglobulin preparations in terms of specificity, purity, low risk of blood-borne pathogen contamination, and safety may be overcome by the use of monoclonal antibodies. The effective treatment options against SARS-CoV-2 can directly interrupt any stage of the viral life cycle or the receptor proteins located in the host cell surface to restrain the virus from binding, thereby blocking viral attachment and entry. These can be accomplished by using peptidic fusion inhibitors, anti-SARS-CoV-2 nMAbs, anti-ACE2 monoclonal antibodies, and protease inhibitors.

Passive antibody therapy can be an important approach to limit COVID-19 epidemics. The viral replication and disease severity can be reduced by passive immunization with an antibody that can recognize epitopic regions in the foreign virus particle. Monoclonal antibodies represent the major class of biotherapeutics for passive immunotherapy to fight against viral infection. The therapeutic potential of monoclonal antibodies has been well-recognized in the treatment of many diseases. The blood of infected patients can be the source of antibodies for passive immunotherapy. The convalescent sera of infected patients may be effective in neutralizing the virus and preventing further infection in humans. The early administration of convalescent plasma or hyper-immune immunoglobulin from patients having significant antibody titers can likely reduce the viral load and disease mortality as evidenced by prior experience in treating other viral infections such as influenza, SARS, MERS, and Ebola.

Table 2. Vaccines and immunotherapy potentials of different approaches.

| Treatment by | Specific or for similar viruses | Type of immunotherapy/vaccine | Outcomes | Reference |
|--------------|---------------------------------|------------------------------|----------|-----------|
| Plasma therapy (Convalescent plasma) | COVID-19 Specific | polyclonal antibody immune response (passive antibody) | Clinical improvement | 83 |
| Immunoglobin | COVID-19 Specific | Specific (for COVID-19) | Clinical improvement | 83 |
| Thymosin | COVID-19 Specific | Polypeptide hormone for maturation of T cells | Lung injury score | 83 |
| Tocilizumab | COVID-19 Specific | monoclonal antibody against interleukin-6 receptor (IL-6 R) | Cure rate | 83 |
| Cytoxic T lymphocyte(CTL) | COVID-19 Specific | Vaccine | Untested | 84 |
| Immunoglobin Fc domain | COVID-19 Specific | ACE2 immunoadhesin | Untested | 85 |
| Viral-vector | MERS-CoV | Vaccine | Acceptable | 86 |
| Vectors that encoding S or S1 protein | MERS-CoV | Vaccine | Induce both Th1 and Th2 immune responses | 86 |
| Viral-vector and nanoparticle | MERS-CoV | Vaccine | Acceptable | 86 |
| DNA encoding S or S1 Protein | MERS-CoV | Vaccine | In some features is acceptable | 86 |
| Inactivated whole-virus | MERS-CoV | vaccine | In some features is acceptable | 86 |
| Live-attenuated | MERS-CoV mutant | Vaccine | In some features are acceptable | 86 |
| Subunits or nanoparticle | MERS-CoV | vaccine | In some features are acceptable | 86 |
| Monoclonal Antibody CR3022 | SARS-CoV | monoclonal antibody cross-reactive antibodies alone or in combination with other neutralizing antibodies (e.g. m396, CR3014) | Un-tested | 61 |
| Based T cell epitope proteins | SARS-CoV-2 | vaccine | Only about SARS-CoV | 87 |
| Recombinant subunit Trimeric S Protein | SARS-CoV-2 | Vaccine | Preliminary study | 88 |
| mRNA – 1273 | SARS-CoV-2 | Vaccine | Phase 2 clinical trials | 72 |
| INO 4800 | SARS-CoV-2 | Vaccine | Phase 1/2 clinical trials | 70 |
| DNA plasmid | SARS-CoV-2 | Vaccine | Phase 1/2 clinical trials | 82 |
| Inactivated whole-virion | SARS-CoV-2 | Vaccine | Phase 1/2 clinical trials | 82 |
| DNA GX-19 | SARS-CoV-2 | Vaccine | Phase 1 clinical trial | 82 |
| Plant derived Virus like particle adjuvanted Protein subunit full length SARS-CoV-2 glycoprotein nanoparticle | SARS-CoV-2 | Vaccine | Phase 1 clinical trial | 82 |
| Protein subunit SARS-CoV RBD-dimer | SARS-CoV-2 | Vaccine | Phase 2 | 82 |
| Non- replicating viral vector ChAdOx1-N | SARS-CoV-2 | Vaccine | Phase 3 | 82 |
| Inactivated alum | SARS-CoV-2 | Vaccine | Phase 3 clinical trials | 82 |

(Adapted/modified from AminJafari and Ghesemi, 2020; Ahn et al., 2020)
specific nMAbs either against the RBD in the spike protein or specific antibody that binds to ACE2. In addition, RBM-specific nMAbs were reported to block the ACE2 receptor interactions and subsequently the SARS-CoV-2 infection, hence could be potentially used as a crucial passive antibody-based agent for COVID-19 in the absence of a specific vaccine.66 Suitable expression systems such as mammalian, yeast, or plant could be used to clone and express the sequences of monoclonal antibodies effective against SARS-CoV, and recombinant monoclonal antibodies could be tested against SARS-CoV-2. Plasmid expression systems could be considered for the rapid production of monoclonal antibodies in a short time at an affordable cost.7,99,100

Monoclonal antibody therapy is one of the best types of passive immunotherapy. A human IgG1 monoclonal antibody, CR3014, has been generated and found to be reactive with whole inactivated SARS-CoV and could be used as prophylaxis for SARS-CoV infection in ferrets.60

Viral infectivity is reduced by NAbs, which bind the surface epitopes of viral particles and block the entry of the virus to an infected cell.101 NAbs elicit their protective activities by preventing the attachment of the virion to their receptors on targeted cells, causing aggregation of virus particles and by lysis of viruses through the constant (C) region of antibody-mediated opsonization or complement activation.102

Explication of the immunopathogenesis of SARS-CoV-2 is useful for developing passive antibody therapy, designing vaccines, and understanding of clinical drug interventions. The human-to-human transmission of SARS-CoV-2 may be enhanced by the high affinity of the S protein for human ACE2, and the S protein might be the main target for antibody-mediated neutralization.

Both the innate and adaptive immune responses are involved in resistance to SARS-CoV infections.103 Excessive proinflammatory cytokine responses are induced because of the activation of dendritic cells and macrophages by SARS-CoV.104 Generally, the levels of IFN-γ, IL-1β IL-6, IL-12, IL-8, MCP-1, and IP-10 are increased in the early phase of infection and later reduced in the recovery stage. Notably, T-lymphopenia was recorded in the CD4+ and the CD8+ populations as evidenced by flow cytometry analysis, which inversely correlated with increased serum levels of the proinflammatory cytokines IL-6, IL-10, and TNF-α. A progressive increase in the expression of programmed cell death marker-1 (PD-1) and T cell immunoglobulin and mucin domain 3 (Tim-3) was observed as patients (n = 14) deteriorated from prodromal to symptomatic COVID-19 requiring intensive care.105

Uncontrolled systemic inflammation or cytokine storm results in severe illness, which has been observed in SARS-CoV-2 infection. The inflammatory cytokines and chemokines (IL-1β, IFN-γ, IP-10, and MCP-1) were upregulated.107,108 T cell-mediated responses in SARS-CoV infection have been well elucidated109 and both CD4+ and CD8 + T-cells have been proven to provide broad and long-term protection. Elucidation of T-cell-mediated response in SARS-CoV-2 infection may provide important hints for the design of a vaccine composed of viral structural proteins.

A model in which complement activation in the lung and in other organs is a critical host mediator of SARS-CoV-2-induced development of atypical ARDS and thrombotic microangiopathy (TMA) has been suggested.110 The complement activation has been said to occur primarily in the lower airways and result in the release of C5α into the circulation. It activates proinflammatory immune cells as a key mechanism that drives the “cytokine and chemokine storm” associated with fatal lung injury and TMA development. Thus, for alleviation of the proinflammatory effects, reduce lung pathology, and increase the survival of COVID-19 patients, C5a should be targeted.110

Perspectives on the development of neutralizing antibodies against SARS-CoV-2

Convalescent plasma is chosen when there are no specific vaccines or drugs available for emerging infection-related diseases.111 The feasibility of convalescent plasma therapy as well as its safety and clinical efficacy in critically ill MERS patients was tested96 and observed to be of immunotherapeutic potential for the treatment of MERS-CoV infection. The use of convalescent plasma from recovered SARS patients had been used for treating other SARS patients.112,113 Notably, the World Health Organization has suggested the use of convalescent plasma or serum under Blood Regulators Network when vaccines and antiviral drugs were unavailable for an emerging virus.83 Use of plasma from the convalescent patients might be the simplest and most direct approach to combat SARS-CoV-2 during the outbreak.85 Polyclonal NAbs that are induced in convalescent patients would be effective in treating SARS-CoV-2.34 Earlier, SARS and Ebola patients were treated using convalescent plasma.112,114 The SARS-CoV-2 ‘S’ protein forms an important target for developing NAbs to block binding and fusion of SARS-CoV-2.

A cocktail antibody approach for SARS-CoV-2 could be undertaken as concoction of NAbs has shown the stronger neutralization than alone in treatment of both Ebola and SARS viruses.115,116 Therefore, generation of NAbs targeting different epitopes on SARS-CoV-2 would be a practical approach.

Effects of COVID-19 on current vaccinations

The COVID-19 pandemic has encouraged intense debates on current (and future) preventive measures, including vaccination. A topic of intense debate and a matter of scientific interest for future research is the role of bacillus Calmette-Guérin (BCG) vaccination in this situation.117 An analysis of data on COVID-19 in countries with BCG vaccination and countries without such a program revealed a daily incidence of 0.8 - per million compared with 34.8 per million, respectively. The respective data on the mortality were 0.08 and 34.8 per million, the crude case fatality rate was 4.1% and 5.1% in countries with BCG vaccination and countries without BCG vaccination.117

The innate immune system and trained immunity can be considered in the fight against viruses including COVID-19.118 It has been shown that BCG vaccination before influenza vaccination in healthy individuals resulted in a pronounced antibody response against influenza A (H1N1) compared to the placebo.119 Based on these observations, BCG vaccination trials have been initiated to fight infections such as COVID-19, particularly in the elderly population, and to prevent severe COVID-19 infection in health care workers.117 Two
randomized-controlled trials are currently testing BCG vaccination for COVID-19 prevention in Australia (NCT04327206) and the Netherlands (NCT04328441).

Conclusions and perspective

Animal health surveillance systems have an important role in anticipating, detecting and CONTAINING outbreaks of emerging diseases. There is an urgent need to integrate these with human public health surveillance systems and ecological systems, underlining the essence of ‘one health’ concept. In the era of globalization, it is difficult for any country to neglect or hide an emerging epidemic. The recent and past occurrences of coronavirus outbreaks do not seem to be inconsequential but a result of inappropriate human activities. To have a better understanding on the ecology of CoVs and further to prevent its animal-to-human transmission and epidemics in the future, continuous surveillance in mammals and birds is essential.

Approximately 60% of emerging transferable diseases originate from animals, and 70% of these are reported to originate from wild animals, indicating that the unrestricted wildlife trade might enhance the risks of emerging infections. There have been rising calls from different countries to permanently ban wildlife markets and trades. These actions, partly, would help to protect human lives from future pandemics, like COVID-19. Therefore, it is indispensable to globally ban wildlife markets and trades considering national security, biosafety, and public health.

The development of therapeutic NAbs against SARS-CoV-2 may offer benefits for the control of the current pandemic and the possible reemergence of the virus in the future, and their development, therefore, remains a high priority. Vaccines are being developed rapidly; however, they will likely arrive too late to affect the first wave of the pandemic. Establishing an animal model of infection and disease pathogenesis is imperative for understanding several essential elements of a viral disease in the infected host, including host tropism, immune responses, and modes of transmission, as well as for the progression of therapeutic development.

A detailed understanding of the pathogenesis of COVID-19 might increase opportunities for the realistic design of vaccines and immunotherapies for the novel SARS-CoV-2.

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