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Current Knowledge about the Pathophysiology, Clinical Manifestation, and Treatment of COVID-19

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Abstract: The current wave of acute atypical respiratory infections that began in Wuhan, China, is suspected to be caused by SARS coronavirus-2, a novel coronavirus in the Coronaviridae family. COVID-19, or coronavirus disease 19, is the name of the virus that causes this illness. On March 11, 2020, the World Health Organisation (WHO) proclaimed it a pandemic after it spread terrifyingly swiftly across the globe. This publication provides an update on the aetiology, clinical manifestations, and most recent COVID-19 therapeutic decisions. PUBMED/MEDLINE was searched for literature and various articles/case reports from 1997 to 2020 using the terms coronavirus, SARS, Middle East respiratory disease, and mRNA virus. Because of the global spread of COVID-19, all populations are experiencing an increase in illness and mortality. In the absence of an adequate and accurate antibody test, reverse-transcription PCR of nasopharyngeal and oropharyngeal swab samples is employed for diagnosis. Throughout the clinical range, the sickness expresses itself in mild, moderate, and severe ways. The majority of patients have a slight influenza-like disease that cannot be separated from a simple upper respiratory tract infection, or they are asymptomatic carriers who, despite their asymptomatic status, have the potential to infect anyone with whom they come into contact. For moderate and severe cases, hospitalisation and intensive care (including non-invasive and invasive ventilation, antipyretics, antivirals, antibiotics, and steroids) are required. Immunomodulatory drugs and plasma exchange therapy may aid difficult patients. Pharmaceutical companies have begun human research in a number of countries as part of their continuous search for a COVID-19 vaccine.

Keywords: *Sars, Pcr, Covid19 and Virus.*

1. Introduction

There were many reports of acute atypical respiratory illnesses in Wuhan, China, in December 2019. This quickly spread from Wuhan to neighbouring cities. The culprit was quickly identified as a novel coronavirus. The new coronavirus was dubbed SARS-CoV-2 (2019-nCoV) because it shared more than 80% of its DNA with SARS-CoV, the virus that caused acute respiratory distress syndrome (ARDS) and considerable mortality in 2002-2003 [1]. It was previously thought that the SARS-CoV-2 epidemic was caused by a zoonotic transmission

connected to a seafood market in Wuhan, China. Following study, it was determined that human-to-human transmission was responsible for a significant portion of the pandemic [2].

The sickness was caused by the coronavirus disease 19 (COVID-19) virus, and the World Health Organisation (WHO) declared a pandemic. COVID-19 has been documented in about 200 countries and territories, affecting a significant portion of the global population [3, 4]. The John Hopkins University Centre for Systems Science and Engineering (CSSE) [5] projected that over 1,400,000 instances have been registered globally as of April 7, 2020. Although the SARS-CoV-2 virus affects other organ systems, the respiratory system is its major target. In the initial case series from Wuhan, China, fever, dry cough, and dyspnea were recorded as symptoms of lower respiratory tract infections [6].

The COVID-19 respiratory symptom spectrum, which ranges from moderate to severe hypoxia with acute respiratory distress syndrome (ARDS), is now extensively recognised. According to the previously stated Wuhan trial, there was a fast escalation of symptoms, with ARDS developing within 9 days after the onset of respiratory symptoms [6]. This illness has the potential to be deadly. Globally, the number of individuals dying from major diseases has grown. According to epidemiological studies, the prevalence is greater in the elderly [8] and significantly lower in children [9, 10].

Because there is no feasible targeted treatment at this time, most medical care is supportive. Clinical studies have been conducted on a variety of medications, including azithromycin, lopinavir-ritonavir, remdesivir, and hydroxychloroquine [8, 11, 12], but none have yet exhibited therapeutic promise. Clinical trials are testing a greater number of medications. Several nations have used social distancing and lockdowns to attempt to restrict the spread of the illness. This section tries to present an overview of current COVID-19 knowledge and address the underlying processes driving the disease's varied spectrum of symptoms, with a particular emphasis on the differences between adult and paediatric patients.

2. Epidemiological data of COVID-19

Numerous research have been conducted on Chinese experiences to date. The bulk of COVID-19 cases reported at the outset of the epidemic were in older people [13]. As the epidemic progressed, there was a slight rise in cases among youngsters under the age of 18, but also among persons 65 and older. There was a clear gender difference at initially, but as the number of cases grew, male patients became more common. On average, 5.2 days were needed for incubation. Overall, 2.3% of cases ended in mortality [14, 15].

Researchers examined the risk variables associated with hospital-related mortality by analysing data from two Wuhan hospitals. The multivariable analysis showed three risk factors: d-dimer more than 1 g/mL at admission, a higher SOFA score, and older age [8]. Coronary artery disease, diabetes, and hypertension were also included risk factors in the univariable analysis. Multi-organ failure accounted for the majority of COVID-19 fatalities in Wuhan, with a median age of 65; 94% of patients had respiratory failure, 94% had shock, and 94% had ARDS [16].

Since the epidemic in China, SARS-CoV-2 has expanded globally. In terms of COVID-19 instances documented as of early April 2020, the United States leads China, Germany, France, Spain, and Italy. The epidemic in China had a significant influence on Italy. The mortality rate among the elderly was also higher in the Chinese series. Italy had a case-fatality rate of 7.2%, which was three times higher than China's rate [15, 18].

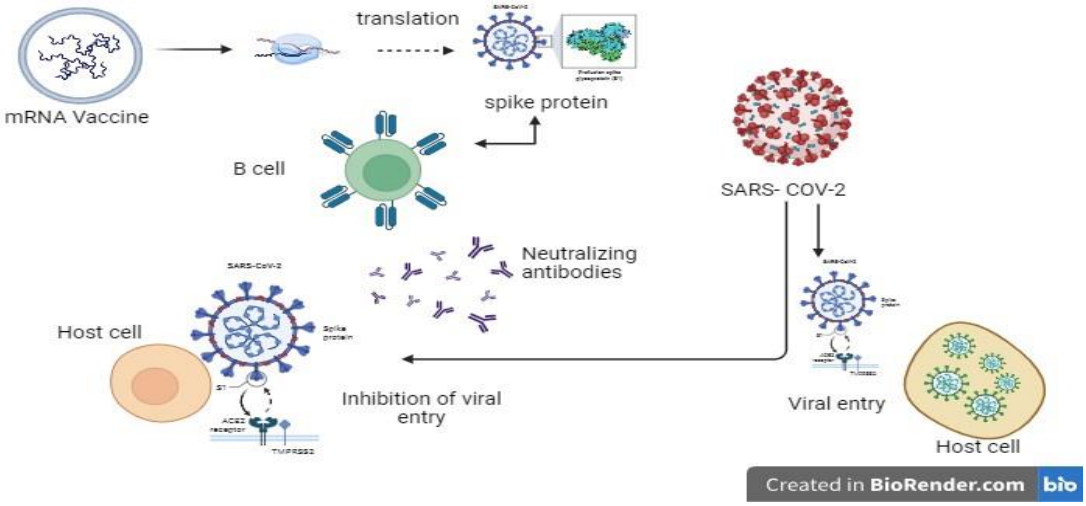
Children have made up a very small proportion of all COVID-19 cases since the pandemic began. The Chinese Centre for Disease Control and Prevention (China CDC) projected that 1% of all cases included children under the age of 10 and those between the ages of 11 and 19 based on data from February 2020 [14]. Because around 20% of the population is under the age of fifty, the paediatric population may have a lower COVID-19 prevalence. If children with less symptoms had fewer tests performed, the real prevalence in the paediatric population was most likely underestimated.

If children were tested less often because they came with fewer symptoms, the real prevalence in the paediatric population would most certainly be underestimated. Due of the Chinese New Year holidays, Chinese schools

were closed for the most of the epidemic, which may have reduced exposure among youngsters. The China CDC received reports of 2134 paediatric COVID-19 cases [20]. 4.4%, 50.9%, 38.8%, and 5.9% of these individuals were classified as asymptomatic, mild, moderate, or severe, respectively. Table 1 summarises the categories for asymptomatic, mild, moderate, severe, and critical. In contrast, 18.5% of adult patients had severe diseases [20].The equivalent percentages of severe and critical cases were 10.6%, 7.3%, 4.2%, 4.1%, and 3.0% for the age categories of 1, 1-5, 6-10, 11-15, and 16 years. Children under the age of five were especially prone to severe illnesses. The age groups with the lowest case-fatality rate were 0 to 9 and 10 to 19. In Italy, the prevalence of COVID-19 patients aged 8 to 18 was just 1.2% [18]. In comparison to Chinese statistics, the case-fatality rates for ages 0-9 and 10-19 were 0.2% and 0%, respectively. The Korean Centres for Disease Control and Prevention released statistics in late March revealing that 6.3% of all COVID-19 positive cases were in youngsters under the age of 19 [21]. On April 6, 2020, the US Centres for Disease Control and Prevention (CDC) issued a study that included 2572 COVID-19 cases among children under the age of 18. Despite accounting for 22% of the population, this age group accounted for just 1.7% of all cases reported in the United States. Overall, the results contradicted Chinese officials' statements, demonstrating that youngsters did not seem to be as ill as adults. Only 73% of the children with data suffered fever, coughing, or dyspnea. In comparison, 93% of individuals aged 18 to 64 who reported within the same time period did not. The highest expected hospitalisation rate for children aged 1 to 17 was 14% [22]. According to Chinese CDC statistics, however, babies had the greatest prevalence of hospitalisation (15-62%). Though the general prognosis for the paediatric population is favourable, numerous deaths have been documented in the United States and other countries, and further study is required to understand the true severity of COVID-19. Even though the Chinese series revealed that men were involved in an equal number of instances, data revealed that more men than women suffered from severe illness and died [23, 24]. Using data from other nations, similar findings were observed [25]. The COVID-19 virus has a negative impact on comorbid conditions such as illness, hypertension, lung disease, and cardiovascular disease. These disorders are more frequent in males and are connected to tobacco and alcohol usage [25]. Immunological variations between sexes have also been proposed [13]. Furthermore, a research investigating the variables affecting the adoption of protective behaviours, especially in the setting of pandemics, found that women were about 50% more likely than males to participate in non-pharmaceutical activities like as hand washing, wearing face masks, and avoiding crowds [26]. This theory may have some validity.

The process by which SARS-CoV-2 enters host cells

Coronaviruses are single-stranded, positive-sense, enclosed RNA viruses with a diameter of about 30 kilobases. They disperse among numerous host species [27]. Their genetic makeup allows for a broad classification into four genera: α, β, η, and δ. The coronaviruses α and β only infect mammals [28]. Human coronaviruses, which cause croup and the common cold, include NL63 and 229E. They are members of the α coronavirus family. On the other hand, the β coronavirus family includes SARS-CoV, MERS-CoV, and SARS-CoV-2. A virus goes through five stages in its host's life cycle: attachment, penetration, biosynthesis, maturity, and release. Viruses cling to host receptors and then penetrate the cell by membrane fusion or endocytosis. The virus's components are released into the host cell, and then viral RNA enters the nucleus to replicate. Viral mRNA is used to biosynthesize viral proteins. A virus produces and releases new particles when it achieves maturity. The coronavirus's four structural proteins are the spike (S), envelop (E), membrane (M), and nucleocapsid (N) [29].



Spike's S1 component attaches to the host cell receptor, while the S2 subunit links the virus's and the cell's membranes. These are spike's two operational subunits. It was discovered that angiotensin converting enzyme 2 (ACE2) had SARS-CoV receptor activity [30]. According to structural and functional studies, ACE2 was also connected to the SARS-CoV-2 spike [31–33]. In the kidney, bladder, ileum, heart, and lung, ACE2 expression was elevated [34].

Table 1 Classification of COVID-19 patients

Asymptomatic	COVID nucleic acid test positive. Without any clinical symptoms and signs and the chest imaging is normal
Mild	Symptoms of acute upper respiratory tract infection (fever, fatigue, myalgia, cough, sore throat, runny nose, sneezing) or digestive symptoms (nausea, vomiting, abdominal pain, diarrhea)
Moderate	Pneumonia (frequent fever, cough) with no obvious hypoxemia, chest CT with lesions.
Severe	Pneumonia with hypoxemia (SpO2 < 92%)
Critical	Acute respiratory distress syndrome (ARDS), may have shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction and acute kidney injury

The protein ACE2 was found to be significantly expressed on lung epithelial cells. More study is required to discover if SARS-CoV-2 binds to other targets. Proteases degrade the spike protein when SARS-CoV2 connects to the host protein. This idea proposes a two-step sequential protease cleavage to activate the SARSCoV and MERS-CoV spike protein. Following priming at the S1/S2 cleavage site, activation occurs at a fusion peptide in the S2 subunit at the S′2 position [35-37]. The S1 and S2 subunits remain non-covalently linked after the S1/S2 cleavage point, and the distal S1 subunit aids in keeping the membrane-anchored S2 subunit in the prefusion condition [32]. .. The spike for membrane fusion is triggered after cleavage at the S′2 location, perhaps due to

irreversible conformational changes. It differs from other viruses in that it may be cleaved and activated by proteases [38]. SARS-CoV-2 is distinguished from other coronaviruses by the presence of a furin cleavage site at the S1/S2 site, known as the "RPPA" sequence. The SARS-CoV spike was not cleaved during assembly, while the S1/S2 site was cleaved completely during biosynthesis [32]. Although a variety of proteases, including cathepsin L and transmembrane protease serine 2 (TMPRSS2), have been shown to cleave the S1/S2 site [37, 39], the virus's widespread expression of furin makes it very dangerous.

3. The host's reaction to SARS-CoV-2

People infected with SARS-CoV-2 can develop mild symptoms all the way to severe respiratory failure and multiple organ failure. Even in people who are asymptomatic, a CT scan can detect the unique pulmonary ground glass opacification [40]. Increased expression of ACE2 on the apical surface of lung epithelial cells in the alveolar region demonstrates the virus's ability to penetrate and kill these cells [41, 42]. This is in line with the finding that the distal airway is frequently the site of the initial lung injury. Airway innate immunity is mostly made up of epithelial cells, alveolar macrophages, and dendritic cells (DCs) [43]. DC-SIGN-related protein (DC-SIGNR, L-SIGN), and DC-SIGN, an intercellular adhesion molecule exclusive to dendritic cells that binds to nonintegrin [45-47]. SARS-CoV can also bind to ACE2. DC-SIGN is highly expressed in cells like macrophages and dendritic cells. It is possible that SARS-CoV-2 can infect DCs and alveolar macrophages directly if it has another target. More research is needed into this matter. By emptying lymph nodes, these antigen-presenting cells deliver viral antigens to T cells. It's crucial to have both CD4+ and CD8+ T cells. Virus-infected cells can be eliminated by CD8+ T cells, and CD4+ T cells can stimulate B cells to produce antibodies against the virus.

Publishing decisions were made for the vast majority of immunological research involving individuals with severe COVID-19. In extreme cases, symptoms of lymphopenia, or a lack of T lymphocytes in the bloodstream, were observed [48, 49]

Routes of transmission

SARS-CoV-2 is mostly transmitted by inhalational droplets and direct skin contact. Aerosol and fecal-oral transmissions are possible but have not been confirmed, according to the Chinese Preventive Medicine Association's Special Expert Group for Control of the Epidemic of Novel Coronavirus Pneumonia and the People's Republic of China's General Office of the National Health Commission.

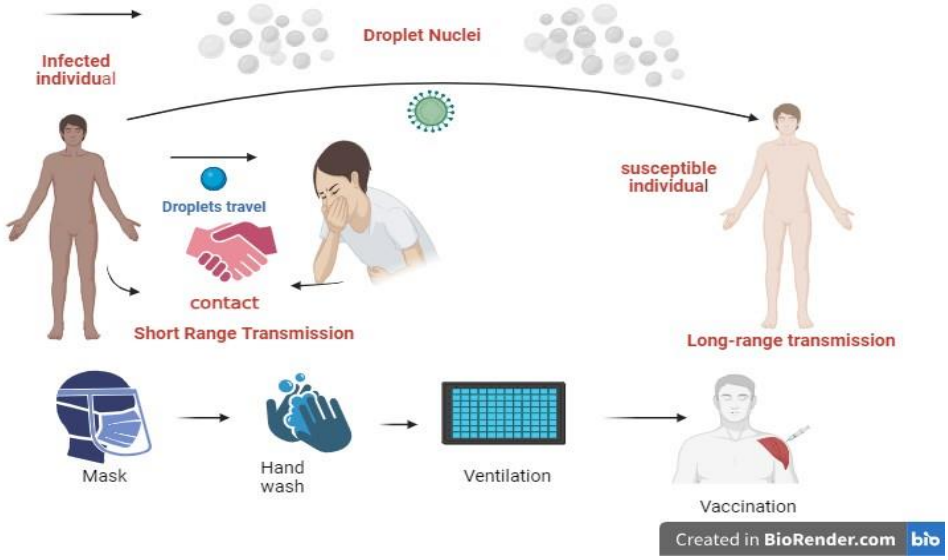
Respiratory droplet movement: Respiratory droplets, like other respiratory viral diseases, are assumed to be the major mechanism of transmission. Although SARS-CoV-2 was discovered to survive in infected people's environments in Guangzhou, China (household surfaces, door handles, mobile phones, and the like), it is still unclear whether the virus can be transmitted through direct or indirect contact with virions (General Office of the People's Republic of China, 2020). When susceptible persons come into touch with bodily fluids (sputum, saliva, or faeces) from infected humans or animals, the SARS-CoV-2 virus may spread via the mouth, nasal cavity, and other mucosal membranes. In the same way, vulnerable people may get infected with SARS-CoV-2 via indirect contact with infected things contaminated with human fluids.

Aerosol transmission: biological aerosols are airborne droplets that contain infections, such as bacteria or viruses, and hang there for a while before evaporating. The disease may then spread over vast distances by droplet cores, which are formed when the remaining proteins and pathogens combine. severe SARS-CoV-2 infection, droplet cores can travel a specific distance when carried by air currents. Patients may release more virus during various medical procedures (tracheal intubation, mask breathing, and non-invasive ventilation); this could lead to local aerosols, which increase the risk to nearby individuals [50].

SARS-CoV-2, the virus responsible for fecal-oral and urinary transmission, has been isolated from the waste of COVID-19 patients. The research teams identifying this virus were directed by Lan-juan LI and Nan-shan ZHONG. SARS-CoV-2, the virus responsible for fecal-oral and urinary transmission, has been isolated from the waste of COVID-19 patients. The research teams identifying this virus were directed by Lan-juan LI and Nan-

shan ZHONG. These results show that SARS-CoV-2 can transmit through feces or urine due to the virus's capacity to persist in the urethra and digestive system [51, 52]. The virus's ability to persist in human waste is the subject of ongoing study.analyze.

The role of the mother in the transmission of SARS-CoV-2: A kid born to a woman infected with the virus on February 6, 2020, tested positive for the virus 36 hours after birth, according to a report from Wuhan Tongji Hospital. These results suggested that viral transmission from mother to child was a real possibility.



Diagnosis and assessment of severity

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Droplet dispersion in the lungs: Respiratory droplets, like with other respiratory viral infections, are assumed to be the primary mechanism of transmission. Although SARS-CoV-2 was discovered to survive in the environments of infected people in Guangzhou, China (household surfaces, door handles, mobile phones, and the like), it is still unknown whether the virus can be transmitted through direct or indirect contact with virions (General Office of the People's Republic of China, 2020). The SARS-CoV-2 virus may spread via the mouth, nasal cavity, and other mucosal membranes when susceptible persons come into contact with bodily fluids (sputum, saliva, or faeces) from infected humans or animals. Similarly, vulnerable individuals may get infected with SARS-CoV-2 via indirect contact with infected things contaminated with human fluids.

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Fecal-oral and urine transmission: SARS-CoV-2 has been successfully identified from the feces and urine of COVID-19 patients by teams led by Lan-juan LI and Nan-shan ZHONG. Fecal-oral and urine transmission: SARS-CoV-2 has been successfully identified from the feces and urine of COVID-19 patients by teams led by Lan-juan LI and Nan-shan ZHONG. These results imply that SARS-CoV-2 can spread through feces or urine

due to the virus's ability to survive in the urethra and digestive tract [51, 52]. More research is currently being done to determine how the virus survives in urine and feces.analyze.

Maternal transmission of the SARS-CoV-2 virus: On February 6, 2020, Wuhan Tongji Hospital reported that a pregnant patient with the virus gave birth to a child who tested positive for the virus 36 hours after the delivery. These findings raised the possibility that a mother could transmit the virus to her offspring.

Imaging Research:

Chest X-rays and CT scans: Imaging tests are one method of assessing the degree of lung involvement in COVID-19. Ground-glass opacities and other characteristic patterns may be seen in the lungs.

Systems for Clinical Scoring: Clinical Severity Evaluation By assessing the severity of a condition, a number of scoring systems, like the CURB-65 and the Modified Early Warning Score (MEWS), can be used to inform hospitalization decisions.

Blood examinations: Monitoring blood indicators such as C-reactive protein (CRP), D-dimer, and others may provide information on a patient's inflammatory and coagulation problems.

Telemedicine and remote monitoring:

Providers of Telemedicine: When assessing symptoms and providing guidance on whether additional testing or an in-person assessment is necessary, remote consultations can be a helpful tool.

At-home monitoring: For those with mild symptoms, monitoring vital signs and symptoms remotely can help identify worsening conditions before they worsen.

Following the advice and guidelines given by medical professionals and regional health authorities is essential. Depending on the region and the stage of the pandemic, different testing, protocols, and treatment options may be available. Always seek the guidance of healthcare professionals for the most up-to-date information and recommendations. Furthermore, it is important to thoroughly review any information regarding intimate contact with confirmed or probable patients at home, at work, or at medical facilities where hospital-associated cases have been documented within the 14 days before symptom onset. When a patient presents with symptoms that could be related to COVID-19, an epidemiological history should be obtained. This would include a past history of visiting or living in Wuhan, Hubei Province, or in any other locations and communities impacted by COVID-19[41,46,51].

Management: The current cornerstones of COVID-19 population management are close observation, supportive care, and sickness prevention and control. These patients usually need oxygen therapy and prompt care since severe or critical disease often develops and can result in complications including ARDS, respiratory failure, and septic shock.

Despite advanced medical care, the mortality rate for intensive care unit (ICU) patients is over 40%. In an effort to reduce the mortality rate associated with severe COVID-19, a number of treatments have been tried that either limit the virus's ability to proliferate or affect the host immune response. However, systemic glucocorticoids have been tested in a number of individuals with moderate disease, and while there is some controversy about whether or not this treatment lengthens the time that the virus is shed, the data that has been collected so far indicates that it is safe and effective. Interferon- (IFN-), an antiviral immunomodulatory medication, was also evaluated for its interaction with glucocorticoids. Blood purification therapy, or "Li's artificial liver," has showed promise in lowering cytokine storm and associated difficulties in critically ill patients [53, 54].

4. Vaccine development and drugs in the pipeline for COVID-19

One of the most important methods for stopping the spread of viral diseases and lowering rates of morbidity and mortality is the development of vaccinations. The genome sequence of the novel virus SARS-CoV-2, which was initially discovered by Chinese scientists, is currently accessible to the general public [56,57]. Numerous SARS-CoV-2 vaccine candidates can be developed thanks to these developments, collaboration, and open-source data.

Vaccinations can be classified into several types, such as vectored vaccines, live attenuated vaccines, recombinant subunit vaccines, and vaccinations based on nucleic acids [58].vaccinations that are live-attenuated and inactivated

Live attenuated and inactivated vaccines are based on the virus's antigenicity in its weaker and dead forms, respectively. Certain viral components, whole inactivated virus particles, or toxoids that have undergone chemical modification to make them non-pathogenic can all be used in inactivated vaccines (Stauffer et al., 2006) [59]. The China National Biotec Group is actively testing a few inactivated vaccine candidates to determine their immunogenicity and efficacy using experimental animals. According to Baggett et al. (2002)[60], live attenuated vaccines are made in a lab setting utilizing microorganisms that have undergone physiological, chemical, or physical weakening.immunisations using vectors

Vaccines that use other viruses as carriers of the SARS-CoV-2 protein include adenovirus, rabies virus, modified vaccinia Ankara (MVA) virus, chimeric parainfluenza virus, and vesicular stomatitis virus (VSV). Researchers at Oxford University in the United Kingdom and Rocky Mountain Laboratories in the United States are working together to create a chimpanzee adenovirus-vectored immunization that protects against SARS-CoV-2. Additionally, a live attenuated recombinant measles virus (rMV) vectored vaccine for the new coronavirus SARS-CoV-2 is being developed by Zydus Cadila, an Indian pharmaceutical company. Reverse genetics is used to create the rMV, which expresses codonoptimized SARS-CoV-2 proteins to produce certain neutralizing antibodies.vaccines derived from nucleic acids

It is possible to stimulate both humoral and cellular immune responses by injecting nucleic acid constructs that express bacterial or viral genes.

The goal of a project headed by Zydus Cadila is to create a DNA vaccine that can protect against the S protein in the primary viral membrane, which allows SARS-CoV-2 to infect cells. Following insertion into the host cells, the plasmid DNA changes into the viral protein and triggers an immune response. This shields against infection and may even get rid of the virus. Medication As a potential vaccination against SARS-CoV-2, Inovio Beijing Advaccine Biotechnology Company (China) and (USA) are currently collaborating to advance the development of INO-4800. Preclinical testing for the vaccine is currently underway, and clinical product production is underway for a phase I clinical trial that will take place concurrently in China. Using PCR-based DNA manufacturing technology, Takis Biotech (Rome, Italy), a division of Applied DNA Sciences (New York, USA), and LineaRx (New York, USA) are developing a linear DNA vaccine against SARS-CoV-2. Moderna (USA) and the National Institutes of Health (USA) are working together to create a messenger RNA (mRNA) vaccine against SARS-CoV-2, which codes for the viral S protein.immunizations using recombinant components

Numerous microbial components produced in a heterologous expression system make up recombinant subunit vaccines [61]. One of the main advantages of subunit vaccines over inactivated and live attenuated vaccines is their excellent safety profile, which is attributed to the fact that they only include synthetic peptides or noninfectious recombinant proteins—no viral viruses—instead of other components [62].

According to Huang et al. (2020) and Ji et al. (2020)[63,64], vaccines based on the S protein of SARS-CoV-2 may be able to create antibodies to block virus binding and fusion and so neutralize virus infection. This is true because the S protein is necessary for both membrane fusion and receptor binding. One of the most significant antigenic elements of the coronavirus structural proteins is the S protein, which elicits neutralizing antibodies and host immunological responses. As a result, he and Jiang (2005) decided to consider it as a potential target for immunization. Using S protein subunit-trimer antigens, Clover Biopharmaceuticals (Chengdu, China) has started to create a recombinant subunit vaccine against SARS-CoV-2.

5. Drugs in the pipeline for COVID-19

Conventional medicine manufacturing methods are manifestly inadequate for the current crisis and require years of research. In this setting, research on the compassionate use of experimental medicines is routinely conducted, and clinical trial approvals are expedited.

Many treatment approaches could be researched as COVID-19 first-line therapy, despite our little understanding of the disease. People who have been diagnosed with SARS-CoV-2 infection could be treated using these techniques in a timely manner.

Antibodies that neutralize the virus S protein

SARS-CoV-2 has been found to share the cellular entry receptor ACE2 [66]. Before the virus multiplies, during SARS-CoV-2 entrance—which is triggered by the S protein attaching to ACE2 on the cell surface—the viral nucleocapsid is introduced into the cell. Since the S protein is involved in both receptor identification and viral attachment and entry, it is a desirable target for the development of COVID-19 therapy medications. According to Zhao et al. (2016), neutralizing antibodies that specifically target the S protein of SARS-CoV-2 may offer a transient passive protection to the illness. It has been discovered that ACE2 is a cellular entry receptor of SARS-CoV-2, just like SARS-CoV [65]. The S protein attaches to ACE2 on the cell surface to start the SARS-CoV-2 entry process. As a result, the virus can enter the cell and release its nucleocapsid before replicating. The S protein is a top choice for therapeutic research projects meant to counteract COVID-19 since it is involved in both receptor recognition and viral attachment and entry. Neutralizing antibodies that particularly target the S protein of SARS-CoV-2 have the potential to temporarily offer passive protection against the disease [66,67].
The ACE2 inhibitors
ACE2 inhibitors may be anti-SARS-CoV-2 because ACE2 is necessary for the viral infection process. Biologics, traditional Chinese medicines, and thousands of chemicals were screened from databases. As a means of creating anti-COVID-19 therapy, the results of these techniques suggest that valproic acid, butyrate, epoxomicin, sambucus, astragalus, urtica, azathioprine, andrographis, may be effective [68].

6. Opionucleotides that oppose the SARS-CoV-2 RNA genome

Creating novel uses for antiviral drugs that are already on the market
Small molecule compounds may be good candidates for COVID-19 treatment if they have already been approved as antiviral (or other) drugs. Antivirals frequently target viruses during various stages of infection and replication [71]. Antiviral regimens frequently target proteases and viral polymerases [71, 72].There have been prior pilot clinical trials on the repurposing of antiviral medications. SARS-CoV-2 is among the coronaviruses that arbidol (umifenovir) effectively combats in vitro. Favipiravir inhibits RNA-dependent RNA polymerase (RdRp). Antiviral medications could be useful short-term tactics in the fight against SARS-CoV-2 due to our current knowledge of their safety profiles and effectiveness against viruses that are closely related. Arbidol, also known as umifenovir, has been approved.
SARS-CoV-2 is among the coronaviruses that arbidol (umifenovir) effectively combats in vitro. It is permitted for use in China and Russia to treat influenza [77]. Consequently, arbidol is being administered in phase IV clinical trials (NCT04260594, NCT04254874, and NCT04255017) and as empirical therapy for COVID-19 patients. Favipiravir, an inhibitor of RNA-dependent RNA polymerase (RdRp), is being reexamined for randomized clinical studies against COVID-19 [76]. Given our existing understanding of antiviral medicines' safety profiles and efficacy against closely comparable viruses, they may be useful as short-term therapy for SARS-CoV-2.

Remdesivir was given to the first COVID-19 case in the US on a compassionate use basis after showing promise against MERS in preclinical models [77].
Adult hospitalized patients with mild to moderate SARSCoV-2 infections are currently being evaluated for Remdesivir in a phase III trial being carried out in China [78].

Recuperated patient serum

After recovering from the SARSCoV-2 infection, patients will respond to viral antigens by developing polyclonal antibodies. These polyclonal antibodies' neutralizing effect might shield the recuperated host from

contracting fresh infections [79, 80].As a result, serum from recuperating patients might be useful as a preventative or therapeutic measure for additional diseases linked to this outbreak. According to a paper [81], serum from a convalescent SARS patient decreased the entry of the SARS-CoV-2 virus and prevented the entry of the SARS-S protein-driven virus. Passive transfer of antibodies from recovered patients' serum is currently being studied as a potential treatment for COVID-19 patients with severe illness.

Traditional applications of herbal remedies and pharmaceuticals

The immune system can be bolstered and antiviral and antibacterial properties discovered in several traditional herbal therapies [82]. Treatments for pneumonia caused by SARS-CoV-2 infection would follow standard medical practice and be tailored to each individual patient depending on their specific clinical presentation. Traditional herbal medicine and Chinese patent drugs like Xiyanping and Xuebijing injections have both been utilized in clinical treatment, and both are recommended for patients at different stages of the condition.

Developing and deploying medicines that effectively halt SARS-CoV-2 infection as soon as possible is a challenging task. Research and development of vaccines and broad-spectrum antiviral medicines that target coronavirus infections are urgently needed in light of the present pandemic. We hope that this outbreak will soon be over if we can keep the virus under control and implement good treatment and vaccination plans.

7. References

1. T.G. Ksiazek, D. Erdman, C.S. Goldsmith, S.R. Zaki, T. Peret, S. Emery, S. Tong,C. Urbani, J.A. Comer, W. Lim, P.E. Rollin, S.F. Dowell, A.E. Ling, C.D. Humphrey, W.J. Shieh, J. Guarner, C.D. Paddock, P. Rota, B. Fields, J. DeRisi, J.Y. Yang, N. Cox, J.M. Hughes, J.W. LeDuc, W.J. Bellini, L.J. Anderson, SW Group, A novel coronavirus associated with severe acute respiratory syndrome, N Engl J Med. 348 (2003) 1953–1966.
2. Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, R. Ren, K.S.M. Leung, E.H.Y. Lau,J.Y. Wong, X. Xing, N. Xiang, Y. Wu, C. Li, Q. Chen, D. Li, T. Liu, J. Zhao, M. Liu,W. Tu, C. Chen, L.Jin, R. Yang, Q. Wang, S. Zhou, R. Wang, H. Liu, Y. Luo, Y. Liu,G. Shao, H. Li, Z. Tao, Y. Yang, Z. Deng, B. Liu, Z. Ma, Y. Zhang, G. Shi, T.T.Y. Lam,J.T. Wu, G.F. Gao, B.J. Cowling, B. Yang, G.M. Leung, Z. Feng, Early transmission dynamics in Wuhan, China, of Novel Coronavirus-infected pneumonia, N Engl JMed. 382 (2020) 1199–1207.
3. M. Zheng, Y. Gao, G. Wang, G. Song, S. Liu, D. Sun, Y. Xu, Z. Tian, Functional exhaustion of antiviral lymphocytes in COVID-19 patients, Cell Mol Immunol. (2020), https://doi.org/10.1038/s41423-020-0402-2.
4. J. Zhang, M. Litvinova, W. Wang, Y. Wang, X. Deng, X. Chen, M. Li, W. Zheng, L. Yi, X. Chen, Q. Wu, Y. Liang, X. Wang, J. Yang, K. Sun, I.M. Longini Jr., M.E. Halloran, Wu, B.J. Cowling, S. Merler, C. Viboud, A. Vespignani, M. Ajelli, H. Yu, Evolving epidemiology and transmission dynamics of coronavirus disease 2019 outside Hubei province, China: a descriptive and modelling study, Lancet Infect Dis. (2020),Fig. 2. Age-dependent ACE2 expression profiles in the mouse lung.Using Lung Gene Expression Analysis Web Portal (https://research.cchmc.org/pbge/lunggens/mainportal.html), the expression of ACE2 was examined. This datawas obtained from microarray experiments of three mice strains A/J mice, C57BL/6J mice and C3H/HeJ mice at different ages [72]. X axis showed age and mouse strain, and y axis showed ACE2 expression level. M.K. Yuki, et al. Clinical Immunology 215 (2020) 1084275 https://doi.org/10.1016/S1473-3099 (20)30230-9.
5. JHUoMCr center, Journal (2020), https://coronavirus.jhu.edu/map.html.
6. C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020)497–506.
7. H. Shi, X. Han, N. Jiang, Y. Cao, O. Alwalid, J. Gu, Y. Fan, C. Zheng, Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study, Lancet Infect Dis. 20 (2020) 425–434.

8. F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, L. Guan, Y. Wei, H. Li, X. Wu, J. Xu, S. Tu, Y. Zhang, H. Chen, B. Cao, Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (2020) 1054–1062.
9. X. Lu, L. Zhang, H. Du, J. Zhang, Y.Y. Li, J. Qu, W. Zhang, Y. Wang, S. Bao, Y. Li, C. Wu, H. Liu, D. Liu, J. Shao, X. Peng, Y. Yang, Z. Liu, Y. Xiang, F. Zhang, R.M. Silva, K.E. Pinkerton, K. Shen, H. Xiao, S. Xu, G.W.K. Wong, T Chinese Pediatric Novel Coronavirus Study, SARS-CoV-2 infection in children, N Engl J Med. (2020), https://doi.org/10.1056/NEJMc2005073.
10. H. Qiu, J. Wu, L. Hong, Y. Luo, Q. Song, D. Chen, Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study, Lancet Infect Dis. (2020), https://doi.org/10. 1016/S1473-3099(20)30198-5.
11. B. Cao, et al., A trial of Lopinavir-ritonavir in adults hospitalized with severe Covid19, N Engl J Med. (2020), https://doi.org/10.1056/NEJMoa2001282.
12. P. Gautret, J.C. Lagier, P. Parola, V.T. Hoang, L. Meddeb, M. Mailhe, B. Doudier, J. Courjon, V. Giordanengo, V.E. Vieira, H.T. Dupont, S. Honore, P. Colson,E. Chabriere, B. La Scola, J.M. Rolain, P. Brouqui, D. Raoult, Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, Int J Antimicrob Agents 105949 (2020).
13. N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (2020) 507–513.
14. Z. Wu, J.M. McGoogan, Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention, JAMA (2020), https://doi.org/10.1001/jama.2020.2648.
15. G. Onder, G. Rezza, S. Brusaferro, Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy, JAMA (2020), https://doi.org/10.1001/ jama.2020.4683.
16. Y. Du, L. Tu, P. Zhu, M. Mu, R. Wang, P. Yang, X. Wang, C. Hu, R. Ping, P. Hu, T. Li, F. Cao, C. Chang, Q. Hu, Y. Jin, G. Xu, Clinical features of 85 fatal cases of COVID19 from Wuhan: a retrospective observational Study, Am J Respir Crit Care Med. (2020), https://doi.org/10.1164/rccm.202003-0543OC.
17. Y. Gao, T. Li, M. Han, X. Li, D. Wu, Y. Xu, Y. Zhu, Y. Liu, X. Wang, L. Wang,Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19, J Med Virol. (2020), https://doi.org/10.1002/jmv.25770.
18. E. Livingston, K. Bucher, Coronavirus disease 2019 (COVID-19) in Italy, Journal. (2020), https://doi.org/10.1001/jama.2020.4344.
19. W. Li, M.J. Moore, N. Vasilieva, J. Sui, S.K. Wong, M.A. Berne, M. Somasundaran, J.L. Sullivan, K. Luzuriaga, T.C. Greenough, H. Choe, M. Farzan, Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus, Journal 426 (2003) 450–454.
20. Y. Chen, Y. Guo, Y. Pan, Z.J. Zhao, Structure analysis of the receptor binding of 2019-nCoV, Journal. (2020), https://doi.org/10.1016/j.bbrc.2020.02.071.
21. A.C. Walls, Y.J. Park, M.A. Tortorici, A. Wall, A.T. McGuire, D. Veesler, Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein, Journal. (2020), https://doi.org/10.1016/j.cell.2020.02.058.
22. M. Letko, A. Marzi, V. Munster, Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses, Journal 5 (2020) 562–569.
23. X. Zou, K. Chen, J. Zou, P. Han, J. Hao, Z. Han, Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection, Journal. (2020), https://doi.org/10.1007/ s11684-020-0754-0.
24. S. Belouzard, V.C. Chu, G.R. Whittaker, Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites, Journal 106 (2009)5871–5876.
25. J.K. Millet, G.R. Whittaker, Host cell entry of Middle East respiratory syndrome coronavirus after two-step, furin-mediated activation of the spike protein, Journal 111 (2014) 15214–15219.

26. X. Ou, Y. Liu, X. Lei, P. Li, D. Mi, L. Ren, L. Guo, R. Guo, T. Chen, J. Hu, Z. Xiang, Z. Mu, X. Chen, J. Chen, K. Hu, Q. Jin, J. Wang, Z. Qian, Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV, Journal 11 (2020) 1620.
27. S. Belouzard, J.K. Millet, B.N. Licitra, G.R. Whittaker, Mechanisms of coronavirus cell entry mediated by the viral spike protein, Journal 4 (2012) 1011–1033.
28. M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Kruger, T. Herrler, S. Erichsen, T.S. Schiergens, G. Herrler, N.H. Wu, A. Nitsche, M.A. Muller, C. Drosten, S. Pohlmann, SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked mby a clinically proven protease inhibitor, Journal. (2020), https://doi.org/10.1016/ j.cell.2020.02.052.
29. W.J. Guan, Z.Y. Ni, Y. Hu, W.H. Liang, C.Q. Ou, J.X. He, L. Liu, H. Shan, C.L. Lei,D.S.C. Hui, B. Du, L.J. Li, G. Zeng, K.Y. Yuen, R.C. Chen, C.L. Tang, T. Wang,P.Y. Chen, J. Xiang, S.Y. Li, J.L. Wang, Z.J. Liang, Y.X. Peng, L. Wei, Y. Liu, Y.H. Hu,P. Peng, J.M. Wang, J.Y. Liu, Z. Chen, G. Li, Z.J. Zheng, S.Q. Qiu, J. Luo, C.J. Ye, S.Y. Zhu, N.S. Zhong, C China Medical Treatment Expert Group for, Clinical characteristics of coronavirus disease 2019 in China, Journal. (2020), https://doi.org/ 10.1056/NEJMoa2002032.
30. I. Hamming, W. Timens, M.L. Bulthuis, A.T. Lely, G. Navis, H. van Goor, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis, Journal 203 (2004) 631–637.
31. H.P. Jia, D.C. Look, L. Shi, M. Hickey, L. Pewe, J. Netland, M. Farzan, C. WohlfordLenane, S. Perlman, P.B. McCray Jr., ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia, Journal 79 (2005) 14614–14621.
32. T. Yoshikawa, T. Hill, K. Li, C.J. Peters, C.T. Tseng, Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages anddendritic cells, Journal 83 (2009) 3039–3048.
33. I. Fujimoto, J. Pan, T. Takizawa, Y. Nakanishi, Virus clearance through apoptosisdependent phagocytosis of influenza A virus-infected cells by macrophages, Journal 74 (2000) 3399–3403.
34. S.A. Jeffers, S.M. Tusell, L. Gillim-Ross, E.M. Hemmila, J.E. Achenbach, G.J. Babcock, W.D. Thomas Jr., L.B. Thackray, M.D. Young, R.J. Mason, D.M. Ambrosino, D.E. Wentworth, J.C. Demartini, K.V. Holmes, CD209L (L-SIGN) is a receptor for severe acute respiratory syndrome coronavirus, Journal 101 (2004) 15748–15753.
35. A. Marzi, T. Gramberg, G. Simmons, P. Moller, A.J. Rennekamp, M. Krumbiegel, M. Geier, J. Eisemann, N. Turza, B. Saunier, A. Steinkasserer, S. Becker, P. Bates, H. Hofmann, S. Pohlmann, DC-SIGN and DC-SIGNR interact with the glycoprotein of Marburg virus and the S protein of severe acute respiratory syndrome coronavirus, Journal 78 (2004) 12090–12095.
36. Z.Y. Yang, Y. Huang, L. Ganesh, K. Leung, W.P. Kong, O. Schwartz, K. Subbarao, G.J. Nabel, pH-dependent entry of severe acute respiratory syndrome coronavirus is mediated by the spike glycoprotein and enhanced by dendritic cell transfer through DC-SIGN, Journal 78 (2004) 5642–5650.
37. Y. Zhou, B. Fu, X. Zheng, D. Wnag, C. Zhao, Y. Qi, R. Sun, Z. Tian, X. Xu, H. Wei, Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients, Journal. (2020).
38. C. Qin, L. Zhou, Z. Hu, S. Zhang, S. Yang, Y. Tao, C. Xie, K. Ma, K. Shang, W. Wang, D.S. Tian, Dysregulation of immune response in patients with COVID-19 in Wuhan, China, Journal (2020), https://doi.org/10.1093/cid/ciaa248.
39. Wax RS, Christian MD, 2020. Practical recommendations for critical care and anesthesiology teams caring for novel coronavirus (2019-nCoV) patients. Can J Anesth/J Can Anesth, 67:568-576
40. Fang Q, 2020. Nan-shan ZHONG's team isolated neocoronavirus from a patient's urine specimen. Guangzhou Daily. https://gzdaily.dayoo.com/pc/html/2020-02/23/content_12 7574_683801.htm [Accessed on Feb. 28, 2020] (in Chinese). Favre G, Pomar L, Musso D, et al., 2020. 2019-nCoV epidemic: what about pregnancies? Lancet, 389(10224):E40

41. Xinhuanet, 2020. Nan-shan ZHONG's and Lan-juan LI's teams isolated the virus from the stools of patients with new coronary pneumonia. Xinhuanet. http://m.xinhuanet. com/hb/2020-02/13/c_1125570909.htm [Accessed on Feb. 28, 2020] (in Chinese)
42. Xu KJ, Cai HL, Shen YH, et al., 2020. Management of corona virus disease-19 (COVID-19): the Zhejiang experience. J Zhejiang Univ (Med Sci) (in Chinese). https://doi.org/10.3785/j.issn.1008-9292.2020.02.02
43. Xu XT, Chen P, Wang JF, et al., 2020. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci, 63(3):457-460. https://doi.org/10.1007/s11427-020-1637-5
44. Gao S, Song SQ, Zhang LL, 2019. Recent progress in vaccine development against chikungunya virus. Front Microbiol, 10:2881. https://doi.org/10.3389/fmicb.2019.02881
45. Chan JFW, Yuan SF, Kok KH, et al., 2020a. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet, 395(10223):514-523. https://doi.org/10.1016/S0140-6736(20)30154-9
46. Zhu N, Zhang DY, Wang WL, et al., 2020. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med, 382(8):727-733. https://doi.org/10.1056/NEJMoa2001017
47. Gao S, Song SQ, Zhang LL, 2019. Recent progress in vaccine development against chikungunya virus. Front Microbiol, 10:2881. https://doi.org/10.3389/fmicb.2019.02881
48. Stauffer F, El-Bacha T, da Poian AT, 2006. Advances in the development of inactivated virus vaccines. Recent Pat Anti-Infect Drug Discov, 1(3):291-296. https://doi.org/10.2174/157489106778777673
49. Zhou YY, Zeng YY, Tong YQ, et al., 2020. Ophthalmologic evidence against the interpersonal transmission of 2019 novel coronavirus through conjunctiva. medRxiv, preprint. https://doi.org/10.1101/2020.02.11.20021956
50. Plotkin SA, 2005. Vaccines: past, present and future. Nat Med, 11(4):S5-S11. https://doi.org/10.1038/nm1209
51. Zheng QL, Duan T, Jin LP, 2020. Single-cell RNA expressionprofiling of ACE2 and AXL in the human maternal-fetalinterface. Reprod Dev Med, 4(1):7-10. https://doi.org/10.4103/2096-2924.278679
52. Huang CL, Wang YM, Li XW, et al., 2020. Clinical features ofpatients infected with 2019 novel coronavirus in Wuhan,China. Lancet, 395(10223):497-506. https://doi.org/10.1016/s0140-6736(20)30183-5
53. Jin YH, Cai L, Cheng ZS, et al., 2020. A rapid advice guidelinefor the diagnosis and treatment of 2019 novel coronavirus(2019-nCoV) infected pneumonia (standard version). Mil Med Res, 7(1):4.
54. Zhou P, Yang XL, Wang XG, et al., 2020b. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, 579(7798):270-273. https://doi.org/10.1038/s41586-020-2012-7.
55. Zhou P, Yang XL, Wang XG, et al., 2020a. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. bioRxiv, preprint. https://doi.org/10.1101/2020.01.22.914952
56. Zou LR, Ruan F, Huang MX, et al., 2020. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med, 382(12):1177-1179. https://doi.org/10.1056/NEJMc2001737.
57. Cui QH, Huang CB, Ji XW, et al., 2020. Possible inhibitors of ACE2, the receptor of 2019-nCoV. Preprints, 2020020047. https://doi.org/10.20944/Preprints202002.0047.V1
58. Leonard JN, Schaffer DV, 2006. Antiviral RNAi therapy: emerging approaches for hitting a moving target. Gene Ther, 13(6):532-540. https://doi.org/10.1038/sj.gt.3302645
59. Watts JK, Corey DR, 2012. Silencing disease genes in the laboratory and the clinic. J Pathol, 226(2):365-379. https://doi.org/10.1002/path.2993
60. Li GD, de Clercq E, 2020. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Dis, 19(3): 149-150. https://doi.org/10.1038/d41573-020-00016-0
61. Patick AK, Potts KE, 1998. Protease inhibitors as antiviral agents. Clin Microbiol Rev, 11(4):614-627. https://doi.org/10.1128/cmr.11.4.614

62. Plotkin SA, 2005. Vaccines: past, present and future. Nat Med, 11(4):S5-S11. https://doi.org/10.1038/nm1209
63. Chu CM, Cheng VCC, Hung IFN, et al., 2004. Role oflopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax, 59(3):252-256. https://doi.org/10.1136/thorax.2003.012658
64. Liu P, Chen W, Chen JP, 2019. Viral metagenomics revealed Sendai virus and coronavirus infection of Malayan Pangolins (Manis javanica). Viruses, 11(11):979. https://doi.org/10.3390/v11110979
65. Lu RJ, Zhao X, Li J, et al., 2020. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet, 395(10224): 565-574. https://doi.org/10.1016/s0140-6736(20)30251-8
66. Sheahan TP, Sims AC, Leist SR, et al., 2020. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun, 11:222. https://doi.org/10.1038/s41467-019-13940-6
67. Wang M, Cao R, Zhang L, et al., 2020. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res, 30(3):269-271. https://doi.org/10.1038/s41422-020-0282-0
68. Al-Tawfiq JA, Alfaraj SH, Altuwaijri TA, et al., 2017. A cohort-study of patients suspected for MERS-CoV in a referral hospital in Saudi Arabia. J Infect, 75(4):378-379. https://doi.org/10.1016/j.jinf.2017.06.002
69. Arabi Y, Balkhy H, Hajeer AH, et al., 2015. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. SpringerPlus, 4:709. https://doi.org/10.1186/s40064-015-1490-9
70. Hofmann H, Pöhlmann S, 2004. Cellular entry of the SARS coronavirus. Trends Microbiol, 12(10):466-472. https://doi.org/10.1016/j.tim.2004.08.008
71. Jin YH, Cai L, Cheng ZS, et al., 2020. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res, 7(1):4. https://doi.org/10.1186/s40779-020-0233-6