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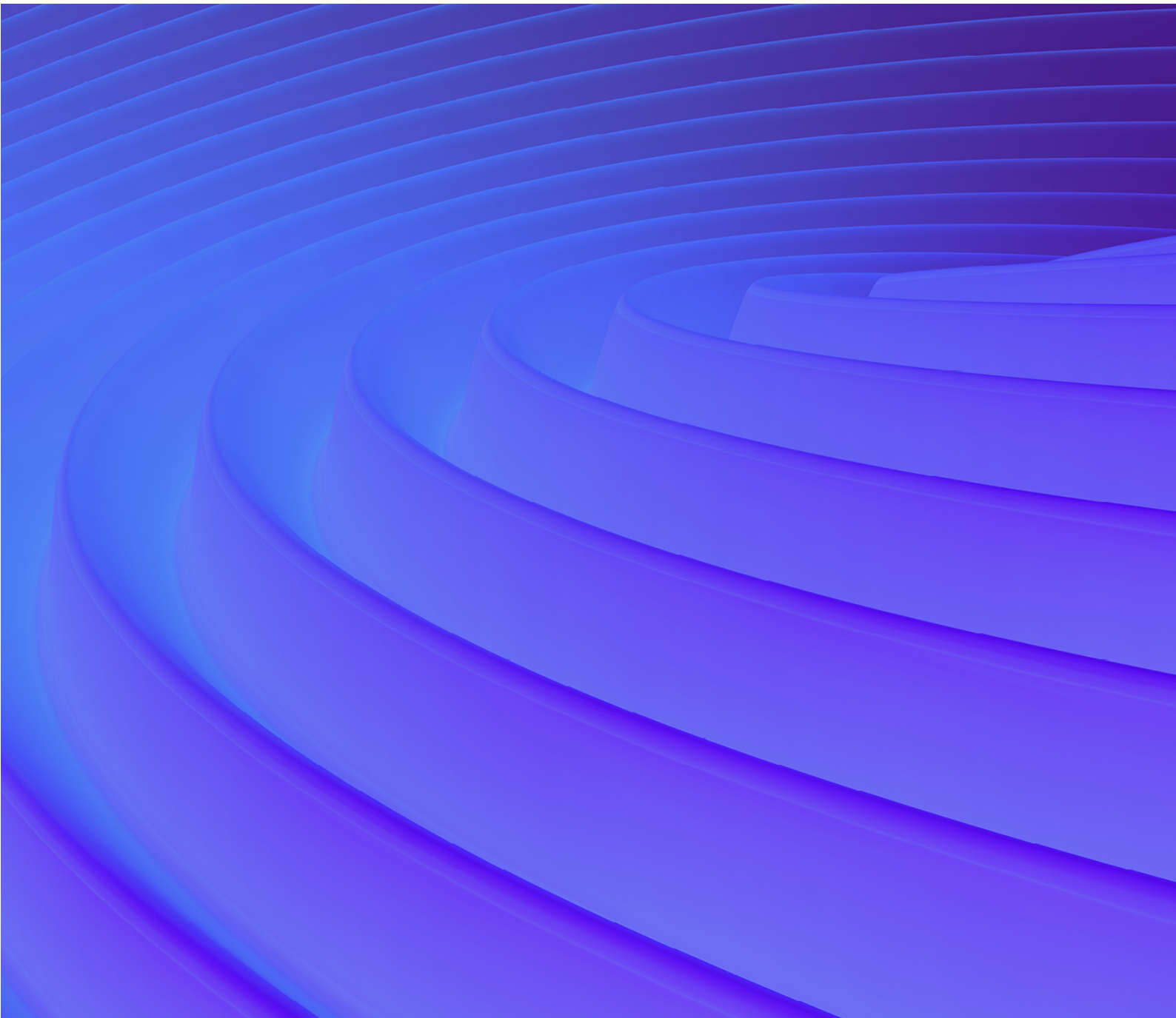
Disease Briefing: Coronaviruses



Contents

Facts about Coronaviruses

Coronaviruses are a group of large, enveloped, positive-sense, single-stranded RNA viruses belonging to the order Nidovirales, family Coronaviridae, subfamily Coronavirinae. More than two dozen different species are known and have been divided into four genera (alpha, beta, gamma and delta) characterized by different antigenic cross-reactivity and genetic makeup. Only the alpha- and betacoronavirus genera include strains pathogenic to humans and other mammals (Paules, C.I. et al (2020); Chen, Y. et al (2020)).

The first known coronavirus, the avian infectious bronchitis virus, was isolated in 1937 and was the cause of devastating infections in chickens. The first human coronavirus was isolated from the nasal cavity and propagated on human ciliated embryonic trachea cells in vitro by Tyrrell and Bynoe in 1965. However, coronaviruses have been present in humans for at least 500-800 years, and all originated in bats (Su, S. et al (2016); Yang, Y. et al (2020); Pooladanda, V. et al (2020)).

Coronaviruses have long been recognized as important veterinary pathogens, causing respiratory and enteric diseases in mammals as well as in birds. Until 2019, only six coronaviruses were known to cause disease in humans: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory virus coronavirus (MERS-CoV) (Skariyachan, S. et al (2019); Bonilla-Aldana, D.K. et al (2020)). HCoV-229E and HCoV-NL63 are alphacoronaviruses; the rest are betacoronaviruses (Yang, Y. et al (2020)). The first four are endemic locally; they have been associated mainly with mild, self-limiting disease, although HCoV-HKU1 can cause pneumonia. SARS-CoV and MERS-CoV can cause severe illness (Song, Z. et al (2019); Paules, C.I. et al (2020)). SARS-CoV and MERS-CoV are among the pathogens included in the World Health Organization's Blueprint List of Priority Diseases (Bonilla-Aldana, D.K. et al (2020)).

Given the high prevalence and wide distribution of coronaviruses, their large genetic diversity as well as the frequent recombination of their genomes, and increasing activity at the human-animal interface, these viruses are recognized as an ongoing threat to human health (Hui, D.S. et al (2020); Zhu, N. et al (2020)). This fact again became strikingly evident in late 2019 and early 2020, when a novel coronavirus was discovered to be the cause of a large and rapidly spreading outbreak of lower respiratory tract infection and disease, including potentially fatal pneumonia, in Wuhan, China (WHO statement regarding cluster of pneumonia cases in Wuhan, China (World Health Organization, January 9, 2020); Coronavirus disease (Covid-19) pandemic (World Health Organization)). The virus--provisionally designated 2019-nCoV and later given the official name SARS-CoV-2, due to its similarity to SARS-CoV--was isolated and the viral genome sequenced. SARS-CoV-2 was characterized as a betacoronavirus and recognized as the seventh discrete coronavirus species capable of causing human disease (Zhu, N. et al (2020)). The disease caused by the virus was officially named Coronavirus Disease 2019 (Covid-19) by WHO.

Morphology, Structure and Replication

Coronaviruses are so named because of their characteristic solar corona (crown-like) appearance when observed under an electron microscope. This appearance is produced by the peplomers of the surface (or spike; designated S) glycoprotein radiating from the virus lipid envelope (Chen, Y. et al (2020); Yang, Y. et al (2020)).

Coronaviruses have four major structural proteins. The S glycoprotein is a major antigen responsible for both receptor binding and cell fusion (Song, Z. et al (2019)) and the membrane glycoprotein (M) is involved in budding and envelope formation; the M protein has also been found to play a pivotal role in virion assembly. The viral genome is associated with the basic phosphoprotein nucleocapsid (N) within the capsid. The envelope (E) protein is a highly hydrophobic protein encasing the entire structure of the coronavirus. The genome is nonsegmented, positive single-stranded RNA of about 26-32 kb, making it the longest RNA viral genome known, and contains at least six different open reading frames. The RNA molecule has a

methylated cap in 5' and a poly-A tail in 3' (Schoeman, D. et al (2019); Chen, Y. et al (2020): Pillaiyar, T. et al (2020)).

Coronaviruses are capable of adapting quickly to new hosts through the processes of genetic recombination and mutation in vivo. As RNA viruses, coronaviruses rely on RNA-dependent RNA polymerase (RdRp) to replicate the virus genome. The intrinsic error rate of RdRp is approximately 1,000,000 mutation/site/replication, resulting in continuous point mutations. Point mutations alone are not sufficient to create a new virus, however; this can only occur when the same host is simultaneously infected with two coronavirus strains, enabling recombination. One coronavirus can gain a genomic fragment of hundreds or thousands base-pair long from another CoV strain when the two co-infect the same host, enabling the virus to increase its ecological niche or to make the leap to a new species (Gralinski, L.E. et al (2015); Makarov, V. et al (2020)). This susceptibility enabled the emergence in approximately two decades of three new human coronavirus species with epidemic potential: SARS-CoV, MERS-CoV and SARS-CoV-2 (Chen, J. (2020)).

Epidemiology, Morbidity and Mortality

Coronaviruses, along with influenza, parainfluenza, RSV and rhinoviruses, cause mild, self-limited upper respiratory tract infections including the common cold (Pillaiyar, T. et al (2020)) and pneumonia. Coronaviruses are responsible for one-third of cold cases. Coronaviruses can also cause gastroenteritis in humans as well as a plethora of diseases in other animals (Berry, M. et al (2015); Su, S. et al (2016)). Unlike other coronaviruses pathogenic in humans, which only rarely cause severe disease and death (Veiga, A.B.G.D. et al (2020)), the pandemic strains SARS-CoV, MERS-CoV and SARS-CoV-2 are capable of causing severe acute respiratory disease, multi-organ failure and/or death.

The coronavirus strains OC43, NL63, HKU1 and 229E are found worldwide in temperate as well as tropical zones. They cause outbreaks throughout the year, although at a higher rate during winter and spring months in temperate climates. All four strains are in circulation yearly, and may be present in the same community simultaneously (Ogimi, C. et al (2020)).

In a comprehensive epidemiology study conducted over a nine-year period in Sao Paulo, Brazil, human coronaviruses were detected in 7.7% of respiratory samples analyzed. The researchers looked at 1,137 samples obtained from asymptomatic individuals, general community, patients with comorbidities and hospitalized patients. NL63 was the most frequently detected coronavirus overall (50.0%), followed by OC43 (27.3%), albeit with variations by year: in 2004, HCoV-229E was the predominant strain circulating (61.5%) (Cabeça, T.K. et al (2013)). 229E is distributed globally (Su, S. et al (2016)).

A study of 559 upper respiratory samples obtained from adults with acute respiratory infections in Beijing, China in 2014 showed that HCoV-OC43 was present in 12.5%, with prevalence peaking in autumn (Hu, Q. et al (2014)). OC43, which has diverged into five distinct genotypes, is distributed globally (Su, S. et al (2016)) and is often the most common species detected through viral surveillance (Ogimi, C. et al (2020)).

HCoV-NL63 was first isolated from a respiratory sample obtained from pediatric patients in different geographic areas in 2004. The virus, which is now known to be distributed globally, accounts for approximately 4.7% of common respiratory illness worldwide (Su, S. et al (2016)). HKU1 is less commonly isolated, causing a generally mild and self-limited infection that is indistinguishable from other respiratory viruses. It appears to be globally distributed (Su, S. et al (2016)).

An analysis of 686 adult patients presenting with acute respiratory infections in Mallorca, Spain (January 2013-February 2014) showed that 7% overall were caused by a coronavirus, including 21.6% of patients in whom viral infection was implicated. The most prevalent strain identified was OC43 (50.0%), followed by NL63 (29%) and 229E (21%). Fifty-two percent of patients with CoV infections required hospitalization, and two patients required intensive care. No CoV infections were fatal in this study (Reina, J. et al (2014)).

A coronavirus that killed nearly 25,000 piglets in 2016-2017 in China emerged from horseshoe bats near the origin of the SARS-CoV, which emerged in 2002 in the same species of bats (Rhinolophus spp). The virus, named swine acute diarrhea syndrome coronavirus (SADS-CoV), has not been confirmed to infect humans (Zhou, P. et al (2018)).

Facts about SARS-CoV

Severe acute respiratory syndrome (SARS) was a viral illness caused by a novel coronavirus (SARS-CoV) and affecting the respiratory system. It originated in the Chinese province of Guangdong in November 2002 and soon spread throughout Asia, North America and Europe. Worldwide, 33 countries and regions on five continents reported SARS cases, although the most severely affected were mainland China and Hong Kong. By spring 2003, SARS became recognized as a global health threat. The rapid spread of the virus to different continents following the initial outbreak underscored the ease with which infectious diseases can be spread internationally within a highly mobile global population (Heymann, D.L. et al (2013); Yang, Y. et al (2020)).

Although the disease has been absent since 2003, the swift and extensive spread of SARS underlined the need for ongoing surveillance of this and related coronavirus, as well as the maintenance of capacity for rapid response should it reemerge. Equally important lessons of the SARS outbreak were the need for transparency in information sharing and the importance of international coordination of response (McCloskey, B. et al (2020)). In the post-SARS era, the government of mainland China has invested heavily in public health, infectious disease surveillance, response and reporting, enabling the country to respond more effectively to subsequent health threats such as H7N9 avian influenza (Zhang, Y. et al (2013)) and Covid-19 (Hui, D.S. et al (2020)).

The lessons learned from SARS have also been applied effectively on the international level in terms of response to the ongoing Middle East respiratory virus (MERS-CoV) outbreak, which emerged in 2012 and is caused by a different strain of coronavirus. These lessons were again put to test in 2020 with the emergence and explosive spread of Covid-19, initially in mainland China and later globally (Perlman, S. (2020)).

SARS-CoV Morphology, Structure and Replication

On March 24, 2003, scientists in Hong Kong and at the U.S. Centers for Disease Control and Prevention (CDC) reported the first preliminary evidence that a new coronavirus was the causative agent of SARS. On April 17, 2003, the WHO formally announced that the causative agent of SARS was a newly discovered member of the coronavirus family, which was not known to exist in humans before the disease was recognized. The new coronavirus was only distantly related to previously known and characterized coronaviruses (Berry, M. et al (2015)). Its origin was eventually traced to bats, with the masked palm civet (Civettictis civetta), a tree-dwelling cat, serving as a possible intermediary host that enabled the jump to humans (Song, Z. et al (2019)).

The SARS-CoV virion is spherical with an average diameter of 78 nm. The helical nucleocapsid is enclosed by an envelope (Goldsmith, C.S. et al (2004)) that is covered with club-shaped, long peplomers about 20 nm long, giving it the typical crown-like appearance.

The organization of SARS-CoV is similar to that of other coronaviruses, with the gene order being 5', replicase [rep], spike [S], envelope [E], membrane [M], nucleocapsid [N], 3', flanked by short untranslated regions (Du, L. et al (2009); Song, Z. et al (2019)). Sequences potentially coding for five more nonstructural proteins are interspersed between the ORF S and N.

The genome contains a total of 11 predicted open reading frames that potentially encode as many as 23 mature proteins (Ruan, Y.J. et al (2003)). The two principal ORFs, occupying about two-thirds of the genome, code for two major polyproteins, ORF1a and ORF1b. The polyproteins are cleaved by proteolysis to produce nonstructural proteins, the most important of which are the RNA-dependent RNA polymerase (Rep) and an ATPase helicase (Hel). The SARS-

CoV has some genetic characteristics that are slightly different from other coronaviruses. There is a short anchor in the S protein, the number and location of the small ORFs are different, there is only one PLP-protease, and a unique, short lysine-rich region exists in the nucleocapsid protein. The biologic significance of these variations is unknown (Rota, P.A. et al (2003); Marra, M.A. et al (2003)).

Coronaviruses enter cells via binding to a host receptor followed by membrane fusion. ACE2 was identified as the cell receptor for SARS-CoV (Wan, Y. et al (2020)). The SARS-CoV virus acidification of endosomes for a productive infection, suggesting a pH-dependent mechanism (Simmons, G. et al (2004)). Coronaviruses replicate in the cytoplasm, where viral RNA is synthesized in a specific, flask-shaped compartment surrounded by a double membrane (Gosert, R. et al (2002)). The SARS-CoV infection is associated with ultrastructural changes both in vivo and in cultured cells. These changes include formation of double-membrane vesicles, presence of nucleocapsid inclusions and granulations in the cytoplasm (Goldsmith, C.S. et al (2004)).

The first gene to be translated is a viral RNA polymerase, called replicase, which initially transcribes full-length, negative strand (or antisense) copies of the genome. These negative strands are then used as templates to produce mRNAs that transcribe viral genes. Those subgenomic transcripts are nested, and have identical 5' regions, non-translated, and a poly-A tail in 3'. The different, nested transcripts are not produced by splicing, but by the activity of the viral RNA polymerase. The viral RNA polymerase interacts with a repeated intergenic sequence (TRS, transcription regulating sequence) located between the viral genes and allows the link between the 5' leader sequence and the start of each gene. The replication mechanism has not been completely described, but it is likely to proceed through subgenomic-size, minus-strand RNAs containing the anti-leader sequence. Large granular areas containing viral RNA and proteins that are not seen in cells infected by other coronaviruses may be observed in cells infected by the SARS-CoV. These regions may be viral translation centers (Goldsmith, C.S. et al (2004); Song, Z. et al (2019)).

The viral particles assemble in the Golgi, accumulate in dilated vesicles that are then transported and secreted to the cell surface, where they are released by exocytosis.

The SARS-CoV has biological characteristics that differ from previously known coronaviruses. SARS-CoV is tropic for Vero cells (a cell line derived from the African green monkey kidney epithelial cells), it grows at 37°C in contrast to other coronaviruses that grow at lower temperature, and can infect the lower respiratory tract (Vicenzi, E. et al (2004)). The SARS coronavirus genome is between 29705 and 29751 nucleotides (NCBI Sequence Viewer: SARS coronavirus). The SARS virus genome did not match any of the three previously known groups of coronaviruses, and had only a weak antigenic relationship to coronaviruses 229E and OC43. The polymerase gene is closely related to the bovine and murine coronaviruses in group 2, but also has some characteristics of avian coronaviruses in group 3. The SARS-CoV does not have a hemagglutinin-esterase present in group 2 and some group 3 coronaviruses, but it has a single papain-like proteinase that is present in group 3 coronaviruses (Holmes, K.V. et al (2003)). The differences between SARS-CoV and other coronaviruses pointed to a new group (Marra, M.A. et al (2003); Rota, P.A. et al (2003)) that was phylogenetically equidistant from the three known groups at that time. A new coronaviruses group 4 was proposed, of which the SARS-CoV is the only member. The discovery of SARS-CoV drove the search for other, previously unknown, human coronaviruses. Two such viruses were identified shortly thereafter: HCoV-NL63 (2004) and HCoV-HKU1 (2005). Both appear to be distributed worldwide, and at least the former has been circulating in human populations for centuries (Berry, M. et al (2015); Abdel-Moneim, A.S. (2014)).

Transmission

The SARS coronavirus was transmitted through large droplets and via direct contact (Wong, S.S. et al (2008)). The virus can reach a concentration of about 100 million particles per mL in sputum (Drosten, C. et al (2003)) and can survive on contaminated surfaces and objects at room temperature for up to six days (Cleri, D.J. et al (2010)).

Two major factors contributed to the rapid spread of SARS: a highly mobile international population and high urban population densities (Arita, I. et al (2003)).

Attack rates were higher than 50% in the healthcare setting during the outbreak, while household transmission was less efficient (6-8%) (Goh, D.L. et al (2004); Lau, J.T. et al (2004)). Simulation studies performed after the outbreak suggested that physicians and other health care workers were the principal vectors of SARS transmission in the hospital setting (Cleri, D.J. et al (2010)). Practices such as use of ventilators and nebulized bronchodilators may cause aerosols and spread of droplets containing virus. The risk of spreading the virus may also be increased by cardiopulmonary resuscitation, bronchoscopy, endotracheal intubation, airway and sputum suction (Cleri, D.J. et al (2010); Chen, W.Q. et al (2009)).

Virus load and shedding peaked at approximately 10 days from the appearance of clinical symptoms, when the patient's status worsened and required medical attention. Thus patients were most infectious at the time of seeking health care. Viral shedding continued for at least 13 more days (range 2-60 days) (Cleri, D.J. et al (2010)). Patients were not infectious during the incubation period (Zeng, G. et al (2009)).

A few patients were identified as SARS "superspreaders" who spread the virus efficiently because they harbored above-normal levels of virus (Yang, Y. et al (2020)). Superspreading seems to be associated with high virus titer, aerosol generation, contamination of the environment, and close contact with others in a healthcare setting (Cleri, D.J. et al (2010)).

Symptoms and Disease

The SARS-CoV preferentially infects the lower respiratory tract, resulting in a severe, acute viral pneumonia. The WHO case definition for probable SARS included high fever (>38°C) or history of fever in the previous 48 hours; new infiltrates on chest x-ray suggestive of pneumonia; flu-like symptoms (chills, cough, malaise, myalgia) or history of exposure to SARS-CoV; and one or more positive diagnostic tests for SARS (Cleri, D.J. et al (2010)). Unfortunately, the initial symptoms and clinical appearance were not easily distinguishable from other common respiratory infections, and fever was sometimes absent in older adults.

Analysis of both autopsy samples and experimentally infected animals indicates that the SARS-CoV infection in the lung affects the pneumonic areas and is detected in type 2 pneumocytes (Gralinski, L.E. et al (2015)). Morphological changes in tissues included diffuse alveolar damage, denudation of the bronchial epithelium, loss of cilia, and squamous metaplasia. Giant-cell infiltration, hemophagocytosis and cytomegalic alveolar pneumocytes were also observed in some cases (Liu, J. et al (2020)). The infection progresses through an inflammatory or exudative phase (characterized by hyaline-membrane formation, pneumocyte proliferation and edema), a proliferative phase and a fibrotic phase (Gralinski, L.E. et al (2015)).

The respiratory tract was the main target of the SARS-CoV, although the gastrointestinal tract could also be involved (Paules, C.I. et al (2020)). Infection of the central nervous system was also reported (Zhang, D.M. et al (2008)). Symptomatically, SARS generally followed a triphasic pattern. In the first week after infection, symptoms usually consisted of fever and myalgia. These early symptoms may have been related to direct viral cytopathic effects, since increases in viral load could be detected by PCR during this phase of the disease. Seroconversion was detected during the second week and was followed by a reduction of viral load. The innate immune response was insufficient to control the SARS-CoV infection because decreases in viral load are coincident with the specific antibody response (Peiris, J.S. et al (2003)). A third phase occurred in 20% of infected patients and was characterized clinically by disease progression that could not be explained by uncontrolled viral replication. This phase could be the result of an excessive and aberrant albeit ineffective host immune response, ultimately leading to SARS-associated lung damage and, potentially, death (Gralinski, L.E. et al (2015); Zumla, A. et al (2020)).

Symptoms of SARS during the 2003 outbreak were not identical in all patients. Nearly 100% of adults and children presented with fever, and approximately half with cough and/or myalgia. Only a few patients had upper respiratory symptoms. Diarrhea was reported in 11-15% of patients at presentation (Cleri, D.J. et al (2010)) and in up to 40-70% of hospitalized patients (Hui,

D.S. (2005)). Lymphopenia, leukopenia, thrombocytopenia were detected in some patients. Elevation of enzymes such as lactate dehydrogenase, aspartate aminotransferase and creatinine kinase levels indicated an effect of SARS on the liver in some patients (Drosten, C. et al (2003): Cleri, D.J. et al (2010)). Others presented with symptoms unexpected in a respiratory infection, such as acute abdominal pain (Poutanen, S.M. et al (2003)). Pulmonary infiltrates were present on chest radiography. The changes in lung tissue pointed to damage inflicted by cytokines and chemokines (Gralinski, L.E. et al (2015)).

During the outbreak, about 40% of infected patients developed respiratory failure requiring assisted ventilation, however 90% of patients recovered within a week after the first appearance of symptoms. Smokers required mechanical ventilation more frequently than nonsmokers (Poutanen, S.M. et al (2003)). Older patients had greater morbidity and mortality, the result of an aging-related attenuation in the adaptive immune response (Frieman, M. et al (2008); Schäfer, A. et al (2014)).

Fatal SARS was the result of progressive respiratory impairment caused by damage to the lung alveoli. While the mortality rate during the SARS outbreak was <1% for patients under age 24 (Hui, D.S. et al (2010)), it increased to about 13% in patients under age 60, and was much higher (approximately 50%) in those over 60 and in those developing acute respiratory distress syndrome (approximately 50%) (Cleri, D.J. et al (2010); Schäfer, A. et al (2014)). The overall mortality rate during the outbreak was approximately 10%. Fatal cases of SARS-CoV infection were characterized by aberrant interferon signaling and a dysregulated adaptive immune response, or "cytokine storm" (Liu, J. et al (2020)).

Independent correlates of adverse clinical outcome included known history of diabetes/hyperglycemia, advanced age, male gender, comorbid hepatitis, high neutrophil counts at admission and high levels of lactate dehydrogenase, reflecting tissue necrosis related to the immune hyperactivity (Cleri, D.J. et al (2010); Hui, D.S. et al (2010)). A positive association was reported between air pollution and higher case-fatality rates (Cleri, D.J. et al (2010)). Host genetic variants may have also influenced variations in disease response (Schäfer, A. et al (2014)).

SARS infection was less prevalent as well as less aggressive in young children (Berry, M. et al (2015)). The highest rates of infection occurred in people of 20-39 years of age, whereas only 1% of cases occurred in children under age 10 years (Liang, W. et al (2004)). High rates among young adults may reflect cases among healthcare workers, while similar high rates in older people may be the consequence of nosocomial infections.

A prospective, observational study reported in 2007 was the first to provide comprehensive information regarding the long-term outcomes of SARS survivors. The 117 SARS survivors from Toronto, Ontario, underwent physical examination, pulmonary function testing, chest radiography and the six-minute walk test, filled out quality-of-life surveys and provided information regarding healthcare utilization at three different points (3, 6 and 12 months) following hospital discharge. The results showed that most SARS survivors had recovered fully from the physical illness by one year. However, general health, vitality and social functioning were below normal in many SARS survivors one year after illness, and many patients reported being unable to return to their pre-SARS level of work. Health care utilization, especially with respect to psychiatric care, was significantly higher than normal during the period of evaluation, and patients reported important decrements in mental health. Family caregivers of SARS survivors also reported suffering psychological consequences (Tansey, C.M. et al (2007)). A later study of 22 long-term survivors in Toronto established that chronic post-SARS morbidity persisted for up to 20 months after onset of illness. Symptoms included chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep (Moldofsky, H. et al (2011)). A long-term follow-up study reported by Hong Kong researchers also found significant psychiatric morbidities and persistent fatigue in 233 SARS survivors at the fourth year of follow-up (Lam, M.H. et al (2009)); another Hong Kong follow-up study suggested that long-term impairment was more pronounced in health care workers (Ngai, J.C. et al (2010)). Twelve years after surviving SARS, former patients were found to have increased susceptibility to pulmonary infections, tumors, cardiovascular disorders and abnormal glucose metabolism as compared to healthy controls. Particularly among patients who had been treated with high-dose methylprednisolone,

there appeared to be a risk of long-term systemic damage due to serum metabolic alterations (Wu, Q. et al (2017)).

Epidemiology and Cost of the SARS Epidemic

A total of 8,422 cases and 919 resulting deaths resulted worldwide during the SARS outbreak. Mainland China was hardest hit, with 5,328 cases and 349 deaths (Yang, Y. et al (2020)). Epidemiologic studies estimated that the average incubation time was 6.4 days. Mortality was 6.8% in younger patients and was as high as 43% in patients over the age of 60 years (Cleri, D.J. et al (2010)). The global case-fatality rate was 11% (Wong, S.S. et al (2008)), albeit with significant variation between regions (Lau, E.H. et al (2010)).

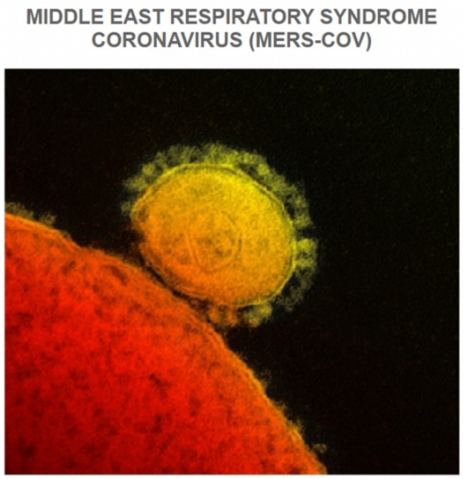
The SARS epidemic had important economic implications, with a global economic impact over two years estimated at between USD 40 billion (Ayittey, F.K. et al (2020)) and up to USD 100 billion (Paules, C.I. et al (2020)). The total economic impact of SARS in mainland China in 2003 has been estimated at USD 25.3 billion (Zhang, Y. et al (2013)), including losses to the tourism sector in Beijing alone estimated at USD 1.4 billion (Beutels, P. et al (2009)).

The rapid and effective containment of SARS just months after its international recognition was achieved thanks to an unprecedented international collaboration between researchers, healthcare providers and health authorities (Braden, C.R. et al (2013)). However, factors and circumstances that caused the emergence of SARS are not understood and a reemergence of the disease remains possible, particularly in light of the fact that animal reservoirs of this and other coronaviruses still exist (Berry, M. et al (2015); Yang, Y. et al (2020)).

For more epidemiology information, consult the Incidence and Prevalence Database (IPD): IPD: Severe acute respiratory syndrome (SARS).

Facts about MERS-CoV

In September 2012, WHO reported two cases of acute respiratory illness, ultimately fatal, accompanied by renal failure and caused by a previously unknown human coronavirus. The earliest known case was retrospectively traced to April 2012 (Mostafa, A. et al (2020)). The novel betacoronavirus responsible for the disease, formally named Middle East respiratory syndrome coronavirus (MERS-CoV), appears to have originated in bats (Zumla, A. et al (2015)) and uses dromedary camels as intermediate hosts (Cho, H. et al (2018)). Although it also pertains to the Coronavirinae family, the new virus was shown to be genetically different from the SARS coronavirus and to use a different host-cell receptor, identified as dipeptidyl peptidase 4 (DPP4, also known as CD26) (Li, F. et al (2019)). In a human lung epithelial cell assay, MERS-CoV was shown to elicit a distinct pattern of host gene expression responses. The virus is a cause for concern due to its zoonotic potential and the high case fatality rate (approximately 35%) (Li, F. et al (2019)).



Transmission electron micrograph of a single Middle East Respiratory Syndrome Coronavirus (MERS-CoV) virion. Credit: NIAID/RML

WHO has released interim guidelines for the appropriate care of patients in whom this infection is suspected (see Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected - Interim guidance (World Health Organization, 2019)). See WHO Global Alert and Response (GAR): Coronavirus infections and CDC - Coronavirus home page for up-to-date information from WHO and CDC.

MERS-CoV Morphology, Structure and Replication

MERS-CoV is a positive-sense, enveloped, single-stranded RNA virus with a genome size of 30.1 kB (Mostafa, A. et al (2020)). It is classified as a betacoronavirus, and is more closely related to bat coronaviruses such as HKU4 and HKU5 than it is to SARS-CoV. Seroepidemiology studies have failed to uncover evidence of past infections with MERS-CoV in the general population of the affected geographic region, supporting the affirmation that this was a new virus (Chan, J.F. et al (2015)).

The genome arrangement of MERS-CoV is 5' - replicase - structural proteins (S - E - M - N) - poly(A) - 3', similar to other coronaviruses. The virus has 10 open reading frames (ORFs) and 16 putative nonstructural proteins that are involved in the processes of viral transcription and replication (Chan, J.F. et al (2015); Skariyachan, S. et al (2019)).

The virus gains entry into the host cell by binding to DPP4 receptors expressed in the lower airway as well as in the kidney and other organs (Paules, C.I. et al (2020)); the fact that DPP4 receptors are not expressed in the upper respiratory tract may explain why MERS-CoV is less transmissible than other coronaviruses (Mostafa, A. et al (2020)). It uses host proteases to gain entry into lung cells. The protease furin activates the S protein on the viral envelope, mediating membrane fusion and enabling virus entry into the host cell (Banik, G.R. et al (2015); Tang, T. et al (2020)). Like the SARS-CoV, the Middle East respiratory virus is able to overcome the host innate immune response until high virus titers have been achieved, and induces cytokine dysregulation (Gralinski, L.E. et al (2015); Skariyachan, S. et al (2019)).

Transmission

The MERS-CoV virus presumably originated in bats, although it was initially unclear how it made the leap from bats to humans (Abdel-Moneim, A.S. (2014)). CDC investigators were first to identify dromedary camels as an intermediate or amplifying host and the most likely source of zoonotic transmission in the Middle East (Arabi, Y.M. et al (2017); Killerby, M.E. et al (2020)). Several possible routes of spread exist, including direct close contact with the animals--particularly juvenile camels--and their bodily fluids, as well as meat handling and/or consumption of unpasteurized camels' milk (Widagdo, W. et al (2019); Killerby, M.E. et al (2020)).

Although it is primarily a zoonotic virus, nonsustained human-to-human transmission has been confirmed in 53-60% of all cases, albeit predominantly in health care settings and family clusters. Humans are considered terminal or transient hosts, however, with an R0 of <1 (Killerby, M.E. et al (2020)). Patients with severe to fatal infection are more likely to transmit the virus, since they shed a higher amount of virus progeny in comparison to those with asymptomatic or mild infection (Widagdo, W. et al (2019)). Like SARS-CoV, droplets are believed to constitute the principal mode of transmission of MERS-CoV (Cho, H. et al (2018)). Nosocomial spread, i.e. contamination via contact with virus on environmental surfaces, was also confirmed during the Korean outbreak in 2015 (Bin, S.Y. et al (2016); Cho, H. et al (2018)).

Symptoms and Disease

The incubation period is approximately 5 days (range 2-15 days), with 94% of patients showing signs of disease by day 12 (Chan, J.F. et al (2015)). Typical presenting symptoms are

nonspecific and include fever, chills, nonproductive cough, dyspnea, rigor, headache, myalgia and malaise. Some patients present with gastrointestinal symptoms, including diarrhea, nausea and vomiting, and abdominal pain. Acute renal impairment is a unique feature of MERS and occurs with significantly greater frequency than was seen in patients with SARS (Song, Z. et al (2019); Paules, C.I. et al (2020)).

Pathological features of MERS-CoV infection include exudative pulmonary edema, diffuse alveolar damage with hyaline membranes, type II pneumocyte hyperplasia, interstitial pneumonia, and necrosis of the bronchial submucosal glands (Liu, J. et al (2020)).

Symptoms and manifestations of Middle East respiratory syndrome range from mild or asymptomatic infection to severe pneumonia, acute respiratory distress, septic shock and multiorgan failure resulting in death (Zumla, A. et al (2015); Zumla, A. et al (2016)). Respiratory failure with ARDS and multiorgan dysfunction syndrome are not uncommon, and the majority of patients with these complications will require admission to the intensive care unit within 2-5 days of symptom onset. The median time from symptom onset to invasive ventilation and/or extracorporeal membrane oxygenation in these patients is 4.5 to 7 days (Chan, J.F. et al (2015)). Risk of severe disease is higher in men over age 45, people with preexisting medical conditions including diabetes, obesity, chronic kidney disease, chronic cardiac disease and COPD (Zumla, A. et al (2016); Mostafa, A. et al (2020)), and in health care workers.

While the early case-fatality rate was close to 60%, this has decreased with improved awareness and surveillance; however, mortality remains above 35% (Al-Tawfiq, J.A. et al (2014); Chafekar, A. et al (2018)). The probability of a fatal outcome is much greater among patients aged 50 years and older as compared to younger patients (77% vs. 22%, respectively) (Cauchemez, S. et al (2014)). Mortality is also higher in men and in patients with multiple comorbidities (Banik, G.R. et al (2015); Chan, J.F. et al (2015)). Nonetheless, given that asymptomatic or mild cases are generally not reported, the actual case-fatality rate is presumably below the reported rate of 35% (Mostafa, A. et al (2020)).

Epidemiology of MERS

Since September 2012, cases of MERS-CoV have been reported in 27 countries including the Kingdom of Saudi Arabia, Italy, the Netherlands, France, Germany, Italy, Tunisia, Malaysia, United Kingdom, United States, Iran, Egypt, Lebanon and Turkey (Chafekar, A. et al (2018); Middle East respiratory syndrome coronavirus (MERS-CoV) (World Health Organization), consulted March 19, 2020). Initial cases were restricted to the Middle East as well as two cases in the U.K. among family members of an infected individual who had recently traveled from Saudi Arabia. Several cases later occurred in clusters, including a hospital outbreak in Saudi Arabia, and confirmed that the virus can be transmitted between humans during close contact (Assiri, A. et al (2013); Zumla, A. et al (2015)). As of May 31, 2020, the World Health Organization had been notified of 2,562 laboratory-confirmed human cases of infection with the virus and 881 resulting deaths (Middle East respiratory syndrome coronavirus (MERS-CoV) -- Saudi Arabia. Disease outbreak news: update (World Health Organization, July 2, 2020). The case-fatality rate remains extremely high: in excess of 35% (Mostafa, A. et al (2020)).

Published epidemiology figures reflect only the number of patients with clinical manifestations of MERS. However, a study of the general population of Saudi Arabia suggests that the rate of asymptomatic disease is much higher. Based on a serosurvey of individuals aged 15 and older who were seen by a health care professional or participated in a national burden-of-disease study between December 2012 and December 2013, nearly 45,000 people in that country were estimated to be seroprevalent for MERS-CoV, and may constitute a source of infection for individuals who do not come into contact with camels (Müller, M.A. et al (2015)). Moreover, a study of travelers to countries affected by MERS between September 2012-2016 has enabled a more precise estimate of the number of severe MERS cases in those countries (Saudi Arabia, United Arab Emirates, Jordan and Qatar). The researchers estimated that approximately 3,300 cases of severe disease occurred in that span of time, a number that is 2.3 times greater than the total number of laboratory-confirmed infections (O'Hagan, J.J. et al (2016)).

On May 20, 2015, the index case in what became the largest outbreak of MERS-CoV outside the kingdom of Saudi Arabia was reported in the Republic of Korea. The index patient had recently traveled to four countries in the Middle East, and returned to Korea while still asymptomatic. Between May 2015 and June 2016, there were 185 laboratory-confirmed cases, including 38 fatalities, in Korea, as well as an additional case in China. The outbreak cost the central government of the Republic of Korea USD 860 million in concept of quarantine system reform, emergency support for hospitals and other MERS response activities, and loans for affected medical institutions. Direct medical costs of the outbreak were approximately USD 12 million (Joo, H. et al (2019)).

The epidemiology of new MERS infections appears to follow a seasonal pattern, with outbreaks in the spring of 2013, 2014 and 2015 coinciding with the months when camels give birth (Al-Tawfiq, J.A. et al (2014)).

Although the data is still evolving, the basic reproduction number (R0) for the MERS-CoV is generally considered to be less than 1, indicating low pandemic potential unless the virus mutates (Killerby, M.E. et al (2020)).

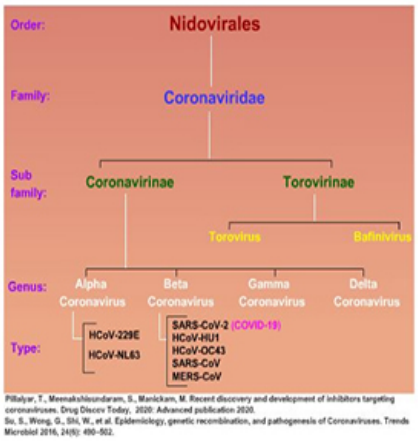
For more epidemiology information, consult the Incidence and Prevalence Database (IPD): **IPD: Middle East respiratory syndrome coronavirus (MERS-CoV)**.

Facts about Covid-19

In December 2019, a new coronavirus began causing febrile respiratory illness in mainland China; two months later, the rapidly spreading disease was officially named Coronavirus Disease 2019 (Covid-19) by WHO (Lai, C.C. et al (2020)). Earliest reports of the illness were issued by doctors in the densely populated city of Wuhan, Hubei province. Index cases were linked to the Huanan wholesale seafood market, which was immediately closed. Although the initial cases were traced to zoonotic transmission, human-to-human transmission was soon documented, both in healthcare settings and in familial clusters (Chan, J.F. et al (2020); Li, Q. et al (2020)). In fact, following the initial leap across the species barrier, human-to-human transmission quickly became responsible for widespread and rapid dissemination of the virus across populations with no preexisting immunity (Chen, J. (2020)); the disease spread from a single focal point across the entire country of China in just 30 days (Wu, Z. et al (2020)). By the end of January 2020, the new coronavirus had already established a foothold on four continents (Asia, Australia, Europe and North America) (Triggle, C.R. et al (2020)). Within three months, the new disease had become a global pandemic (Sanche, S. et al (2020)).

The pathogen--originally termed 2019-nCoV and later designated SARS-CoV-2--was sequenced and identified as a betacoronavirus belonging to the sarbecovirus subgenus, with approximately 80% similarity in genetic sequence to SARS-CoV (Zhu, N. et al (2020); Perlman, S. (2020)) overall, and more than 90% sequence identity with respect to various essential enzymes (Morse, J.S. et al (2020)). The new virus is even more closely related (more than 90% sequence homology) to Bat-CoV-RaTG13, which was previously identified in Rhinolophus affinis (intermediate horseshoe bat) from Yunnan Province (Yang, Y. et al (2020); He, F. et al (2020)).

Coronavirus Taxonomy



SARS-CoV-2 Morphology, Structure and Replication

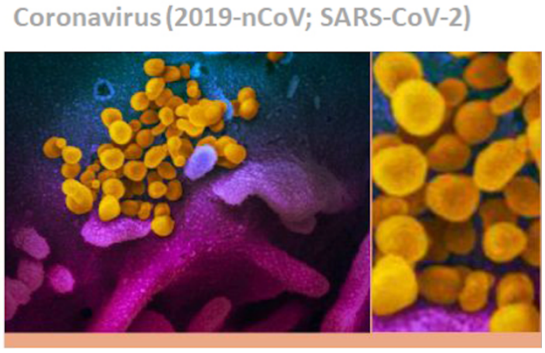
The SARS-CoV-2 virus has a diameter of 60-140 nm and the typical solar corona appearance (Wiersinga, W.J. et al (2020)). The viral genome is a single-stranded, positive-sense RNA with 10 open reading frames (ORFs) encoding for four structural (S, E, M and N), 16 nonstructural (including 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase) and several accessory proteins (Li, G. et al (2020); Tang, T. et al (2020); Pooladanda, V. et al (2020)).

Due to its similarities to SARS virus, the Coronavirus Study Group of the International Committee on Taxonomy of Viruses (ICTV) named the new virus SARS-CoV-2. The native animal host of SARS-CoV-2 is presumed to be a bat; a wild animal--the pangolin is one suspect--is believed to have served as an amplifying intermediate host (Lu, R. et al (2020); Yang, Y. et al (2020); Zhang, T. et al (2020)), as bat-derived coronaviruses cannot directly infect humans (Wang, R. et al (2020)). The binding affinity of the SARS-CoV-2 S protein for ACE2 is 10- to 20-fold greater than that of SARS-CoV, which may help to explain its more rapid spread through human populations (He, F. et al (2020); Wrapp, D. et al (2020)). As the virus began to spread beyond it s initial foothold in China, a missense mutation in the spike protein, designated D614G, first emerged as a predominant clade in Europe (66% of sequences) and soon became the most common variant worldwide (Isabel, S. et al (2020); Koyama, T. et al (2020)). This mutation appears to render the virus more infectious, but not to cause more severe disease (Korber, B. et al (2020)).

Like SARS-CoV, the new coronavirus deploys the densely glycosylated S protein (which consists of S1 and S2 subunits) for virus-host cell receptor interaction and viral entry via the membrane pathway (Walls, A.C. et al (2020)), with ACE2 serving as its binding receptor on the host cell (Wan, Y. et al (2020)). The S protein is also the major antigenic determinant, and is targeted by the host antibody response (Tang, T. et al (2020)). The S1 subunit, as the receptor binding domain, engages with the ACE2 receptor on the host cell surface (Kumar, G.V. et al (2020); Walls, A.C. et al (2020)). The virus uses the host cellular serine protease TMPRSS2--or alternatively, the enzyme furin--for S protein priming (also known as cleavage). During this step, which is essential for entry into the host cell, the S protein is cleaved and its subunits are separated, exposing the S2 subunit, which mediates cell membrane fusion (Hoffmann, M. et al (2020); Wiersinga, W.J. et al (2020); Bestle, D. et al (2020)). ACE2 receptors are expressed on a variety of cells, including arterial and venous endothelial cells, arterial smooth muscle, upper and lower respiratory tract epithelial cells, small intestinal epithelial, renal and immune cells (Madjid, M. et al (2020)). However, TMPRSS2 must be expressed on the same cell at the same time in

order for the virus to successfully enter. ACE2/TMPRSS2 co-expressing cell subsets--and hence, those at the greatest risk of infection--include mucus-secreting goblet cells in the nose, type II pneumocytes in the alveoli of the lung, and absorptive enterocytes in the intestines. In the absence of host proteases, coronaviruses are alternatively able to penetrate the host cell via clathrin- and non-clathrin-mediated endocytosis (Tang, T. et al (2020)). Within the host cell, the RNA-directed RNA-polymerase (RdRp) directs the processes of viral genome replication and transcription (Makarov, V. et al (2020)). In contrast with the SARS virus, SARS-CoV-2 appears to replicate actively in cells of the upper respiratory tract, which may contribute to increased transmissibility (Wölfel, R. et al (2020)).

Integrity of the epithelial-endothelial barrier integrity begins to deteriorate in the later stages of infection, when viral replication accelerates and host defenses simultaneously become severely dysregulated. In addition to epithelial cells, SARS-CoV-2 begins to infect pulmonary capillary endothelial cells, heightening the inflammatory response and triggering an influx of monocytes and neutrophils. As revealed in autopsy studies, there is a diffuse thickening of the alveolar wall with mononuclear cells and macrophages infiltrating airspaces, manifesting as pulmonary edema and visible on computed tomographic imaging as bilateral, lower-lobe ground-glass opacities. This manifests as pneumonia and acute respiratory distress syndrome (ARDS). Fulminant activation of coagulation factors may lead to disseminated intravascular coagulation (Wiersinga, W.J. et al (2020)).



Source: NIAID-RML NIAID had producted images of the novel coronavirus (SARS-CoV-2, previously known as 2019-nCoV) on its scanning and transmission eletron microscopes on Tuesday Feb 11, 2020. SARS-CoV-2 causes COVID-19 disease, which has grown to be a global public health emergency since cases were first detected in Wuhan, China in December 2019.

Transmission

Person-to-person transmission of SARS-CoV-2 was first linked to the inhalation of suspended respiratory droplets (>5 mcm) generated when an infected individual coughs, sneezes or speaks, or through direct contact with an infected patient (Lai, C.C. et al (2020); Guo, Z.-D. et al (2020)). However, it is now generally accepted that the virus can also be transmitted in aerosolized microparticles (less than or equal to 5 mcm) of saliva, e.g., those produced when speaking, and that in a confined environment with poor ventilation, infectious particles can remain suspended in the air for prolonged periods, facilitating long-range transmission (Stadnytskyi, V. et al (2020); Fears, A.C. et al (2020); Alwan, N.A. et al (2020)). Viral load in saliva peaks at presentation and remains high for at least the first week of symptomatic illness, gradually declining thereafter but remaining detectable for 20 days or more (Kai-Wang, K. et al (2020)). The virus can also be transmitted via fomites, although this method of transmission appears to be less important. SARS-CoV-2 remains viable for up to 24 hours on cardboard and for up to 72 hours on plastic and stainless steel (van Doremalen, N. et al (2020)). Infectious droplets and body fluids can also contaminate the human conjunctival epithelium, producing ocular complications that may then progress to respiratory infection; this route of transmission was reported in Wuhan, China (Lu, C.W. et al (2020)). At later stages of infection, viral persistence has been detected in anal swabs, blood and serum, suggesting additional shedding mechanisms and the potential for transmission via the oral-fecal or body fluid routes (Zhang, W. et al (2020)). A systematic review and analysis of 49 studies involving 655 mothers and 666

neonates has concluded that the risk of vertical transmission of Covid-19 is very low. The rate of neonatal infection was similar regardless of whether the baby was born vaginally or by Caesarean section, breast- or bottle-fed, and allowed contact with the mother or isolated (Walker, K.F. et al (2020)).

A study of the transmission dynamics in the first 425 confirmed cases in Wuhan concluded that SARS-CoV-2 is extremely contagious, and estimated a basic reproduction number (R0) of 2.2 (Li, Q. et al (2020)); later studies with more data suggested a higher R0 of 2.24-3.58 (Lai, C.C. et al (2020)), although one modeling study pegged R0 even higher, at 5.7 (Sanche, S. et al (2020)). An active monitoring study of U.S. patients infected with Covid-19 found that the symptomatic secondary attack rate was just 0.45% among all close contacts, but increased to 10.5% among household members (Burke, R.M. et al (2020)), while a contact tracing study in Taiwan found an overall secondary clinical attack rate of 0.7%, increasing to 4.6% in household family contacts and 5.3% in non-household family contacts (Cheng, H.Y. et al (2020)). A retrospective cohort study analyzed 391 Covid-19 cases and 1,286 close contacts in the Chinese city of Shenzhen between January 14 and February 12, 2020. The household secondary attack rate in this cohort was 11.2%, with children as likely as adults to become infected but less likely to have severe symptoms. The R0 was 0.4 (Bi, Q. et al (2020)). Similar to SARS, superspreading events have been reported during the Covid-19 outbreak (Liu, Y. et al (2020)).

It soon became apparent that the infection could be transmitted via pharyngeal viral shedding by individuals during the prodromal period (Heymann, D.L. et al (2020); Wölfel, R. et al (2020)), as well as by those who remain asymptomatic throughout their infection (Yang, Y. et al (2020)). According to a study of 28 infector-infectee pairs, the serial interval--the time from symptom onset in a primary patient to the onset of symptoms in a secondary patient--of Covid-19 (4.0 to 4.6 days) is close to or shorter than its median incubation period (5.1 days). This finding is significant because it suggests a more important role of presymptomatic transmission, implying that the isolation of cases as a means of curtailing the outbreak might not be as effective as initially believed (Lauer, S.A. et al (2020); Nishiura, H. et al (2020)). This finding was reinforced in a study of 77 transmission pairs, in which 44% of secondary cases were infected during the presymptomatic stage of the index case's illness. Assuming an incubation period of 5.2 days, viral shedding began 2.3 days before symptom onset, peaking at 0.7 days before onset of symptoms, and appeared to decline quickly over the next 7 days (He, X. et al (2020)). Presymptomatic individuals accounted for 48-62% of transmission in modeling studies in Singapore and Tianjin, China (Ganyani, T. et al (2020)). The rate of transmission by truly asymptomatic individuals, i.e., those who remain asymptomatic throughout their infection, has been estimated at 4% to 32%; however, further study is required to confirm the existence and frequency of asymptomatic transmission (Wiersinga, W.J. et al (2020)). Replication-competent virus can be isolated for up to 7 days after onset of symptoms. To prevent infecting others, CDC recommends isolation of symptomatic individuals for 10 days after symptom onset as well as at least 24 hours after resolution of fever, without the use of fever-reducing medications, and with improvement of other symptoms. Individuals who never develop symptoms should isolate for 10 days after the date of their first positive RT-PCR test for SARS-CoV-2 RNA (Duration of isolation and precautions for adults with COVID-19 (Centers for Disease Control and Prevention, updated October 19, 2020)).

Symptoms and Disease

The incubation period ranges from 2-14 days (median 5.1 days) (Lauer, S.A. et al (2020)), after which Covid-19 disease manifestation varies widely, from an asymptomatic carrier state to pneumonia or acute respiratory distress syndrome (ARDS). Up to 30% of infections are asymptomatic (Lai, C.C. et al (2020); Nishiura, H. et al (2020)). Symptomatic respiratory illness ranges from mild to severe, with symptoms that include fever, cough, dyspnea, myalgia, headache and diarrhea. Chest CT scan reveals the presence of bilateral ground-glass opacities (Huang, C. et al (2020); Wu, Z. et al (2020); Lai, C.C. et al (2020)). First reported anecdotally, acute anosmia and/or ageusia (sudden loss of olfactory and gustatory function, respectively) is now recognized as a strong indicator of Covid-19, particularly that of mild to moderate severity (Vaira, L.A. et al (2020)).

In an early description of 41 clinical cases in Wuhan, China, clinical presentations were very similar to those of SARS and included fever (98%), cough (76%) and myalgia or fatigue (44%). All patients had pneumonia with abnormal findings on chest CT; 32% had underlying diseases including diabetes, hypertension and cardiovascular disease. The most severely ill patients developed ARDS, a syndrome characterized by the acute onset of hypoxemic respiratory failure with bilateral infiltrates, requiring ICU admission and oxygen therapy. Critically ill patients showed elevated plasma levels of IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A and TNF-alpha--often called a "cytokine storm"--which corresponded with disease severity. The mortality rate in this early patient set was approximately 15% (Huang, C. et al (2020); Zumla, A. et al (2020)), and primarily involved older patients with serious underlying diseases or conditions. A later analysis of a larger group of Chinese patients (N = 44,672) found an overall mortality rate of 2.3%, which increased with age, from zero in children under 9 to 14.8% in those over 80 (Unknown Author (2020); Wu, Z. et al (2020)).

Several highly prevalent underlying conditions--including cardiovascular disease, hypertension, obesity, cancer, asthma and diabetes--have been shown in various patient series to be associated with a significantly higher risk of hospitalization and mortality (Docherty, A.B. et al (2020); Adams, M.L. et al (2020)). A systematic review and meta-analysis of 75 published studies found that individuals with overweight/obesity were at 46% higher risk of infection, 113% higher risk of hospitalization, 74% higher risk of ICU admission and 48% higher risk of death (Popkin, B.M. et al (2020)). Other factors associated with poor prognosis include indicators of increased disease severity (oxygenation, respiratory rate, lymphopenia, chest imaging findings), disseminated intravascular coagulation, older age and delay in diagnosis. Male gender and African American race have been linked to more severe disease and worse outcomes in several patient groups (Lai, C.C. et al (2020); Kragholm, K. et al (2020)). History of cigarette smoking (current or former) is associated with an increased risk of disease progression (Patanavanich, R. et al (2020)). CDC data on women of reproductive age with Covid-19 suggest that pregnant women are more likely to be hospitalized and are at increased risk for ICU admission and mechanical ventilation as compared to nonpregnant women, although their risk for death is similar (Ellington, S. et al (2020)). A Swedish study of pregnant women found that, although Covid-19 is less severe in pregnancy than either SARS or MERS, women infected with SARS-CoV-2 had a higher rate of preeclampsia than matched controls (Ahlberg, M. et al (2020)). A genome-wide association study conducted in Italy and Spain identified an association signal at locus 9q34.2, which coincides with the ABO blood group locus. In their sample of 1,610 patients and 2,205 controls, the risk of severe Covid-19 with respiratory failure was higher in patients with blood group A compared to other groups, and was lower in those with blood group O compared to other groups (Ellinghaus, D. et al (2020)). Individuals with inborn errors of type I interferons, an important component of the immune system for overcoming the virus, are at risk of more severe and potentially life-threatening Covid-19 disease (Bastard, P. et al (2020)).

As the numbers of infected and seriously ill patients grow worldwide, there is a growing understanding of the full scope and impact of SARS-CoV-2 infection on the body. In addition to its well-known respiratory effects, the viral infection--as well as the drugs used to treat it and the host inflammatory and immune response--are capable of potentially causing much broader acute and chronic damage to organs ranging from the brain and eyes to the gastrointestinal tract, liver, kidneys, heart and circulatory system (How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes (Science news, April 17, 2020)) as well as peripheral and central nervous system and skeletal muscle (Mao, L. et al (2020)). There is a growing awareness of potentially severe neurological effects of Covid-19 disease, including encephalopathy, encephalitis and Guillain-Barre syndrome. Encephalopathy in particular is associated with increased morbidity and mortality, independent of the severity of respiratory disease (Ellul, M.A. et al (2020); Liotta, E.M. et al (2020)).

An usually high incidence of disseminated intravascular coagulation, localized pulmonary thrombotic microangiopathy and venous thromboembolism has been reported in severely ill patients as well as those with only mild to moderate disease; coagulopathy in the Covid-19 patient population is driven by the immune response and is associated with increased risk of fatal outcome (Tang, N. et al (2020); Levi, M. et al (2020)). In a preliminary report of 184 Dutch ICU patients with laboratory-confirmed Covid-19 pneumonia, the incidence of thrombotic

complications was remarkably high: 31% (Klok, F.A. et al (2020)); in a follow-up analysis of the same 184 critically ill patients, the investigators found that the incidence of a composite endpoint comprising symptomatic acute pulmonary embolism, deep vein thrombosis, ischemic stroke, myocardial infarction and/or systemic arterial embolism was 49% (Klok, F.A. et al (2020)). Of special concern, large-vessel ischemic stroke and other severe consequences of thrombotic disease have been described as presenting symptoms of Covid-19 in younger, otherwise healthy individuals (Oxley, T.J. et al (2020)). Although most commonly described in the ICU setting, thrombotic complications have been reported in hospitalized patients of all degrees of severity. In a study of 3,334 consecutive patients hospitalized in a large New York City health system, the incidence of any thrombotic event was 29.4% and 11.5% among ICU and non-ICU patients, respectively (Bilaloglu, S. et al (2020)).

The risk of symptomatic and severe Covid-19 increases with age, although children are not immune. An analysis of data on 2,135 pediatric cases of Covid-19 reported to the Chinese Center for Disease Control and Prevention between January 16 and February 8, 2020 confirmed that the disease could affect children, although manifestations may be more mild. Infants were especially vulnerable (Dong, Y. et al (2020)). A growing body of evidence since those early months suggests that children are as likely as adults to be infected with SARS-CoV-2, but are less likely to have symptomatic disease or to develop severe symptoms. When they do have symptoms, fever and cough are the most common. Gastrointestinal symptoms of Covid-19 are more frequent in children than adults (Zimmermann, P. et al (2020)). Reports from Europe and North America have described clusters of children and adolescents requiring admission to intensive care units, who presented with a multisystem inflammatory syndrome in children (MIS-C) sharing some features of Kawasaki disease and toxic shock syndrome. Case reports and small series have described a presentation of acute illness accompanied by a hyperinflammatory syndrome, leading to multiorgan failure and shock (Feldstein, L.R. et al (2020)). The WHO has developed a preliminary case definition and established a digital platform for standardized, anonymized clinical data collection in order to obtain greater understanding of this syndrome (Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19 -- Scientific brief (World Health Organization, May 15, 2020)). Disease descriptions have also been developed by the CDC, European CDC and U.K. National Health Service, contributing to increased awareness and improved reporting (Whittaker, E. et al (2020)). In New York State--site of an early and large Covid-19 outbreak in the U.S.--clinicians reported nearly 200 cases of hyperinflammatory syndromes with dermatologic, mucocutaneous and gastrointestinal manifestations together with cardiac dysfunction. Ninety-five children were confirmed to have MIS-C, of whom 80% were admitted to the ICU and two died (Dufort, E.M. et al (2020)). In a case series of 58 hospitalized children in the U.K. who met broad definitions for MIS-C as proposed by the NHS, CDC or WHO, three distinct disease patterns were discerned. One group of children had persistent fever and elevated levels of inflammatory markers, but without features of Kawasaki disease, shock or organ failure. A second group fulfilled the diagnostic criteria for Kawasaki disease, whereas the third group had shock together with clinical, echocardiographic and laboratory evidence of myocardial injury (Whittaker, E. et al (2020)).

A subset of patients--mostly adults--have been described with long-term, often debilitating symptoms that persist long after recovery from acute Covid-19 (Carfì, A. et al (2020)). These include cardiomyopathy, lasting pulmonary damage, fatigue and other neurological complications, and a compromised immune system. The mechanisms underlying the diverse manifestations of long Covid-19 are poorly understood at this time (Chiappelli, F. (2020)), but appear to involve the immune system's reaction to the virus rather than lasting effects of the pathogen itself. Post-viral autoimmunity, inflammation, fibrosis and thrombosis cause damage to a range of organs and organ systems, including the lungs, heart and circulatory system, kidneys, liver, adrenal glands and gastrointestinal tract (Long-term immunological health consequences of Covid-19 (British Society for Immunology, August 2020)).

As the pandemic matures, a wide range of disease sequelae have begun to come to light. U.K. researchers, concerned about findings of new-onset diabetes and sometimes severe ketoacidosis in Covid-19 patients, have initiated the CoviDiab Registry to learn more about this complication. The data obtained will help to answer questions such as the frequency of new-

onset diabetes in this patient population; whether it is classic type 1 or type 2 diabetes, or a new type of diabetes altogether; whether patients remain at higher risk for diabetes or diabetic ketoacidosis following resolution of the viral disease; and whether Covid-19 affects the underlying pathophysiology and natural history of diabetes in patients with preexisting diabetes (Rubino, F. et al (2020)).

Epidemiology

According to WHO, as of December 2, 2020, more than 63 million laboratory-confirmed cases of Covid-19 had been diagnosed and reported worldwide. Also as of this date, WHO had confirmed more than 1.46 million deaths from Covid-19 worldwide (WHO coronavirus disease (COVID-19) dashboard (World Health Organization), consulted December 2, 2020). On January 30, under recommendation from the International Health Regulations (2005) Emergency Committee, the Director-General of WHO declared the Covid-19 outbreak a Public Health Emergency of International Concern (PHEIC) (Unknown Author (2020)). On March 11, WHO officially designated the outbreak a global pandemic (WHO Director-General's opening remarks at the media briefing on COVID-19 -- 11 March 2020 (World Health Organization press release)). To track the outbreak in real time, click here: Coronavirus COVID-19 global cases dashboard (Johns Hopkins University Center for Systems Science and Engineering).

A U.S. study provided further insight into the rate of clinical disease by underlying condition and by age. A total of 1,320,488 laboratory-confirmed Covid-19 cases were reported to CDC between January 22 and May 30, 2020. The cumulative incidence was 403.6 cases per 100,000 persons, and was similar among males (401.1) and females (406.0). The proportion of patients with an underlying health condition was 21.8%. The distribution by type of underlying condition was reported as follows: any cardiovascular disease, 32.2%; any chronic lung disease, 17.5%; renal disease, 7.6%; diabetes, 30.2%; liver disease, 1.4%; immunocompromised, 5.3%; neurologic/neurodevelopmental disability, 4.8%. The distribution of patients by age was reported as follows: 0-9 years, 1.5%; 10-19 years, 3.7%; 20-29 years, 13.8%; 30-39 years, 16.3%; 40-49 years, 16.6%; 50-59 years, 17.9%; 60-69 years, 13.6%; 70-79 years, 8.0%; 80 years or older, 8.7%. The highest incidence rate was among persons aged 80 years and older (902.0 per 100,000) (Stokes, E.K. et al (2020)). According to the American Academy of Pediatrics, the overall cumulative rate of Covid-19 in the pediatric population of the U.S. was 1,777 cases per 100,000 children as of November 26, 2020. Cumulatively, children represent 12% of all cases in the U.S. (Children and Covid-19: State data report (American Academy of Pediatrics/Children's Hospital Association, November 26, 2020)).

The rapid spread and ease of transmission of the virus are causing global alarm. Experts point out that although the virus poses a relatively low health threat at the individual level, it is easily transmissible and thus poses a significant risk at the population level. Careful surveillance of SARS-CoV-2 virus is critical to monitor its future host adaption, viral evolution, infectivity, transmissibility and pathogenicity (Huang, C. et al (2020)). Modeling studies suggest that the initial, most severe pandemic wave of SARS-CoV-2 will be followed by recurrent wintertime outbreaks until herd immunity is achieved, either through natural infection or vaccination. If immunity is short-lasting, pandemic waves may recur every year or two. If immunity is permanent, however, the virus could largely disappear within five or more years of the first major outbreak (Kissler, S.M. et al (2020)).

For more epidemiology information, consult the Incidence and Prevalence Database (IPD): IPD: Covid-19 (2019 novel coronavirus).

Morbidity and Mortality

The case-fatality rate in a study of the first 44,000 cases of Covid-19 in mainland China was 2.3% (Unknown Author (2020)). Mortality among symptomatic patients is estimated to be in the range of 0.5% to 4%, while among patients who require hospitalization, the rate increases to 5% to 15%. In the early Hubei Province case series, mortality among critically ill patients ranged from 22% to 62%. These numbers will change as the outbreak evolves (Murthy, S. et al (2020)). As the

pandemic continued to progress, and taking into account the total spectrum of disease, the overall case-fatality ratio in mainland China was estimated in a modeling study at 1.38%, ranging from 0.31% in those under 60 years of age to 6.38% in those 60 years and older. In an international sample of patients included in the same modeling study, the case-fatality ratio was estimated at 2.7% overall, ranging from 1.4% in patients aged < 60 years to 4.5% in those aged 60 years and older (Verity, R. et al (2020)).

In Italy, a much higher case-fatality rate of 7.2% (as of March 17, 2020) was reported. Three factors that potentially explain this difference were identified: the older age of the population (23% aged 65 years or older), testing strategies (only symptomatic individuals are tested) and the definition of Covid-19-related death applied in that country. Uniform testing and reporting guidelines are needed in order to generate standard epidemiology data across all affected countries (Onder, G. et al (2020)). As of June 8, the mortality rate in Lombardy--the most severely affected region of Italy--was 159 per 100,000 population (Petersen, E. et al (2020)). Throughout the entire EU/European Economic Area (EEA) plus U.K., the 14-day Covid-19 mortality rate for the week ending November 26, 2020 was 95.3 (country range: 2.4-226.7) per million population (Covid-19 surveillance report - Week 47 (European Centre for Disease Prevention and Control), consulted December 2, 2020).

Early in the U.S. outbreak, the mortality rate among residents of a long-term care facility in Washington state was 33.7% (McMichael, T.M. et al (2020)). In the U.S. overall during the early months of the outbreak (March-April 2020), more than 87,000 excess deaths (expected vs. observed deaths) were reported; of these, 65% were attributed to Covid-19 (any mention) and 35% were attributed to other causes. The most common nonrespiratory causes of excess deaths in this sample were diabetes, heart disease, Alzheimer's disease and cerebrovascular disease; the researchers concluded that up to one-third of early Covid-19 deaths were unreported due to misattribution or delayed reporting (Woolf, S.H. et al (2020)).

The population of the Diamond Princess cruise ship provides a unique opportunity to study the evolution of the disease, given the prolonged quarantine and close observation of the 3,711 passengers and crew. From February 1, when the index case was reported, until February 20, when the passengers were allowed to leave the ship, there were 619 PCR-confirmed cases on board (318 symptomatic and 301 asymptomatic), giving an infection rate of 17%. The average age of patients on board was 58 years, and the all-age corrected infection-fatality rate (cIFR) was 1.3% and the corrected case-fatality rate (cCFR) was 2.6% (Russell, T.W. et al (2020)).

For the 20 countries most affected by Covid-19 as of July 3, 2020, mortality rates per 100,000 population were reported as follows, with the observed case-fatality rates in parentheses: United Kingdom, 67.54 (15.4%); United States, 41.33 (4.1%); Chile, 37.26 (2.2%); Peru, 37.11 (3.6%); Brazil, 34.42 (3.9%); Mexico, 27.74 (11.7%); Bolivia, 15.92 (3.7%); Iran, 15.68 (5.0%); Colombia, 10.93 (3.7%); Iraq, 8.20 (4.1%); Russia, 7.83 (1.6%); Guatemala, 7.07 (4.2%); South Africa, 7.06 (1.5%); Saudi Arabia, 6.60 (1.0%); Argentina, 4.15 (1.8%); Egypt, 3.92 (4.7%); Pakistan, 2.48 (2.1%); India, 1.71 (2.6%); Bangladesh, 1.46 (1.3%); Indonesia, 1.35 (4.8%) (Johns Hopkins University coronavirus resource center - Mortality analysis, consulted July 13, 2020).

As the pandemic progresses, racial differences in outcomes have increasingly been reported, particularly in the U.S., where a retrospective cohort study has explored racial and ethnic differences in the clinical course and outcomes of U.S. Covid-19 patients. The study was conducted in Louisiana and included patients from an integrated-delivery health system from March 1 and April 11, 2020. A total of 3,481 Covid-19 patients were included in the study, of whom 1,382 were hospitalized (39.7%; 319 White non-Hispanics and 1,063 Black non-Hispanics). Among hospitalized Covid-19 patients, 76.9% were Black. The hospital course of Covid-19 patients who were hospitalized during the study period was reported as follows for White versus Black non-Hispanics: coinfection with pneumonia, 36.4% vs 38.3%; acute renal failure, 10.7% vs 15.3%; acute hepatic injury, 0.6% vs 0.2%; cardiomyopathy or congestive heart failure, 0% vs 0.2%; hypoxic respiratory failure, 24.8% vs 25.4%. The clinical outcomes of Covid-19 patients who were hospitalized in the same period were reported as follows for White versus Black non-Hispanics: still admitted, 4.1% vs 4.6%; discharged alive from the hospital, 65.8% vs 73.8%; died, 30.1% vs 21.6%. The median length of hospital stay in the two groups was 7.0 days and 6.0 days,

respectively. Of 326 patients who died from Covid-19, 70.6% were Black (Price-Haywood, E.G. et al (2020)).

The leading causes of death in patients with Covid-19 are respiratory failure subsequent to ARDS (70%) and sepsis (28%) (Tay, M.Z. et al (2020)). An autopsy study of 12 consecutive Covid-19 deaths in Hamburg, Germany, revealed deep venous thrombosis in 7 of 12 patients (58%); venous thromboembolism was not suspected before their deaths. In four patients, pulmonary embolism was the direct cause of death (Wichmann, D. et al (2020)). Risk of death is highest among the elderly and patients with comorbidities.

Covid-19 mortality is believed to be much higher than official numbers reflect, particularly in the early months of the pandemic, which overlapped with the end of the 2019-2020 flu season and reporting mechanisms were not standardized. Excess mortality may provide some additional information. According to EuroMOMO network data, by age group, the cumulative proportion of excess mortality in for 24 participating European countries/federal states for weeks 1 to 18 of 2020 was reported as follows: 15-44 years, 1%; 45-64 years, 8%; 65-74 years, 13%; 75-84, 30%; 85 years or older, 48% (Vestergaard, L.S. et al (2020)). In the U.S., the median estimated number of excess all-cause deaths between January and October 2020 was 299,028. Two-thirds of excess deaths during that period (66.2%; n=198,081) were attributed to Covid-19, while the remainder were linked to other causes (Rossen, L.M. et al (2020)).U.K. researchers conducted a modeling study to estimate the overall impact of Covid-19 on mortality during government-mandated lockdowns. This includes not only deaths directly caused by the viral infection, but also excess deaths in individuals indirectly affected by the pandemic, e.g., by altered access to health services; the physical, psychological and social effects of distancing; or adverse economic changes. They estimated one-year mortality under various scenarios including full suppression, partial suppression, mitigation and doing nothing. Excess deaths in the U.K. under these scenarios ranged from 2-7 excess deaths with full suppression to between 18,374 and 73,498 in a mitigation scenario, and would be between 146,996 to 587,982 under a policy of "do nothing" (Banerjee, A. et al (2020)). Moreover, disruption of health services and redirection of resources to Covid-19 that would otherwise be deployed to the prevention and treatment of other infectious diseases could have a significant impact in low-resource settings. Assuming an R0 of 3.0, a modeling study shows that deaths due to HIV, tuberculosis and malaria in high-burden settings could increase over five years by up to 10%, 20% and 36%, respectively, compared with if there was no Covid-19 pandemic (Hogan, A.B. et al (2020)).

Economic Impact

In an intricately intertwined global economy, the costs of disruption due to the Covid-19 pandemic are becoming starkly apparent. This unprecedented event has interrupted global trade and supply chains, depressed asset prices, and forced multinational corporations to make difficult decisions based on limited and constantly evolving information (Ayittey, F.K. et al (2020)).

The eventual impact of the Covid-19 pandemic on industries including tourism, manufacturing, commerce and trade, as well as its impact on global supply chains, has been and will continue be vast, beginning in China and ultimately at the global level. According to one estimate, China's GDP year-on-year growth during Q1 2020 would be down at least 4.5%, while global GDP would be suppressed by approximately 0.42% during Q1. This is comparable to the World Bank's estimates of global GDP loss due to a severe influenza outbreak: 0.5%, equivalent to USD 300 billion, and dwarfs the losses attributed to the 2002-03 SARS outbreak, when China played a much smaller role in the global economy (Ayittey, F.K. et al (2020)).

The economic impact of the Covid-19 pandemic and resulting partial economic shutdown in the U.S. was estimated at 5% of GDP per month, equivalent to USD two trillion for a two-month shutdown (Walensky, R.P. et al (2020); Policy brief - The cost of COVID-19: A rough estimate of the 2020 US GDP impact (Mercatus Center at George Mason University, April 2020)). Assuming successful containment by fall of 2021, Harvard University economists have projected that the economic impact of the Covid-19 pandemic in the U.S. will be USD 16 trillion (Cutler, D.M. et al (2020)).

The cost to low- and middle-income countries (LMICs) is also significant. A WHO modeling study showed that total health care resources (human resources, commodities and capital inputs) to address Covid-19 in 73 LMICs at current transmission rates (as of June 26, 2020) over a four-week period would incur costs of USD 52.45 billion. If transmission rates were to decrease by 50%, this cost would be USD 33.08 billion, whereas if transmission were to increase by 50%, cost would increase to USD 61.92 billion (Edejer, T.T.-T. et al (2020)).

The economic impact of Covid-19 at the individual patient level has been estimated by FAIR Health, using private U.S. healthcare claims data. Nationally, the median charge amount for hospitalization of a COVID-19 patient ranged from USD 34,662 for the 23-30 age group to USD 45,683 for the 51-60 age group. Males were associated with a larger share of the distribution of COVID-19 claim lines than females (54% vs 46%). The 50-61 age group accounted for the largest share by age (29.9%), while children (0-18 years) accounted for just 1.5% (Key characteristics of Covid-19 patients - Profiles based on analysis of private healthcare claims (FAIR Health brief, July 14, 2020)).

Diagnosis

During the SARS epidemic, approaches to diagnostic testing include serologic detection, virus isolation in cell culture, electron microscopy and detection of viral RNA by molecular methods. Both ELISA and immunofluorescent serologic tests for detecting coronavirus antibodies were developed (Suresh, M.R. et al (2008)). The availability of RNA sequence information on a number of strains of SARS viruses facilitated the subsequent development of rapid diagnostic tests. Molecular tests based on reverse transcription polymerase chain reaction (RT-PCR) detect viral RNA. A comparison of molecular and serological tests employed during the SARS epidemic indicated increased sensitivity and specificity for molecular assays (Caruana, G. et al (2020).

Two-step conventional and one-step quantitative RT-PCR techniques were routinely used during the SARS outbreak (Peiris, J.S. et al (2008)). A report from the CDC indicated that real-time RT-PCR was more sensitive than conventional RT-PCR, potentially providing a useful technique for detecting virus in the early phases of the diseases, when virus titer was low (Emery, S.L. et al (2004)). ELISA detection of anti-nucleocapsid protein (NP) antibodies, which peak early in infection, was identified by Canadian investigators as a more reliable and specific method of diagnosing SARS (Suresh,

Various diagnostic tests have been used in the detection of MERS-CoV infection, including serological assays, immunofluorescence assays, ELISA, protein microarray, micro-neutralization assays, Western blot--all of which have limitations (Banik, G.R. et al (2015))--and RT-PCR, the latter being most specific and sensitive (Skariyachan, S. et al (2019)). WHO recommends that screening RT-PCR target the upE gene, and that positive samples be retested targeting the ORF1a, ORF1b or N gene. Testing should use samples obtained from the lower respiratory tract, e.g., bronchoalveolar lavage or tracheal aspirate, where viral load is greatest (Banik, G.R. et al (2015); Zumla, A. et al (2015)). However as the procedure for collecting these specimens is invasive, upper respiratory specimens are sometimes used instead (Chan, J.F. et al (2015)).

Researchers at the University of Texas and NIH have developed asymmetric five-primer reverse transcription loop-mediated isothermal amplification (RT-LAMP) assays for the detection of MERS-CoV. The RT-LAMP assays are designed to amplify MERS-CoV genomic loci located within the ORF1a and ORF1b genes and the upE gene, and will enable the development of portable point-of-care diagnostics (Bhadra, S. et al (2015)).

In December 2019, a novel coronavirus, later identified as SARS-CoV-2, was first identified in samples taken from three patients with acute respiratory disease in Wuhan, China. The genetic sequence of SARS-CoV-2 was made available to the WHO on January 12, 2020, facilitating the production of specific diagnostic PCR tests to detect the novel coronavirus infection (Hui, D.S. et al (2020); Zhu, N. et al (2020)). The virus was first isolated from bronchoalveolar lavage fluid; however, viral RNA has also been detected in blood and stool samples (Wang, W. et al (2020)). With increased experience, the most commonly used diagnostic samples are those taken from the upper (nasopharyngeal) or lower (induced sputum, endotracheal aspirates, bronchoalveolar lavage) respiratory tract (Murthy, S. et al (2020); Caruana, G. et al (2020)). The Beijing Center for

Disease Prevention and Control and the University of Hong Kong (Chu, D.K.W. et al (2020)) as well as several Chinese biotech companies quickly developed the first nucleic acid amplification tests (NAATs), which were soon improved upon. RT-PCR, RT-LAMP, RT-insulated isothermal PCR (RT-iiPCR) and one-step rRT-PCR assays diagnose SARS-CoV-2 genetic material (Pang, J. et al (2020)). Quantitative RT-PCR based assays need expensive lab instrumentation and are usually conducted in public health laboratories.

On February 5, 2020, the U.S. FDA issued an emergency use authorization (EUA) that would allow emergency use of the CDC's own 2019-nCoV Real-Time RT-PCR Diagnostic Panel (FDA takes significant step in coronavirus response efforts, issues emergency use authorization for the first 2019 novel coronavirus diagnostic (FDA news release, February 4, 2020)), a RT-PCR test for detection of SARS-CoV-2 from respiratory secretions (nasal or oral swabs). The CDC's diagnostic was initially plagued with a high rate of inconclusive or invalid results (Sharfstein, J.M. et al (2020)). Covid-19 PCR tests in general have false-negative rates in the range of 20-67%, depending upon the quality and timing of testing (Wiersinga, W.J. et al (2020)). The National Institutes of Health has established the RADx initiative to stimulate and support the development, production scale-up and deployment of accurate and rapid new Covid-19 diagnostic tests. One objective of the program is that by December 2020, approximately 2% of the U.S. population (6 million persons) can be tested each day. Another goal is specifically to improve access to testing in underserved and vulnerable sectors of the U.S. population (Tromberg, B.J. et al (2020)).

Hong Kong researchers developed three different PCR assays targeting the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp)/helicase (Hel), spike (S) and nucleocapsid (N) genes, and compared each of them with the RdRp-P2 assay used in many European laboratories. They found that the COVID-19-RdRp/Hel assay did not cross-react with other human-pathogenic coronaviruses and respiratory pathogens in cell culture and clinical specimens; in contrast, the RdRp-P2 assay did cross-react with SARS-CoV in cell culture (Chan, J.F. et al (2020)). In March, WHO issued diagnostic guidelines recommending NAATs targeting RdRp, E, N and S genes, with various potential combinations (Caruana, G. et al (2020)).

In July 2020, the FDA granted the first EUA for pooled sampling in diagnostic testing for Covid-19. The authorization was granted to Quest Diagnostics for its Quest SARS-CoV-2 rRT-PCR test, to be used with pooled samples containing up to four individual swab specimens collected under observation. Sample pooling allows for more people to be tested quickly using fewer testing resources. Sample pooling does this by allowing multiple individuals to be tested at once. The samples collected from the individuals are then tested in a pool or batch using just one test, rather than running each individual sample on its own test. If the pool is positive, it means that one or more of the individuals tested in that pool may be infected, so each of the samples in that pool are tested again individually. Because the samples are pooled, it is expected that fewer tests will be run overall, meaning fewer testing supplies are used and more tests can be run at the same time allowing patients to receive their results more quickly in most cases. This testing strategy is most efficient in areas with low prevalence, when most results are expected to be negative (Coronavirus (COVID-19) update: FDA issues first emergency authorization for sample pooling in diagnostic testing (FDA news release, July 18, 2020)).

In the U.S., Mammoth Biosciences and Sherlock Biosciences are using CRISPR (clustered regularly interspaced short palindromic repeats)-Cas12 technology to develop rapid point-of-care SARS-CoV-2 tests (Fast, portable tests come online to curb coronavirus pandemic (Nature Biotechnology News, March 23, 2020)). Mammoth scientists have created the SARS-CoV-2 DETECTR, a CRISPR-Cas12 based lateral flow assay that detects SARS-CoV-2 from extracted patient sample RNA and takes 30 minutes to perform. The assay involves simultaneous reverse transcription and isothermal amplification using loop-mediated amplification (RT-LAMP) from RNA extracted from nasopharyngeal or oropharyngeal swabs in universal transport media. This is followed by Cas12 detection of predefined coronavirus sequences and then cleavage of a reporter molecule confirms detection of the virus. Sherlock Biosciences developed the SHERLOCK CRISPR SARS-CoV-2 test, which works by programming a CRISPR molecule to detect the specific genetic signature for SARS-CoV-2 in a nasal, nasopharyngeal or oropharyngeal swab or specimen of bronchoalveolar lavage. When the signature is found, the CRISPR enzyme is activated and releases a detectable signal. In May 2020, Sherlock received an

EUA for the test kit, which provides results in less than one hour (First CRISPR test for the coronavirus approved in the United States (Nature News, May 8, 2020)).

Rapid diagnostics now include serological tests that screen for immunoglobulins generated soon after a primary infection. IgM antibodies are detectable within 5 days of infection and increase for 2-3 weeks thereafter. IgG antibodies can be detected approximately 14 days after symptom onset. In both cases, antibody levels correlate with severity of infection (Wiersinga, W.J. et al (2020)). A wide variety of antibody tests for SARS-CoV-2, including point-of-care assays and high-throughput enzyme immunoassays, have been given emergency use authorization by the FDA (qSARS-CoV-2 IgG/IgM Rapid Test - Letter of Authorization (FDA news release, April 1, 2020)); however, only high-quality assays with sensitivity >95% and specificity of at least 98% should be used (Caruana, G. et al (2020)).

In August 2020, the FDA issued an EUA to Abbott Diagnostics for its BinaxNOW COVID-19 Ag Card, a rapid point-of-care diagnostic that uses lateral flow technology to detect SARS-CoV-2 nucleocapsid protein antigens in a nasal swab sample. The credit card-sized device produces results in just 15 minutes, and can be used in doctors' offices, emergency rooms and some schools to detect acute Covid-19 infection (BinaxNOW COVID-19 Ag Card emergency use authorization letter (Food and Drug Administration, August 26, 2020)).

In mid-November, the FDA issued an EUA to Lucira Health for the Lucira COVID-19 All-In-One Test Kit, the first Covid-19 diagnostic test for self-testing at home. It is a molecular (real-time loop mediated amplification reaction) single-use test to detect SARS-CoV-2 and provides results in 30 minutes or less. It is authorized, by prescription only, for home use with self-collected nasal swab samples in individuals age 14 and older who are suspected of having Covid-19. The test can also be used in the health care setting.

Patients testing positive for Covid-19 on PCR should undergo imaging studies in order to detect lung damage at the early stages. Non-contrast-enhanced chest computed tomography (CT) plays an important role at this stage of diagnosis, and enables the detection of bilateral, multifocal patchy ground glass opacities, which are characteristic chest CT imaging features of Covid-19 pneumonia (Xu, X. et al (2020); Li, Y. et al (2020)). Patients should also be tested for influenza and other viruses, as coinfection is associated with worse outcomes (Yang, Y. et al (2020)).

Differential Diagnosis

Pneumonia of other viral or bacterial origin--especially Streptococcus pneumonia, Haemophilus influenzae, Moraxella catarrhalis, methicillin-resistant Staphylococcus aureus and Legionella spp.--were included in the differential diagnosis of SARS. Other febrile viral diseases included in the differential diagnosis were seasonal and avian influenza, respiratory syncytial virus, varicella zoster virus, human metapneumovirus and hantavirus. When appropriate, other epidemic or population-wide diseases were taken into consideration, e.g. smallpox, tularemia, anthrax, viral hemorrhagic fever or plague (Cleri, D.J. et al (2010)).

In the case of Covid-19, the differential diagnosis includes most of the aforementioned infections as well as noninfectious diffuse pulmonary diseases, e.g., dermatomyositis or vasculitis. Travel history and contact tracing may help to inform the diagnosis (Tian, X.L. et al (2020); Yang, Y. et al (2020)). In anticipation of the 2020-21 flu season, various nucleic acid tests were approved in the U.S. for the simultaneous detection and differentiation of SARS-CoV-2, influenza A virus, and/or influenza B virus as well as, in some cases, multiple other respiratory viral and bacterial organisms (Coronavirus (COVID-19) update: FDA authorizes additional COVID-19 combination diagnostic test ahead of flu season (Food and Drug Administration news release, July 2, 2020)).

Prevention

Without effective drugs or vaccines against the infectious agents (Li, G. et al (2020)), society-level interventions such as quarantining, community containment, case identification and

contact tracing are the most effective means of controlling a coronavirus outbreak with epidemic potential (Wilder-Smith, A. et al (2020); Alwan, N.A. et al (2020)). Although authorities may be reluctant to impose these measures due to their economic and social impact, the success of these strategies was demonstrated during the SARS outbreak in Singapore, where application of infection control measures resulted in a decrease in R0 (secondary infection rate) from 7 at week 1 to <1 after week 2 (Cleri, D.J. et al (2010)). Soon after the Covid-19 outbreak began to expand, Chinese authorities imposed restrictions on movement in and around Wuhan, the major air and train transportation hub of central mainland China. Transportation and activities throughout the country were subsequently limited (Wu, Z. et al (2020)). Similar measures were implanted in Europe during the first wave of the pandemic and were successful in reducing the R0 to below 1 (Flaxman, S. et al (2020)). Based on assumptions of exponential growth of the outbreak (estimated R0 = 2.68), in the time until a vaccine is widely available, WHO-linked epidemiology experts recommended stringent controls in order to prevent independent, self-sustaining outbreaks in countries around the world (Wu, J.T. et al (2020)). This is especially important given the increasingly clear role of asymptomatic individuals in spreading Covid-19.

On the personal level, hygiene measures are recommended to prevent the spread of disease in situations where individuals are in contact with patients, potentially infected individuals or contaminated fomites (Chen, Y. et al (2020)). These include maintaining physical distance of at least 1 m, use of masks or other facial coverings, and eye protection (Chu, D.K. et al (2020); Lerner, A.M. et al (2020)). Washing hands with soap and water or with alcohol-based hand rubs is effective for interrupting virus transmission. In general, coronaviruses are able to survive on metal, glass and plastic surfaces at room temperature for up to nine days, but can be inactivated by disinfection with ethanol (62-71%), hydrogen peroxide (0.5%) or sodium hypochlorite (0.1%) (Kampf, G. et al (2020)). The MERS virus is capable of surviving in the environment for up to 48 hours at 20°C and for 24 hours at 30°C (Chan, J.F. et al (2015)). The SARS-CoV-2 virus is stable and viable on surfaces made of plastic or stainless steel for up to 72 hours, on cardboard for up to 24 hours, and on copper for up to four hours. The virus is viable in aerosols for at least three hours (van Doremalen, N. et al (2020)). Personal protective equipment, including eye protection, is thus recommended for health care personnel, as well as surgical masks or N95 disposable filtering respirators (Huang, C. et al (2020)). Airborne precautions should be applied especially when performing aerosol-generating procedures such as intubation (Paules, C.I. et al (2020)). All potentially infectious specimens should be handled and transported with caution, and must be tested in laboratories meeting WHO BSL3 standards (Chan, J.F. et al (2015)).

As a result of the SARS outbreak, WHO revised the rules for reporting infectious diseases by its member states. The previous reporting requirements, formulated in 1951, required reporting for plague, cholera and yellow fever only, and the resulting delay in reporting cases early in the outbreak was likely to have contributed to its rapid spread (Wu, Z. et al (2020)). The efficient and collaborative international response to the MERS outbreak beginning in 2012, and again to the Covid-19 outbreak in late 2019, testifies to the improvements made (Chan, J.F. et al (2015); Paules, C.I. et al (2020)). In 2017, WHO placed SARS-CoV and MERS-CoV on its Priority Pathogen list, with the goal of galvanizing research and development into countermeasures against CoVs (Paules, C.I. et al (2020)).

As the three major coronavirus outbreaks have clearly demonstrated, increasing overlap between human and animal ecosystems provides greater opportunities for viruses to cross the species barrier. Prevention of future outbreaks of zoonotic disease requires improved coordination between experts in human and veterinary medicine as well as stricter laws governing the raising, transportation, slaughter and sale of wild animals (Wang, R. et al (2020); Yang, Y. et al (2020)).

Chemoprophylaxis

Studies such as Mexico's PHYDRA trial (NCT04318015) and the U.K.'s COPCOV trial (NCT04303507) are evaluating the potential efficacy of the antimalarial drugs chloroquine/hydroxychloroquine for chemoprophylaxis in health care personnel who are in contact with Covid-19 patients. The Indian Council of Medical Research recommends the prophylactic use of hydroxychloroquine (HCQ) by all health care professionals in that country

who are in contact with patients known or suspected to be infected with SARS-CoV-2, as well as for asymptomatic household contacts of confirmed cases (Agrawal, S. et al (2020); Rathi, S. et al (2020)). In June, U.S. and Canadian researchers published results of a randomized, double-blind, placebo-controlled trial evaluating HCQ for postexposure prophylaxis. They enrolled 821 asymptomatic adults who had a high- or moderate-risk household or occupational exposure to someone with confirmed Covid-19, i.e., at a close distance for a period of >10 minutes while wearing insufficient personal protective equipment. Subjects were treated with placebo or active drug within four days of exposure. The incidence at 14 days of new illness compatible with Covid-19 did not differ significantly between subjects receiving HCQ (11.8%) versus placebo (14.3%) (Boulware, D.R. et al (2020)). Another U.S. study failed to demonstrate efficacy for HCQ, taken daily for 8 weeks as a pre-exposure prophylaxis strategy, when used by hospital-based health care workers. The study was terminated early on the basis of futility (Abella, B.S. et al (2020)).

Appili Therapeutics is conducting a phase II study in Canada and the U.S. to evaluate the broad-spectrum antiviral agent favipiravir as a preventative measure against Covid-19 outbreaks in long-term care facilities. Approximately 760 participants will be enroll in the partially blinded, cluster-randomized, placebo-controlled trial, the primary objective of which will be to evaluate the efficacy of oral favipiravir for 25 days compared with placebo as a prophylaxis to prevent Covid-19 outbreaks in these high-risk settings. The primary endpoint will be outbreak control, defined as no new cases of Covid-19 in residents for 24 consecutive days up to day 40 after the start of prophylaxis, with secondary objectives including measures of safety, rates of infection, disease progression and fatality rates.

Vitamin D is known to enhance the production of antimicrobial peptides (cathelicidins and defensins) in the respiratory epithelium, and may help tamper the inflammatory response to infection by modulating immune cell function (Laird, E. et al (2020); Grant, W.B. et al (2020)). In a systematic review and meta-analysis conducted prior to the Covid-19 pandemic, vitamin D supplementation was shown to be safe and provide some protection against acute respiratory tract infections. The reviewers analyzed individual participant data (N=10,933) obtained in 25 randomized controlled trials. Protective effects were observed with daily or weekly doses of vitamin D, albeit not with bolus dosing, and were strongest in individuals with the most severe vitamin D deficiency at baseline (25(OH)D < 25 nmol/L) (Martineau, A.R. et al (2017)). A growing body of circumstantial evidence links vitamin D status with outcomes in Covid-19 patients. The administration of vitamin D supplements to vulnerable individuals, such as nursing home residents, may be warranted during the current pandemic (Mitchell, F. (2020)), although relatively high doses are required. For chemoprophylaxis, at-risk individuals should consider taking a loading dose of 10,000 IU/day of vitamin D3 for a few weeks, decreasing to 5000 IU/day, with a goal of elevating 25(OH)D concentrations above 40-60 ng/mL (100-150 nmol/L) (Grant, W.B. et al (2020)). The COVIDENCE UK study, now recruiting volunteers, will assess how diet and lifestyle factors--including vitamin D status--affect the transmission of SARS-CoV-2, severity of Covid-19 symptoms, speed of recovery and long-term effects.

Vaccines

The successful containment of coronavirus epidemics in farm animals by vaccines, including those based on either killed or attenuated virus, supports the initiation of vaccine development. However, it remains unknown whether coronavirus infections in humans produce a lasting immune response that could be replicated with a vaccine. Nonetheless, given the rapid propagation of SARS-CoV-2 throughout the global population and the complete lack of preexisting immunity in humans to this highly contagious virus, a vaccine is widely accepted as the only tool available to enable an eventual return to normalcy. The pandemic has created an urgent need to develop and test one or more safe and effective vaccines, and then to manufacture and quickly distribute them in quantities sufficient to immunize a sufficiently large number of individuals to provide herd immunity, which would protect the entire global community (Corey, L. et al (2020)). Assuming an R0 of 2.2, 55% of the population would have to be exposed (through infection or vaccination) in order to achieve herd immunity; if R0 is 5.7, this threshold increases to 82% (Sanche, S. et al (2020)). A challenge of this magnitude requires full

and unprecedented collaboration from industries, governments and academia (Corey, L. et al (2020)). Experts have stressed that there is no evidence that sufficient population-wide protection can be achieved through widespread natural infection. It is unclear how long acquired immunity against SARS-CoV-2 will last; case reports show that the virus is capable of reinfecting individuals who have already had the disease, although the frequency of reinfection remains unknown (Alwan, N.A. et al (2020)).

The S protein is widely regarded as one of the most promising targets for coronavirus vaccine development (Li, F. et al (2019); Song, Z. et al (2019)), due to its ability to induce neutralizing antibodies, and hence is being targeted for the development of anti-MERS-CoV (Yong, C.Y. et al (2019)) as well as anti-SARS-CoV-2 vaccines. Upon emergence of SARS-CoV-2, both the S and N proteins were identified as potential vaccine antigens, based on their previously demonstrated ability to induce potent and long-lived immune responses in SARS-CoV (Ahmed, S.F. et al (2020); Le, T.T. et al (2020)).

Vaccine platforms with potential application in human coronavirus vaccine development include gene-based vaccines (e.g., nucleic acid DNA and mRNA, replicating and non-replicating viral vectors), protein-based vaccines (e.g., whole inactivated virus or recombinant protein subunits), peptide-based and virus-like particle vaccines (Le, T.T. et al (2020); Mostafa, A. et al (2020)). DNA- and mRNA-based platforms have the greatest potential for rapid development in an outbreak situation. They can be made quickly because they require no culture or fermentation, being based instead on a viral sequence (Lurie, N. et al (2020); Corey, L. et al (2020); Graham, B.S. (2020)). The two main types of RNA vaccines are non-replicating mRNA and self-amplifying (also known as replicon) RNA vaccines. mRNA vaccines are designed to induce the cytoplasmic expression of chimeric mRNAs containing curated ORF viral sequences. Once injected, the delivered mRNA is processed by immune cells and begins to produce the targeted functional protein (generally S) directly via translation, at the same time activating other immune cells (B cells and T cells) to recognize the newly produced viral protein and to generate antibodies (Wang, F. et al (2020)). Adjuvants can be added to these vaccines to boost and prolong the immune response (Graham, B.S. (2020); Le, T.T. et al (2020)).

Several companies are focusing on nucleic acid vaccine platforms for rapid development of a Covid-19 vaccine (Corey, L. et al (2020)). One such vaccine is mRNA-1273, an mRNA vaccine against SARS-CoV-2 encoding for a pre-fusion, stabilized form of the S protein. The vaccine candidate was selected by Moderna in collaboration with investigators from Vaccine Research Center at NIAID and is undergoing an extremely accelerated development timeline. The first clinical batch of the vaccine was completed on February 7, 2020 and underwent analytical testing; it was shipped to NIH on February 24, just 42 days from sequence selection, and the first participant in the NIAID-led phase I study of mRNA-1273 was dosed on March 16. The vaccine has received fast-track designation from FDA. In July, Moderna reported results of a phase I, dose-escalation, open-label trial including 45 healthy adults (18-55 years), who received two doses of the mRNA-1273 vaccine (25, 100 or 250 mcg) at a 28-day interval. Following the first dose, antibody responses increased in all participants and were higher in those receiving higher doses; further increases were registered following the second dose. The most common adverse events were fatigue, chills, headache, myalgia, and pain; systemic adverse events were more frequent after the second dose, and were severe in three patients at the highest dose level. Further evaluation of mRNA-1273 was deemed to be warranted (Jackson, L.A. et al (2020)). In late July, Moderna announced the initiation of a phase III study, named COVE (NCT04470427), in collaboration with NIAID and BARDA, to evaluate mRNA-1273. The randomized (1:1), placebo-controlled trial, the protocol of which follows the FDA guidance on clinical trial design for COVID-19 vaccine studies, enrolled more than 30,000 participants in the U.S. and has a primary endpoint of prevention of symptomatic Covid-19 disease. Key secondary endpoints include prevention of severe Covid-19 disease (as defined by the need for hospitalization) and prevention of infection by SARS-CoV-2. In November, Moderna released positive findings of an interim analysis of the study. This first interim analysis was based on 95 cases of Covid-19, of which 90 cases were observed in the placebo group versus 5 cases observed in the mRNA-1273 group, resulting in a point estimate of vaccine efficacy of 94.5%. Regarding the secondary endpoint, 11 severe cases of Covid-19 were reported, all in the placebo group. There were no significant safety concerns and a review of solicited adverse events indicated that the vaccine

was generally well tolerated. The majority of adverse events were mild or moderate in severity. Based on these interim safety and efficacy data, Moderna has requested emergency use authorization in the U.S. and will file for conditional approval in the E.U. Moderna also plans to submit applications for authorizations to global regulatory agencies. By year-end, the company expects to have approximately 20 million doses of mRNA-1273 ready to ship in the U.S.

In November, Pfizer and BioNTech announced that their mRNA-based vaccine candidate, BNT-162b2 demonstrated evidence of efficacy against COVID-19 in participants without prior evidence of SARS-CoV-2 infection, based on the first interim efficacy analysis of an ongoing phase III trial (NCT04368728) conducted by an external, independent data monitoring committee. At the point of the interim analysis, 94 cases of Covid-19 had developed among study participants. The case split between vaccinated individuals and those who received the placebo indicates a vaccine efficacy rate above 90%, at seven days after the second dose. This means that protection is achieved 28 days after the initiation of the vaccination, which consists of a two-dose schedule. The DMC did not report any serious safety concerns and recommended that the study continue through the final analysis, which would occur when a total of 164 confirmed Covid-19 cases have accrued. The trial had enrolled 43,538 participants as of the interim reporting date, of whom 38,955 had received a second vaccine dose as of November 8, 2020. Of note, approximately 42% of global participants and 30% of U.S. participants had racially and ethnically diverse backgrounds. On November 18, with 170 confirmed cases of Covid-19 registered, Pfizer announced the final efficacy analysis of that study. The efficacy rate of BNT-162b2 was determined to be 95% in participants without prior SARS-CoV-2 infection (first primary objective) and also in participants with and without prior SARS-CoV-2 infection (second primary objective), in each case measured from 7 days after the second dose. The first primary objective analysis is based on 170 cases of Covid-19, as specified in the study protocol, of which 162 cases were observed in the placebo group versus 8 cases in the BNT-162b2 group. Efficacy was consistent across age, gender, race and ethnicity demographics. The observed efficacy in adults over 65 years was over 94%. There were 10 severe cases of Covid-19 observed in the trial, with 9 of the cases occurring in the placebo group and 1 in the BNT-162b2 vaccinated group. Pfizer and BioNTech announced their plan to submit a request within days to the FDA for an EUA based on the totality of safety and efficacy data collected to date, as well as manufacturing data relating to the quality and consistency of the vaccine. These data also will be submitted to other regulatory agencies around the world. The trial will continue to collect efficacy and safety data in participants for an additional two years. On December 2, the U.K.'s Medicines & Healthcare Products Regulatory Agency (MHRA) granted a temporary authorization for emergency use for BNT162b-2 against Covid-19. This constitutes the first Emergency Use Authorization for the mRNA vaccine worldwide. Administration of the vaccine was expected to begin within a week of this decision.

Coalition for Epidemic Preparedness Innovation (CEPI) provided early funding for Oxford University to develop a vaccine candidate against Covid-19 based on their ChAdOx1 viral vector technology. ChAdOx1 is a replication-deficient simian adenoviral vaccine vector; the platform had previously been used to produce vaccine candidates against influenza, chikungunya and Zika. CEPI's early funding supported the manufacture of Covid-19 vaccine materials required for preclinical and phase I development, enabling Oxford to begin phase I/II studies of their ChAdOx1 nCoV-19 vaccine candidate just six weeks later. In May, the vaccine was licensed to AstraZeneca for global development and distribution. In July, published study results showed that the vaccine, now known as AZD-1222, was well tolerated and generated robust immune responses against the SARS-CoV-2 virus in all 1,077 healthy adult participants, aged 18-55 years. The results confirmed that a single dose of AZD-1222 resulted in a four-fold increase in antibodies to the SARS-CoV-2 virus spike protein in 95% of participants one month after injection. By 28 days after vaccination, neutralizing antibody responses against SARS-CoV-2 were detected in 32 of 35 participants using one assay, and in 35 of 35 participants when measured by another assay. Antibody responses remained high until day 56. There was an increased level of antibodies in 10 subjects who received a second dose of the vaccine, indicating that recipients do not develop immunity to the chimpanzee adenoviral vector. T-cell responses targeting the SARS-CoV-2 spike protein also were markedly increased, peaking 14 days after vaccination, compared with placebo. The level had declined slightly by day 56 of the trial. The T-cell response did not increase in 10 subjects who had a second dose of the vaccine,

which the researchers at Oxford University say is consistent with other vaccines of this kind (Folegatti, P.M. et al (2020)).

CanSino and the Beijing Institute of Biotechnology are also developing an adenoviral vector-based Covid-19 vaccine. The vaccine, a replication-defective Ad5-vectored vaccine expressing the spike glycoprotein of SARS-CoV-2, was evaluated in a phase I safety study enrolling 108 healthy adults. The vaccine was tolerable and immunogenic at 28 days post-vaccination, inducing rapid and specific T-cell responses beginning 14 days post-injection; SARS-CoV-2-specific antibody and T-cell responses were lowest in those subjects with high preexisting Ad5 neutralizing antibody titers. The incidence of adverse effects was high and included injection-site pain, fever, fatigue and headache, although these were generally transient and self-limiting. The investigators concluded that further evaluation of the vaccine was warranted (Zhu, F.C. et al (2020)). In a subsequent phase II trial in 508 subjects, 95% of those enrolled in the high-dose group and 91% in the low-dose group showed antibody responses at 28 days post-immunization. T-cell responses occurred in 90% of the high-dose group and 88% of those getting the low dose. Compared with the younger population, older volunteers generally had significantly lower immune responses, indicating that a second dose may be needed to boost protection in the elderly (Zhu, F.-C. et al (2020)).

In August 2020, the Russian Federation undertook the highly controversial action of issuing a 'registration certificate' for a nationally developed Covid-19 vaccine candidate that had been tested in just 76 people in phase I/II studies. The adenovirus vector-based vaccine, dubbed Sputnik V, was developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Moscow. Albeit the first regulatory approval worldwide for a Covid-19 vaccine, the action was widely denounced by scientists both outside and within the country as being premature and inappropriate, given the extremely small number of doses that had been administered (Russia's approval of a COVID-19 vaccine is less than meets the press release (Science News, August 11, 2020)). In September, the results of two phase I/II studies, which included more detail about the vaccine, appeared in print. The vaccine consists of two components: a recombinant adenovirus type 26 (rAd26) vector and a recombinant adenovirus type 5 (rAd5) vector, each carrying the gene for the SARS-CoV-2 spike glycoprotein. In these studies, rAd26-S and rAd5-S demonstrated a favorable safety profile and induced strong cellular as well as humoral immune responses (Logunov, D.Y. et al (2020)).

Given the rapid increase in and accelerated pace of vaccine development during the Covid-19 pandemic, the WHO designed the SOLIDARITY vaccine trial. This large, international, multisite trial has an adaptive design and will enable the concurrent evaluation of the benefits and risks of various candidate vaccines that are deemed promising. Different candidate vaccines may be available or suitable to enter the trial at different times; for each candidate vaccine, the primary efficacy results are expected within 3-6 months of the vaccine entering the trial. In a novel design, SOLIDARITY will use a shared placebo/control group and a common Core protocol, so that resources allocated to the evaluation of each candidate vaccine are judiciously saved while ensuring a high standard of scientific rigor and efficiency (WHO R&D Blueprint: An international randomised trial of candidate vaccines against COVID-19 (World Health Organization, May 28, 2020)).

In the U.S., the National Institutes of Health established the Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV) partnership and Operation Warp Speed. ACTIV has developed a collaborative framework for prioritizing vaccines as well as drug candidates, including streamlining clinical trials, coordinating regulatory processes and/or leveraging assets among all partners to rapidly respond to the Covid-19 and future pandemics (NIH to launch public-private partnership to speed COVID-19 vaccine and treatment options (National Institutes of Health news release, April 17, 2020)). Operation Warp Speed was launched as a partnership between the U.S. government and industry with the goal of delivering 300 million doses of a safe and effective Covid-19 vaccine by January 2021 (O'Callaghan, K.P. et al (2020)).

Albeit controversial, human challenge studies have been proposed as a method of accelerating the testing of vaccines under conditions of urgency, such as a pandemic. These would be conducted later in the testing process, following the successful completion of safety, dose finding and immunogenicity studies. Challenge studies involve the deliberate infection of

human volunteers with a viral pathogen in order to evaluate efficacy of a candidate vaccine(s), and would entail a significantly shorter timeframe than that needed for standard phase III field trials. Study participation would be limited to previously uninfected individuals deemed to be at low risk of complications or mortality, who would be randomized to receive either an investigational vaccine or placebo in order to detect differences in response to the viral challenge (Eyal, N. et al (2020)). The WHO has published a policy brief outlining key criteria that would need to be satisfied in order for such unconventional studies to be ethically acceptable (Key criteria for the ethical acceptability of COVID-19 human challenge studies - WHO Working Group for Guidance on Human Challenge Studies in COVID-19 (World Health Organization, May 6, 2020)).

A potential risk of any antiviral vaccine, and one that also exists with coronavirus vaccines, is that of vaccine-mediated disease enhancement (Zellweger, R.M. et al (2020)). One such syndrome, known as antibody-dependent enhancement (ADE), occurs when exposure to the virus upregulates the expression of both neutralizing and non-neutralizing antibodies, rendering the individual's immune system more, rather than less, reactive to a secondary infection. ADE has been observed in cats vaccinated against feline infectious peritonitis virus, a member of the coronavirus family. A related syndrome, known as vaccine-associated enhanced respiratory disease (VAERD), may emerge in individuals vaccinated with conformationally incorrect antigens. This results in two major types of immunological phenomena that correlate with VAERD: one is a relatively high ratio of binding antibody to neutralizing antibody. The other is induction of a Th2-driven allergic immune response, which may paradoxically potentiate airway dysfunction and delay viral clearance. Prior to widespread vaccination of citizens, rigorous testing in appropriate animal models and early-stage clinical studies must be conducted to detect the risk of both ADE and VAERD, as well as longer-term studies to determine the risk of enhancement following reexposure to a virus that continues to circulate in the population (Lurie, N. et al (2020); Corey, L. et al (2020); Graham, B.S. (2020)). Vaccine-induced disease enhancement has been observed in experimental animal inoculated against SARS and MERS, leading to concerns that this risk also exists with SARS-CoV-2 vaccines (Zellweger, R.M. et al (2020)).

Development of a MERS vaccine has been facilitated by the recent development of small animal models that effectively replicate MERS-CoV transmission and symptomatic human disease (Schindewolf, C. et al (2019)). In contrast, vaccine research for Covid-19 was initially hindered by the lack of a suitable animal model for testing. Transgenic mice expressing the human ACE2 (hACE2) receptor, first developed during the SARS outbreak, were again bred (Labs rush to study coronavirus in transgenic animals -- some are in short supply (Nature News, March 9, 2020)). Investigators at Beijing Institute of Microbiology and Epidemiology developed an ACE2 humanized mouse model (hACE2) using CRISPR/Cas9 knockin technology and confirmed that infection of these mice with SARS-CoV-2 led to a disease mimicking that in humans (Sun, S.H. et al (2020)). Russian investigators proposed a new mouse model of Covid-19 in which both hACE2 and human TMPRSS2 (hTMPRSS2) would be introduced in the murine genome using CRISPRcas9 technology. The researchers intend to place LoxP sites in front of the hTMPRSS2, creating an inducible hACE2/hTMPRSS2 expression to control the sensitiveness of the mice to infection. In this way, the new mouse model would be safer for research conditions. This murine model, presenting two human genes that are essential for cell invasion of the virus, would better mimic the human syndrome (Soldatov, V.O. et al (2020)).

The following tables present an up-to-date overview of the development of potential coronavirus vaccines against Covid-19 and MERS.

Experimental vaccines for prevention of Covid-19 in active preclinical and clinical development

Drug name	Organizations	Description	Phase
Gam-COVID-Vac	Gamaleya Research Institute of Epidemiology and Microbiology	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of recombinant adenovirus vector encoding SARS - CoV - 2 spike (S)	Registered
BNT-162b2	Pfizer; BioNTech	Human SARS - CoV - 2 (Covid - 19 coronavirus) mRNA vaccine	Pre-Registered
ChAdOx1-nCoV19	AstraZeneca	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of replication - deficient chimpanzee adenovirus Oxford 1(ChAdOx1) vector encoding SARS - CoV - 2 spike (S) gene	Pre-Registered
mRNA-1273	Moderna	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of mRNA encoding S - 2P antigen comprising SARS - CoV - 2 Spike (S) glycoprotein with a transmembrane anchor and an intact S1 - S2 cleavage site, harboring two consecutive proline substitutions at positions 986 and 987 of the S2 subunit; encapsulated in lipid nanoparticles	Pre-Registered
Ad5-nCoV	CanSino Biologics	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of a replication - defective adenovirus type 5 vector encoding SARS - CoV - 2 spike (S) gene	Phase III
CoronaVac	Sinovac; Instituto Butantan	Human SARS - CoV - 2 (Covid - 19 coronavirus) inactivated vaccine; expressed in Vero cells	Phase III
Covovax	Novavax	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising recombinant COVID - 19 spike glycoprotein; encapsulated in nanoparticles	Phase III
IMM-101	Immodulon Therapeutics	Cancer vaccine consisting of heat - killed Mycobacterium obuense (whole cell)	Phase III
MV-130	Inmunotek	Multivalent bacterial vaccine consisting of inactivated Staphylococcus aureus (15%), Staphylococcus epidermidis (15%), Streptococcus pneumoniae (60%), Klebsiella pneumoniae (4%), Branhamella catarrhalis (3%) and Haemophilus influenzae (3%)	Phase III

VAC-31518	Janssen	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of replication - incompetent adenovirus vector serotype 26 (Ad26) encoding SARS - CoV - 2 proteins; produced based on AdVac(R) technology and expressed in human PER.C6® cell line	Phase III
VPM-1002	Vakzine Projekt Management	Tuberculosis vaccine consisting of a live attenuated recombinant Mycobacterium bovis BCG strain with deleted urease C gene (UreC), expressing fusion protein comprising Mycobacterium bovis Ag85B antigen fused to listeriolysin (Hly) from Listeria monocytogenes	Phase III
1088181	China National Pharma Group (SINOPHARM)	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising beta - propiolactone - inactivated SARS - CoV - 2 WIV04 strain; propagated in Vero cells	Phase III
CoVLP	Mitsubishi Tanabe Pharma	Human SARS - CoV - 2 (Covid - 19 coronavirus) plant - derived virus - like particle (VLP) vaccine	Phase II/III
INO-4800	Inovio Pharmaceuticals	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of pGX0001 DNA plasmid encoding for an optimized SARS - CoV - 2 spike glycoprotein sequence and an N - terminal IgE leader sequence, under the control of human cytomegalovirus immediate - early promoter and a bovine growth hormone polyadenylation signal	Phase II/III
CVnCoV	CureVac	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of mRNA encoding the full - length spike (S) protein of SARS - CoV - 2 encapsulated in lipid nanoparticles (LNP)	Phase II
Eftilagimod alfa	Immutep	Soluble fusion protein consisting of human lymphocyte activation gene 3 protein (LAG - 3) dimer fused to the Fc domain of human IgG1 antibody via a linker peptide; produced in CHO cells	Phase II
NasoVAX Seasonal Influenza	Altimmune	Influenza A vaccine consisting of an adenoviral vector encoding hemagglutinin (HA) protein from influenza subtype (H1N1)	Phase II

1098235	Zhifei Longcom	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of recombinant dimer comprising two RBD domains (R319 - K527) of spike protein of SARS - CoV - 2 fused via a disulfide link; expressed in CHO cells	Phase II
AG-0301-COVID19	Osaka University; AnGes	Human SARS - CoV - 2 (Covid - 19 coronavirus) plasmid DNA vaccine	Phase I/II
AG-0302-COVID19	AnGes	Human SARS - CoV - 2 (Covid - 19 coronavirus) plasmid DNA vaccine	Phase I/II
ARCT-021	Arcturus Therapeutics	Human SARS - CoV - 2 (Covid - 19 coronavirus) mRNA vaccine comprising a self - replicating RNA based on STARR technology platform delivered using Lipid - enabled and Unlocked Nucleomonomer Agent modified RNA (LUNAR(R)) platform	Phase I/II
BBIBP-CorV	Beijing Institute of Biological Products	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising beta - propiolactone (BPL) - inactivated SARS - CoV - 2 19nCoV - CDC - Tan - HB02 (HB02) strain; propagated in Vero cells	Phase I/II
BNT-162a1	Pfizer; BioNTech	Human SARS - CoV - 2 (Covid - 19 coronavirus) mRNA vaccine	Phase I/II
BNT-162b1	Pfizer; BioNTech	Human SARS - CoV - 2 (Covid - 19 coronavirus) mRNA vaccine	Phase I/II
BNT-162c2	Pfizer; BioNTech	Human SARS - CoV - 2 (Covid - 19 coronavirus) mRNA vaccine	Phase I/II
Covaxin	Bharat Biotech	Human SARS - CoV - 2 (Covid - 19 coronavirus) inactivated vaccine	Phase I/II
FINLAY-FR-1	Instituto Finlay	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine based on the receptor - binding domain (RBD) of Spike glycoprotein	Phase I/II
GX-19	Genexine	Human SARS - CoV - 2 (Covid - 19 coronavirus) DNA vaccine encoding spike (S) protein of SARS - CoV - 2	Phase I/II
LV-SMENP-DC	Shenzhen Genoimmune Medical Institute	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of dendritic cells modified with lentiviral vectors (NHP/TYF) expressing a SARS - CoV - 2 SMENP minigene encoding multiple viral genes (spike (S), membrane (M), envelope (E), nucleocapsid (N) and protease (P))	Phase I/II

		and immune - stimulating regulatory genes (CNX, GM - CSF and IL - 15); administered together with SARS - CoV - 2 antigens - specific peripheral blood mononuclear cells (PBMC) - derived cytotoxic T lymphocytes (CTLs)	
QazCovid-in	RGE Research Institute Biol Saf Problems	Human SARS - CoV - 2 (Covid - 19 coronavirus) inactivated vaccine	Phase I/II
V-591	Merck & Co.	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising measles vector encoding SARS - CoV - 2 antigens	Phase I/II
V-SARS	Immunitor	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine produced using heat - inactivated plasma from Covid - 19 patients	Phase I/II
ZyCoV-D	Cadila Healthcare (d/b/a Zydus Cadila)	Human SARS - CoV - 2 (Covid - 19 coronavirus) DNA vaccine	Phase I/II
1100340	Imperial College	Human SARS - CoV2 (Covid - 19 coronavirus) vaccine consisting of self - amplifying RNA (saRNA) encoding for the alphaviral replicase and a pre - fusion stabilized SARS - CoV - 2 spike protein, encapsulated in lipid nanoparticles	Phase I/II
1105637	Biological E	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising the receptor binding domain of the spike (S) glycoprotein of SARS - CoV - 2	Phase I/II
1094634	Chinese Academy of Medical Sciences	Human SARS - CoV - 2 (Covid - 19 coronavirus) inactivated vaccine	Phase I/II
1080989	Sanofi	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine produced using a baculovirus expression vector system (BEVS)	Phase I/II
1105779	Serum Institute of India; SpyBiotech	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine based on Hepatitis B surface antigen (HBsAg) virus - like particles (VLPs) displaying the SARS - CoV - 2 Spike protein on the surface; produced with the proprietary SpyCatcher/SpyTag technology	Phase I/II
ARCoV	Academy of Military Medical Sciences; Walvax Biotechnology	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of mRNA encoding receptor binding domain (RBD, aa 319 - 541) of SARS -	Phase I

		CoV - 2 encapsulated in lipid nanoparticles (LNP)	
COH04S1	City of Hope National Medical Center	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of synthetic modified vaccinia Ankara (MVA) encoding spike (S) glycoprotein and nucelocapsid proteins of SARS - CoV - 2	Phase I
COVAX-19	Vaxine	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine based on SARS - CoV - 2 spike (S) glycoprotein	Phase I
Covax-19	GeneCure	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of a replication - defective genetically engineered simian immunodeficiency virus (SIV) pseudotyped with SARS - CoV - 2 antigens; generated using SimVec platform technology	Phase I
GRAd-COV2	ReiThera	Human SARS - CoV - 2 (COVID - 19 coronavirus) vaccine based on a proprietary replication - defective gorilla adenoviral vector (GRAd) encoding the full - length SARS - CoV - 2 spike protein comprising the K986P and V987P trimer stabilizing mutations; linked at the C terminus to a HA tag	Phase I
S-2P	Medigen Vaccine Biologics (MVC)	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine based on recombinant mutant Spike protein (comprising a 682 - RRAR - 685 to GSAS mutation in the S1/S2 furin - recognition site, and a 986 - KV - 987 to PP mutation)	Phase I
SCB-2019	Clover Biopharmaceuticals	Human SARS - CoV - 2 (Covid - 19 coronavirus) subunit trimer vaccine comprising recombinant COVID - 19 spike glycoprotein; produced using Trimer - Tag(R) technology	Phase I
UB-612	COVAXX	Human SARS - CoV - 2 (Covid - 19 coronavirus) multi - peptide vaccine consisting of fragments from the receptor binding domain (RBD) of the SARS - CoV - 2 Spike protein and Th and CTL epitope peptides derived from the S2 Spike subunit, membrane and nucleoprotein regions	Phase I
UQ/CSL-V451	CSL; University of Queensland	Human SARS - CoV - 2 (Covid - 19 coronavirus) subunit vaccine	Phase I

		consisting of recombinant Spike (S) glycoprotein	
V-590	Merck & Co.	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of replicating vesicular stomatitis vector (rVSV) harboring a deletion of glycoprotein (G), encoding SARS - CoV - 2 spike (S) gene (rVSVdeltaG - SARS - CoV - 2)	Phase I
VXA-CoV2-1	Vaxart	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising replication incompetent adenovirus 5 (rAd) vector encoding a SARS - COV - 2 antigen and a dsRNA TLR3 ligand as an adjuvant	Phase I
bacTRL-Spike	Symvivo	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of probiotic composition comprising Bifidobacterium longum transduced with a DNA plasmid encoding spike protein from SARS - CoV - 2	Phase I
hAd5-S-Fusion+N-ETSD	ImmunityBio	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of an E1, E2b, E3 - deleted adenovirus type 5 vector encoding SARS - CoV - 2 spike (S) and nucleocapsid (N) gene with an enhanced T - cell stimulation domain	Phase I
1098305	University of Queensland	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of recombinant fusion proteins produced with the Molecular Clamp technology	Phase I
1084319	Shenzhen Genoimmune Medical Institute	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of artificial antigen presenting cells (aAPC) carrying SARS - CoV - 2 antigens	Phase I
Immuvac	Cadila Pharmaceuticals	Poly - TLR agonist polyantigenic vaccine containing heat - killed Mycobacterium W	Clinical
AdCOVID	Altimmune	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of adenovirus type 5 vector encoding SARS - CoV - 2 spike (S) gene	IND Filed
CORVax12	OncoSec Medical	Composition comprising human SARS - CoV - 2 (Covid - 19 coronavirus) DNA vaccine encoding SARS - CoV - 2 spike and a plasmid encoding human interleukin - 12 (IL - 12) (TAVO(TM))	IND Filed

T-COVID	Altimmune	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine based on adenovirus type 5 vector	IND Filed
AAVCOVID	General Hospital Corp.	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of adeno - associated viral (AAV) vector encoding Spike glycoprotein (S) of SARS - CoV - 2	Preclinical
ACvac1	Axon Neuroscience	Human SARS - CoV - 2 (Covid - 19 coronavirus) peptide vaccine based on the Spike (S) glycoprotein	Preclinical
AKS-452	Akston	Human SARS - CoV2 (Covid - 19 coronavirus) vaccine consisting of the receptor binding domain (RBD) from SARS - CoV - 2 S protein fused to an IgG Fc domain	Preclinical
AV-COVID-19	Aivita	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of autologous dendritic cells loaded with SARS - CoV - 2 antigens	Preclinical
AVI-205	Abvision (AVI)	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine based on the Spike protein, produced on the ImmunoBuster - II(TM) platform	Preclinical
BC-PIV SARS-CoV-2	MediciNova; BioComo; Mie University	Human SARS - CoV2 (Covid - 19 coronavirus) vaccine consisting of a non - transmissible human parainfluenza virus type 2 (hPIV2) with the F - envelope gene deleted (BC - PIV) and carrying a mutated SARS - CoV2 spike (S) gene	Preclinical
BVX-0320	BioVaxys	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of haptenized spike glycoprotein (S) of SARS - CoV - 2	Preclinical
CDX-005	Codagenix	Live - attenuated human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine	Preclinical
COVID-eVax	Rottapharm Biotech; Takis	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising a DNA vector encoding a portion of spike (S) protein of SARS - CoV - 2	Preclinical
CoVepiT	OSE Immunotherapeutics	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine based on optimized peptides from SARS - CoV - 2	Preclinical
CorVax	Vaxil	Human SARS - CoV - 2 (Covid - 19 coronavirus) multi - epitope peptide vaccine comprising VXL - 301, VXL -	Preclinical

		302 and VXL - 303 peptides; generated using VaxHit(TM) platform	
Coravax	Thomas Jefferson University; Bharat Biotech	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising killed rabies virus vector encoding SARS - CoV - 2 spike (S) gene	Preclinical
Covigenix	Entos Pharmaceuticals	Pan - coronavirus plasmid DNA vaccine comprising in silico - optimized and conserved regions of the SARS - CoV - 2 spike protein; based on the Fusogenix platform	Preclinical
DPX-COVID-19	IMV Inc.	Human SARS - CoV - 2 (Covid - 19 coronavirus) peptide vaccine formulated with the DepoVax(TM) vaccine delivery technology	Preclinical
DS-5670	Daiichi Sankyo	Human SARS - CoV - 2 (Covid - 19 coronavirus) mRNA vaccine	Preclinical
ELI-005	Elicio Therapeutics	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising recombinant SARS - CoV - 2 Spike receptor binding domain (RBD) protein and the amphiphile adjuvant ELI - 004 (CpG DNA conjugated to diacyl lipid (AMP - CpG))	Preclinical
EXG-5003	Elixirgen Therapeutics	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising self - replicating RNA (srRNA) expressing the receptor binding domain (RBD) of the SARS - CoV - 2 spike protein	Preclinical
GEO-CM01	GeoVax Labs	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of virus - like particles (VLPs) based on recombinant modified vaccinia Ankara (MVA) vector encoding SARS - CoV - 2 spike glycoprotein (S) envelope protein (E) and matrix protein (M); generated using GV - MVA - VLP(TM) vaccine platform	Preclinical
HDT-301	Gennova Biopharmaceuticals; HDT Bio	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine based on a mRNA encoding for SARS - CoV - 2 Spike protein, formulated in a hybrid lipid inorganic nanoparticle (LION(TM)) platform	Preclinical
IBIO-200	iBio (US)	Human SARS - CoV - 2 (Covid - 19 coronavirus) recombinant virus - like particle (VLP) vaccine comprising the receptor binding motif (RBM) of the SARS - CoV - 2 spike protein fused to a self - assembling protein and displayed in a repetitive structure	Preclinical

		and geometry, containing oligomannose molecules; produced with the FastPharming manufacturing platform in plant viruses	
IBIO-200	iBio (US)	Human SARS - CoV - 2 (Covid - 19 coronavirus) virus - like particle vaccine; generated by FastPharming System(TM)	Preclinical
IBIO-201	iBio (US)	Human SARS - CoV - 2 (Covid - 19 coronavirus) recombinant subunit vaccine comprising antigens derived from the SARS - CoV - 2 spike protein fused with the proprietary LicKM booster molecule (modified thermostable variant of the lichenase protein from Clostridium thermocellum)	Preclinical
IPT-001	INTELLiSTEM Technologies	Human SARS - CoV - 2 (Covid - 19 coronavirus) peptide vaccine based on the Spike (S) and Nucleocapsid (N) proteins, developed using the Intellipeptidome(TM) platform	Preclinical
IVX-411	Icosavax	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of virus - like particle (VLP) - based self - assembling protein nanoparticle displaying 60 copies of the SARS - CoV - 2 Spike (S) glycoprotein receptor - binding domain (RBD)	Preclinical
Ii-Key-SARS-CoV-2	Generex	Human SARS - CoV - 2 (Covid - 19 coronavirus) peptide vaccine	Preclinical
MRT-5500	Translate Bio; Sanofi Pasteur	Human SARS - CoV - 2 (Covid - 19 coronavirus) mRNA vaccine based on spike (S) glycoprotein of SARS - CoV - 2, encapsulated in cationic lipid nanoparticles (LNP)	Preclinical
MV-014-210	Meissa Vaccines	Human SARS - CoV - 2 (Covid - 19 coronavirus) live - attenuated vaccine	Preclinical
PDS-0203	PDS Biotechnology	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of recombinant native SARS - CoV - 2 protein loaded into Versamune(R) nanoparticles	Preclinical
PDS-0204	PDS Biotechnology; Farmacore	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of recombinant SARS - CoV - 2 fusion protein loaded into Versamune(R) nanoparticles	Preclinical

PRAK-03202	PREMAS Biotech	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of virus - like particles (VLPs) encoding three SARS - CoV - 2 antigens	Preclinical
PTX-COVID19-B	Providence Therapeutics	Human SARS - CoV - 2 (Covid - 19 coronavirus) mRNA vaccine	Preclinical
PittCoVacc	University of Pittsburgh	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of microneedle (MNA) patch comprising recombinant spike glycoprotein (S) of SARS - CoV - 2 expressed in 293HEK cells	Preclinical
S-268019	Shionogi	Human SARS - CoV - 2 (Covid - 19 coronavirus) recombinant protein vaccine	Preclinical
SPOR-COV	Destiny Pharma	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of modified Bacillus subtilis spores engineered to express human SARS - CoV - 2 antigens	Preclinical
STI-3333	Sorrento Therapeutics	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of the S1 domain of Spike glycoprotein (S) of SARS - CoV - 2 fused to the Fc portion of human IgG1 antibody	Preclinical
STI-6991	Sorrento Therapeutics	Human SARS - CoV - 2 (Covid - 19 coronavirus) decoy cellular vaccine consisting of irradiated replication - deficient K562 human myelogenous leukemia cells expressing spike protein of SARS - CoV - 2 virus	Preclinical
TNX-1800	Tonix Pharmaceuticals	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising an engineered, live replicating strain of horsepox virus (HPXV) encoding the Spike glycoprotein (S) of SARS - CoV - 2	Preclinical
TNX-1810	Tonix Pharmaceuticals	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising an engineered, live replicating strain of horsepox virus (HPXV) encoding a protein of COVID - 19 virus	Preclinical
TNX-1820	Tonix Pharmaceuticals	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising an engineered, live replicating strain of horsepox virus (HPXV) encoding a protein of COVID - 19 virus	Preclinical

TNX-1830	Tonix Pharmaceuticals	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising an engineered, live replicating strain of horsepox virus (HPXV) encoding a protein of COVID - 19 virus	Preclinical
TNX-2300	Kansas State University	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising a live replicating bovine parainfluenza virus encoding CD40 - ligand and the spike glycoprotein (S) of SARS - CoV - 2	Preclinical
TerraCoV2	Noachis Terra	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine based on SARS - CoV - 2 spike (S) glycoprotein	Preclinical
VBI-2902	VBI Vaccines	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of enveloped virus - like particles (eVLPs) comprising the SARS - CoV - 2 (COVID - 19) spike protein	Preclinical
VLA-2001	Valneva	Human SARS - CoV - 2 (Covid - 19 coronavirus) inactivated vaccine; expressed in Vero cells	Preclinical
ZIP-1642	Ziphius Therapeutics	Human SARS - CoV - 2 (Covid - 19 coronavirus) mRNA vaccine encoding different Covid - 19 antigens, including Spike (S) protein	Preclinical
1092384	Abnova	Human SARS - CoV - 2 (Covid - 19 coronavirus) self - amplifying mRNA vaccine encapsulated in lipid nanoparticles	Preclinical
1105780	Aegis Life	Human SARS - CoV - 2 (COVID - 19 coronavirus) DNA vaccine based on the expression of Spike (S) and Nucleocapsid (N) via the proprietary Fusogenix gene delivery technology	Preclinical
1090209	AdaptVac	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of virus - like particles conjugated through a catcher/tag system to the receptor binding domain of spike (S) SARS - CoV - 2 glycoprotein	Preclinical
1086209	Kentucky BioProcessing (KBP)	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine; expressed in tobacco plant cells	Preclinical
1091995	Verndari	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of microneedle array dermal patch (VaxiPatch(TM)) comprising purified recombinant spike glycoprotein (S)	Preclinical

		of SARS - CoV - 2	
1109683	University of Hong Kong	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising DelNS1 - deleted live attenuated influenza virus encoding receptor binding domain (RBD) of the spike (S) glycoprotein of SARS - CoV - 2 (DelNS1 - SARS - CoV2 - RBD LAIV)	Preclinical
1110132	LiteVax; ImmunoPrecise	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising SARS - CoV - 2 spike glycoprotein	Preclinical
1112949	DIOSynVax	Human SARS - CoV - 2 (Covid - 19 coronavirus) plasmid DNA vaccine; produced using DIOSynVAx technology	Preclinical
1085907	Ufovax; Scripps Research	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine based on self - assembling protein - nanoparticle virus - like particles (VLPs) based on identical Covid - 19 Spike (S) proteins; based on the 1c - SApNP platform	Preclinical
1085271	Halovax; Voltron Therapeutics; Hoth Therapeutics	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine based on self - assembling vaccine (SAV) platform	Preclinical
1105799	Vaxess Technologies	Combination of human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of a recombinant stabilized form of Spike (S) glycoprotein and quadrivalent seasonal influenza vaccine (QIV)	Preclinical
1095015	Phylex BioSciences	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of self - assembling virus - like particles (VLPs) containing conserved epitopes close to the receptor - binding domain (RBD) of Spike glycoprotein of SARS - CoV - 2	Preclinical
1104341	City University of New York (CUNY); TechnoVax	Human SARS - CoV2 (Covid - 19 coronavirus) vaccine consisting of virus - like particles comprising coronavirus structural elements and modified surface spike molecules	Preclinical
1114834	Cel-Sci	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of peptides derived from the nucleocapsid of SARS - CoV - 2; based on ligand epitope antigen presentation system (LEAPS) approach	Preclinical

1092152	Heat Biologics	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising engineered heat shock protein gp96 and SARS - CoV - 2 antigens	Preclinical
1099795	Sinovac; Beijing Advaccine Biotechnology	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of the SARS - CoV - derived spike S1 protein (Q14 - R685) fused to human IgG1 Fc domain (E98 - K329), expressed in Chinese hamster ovary (CHO) - K1 cells	Preclinical

Experimental vaccines for prevention of MERS-CoV in active preclinical and clinical development

Drug name	Organizations	Description	Phase
BVRS-GamVac-Combi	Ministry Healthcare Russian Federation	Middle East respiratory syndrome coronavirus (MERS - CoV) vaccine comprising a combined heterolgous adenoviral vector	Phase I/II
GLS-5300	Inovio Pharmaceuticals; GeneOne Life Science	Middle East Respiratory Syndrome DNA vaccine using the SynCon (TM) technology, encoding MERS spike protein	Phase I/II
ChAdOx1 MERS	Vaccitech Ltd.; University of Oxford	Middle East respiratory syndrome recombinant (MERS) vaccine consisting of replication - deficient simian adenovirus vector ChAdOx1 carrying full - length spike gene of MERS - CoV camel isolate; under the control of human cytomegalovirus major immediate early promoter (IE CMV)	Phase I
MVA-MERS-S	Universitaetsklinikum Hamburg-Eppendorf	Middle East respiratory syndrome coronavirus (MERS - CoV) vaccine comprising modified vaccinia virus encoding full - length S protein of MERS - CoV, under the control of early/late promoter PmH5	Phase I

GREVAX/MERS	Greffex	Recombinant adenoviral vector developed using GREVAX Universal Platform (GREVAX vector) encoding Middle East respiratory syndrome coronavirus (MERS - CoV) antigens	Preclinical

Treatment

Early diagnosis, isolation and supportive care, including fever control, i.v. fluids and supplemental oxygen for patients with severe disease, are the mainstay of treatment for SARS, MERS and Covid-19 (Murthy, S. et al (2020); Yang, Y. et al (2020)). Pharmacological approaches target either the virus itself or the host response. For patients with severe disease, a combination regimen incorporating both of these strategies--with different modalities emphasized at different stages of disease progression--might be most effective (Wiersinga, W.J. et al (2020)).

When it emerged in 2003, SARS was an unknown disease and treatment was empirical. Initial efforts to treat the disease with broad-spectrum antibodies from human immune serum globulins were unsuccessful. Some nonspecific immunosuppressive treatments or broad-spectrum antiviral agents, such as ribavirin, were of limited success (Zumla, A. et al (2016)). Combination therapy with ribavirin and corticosteroids was frequently administered as first-line treatment for SARS, based on promising results observed in some of the earliest patients treated, although data obtained subsequently failed to confirm ribavirin's anticipated anti-SARS-CoV activity in vitro (Cleri, D.J. et al (2010)). Some physicians preferred to delay administration of corticosteroids until the second week of infection in order to reduce side effects. The HIV protease inhibitor combination lopinavir/ritonavir, which inhibits the major CoV protease 3CLpro, was the most effective treatment for SARS (Zumla, A. et al (2016)). Twenty-one-day rates of ARDS and mortality were lowest in subjects treated with a combination of ribavirin, lopinavir/ritonavir and a corticosteroid (Pillaiyar, T. et al (2020)).

At the outset of the MERS-CoV outbreak, NIH researchers screened a panel of 290 approved and investigational drugs with defined cellular targets in order to determine the potential for repurposing any of them to treat SARS and/or MERS. They found that 33 compounds were active against MERS-CoV, 6 against SARS-CoV and 27 against both coronaviruses. The active drugs were grouped into 13 therapeutic classes and included antibacterial and antiparasitic agents, neurotransmitter inhibitors, estrogen receptor antagonists, kinase signaling inhibitors, inhibitors of lipid or sterol metabolism, protein-processing inhibitors, and inhibitors of DNA synthesis/repair (Dyall, J. et al (2014)). In another repurposing study, Dutch investigators screened a library of 348 FDA-approved drugs for anti-MERS-CoV activity in cell culture and found four (chloroquine, chlorpromazine, loperamide, and lopinavir) that were capable of inhibiting MERS-CoV replication at low micromolar concentrations, and further evaluation of these compounds was recommended (de Wilde, A.H. et al (2014)). A systematic review of drugs evaluated in preclinical and clinical studies against MERS-CoV found that the combination of lopinavir/ritonavir and interferon-beta-1b gave excellent results in common marmosets, and has progressed to testing in a randomized control trial setting. Ribavirin and interferon were the most widely used combination in observational studies, and may warrant further investigation (Momattin, H. et al (2019)).

In early 2020, as the number of people affected by the Covid-19 outbreak steadily multiplied and with a lack of virus-specific therapies, scientists began to investigate various host-directed therapies with demonstrated safety that could be repurposed to treat the most seriously ill patients (Zumla, A. et al (2020); Stebbing, J. et al (2020); Wiersinga, W.J. et al (2020)), nutritional interventions (vitamins A, C, D and E, B vitamins, omega-3 polyunsaturated fatty acids, selenium, zinc and iron), immunoenhancing agents, convalescent plasma and traditional Chinese

medicine. Virus-directed approaches were also pursued (Jeon, S. et al (2020);Zhang, L. et al (2020); Pillaiyar, T. et al (2020)), and resulted in the introduction of remdesivir in Japan (see table below). The drug is available there exclusively through the government.

In March, WHO announced the initiation of the SOLIDARITY Therapeutics Trial, a large international study designed to test various treatment approaches. More than 30 countries ultimately joined the study, which evaluated four different drugs or combinations--remdesivir, lopinavir/ritonavir (Kaletra), interferon-beta and hydroxychloroquine--regarding their effects on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients. Also in March, SOLIDARITY's European counterpart, DISCOVERY, was launched in various European countries (Belgium, France, Germany Luxembourg, the Netherlands, Spain, Sweden and the U.K.). This study planned to enroll 3,200 patients who would be treated with remdesivir, Kaletra with or without IFN-beta, or hydroxychloroquine. Both SOLIDARITY and DISCOVERY are adaptive trials, meaning that ineffective experimental treatments can very quickly be dropped and replaced by other molecules that emerge from research efforts. Both studies will compare the active treatments to standard of care. The U.K.'s adaptive RECOVERY trial was initiated in early April to evaluate the following treatments: lopinavir/ritonavir, dexamethasone, hydroxychloroquine, azithromycin, tocilizumab and convalescent plasma.

Interim results of SOLIDARITY were announced by WHO in October. In 405 hospitals, 11,266 adults were randomized, with 2,750 allocated remdesivir, 954 hydroxychloroquine, 1,411 lopinavir/ritonavir, 651 interferon plus lopinavir, 1,412 only interferon, and 4,088 no study drug. Compliance was 94% to 96% midway through treatment, with 2% to 6% crossover. In all, 1,253 deaths were reported (at median day 8, interquartile range 4-14). Kaplan-Meier 28-day mortality turned up at 12% (39% if already ventilated at randomization, 10% otherwise). The number of deaths in each treatment group versus its control were as follows: remdesivir 301/2743 vs. 303/2708 control; hydroxychloroquine 104/947 vs. 84/906 control; lopinavir 148/1399 vs. 146/1372 control; and interferon 243/2050 vs. 216/2050 control. None of the drugs definitively reduced mortality (in unventilated patients or any other subgroup of entry characteristics), initiation of ventilation or hospitalization duration. The results of the trial are under review for publication in a medical journal. The global platform of the Solidarity Trial is ready to rapidly evaluate promising new treatment options, with nearly 500 hospitals open as trial sites. Newer antiviral drugs, immunomodulators and anti-SARS-CoV-2 monoclonal antibodies are now being considered for evaluation (Solidarity Therapeutics Trial produces conclusive evidence on the effectiveness of repurposed drugs for COVID-19 in record time (World Health Organization news release, October 15, 2020)).

Drugs and biologics marketed for the treatment of coronavirus infection

Drug name	Organizations	Description	Phase
Antiviral agents			
Remdesivir (Veklury)	Gilead	2020 (Japan)	Remdesivir (Veklury)
Treatment of cytokine storm			
Levilimab (Ilsira)	Biocad	2020 (Russia)	Levilimab (Ilsira)

Broad-Spectrum Antiviral Agents

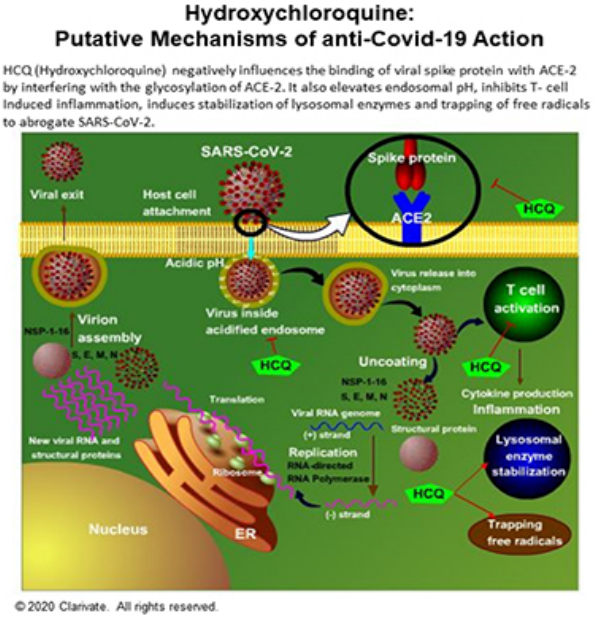
The aminoquinoline antimalarial agents chloroquine and its more soluble and better tolerated metabolite hydroxychloroquine (HCQ) have broad antiviral spectrums in vitro, with activity against DNA as well as RNA viruses. They also exert antiinflammatory and immunomodulatory effects. Chloroquine has a variety of effects: it acts by increasing endosomal pH required for fusion of a virus with the host cell, as well as by interfering with glycosylation of virus cell surface receptors. Chloroquine may also interfere with posttranslational modification of viral proteins, interrupting the process of viral replication and reducing infectivity (Colson, P. et al (2020); Devaux, C.A. et al (2020)).

Investigational use of chloroquine in Chinese patients with Covid-19 early in the pandemic was reported to lead to more rapid declines in fever and improvements in lung CT images, and was associated with a shorter recovery time as compared with control groups. Based on this promising profile, low cost, favorable safety profile and easy availability of the drug, more than 200 clinical trials were initiated to evaluate chloroquine/hydroxychloroquine for the treatment of Covid-19 pneumonia (Wiersinga, W.J. et al (2020)). Some studies assessed a combination of HCQ with azithromycin, based on the CYP450-inhibitory effects of the latter, which may slow metabolism of the antimalarial agent. Of note, chloroquine, HCQ and azithromycin are all known to prolong QT interval, raising concerns about the risk of arrhythmic death from individual or concurrent use of these medications, and patients should be closely monitored (Ventricular arrhythmia risk due to hydroxychloroquine-azithromycin treatment for COVID-19 (American College of Cardiology, March 29, 2020)). This cardiotoxic effect was reported in a Brazilian study, and led to a recommendation against use of high-dose chloroquine in combination with azithromycin and oseltamivir in critically ill patients (Silva Borba, M.G. et al (2020)). Overall, in spite of the large number of studies conducted to date using a variety of endpoints, none have confirmed any significant benefit for chloroquine/HCQ. This includes effect on 28-day negative conversion of SARS-CoV-2, risk of intubation or in-hospital mortality (Wiersinga, W.J. et al (2020)).

During the peak of the outbreak in that country, Chinese experts issued a consensus statement regarding the use and appropriate dosing of chloroquine (Unknown Author (2020)). In late March, in response to a request from the Biomedical Advanced Research and Development Authority (BARDA), the U.S. FDA issued an Emergency Use Authorization (EUA) to allow the donation of hydroxychloroquine sulfate and chloroquine phosphate to the Strategic National Stockpile. Under the EUA, the drugs could be distributed and used for hospitalized adult and adolescent patients with Covid-19, as appropriate, when a clinical trial was not available or feasible (Chloroquine phosphate and hydroxychloroquine sulfate for treatment of COVID-19 - Letter of authorization (Food and Drug Administration, March 28, 2020)). In June, having determined that chloroquine and hydroxychloroquine are unlikely to be effective in treating COVID-19 for the authorized uses in the EUA, the authorization was withdrawn by FDA (Coronavirus (COVID-19) update: FDA revokes emergency use authorization for chloroquine and hydroxychloroquine (Food and Drug Administration news release, June 15, 2020)). The EMA, in contrast, issued a statement in March emphasizing that the antimalarials should be used to treat Covid-19 only in the context of a clinical trial or EUA program (COVID-19: chloroquine and hydroxychloroquine only to be used in clinical trials or emergency use programmes (European Medicines Agency, April 1, 2020)).

In May 2020, researchers from Harvard Medical School and collaborators published a multinational registry analysis of real-world outcomes obtained in more than 96,000 Covid-19 patients, including those who were (n=14,888) treated with chloroquine or HCQ, with or without a macrolide, and control patients (n=81,144) who did not receive any of these regimens. The article (since retracted) reported no evidence of benefit with any of these regimens; in fact, each of the antimalarial drug-containing regimens was associated with decreased in-hospital survival as well as an increased frequency of ventricular arrhythmias when used for treatment of Covid-19. On the basis of this report, on May 25, WHO temporarily paused the HCQ arm of the SOLIDARITY Trial in order for the Data Safety Monitoring Board (DSMB) to review safety and mortality data. Following this review, the DSMB found no reasons to modify the trial, and investigators involved in SOLIDARITY were notified by WHO to resume hydroxychloroquine treatment on June 3. That same day, the editors of the Lancet issued an 'Expression of Concern'

to alert readers to the fact that serious scientific questions regarding the data analysis had been brought to their attention (see An open letter to Mehra et al and The Lancet (J. Watson et al., May 28, 2020)). On June 4, the authors of the Lancet study retracted their article, stating that third-party peer reviewers were unable to replicate the analyses presented in the paper. On June 5, the lead investigators of the RECOVERY Trial announced preliminary results finding that HCQ does not reduce the risk of death among hospitalized patients with Covid-19, and said that recruitment into that arm of the trial would be discontinued. WHO announced on July 4 that the HCQ treatment arm of SOLIDARITY would be discontinued (WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19 (World Health Organization news release, July 4, 2020)). In August, French/Swiss researchers published another systematic review and meta-analysis designed to assess whether HCQ, with or without azithromycin, decreased Covid-19 mortality in adult patients compared to standard of care. Their analysis included 29 studies (3 randomized controlled trials, non-randomized trial and 25 observational studies) enrolling nearly 33,000 patients (11,932 in the HCQ group, 8,081 in the HCQ/azithromycin group and 12,930 in the control group). The researchers concluded that HCQ alone was not associated with reduced mortality in hospitalized Covid-19 patients; moreover, they found that the combination of HCQ plus azithromycin significantly increased mortality (Fiolet, T. et al (2020)).



Defensins, including alpha- and beta-defensins, are constitutively or inducibly expressed by humans and other organisms to protect against invading microorganisms. They have broad-spectrum antimicrobial activity, with potent killing effects against bacteria, fungi, mycoplasma, viruses and tumor cells (Park, M.S. et al (2018); Li, G. et al (2020)). Defensin-mimetic therapeutics are a novel class of antimicrobial peptide (AMPs) mimetics, also termed host defense protein (HDPs) mimetics, that are more stable and potent than natural defensins. These compounds show antibacterial, antiviral, antifungal, antiinflammatory and anticancer activities through their effects on the innate and adaptive human immune system. Defensin mimetics may be useful in the treatment of coronavirus infections, including Covid-19.

Ribavirin is a ribonucleoside analogue that is active against some coronaviruses, as well as respiratory syncytial virus and metapneumoviruses. Because of its relatively broad spectrum of antiviral activity, ribavirin was one of the first compounds tested for its clinical efficacy against SARS. Early therapy with ribavirin, particularly when combined with corticosteroids, was associated with variable outcomes in SARS patients (Cleri, D.J. et al (2010); Sanders, J.M. et al (2020)). Ribavirin has also been tested in the rhesus macaque model of MERS-CoV, which is a model of mild to moderate human disease. The results obtained--IFN-a2b plus ribavirin reduced virus replication, moderated the host response and improved clinical outcome--support use of the combination to treat patients with MERS (Falzarano, D. et al (2013)). However, in an

observational study of 349 critically ill MERS patients, of whom 144 received ribavirin/rIFN (ribavirin and/or rIFN-alfa2a, rIFN-alfa2b or rIFN-beta1a), the treatment was not associated with any reduction in 90-day mortality or in faster MERS-CoV RNA clearance (Arabi, Y.M. et al (2020)). Adverse events, including dose-dependent anemia, are a significant concern with ribavirin, and have been cited as one factor potentially limiting its utility in patients with Covid-19 (Li, G. et al (2020)). Nonetheless, in mid-April 2020, Bausch Health announced that it would initiate a clinical trial in Canada evaluating ribavirin for inhalation in combination with standard-of-care therapy for the treatment of hospitalized adult patients with respiratory distress resulting from Covid-19 infection. The clinical study (NCT04356677) has been approved by Health Canada but is not yet enrolling patients (ClinicalTrials.gov website consulted December 2,2020). The company was also in discussions with health authorities in multiple countries regarding additional studies to evaluate ribavirin as a treatment for Covid-19 infection.

Viral Entry Inhibitors

The process of coronavirus replication is well understood. Several unique steps have been identified as potential targets for antiviral drugs. The first step in the replication process--viral fusion with the host cell--could potentially be blocked by entry inhibitors or membrane fusion inhibitors, similar to antivirals used for HIV infection.

Angiotensin-converting enzyme 2 (ACE2) receptors are highly expressed on pulmonary cells, primarily in type II alveolar epithelial cells. Type II alveolar cells produce pulmonary surfactant, which maintains the stability of pulmonary tissue by reducing the surface tension of fluids that coat the lung. However, ACE2 also serves as the entry receptor for some coronaviruses, including SARS-CoV and SARS-CoV-2. The spike (S) protein of SARS engages ACE2 as the entry receptor and then uses the host cell-surface protein TMPRSS2 (transmembrane serine protease 2), which is co-expressed on bronchial epithelial cells, for S priming. The latter step enables fusion of viral and cellular membranes and viral entry into the cell (Stopsack, K.H. et al (2020)). The resulting injury to type II alveolar cells may help to explain the severe lung injury observed in Covid-19 patients.

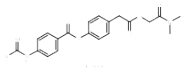
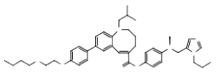
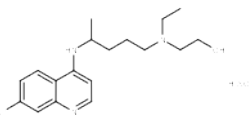
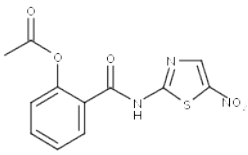
Umifenovir (also known as Arbidol), marketed in some countries for the treatment of influenza, has long been studied as a potential treatment for other viral infections. It is an efficient inhibitor of SARS-CoV-2 virus infection in vitro (Wang, X. et al (2020)). Umifenovir has a unique mechanism of action targeting the S protein/ACE2 interaction, and thus is capable of inhibiting membrane fusion of the viral envelope (Sanders, J.M. et al (2020)). Chinese researchers evaluated the antiviral effects and safety of umifenovir in combination with lopinavir/ritonavir in patients with laboratory-confirmed Covid-19. Fifty patients were enrolled and were divided into two treatment groups, receiving either lopinavir/ritonavir (400 mg/100 mg) twice a day for a week (n = 34), or umifenovir (0.2 g) given three times a day (n = 16). None of the patients developed severe pneumonia or ARDS. Fever was the most common symptom at the onset of illness, with most patients having a short duration of fever (< 7 days); there was no difference in fever duration between the two groups. On day 7 after admission, the viral load was undetectable in half of the patients receiving umifenovir and in 23.5% of those treated with lopinavir/ritonavir. On day 14 after the admission, viral load was undetectable in all the patients in the umifenovir group; however, viral load was detectable in 44.1% of patients who received lopinavir/ritonavir. Patients treated with umifenovir had a shorter duration of positive RNA test versus those treated with lopinavir/ritonavir. As for safety, no apparent side effects were found in either treatment group. Overall, these findings indicate that umifenovir monotherapy could be superior to lopinavir/ritonavir in treating Covid-19 (Zhu, Z. et al (2020)).

Administration of human recombinant soluble ACE2 has been explored as a method of preventing viral entry into host cells, i.e., as a neutralizing agent (Tay, M.Z. et al (2020)). This approach, known as ACE2 enhancement therapy, has been tested successfully in vitro and in human capillary and human kidney organoids. It should be noted that viral inhibition in these models, albeit dose-dependent, was not complete, suggesting that in addition to ACE2, SARS-CoV-2 may also use some other co-receptor. Alternatively, there may be other as-yet-unknown factors that mediate infection of ACE2-expressing cells in the upper respiratory tract (Monteil, V. et al (2020)). In April, a phase II clinical trial (NCT04335136) was initiated to assess APN-01, a

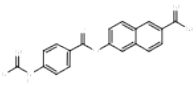
proprietary recombinant human ACE2 (rhACE2), in up to 200 patients with severe Covid-19, including patients requiring invasive mechanical ventilation.

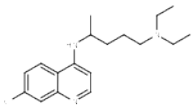
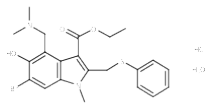
As explained above (see SARS-CoV-2 Morphology, Structure and Replication), the S protein consists of S1 and S2 subunits, which are the receptor binding domain and membrane fusion domain, respectively. The S1 domain is poorly conserved across different members of the coronavirus family, which may explain why monoclonal antibodies developed for SARS--most of which were targeted at S1--have shown limited efficacy against SARS-CoV-2. The membrane fusion domain, on the other hand, is one of the best conserved regions of the S protein across all species. Drugs and biologics targeted to S2, therefore, may be more broadly applicable in the treatment of this and future CoV outbreaks (Tang, T. et al (2020)).

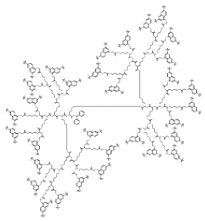
Viral entry inhibitors under active development for the treatment of coronavirus infection

Drug Name	Organizations	Mechanisms	Phase	Structure
Bamlanivimab	Lilly	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase III	
Camostat mesylate	Ono	Transmembrane Protease Serine 2 (TMPRSS2) Inhibitors; Trypsin Inhibitors; Viral Entry Inhibitors	Phase III	
Casirivimab/Imdevimab	Regeneron	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)/ACE2 Interaction Inhibitors; Viral Attachment Inhibitors; Viral Fusion Inhibitors	Phase III	
Cenicriviroc mesilate	National Institutes of Health (NIH)	Chemokine CCR2B Receptor Ligands; Chemokine CCR5 Receptor Antagonists; Signal Transduction Modulators; Viral Attachment Inhibitors	Phase III	
DAS-181	Ansun Biopharma	Viral Attachment Inhibitors	Phase III	
Hydroxychloroquine sulfate	Sanofi	Autophagy Inhibitors; Palmitoyl-Protein Thioesterase 1 (PPT1) Inhibitors; Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)/ACE2 Interaction Inhibitors; Viral Attachment Inhibitors	Phase III	
Nitazoxanide	Romark	Hemagglutinin (HA) (Viral) Inhibitors; Myc Proto-Oncogene Protein (c-Myc) Inhibitors; Protein Disulfide-	Phase III	

		Isomerase A3 (PDIA3) Inhibitors; Pyruvate Synthase (Pyruvate-Ferredoxin Oxidoreductase; PFOR) (Bacterial) Inhibitors; Pyruvate Synthase (Pyruvate-Ferredoxin Oxidoreductase; PFOR) (Protozoal) Inhibitors; Signal Transduction Modulators; Viral Fusion Inhibitors; Viral Maturation Inhibitors	
Regdanvimab	Celltrion	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase III
GSK-4182136	Vir Biotechnology; GlaxoSmithKline	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase II/III
Leronlimab	CytoDyn	Anti-CD195 (CCR5); Signal Transduction Modulators; Viral Entry Inhibitors	Phase II/III
LY-CoV016	Lilly	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase II
XAV-19	Xenothera	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase II
VIR-7832	Vir Biotechnology; GlaxoSmithKline	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase I/II
1086612	Chongqing Sidemu Biotechnology	Anti-GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor; CSF2); Drugs Acting on NKG2D; Drugs Targeting Angiotensin-Converting Enzyme 2 (ACE2); Signal Transduction Modulators; Viral Fusion Inhibitors	Phase I/II
ABL-901	HiFiBiO	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase I
ABP-300	Abpro	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase I

AT-301	Atossa Therapeutics	Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus) Inhibitors; Viral Fusion Inhibitors	Phase I	
BRII-196	Brii Biosciences	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase I	
BRII-198	Brii Biosciences	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase I	
Ensovibep	Molecular Partners	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase I	
Liposomal hydroxychloroquine	Taiwan Liposome Co.	Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)/ACE2 Interaction Inhibitors; Viral Attachment Inhibitors	Phase I	
Nafamostat mesilate	Covistat	Transmembrane Protease Serine 2 (TMPRSS2) Inhibitors; Tryptase Inhibitors; Viral Entry Inhibitors	Phase I	
REGN-3048	Regeneron	Anti-Spike Glycoprotein (MERS-CoV); Viral Fusion Inhibitors	Phase I	
REGN-3051	Regeneron	Anti-Spike Glycoprotein (MERS-CoV); Viral Fusion Inhibitors	Phase I	
SAB-301	SAB Biotherapeutics	Anti-Spike Glycoprotein (MERS-CoV); Viral Fusion Inhibitors	Phase I	
STI-1499	Sorrento Therapeutics	Angiotensin-Converting Enzyme 2 (ACE2) Inhibitors; Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Signal Transduction Modulators; Viral Fusion Inhibitors	Phase I	
BD-368-2	Peking University (PKU)	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)/ACE2 Interaction Inhibitors; Viral Attachment	Clinical	

		Inhibitors; Viral Fusion Inhibitors		
Chloroquine phosphate	Guangdong Zhongsheng Pharmaceutical; University of Oxford	Apoptosis Inducers; Histamine N-Methyltransferase (HNMT) Inhibitors; Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)/ACE2 Interaction Inhibitors; Viral Attachment Inhibitors	Clinical	
Umifenovir hydrochloride	Wuhan Tongji Hospital	Capsid Assembly (Hepatitis B Virus) Modulators; Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)/ACE2 Interaction Inhibitors; Viral Attachment Inhibitors	Clinical	
HLX-70	Shanghai Henlius Biotech	Anti-Spike Glycoprotein (SARS-CoV); Viral Fusion Inhibitors	IND Filed	
STI-2020	Sorrento Therapeutics	Angiotensin-Converting Enzyme 2 (ACE2) Inhibitors; Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Signal Transduction Modulators; Viral Fusion Inhibitors	IND Filed	
STI-2099	Sorrento Therapeutics	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	IND Filed	
2-43	Columbia University	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical	
ACE2-Fc	iBio (US); Planet Biotechnology	Viral Entry Inhibitors	Preclinical	
AR-701	Aridis Pharmaceuticals	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)/ACE2 Interaction Inhibitors; Viral Attachment Inhibitors; Viral Fusion Inhibitors	Preclinical	
AR-711	Aridis Pharmaceuticals	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical	

Astrodimer sodium	Starpharma	Reverse Transcriptase/Ribonuclease H (Viral) Inhibitors; Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus) Inhibitors; Viral Fusion Inhibitors	Preclinical	
CMAB-020	Mabpharm	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Basigin (BSG; CD147)/ACE2 Interaction Modulators; Viral Fusion Inhibitors	Preclinical	
COVI-SHIELD	Sorrento Therapeutics	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical	
Dioguard	Diomics	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical	
IgY-110	IGY Immune Technologies & Life Sciences	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical	
KEPTIDE Covid	Sotira	Drugs Targeting Angiotensin-Converting Enzyme 2 (ACE2); Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)/ACE2 Interaction Inhibitors; Viral Attachment Inhibitors	Preclinical	
LCA-60	Vir Biotechnology	Anti-Spike Glycoprotein (MERS-CoV); Viral Fusion Inhibitors	Preclinical	
MP-0423	Molecular Partners	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical	
Sybody 23	Universitaet Zuerich	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical	
TB-181-36	Twist Bioscience	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical	

TB-202-3	Twist Bioscience	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical
1098546	Centivax	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical

Inhibitors of Host Proteases

A number of host proteases have been shown to proteolytically process the S protein, which determines coronaviral entry into the host cell. These include cathepsin, furin, trypsin (Millet, J.K. et al (2015); Kilianski, A. et al (2014)), and type II transmembrane serine protease (TMPRSS2) (Stopsack, K.H. et al (2020)).

Following attachment of the SARS-CoV-2 S protein to the ACE2 receptor on the host cell, the spike protein is cleaved by TMPRSS2, allowing the S2 subunit virus to drive fusion of the viral membrane with the host cell (Profile of a killer: The complex biology powering the coronavirus pandemic (Nature News, May 4, 2020)). TMPRSS2 has been identified as a promising anti-Covid-19 drug target, with the advantage that drugs acting on this target are already approved for marketing. The TMPRSS2 inhibitor camostat mesilate is marketed in Japan for the treatment of pancreatitis, and has been identified as a suitable candidate for repurposing in the treatment of Covid-19 (Hoffmann, M. et al (2020)). In April, Danish investigators began enrolling patients with PCR-confirmed SARS-CoV-2 in a placebo-controlled study (NCT04321096) designed to determine whether camostat mesilate is able to act on the lung cells targeted by the virus and prevent it from infecting them.

In a comparative study, the related TMPRSS2 inhibitor nafamostat mesylate was found to be 15-fold more potent than camostat in blocking SARS-CoV-2 entry in vitro, with significantly higher antiviral efficiency. Nafamostat is already approved by the FDA and has a proven safety profile, supporting its evaluation in patients with Covid-19 infection (Hoffmann, M. et al (2020)).

The mucolytic agent bromhexine was found in a repurposing study to be a potent and specific TMPRSS2 inhibitor with a potentially superior safety profile (Maggio, R. et al (2020)), supporting its evaluation in patients with Covid-19.

Viral Enzyme Inhibitors

Viral enzymes involved in the process of replication within the host cell have also been identified as potential drug targets. Inhibitors of viral proteases may block cleavage of the polymerase protein to inhibit viral RNA synthesis. Nucleoside inhibitors might specifically inhibit viral replication without causing damage to the host cell. Targeted inhibitors of the serine proteases, which are required to activate the viral infectivity of some coronaviruses, may block the later stages of the viral life cycle (Kilianski, A. et al (2014); Zhou, Y. et al (2015)).

The HIV protease inhibitor combination lopinavir/ritonavir has progressed furthest in development for treatment of MERS-CoV. Following successful preclinical evaluation of lopinavir/ritonavir plus interferon-beta1b, in which significant reductions in mortality were obtained in a marmoset model, clinical evaluation of the combination was recommended (Chan, J.F. et al (2015)). The MIRACLE trial, a randomized, adaptive, double-blind, placebo-controlled trial that enrolled 95 patients at nine sites in Saudi Arabia, evaluated the efficacy and safety of lopinavir/ritonavir plus recombinant interferon-beta1b compared to placebo in patients with laboratory-confirmed MERS-CoV infection requiring hospital admission. The primary outcome measure was 90-day all-cause mortality, which was found to be lower in patients randomized to the combination regimen. Efficacy was greatest when treatment was initiated within 7 days of onset of symptoms (Arabi, Y.M. et al (2020)). The justification for using the two in

combination is that ritonavir, in addition to inhibiting protease, is also an inhibitor of cytochrome P4503A4. It thereby reduces the metabolism and enhances and prolongs the action of the second protease inhibitor, lopinavir.

Since the combination of lopinavir and ritonavir was already available in the Wuhan, China hospital where early SARS-CoV-2-infected patients were treated, a trial was quickly initiated to assess the efficacy and safety of the combination to treat Covid-19 (Huang, C. et al (2020)). The randomized, controlled, open-label trial, designated LOTUS China, enrolled 199 patients who were SARS-CoV-2-positive on RT-PCR, had confirmed pneumonia on chest imaging and had oxygen saturation (Sao2) of less than or equal to 94% while breathing ambient air or Pao2:Fio2 ratio of less than or equal to 300 mgHg. Eligible patients were randomized to receive either lopinavir/ritonavir twice daily in combination with standard care, or standard care alone, for 14 days; standard care included supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy and extracorporeal membrane oxygenation (ECMO), as required. The results showed no difference overall in time to clinical improvement or mortality between the lopinavir/ritonavir and standard care groups. In the intention-to-treat population, however, initiation of lopinavir/ritonavir therapy within 12 days after the onset of symptoms was associated with shorter time to clinical improvement, whereas initiation of treatment after this point was not. Twenty-eight-day mortality rates were lower in the active treatment vs. standard care groups (19.2% vs. 25.0%), and ICU stay was shorter (6 days vs. 11 days). The percentage of patients with clinical improvement at day 14 was also higher in the lopinavir/ritonavir group versus standard care (45.5% vs. 30.0%). Addition of lopinavir/ritonavir did not result in decreased viral RNA load in throat or duration of viral RNA detectability as compared with standard care alone. Of note, the overall mortality rate (22.1%) was substantially higher than that reported in initial descriptive studies (11% to 14.5%), indicating a high overall degree of severity in the study population (Cao, B. et al (2020)).

Nonetheless, in June 2020 the chief investigators of the U.K. RECOVERY Trial, which was evaluating lopinavir/ritonavir in one treatment arm, announced that the study protocol was being modified and that patients would no longer be randomized to treatment with the anti-HIV combination (No clinical benefit from use of lopinavir-ritonavir in hospitalised COVID-19 patients studied in RECOVERY (Recovery Trial news release, June 29, 2020)). The decision was made on the basis of preliminary results showing that for patients hospitalized with Covid-19 and not on a ventilator, lopinavir/ritonavir was not superior to standard treatment alone: there was no significant difference in the primary endpoint of 28-day mortality (23% for lopinavir/ritonavir vs. 22% usual care). There was also no evidence of beneficial effects on the risk of progression to mechanical ventilation or length of hospital stay (Horby, P.W. et al (2020)). In light of the evidence for lopinavir/ritonavir vs. standard of care from SOLIDARITY trial interim results, and supported by a review of the evidence from all trials presented at the 1-2 July WHO Summit on COVID-19 research and innovation, WHO announced on July 4 that the lopinavir/ritonavir treatment arm of SOLIDARITY would be discontinued (WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19 (World Health Organization news release, July 4, 2020)).

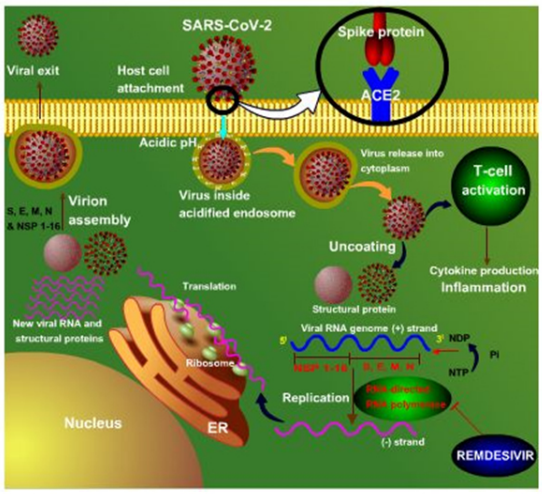
In the case of RNA viruses such as coronavirus, the most specific target is the RNA-directed RNA-polymerase (RdRp), which directs the processes of viral genome replication and transcription. This key enzyme shows significant differences between positive-sense viruses, such as SARS-CoV-2, and negative-sense RNA viruses (Buonaguro, L. et al (2020)). The RdRp inhibitor remdesivir showed broad-spectrum antiviral activity against coronaviruses in vitro and in vivo, inhibiting the replication of both endemic and zoonotic strains in cell culture. In a relevant murine model of SARS-CoV infection, prophylactic administration of remdesivir prevented development of symptomatic disease; postexposure administration was also effective in mitigating the immunopathological phase of disease, improving respiratory function and reducing viral load (Sheahan, T.P. et al (2017)). In 2020, based on these and other studies suggesting its anti-CoV activity (Sheahan, T.P. et al (2020); Wang, M. et al (2020)) and at the request of treating physicians, remdesivir was supplied by the manufacturer for experimental use in China, to treat hospitalized adult patients with Covid-19 illness. In January, in its R&D Blueprint report, WHO said it considered remdesivir to be the most promising candidate for treatment of Covid-19, based on its broad antiviral spectrum, available in vitro and in vivo data,

and the extensive clinical safety database (WHO R&D blueprint report - Informal consultation on prioritization of candidate therapeutic agents for use in novel coronavirus 2019 infection (World Health Organization, January 24, 2020)). In April, results were announced from a compassionate-use study in 53 hospitalized patients (22 in the U.S., 22 in Europe or Canada, and 9 in Japan) who were treated with a 10-day course of remdesivir. At baseline, 30 patients (57%) were receiving mechanical ventilation and four (8%) were receiving ECMO. At a median follow-up of 18 days, 36 patients (68%) registered improvement in oxygen-support class, including 17 of 30 mechanically ventilated patients (57%) who were successfully extubated. Twenty-five patients (47%) were released from the hospital, while seven (13%) died (Grein, J. et al (2020)). Later that month, preliminary results of the NIAID-sponsored ACTT-1 trial, which enrolled 1,063 hospitalized adults with laboratory-confirmed Covid-19, were announced. The preliminary findings indicate that patients randomized to a 10-day course of treatment with remdesivir had a 31% faster time to recovery than those who received placebo (11 days vs. 15 days, respectively). Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group (Beigel, J.H. et al (2020)). In the open-label, phase III SIMPLE trial, patients who received a shorter, 5-day course of remdesivir experienced similar clinical improvement as patients who received a 10-day treatment course. As this study lacked a control group, however, the magnitude of difference could not be calculated (Goldman, J.D. et al (2020)).

On May 1, the FDA issued an emergency use authorization (EUA) for remdesivir in the U.S., allowing the drug to be distributed and used by licensed health care providers to treat adults and children hospitalized with severe Covid-19. Severe Covid-19 is defined as patients with an oxygen saturation of less than or equal to 94% on room air, or requiring supplemental oxygen, mechanical ventilation or ECMO (Coronavirus (COVID-19) update: FDA issues emergency use authorization for potential COVID-19 treatment (FDA news release, May 1, 2020)). In August, following a revision of the EUA, use was broadened to all hospitalized adult and pediatric patients with suspected or laboratory-confirmed Covid-19, irrespective of their severity of disease. Also in May, the Japanese Ministry of Health, Labour and Welfare (MHLW) granted regulatory approval of remdesivir as a treatment for SARS-CoV-2 infection under an exceptional approval pathway. The exceptional approval was granted due to the Covid-19 pandemic and references the EUA for remdesivir in the United States. Of note, the Japanese regulatory process does not include an emergency use provision. In July, the European Medicines Agency issued a conditional marketing authorization of remdesivir, indicated for the treatment of Covid-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen. The authorization allows the drug to be marketed throughout the E.U. In October, remdesivir was approved by the U.S. FDA, indicated for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kg for the treatment of Covid-19 requiring hospitalization. The EUA has been modified to ensure continued access to the previously covered pediatric population. The FDA approval was based on results of ACTT-1 (Beigel, J.H. et al (2020)) as well as two other international phase III trials. On November 20, WHO issued a conditional recommendation against the use of remdesivir in hospitalized patients, regardless of disease severity, stating that there was no evidence at that time to confirm that remdesivir improves survival and other outcomes in these patients. That includes no important effect on mortality, need for mechanical ventilation, time to clinical improvement, and other patient-important outcomes. WHO stressed that further clinical evaluation of the antiviral agent is needed.

Remdesivir: Treatment for SARS-CoV-2 Infection (COVID-19)

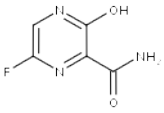
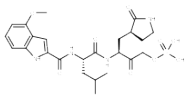
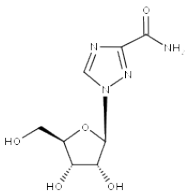
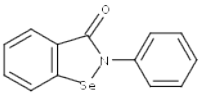
Remdesivir is an investigational antiviral drug that inhibits viral RNA-directed RNA polymerase to disrupt replication of a new viral genome. It functions by blocking addition of new nucleotides to the 3' OH group of template RNA.

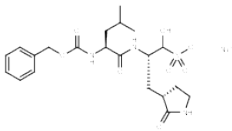
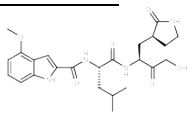


Favipiravir, a nucleoside analogue that is marketed in Japan for the treatment of influenza A and B, is being evaluated as a potential broad-spectrum antiviral for use in the Covid-19 outbreak (Sanders, J.M. et al (2020)). Like remdesivir, favipiravir inhibits RNA-directed RNA polymerase of various RNA viruses; in addition to influenza, it has been found to inhibit the replication of yellow fever virus, Ebola virus, norovirus and chikungunya virus (Li, G. et al (2020)). Although favipiravir was not highly active against SARS-CoV-2 in vitro (Wang, M. et al (2020)), its commercial availability and favorable tolerability profile support clinical testing in Covid-19 patients, with studies evaluating the originator product underway in several countries. In June 2020, Glenmark Pharmaceuticals obtained accelerated approval in India for its generic version of favipiravir (FabiFlu), indicated for the treatment of mild to moderate Covid-19. The approval's restricted use requires every patient to have signed informed consent before treatment initiation. Another generic version of favipiravir developed by R-Pharm (Coronavir) has been approved in Russia, indicated for out-patient treatment of mild to moderate Covid-19 coronavirus infection.

The 33.8-kDa main protease (Mpro) of SARS-CoV-2 constitutes an attractive drug target because of its essential role in viral replication and transcription and its lack of closely related homologues in humans (Jin, Z. et al (2020)). Mpro, together with the papain-like proteases, is required for processing polyproteins that are translated from the viral RNA (Zhang, L. et al (2020)). Chinese researchers applied a strategy combining structure-assisted drug design, virtual drug screening and high-throughput screening to repurpose drugs to target viral Mpro. Using computer-aided drug design, the team identified a mechanism-based irreversible inhibitor (N3) and determined the crystal structure of the Mpro-N3 complex. They then used structure-based virtual and high-throughput screening of around 10,000 compounds (including approved drugs, drug candidates under clinical development, and other pharmacologically active compounds) to identify Mpro inhibitors and found that ebselen--an organoselenium compound with antiinflammatory, antioxidant and cytoprotective properties and very low cytotoxicity--was the most potent Mpro inhibitor in the series (Jin, Z. et al (2020)).

Viral enzyme inhibitors under active development for coronavirus infection

Drug name	Organizations	Description	Phase	Structure
Favipiravir	FUJIFILM Toyama Chemical	RNA-Directed RNA Polymerase (RdRp) (Influenza A Virus H1N1) Inhibitors; RNA-Directed RNA Polymerase (RdRp) (NS5B) (HCV) Inhibitors; RNA-Directed RNA Polymerase (RdRp) (SARS-CoV-2; COVID-19 Virus) Inhibitors; Viral Replication Inhibitors	Pre-Registered	
ASC-09/ritonavir	Ascletis	HIV Protease Inhibitors; HIV-1 Protease Inhibitors; Tumor Necrosis Factor Receptor Superfamily Member 6 (CD95)/PLC-gamma-1 Interaction Inhibitors	Phase III	
Darunavir/cobicistat	Shanghai Public Health Clinical Center	Cytochrome P450 CYP3A4 Inhibitors; HIV Protease Inhibitors	Phase III	
Lopinavir/ritonavir	King Abdullah International Med Res Cent	HIV Protease Inhibitors; HIV-1 Protease Inhibitors; Tumor Necrosis Factor Receptor Superfamily Member 6 (CD95)/PLC-gamma-1 Interaction Inhibitors	Phase II/III	
PF-07304814	Pfizer	3C-Like Proteinase (3CLpro; Mpro; nsp5) (SARS-CoV-2; COVID-19 Virus) Inhibitors; Viral Replication Inhibitors	Phase I	
Ribavirin	Bausch Health	Equilibrative Nucleoside Transporter ENT1 Inhibitors; Inosine 5'-Monophosphate Dehydrogenase (IMPDH) Inhibitors; RNA-Directed RNA Polymerase (RdRp) (SARS-CoV-2; COVID-19 Virus) Inhibitors; Viral Replication Inhibitors	Clinical	
Ebselen	Sound Pharmaceuticals	3C-Like Proteinase (3CLpro; Mpro; nsp5) (SARS-CoV-2; COVID-19 Virus) Inhibitors; Antioxidants; Diacylglycerol Acyltransferase/Mycolyltransferase Ag85C (Mycobacterium tuberculosis) Inhibitors; Ferroptosis Inhibitors; Glutathione Peroxidase (GPx) Mimetics; NADPH Oxidase (NOX) Inhibitors; Phosphotransferase (HK) (Trypanosoma brucei) Inhibitors; Protein Kinase C (PKC) Inhibitors; Serine Protease NS3 (HCV) Inhibitors; Signal Transduction Modulators;	IND Filed	

		Sulfhydryl Oxidase 1 (hQSOX) Inhibitors; Viral Replication Inhibitors		
GC-376	Anivive Lifesciences	3C-Like Protease (Norovirus) Inhibitors; 3C-Like Proteinase (3CLpro; Mpro; nsp5) (SARS-CoV-2; COVID-19 Virus) Inhibitors; Viral Replication Inhibitors	Preclinical	
NV-CoV-1-R	NanoViricides	Drugs Targeting Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus); RNA-Directed RNA Polymerase (RdRp) (Ebola Virus) Inhibitors; RNA-Directed RNA Polymerase (RdRp) (MERS-CoV) Inhibitors; RNA-Directed RNA Polymerase (RdRp) (SARS-CoV) Inhibitors; RNA-Directed RNA Polymerase (RdRp) (SARS-CoV-2; COVID-19 Virus) Inhibitors; Viral Replication Inhibitors	Preclinical	
PF-835231	Pfizer	3C-Like Proteinase (3CLpro; Mpro; nsp5) (SARS-CoV-2; COVID-19 Virus) Inhibitors; Viral Replication Inhibitors	Preclinical	
SBFM-PL4	Sunshine Biopharma	Drugs Targeting Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteases	Preclinical	

Other Viral Replication Inhibitors

In late April 2020, the first patient was treated in a randomized phase II study evaluating low-dose oral selinexor in hospitalized patients with severe Covid-19 (XPORT-CoV-1001; NCT04349098). Selinexor is a selective inhibitor of nuclear export (SINE) compound that blocks Exp1, a cellular protein encoded by the gene XPO1 which is involved in both the replication of SARS-CoV-2 and the host inflammatory response to the virus. SINE compounds have been identified as having the potential to interfere with key host protein interactions with influenza, RSV and other viruses including SARS-CoV-2, with Exp1 being one of the host proteins with the highest number of functional connections with SARS-CoV proteins. SINE compounds have also demonstrated potent antiinflammatory activity through the inhibition of nuclear factor kappaB (NF-kappaB), leading to reductions in cytokines such as IL-6, IL-1, IFN-gamma and others in a variety of models, which may be particularly beneficial to hospitalized patients with Covid-19 and other severe viral infections (Uddin, M.H. et al (2020)).

Interferons

The host immune response, including the innate interferon response, is crucial for controlling viral replication. This response involves stimulation by the virus of pattern recognition receptors, which triggers the transcriptional induction of type I interferons (Bastard, P. et al (2020)), activation of the Jak1/Tyk2-STAT1/2 pathway and the subsequent upregulation of IFN-stimulated genes (ISGs). Coronaviruses are capable of suppressing this response in order to evade the host immune system and continue replicating unchecked; SARS-CoV-2 is particularly adept at such evasion. However, they may be responsive to treatment with interferons, particularly recombinant forms (Zumla, A. et al (2016); Blanco-Melo, D. et al (2020); Jamilloux, Y. et al (2020)).

The antiviral activity of interferon-beta, interferon-alfa and interferon-gamma was evaluated in SARS-CoV strains isolated from patients in Frankfurt and Hong Kong and replicated in Vero and Caco-2 cell lines (Hensley, L.E. et al (2004)). IFN-beta showed good antiviral activity, inhibiting SARS-CoV replication in both cell lines. IFN-alfa was also active, but with a sensitivity index 50-90 times lower than that for IFN-beta. IFN-gamma was slightly more active than IFN-alfa in one cell line but was completely inactive in the other (Cinatl, J. et al (2003)). MERS-CoV has been shown to be 50-100 times more susceptible in vitro than SARS-CoV to treatment with IFN-alfa (Abdel-Moneim, A.S. (2014)). In vitro in Vero cells, SARS-CoV-2 was more susceptible than SARS-CoV to both IFN-alfa and IFN-beta, the latter being slightly more effective in reducing viral titers (Mantlo, E. et al (2020)).In early 2020, a phase II trial was launched in Hong Kong to test the efficacy of lopinavir/ritonavir, with or without the addition of ribavirin and IFN-beta-1b, in 127 hospitalized patients with mild to moderate Covid-19. The combination regimen incorporating IFN-1beta and ribavirin was shown to be safe, and was superior to lopinavir/ritonavir alone in alleviating symptoms as well as shortening the duration of viral shedding and hospital stay. The investigators concluded that future placebo-controlled clinical studies evaluating IFN beta-1b as a backbone of antiviral therapy are warranted (Hung, I.F. et al (2020)). Chinese Covid-19 guidelines list interferons as an alternative for use in the setting of combination therapy (Sanders, J.M. et al (2020)).

SNG-001, an inhaled formulation of interferon-beta, was evaluated in hospitalized patients with Covid-19 (NCT04385095). The double-blind, placebo-controlled phase II trial recruited 101 patients at 9 U.K. sites between March 30-May 27, 2020. Patient groups were evenly matched in terms of average age (56.5 years for placebo and 57.8 years for SNG-001), comorbidities and average duration of Covid-19 symptoms prior to enrollment (9.8 days for placebo and 9.6 days for SNG-001). The odds of developing severe disease (e.g., requiring ventilation or resulting in death) during the treatment period (day 1-16) were significantly reduced by 79% for patients receiving SNG-001 compared to patients who received placebo. Patients who received SNG-001 were more than twice as likely to recover (defined as 'no limitation of activities' or 'no clinical or virological evidence of infection') over the course of the treatment period compared to those receiving placebo. Over the treatment period, the measure of breathlessness was markedly reduced in patients who received SNG-001 compared to those receiving placebo. Three subjects (6%) died after being randomized to placebo. There were no deaths among subjects treated with SNG-001. In the patients with more severe disease at time of admission (i.e., requiring treatment with supplemental oxygen), SNG-001 treatment increased the likelihood of hospital discharge during the study, although the difference was not statistically significant. Median time to discharge was 6 days for patients treated with SNG-001 and 9 days for those receiving placebo. Furthermore, patients receiving SNG-001 appeared to be more than twice as likely to have recovered by the end of the treatment period although this strong trend did not reach statistical significance. However by day 28, patients receiving SNG-001 treatment had statistically significantly better odds of recovery. The efficacy analyses indicate that SNG-001 positive treatment effects were independent of prior duration of Covid-19 symptoms.In an uncontrolled, exploratory study, 77 hospitalized patients with confirmed Covid-19 were treated with nebulized IFN-alfa2b, oral umifenovir (Arbidol) or their combination. No patients in any treatment group progressed to end-organ dysfunction. Of note, the IFN-alfa-containing regimens shortened the duration of viral shedding and reduced expression of IL-6 and CRP, indicating suppression of inflammatory response (Zhou, Q. et al (2020)).

Recombinant interferon therapy has long focused on type I IFNs (IFN-alfa and -beta) for potentiation of the innate antiviral response. During the Covid-19 pandemic, attention turned to the potential contribution by type III interferons, particularly IFN-lambda, in mediating antiviral resistance in cells. Type III IFNs have antiviral and tissue-protective activities; their expression is induced at a lower viral burden compared to type I IFNs. Also in contrast with type I IFNs, which signal through a receptor complex (IFNAR) present on a multitude of host cells, type III IFNs signal through a unique heterodimeric receptor complex (IFNLR), the expression of which is limited to epithelial cells and a subpopulation of immune cells, including neutrophils and B cells. Administration of recombinant or pegylated IFN-lambda, either as prophylactic therapy or at an early stage of Covid-19, could result in expression of ISGs and induce a localized antiviral response in respiratory epithelial cells, while reducing the systemic side effects and inflammation associated with type I IFNs (Prokunina-Olsson, L. et al (2020); Andreakos, E. et al (2020)).

Interferons under active development for treatment of coronavirus infection

Drug name	Organizations	Description	Phase
1086588	Shanghai Jiao Tong University (SJTU)	Recombinant human interferon alpha - 1b	Phase III
Interferon-beta	Synairgen	Interferon beta 1a (IFN - b1a)	Phase II
Peginterferon lambda-1a	Eiger BioPharmaceuticals	Pegylated (20kD) recombinant human interferon lambda 1 (IFNL1/IL29)	Phase II
Pegylated interferon alpha-2b	Cadila Healthcare (d/b/a Zydus Cadila)	Long - acting pegylated interferon alpha - 2b	Phase II
FP-1201	Faron	Recombinant human interferon beta - 1a	Clinical
pSV1.0-IFN-K	Shanghai Public Utilities Institute	Plasmid vector (pSV1.0) encoding full - length human interferon - kappa (IFN - K); under the control of cytomegalovirus (CMV) promoter	Phase 0
AP-003	BetterLife Pharma	Interferon alfa - 2b	Preclinical
BBT-032	Bolder Biotechnology	Long - acting pegylated interferon beta - 1b analog	Preclinical
Human leukocyte interferon alpha	AIM ImmunoTech	Interferon alpha proteins comprising approximately 166 amino acids ranging in molecular weights from 16, 000 to 27, 000 daltons	Preclinical

Antibodies

Monoclonal antibodies (MAbs), including MAbs directed at neutralizing the virus or those designed to modulate the host response, often represent the first line of investigation and defense against emerging diseases. Murine, chimeric and fully human monoclonal antibodies have been tested; the latter are preferred due to their reduced immunogenicity (Jin, Y. et al (2017); Shanmugaraj, B. et al (2020)). Virus-specific MAbs are potentially useful both in the setting of prevention--preexposure or postexposure prophylaxis--and for the treatment (i.e., to block disease progression) of coronavirus disease (Marovich, M. et al (2020)).

Various MAbs were evaluated during the SARS outbreak. Most of these were directed at the S1 fragment of the spike protein, with the aim of blocking its interaction with the cellular binding receptor ACE2 (Shanmugaraj, B. et al (2020)). Neutralization of Middle East respiratory syndrome coronavirus has been attempted using a related strategy targeting the receptor (CD26/DPP4) binding domain of the MERS-CoV spike glycoprotein. One such MAb designated m336 neutralized the virus with exceptional potency, and was reported to have great potential as a candidate therapeutic or as a reagent to facilitate the development of MERS-CoV vaccines (Ying, T. et al (2014)). Japanese researchers also investigated anti-CD26 MAbs for MERS-CoV and identified the humanized MAb YS110 as a promising candidate, with the advantage that this agent had already undergone clinical testing for other indications (Ohnuma, K. et al (2013)).MAbs directed to the S protein of SARS-CoV-2 have also been described in the literature. Such neutralizing antibodies could be used to reduce the course of infection or in the setting of prevention (Tian, X. et al (2020); Kumar, G.V. et al (2020)). The specific human monoclonal antibody CB6, isolated from a recovered Covid-19 patient, demonstrated substantial neutralization activity in vitro against SARS-CoV-2. CB6 reduced virus levels by about 3 logs in rhesus monkeys when administered one day after infection. When given one day before viral challenge, CB6 was able to keep viral load at no more than 103 RNA copies/mL, demonstrating strong prophylactic protection. Structural studies showed that CB6 recognizes epitopes in SARS-CoV-2 receptor binding domain that overlap with ACE2 binding sites, thereby directly obstructing virus/receptor interactions. The Fc portion of CB6 was modified in order to reduce the risk of antibody-dependent enhancement, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis (Shi, R. et al (2020)). The MAb, renamed JS-016, was one of the first virus-specific MAbs to progress to clinical testing; several other anti-S MAbs have followed, as shown in the table below.

In November 2020, the U.S. FDA granted Emergency Use Authorization for the investigational neutralizing antibody bamlanivimab (LY-CoV555) for the treatment of mild to moderate Covid-19 in adults and pediatric patients 12 years and older with a positive Covid-19 test, who are at high risk for progressing to severe disease and/or hospitalization. Bamlanivimab should be administered as soon as possible after a positive Covid-19 test and within 10 days of symptom onset. The authorization allows for the distribution and emergency use of bamlanivimab, which is administered via a single intravenous infusion.

Polyclonal antibodies (pAbs) are secreted by different B cell lineages, whereas MAbs are secreted from one lineage. pAbs include several immunoglobulin molecules that each react to a specific antigen. Each pAb recognizes a unique epitope on that antigen. These antibodies have the advantage of being extremely easy and cheap to produce. In June 2020, the dual polyclonal antibody REGN-COV2 (casirivimab/imdevimab) entered an adaptive phase I/II/III clinical testing program for the prevention and treatment of Covid-19. The REGN-COV2 clinical program was designed to evaluate the therapy in four separate study populations: hospitalized Covid-19 patients, nonhospitalized symptomatic Covid-19 patients, uninfected people in groups that are at high-risk of exposure (e.g., healthcare workers or first responders) and uninfected people with close exposure to a Covid-19 patient (e.g., a housemate). REGN-COV2 has the potential both to prevent and treat infection, and also to preempt viral escape. The two antibodies bind noncompetitively to the critical receptor binding domain of the spike protein, which diminishes the ability of mutant viruses to escape treatment. REGN-COV2's preclinical development and preclinical/clinical manufacturing was funded in part by BARDA. On November 21, the FDA granted EUA to the antibody cocktail for the treatment of mild to moderate Covid-19 in adults, as well as in pediatric patients at least 12 years of age and weighing

at least 40 kg, who have received positive results of direct SARS-CoV-2 viral testing and are at high risk for progressing to severe Covid-19 and/or hospitalization.

In addition to MAbs targeted the virus itself, many others in development for Covid-19 target the host immune response and cytokine storm. These are discussed in later sections of this report.

Monoclonal and polyclonal antibodies under active development for coronavirus infections

Drug name	Organizations	Description	Phase
Bamlanivimab	Lilly	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase III
COVID-HIG	Grifols; Emergent BioSolutions		Phase III
Canakinumab	Novartis	Anti-IL1B (Interleukin-1beta); Signal Transduction Modulators	Phase III
Casirivimab/Imdevimab	Regeneron	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)/ACE2 Interaction Inhibitors; Viral Attachment Inhibitors; Viral Fusion Inhibitors	Phase III
CoVIg-19	CSL Behring; Takeda	Drugs Targeting Human SARS Coronavirus (SARS-CoV) Proteins	Phase III
Infliximab	National Institutes of Health (NIH)	Anti-TNF-alpha; Signal Transduction Modulators	Phase III
Lenzilumab	Humanigen	Anti-GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor; CSF2); Signal Transduction Modulators	Phase III
Ravulizumab	Alexion Pharmaceuticals	Anti-C5 (Complement 5)	Phase III
Regdanvimab	Celltrion	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase III
Sarilumab	Sanofi	Anti-IL6R (Interleukin-6 Receptor Subunit alpha; CD126); Signal Transduction Modulators	Phase III
Tocilizumab	Roche; Chugai Pharmaceutical	Anti-IL6R (Interleukin-6 Receptor Subunit alpha;	Phase III

		CD126); Signal Transduction Modulators	
BDB-001	Staidson (Beijing) Biopharmaceuticals	Anti-C5 (Complement 5)	Phase II/III
EB-05	Edesa Biotech	Anti-TLR4; Signal Transduction Modulators	Phase II/III
Emapalumab	Swedish Orphan Biovitrum	Anti-IFN-gamma (Interferon gamma); Signal Transduction Modulators	Phase II/III
GSK-4182136	Vir Biotechnology; GlaxoSmithKline	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase II/III
INM-005	Inmunova		Phase II/III
Leronlimab	CytoDyn	Anti-CD195 (CCR5); Signal Transduction Modulators; Viral Entry Inhibitors	Phase II/III
Mavrilimumab	Kiniksa Pharmaceuticals	Anti-CSF2RA (Granulocyte-Macrophage Colony-Stimulating Factor Receptor Subunit alpha); Signal Transduction Modulators	Phase II/III
Olokizumab	R-Pharm	Anti-IL-6 (Interleukin-6); Signal Transduction Modulators	Phase II/III
Vilobelimab	InflaRx	Anti-C5 (Complement 5)	Phase II/III
Astegolimab	Genentech	Anti-IL1RL1 (Interleukin-1 Receptor-Like 1; ST2)	Phase II
Avdoralimab	Innate Pharma	Anti-Anaphylatoxin Chemotactic Receptor 1 (C5aR; CD88); Signal Transduction Modulators	Phase II
Axatilimab	Syndax Pharmaceuticals	Anti-CSF1R (Macrophage Colony-Stimulating Factor 1 Receptor; CD115); Signal Transduction Modulators	Phase II
CERC-002	Cerecor	Anti-TNFSF14 (Tumor Necrosis Factor Ligand Superfamily Member 14; LIGHT)	Phase II
Camrelizumab	Southeast University	Anti-PD-1; Immune Checkpoint Inhibitors	Phase II
Garadacimab	CSL Behring	Anti-Factor XII; Inhibitors of Blood Coagulation Pathways	Phase II

Gimsilumab	Kinevant Sciences	Anti-GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor; CSF2); Signal Transduction Modulators	Phase II
LY-CoV016	Lilly	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase II
MEDI-3506	AstraZeneca	Anti-IL-33 (Interleukin-33); Signal Transduction Modulators	Phase II
Otilimab	GlaxoSmithKline	Anti-GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor; CSF2); Signal Transduction Modulators	Phase II
Pamrevlumab	FibroGen	Anti-CTGF (Connective Tissue Growth Factor)	Phase II
Plonmarlimab	I-Mab Biopharma	Anti-GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor; CSF2); Signal Transduction Modulators	Phase II
Risankizumab	National Institute Allergy Infect Dis	Anti-IL-23A (Interleukin-23 subunit alpha; IL-23p19); Signal Transduction Modulators	Phase II
Sirukumab	Janssen	Anti-IL-6 (Interleukin-6); Signal Transduction Modulators	Phase II
Trimodulin	Biotest AG		Phase II
XAV-19	Xenothera	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase II
NGM-621	NGM Biopharmaceuticals	Anti-C3 (Complement C3)	Phase I/II
VIR-7832	Vir Biotechnology; GlaxoSmithKline	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase I/II
[131I]-Metuximab injection	Fourth Military Medical University	Anti-CD147 (Basigin (BSG; CD147); Signal Transduction Modulators	Phase I/II
1086612	Chongqing Sidemu Biotechnology	Anti-GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor; CSF2); Drugs Acting on NKG2D; Drugs Targeting Angiotensin-	Phase I/II

		Converting Enzyme 2 (ACE2); Signal Transduction Modulators; Viral Fusion Inhibitors	
1083678	Kamada		Phase I/II
ABL-901	HiFiBiO	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase I
ABP-300	Abpro	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase I
AK-119	Akeso Biopharma	Anti-5'-nucleotidase (NT5E; CD73); Immune Checkpoint Inhibitors	Phase I
ARGX-117	argenx	Anti-C2 (Complement C2)	Phase I
AZD-7442	AstraZeneca	Drugs Targeting Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins	Phase I
Adalimumab	University of Oxford	Anti-TNF-alpha; Signal Transduction Modulators	Phase I
Anti-SARS-CoV-2 IgY	Stanford University	Drugs Targeting Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins	Phase I
BGB-DX-P593	BeiGene	Drugs Targeting Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins	Phase I
BRII-196	Brii Biosciences	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase I
BRII-198	Brii Biosciences	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Phase I
CPI-006	Corvus Pharmaceuticals	Anti-5'-nucleotidase (NT5E; CD73); Immune Checkpoint Inhibitors	Phase I
Daxdilimab	Viela Bio	Anti-ILT7 (Leukocyte Immunoglobulin-Like Receptor Subfamily A Member 4; LILRA4)	Phase I
REGN-3048	Regeneron	Anti-Spike Glycoprotein (MERS-CoV); Viral Fusion Inhibitors	Phase I

REGN-3051	Regeneron	Anti-Spike Glycoprotein (MERS-CoV); Viral Fusion Inhibitors	Phase I
SAB-185	SAB Biotherapeutics	Drugs Targeting Human SARS Coronavirus (SARS-CoV) Proteins	Phase I
SAB-301	SAB Biotherapeutics	Anti-Spike Glycoprotein (MERS-CoV); Viral Fusion Inhibitors	Phase I
STI-1499	Sorrento Therapeutics	Angiotensin-Converting Enzyme 2 (ACE2) Inhibitors; Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Signal Transduction Modulators; Viral Fusion Inhibitors	Phase I
TY-027	Tychan	Drugs Targeting Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins	Phase I
[18F] alphavbeta6-diabody	University of California, Davis	Anti-Alphavbeta6	Phase I
Atibuclimab	Implicit Bioscience	Anti-CD14	Clinical
BD-368-2	Peking University (PKU)	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)/ACE2 Interaction Inhibitors; Viral Attachment Inhibitors; Viral Fusion Inhibitors	Clinical
Eculizumab	Alexion Pharmaceuticals	Anti-C5 (Complement 5)	Clinical
Foralumab	Tiziana Life Sciences	Anti-CD3; Signal Transduction Modulators	Clinical
Itolizumab	Biocon	Anti-CD6 (T-Cell Differentiation Antigen CD6)	Clinical
Lanadelumab	Takeda	Anti-KLKB1 (Plasma Kallikrein)	Clinical
MW-33	Mabwell (Shanghai) Bioscience	Drugs Targeting Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins	Clinical
NI-0801	Edesa Biotech	Anti-CXCL10 (C-X-C Motif Chemokine 10); Signal Transduction Modulators	Clinical

Namilumab	Izana Bioscience	Anti-GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor; CSF2); Signal Transduction Modulators	Clinical
Narsoplimab	Omeros	Anti-MASP2 (Mannan-Binding Lectin Serine Protease 2)	Clinical
Siltuximab	EUSA Pharma	Anti-IL-6 (Interleukin-6); Signal Transduction Modulators	Clinical
1106921	University of Health Sciences Lahore		Clinical
1085777	Shenzhen Third People's Hospital		Clinical
HLX-70	Shanghai Henlius Biotech	Anti-Spike Glycoprotein (SARS-CoV); Viral Fusion Inhibitors	IND Filed
Itolizumab	Equillium	Anti-CD6 (T-Cell Differentiation Antigen CD6)	IND Filed
STI-2020	Sorrento Therapeutics	Angiotensin-Converting Enzyme 2 (ACE2) Inhibitors; Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Signal Transduction Modulators; Viral Fusion Inhibitors	IND Filed
STI-2099	Sorrento Therapeutics	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	IND Filed
2-43	Columbia University	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical
ADG-2	Adagio Therapeutics	Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers	Preclinical
ADM-03820	Ology Bioservices	Drugs Targeting Human SARS Coronavirus (SARS-CoV) Proteins	Preclinical
AR-701	Aridis Pharmaceuticals	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)/ACE2 Interaction Inhibitors; Viral Attachment Inhibitors; Viral Fusion Inhibitors	Preclinical

AR-711	Aridis Pharmaceuticals	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical
CMAB-020	Mabpharm	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Basigin (BSG; CD147)/ACE2 Interaction Modulators; Viral Fusion Inhibitors	Preclinical
COVI-SHIELD	Sorrento Therapeutics	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical
CT-P38	Celltrion	Drugs Targeting Human MERS Coronavirus (MERS-CoV) Proteins	Preclinical
DXP-604	Beijing DanXu Pharmaceuticals	Drugs Targeting Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins	Preclinical
DZIF-10c	Universitaet zu Koeln	Drugs Targeting Coronavirus Proteins	Preclinical
Dioguard	Diomics	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical
Enamptcumab	Aqualung Therapeutics	Anti-NAMPT (Nicotinamide Phosphoribosyltransferase)	Preclinical
IMM-124-E	Immuron		Preclinical
IqY-110	IGY Immune Technologies & Life Sciences	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical
LCA-60	Vir Biotechnology	Anti-Spike Glycoprotein (MERS-CoV); Viral Fusion Inhibitors	Preclinical
LCTG-001	Lactiga		Preclinical
Quetmolimab	Eisai	Anti-CX3CL1 (Fractalkine; FKN)	Preclinical
Sybody 23	Universitaet Zuerich	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical
TB-181-36	Twist Bioscience	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical

TB-202-3	Twist Bioscience	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical
1086205	GigaGen	Drugs Targeting Human SARS Coronavirus (SARS-CoV) Proteins	Preclinical
1098546	Centivax	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Viral Fusion Inhibitors	Preclinical

Immunoglobulin Therapy

Experimental use of passive antibody therapy, including i.v. immunoglobulins or convalescent plasma, was described during the 2003 SARS epidemic (Mair-Jenkins, J. et al (2015); Roback, J.D. et al (2020)). The principal mechanism of action of convalescent plasma--i.e., blood plasma obtained from patients who have overcome a specific infection--is expected to be virus neutralization via transfer of high titers of neutralizing antibodies, although other mechanisms may also be involved, such as antibody-dependent cellular cytotoxicity and/or phagocytosis, or modification of the inflammatory response. Convalescent plasma therapy is most effective when administered in the early stages of infection, when the inoculum size is smaller (Casadevall, A. et al (2020)).

Again during the MERS-CoV outbreak in 2015, some South Korean patients were treated with convalescent plasma. A systematic review and meta-analysis of health care databases and so-called grey literature describing the use of convalescent plasma, serum or hyperimmune immunoglobulin derived from convalescent plasma to treat severe acute respiratory infections of viral origin concluded that the approach was safe and may decrease the risk of mortality (Mair-Jenkins, J. et al (2015)). However, Saudi Arabian scientists reported that clinical trials evaluating this therapy would be challenging due to the limited availability of suitable donors, i.e., individuals with sufficiently high neutralizing antibody titers (Arabi, Y. et al (2016)).

Convalescent plasma was used in China to treat some patients with Covid-19, although not in the setting of controlled clinical trials (Roback, J.D. et al (2020)). The potential of the treatment to improve clinical outcomes in patients with laboratory-confirmed Covid-19 and acute respiratory distress syndrome was evaluated in 5 critically ill patients who had severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment and who were receiving mechanical ventilation. The treatment consisted of convalescent plasma with a SARS-CoV-2-specific antibody (IgG) binding titer greater than 1:1000 and a neutralization titer greater than 40 that had been obtained from 5 patients who recovered from COVID-19; it was administered 10-22 days after admission. Following the transfusion, body temperature normalized within 3 days in 4 of 5 subjects, the Sequential Organ Failure Assessment (SOFA) score decreased from 2-20 before to 1-4 after and Pao2/Fio2 improved in 4 of 5 patients, increasing within 12 days from 172-276 to 284-366. Viral loads became negative within 12 days and SARS-CoV-2-specific ELISA and neutralizing antibody titers increased from 40-60 before to 80-320 on day 7. ARDS resolved in 4 patients at 12 days after transfusion and 3 patients were weaned from mechanical ventilation within 2 weeks. Three patients had been discharged from the hospital at the time of reporting and two were in stable condition 37 days after transfusion. Though the effects of treatment may have been influenced by the fact that other treatments such as antivirals were also given, further study in a larger number of patients appeared warranted (Shen, C. et al (2020)). A subsequent larger study, conducted in Wuhan, China, was terminated after enrolling 103 of a planned 200 patients due to containment of the epidemic in that city. Patients with laboratory-confirmed, severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, or requiring mechanical ventilation) Covid-19 were randomized to standard therapy with or without convalescent plasma. Clinical improvement within 28 days was met by 51.9% and 43.1% of the convalescent plasma and control group, respectively; however, there was no statistical difference in the primary outcome measure of

time to clinical improvement (Li, L. et al (2020)). As stated above, this treatment is thought to work by suppressing viremia, which typically peaks in the first 10-14 days of illness; therefore, if convalescent plasma is administered in the early stages of disease, or in the setting of prophylaxis, it might be more effective (Chen, L. et al (2020); Casadevall, A. et al (2020)).

In March 2020, the U.S. FDA issued a notice stating that investigators wishing to study the compassionate use of convalescent plasma to treat patients with Covid-19 were encouraged to submit requests to FDA for investigational use under the traditional IND regulatory pathway (Investigational COVID-19 convalescent plasma - Emergency INDs (Food and Drug Administration, March 25, 2020)). In April, the FDA issued guidance for health care providers and investigators regarding the administration and study of Covid-19 convalescent plasma during the public health emergency (Investigational Covid-19 convalescent plasma - Guidance for industry (Food and Drug Administration, April 2020)). In August, the FDA issued an emergency use authorization for convalescent plasma as a passive immune therapy for the treatment of hospitalized patients with Covid-19 (Covid-19 convalescent plasma EUA decision memo (Food and Drug Administration, August 23, 2020)). Just a week later, however, the NIH released a statement on behalf of the Covid-19 Treatment Guidelines Panel. The panel concluded that there are insufficient data at this time to recommend either for or against the use of convalescent plasma for the treatment of Covid-19, and that it should not be considered the standard of care. The NIH panel called for prospective, well-controlled, adequately powered randomized trials (The COVID-19 Treatment Guidelines Panel's statement on the emergency use authorization of convalescent plasma for the treatment of COVID-19 (National Institutes of Health news release, September 1, 2020)).

In a study conducted at Brown University Medical School, 64 hospitalized patients with severe Covid-19 were treated within 7 days of symptom onset with convalescent plasma, and outcomes were compared to those in a matched control group of 177 patients. In-hospital mortality, the primary outcome measure, was 12.5% in the convalescent plasma ground and 15.8% in controls; the difference was not statistically significant. Similarly, there was no significant difference in the overall rate of hospital discharge between the two groups, although this rate did improve significantly among patients aged 65 years and older who received the experimental therapy. The investigators concluded that further studies should target this subgroup of the population (Rogers, R. et al (2020)).

An alternative to convalescent plasma, which contains both IgG and IgM but varies in antibody specificity and titer depending upon donor characteristics, is hyperimmune globulin (H-Ig), which contains standardized antibody doses but is devoid of IgM due to fractionation (Roback, J.D. et al (2020)). In March 2020, Takeda announced that it was initiating the development of a highly purified anti-SARS-CoV-2 polyclonal H-Ig designated TAK-888 to treat high-risk individuals with Covid-19. Takeda is in discussions with national health and regulatory agencies and healthcare partners in the U.S., Asia and Europe to rapidly advance research into TAK-888. This requires access to source plasma from people who have successfully recovered from Covid-19 or who have been vaccinated, once a vaccine is developed.

Corticosteroids

Corticosteroids were widely used during the SARS epidemic, although there was little consensus at the time regarding optimal treatment regimens. A review published some years later by Chinese researchers concluded that corticosteroid therapy had a positive impact on oxygenation index (OI), used as a measure of efficacy. Among the 225 SARS patients treated at a single Chinese center in 2003, the use of corticosteroids increased OI from an average of 237 mmHg at baseline to 335 mmHg after steroid administration. The optimum dose was determined to be 1-3 mg/kg (or 160-240 mg/day) for a total accumulated dose of 1000-2000 mg. The optimum duration of treatment was 8-14 days (Jia, W.D. et al (2009)).

Data obtained in a Hong Kong hospital support use of pulsed methylprednisolone as rescue therapy only during the later stages of SARS; administration during the earlier phases of disease appeared to actually prolong viremia (Hui, D.S. et al (2010)). In fact, later analysis showed that prolonged methylprednisolone use was associated with worse outcomes, including

disseminated fungal infection and avascular osteonecrosis, and increased 30-day mortality (Pillaiyar, T. et al (2020)); as such, corticosteroids should be used only with caution in the treatment of patients with MERS (Zumla, A. et al (2015)).

Based on previous experience with SARS and MERS, routine use of corticosteroids was not initially recommended in patients in Wuhan with Covid-19 (Huang, C. et al (2020); Lai, C.C. et al (2020)), although this guidance has evolved significantly since those early days. Based on the results of multiple clinical studies described below, in September 2020, WHO issued new treatment guidelines that recommend strongly in favor of the administration of systemic corticosteroids to treat patients with severe and critical Covid-19. A second recommendation is against use of corticosteroids in patients with mild Covid-19 (Corticosteroids for COVID-19 - Living guidance (World Health Organization, September 2020)).

Dexamethasone is a synthetic adrenocortical steroid that is 4-5 times more potent than prednisone. A multicenter study conducted in Spain was the first to find that addition of dexamethasone to routine ICU care reduced the duration of mechanical ventilation and decrease ICU, in-hospital and all-cause mortality in patients with moderate to severe ARDS. Although the patients in this study did not have Covid-19, the trial provided convincing evidence of the efficacy of dexamethasone for treatment of severe respiratory disease, including that caused by SARS-CoV-2 (Villar, J. et al (2020)).

In June 2020, researchers from the U.K. RECOVERY trial--which is testing a range of potential treatments for COVID-19, including dexamethasone--announced that recruitment into the dexamethasone arm of the study was being halted upon determining that sufficient patients had been enrolled to establish whether or not the drug had a meaningful benefit. A total of 2,104 patients had been randomized at that point to receive dexamethasone 6 mg once per day (orally or by i.v. injection) for ten days and were compared with 4,321 patients randomized to usual care alone. Among the patients who received usual care alone, 28-day mortality was highest in those who required ventilation (41%), intermediate in those patients who required oxygen only (25%) and lowest among those who did not require any respiratory intervention (13%). As compared to patients receiving usual care alone, dexamethasone reduced deaths by one-third in mechanically ventilated patients (29.3% vs. 41.4%) and by one-fifth (23.3% vs. 26.2%) in patients receiving oxygen without invasive mechanical ventilation. There was no benefit among those patients who did not require respiratory support at randomization (Horby, P. et al (2020)).

In September 2020, three clinical studies and a meta-analysis were published simultaneously in the Journal of the American Medical Association. One of the studies, the CoDEX randomized, open-label clinical trial, enrolled 299 Brazilian patients with moderate to severe Covid-19 and ARDS who were randomized to dexamethasone plus standard of care or standard care alone. In this study, treatment with the steroid resulted in a statistically significant increase in the number of days alive and free from mechanical ventilation during the first 28 days (Tomazini, B.M. et al (2020)). The REMAP-CAP study was designed to determine whether intravenous hydrocortisone (administered either as a 7-day fixed-dose course or given only when shock is clinically evident) improves 21-day organ support-free days in patients with severe Covid-19. The study was terminated prematurely when results of another study were published; however, an analysis of the data generated before termination suggested that treatment with the afore-mentioned hydrocortisone regimens, compared with no hydrocortisone, yielded 93% and 80% probabilities of superiority, respectively (Angus, D.C. et al (2020)). A French study, which was also terminated prematurely, enrolled 149 of a planned 290 critically ill patients who were randomized to hydrocortisone or placebo. The multicenter, randomized, double-blind sequential trial included an interim analysis after every 50 new patients were enrolled; the DSMB recommended early termination due to slowing of the outbreak in France together with results of the RECOVERY trial. In the post hoc analysis, the difference in 21-day mortality was not statistically significant; however, the trial is likely underpowered due to the early termination (Dequin, P.-F. et al (2020)). The meta-analysis included 7 studies conducted between February and June 2020 and enrolling a total of 1,703 hospitalized, critically ill patients with suspected or confirmed Covid-19, including those who were or were not receiving invasive mechanical ventilation at randomization. The primary outcome measure was all-cause mortality at 28 days after randomization. These meta-analysis found that treatment with corticosteroids

(dexamethasone or hydrocortisone) reduced mortality in the most severely ill patients from 40% to 32%, equivalent to a a 20% relative reduction (Sterne, J.A.C. et al (2020)).

Corticosteroids have multiple mechanisms of action, including immunomodulation as well as inhibition of the hyperinflammatory response. This appears to be a class effect; thus, no one steroid is recommended over any other (Corticosteroids for COVID-19 - Living guidance (World Health Organization, September 2020)).

Stem Cell Therapy

Cell-based approaches--particularly mesenchymal stem cells (MSCs)--are considered one of the more promising potential therapies for acute respiratory distress syndrome (ARDS) in patients with Covid-19, particularly severe or critical cases (Liu, S. et al (2020)). An attractive feature of MSCs is their potential to treat sepsis as well as acute lung injury, given the high rate of comorbidity of these two disorders.

Exogenous stem cells can be delivered to the lung intravenously, intratracheally or by direct injection. Following systemic administration, MSCs migrate to the lungs and become lodged in pulmonary vascular bed. Due to their pluripotent nature, MSCs are capable of secreting various paracrine factors such as growth factors, endothelial and epithelial permeability-regulating factors, as well as antiinflammatory cytokines and antimicrobial peptides. As such, they can potentially treat several of the major pathological features of ALI, including impaired alveolar fluid clearance, altered lung endothelial permeability and dysregulated inflammation; they can also enhance tissue repair, inhibit bacterial growth and exert immunomodulatory effects (Rogers, C.J. et al (2020); Khoury, M. et al (2020); Leng, Z. et al (2020)). In addition to bone marrow- or adipose-derived MSCs, other stem cell populations with potential application in the treatment of Covid-19-related acute lung injury include embryonic stem cells, circulating endothelial progenitor cells, and amniotic fluid stem/progenitor cells (Warburton, D. et al (2008); Rogers, C.J. et al (2020)).

Stem cell therapies under active development for coronavirus infection and disease

Drug name	Organizations	Description	Phase
Remestemcel-L	Mesoblast	Allogeneic bone marrow (iliac crest) - derived mesenchymal stem cells	Phase III
MAPC	Athersys	Allogenic human bone marrow - derived multipotent adult progenitor cells (MAPCs)	Phase II/III
AD-MSCs (allogeneic)	Hope Biosciences	Human allogeneic adipose tissue - derived mesenchymal stem cells	Phase II
CAP-1002	Capricor Therapeutics	Allogeneic cardiosphere - derived stem cells (CDCs)	Phase II
DB-001	Direct Biologics	Human allogeneic bone marrow mesenchymal stem or stromal cells - derived exosomes	Phase II
Emiplacel	Pluristem	Human allogeneic placenta - derived adherent mesenchymal stromal - like cells expressing cell surface markers CD29, CD73 and CD105	Phase II

CB-MSCs	Duke University; Restem	Human allogeneic umbilical cord blood - derived mesenchymal stem cells	Phase I/II
Descartes-30	Cartesian Therapeutics	Human allogeneic mesenchymal stem cells (MSCs) RNA - engineered to secrete a combination of DNases; generated using Cartesian's RNA Armory(SM) technology	Phase I/II
HC-016	Histocell	Human allogeneic adipose tissue - derived mesenchymal stem cells expanded and pulsed with H2O2	Phase I/II
JadiCell	University of Miami (UM)	Universal donor human umbilical cord - derived mesenchymal stem cells	Phase I/II
Orbcel-C	Orbsen Therapeutics	Human umbilical cord - derived CD362+ mesenchymal stromal cells	Phase I/II
SBI-101	Sentien Biotechnologies	Human allogeneic mesenchymal stromal cells	Phase I/II
WJ-MSC	Hopitaux de Paris	Human umbilical Wharton's jelly (WJ) - derived mesenchymal stem cells	Phase I/II
1087610	Renmin Hospital of Wuhan University	Human allogeneic dental pulp - derived mesenchymal stem cells	Phase I/II
CLBS-119	Caladrius Biosciences	Peripheral blood - derived autologous CD34+ cells	Phase I
AD-MSCs (autologous)	Hope Biosciences; Celltex Therapeutics	Human autologous adipose tissue - derived mesenchymal stem cells	IND Filed
AstroStem-V	Nature Cell	Human allogeneic adipose tissue - derived mesenchymal stem cells	IND Filed
BM-MSCs (allogeneic)	NantKwest	Human allogeneic bone marrow - derived mesenchymal stem cells	IND Filed
BX-U001	Baylx	Human allogeneic umbilical cord tissue - derived mesenchymal stem cells	IND Filed
CYP-001	Cynata Therapeutics	Induced pluripotent stem cell (iPSC) and mesenchymoangioblast - derived mesenchymal stem cells (MCA - MSCs); manufactured using Cymerus technology	IND Filed
DWP-710	Daewoong	Human mesenchymal stem cells	IND Filed

PSC-04	Personalized Stem Cells	Human allogeneic adipose tissue - derived mesenchymal stem cells (MSCs)	IND Filed
ProTrans	NextCell Pharma	Human allogeneic umbilical Wharton's jelly (WJ) - derived mesenchymal stem cells	IND Filed
aMBMC	Stemedica	Human allogeneic bone marrow - derived ischemia - tolerant mesenchymal stem cells (itMSCs)	IND Filed
CB-MSC-1	Avalon Globocare	Allogeneic umbilical cord blood - derived mesenchymal stromal cells (MSCs)	Preclinical
NestCell	Cellavitta Pesquisas Cientificas	Mesenchymal stem cells	Preclinical
XSTEM-ARDS	Xintela	Human mesenchymal stem cells	Preclinical

Targeting the Cytokine Storm

A model has been proposed of the pathogenesis of acute respiratory distress syndrome, such as that occurring in patients with advanced Covid-19. Lung vascular permeability increases in the early or exudative stage, causing the alveolar air space and interstitium to become flooded with protein-rich edema fluid and triggering an inflammatory response (Sapru, A. et al (2015); Tay, M.Z. et al (2020)). Pulmonary or systemic inflammation is both triggered by and prompts the further systemic release of proinflammatory cytokines, sometimes termed a "cytokine storm." Alveolar macrophages release cytokines (IL-6, IL-10 and TNF-alpha), which recruit and activating neutrophils in the lungs (Pedersen, S.F. et al (2020)), leading to further release of inflammatory mediators (leukotrienes, antioxidants, platelet-activating factor and neutrophil elastase). All of these substances have harmful effects on the capillary endothelium and alveolar epithelium, and hence disrupt the epithelial barrier between capillaries and airspaces. As a result, the airspaces and interstitium are flooded with edema fluid, protein and cellular debris. In the resulting cascade of events, surfactant is disrupted, airspaces collapse and there is an imbalance ("mismatch") between ventilation and perfusion, causing hypoxemia (Sweeney, R.M. et al (2016); Tay, M.Z. et al (2020)). In patients with severe Covid-19, the cytokine storm is manifested by an increase in white blood cell count but a simultaneous and significant decrease in CD4+ and CD8+ T cell and natural killer (NK) cell counts, indicating suppression of the adaptive immune response (Pedersen, S.F. et al (2020); Zhang, W. et al (2020)). These patients progress rapidly to cardiovascular collapse, multiorgan dysfunction, sepsis and death (Luo, P. et al (2020)). It should be noted, however, that much remains unknown about the cytokine storm in the context of Covid-19. For example, in comparison to other causes of ARDS, Covid-19 is characterized by lower levels of circulating cytokine responses (Sinha, P. et al (2020)).

Even as more is being learned about the role and scope of cytokine dysregulation in the disease process, several therapeutic approaches targeting the cytokine storm are being evaluated in clinical trials. These agents, which address aspects of the disease that may not improve with antiviral drug therapy, include NSAIDs, glucocorticoids, immunosuppressants, antagonists/inhibitors of proinflammatory cytokines and Janus kinase (JAK) inhibitors (Zhang, W. et al (2020); Yi, Y. et al (2020)).

Transient production of the proinflammatory cytokine interleukin-6 (IL-6) is triggered in response to infection or tissue injury. The cytokine contributes to host defense by stimulating acute phase responses, hematopoiesis and immune reaction. Elevated levels of IL-6 in serum are frequently detected in patients with severe Covid-19, and may correlate with poor prognosis. As such, IL-6 has been identified as a primary driver of the cytokine storm in severe Covid-19 (Russell, B. et al

(2020); Seif, F. et al (2020)), and several early reports in the literature described compassionate use or small trials of monoclonal antibodies targeting IL-6 or its receptor (Sanders, J.M. et al (2020)). In a retrospective observational study conducted in China, a single dose of the humanized anti-IL-6R MAb tocilizumab was administered to 15 patients with various degrees of disease severity and/or comorbidities. Following the treatment, disease stabilized in 10 patients, worsened in 2, and was unable to prevent the deaths of 3 critically ill patients. Nonetheless, the investigators concluded that further evaluation was warranted to determine the appropriate dose and timing of administration, as well as the profile of patients who would benefit from the treatment (Luo, P. et al (2020)). Based on these and other positive findings, a multicenter, large-scale clinical trial was initiated in China (ChiCTR2000029765) and resulted in the treatment of approximately 500 severe or critically patients (Fu, B. et al (2020)). Moreover, according to Chinese Covid-19 treatment guidelines, tocilizumab could be used to reduce Covid-19 mortality in patients with extensive bilateral lung lesions (i.e., ground-glass opacity) or in severe or critical patients who have elevated laboratory detected IL-6 levels (Fu, B. et al (2020)). Subsequent studies conducted in Europe and the U.S. failed to demonstrate a favorable impact on disease outcomes for tocilizumab (Gupta, S. et al (2020); Salvarani, C. et al (2020); Hermine, O. et al (2020)).

Another clinical program has evaluating the anti-IL-6R antibody sarilumab in U.S. patients hospitalized with severe Covid-19 infection (Sanders, J.M. et al (2020)). The randomized, double-blind, placebo-controlled phase II/III trial assessed the safety and efficacy of adding sarilumab to usual supportive care, compared to supportive care plus placebo. The BARDA-supported trial incorporated an adaptive design to evaluate the MAb in adults hospitalized with laboratory-confirmed Covid-19 classified as severe or critical, or who were suffering from multiorgan dysfunction. In April, following a review by the trial's independent data monitoring committee of all available phase II and phase III data and the observation of negative trends in the severe group, the trial was amended so that only patients classified as critical would continue to be enrolled. In July, upon finding that neither primary nor secondary efficacy endpoints had been met in the active treatment arm, and furthermore with adverse events reported by up to 80% of patients, including 3% with serious AEs, the U.S. study was stopped. A separate trial outside the U.S., which is evaluating sarilumab in hospitalized patients with severe and critical Covid-19 but uses a different dosing regimen, remains ongoing.

In September 2020, the Ministry of Health of the Russian Federation approved levilimab, a monoclonal antibody that blocks the interleukin-6 receptor, indicated to prevent the cytokine storm in hospitalized patients with severe Covid-19. With this action, levilimab became the first agent to be approved for this indication in any country.

In July, the Drugs Controller General of India authorized emergency use of the anti-CD6 MAb itolizumab in the treatment of cytokine release syndrome (CRS) in patients with moderate to severe ARDS due to Covid-19. Approval was based on the results of a randomized, controlled clinical trial at multiple hospitals in India in preventing CRS in patients with moderate to severe ARDS due to Covid-19. The primary endpoints for reduction in mortality rate were met and other key secondary endpoints for efficacy and biomarkers were also achieved. Itolizumab demonstrated a statistically significant advantage over the control arm in one-month mortality rate. Statistically significant advantages for itolizumab were also seen over control on key efficacy parameters such as PaO2 and SpO2 (oxygen saturation) improvement without increasing FiO2 (oxygen flow). All the patients in the itolizumab arm were weaned off oxygen by day 30, and none needed ventilator support, unlike the control arm. Key secondary endpoints of clinical markers of inflammation such as IL-6, TNF-alpha, serum ferritin, D-dimer, LDH and CRP showed clinically significant suppression post-dosing and correlated well with clinical improvement in symptoms and chest X-ray images. Itolizumab was well tolerated and was found to be safe. Itolizumab, an anti-CD6 IgG1 monoclonal antibody, has been available in India since 2013 for the treatment of chronic plaque psoriasis.

The interleukin-1 family of soluble protein cytokines includes IL-1alpha, IL-1beta and IL-1 receptor antagonist (IL-1RA). IL-1alpha and IL-beta are proinflammatory cytokines that are involved in inflammatory and immune responses while IL-1RA competes for receptor binding with these two isotypes, thus blocking inflammatory and/or immune activation. Both isotypes are secreted by monocytes, macrophages and accessory cells early during an immune response

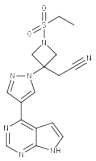
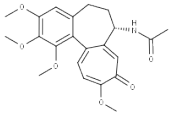
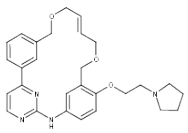
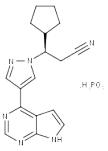
and they activate T and B cells, stimulate T-cell proliferation and enhance T- and B-cell responses to antigens. Overproduction of IL-1 has been implicated in several diseases and may contribute to severe Covid-19. Anakinra, a recombinant IL-1RA, might help to neutralize the hyperinflammatory state in patients with severe disease. In a small study conducted in France, patients with severe Covid-19-related bilateral pneumonia on chest x-ray or lung CT scan who were administered anakinra has less need for invasive mechanical ventilation and reduced risk of death as compared to those receiving standard treatment (Huet, T. et al (2020)).

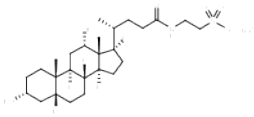
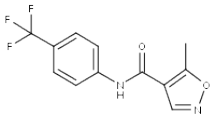
The Janus kinase family (JAK1, JAK2, JAK3 and Tyk2) of kinases are involved in cytokine signaling. JAKs are closely associated with cell surface cytokine receptors, as the latter lack enzymatic activity and require phosphorylation by JAKs to propagate the cytokine signal. Manipulation of the JAK/STAT signaling pathway is being evaluated as a way of indirectly suppressing a range of proinflammatory mediators, including IL-6, thereby reducing viral entry and inflammation in patients with coronavirus (Russell, B. et al (2020); Luo, W. et al (2020)). Several small-molecule JAK inhibitors are approved for marketing and have been suggested for off-label use in treating Covid-19 (Seif, F. et al (2020)), including the reversible JAK1/2 inhibitor baricitinib (Cj Jorgensen, S. et al (2020)). The randomized, double-blind, placebo-controlled, NIH-sponsored ACTT 2 study evaluated the antiviral agent remdesivir, with or without addition of baricitinib, in more than 1,000 hospitalized adult patients with Covid-19. On the basis of the results of this study, in November 2020, the FDA granted an EUA to the combination of baricitinib plus remdesivir for adult and pediatric patients 12 years of age and older and weighing at least 40 kg for the treatment of Covid-19 requiring hospitalization. One concern about JAK inhibitors is that they can also block production of IFN alfa, which has beneficial, infection-fighting effects (Zhang, W. et al (2020); Seif, F. et al (2020)).

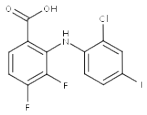
The anti-CCR5 MAb leronlimab (PRO-140) is being evaluated as a potential treatment for patients infected with SARS-CoV-2. Leronlimab has the potential to enhance the cellular immune response by suppressing Treg cells that, in turn, inhibit the antiviral T-cell responses and the potential to repolarize macrophage activity. Leronlimab has shown no drug-related serious adverse events in 9 clinical trials involving more than 800 patients, and has been previously used in combination with protease inhibitors used in HIV therapy, which could be potentially used to treat Covid-19. Preliminary results from the first 10 patients treated in the study suggested significant improvements in several important immunologic biomarkers in 8 of the 10 severely ill patients, with improvements in cytokines and IL-6, and a trend toward normalization of the CD4/CD8 ratio.

The NLRP3 inflammasome has been identified as a potential pathophysiological component determining the clinical course of patients with Covid-19. Inflammasomes are large multiprotein complexes composed of multiple members of the NOD-like receptor family: NLRP3 (sensor), PYCARD (adaptor) and CASP1 (effector). These complexes are responsible for the activation of inflammatory process and innate immune responses associated with host defense. Inflammasomes can rapidly detect invading pathogenic microbes and eliminate them. They are assembled in response to microbial or endogenous products released from damaged or dying cells and the composition of an inflammasome is dependent on the activator that initiates its assembly (Freeman, T.L. et al (2020)). Dysregulation of inflammasomes has been associated with several autoinflammatory and autoimmune disorders, including gout; NLRP3 inflammasomes are also implicated in the pathogenesis of acute respiratory distress syndrome in patients with Covid-19. The marketed uricosuric drug colchicine is a nonselective inhibitor of NLRP3 inflammasomes with an established safety profile; as such, it has been selected for clinical evaluation for the prevention of complications in patients with laboratory-confirmed Covid-19 (Deftereos, S.G. et al (2020); Deftereos, S.G. et al (2020)).

Drugs and biologics targeting the cytokine storm for treatment of Covid-19

Drug name	Organizations	Description	Phase	Structure
Baricitinib	Lilly	Jak1 Inhibitors; Jak2 Inhibitors; Signal Transduction Modulators	Phase III	
Canakinumab	Novartis	Anti-IL1B (Interleukin-1beta); Signal Transduction Modulators	Phase III	
Colchicine	Montreal Heart Institute (MHI)	Antimitotic Drugs; Microtubule Destabilizers (Tubulin Polymerization Inhibitors); NLRP3 Inflammasome Inhibitors	Phase III	
Lenzilumab	Humanigen	Anti-GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor; CSF2); Signal Transduction Modulators	Phase III	
Pacritinib	CTI BioPharma	Angiogenesis Inhibitors; Cyclin-Dependent Kinase 2 (CDK2) Inhibitors; FLT3 (FLK2/STK1) Inhibitors; Interleukin-1 Receptor-Associated Kinase 1 (IRAK-1) Inhibitors; Jak2 Inhibitors; Macrophage Colony-Stimulating Factor 1 Receptor (CSF1R; CD115; c-Fms) Inhibitors; Signal Transduction Modulators	Phase III	
Ruxolitinib phosphate	Novartis; Incyte	Jak1 Inhibitors; Jak2 Inhibitors; Signal Transduction Modulators; Tyk2 Inhibitors	Phase III	
Sarilumab	Sanofi	Anti-IL6R (Interleukin-6 Receptor Subunit alpha; CD126); Signal Transduction Modulators	Phase III	
Tocilizumab	Roche; Chugai Pharmaceutical	Anti-IL6R (Interleukin-6 Receptor Subunit alpha; CD126); Signal Transduction Modulators	Phase III	

Anakinra	Swedish Orphan Biovitrum	Interleukin-1 Receptor Type 1 (IL1R1; CD121a) Antagonists; Signal Transduction Modulators	Phase II/III	
Olokizumab	R-Pharm	Anti-IL-6 (Interleukin-6); Signal Transduction Modulators	Phase II/III	
RPH-104	R-Pharm	Interleukin-1 (IL-1) Inhibitors; Signal Transduction Modulators	Phase II/III	
Dapansutrile	Olatec Therapeutics	NLRP3 Inflammasome Inhibitors	Phase II	
Gimsilumab	Kinevant Sciences	Anti-GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor; CSF2); Signal Transduction Modulators	Phase II	
Otilimab	GlaxoSmithKline	Anti-GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor; CSF2); Signal Transduction Modulators	Phase II	
Plonmarlimab	I-Mab Biopharma	Anti-GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor; CSF2); Signal Transduction Modulators	Phase II	
Sirukumab	Janssen	Anti-IL-6 (Interleukin-6); Signal Transduction Modulators	Phase II	
Sodium taurodeoxycholate	Shaperon	G-Protein Coupled Bile Acid Receptor 1 (GPBAR1; TGR5; GPCR19; GPR131) Agonists; NLRP3 Inflammasome Inhibitors; Signal Transduction Modulators	Phase II	
TD-0903	Theravance Biopharma	Janus Kinase (Jak) Inhibitors; Signal Transduction Modulators	Phase II	
Leflunomide	City of Hope National Medical Center	Angiogenesis Inhibitors; Dihydroorotate Dehydrogenase (DHODH) Inhibitors; Jak3 Inhibitors; PDGFR Family Inhibitors; Signal Transducer and Activator of Transcription 6 (STAT6) Inhibitors; Signal Transduction Modulators	Phase I/II	

1086612	Chongqing Sidemu Biotechnology	Anti-GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor; CSF2); Drugs Acting on NKG2D; Drugs Targeting Angiotensin-Converting Enzyme 2 (ACE2); Signal Transduction Modulators; Viral Fusion Inhibitors	Phase I/II
Itolizumab	Biocon	Anti-CD6 (T-Cell Differentiation Antigen CD6)	Clinical
Jaktinib dihydrochloride monohydrate	Suzhou Zelgen Biosciences	Jak2 Inhibitors; Signal Transduction Modulators	Clinical
Namilumab	Izana Bioscience	Anti-GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor; CSF2); Signal Transduction Modulators	Clinical
Siltuximab	EUSA Pharma	Anti-IL-6 (Interleukin-6); Signal Transduction Modulators	Clinical
Itolizumab	Equillium	Anti-CD6 (T-Cell Differentiation Antigen CD6)	IND Filed
ATR-002	Atriva	Mitogen-Activated Protein (MAP) Kinase Kinase (MEK) Inhibitors; Signal Transduction Modulators	Preclinical 

Targeting Coagulation Disorders

Thrombotic and thromboembolic disease have emerged as potential complications of Covid-19. Potentially due to excessive inflammation, platelet activation, endothelial dysfunction and/or stasis, SARS-CoV-2 infection may predispose to thrombosis in the venous or arterial circulation, manifesting as stroke or venous thromboembolism (Kollias, A. et al (2020); Connors, J.M. et al (2020)). Stroke has been reported as a presenting symptom of Covid-19, including in younger patients without underlying conditions (Oxley, T.J. et al (2020)). Moreover, some investigational agents being tested in patients with Covid-19 may carry the risk of thrombotic events, or may interact with antiplatelet agents, in patients who were taking them prior to becoming infected (Connors, J.M. et al (2020)).

Covid-19-associated coagulopathy (CAC) appears to be linked to the systemic hyperinflammatory host response, rather than a procoagulatory effect of the virus itself. In response to the viral infection, the innate immune system initiates a complex systemic immune cascade which results in the activation of coagulation systems and generation of thrombin, a phenomenon known as immunothrombosis (Bikdeli, B. et al (2020); Levi, M. et al (2020)). Elevated D-dimer level is associated with poor prognosis, and disseminated intravascular coagulation is thought to be involved in the majority of Covid-19 deaths (Tang, N. et al (2020); Kollias, A. et al (2020)).

WHO treatment guidelines recommend pharmacological prophylaxis (low-molecular-weight heparin or heparin) to prevent venous thromboembolism in severely ill adolescents and adults without contraindications, both during acute illness in the hospital and following discharge (Clinical management of severe acute respiratory infection (SARI) when Covid-19 disease is suspected - Interim guidance (World Health Organization, updated March 13, 2020)). Higher than the standard therapeutic dose may be required in Covid-19 patients, particularly those who are obese. Current data do not support the use of anticoagulants to treat microvascular thrombosis (Bikdeli, B. et al (2020)).

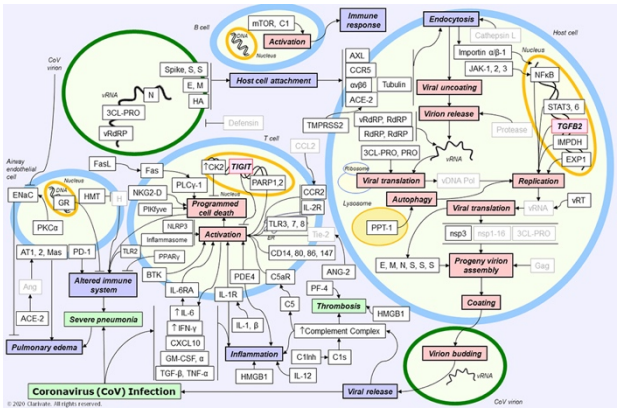
Several investigational agents targeting Covid-19-associated coagulopathy are being evaluated in the clinic, including dociparstat sodium, a non-anticoagulant heparin derivative (2-O, 3-O desulfated heparin) that retains antiinflammatory activity. The drug is being evaluated in phase II/III clinical trials at Chimerix for the treatment of acute lung injury (ALI) in patients with severe Covid-19. The mechanistic rationale supporting dociparstat's potential in ALI patients with Covid-19 is two-fold. The first is based in its potential to decrease inflammation/immune cell infiltration in Covid-19 patients with ALI, and the second in its potential to alleviate the underlying causes of coagulation disorders by inhibiting HMGB1 and platelet factor 4 (PF4) activities. HMGB1, an endogenous damage-associated molecular pattern (DAMP) molecule, has been identified as a therapeutic target for Covid-19 (Andersson, U. et al (2020)).

The complement system comprises more than 30 members, which are implicated in the host defense response to infection and injury. This family of serum molecules mediates inflammation and opsonization of antigens and microorganisms in addition to controlling lysis of pathogens or cells sensitized with antibody. These serum molecules may be activated via the classical pathway involving activation by immune complexes binding to C1q subcomponent of C1, which has six Fc binding sites, or by an alternative pathway that can involve activation in the presence of suitable surface molecules. In the case of SARS-CoV-2, the spike protein (subunits 1 and 2) is capable of activating the alternative pathway. Complement components interact with each other, so that a small stimulus can result in a cascade of activity (Gralinski, L.E. et al (2018); Yu, J. et al (2020)). Alternative pathway of complement activation has also been implicated in the formation of diffuse thrombotic microangiopathy and end organ dysfunction, both of which are associated with increased morbidity and mortality in Covid-19 patients. Inhibition of the complement system has been identified as a potential method of treating patients with severe disease due to SARS-CoV-2 infection (Diurno, F. et al (2020); Campbell, C.M. et al (2020); Yu, J. et al (2020)).

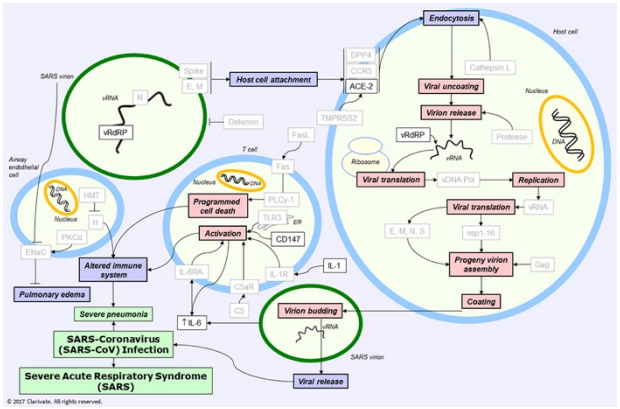
Targets for Therapeutic Intervention

For an overview of validated therapeutic targets for this indication, consult the targetscape below. The targetscape shows an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of the condition and their biological actions. An arrow indicates a positive effect; a dash indicates a negative effect. Gray or lighter symbols are protein targets that are not validated (i.e., not under active development [UAD]). Pink text boxes with red borders indicate validated gene targets. Yellow text boxes are gene targets not UAD. Purple and pink text boxes indicate extracellular and intracellular effects, respectively. Green text boxes indicate a related disease/condition/symptom. For in-depth information on a specific target or mechanism of action, see the corresponding section in this report.

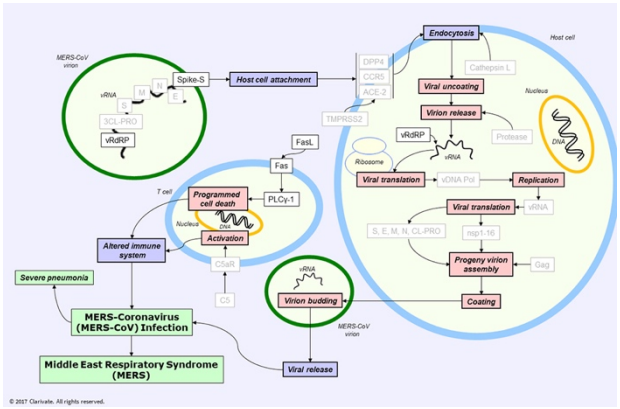
Coronavirus (CoV) Infection Targetscape



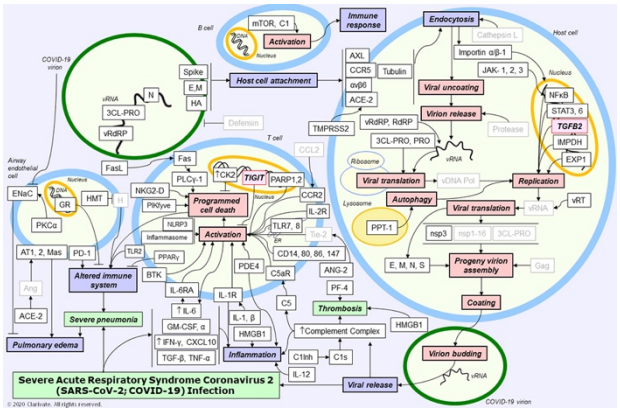
Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV) Infection Targetscape



Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection Targetscape



Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2; COVID-19) Infection Targetscape



02-Dec-2020

RS-5614 studied in investigator-initiated trial for severe COVID-19

Renascience has reported the start of an investigator-initiated trial of the plasminogen activator inhibitor-1 (PAI-1) RS-5614 (TM-5614) to treat lung injuries associated with COVID-19 infections (ClinicalTrials.gov Identifier NCT04634799). The single-center, randomized, double-blind, placebo-controlled trial, at Northwestern University will enroll high-risk patients hospitalized with severe COVID-19 and requiring supplemental oxygen, specifically those age 65 years or older, or those under 65 years with at least one major cardiometabolic comorbidity (diabetes, hypertension or cardiovascular disease). Patients will be randomized in a 1:1 ratio to receive standard of care plus RS-5614 or standard of care plus placebo. The primary endpoint is clinical improvement at 7 days, defined as change of at least 2 points in the NIAID-defined ordinal scale. Secondary outcome measures will assess: change in sequential organ failure assessment (SOFA) score; change in PAI-1 levels; and ventilator free days. In animal models, RS-5614 has been found to strongly inhibit the formation of micro-thrombi and significantly reduce airway inflammation, fibrosis and emphysema in the lungs

02-Dec-2020

Edesa initiates phase II/III study of EB-05 for hospitalized patients with COVID-19

Edesa Biotech has enrolled the first patient in a phase II/III trial evaluating the company's investigational drug, EB-05, as a therapy for hospitalized COVID-19 patients (ClinicalTrials.gov Identifier NCT04401475). The company plans to enroll approximately 316 patients in the phase II portion of the multicenter, double-blind, placebo-controlled study. Up to 40 hospitals are expected to take part. Pending favorable outcomes in the phase II part of the trial, Edesa will continue with a pivotal phase III study. Edesa believes EB-05, a monoclonal antibody, could regulate the overactive and dysfunctional immune response associated with acute respiratory distress syndrome (ARDS) by modulating the Toll-like receptor 4 (TLR4) signaling pathway. The drug is delivered intravenously in a single infusion to hospitalized COVID-19 patients (Edesa Biotech News Release).

02-Dec-2020

Investigator-initiated trial to study Carragelose nasal spray for COVID-19 prophylaxis

Swansea University Medical School plans to conduct a clinical trial with Carragelose (iota-/kappa-carrageenan) nasal spray as a COVID-19 prophylaxis for healthcare professionals (ClinicalTrials.gov Identifier NCT04590365). The investigator-initiated, double-blind, randomized trial, named ICE-COVID, will recruit 480 healthcare professionals managing COVID-19 patients during the pandemic. Subjects will be equally randomized into a treatment group (0.12 mg/mL iota-carrageenan / 0.4 mg/mL kappa-carrageenan in 0.5% saline) and a placebo group (0.5 % saline) and will apply this study regime three times a day, one dose into each nostril and three throat sprays, over the course of 8 weeks. The objective of the study is to assess the efficacy of Carragelose nasal and throat spray in reducing the rate, severity and duration of COVID-19 infections. Further endpoints include infection with other respiratory viruses, usability of the spray for prophylaxis and the effects on quality adjusted life years (QALYs). Carragelose is a sulfated polymer from red seaweed and a unique, broadly active antiviral compound. Several clinical and preclinical studies have shown that Carragelose forms a layer on the mucosa wrapping entering viruses, thereby inactivating them, and preventing them from infecting cells. The new trial is supported by Marinomed Biotech, the originator and licensor of Carragelose, and Boots UK. The Carragelose nasal spray used in the study is marketed as Boots Dual Defence in the U.K. (Marinomed Biotech News Release).

02-Dec-2020

DMC completes positive safety review of CYNKCOVID study

Celularity announced that the independent Data Monitoring Committee (DMC) completed the first assessment of the ongoing phase I/II CYNK-001-COVID-19 study (CYNKCOVID; ClinicalTrials.gov Identifier NCT04365101) with CYNK-001 off-the-shelf, allogeneic, natural killer (NK) cell therapy in adults patients with COVID-19. The DMC confirmed the absence of dose-limiting toxicities (DLTs) and recommended to move forward with the trial. Additionally, there was no evidence of worsening of inflammatory biomarkers, and the observed clinical findings justify the continuation of the trial. Enrollment is currently ongoing in this multicenter study, with active sites in Arizona, Arkansas, California, New Jersey and Washington. The phase I/II CYNKCOVID clinical trial is continuing to enroll to the next evaluation milestone where the external, independent DMC will review the phase I data for both safety and efficacy. Celularity continues to accumulate safety data on CYNK-001 across a broad platform of programs including COVID-19, as well as hematologic and solid tumor malignancies (Celularity News Release).

02-Dec-2020

FDA clears IND for phase I study of DHOHD inhibitor RP-7214 for COVID-19

The FDA has approved Rhizen Pharmaceuticals' IND application to study its oral dihydroorotate dehydrogenase (DHOHD) inhibitor, RP-7214, for SARS-CoV-2 infection. The initial phase I study, which will begin dosing this month, will evaluate single ascending doses of RP-7214 in healthy volunteers. A follow-up to this study would assess multiple ascending doses in patients with COVID-19. RP-7214 has shown potent inhibition of COVID-19 viral replication. Its host-based mechanism could allow complementary combinations with direct acting antiviral drugs, while its broad anti-inflammatory action could potentially mitigate the cytokine mediated inflammatory symptoms typically seen in SARS-CoV-2 and other viral infections. RP-7214 has also been studied across multiple inflammation models where it has demonstrated encouraging anti-inflammatory activity. IND-enabling preclinical studies show RP-7214 to be orally available, safe and tolerable with predictable dose-linear pharmacokinetics (Rhizen Pharmaceuticals News Release).

02-Dec-2020

U.K. approval for Pfizer and BioNTech's COVID-19 mRNA vaccine BNT-162b2

The U.K.'s Medicines & Healthcare Products Regulatory Agency (MHRA) has granted a temporary authorization for emergency use for Pfizer and BioNTech's COVID-19 mRNA vaccine BNT-162b2 against COVID-19. This constitutes the first emergency use authorization following a worldwide phase III trial of a vaccine to help fight the pandemic. The MHRA's decision was based on a rolling submission, including data from the phase III study, which demonstrated a vaccine efficacy rate of 95% for BNT-162b2 in participants without prior SARS-CoV-2 infection (first primary objective) and also in participants with and without prior SARS-CoV-2 infection (second primary objective), in each case measured from 7 days after the second dose. The first primary objective analysis is based on 170 cases of COVID-19, as specified in the study protocol. Efficacy was consistent across age, gender, race and ethnicity demographics, with an observed efficacy of more than 94% in adults age 65 years and older. BNT-162b2 was generally well tolerated. Pfizer and BioNTech previously signed an agreement to supply a total of 40 million doses to the U.K. with the first doses expected to arrive in the coming days and delivery fulfilment expected to be completed next year. The companies have developed temperature-controlled shippers for the BNT-162b2 vaccine candidate, which can maintain recommended storage conditions (-70 C +/-10 C) for extended periods of time without any additional equipment but dry ice. Regulatory decisions by the FDA and the E.U.'s EMA are expected this month. BioNTech will hold the regulatory authorization in the U.K., and, if granted, in the U.S.,

the E.U., Canada and other countries. Pfizer will have the commercialization right worldwide with the exception of China, Germany and Turkey (BioNTech News Release).

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01-Dec-2020

Antiviral novaferon exhibits anti-SARS-CoV-2 effects both at cellular level and in COVID-19 patients

Novaferon (rIFN-a2b) is a recombinant antiviral protein produced by DNA shuffling of IFN-alpha. Recently, investigators from The First Hospital of Changsha and collaborators published preclinical and first clinical results of novaferon against SARS-CoV-2 causing COVID-19. Novaferon inhibited viral replication (EC50 = 1.02 ng/mL) in Vero E6 cells infected with SARS-CoV-2 and also prevented viral entry into healthy cells (EC50 = 0.10 ng/mL) in vitro. In a randomized, open-label, parallel-group trial (Chinese Clinical Trial Registry Number ChiCTR2000029496) including 89 COVID-19 patients, the viral clearance rates of novaferon alone (50.0%) or in combination with lopinavir/ritonavir (60.0%) were significantly higher than that of lopinavir/ritonavir (24.1%) on day 6. On day 9, SARS-CoV-2 clearance rates were similar among the three groups: 56.7% in the novaferon group, 70.0% in the novaferon plus lopinavir/ritonavir group, and 51.7% in the lopinavir/ritonavir group. The median time to viral clearance was 6 days for both novaferon and novaferon plus lopinavir/ritonavir, compared with 9 days for the lopinavir/ritonavir group. During the observation period, none of the moderately ill patients receiving novaferon alone or in combination with lopinavir/ritonavir progressed to severe illness, while 4 patients in the lopinavir/ritonavir group progressed to severe illness. No severe adverse events were observed for any of the antiviral drugs, and no specific adverse events were related to novaferon treatment. Authors concluded that novaferon exhibits anti-SARS-CoV-2 effects both at cellular level and in COVID-19 patients, which justifies further large-scale clinical evaluation (Zheng, F. et al. Int J Infect Dis 2020, 99: 84).

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01-Dec-2020

DMX-200 selected for inclusion in CLARITY 2.0 study for COVID-19

Dimerix's DMX-200 (propagermanium) has been selected for inclusion in a new investigator-initiated feasibility/phase III study, CLARITY 2.0, for COVID-19. Led by the University of Sydney, the trial will assess the safety and effectiveness of DMX-200 administered together with an angiotensin receptor blocker (ARB), on clinical outcomes of approximately 600 participants in India who have tested positive for COVID-19. In this prospective, multicenter, randomized, double blind, placebo-controlled study, participants will be treated for up to 28 days and then followed up for a total of 26 weeks. The primary endpoint is the 7-point clinical health score developed by the WHO for COVID-19 trials, scored from no hospitalization or ventilation requirement through to death, at treatment day 14. The DMX-200 therapy is aimed at reducing damage from inflammatory immune cells by blocking their signaling and limiting subsequent movement in the lungs, or other tissues, damaged by the virus. In September, Dimerix was awarded USD 1 million from the Australian Government's Biomedical Translation Bridge program to support the inclusion of DMX-200 in the REMAP-CAP global study in COVID-19 patients with acute respiratory distress syndrome (ARDS) (Dimerix News Release).

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01-Dec-2020

New COMMUNITY adaptive platform trial for COVID-19 begins enrollment

Three members of the COVID R&D Alliance (Amgen, Takeda Pharmaceutical and UCB) have announced enrollment of the first patient into COMMUNITY (COVID-19 MUltiple agents and Modulators UNified IndusTrY members; ClinicalTrials.gov Identifier NCT04590586), an adaptive platform trial designed to evaluate an array of therapeutic candidates in hospitalized COVID-19 patients. Designed and launched by members of the COVID R&D Alliance, the randomized, double-blind, placebo-controlled platform study seeks to identify an effective treatment(s) for hospitalized COVID-19 patients, who are grade 2-5 on a Clinical Severity Status 8-Point Ordinal

Scale. Multiple candidates will be tested against a shared placebo-controlled arm. Initial therapies entering into COMMUNITY were selected based upon their potential to suppress or control the immune response or the resulting inflammation. They include Amgen's Otezla (apremilast), which may suppress immune response inflammation; Takeda's investigational intravenous administration of lanadelumab, which modulates the kallikrein-kinin system and suppresses production of bradykinin, potentially lessening inflammation; and UCB's zilucoplan, an investigational medicine that may reduce overactivation of the immune system that contributes to acute respiratory distress syndrome (ARDS). Otezla entered COMMUNITY this week, and it is expected that lanadelumab and zilucoplan will enter in the coming weeks. Other antiviral, immunomodulating and vascular agents may enter in the coming months. COMMUNITY will onboard global sites in the U.S., Brazil, Mexico, Russia, South Africa and other countries, and will enroll both hospitalized intensive care unit (ICU) and non-ICU patients. The primary endpoint of the trial is time to confirmed clinical recovery without being rehospitalized through day 29 on the basis of the clinical severity status scale, which is defined as achieving a score of 6, 7 or 8. Key secondary endpoints are oxygen-free recovery, improvement from baseline or fit for discharge from baseline, and all-cause mortality (COVID R&D Alliance News Release).

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30-Nov-2020

Initiation of phase I/II study of NGM-621 as therapy in patients with SARS-CoV-2 infection

Enrollment is currently underway in NGM Biopharmaceuticals' phase I/II study of NGM-621, being evaluated as potential treatment of patients with SARS-CoV-2 infection (ClinicalTrials.gov Identifier NCT04582318). A total of 48 participants are expected to enroll in the randomized, double-blind, placebo-controlled, combined phase I/II single dose and multiple dose study, designed to assess the safety, tolerability, and pharmacokinetics (PK) of NGM-621 intravenous infusion in healthy volunteers (part 1), as well as the safety, tolerability, PK, pharmacodynamics, and efficacy in subjects with confirmed SARS-CoV-2 infection (part 2). The study's primary outcome measures include treatment emergent adverse events both in part 1 and part 2, as well as clinical status on days 15 and 29 in part 2 of the trial. the secondary outcome measures include Cmax, mortality at day 29, duration of supplemental oxygen requirement, and change in hemolytic assays (CH50 and AH50) from baseline. The estimated completion date for this trial is set for September 2021 (ClinicalTrials.gov Website).

Suggested reading

Related websites

- Center for Infectious Disease Research & Policy
- Centers for Disease Control and Prevention (CDC) -- Coronavirus (Covid-19)
- Centers for Disease Control and Prevention (CDC) -- SARS information
- Centers for Research in Emerging Infection Diseases (CREID)
- Coalition for Epidemic Preparedness Innovation (CEPI)
- Coronavirus disease 2019 (COVID-19) (Food and Drug Administration)
- Coronavirus Global Health Emergency (United Nations)
- Covid 19 (Infectious Diseases Data Observatory)
- European Centre for Disease Prevention and Control -- Novel coronavirus
- European Commission - Public health - COVID-19 resources
- Gavi - The Vaccine Alliance
- Global research on coronavirus disease (Covid-19) (World Health Organization)
- MEDLINEplus: Coronavirus infections
- Middle East respiratory syndrome coronavirus (MERS-CoV) (World Health Organization)
- National Institute of Allergy and Infectious Diseases
- NCBI web resource: Severe Acute Respiratory Syndrome (SARS)
- SARS information - Health Canada
- Severe acute respiratory syndrome (SARS) (World Health Organization)
- The Covid-19 host genetics initiative

Related articles

- Coronavirus (Covid-19) (New England Journal of Medicine)
- Coronavirus disease 2019 (COVID-19) (JAMA Network)
- Coronavirus: Latest news and resources (The BMJ)
- Coronavirus: Research, commentary, and news (Science)
- COVID-19 resource centre (The Lancet)
- Nature.com collection: Coronavirus
- Novel coronavirus (COVID-19) resource center (Center for Infectious Disease Research and Policy, University of Minnesota)
- SARS Reference by B.S. Kamps and C. Hoffman (Eds.)
- WHO R&D Blueprint: An international randomised trial of candidate vaccines against COVID-19 (World Health Organization, May 28, 2020)

Guidelines

A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version) (February 2020)

Clinical management of Covid-19 - Interim guidance (World Health Organization, May 2020)

Clinical management of severe acute respiratory infection (SARI) when Covid-19 disease is suspected - Interim guidance (World Health Organization, updated March 13, 2020)

Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected - Interim guidance (World Health Organization, 2019)

Collection: Novel coronavirus (2019-nCoV) guidance for health professionals (Public Health England, January 2020)

Coronavirus disease 2019 (Covid-19) treatment guidelines (National Institutes of Health, April 2020)

COVID-19 rapid guideline: Managing suspected or confirmed pneumonia in adults in the community (National Institute for Health and Care Excellence, April 2020)

COVID-19 rapid guideline: Managing symptoms (including at the end of life) in the community (National Institute for Health and Care Excellence, April 2020)

COVID-19: Developing drugs and biological products for treatment or prevention. Guidance for industry (Food and Drug Administration, May 2020)

Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7) (National Health Commission & State Administration of Traditional Chinese Medicine, March 2020)

Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: Expert consensus statement (February 2020)

Infection prevention and control during health care for probable or confirmed cases of novel coronavirus (nCoV) infection - Interim guidance (World Health Organization, May 6, 2013)

Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected - Interim guidance (World Health Organization, updated March 2020)

Initial public health response and interim clinical guidance for the 2019 novel coronavirus outbreak -- United States, December 31, 2019-February 4, 2020 (Centers for Disease Control and Prevention, February 5, 2020)

Interim infection prevention and control recommendations for patients with known or patients under investigation for 2019 novel coronavirus (2019-nCoV) in a healthcare setting (Centers for Disease Control and Prevention, January 2020)

ISTH interim guidance on recognition and management of coagulopathy in COVID-19 (International Society of Thrombosis and Haemostasis, March 2020)

Management of asymptomatic persons who are RTPCR positive for Middle East respiratory syndrome coronavirus (MERS-CoV) - Interim guidance (World Health Organization, January 2018)

Surviving Sepsis Campaign: Guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19) (Surviving Sepsis Campaign, March 2020)

Treatment of MERS-CoV: Information for clinicians - Clinical decision-making support for treatment of MERS-CoV patients (Public Health England, July 2014)

Treatment of patients with nonsevere and severe coronavirus disease 2019: An evidence-based guideline (April 2020)

Update on the epidemiology of Middle East Respiratory Syndrome coronavirus (MERS-CoV) infection, and guidance for the public, clinicians, and public health authorities - January 2015 (Centers for Disease Control and Prevention, January 30, 2015)

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