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An Overview of Covid-19 From the Beginning to the Present

Reza Yaghubi Tabar[1], Amirmohsen Alizadeh[2] and Taiebeh Mohammadi Farsani[3]*

[1]*Department of Medical Biotechnology, Isfahan (Khorasgan) Branch, Islamic Azad University, Iran*

[2]*Assistant Professor of Nutrition, Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Iran*

[3]*PhD of Medical Biotechnology, Department of Medical Biotechnology, Isfahan (Khorasgan) Branch, Islamic Azad University, Iran*

***Corresponding author:** Taiebeh Mohammadi Frasani, PhD of Medical Biotechnology, Department of Medical Biotechnology, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran

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ABSTRACT

Pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection emerged in Wuhan City, Hubei Province, China in December 2019. By Feb. 11, 2020, the World Health Organization (WHO) officially named the disease resulting from infection with SARS-CoV-2 as coronavirus disease 2019 (COVID-19). COVID-19 represents a spectrum of clinical manifestations that typically include fever, dry cough, and fatigue, often with pulmonary involvement. SARS-CoV-2 is highly contagious and most individuals within the population at large are susceptible to infection. It seems that coronaviruses take an important place in the 21th century history. Five of seven human coronavirus was isolated in this century. Unfortunately, last three of them entered our life with a fear of outbreak, pandemic or death. Last human coronavirus which emerged world from Wuhan China. Initial reports showed that, its origin was bats. It transmitted human to human by droplet and contact routes, but some doubt about airborne, fecal or intrauterine transmission also should be removed. The presence of COVID-19 is manifested by several symptoms, ranging from asymptomatic mild symptoms to severe illness and death. Common symptoms include cough, fever, and shortness of breath. Other reported symptoms are weakness, malaise, respiratory distress, muscle pain, sore throat, loss of taste and or smell. Clinical diagnosis of COVID-19 is based on clinical manifestations, molecular diagnostics of the viral genome by RT-PCR, chest x-ray or CT scan, and serology blood tests.

As the body requires time to respond to the antigenic viral attack, symptoms may appear 2 to 14 days after exposure to the virus. SARS-CoV-2 is a betacoronavirus belonging to the subgenus Sarbecovirus. The global spread of SARS-CoV-2 and the thousands of deaths caused by coronavirus disease (COVID-19) led the World Health Organization to declare a pandemic on 12 March 2020.

Abbreviations: RBD: Receptor Binding Domain; AA: Amino Acids; NTD: N-terminal Domain; R0: Reproduction Number; PCR: Polymerase Chain Reaction; CI: Confidence Interval; ELISA: Enzyme-Linked Immunosorbent Assays; CLIA: Chemiluminescence Assays; MVA: Modified Vaccinia Ankara; VSV: Vesicular Stomatitis Virus; WHO: World Health Organization; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

Introduction

Origin of the SARS CoV-2 Virus

The first cases of coronavirus disease COVID-19 were directly related to an animal market in Wuhan, China. Early investigations suggested that the origin of SARSCoV-2 may be bats. Zhou et al. demonstrate that SARS CoV-2 possesses 96% nucleotide identity with a bat coronavirus, for instance BetaCoV/RaTG13/2013 [1]. Since the discovery of the novel coronavirus, SARS-CoV-2, scientists have debated its origin. It has been speculated that SARS-CoV-2 is the product of laboratory manipulations. However, genetic data does not support this hypothesis and shows that SARS-CoV-2 did not derive from a previously known virus backbone. Genomes analysis and comparison with previously known coronavirus genomes indicate that SARS-CoV-2 presents unique features that distinguish it from other corona-

viruses: optimal affinity for angiotensin converting enzyme 2 (ACE2) receptor and a polybasic cleavage site at the S1/S2 spike junction that determines infectivity and host range. SARS-CoV-2 is highly similar to bat SARS-like coronaviruses and bat might be the reservoir host. RaGT13 is 96% identical to SARS-CoV-2 with some differences in the spike receptor binding domain (RBD) that could explain the differences in ACE2 affinity between SARSCoV-2 and SARS-like coronaviruses. The polybasic cleavage site of SARS CoV-2 is not present in pangolin beta-coronavirus, which share similarities with SARS-CoV-2. Also, the sequence of RBD of the spike protein (S) suggests that it arose from a natural evolutionary process.

Estimates of the most recent common ancestor of SARS-CoV-2 date the epidemic to between late November 2019 and the beginning of December 2019, which is compatible with the first reported cases. Thus, there was unnoticed human transmission after the zoonotic event and before the acquisition of the polybasic furin cleavage site [2].

Structure of Coronavirus

There are four main subgroups of coronaviruses (α, β, γ, and δ). There are six members of the α coronavirus group [3], including human pathogens Cov-229E and CoV-HKU1. The β coronavirus group includes the human pathogens CoV-OC43, SARS-CoV, and MERS-CoV. SARS-CoV-2 is also a β coronavirus; the amino acid sequences within the seven conserved domains within the genomic open reading frame 1ab (ORF1ab) are 94.6% identical to that of the original SARS-CoV. The coronavirus virion particle is typically round or multi-shaped. It measures 120-160 nm in diameter and includes a petal shaped projection consisting of a triple Spike (S) protein, which is common a feature of the coronaviruses. The S protein mediates virus attachment and membrane fusion during infection. In addition to the characteristic S protein, coronavirus genomes generally encode three additional structural proteins, including the Membrane (M) protein, the Envelope (E) protein, and the Nucleocapsid (N) protein. The coronavirus M protein, 218 to 263 amino acids (aa), has an N-terminus modified by an O- or N-glycan and a hydrophilic C-terminal tail. The E protein, 74-109 aa, may be involved in promoting virulence; there are typically about 20 copies of this protein per virion. The coronavirus N protein, 349 to 470 aa, is an RNA-bound phosphorylated protein that facilitates appropriate folding of genomic RNA into the nucleocapsid [1,4].

The structure of SARS-CoV-2 involves a major trimeric envelope glycoprotein called the S-protein, which is expressed on the surface of the virus and is also the main target for vaccines as it binds to host cells. The S-protein is made of two main subunits namely S1 that controls receptor binding and S2, which governs membrane fusion. The S protein also undergoes a significant conformational change from a pre-fusion state to a post-fusion state, achieved by pulling and fusing the cell and viral membranes together. The S protein in coronaviruses is quite diverse as supported by the fact that the S proteins for SARS CoV and MERS CoV only share 44% of the genetic sequence. The differences in the S protein are primarily attributed mainly to the S1 subunit, which is composed of an N-terminal domain (NTD) and a receptor-binding domain (RBD). The diversity of RBD between SARS-CoV and MERS-CoV is attributed to different host cell entry receptors for the two coronaviruses namely angiotensin converting enzyme 2 (ACE2) for SARS-CoV and also for SARSCoV-2 while dipeptidyl peptidase 4 (DPP4) is the receptor for MERS-CoV. Since SARS-CoV and SARS-CoV-2 share the same entry receptor, monoclonal antibodies against SARS-CoV RBD were tested for cross reactivity to SARS-CoV-2 RBD and results showed that no binding was detected to SARS CoV-2 RBD despite the similarity in RBD sequences. In terms of the severity and clinical consequences of the infection, SARS-CoV was more lethal and aggressive but SARS-CoV-2 is highly contagious and spreads more readily [5,6].

Genomic Characterization of Sars-Cov-2

The SARS-CoV-2 virion has a diameter of 60-140 nm and a positive sense, single-stranded 29 891 bp RNA genome. Genome sequence alignment has revealed a 79.5% sequence identity between SARS-CoV-2 and SARS-CoV and a remarkable 93.1% identity with the sequence of the RaTG12 virus isolated from a bat (Rhinolophus affinis) residing in Yunnan Province, China these latter results suggest that SARS-CoV-2 may originate from a virus that is endemic in this bat species [1].

Epidemiology

Several cases of severe unexplained pneumonia were reported from Wuhan, China in December 2019. Bronchoalveolar lavage from an index case was identified as novel Coronavirus (COVID-19) on 3rd January 2020 by Zhu and colleagues and subsequently WHO announced this disease as an 'epidemic'. With rapid increase in COVID-19 infection across the world, WHO declared this as a 'pandemic' on 11th March 2020, an emergency public health situation. Wuhan was the initial epicentre for COVID-19, where first 41 cases of severe pneumonia were reported following exposure to bats and pangolins at the Huanan Seafood Wholesale market. Subsequent cases were reported from the same locality by Chen and colleagues. However, several patients in the outbreak did not have exposure to animals, indicating person to person droplets spread a high possibility. WHO report as of 19th May 2020, confirmed 4,731,458 COVID-19 positive cases from 213 countries worldwide of which 1,477,516 cases were reported in United States of America, 231,606 cases in Spain, 225,886 cases in Italy, 246,410 in United kingdom, China the starting point of this pandemic has 84,500 cases and India has recorded 101,139cases 6. These data indicate the rapid spread of the disease around the world, with a doubling rate of 7.2 days [7,8]. An epidemic curve of infection is a statistical chart used in epidemiology to visualize the onset of the coronavirus outbreak. In an epidemic curve, there are three zones: increasing, plateau, and declining phases.

Increasing phase: This period is affected by many different parameters such as country demographics, age distribution, preparedness of health system to an outbreak, implementation of some preventive measures, country reaction time to a pandemic, reaction of society to new implementing rules. Different countries can exhibit quite different curve patterns and these facts could complicate country. However, it seems that this period takes generally 3 or 4 weeks for COVID-19. Plateau phase: At this phase disease incidence is stable. According to daily country reports it takes 2 or 3 weeks for COVID-19. Decreasing phase: Today we have only China's data about this phase, showing that 2 or 3 weeks later disease activity could be detected very low levels [2].

Pathology and Disease Pathogenesis

An autopsy report of a 50-year old male patient revealed many details of the condition of the lungs of those suffering from the most critical forms of COVID-19. This patient died due to acute respiratory distress syndrome (ARDS) with features that included desquamation of pneumocytes, hyaline membrane formation, and interstitial inflammation and infiltration of large numbers of lymphocytes. Additionally, viral cytopathic-like changes, including multi-nucleated syncytial cells and atypical enlarged pneumocytes, were detected in the intra-alveolar spaces [1].

Disease Presentation: Patients with SARS-CoV-2 infection may present symptoms ranging from mild to severe with a large portion of the population being asymptomatic carriers. The most common reported symptoms include fever (83%), cough (82%) and shortness of breath (31%) [9]. In patients with pneumonia, chest X-ray usually shows multiple mottling and ground-glass opacity. Gastrointestinal symptoms such as vomiting, diarrhea, and abdominal pain are described in 2–10% of the patients with COVID-19, and in 10% of patients, diarrhea and nausea precede the development of fever and respiratory symptoms [10]. COVID-19 patients usually show decrease lymphocyte and eosinophils counts, lower median hemoglobin values as well as increases in WBC, neutrophil counts, and serum levels of CRP, LDH, AST, and ALT. Moreover, initial CRP serum levels have been reported to be an independent predictor for the development of severe COVID-19 infection. Although the main target of coronavirus infection is the lung, the wide distribution of ACE2 receptors in organs may lead to cardiovascular, gastrointestinal, kidney, liver, central nervous system and ocular damage that has to be closely monitored. The cardiovascular system is often affected, with complications including myocardial injury, myocarditis, acute myocardial infarction, heart failure, dysrhythmias, and venous thromboembolic events, and monitoring with high sensitivity cardiac troponin may be useful.

Patients presenting with acute respiratory distress syndrome may worsen rapidly and die of multiple organ failure induced by the so-called "cytokine storm". Indeed, a cytokine profile resembling the secondary hemophagocytic lymphohistiocytosis syndrome has been described in severe COVID-19 cases, and is characterized by increased interleukin (IL)-2, IL-7, granulocyte colony stimulating factor, interferon-c inducible protein-10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-a, and tumor necrosis factor-a. In addition, elevated levels of ferritin and IL-6 are predictors of fatality, and death is likely due to hyper-inflammation induced by the virus. Based on this evidence, tocilizumab (IL-6 receptor blockade) is administered to patients with COVID-19 pneumonia and elevated serum IL-6 to reduce inflammation in the lungs. Elevation of D-dimer levels has been associated with the severity of COVID-19. Subjects with severe COVID-19 have significantly higher values of D-dimer than those without (weighted mean difference 2.97 mg/L;95% CI: 2.47–3.46 mg/L). The elevated D-dimer levels may reflect the risk of disseminated coagulopathy in patients with severe COVID-19, which may require anticoagulant therapy [11].

SARS-COV-2 Transmission: As with other respiratory viruses, SARS-CoV-2 transmission occurs with high efficacy and infectivity mainly through the respiratory route. Droplet transmission is the main recognized route, although aerosols may represent another important route. Estimates of the reproduction number (R0) of SARS-CoV-2 range from 1.4 to 2.5 to 2.24-3.58. Similar to SARS-CoV, the oral-fecal route may be another route of transmission of the virus. SARS-CoV-2 RNA has been detected in the stool of patient with COVID-19 pneumonia [12,13]. Therefore, sewage may have a role in the transmission of SARS-CoV-2. In light of that, technical treatment such as biosorbents capable of retaining and inactivating the virus should be considered. SARS-CoV-2 has been detected in saliva of infected individuals; this can be attributed to the presence of ACE2 receptors in epithelial cells lining the salivary gland ducts. In some studies, patient urine has been tested for SARS-CoV-2 viral RNA. Amongst these studies, the pooled rate of RNA positivity was about 5-6%; nevertheless, the duration of viral shedding in urine samples as well as the infectivity of urine remains to be established. SARS CoV-2 RNA has also been detected on inanimate surfaces such as door handles and the surface of cell phones in residential sites of patients with confirmed COVID-19. Thus, individuals who have come into contact with infected surfaces could be infected if they touch their eyes, mouth or nose.

The vertical transmission of SARS-CoV-2 is debated; a series of nine pregnant women with confirmed COVID-19 showed no mother to child transmission. In addition, SARS-CoV-2 was not detected in breast milk, indicating that the virus cannot be transmitted with breastfeeding. Nevertheless, a newborn with elevated IgM against SARS-CoV-2 born to a mother with COVID-19 has been recently reported. IgM antibodies along with IgG antibodies were detected 2 h after delivery. Il-6 and IL-10 were also elevated, while polymerase chain reaction (PCR) performed on consecutive nasopharyngeal swabs from 2 h to 16 days of age was always negative. Considering that IgM cannot cross the placenta and be transferred to the fetus, it could be hypothesized that the infant was infected in utero even if amniotic fluid was not tested for SARS-CoV-2 RNA. Finally, the eyes may be a route of transmission of SARS-CoV-2. SARS-CoV-2 RNA was

detected in ocular swabs of a patient with confirmed COVID-19 3 days after onset of symptoms and at 27 days when a nasopharyngeal swab tested negative by PCR. Interestingly, the virus from an ocular swab was propagated in Vero E6 cells, suggesting that ocular secretions could be infectious. Although no conclusive data is available, goggles should be worn when examining patients with suspected or confirmed COVID-19 [11].

SARS-CoV-2 Incubation Period: The incubation period of COVID-19 was defined 5.2 days (95% CI, 4.1–12.5 days), 5.1 days (95% CI, 4.5 to 5.8 days) and 4 days in three separate study [14]. However, in a familial cluster of 5 patients, this period was reported between 1 and 19 days. These data show that the incubation period of COVID-19 was similar to MERS and SARS and it's a bit longer than influenza [2]. Determination of the incubation period of SARS-CoV-2 infection is crucial for determining the duration of quarantine, to evaluate the efficacy of entry screening and contact tracing. Based on a Weibull distribution, it was estimated that the mean incubation period is 6.4 days (95% confidence interval (CI): 5.6-7.7), with a range of 2.1-11.1 days (2.5th–97.5th percentile). Similar estimates have been made by other authors. In a study by Lauer et al. it was estimated that the median incubation period was 5.1 days (95% CI, 4.5–5.8 days), and that 97.5% of infected individuals would develop symptoms within 11.5 days (CI, 8.2–15.6 days) of infection. Therefore, the 14-day period of active monitoring recommended by health authorities is justified by the evidence. Longer monitoring can be required in particular cases. It was estimated that 101 out of every 10,000 cases (99th percentile, 482) may develop symptoms after 14 days of active monitoring or quarantine [11,15].

Viral Testing

Reverse Real-Time PCR Assays: Suspected cases of SARS-CoV-2 infection are confirmed by detection of specific and unique viral sequences using a reverse real-time PCR (rRT-PCR) assay. Immediately after the declaration by the Chinese Health Authorities, on 7 January 2020, that the pneumonia outbreak in Wuhan was caused by a novel coronavirus, a European network of laboratories developed an rRT-PCR protocol based on the alignment and comparison of available bat-related coronavirus and SARS-CoV genome sequences plus five sequences from the novel coronavirus SARS-CoV-2 that were released by the Chinese authorities. Three rRT-PCR assays were developed. The first line assay targets the E gene common to the coronaviruses belonging to Sarbecovirus subgenus and encoding the envelope protein. The second assay targets the RdRp gene encoding the RNA-dependent-RNApolymerase. This assay contains two molecular probes: one reacts with the SARS-CoV and SARS-CoV-2 RdRp gene, while the second one (RdRP_SARSr-P2) reacts with SARS-CoV-2 RdRp gene. The third assay targets the N (nucleocapsid) gene. This protocol was adopted in 30 European countries. Recently, a new PCR protocol targeting a different region of the RdRp/Hel gene showed a higher sensitivity and specificity than the RdRP_SARSr-P2 assay. The US Centers for Disease Control and Prevention (CDC) protocol targets the N gene of SARS-CoV-2.

Two primer/probe sets directed toward different regions of N gene were selected. In addition, a primer/probe set that detects the human RNase P gene in control samples and clinical specimens is included. Although amplification tests are sensitive, some infections are missed. The reasons for this may be the quality of the collected specimen, time of collection (very early phase of infection or too late during infection), viral load below the limit of detection of the assay, incorrect handling of the specimen or shipping issues. In the case of low viral load in the upper respiratory tract, a deeper specimen may be required to make a diagnosis. Indeed, in SARS and MERS patients, viral RNA in the upper respiratory tract peaked in the first 7–10 days after symptoms onset, while in the lower respiratory tract, viral RNA was still detected 2–3 weeks after disease onset. Repeat testing can also be performed in the case of nasopharyngeal swabs initially being negative as this increases the chance of detecting SARS-CoV-2 in the nasopharynx. Several real-time PCR assays obtained the CE mark for in vitro diagnostics and are available on the market. Point of Care Tests (POCT) such as XpertVR Xpress SARS-CoV-2 QIAstat-Dx Respiratory 2019-nCoV Panel, and SimplexaTM COVID-19 Direct kit deliver results in about 30-60 min. They do not require skilled technicians and the hands-on time is less than 1 min. These tests can be very useful when clinicians have to make rapid treatment decisions [11,16].

Droplet Digital PCR: Droplet Digital PCR (ddPCR) is a highly sensitive assay for the direct detection and quantification of DNA and RNA targets. It has been increasingly used in infectious disease settings, especially thanks to its ability to consistently and reliably detect down to few copies of viral genomes. Whether the detection of low-level and/or residual viral presence is required, quantitative data obtained by ddPCR are far more informative than those provided by standard RT-PCR assays. Standing the necessity of a limitation (as much as possible) of false negative results in COVID-19 diagnosis, the use of ddPCR could provide a critical support. Its use for SARS-CoV-2 detection, however, is still very poorly investigated in clinical settings, and no data are currently available for European patients [17].

CRISPR-Cas12-Based Lateral Flow Assay for Detection of SARS-CoV-2: Recently, a CRISPR-Cas12-based assay called SARS-CoV-2 DNA endonuclease-targeted CRISPR Trans Reporter (DETECTR) has been developed for the diagnosis of SARS-CoV-2 infection. This assay performs simultaneous reverse transcription and isothermal amplification of RNA extracted from nasopharyngeal or oropharyngeal swabs using loop-mediated amplification (RT-LAMP), followed by Cas12 detection of coronavirus sequences. Detection of the virus is confirmed by cleavage of a reporter molecule. The assay targets the E and N regions but unlike the CDC assay, this one does not target the N1 and N3 regions. Amplification of the E region allows the identification of three SARS-like coronaviruses [SARS-CoV-2 (accession NC_045512), bat SARS-like coronavirus (bat-SL-CoVZC45, ac-

cession MG772933) and SARS-CoV (accession NC_004718)], whereas the N region specifically detects SARS-CoV-2. The DETECTR assay can be run in 30–40 min and is visualized on a lateral flow strip. The test is positive if both E and N genes are detected or presumptive positive if either E or N gene is detected. The limit of detection (LOD) of this DETECTR assay is 10 copies/ml vs 1 copy/ml for the CDC assay. The positive predictive agreement and the negative predictive agreement of DETECTR assay versus the CDC assay were 95% and 100%, respectively [11,18].

Viral Load in Respiratory Samples

Viral load determination performed on nasopharyngeal swabs demonstrated that mild clinical cases had a lower viral load in their respiratory specimens compared with severe cases. The mean viral load in severe cases was 60-fold higher than mild cases. Stratification of the data in relation at the time of sampling after disease onset showed that delta cycle threshold (delta Ct) values were significantly lower in severe cases than mild cases in the first 12 days of disease. In mild cases, viral clearance occurred earlier and after 10 days, 90% of the patients repeatedly tested negative by PCR. By contrast, PCR was still positive at day 10 or beyond in all severe cases. These preliminary data suggest that determination of SARS-CoV-2 load may be useful for monitoring the patients with COVID-19 disease and for predicting prognosis and assessing disease severity [11].

Serology

Several serological assays, including enzyme-linked immunosorbent assays (ELISA), chemiluminescence assays (CLIA), rapid antibody tests, and western blotting, have been developed since the beginning of the SARS-CoV-2 pandemic. The ELISA test developed by Wantai Biological Pharmacy Enterprise Co. detects total antibody, IgM and IgG against SARS-CoV-2. Total antibodies were detected based on a double-antigen sandwich immunoassay using recombinant antigens containing the RBD of the S protein of SARS-CoV-2 as the immobilized antigen and horse radish peroxidase (HRP) as the conjugated antigen. The IgM l-chain capture method was used to detect IgM antibodies (IgM-ELISA), using the same HRP conjugate RBD antigen as in the double-antigen sandwich immunoassay. The IgG antibodies were detected by an indirect ELISA test (IgG-ELISA) based on the recombinant nucleoprotein antigen. The specificity of the assays was determined by testing plasma samples of healthy individuals collected before the SARS-CoV-2 outbreak, and was 99.1%, 98.6% and 99.0% for total antibody, IgM and IgG, respectively. Comparing the results obtained by real-time PCR with those generated by the antibody assays in the first week of illness, PCR showed a higher sensitivity than antibodies assays, 66.7% vs 38.3%. However, from days 8 to 12, the sensitivity of the antibody tests overtook that of the RNA test, and in the late phase of disease, the sensitivity of the antibody tests increased even further compared to the RNA test.

Nevertheless, to date, all the international professional organizations, the US Food and Drug Administration and the CDC do not recommend that serology tests be used for diagnosis. Other research groups developed ELISA assays that used as antigens a modified full-length S protein and the RBD of SARS-CoV2. Using this approach, COVID-19 seroconverters were identified as early as 3 days post symptom onset. Similarly, an antibody test designed to detect E and N antigens detected IgM within one week from disease onset. IgM was detectable for about a month and then gradually disappeared, while IgG was detected after 10 days and was detected for a longer period of time. Using a magnetic chemiluminescence enzyme immunoassay, 100% of patients with COVID-19 were found to be IgG positive 19 days after symptom onset. The median day for both IgG and IgM seroconversion was 13 days post symptoms. Seroconversion for IgM and IgG occurred simultaneously or sequentially. Three groups of patients were identified: patients with synchronous seroconversion of IgG and IgM, patients with IgM seroconversion earlier than IgG seroconversion, and patients with IgG seroconversion earlier than IgM seroconversion. IgM and IgG plateaued 6 days after the first determination. Interestingly, screening of close contacts of patients with COVID-19 showed that few individuals with negative RT-PCR and no symptoms tested positive to IgG and/or IgM, confirming that serology can help in obtaining better estimates of the spread of SARS-CoV-2 [11].

Vaccine Development in the Pipeline for COVID-19

Vaccine Development: Vaccine development is a key strategy for preventing widespread viral infection and reducing morbidity and mortality. The novel virus SARS-CoV-2 was first isolated by Chinese scientists; the genome sequence is currently available to the public. These advances together with cooperation and open-source data make it possible to design multiple SARS-CoV-2 vaccine candidates. Vaccines are typically divided into different types, including inactivated vaccines, live attenuated vaccines, vectored vaccines, nucleic acid-based vaccines, and recombinant subunit vaccines [1].

Inactivated Vaccines and Live Attenuated Vaccines: Inactivated and live attenuated vaccines are based on the antigenicity of killed and weakened versions of the virus, respectively. Inactivated vaccines may include whole inactivated virus particles, specific components derived from the virus or toxoids that are chemically modified to destroy their pathogenicity. China National Biotec Group already has some inactivated vaccine candidates available for testing; their immunogenicity and efficacy are currently under evaluation in experimental animals. Live attenuated vaccines are derived from microbial agents that have been weakened via physical, chemical, or biological means under laboratory conditions. Codagenix (USA) has formed a collaboration with Serum Institute of India in order to develop a rationally designed live attenuated vaccine against SARS-CoV-2 that is synthesized by viral codon deoptimization [1].

Vectored Vaccines: Vectored vaccines are those utilizing other viruses as vectors for SARS-CoV-2 proteins; among such vaccine vectors currently under exploration are the chimeric parainfluenza virus, rabies virus, modified vaccinia Ankara (MVA) virus, vesicular

stomatitis virus (VSV), and adenovirus. Scientists of Rocky Mountain Laboratories (USA) and Oxford University (UK) have been collaborating to develop a chimpanzee adenovirusvectored vaccine against SARS-CoV-2. Likewise, Zydus Cadila, an India-based pharmaceutical company, has launched a program to develop a vectored vaccine for the novel coronavirus SARS-CoV-2 using live attenuated recombinant measles virus (rMV); rMV is generated by reverse genetics and expresses codonoptimized proteins of SARS-CoV-2 in order to induce specific neutralizing antibodies [1].

Nucleic Acid-Based Vaccines: Injection of nucleic acid constructs that can express viral or bacterial genes can result in the activation of both humoral and cellular immune responses. Zydus Cadila has a program to develop a DNA vaccine against the major viral membrane S protein responsible for the cell entry of SARS-CoV-2. After the plasmid DNA is introduced into host cells, it will be translated into the viral protein and elicit immune responses. This provides protection from infection and can lead to viral clearance. Inovio Pharmaceuticals (USA) is currently collaborating with Beijing Advaccine Biotechnology Company (China) to advance the development of INO-4800 as a vaccine candidate targeting SARS-CoV-2. This vaccine is currently undergoing preclinical testing; clinical product manufacturing is in progress for a planned parallel phase I clinical trial in China. Applied DNA Sciences' subsidiary (New York, USA), LineaRx (New York, USA), and Takis Biotech (Rome, Italy) are developing a linear DNA vaccine for the SARS-CoV-2, using PCRbased DNA manufacturing technology. Additionally, Moderna (USA) is also developing a messenger RNA (mRNA) vaccine against SARS-CoV-2 encoding for the viral S protein, in collaboration with the National Institutes of Health (USA) [1].

Recombinant Subunit Vaccines: Recombinant subunit vaccines are composed of several microbial components produced in a heterologous expression systems. Compared with inactivated vaccines and live attenuated vaccines, one of the most important advantages of subunit vaccines is their significant safety profile as they contain only noninfectious recombinant proteins or synthetic peptides, with no infectious viruses. The S protein of SARS-CoV-2 plays a key role in receptor binding and membrane fusion; as such, vaccines based on the S protein may be able to induce antibodies to block virus binding and fusion and thus neutralize virus infection. The S protein is one of the most important antigenic components of the coronavirus structural proteins as it can evoke both host immune responses and neutralizing antibodies. It has therefore been selected as a promising target for a vaccine. Clover Biopharmaceuticals (Chengdu, China) has initiated the development of a recombinant subunit vaccine for SARS-CoV-2 that utilizes S protein subunit-trimer antigens [1].

Drugs in the Pipeline for COVID-19

So far there are no specific antiviral measures available to treat COVID-19. Most of the typical options guiding drug manufacture take years of development and are obviously inadequate for the ongoing outbreak. In this situation, studies are often conducted on compassionate use of unproven therapies and clinical trial approvals expedited. In spite of our limited knowledge, there are several treatment options that could be pursued as first-line therapy for COVID-19. These modalities could be tested rapidly on patients currently diagnosed with SARS-CoV-2 infection [1].

Neutralizing Antibodies Targeting Virus S Protein: ACE2 has been identified as a cellular entry receptor of SARS-CoV-2, similar to that identified for SARS-CoV. SARS-CoV-2 entry starts with the S protein binding to ACE2 on the cell surface, after which the viral nucleocapsid is delivered into the cell prior to virus replication. The S protein is involved in receptor recognition as well as virus attachment and entry, both of which are attractive targets for the development of drugs to treat COVID-19. Neutralizing antibodies that target the S protein of SARS-CoV-2 may provide temporary, passive immunity to the disease. The full genome sequence of SARS-CoV-2 (GenBank: MN908947.3) was clarified and disclosed to the public shortly after the pandemic originated in Wuhan, China. This allows scientists to perform gene synthesis in order to express the S protein as an immunogen. CR3022 and CR3014 developed by Crucell (the Netherlands) are human monoclonal antibodies (mAbs) that can neutralize the original SARS-CoV. These mAbs block the interaction between S protein and its cellular receptor ACE2 and thus completely prevent inflammatory pathology in the lungs of SARS-CoV-infected animal models. Considering that the novel virus SARS-CoV-2 has high sequence similarity to the SARS-CoV virus, these two antibodies may be promising and might be evaluated for the treatment for COVID-19 [1].

Inhibitors of ACE2: Given the critical role of ACE2 in the process of virus infection, ACE2 inhibitors may have anti-SARS-CoV-2 activity. Thousands of compounds, biologics, and traditional Chinese medicines from databases were screened. Results from these methods suggest that azathioprine, andrographis, urtica, sambucus, astragalus, valproic acid, butyrate, and epoxomicin may be effective strategies toward the development of anti-COVID-19 therapy [1].

Oligonucleotides Against SARS-CoV-2 RNA Genome: Modalities that target the virus RNA genome, including small interfering RNA (siRNA) and/or antisense oligonucleotides, might be another therapeutic option. However, the appropriate RNA sequence targets of SARS-CoV-2 remain unknown and delivery of oligonucleotides to the lung is also a challenge. As such, gene therapy can be fully applicable for the design of treatments in the current outbreak [1].

Convalescent Patient Serum: Patients who have recovered from the SARS-CoV2 infection will develop a polyclonal immune response to viral antigens. These polyclonal antibodies may neutralize virus and prevent further infection in the recovered host. Therefore, convalescent patient serum may be a potentially effective tool for treating and preventing further disease related to this outbreak. It was reported that serum from a convalescent SARS patient inhibited SARS-S proteindriven virus entry and reduced SARS-CoV-2 virus entry. Passive transfer of antibodies from convalescent patient serum is currently

under consideration for the treatment of COVID-19 patients with severe disease [1].

Conflict of Interest

Authors declare no conflict of interest.

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