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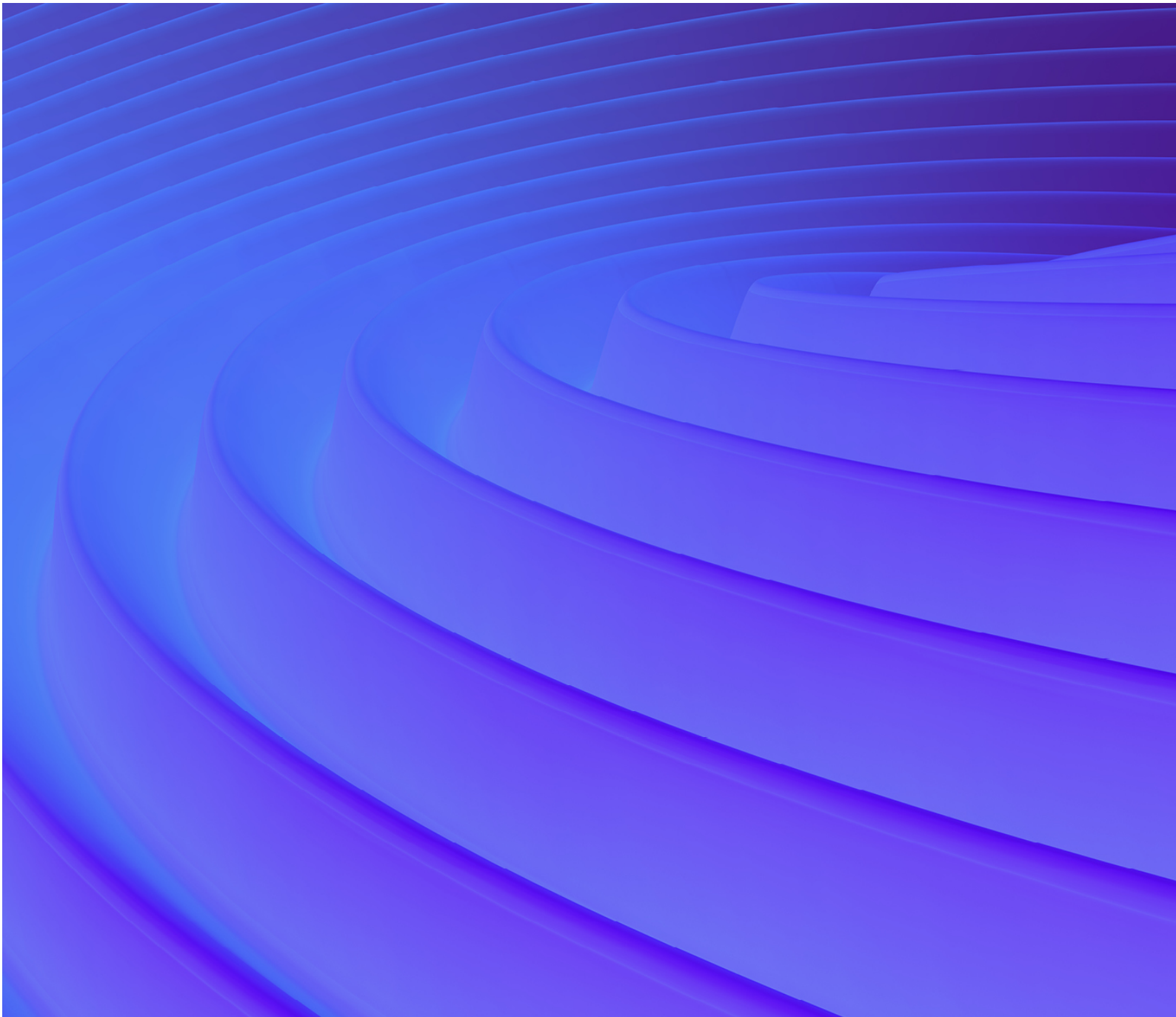
Disease Briefing: Coronaviruses



Contents

Coronavirus: Disease Briefing

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 (Berry, M. et al (2015); Su, S. et al (2016); Yang, Y. 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.

Important RNA viruses and the diseases they produce in humans

Family/Characteristics	Viruses	Diseases
Orthomyxoviruses (Orthomyxoviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; segmented genome)	Influenza A and B virus	Upper respiratory infection, croup

Paramyxoviruses (Paramyxoviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; nonsegmented genome)	Parainfluenza 1-3 virus	Upper respiratory infection, croup
	Respiratory syncytial virus	Upper respiratory infection, croup
	Measles virus	Measles
	Mumps	Aseptic meningitis
Coronaviruses (Coronaviridae) Single-stranded RNA,enveloped (No DNA step in replication; positive-sense genome)	Human coronaviruses	Upper and/or lower respiratory infection
Rhabdoviruses (Rhabdoviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; nonsegmented genome)	Rabies virus	Rabies
Picornaviruses (Picornaviridae) Single-stranded RNA, nonenveloped	Rhinoviruses	Common cold
	Hepatitis A virus	Hepatitis
	Enteroviruses: - Polioviruses - Coxsackie A24 viruses - Coxsackie B viruses - Coxsackie B1-5 viruses - Coxsackie A9 viruses - Echoviruses	 Paralysis Acute hemorrhagic conjunctivitis Myocarditis, pericarditis Aseptic meningitis Aseptic meningitis Aseptic meningitis, encephalitis
Caliciviruses (Calciviridae) Single-stranded RNA, nonenveloped	Norwalk virus	Gastroenteritis
Hepeviruses (Hepeviridae) Single-stranded RNA, nonenveloped	Hepatitis E	Hepatitis
Togaviruses (Togaviridae) Single-stranded RNA, enveloped (No DNA step in replication; positive-sense genome)	Alphaviruses (Group A arboviruses)	Encephalitis, hemorrhagic fever, chikungunya
	Rubivirus	Rubella
Flaviviruses (Flaviviridae) Single-stranded RNA, enveloped (No DNA step in replication; positive-sense genome)	Group B arboviruses	Encephalitis, hemorrhagic fever
	Hepatitis C virus	Hepatitis
	Dengue virus	Dengue fever
	Zika virus	Zika
Bunyaviruses (Bunyaviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome;	Some arboviruses	Encephalitis, hemorrhagic fevers
	Hantavirus	Fever, renal involvement

segmented genome)

Reoviruses (Reoviridae) Double-stranded RNA, nonenveloped	Human rotaviruses	Gastroenteritis
Arenaviruses (Arenaviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome;segmented genome)	Lymphocytic choriomeningitis (LCM virus)	Meningitis
	Lassa virus	Hemorrhagic fever
Retroviruses (Retroviridae) Single-stranded RNA, enveloped (DNA step in replication)	HTLV-I, HTLV-II	T cell leukemia, lymphoma, paresis
	HIV-1, HIV-2	AIDS
Filoviruses (Filoviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; nonsegmented genome)	Marburg virus	Marburg disease
	Ebola virus	Ebola hemorrhagic fever

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 nucleocapside (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 (Raj, V.S. et al (2014); Gralinski, L.E. et al (2015)). 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, SARS-CoV, MERS-CoV and SARS-CoV-2 can cause severe acute respiratory disease, multi-organ failure and/or death.

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)).

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 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 newly identified 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 new 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 and affecting the respiratory system. It originated in the Chinese province of Guandong 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)). SARS-CoV entry into target cells is inhibited by polyanion compounds that have antiviral activity against other enveloped viruses. This data indicates that the SARS-CoV envelope proteins may have positive charges interacting with negative charges on the heparan sulfate proteoglycans present on the surface of target cells (Vicenzi, E. et al (2004)). The SARS-CoV requires 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)). Nocosomial spread was reduced through use of surgical masks, gloves and gowns.

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)).

Viral RNA may persist long after seroconversion, and could be detected in respiratory secretions, plasma and feces for some weeks (Drosten, C. et al (2003)). The SARS outbreak revealed the susceptibility of modern hospitals to nosocomial infections and emphasized the importance of implementing measures to reduce the risk of hospital infections (Gopalakrishna, G. et al (2004)).

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)).

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)).

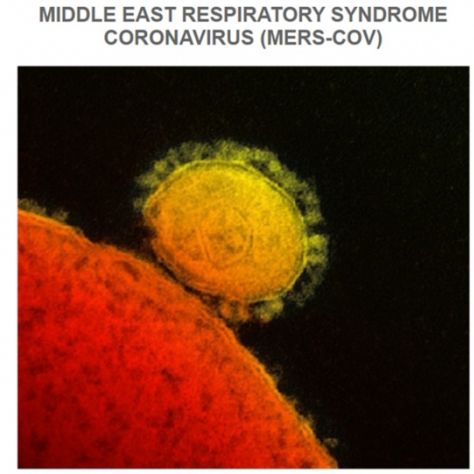
The SARS epidemic had important economic implications, with a global economic impact over two years estimated at between USD 40 billion (Ayittey, F.K. et al (2020)) and up to USD 100 billion (Paules, C.I. et al (2020)). The total economic impact of SARS in mainland China in 2003 has been estimated at 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 (Milne-Price, S. et al (2014); Chan, J.F. et al (2015)). The earliest known case has been traced to April 2012 (Chan, P.K. et al (2013)). 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 29.9 kB. 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 (spike - envelope - membrane - nucleocapsid) - 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)). 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)).

Like the SARS-CoV, the Middle East respiratory virus is able to overcome the host innate immune response until high virus titres 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 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 (Chan, J.F. et al (2015); Zumla, A. et al (2016)), 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)).

Epidemiology of MERS

Since September 2012, cases of MERS-CoV have been reported in 27 countries including 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 Saudia 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 January 2020, the World Health Organization had been notified of 2,519 laboratory-confirmed human cases of infection with the virus and 866 resulting deaths (Middle East respiratory syndrome coronavirus (MERS-CoV) (World Health Organization), consulted March 19, 2020). The case-fatality rate remains extremely high: in excess of 30% (Salamatbakhsh, M. et al (2019)).

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 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).

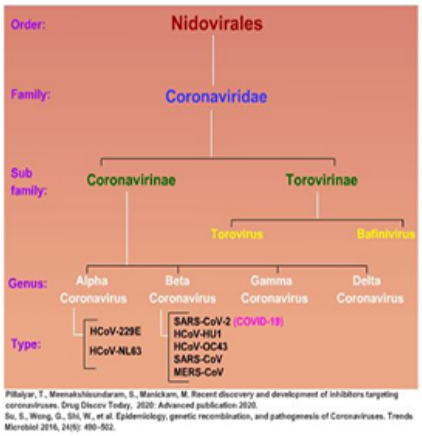
Facts about COVID-19

In late 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)). In January, the Chinese Center for Disease Control and Prevention (China CDC) acknowledged that only 22% of the 198 confirmed Covid-19 cases included in its outbreak analysis could be traced to a Huanan market-related exposure (Wu, J.T. et al (2020)).

The causative virus--originally termed 2019-nCoV--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)).

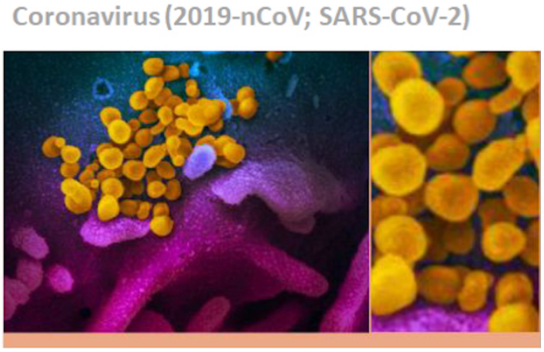
Coronavirus Taxonomy



SARS-CoV-2 Morphology, Structure and Replication

The SARS-CoV-2 viral genome is a single-stranded, positive-sense RNA with 14 open reading frames (ORFs) encoding for four structural (S, E, M and N), 15 nonstructural (including 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase) and 8 accessory proteins (Li, G. et al (2020); Yang, Y. et al (2020)). Like SARS-CoV, the new coronavirus deploys the densely glycosylated S protein (which consists of S1 and S2 subunits) for virus-cell receptor interaction and viral entry (Li, G. et al (2020)), with ACE2 serving as its binding receptor on the host cell (Wan, Y. et al (2020)). ACE2 receptors are found on a variety of cells, including arterial and venous endothelial cells, arterial smooth muscle, respiratory tract epithelium, small intestinal epithelia, respiratory tract epithelium and immune cells (Madjid, M. 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)). The virus uses the host cellular proteases such as TMPRSS2 for S protein priming, an essential step for entry into the host cell (Hoffmann, M. 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 sold at the Huanan market--most likely, a pangolin--is believed to have served as an amplifying intermediate host (Perlman, S. (2020); Lu, R. et al (2020); Yang, Y. et al (2020)), as bat-derived coronaviruses cannot directly infect humans (Wang, R. 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

Transmission of the virus is primarily via inhalation of suspended respiratory secretions, i.e., droplets generated when an infected individual coughs, sneezes or speaks, or through direct contact with an infected patient (Lai, C.C. et al (2020)). There is a possibility that viral RNA may also be transmitted in aerosolized microparticles of saliva, e.g. in exhaled air or when speaking, although this remains to be confirmed and quantified (Cheng, V.C.C. et al (2020); Guo, Z.-D. 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. It 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)). The risk of vertical transmission remains unclear. No virus was detected in amniotic fluid, cord blood, neonatal throat swab or breastmilk samples obtained from six women developing laboratory-confirmed Covid-19 in late pregnancy (Chen, H. et al (2020)). In another sample of 33 Covid-19-positive mothers, three infants presented with early-onset SARS-CoV-2 infection, despite strict infection control and prevention procedures during the delivery. Vertical maternal-fetal transmission could not be ruled out in this cohort (Zeng, L. 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)). An active monitoring study of U.S. patients infected with Covid-19 found that the symptomatic secondary attack rate (R0) was just 0.45% among all close contacts, but increased to 10.5% among household members (Burke, R.M. et al (2020)). In contrast, the R0 for both SARS-CoV and MERS-CoV is less than 1 (Wu, J.T. 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 by individuals during the prodromal period (Heymann, D.L. 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 pre-symptomatic transmission, implying that the isolation of cases as a means of curtailing the outbreak might not be as effective as once believed (Lauer, S.A. et al (2020); Nishiura, H. et al (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 acute respiratory disease or pneumonia. 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 (from most to least common) 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, an growing body of evidence supports the sudden emergence of anosmia and ageusia (loss of olfactory and gustatory function, respectively) as characteristic symptoms of Covid-19 (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 acute respiratory distress syndrome, 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--a so-called "cytokine storm"--, corresponding 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)). The presence of comorbidities, including cardiovascular disease and diabetes, was shown in various patient series to be associated with a significantly higher risk of mortality (Madjid, M. et al (2020)). Other factors associated with poor prognosis include indicators of increased disease severity (oxygenation, respiratory rate, leukocyte/lymphocyte count, chest imaging findings), older age and delay in diagnosis. Male gender has been linked to more severe disease and worse outcomes in several patient groups (Lai, C.C. et al (2020)).

A challenge for scientists studying Covid-19 is that those who are infected with subclinical or mild disease might not present to health care centers, impacting the accuracy of total case counts and calculation of case-fatality rates. Moreover, asymptomatic, seemingly healthy individuals can spread the virus to their contacts at home and at work as well as during travel (Munster, V.J. et al (2020); Bai, Y. et al (2020)).

Epidemiology, Morbidity and Mortality

According to WHO, as of April 16, 2020, nearly two million laboratory-confirmed cases of Covid-19 had been diagnosed and reported in 213 countries, areas or territories worldwide. Although early cases were concentrated in mainland China, the outbreak in that country began slowing in late February, at the same time that it began picking up in other countries. Beginning on February 25, more new cases of Covid-19 were reported each day from countries outside China than from mainland China itself; a week later, the number of daily deaths outside mainland China began to surpass those inside the country, and on March 16, the total number of cases outside mainland China overtook the total number of Chinese cases. As of April 16, WHO confirmed 126,140 deaths from Covid-19 worldwide, with the epicenter of the outbreak now in the European region and the U.S. The risk assessment of this event, as determined by WHO, was very high at the global level (Coronavirus disease (Covid-19) pandemic (World Health Organization), consulted April 16, 2020). For contrast, SARS-CoV caused more than 8,000 symptomatic infections resulting in 800 deaths, and MERS-CoV to date (as of February 4, 2020) has infected 2,494 individuals and caused 858 deaths (Wu, J.T. et al (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 characterized the outbreak a global pandemic. At that point, cases had been reported in 114 countries (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).

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 believed 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)). Risk of death is highest among the elderly and patients with comorbidities, but the disease affects individuals of all ages. An analysis of data on 2,143 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 does not spare children, although manifestations may be more mild. Infants were especially vulnerable (Dong, Y. 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 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)).

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)).

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

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, both within China and globally. According to one estimate, China's GDP year-on-year growth during Q1 2020 will be down at least 4.5%, while global GDP will 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)).

Diagnosis

During the SARS epidemic, the FDA and CDC collaborated on the validation and licensing of SARS diagnostic tests. 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. RT-PCR was an early detection test available for SARS-CoV, but its sensitivity was low, identifying only 37.5-50% of probable cases (Suresh, M.R. et al (2008)).

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, M.R. et al (2008)).

Various diagnostic tests have been used in the detection of MERS-CoV infection, including serological assays, immunofluorescence assays, ELISA, protein microarray, micro-neutralization assays and Western blot--all of which have limitations (Banik, G.R. et al (2015))--, as well as RT-PCR, which is 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)). 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 have developed nucleic acid test kits. Aiming to shorten the diagnosis time, Jiangsu Qitian Gene Technology together with the National Institute for Viral Disease Control and Prevention, developed test kits with an isothermal amplification instrument that automatically interprets the results in minutes, with both sensitivity and specificity values of 100%.

On February 5, 2020, the U.S. FDA issued an emergency use authorization 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)). The diagnostic is a RT-PCR test for the detection of SARS-CoV-2 from respiratory secretions (nasal or oral swabs), but was initially plagued with a high rate of inconclusive or invalid results (Sharfstein, J.M. et al (2020)). Novacyt has also launched a quantitative PCR assay, targeting the unique SARS-CoV-2 genome sequences without the need for cold chain shipping. In addition, Co-Diagnostics is using the Coprimer multiplexing technology to differentiate between similar

genetic sequences, thereby reducing false positive diagnosis. Also, at Meridian Bioscience, the molecular diagnostic test (Meridian Lyo-Ready 1-Step RT-qPCR Mix) can be prepared and freeze-dried, making it highly stable and only requiring the addition of the patient sample to run the assay. In Europe, among others, Ares Genetics is collaborating with BGI Group to make real-time fluorescence PCR tests for the new coronavirus, producing results in several hours. On March 21, the FDA granted emergency use authorization of the first rapid, point-of-care diagnostic for the U.S. market: Cepheid's Xpert Xpress SARS-CoV-2. The test has been designed to operate on any of Cepheid's more than 23,000 automated GeneXpert Systems worldwide, with a detection time of approximately 45 minutes.

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)).

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)).

In the U.S., Mammoth Biosciences and Sherlock Biosciences are using CRISPR (clustered regularly interspaced short palindromic repeats)-Cas12 to develop rapid point-of-care (POC) SARS-CoV-2 tests (**Fast, portable tests come online to curb coronavirus pandemic (Nature Biotechnology News, March 23, 2020)**). For this Sherlock Biosciences is collaborating with Cepheid who is providing the GeneXpert automated molecular diagnostic system. 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.

Quantitative RT-PCR based assays need expensive lab instrumentation and are usually conducted in public health laboratories. The SARS-CoV-2 DETECTR assays have comparable accuracy to qRT-PCR, employ isothermal signal amplification for rapid target detection without the need for thermocycling, show single nucleotide target specificity, are integrated with portable, low-cost lateral flow strips, and follow a quick development cycle.

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 will help to inform the diagnosis (Tian, X.L. et al (2020); Yang, Y. et al (2020)).

Prevention

Without effective drugs or vaccines against the infectious agents (Li, G. et al (2020)), social distancing strategies such as isolation/social distancing, quarantine and community containment are the most effective means of controlling a coronavirus outbreak with epidemic potential (Wilder-Smith, 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)). Based on assumptions of exponential growth of the outbreak (estimated R0 = 2.68), WHO-linked epidemiology experts recommend 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, including children, 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 or contaminated fomites (Chen, Y. 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 30ªC (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)).

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.

Human coronavirus vaccines under development include DNA and RNA vaccines, vector-based, live attenuated and protein subunit vaccines. DNA- and RNA-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 made instead using synthetic processes (Schindewolf, C. et al (2019); Lurie, N. et al (2020)).

The S protein is currently considered to be one of the most promising targets for coronavirus vaccine development (Li, F. et al (2019); Song, Z. et al (2019)), and is being targeted for the development of both anti-MERS-CoV and 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)).

Development 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 has been hindered by the lack of a suitable animal model for testing. Transgenic mice expressing the human ACE2 receptor, first developed during the SARS outbreak, are again being bred for research purposes, but supplies are limited (Labs rush to study coronavirus in transgenic animals -- some are in short supply (Nature News, March 9, 2020)).

A potential risk of any antiviral vaccine, and one that also exists with coronavirus vaccines, is that of antibody-dependent enhancement (ADE). The phenomenon 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. It is believed to be caused by the vaccine inducing a type 2 helper T-cell (Th2) response. Rigorous testing in appropriate animal models is essential to determine the risk of ADE before widespread vaccination of the population (Lurie, N. et al (2020)).

The following tables presents 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
CHAdOx1-nCoV19	University of Oxford	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine consisting of replication - deficient simian adenovirus vector ChAdOx1 encoding SARS - CoV - 2 spike (S) gene	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)) and immune - stimulating regulatory	Phase I/II

		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)	
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 I
INO-4800	Inovio Pharmaceuticals	Human SARS - CoV - 2 (Covid - 19 coronavirus) DNA vaccine	Phase I
mRNA-1273	National Institutes of Health (NIH); Moderna	Human SARS - CoV - 2 (Covid - 19 coronavirus) mRNA vaccine	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
CORVax12	OncoSec Medical	Composition comprising human SARS - CoV - 2 (Covid - 19 coronavirus) DNA vaccine and a plasmid encoding human interleukin - 12 (IL - 12) (TAVO(TM))	IND Filed
Ad26 SARS-CoV-2	Johnson & Johnson	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	Preclinical
IBIO-200	iBio (US)	Human SARS - CoV - 2 (Covid - 19 coronavirus) virus - like particle vaccine; generated by FastPharming System(TM)	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
LUNAR-COV19	Duke University; Arcturus Therapeutics	Human SARS - CoV - 2 (Covid - 19 coronavirus) mRNA vaccine comprising a self - replicating RNA based on STARR technology platform delivered using Lipid -	Preclinical

		enabled and Unlocked Nucleomonomer Agent modified RNA (LUNAR(R)) platform	
NVX-CoV2373	Novavax	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine comprising recombinant COVID - 19 spike glycoprotein; encapsulated in nanoparticles	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
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 a protein of COVID - 19 virus	Preclinical
ZIP-1642	Ziphius Therapeutics	Human SARS - CoV - 2 (Covid - 19 coronavirus) mRNA vaccine encoding different Covid - 19 antigens, including Spike (S) protein	Preclinical
1083739	Mitsubishi Tanabe Pharma	Human SARS - CoV - 2 (Covid - 19 coronavirus) virus - like particle (VLP) vaccine	Preclinical
1086184	Osaka University; AnGes	Human SARS - CoV - 2 (Covid - 19 coronvirus) plasmid DNA vaccine	Preclinical
1080103	CureVac	Human SARS - CoV - 2 (Covid - 19 coronavirus) mRNA vaccine	Preclinical
1086209	Kentucky BioProcessing (KBP)	Human SARS - CoV - 2 (Covid - 19 coronavirus) vaccine; expressed in tobacco plant 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	Ludwig-Maximilians-Univ. Muenchen	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
MVA-MERS-S_DF1	Universitaetsklinikum Hamburg-Eppendorf	Middle east respiratory syndrome (MERS) vaccine consisting of a modified vaccinia ankara (MVA) virus encoding MERS - CoV spike (S) protein antigens	Preclinical

Treatment

There is no approved drug therapy for SARS, MERS, Covid-19 or any other coronavirus infection at this time (Li, G. et al (2020)). Early diagnosis, isolation and supportive care are the mainstay of treatment for patients with severe disease (Murthy, S. et al (2020); Yang, Y. et al (2020)). Treatment approaches, all of which are investigational, are targeted either at the virus itself or the host response.

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 Kaletra (lopinavir/ritonavir), which inhibits the major CoV protease 3CLpro, was the most effective treatment for SARS (Zumla, A. et al (2016)). Twenty-one day ARDS and death rates 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. In MERS-CoV-infected patients, administration of drugs such as these--even if not 100% effective in blocking viral replication--could provide a window of opportunity during which the patient's immune system might begin to respond to the infection (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. Candidate drugs included metformin, glitazones, fibrates, sartans and atorvastin for boosting the immune response; zinc and other metal-containing supplements with antiviral activity; cyclosporine, lopinavir/ritonavir, interferon beta-1b, ribavirin and remdesivir, also for their antiviral activity; various cellular therapies; and anti-IL-6 monoclonal antibodies (MAbs) such as tocilizumab (Zumla, A. et al (2020)). Other host-directed therapeutic options that could be repurposed, based on previous lines of investigation into SARS-CoV and MERS-CoV, include JAK-STAT kinase inhibitors, which have potent antiinflammatory effects (Stebbing, J. et al (2020)), nutritional interventions (vitamins A, C, D and E, B vitamins, omega-3 polyunsaturated fatty acids, selenium, zinc and iron), immuno-enhancing agents (interferons, IVIG, thymosin alpha-1, thymopentin, levamisole and ciclosporin), convalescent plasma and traditional Chinese medicine. Suggested virus-directed approaches include the antimalarial agent chloroquine;

flavonoids, for their antiviral and antioxidant activity; the virucidal anthraquinone emodin and the antipsychotic agent chlorpromazine, both of which block the interaction of the viral S glycoprotein with the ACE2 binding receptor; and MAbs directed against S glycoprotein (Zhang, L. et al (2020); Pillaiyar, T. et al (2020)).

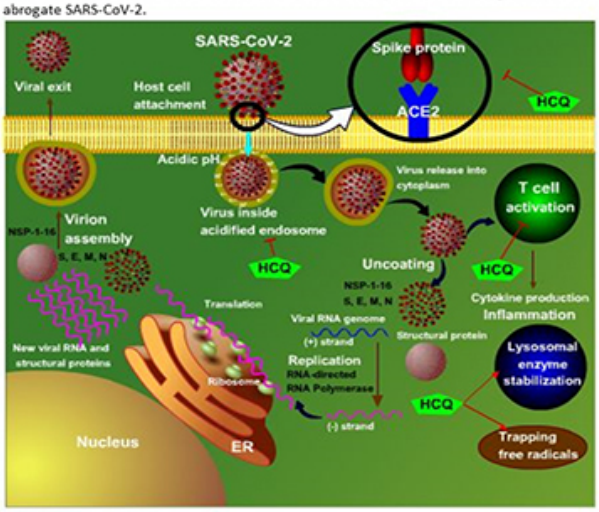
In March, WHO announced the initiation of the SOLIDARITY trial, a large international study designed to evaluate various treatment approaches. The study will enroll patients in Argentina, Bahrain, Canada, France, Iran, Norway, South Africa, Spain, Switzerland and Thailand and will test four different drugs or combinations: remdesivir, lopinavir/ritonavir (Kaletra), Kaletra plus interferon-beta, and chloroquine. 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 will enroll 3,200 patients who will 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.

Broad-Spectrum Antiviral Agents

The aminoquinoline antimalarial agents chloroquine and its more soluble and better tolerated metabolite hydroxychloroquine have a broad antiviral spectrums, with activity against DNA as well as RNA viruses--including anti-SARS-CoV-2--in vitro. They also exert antiinflammatory and immunomodulatory effects. Chloroquine has a variety of effects, although it is still unknown which (if any) of these are relevant to Covid-19. 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 led 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, approximately a dozen clinical trials were initiated to evaluate chloroquine for the treatment of Covid-19 pneumonia (Gao, J. et al (2020)). One small, open-label, nonrandomized French trial reported significant reduction of viral load in patients treated with hydroxychloroquine plus azithromycin (Gautret, P. et al (2020)); however, the poor methodology of the study has been criticized. Others have expressed concern that chloroquine/hydroxychloroquine may adversely affect the host adaptive immune response to the virus by down-regulating IL-2 and the favorable antiinflammatory Th2 response. This paradoxical effect was observed in patients administered the drugs for chikungunya (Guastalegname, M. et al (2020)). The American College of Cardiology notes that chloroquine, hydroxychloroquine and azithromycin all prolong QT interval, raising concerns about the risk of arrhythmic death from individual or concurrent use of these medications, and recommends close clinical monitoring (Ventricular arrhythmia risk due to hydroxychloroquine-azithromycin treatment for COVID-19 (American College of Cardiology, March 29, 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 to allow the donation of hydroxychloroquine sulfate and chloroquine phosphate to the Strategic National Stockpile. The drugs will be distributed and used for hospitalized adult and adolescent patients with Covid-19, as appropriate, when a clinical trial is not available or feasible (Chloroquine phosphate and hydroxychloroquine sulfate for treatment of COVID-19 - Letter of authorization (Food and Drug Administration, March 28, 2020)). The EMA, in contrast, issued a statement just days later emphasizing that the antimalarials should be used to treat Covid-19 only in the context of a clinical trial or emergency use program (COVID-19: chloroquine and hydroxychloroquine only to be used in clinical trials or emergency use programmes (European Medicines Agency, April 1, 2020)).

Hydroxychloroquine:
Putative Mechanisms of anti-Covid-19 Action

HCQ (Hydroxychloroquine) negatively influences the binding of viral spike protein with ACE-2 by interfering with the glycosylation of ACE-2. It also elevates endosomal pH, inhibits T- cell Induced inflammation, induces stabilization of lysosomal enzymes and trapping of free radicals to abrogate SARS-CoV-2.



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)). 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 (2019)). 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 had initiated a clinical trial program 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 initial clinical study has been approved by Health Canada and was expected to be initiated within a few weeks. The company is also in discussions with health authorities in multiple countries regarding additional studies to evaluate ribavirin as a treatment for Covid-19 infection. Additionally, the Bausch Foundation is continuing to work directly with health authorities in Italy to make ribavirin for inhalation available free of charge in compassionate use in Italian hospitals.

Viral Enzyme Inhibitors

The process of coronavirus replication is well understood. Several unique steps have been identified as potential targets for antiviral drugs. Viral fusion with the host cell could potentially be blocked by entry inhibitors or membrane fusion inhibitors, similar to antivirals used for HIV infection. Viral protease inhibitors 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 main protease (Mpro, also called 3CLpro) is one of the best characterized drug targets for coronaviruses. Mpro, together with the papain-like proteases, is required for processing polyproteins that are translated from the viral RNA. It has been identified as a promising target for anti-SARS-CoV-2 compounds (Zhang, L. et al (2020)).

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 ongoing MIRACLE trial is evaluating the efficacy and safety of lopinavir/ritonavir plus recombinant interferon-beta1b compared to placebo--both given in combination with optimal supportive care--in patients with laboratory-confirmed MERS-CoV infection requiring hospital admission (Arabi, Y.M. et al (2018)).

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 (400 mg/100 mg p.o.) 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)).

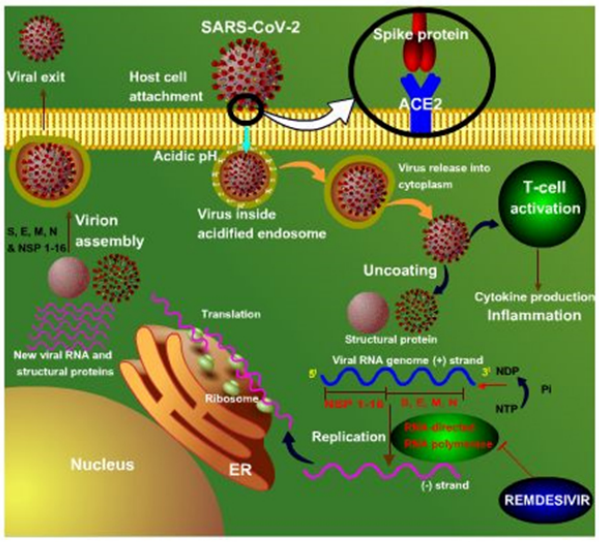
In March 2020, a clinical trial was initiated in Spain to evaluate a novel multidrug approach for reducing the duration of infection and transmission of the SARS-CoV-2 virus. A total of around 200 people testing positive for SARS-CoV-2 will receive the anti-HIV drug combination darunavir/cobicistat plus hydroxychloroquine to try to reduce the number of days they are contagious. In addition, about 3,000 of their direct contacts will receive hydroxychloroquine to see if it prevents infection. It is estimated that people with the virus are contagious for 14 days after first showing symptoms and that they can infect 5-15% of their contacts. The study will determine whether this regimen is able to reduce these numbers.

The RNA-directed RNA polymerase 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 late February, the U.S. NIH announced that a randomized, controlled clinical trial to evaluate the safety and efficacy of remdesivir in hospitalized adults diagnosed with Covid-19 has begun at the University of Nebraska Medical Center in Omaha.

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 approved for use in treating influenza A and B, is being evaluated as a potential broad-spectrum antiviral for use in the Covid-19 outbreak. 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)), clinical results in China were reportedly positive. In one trial, testing favipiravir with interferon in Shenzhen, results showed that patients treated with the combination had significantly reduced the duration of symptoms, as measured by viral load chest imaging, vs. a control group. In another study, clinical recovery rates were higher for Covid-19 patients treated with favipiravir vs. those in a control group. On March 17, the head of the China National Center for Biotechnology Development said in a press conference that based on this "obvious efficacy", favipiravir has been recommended to medical treatment teams and should be included in treatment plans for Covid-19 as soon as possible

Elements of the viral replication process have also been identified as potential therapeutic targets, including viral helicase, features of which are highly conserved among different coronaviruses (Adedeji, A.O. et al (2014)). Other potential antiviral drug targets include virus entry, assembly and exocytosis, which enables the release of virus from host cells. Despite a good understanding of viral targets and the identification of potential antiviral agents in vitro and in animal models, however, these findings have not translated into efficacy in humans (Zumla, A. et al (2016); Chen, Y. et al (2020)).

Monoclonal 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)).

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 MAb for MERS-CoV and have identified the humanized MAb YS110 as a promising candidate, with the advantage that this agent has already undergone clinical testing for other indications (Ohnuma, K. et al (2013)).

Immunomodulators

During the SARS epidemic, the Chinese government granted approval for use of immune system enhancers such as SciClone's Zadaxin (thymosin alpha 1), an immune system enhancer that is marketed in mainland China for hepatitis B, to treat patients with SARS. Zadaxin works by stimulating the production of white blood cells, enhancing the body's ability to fight off infections (Goldstein, A.L. et al (2009)). In vitro studies indicate that the broad-spectrum antiviral agent ribavirin, at concentrations that inhibit other viruses, does not inhibit the replication of the SARS-CoV, and thus that some of its benefits may be due to its immunomodulatory activity (Normile, D. (2003); Mazzulli, T. et al (2004)).

Other treatment options with immunomodulating properties were also used during the SARS epidemic, including passive antibody therapy (i.v. immunoglobulins and convalescent plasma) (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 viral neutralization, although other mechanisms may also be involved, such as antibody-dependent cellular cytotoxicity and/or phagocytosis (Casadevall, A. et al (2020)).

During the MERS-CoV outbreak in 2015, some Korean patients were treated with convalescent plasma. A systematic review and meta-analysis of healthcare 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 has concluded that this approach is 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 been used to treat some patients in China 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 of 5 patients had been discharged from the hospital at the time of reporting and 2 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, and perhaps different timings of administration after admission to hospital (Shen, C. 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; thus, convalescent plasma should be administered in the early stages of disease, or in the setting of prophylaxis, in order to be most 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 are 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)).

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.

Recombinant Proteins

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 serine protease TMPRSS2 for S priming. This enables fusion of viral and cellular membranes and viral entry into the cell. The resulting injury to type II alveolar cells may help to explain the severe lung injury observed in Covid-19 patients. Administration of human recombinant soluble ACE2 has been explored as a method of preventing viral attachment to pulmonary cells, i.e., as a neutralizing agent. This approach 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 late February, a pilot investigator-initiated clinical trial evaluating recombinant human ACE2 (rhACE2), APN-01, was launched to treat patients with severe Covid-19 infection in the People's Republic of China. A total of 24 patients were to be treated for 7 days in the randomized, unblinded study, with the aim of obtaining preliminary data on the impact of rhACE2 on biological, physiologic, and clinical outcomes, as well as safety in patients with severe SARS-CoV-2 infection. These data will be assessed to determine whether a phase IIb clinical trial in a larger number of patients is warranted.

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 and trypsin (Millet, J.K. et al (2015); Kilianski, A. et al (2014)), and--most notably--type II transmembrane serine protease (TMPRSS2).

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 virus to fuse with the cell and begin replicating within. 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) that will attempt to determine whether camostat mesilate is able to act on the lung cells targeted by the virus and prevent it from infecting them.

Interferons

The host immune response, including the innate interferon response, is crucial for controlling viral replication. Coronaviruses suppress this response in order to evade the immune system. However, they may be responsive to treatment with interferons, particularly recombinant forms (Zumla, A. et al (2016)). 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)). In vitro, MERS-CoV has been shown to be 50-100 times more susceptible than SARS-CoV to treatment with IFN-alfa (Abdel-Moneim, A.S. (2014)). In early 2020, a controlled trial was launched in China to test the efficacy of lopinavir/ritonavirin in combination with IFN-alfa-2b in hospitalized patients with SARS-CoV-2 infection.

Targeting the Cytokine Storm

A model has been proposed of the pathogenesis of acute respiratory distress syndrome (ARDS) 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)). 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)). 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 and death (Luo, P. et al (2020)).

With an increased understanding of these processes, several therapeutic approaches targeting the cytokine storm in Covid-19 are now being evaluated. 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)).

Several reports in the literature describe compassionate use or small trials of monoclonal antibodies (MAbs) targeting the proinflammatory cytokine IL-6 or its receptor. 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 is 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)). Note that tocilizumab is approved by the FDA for the treatment of severe life-threatening cytokine release syndrome caused by chimeric antigen receptor T-cell (CART) immunotherapy.

In the U.S., the FDA has approved a phase III trial in collaboration with the Biomedical Advanced Research and Development Authority evaluating intravenous tocilizumab plus standard of care in hospitalized adult patients with severe Covid-19 pneumonia. The randomized, double-blind, placebo-controlled phase III study (COVACTA), which will begin enrolling patients in early April, will evaluate the safety and efficacy of tocilizumab added to standard of care compared to placebo plus standard of care. The trial's primary and secondary endpoints include clinical status, mortality, mechanical ventilation and intensive care unit variables. Patients will be followed for 60 days after randomization, and an interim analysis will be conducted to look for early evidence of efficacy.

Another clinical program is evaluating the anti-IL-6R antibody sarilumab in U.S. patients hospitalized with severe Covid-19 infection. The trial will assess the safety and efficacy of adding sarilumab to usual supportive care, compared to supportive care plus placebo. This randomized, double-blind, placebo-controlled phase II/III trial uses an adaptive design to evaluate the MAb in adults hospitalized with laboratory-confirmed Covid-19 that is classified as severe or critical, or who are suffering from multiorgan dysfunction. All patients must have pneumonia and fever. In the phase II part of the trial, patients will be randomized 2:2:1 into three groups: sarilumab high dose, sarilumab low dose and placebo. The primary endpoint is reduction of fever and the secondary endpoint is decreased need for supplemental oxygen. The phase II findings will be utilized in an adaptive manner to determine transition into phase III, helping to determine the endpoints, patient numbers and doses. The second, larger part of the trial will evaluate the improvement in longer-term outcomes, including preventing death and reducing the need for mechanical ventilation, supplemental oxygen and/or hospitalization. If the trial continues with all three treatment arms to the end, it is expected to enroll approximately 400 patients, depending on the status of the Covid-19 outbreak and the proportion of patients with severe disease and high levels of IL-6.

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 members of the NOD-like receptor family (NLR) such as NLRP3, PYCARD, CASP1 and possibly CASP4 and CASP5. 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. 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.

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)).

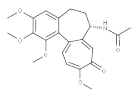
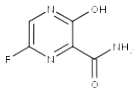
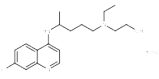
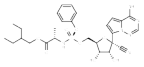
Data obtained in a Hong Kong hospital support use of pulsed methylprednisolone as rescue therapy only during the later stages of SARS; administration during the earlier phases of disease appeared to actually prolong viremia (Hui, D.S. et al (2010)). In fact, later analysis showed that prolonged methylprednisolone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

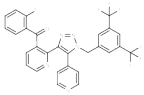
Based on previous experience with SARS and MERS, routine use of corticosteroids was not recommended in patients in Wuhan with Covid-19 (Huang, C. et al (2020); Lai, C.C. et al (2020)), although this guidance is still evolving. Precise use of corticosteroids, adhering strictly to the most recent treatment guidelines, may be warranted to treat appropriately selected patients with novel coronavirus pneumonia in the phase of ARDS, when they may inhibit the cytokine storm and prevent multiorgan damage and septic shock (Zhou, W. et al (2020)).

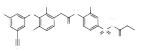
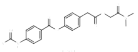
Current Coronavirus Pipeline

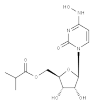
Consult the tables below for an overview of all products mentioned in this review, including drugs, biologics and diagnostic agents that have been marketed or are under active development for this indication. Tables may also include drugs not covered in the preceding sections because their mechanism of action is unknown or not well characterized.

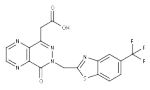
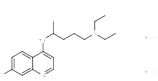
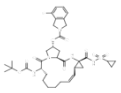
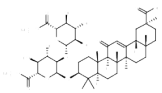
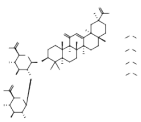
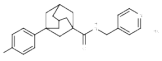
Drugs and biologics in development for the treatment and prevention of coronavirus infections

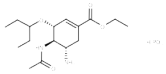
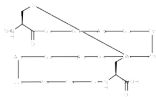
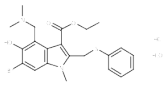
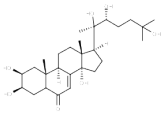
Drug	Organization	Mechanism	Phase	Structure
ASC-09/ritonavir	Ascletis	HIV Protease Inhibitors; HIV-1 Protease Inhibitors; Tumor Necrosis Factor Receptor Superfamily Member 6 (CD95)/PLC-gamma-1 Interaction Inhibitors	Phase III	
CD24Fc	OncoImmune		Phase III	
Colchicine	Montreal Heart Institute (MHI)	Antimitotic Drugs; Microtubule Destabilizers (Tubulin Polymerization Inhibitors)	Phase III	
Darunavir/cobicistat	Shanghai Public Health Clinical Center	Cytochrome P450 CYP3A4 Inhibitors; HIV Protease Inhibitors	Phase III	
Favipiravir	FUJIFILM Toyama Chemical	RNA-Directed RNA Polymerase (Influenza A Virus H1N1) Inhibitors; RNA-Directed RNA Polymerase (NS5B) (HCV) Inhibitors	Phase III	
Hydroxychloroquine sulfate	Shanghai Public Health Clinical Center	Autophagy Inhibitors; Palmitoyl-Protein Thioesterase 1 (PPT1) Inhibitors	Phase III	
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	
Remdesivir	Gilead; National Institute Allergy Infect Dis	RNA-Directed RNA Polymerase (Viral) Inhibitors; Viral Replication Inhibitors	Phase III	

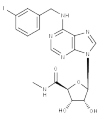
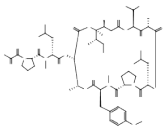
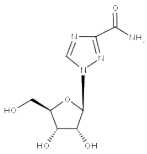
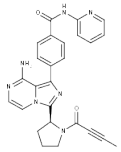
Tradipitant	Vanda Pharmaceuticals	Signal Transduction Modulators; Tachykinin NK1 Receptor Antagonists	Phase III	
1086588	Shanghai Jiao Tong University (SJTU)		Phase III	
Anakinra	Swedish Orphan Biovitrum	IL-1 Receptor Antagonists; Signal Transduction Modulators	Phase II/III	
Emapalumab	Swedish Orphan Biovitrum	Anti-IFN-gamma; Signal Transduction Modulators	Phase II/III	
IFX-1	InflaRx	Anti-C5 (Complement 5)	Phase II/III	
Leronlimab	CytoDyn	Anti-CD195 (CCR5); Signal Transduction Modulators; Viral Entry Inhibitors	Phase II/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	
Sarilumab	Sanofi; Regeneron	Anti-Interleukin-6 Receptor Subunit Alpha (CD126; IL-6R); Signal Transduction Modulators	Phase II/III	
APN-01	Apeiron Biologics		Phase II	
Aviptadil	Relief Therapeutics	Signal Transduction Modulators; VPAC1 (VIP1) Receptor Agonists; cAMP-Dependent Protein Kinase (PKA) Activators	Phase II	
Camrelizumab	Southeast University	Anti-PD-1; Immune Checkpoint Inhibitors	Phase II	

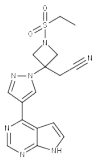
Elsulfavirine sodium	Viriom	Reverse Transcriptase/Ribonuclease H (HIV-1) Inhibitors	Phase II	
Interferon-beta	Synairgen		Phase II	
BVRS-GamVac-Combi	Ministry Healthcare Russian Federation		Phase I/II	
CAStem	Chinese Academy of Sciences		Phase I/II	
CHAdOx1-nCoV19	University of Oxford	Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers; Viral Entry Inhibitors	Phase I/II	
Camostat mesylate	Aarhus University	Transmembrane Protease Serine 2 (TMPRSS2) Inhibitors; Trypsin Inhibitors	Phase I/II	
GLS-5300	Inovio Pharmaceuticals; GeneOne Life Science	Spike Glycoprotein (S) (MERS-CoV)-Directed Immunity Inducers	Phase I/II	
LV-SMENP-DC	Shenzhen Genoimmune Medical Institute	Envelope Protein (E) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers; Membrane Glycoprotein (M) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers; Nucleocapsid Phosphoprotein (N) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers; Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers	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; Drugs Acting on NKG2D; Drugs Targeting Angiotensin-I Converting Enzyme-Related Carboxypeptidase (ACE2); Human Coronavirus Fusion Inhibitors; Signal Transduction Modulators	Phase I/II	

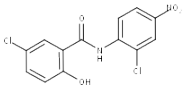
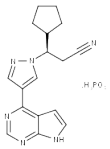
Ad5-nCoV	CanSino Biologics	Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers	Phase I	
AmnioBoost	Lattice Biologics		Phase I	
ChAdOx1 MERS	Vaccitech Ltd.; University of Oxford	Spike Glycoprotein (S) (MERS-CoV)-Directed Immunity Inducers	Phase I	
EIDD-2801	Ridgeback Biotherapeutics		Phase I	
INO-4800	Inovio Pharmaceuticals	Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins-Directed Immunity Inducers	Phase I	
MVA-MERS-S	Ludwig-Maximilians-Univ. Muenchen	Spike Glycoprotein (S) (MERS-CoV)-Directed Immunity Inducers	Phase I	
REGN-3048	Regeneron	Anti-Spike Glycoprotein (MERS-CoV Coronavirus)	Phase I	
REGN-3051	Regeneron	Anti-Spike Glycoprotein (MERS-CoV Coronavirus)	Phase I	
SAB-301	SAB Biotherapeutics	Anti-Spike Glycoprotein (MERS-CoV Coronavirus)	Phase I	
WJ-MSC	Stem Cells Arabia		Phase I	
mRNA-1273	National Institutes of Health (NIH); Moderna	Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins-Directed Immunity Inducers	Phase I	
1084319	Shenzhen Genoimmune Medical Institute	Drugs Targeting Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins	Phase I	

AT-001	Applied Therapeutics	Aldose Reductase Inhibitors	Clinical	
CAP-1002	Capricor Therapeutics		Clinical	
CB-MSCs	Wuhan University of Science Technology		Clinical	
Chloroquine phosphate	Guangdong Zhongsheng Pharmaceutical	Apoptosis Inducers; Histamine N-methyltransferase (HNMT) Inhibitors	Clinical	
DAS-181	Ansun Biopharma		Clinical	
Danoprevir	Ascletis	Serine Protease NS3/Non-Structural Protein 4A (NS3/NS4A) (HCV) Inhibitors	Clinical	
Diammonium glycyrrhizinate	Sino Biopharmaceutical	Microbiome Modulators	Clinical	
Emiplacel	Pluristem	Angiogenesis Inducers	Clinical	
Gimsilumab	Roivant Sciences	Anti-GM-CSF; Signal Transduction Modulators	Clinical	
Magnesium isoglycyrrhizinate	Sino Biopharmaceutical		Clinical	
Namilumab	Izana Bioscience	Anti-GM-CSF; Signal Transduction Modulators	Clinical	
Opaganib hydrochloride	RedHill Biopharma	Angiogenesis Inhibitors; Dihydroceramide Desaturase Inhibitors; Signal Transduction Modulators; Sphingosine Kinase 2 (SPHK2; SPK2) Inhibitors	Clinical	

Oseltamivir phosphate	Wuhan Tongji Hospital	Neuraminidase (Sialidase) (Influenza Virus) Inhibitors	Clinical	
Peginterferon lambda-1a	Eiger BioPharmaceuticals		Clinical	
Sargramostim	Partner Therapeutics		Clinical	
Siltuximab	EUSA Pharma	Anti-IL-6; Signal Transduction Modulators	Clinical	
Solnatide	APEPTICO	Epithelial Sodium Channel (ENaC) Activators; Protein Kinase PKC alpha Inhibitors; Signal Transduction Modulators	Clinical	
Tocilizumab	Roche	Anti-Interleukin-6 Receptor Subunit Alpha (CD126; IL-6R); Signal Transduction Modulators	Clinical	
Umifenovir hydrochloride	Wuhan Tongji Hospital	Capsid Assembly (Hepatitis B Virus) Modulators; Viral Entry Inhibitors	Clinical	
Xiyanping	Jiangxi Qingfeng Pharmaceutical Group	Neuraminidase (Sialidase) (Influenza Virus) Inhibitors	Clinical	
1085777	Shenzhen Third People's Hospital		Clinical	
20-Hydroxyecdysone	Biophytis	Mas-Related G Protein Coupled Receptors (MRG) Ligands; Signal Transduction Modulators	IND Filed	
AD-MSCs (autologous)	Hope Biosciences		IND Filed	
CORVax12	OncoSec Medical	Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins-Directed Immunity Inducers	IND Filed	
CYNK-001	Celularity		IND Filed	

LY-3127804	Lilly	Angiogenesis Inhibitors; Anti-ANGPT2 (Angiopoietin 2)	IND Filed	
MAPC	Athersys	Osteogenesis Inducers	IND Filed	
Piclidenoson	Can-Fite Biopharma	Adenosine A3 Receptor Agonists; Signal Transduction Modulators	IND Filed	
Plitidepsin	PharmaMar	Angiogenesis Inhibitors; Apoptosis Inducers; Autophagy Inhibitors; Elongation Factor 1-alpha 2 (EEF1A2) Inhibitors; Signal Transduction Modulators	IND Filed	
Remestemcel-L	Mesoblast		IND Filed	
Ribavirin	Bausch Health	Equilibrative Nucleoside Transporter ENT1 Inhibitors; Inosine 5'-Monophosphate Dehydrogenase (IMPDH) Inhibitors	IND Filed	
TD-0903	Theravance Biopharma	Janus Kinase (Jak) Inhibitors; Signal Transduction Modulators	IND Filed	
TJ-003234	I-Mab Biopharma	Anti-GM-CSF; Signal Transduction Modulators	IND Filed	
ADX-629	Aldeyra Therapeutics	Aldehyde Scavengers	Preclinical	
Acalabrutinib	Acerta Pharma	Bruton's Tyrosine Kinase (BTK) Inhibitors; Signal Transduction Modulators	Preclinical	
Ad26 SARS-CoV-2	Johnson & Johnson	Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins-Directed Immunity Inducers	Preclinical	

Baricitinib	Lilly	Jak1 Inhibitors; Jak2 Inhibitors; Signal Transduction Modulators	Preclinical	
CK-0802	Cellenkos		Preclinical	
CMAB-020	Mabpharm	Anti-S (Spike Glycoprotein (SARS-CoV-2; COVID-19 Virus); Drugs Targeting Basigin (BSG; CD147)/ACE2 Interaction	Preclinical	
Coravax	Thomas Jefferson University	Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers	Preclinical	
FM-201	Future Medicine		Preclinical	
GREVAX/MERS	Greffex		Preclinical	
Human leukocyte interferon alpha	AIM ImmunoTech		Preclinical	
IBIO-200	iBio (US)	Drugs Targeting Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins	Preclinical	
IPT-001	INTELLiSTEM Technologies	Nucleocapsid Phosphoprotein (N) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers; Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers	Preclinical	
IR-101C	Immune Response BioPharma		Preclinical	
LCA-60	Vir Biotechnology	Anti-Spike Glycoprotein (MERS-CoV Coronavirus)	Preclinical	

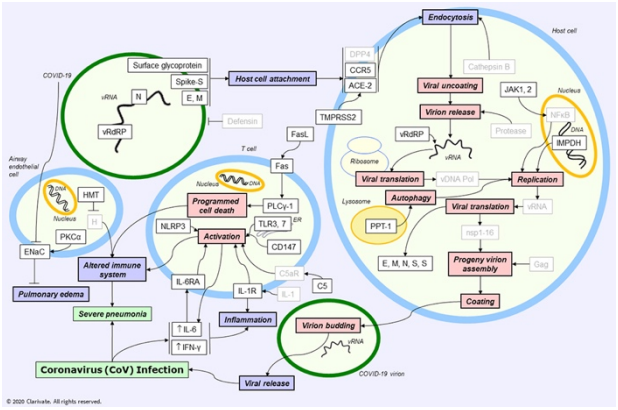
LUNAR-COV19	Duke University; Arcturus Therapeutics	Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins-Directed Immunity Inducers	Preclinical	
MVA-MERS-S_DF1	Universitaetsklinikum Hamburg-Eppendorf	Spike Glycoprotein (S) (MERS-CoV)-Directed Immunity Inducers	Preclinical	
NVX-CoV2373	Novavax	Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers; Viral Entry Inhibitors	Preclinical	
Niclosamide	First Wave Bio; UNION therapeutics	Autophagy Inducers; Neuropeptide Y4 (NPY Y4) Receptor Positive Allosteric Modulators; Quorum Sensing (Pseudomonas aeruginosa) Inhibitors; Wnt Signaling Inhibitors	Preclinical	
PRTX-007	Primmune Therapeutics	Signal Transduction Modulators; Toll-Like Receptor 7 (TLR7) Agonists	Preclinical	
PittCoVacc	University of Pittsburgh	Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers	Preclinical	
Rintatolimod	AIM ImmunoTech	Signal Transduction Modulators; Toll-Like Receptor 3 (TLR3) Agonists	Preclinical	
Ruxolitinib phosphate	Novartis; Incyte	Jak1 Inhibitors; Jak2 Inhibitors; Signal Transduction Modulators; Tyk2 Inhibitors	Preclinical	
STI-4398	Sorrento Therapeutics	Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins-Directed Immunity Inducers; Viral Entry Inhibitors	Preclinical	
STI-6991	Sorrento Therapeutics	Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers	Preclinical	
Sp2CBMTD	Pneumagen		Preclinical	

TNX-1800	Tonix Pharmaceuticals	Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins-Directed Immunity Inducers	Preclinical
ZIP-1642	Ziphius Therapeutics	Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers	Preclinical
rCIG	GigaGen		Preclinical
1086184	Osaka University; AnGes	Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins-Directed Immunity Inducers	Preclinical
1086209	Kentucky BioProcessing (KBP)		Preclinical
1080103	CureVac	Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins-Directed Immunity Inducers	Preclinical
1083739	Mitsubishi Tanabe Pharma	Drugs Targeting Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins	Preclinical

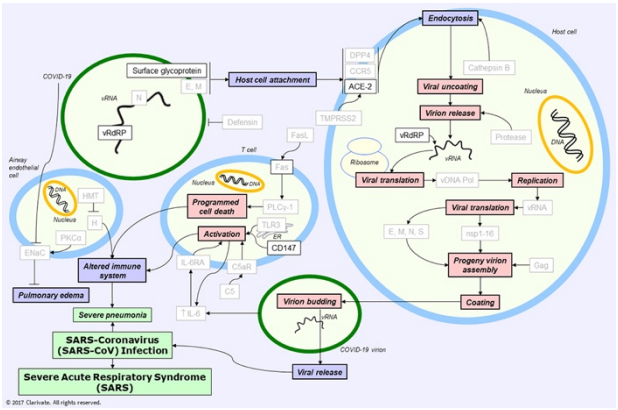
Targets for Therapeutic Intervention

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.

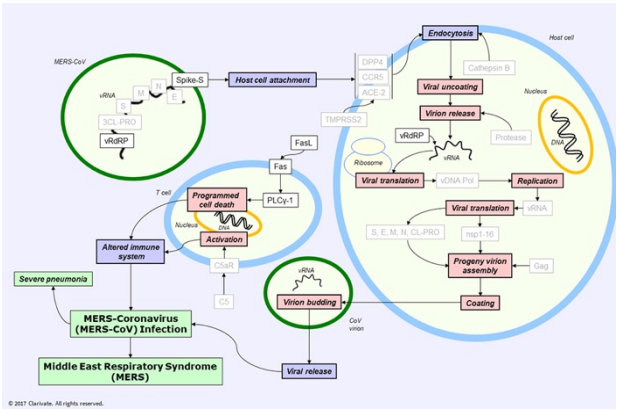
Coronavirus (CoV) Infection Targetscape



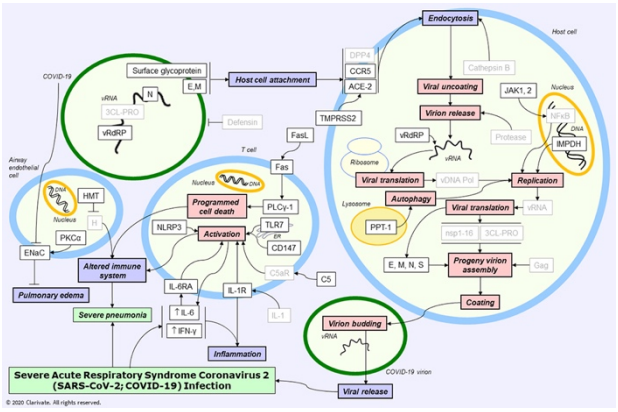
Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV) Infection Targetscape



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



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



Latest Headlines

15-Apr-2020

AstraZeneca initiates CALAVI study of Calquence against COVID-19

AstraZeneca announced that it will initiate a global clinical trial to assess the potential of the next-generation, highly selective Bruton tyrosine kinase (BTK) inhibitor Calquence (acalabrutinib), in the treatment of the exaggerated immune response (cytokine storm) associated with COVID-19 in severely ill patients. Calquence is currently used to treat certain types of blood cancers. The trial, called CALAVI, is based on strong scientific evidence and early clinical data with Calquence demonstrating that a decrease in inflammation caused by BTK inhibition appears to reduce the severity of COVID-19-induced respiratory distress. The goal of the trial is to evaluate the efficacy and safety of adding Calquence to best supportive care (BSC) to reduce mortality and the need for assisted ventilation in patients with life-threatening COVID-19 symptoms. This large, multicenter, global, randomized trial uses a two-part patient-centric design developed in record time to accelerate data capture and analysis. Part one is randomized (2:1) and will evaluate the addition of Calquence to current BSC in patients who are hospitalized but not on assisted ventilation and not in the ICU, while part two will evaluate the addition of Calquence to BSC in a cohort of patients in the ICU with more severe respiratory complications. The study's primary endpoint measures the use of assisted ventilation or death. The CALAVI trial is expected to open for enrollment in the coming days in the U.S. as well as several European countries (AstraZeneca News Release).

15-Apr-2020

Positive topline phase I data reported for ADX-629

Aldeyra Therapeutics announced positive topline phase I data for ADX-629, a first-in-class orally available reactive aldehyde species (RASP) inhibitor in development for the treatment of systemic immune-mediated diseases. Aldeyra also announced phase II clinical development plans for ADX-629. A total of 85 healthy volunteers were enrolled in the single-ascending and multiple-ascending dose phase I clinical trial, designed to evaluate the pharmacokinetic, pharmacodynamic, safety and tolerability profile of oral ADX-629. Of the 85 enrolled subjects, 41 received oral ADX-629 as a single dose, 23 received oral ADX-629 twice per day for 10 days, and 21 received placebo. ADX-629 was well-tolerated, with no treatment-related adverse events (AEs) observed. No clinically meaningful changes in vital signs were reported based on quantitative electrocardiography or blood chemistry data. Additionally, clinically relevant plasma concentrations exceeding known levels of RASP were observed, and reduction in the commonly described proinflammatory RASP malondialdehyde was seen in treated subjects relative to subjects treated with placebo. Unlike most currently available drugs, the RASP targets of ADX-629 are small molecules rather than proteins, therefore, ADX-629 could represent a new pharmacotherapeutic approach with potential applications across a large number of immune-mediated diseases. In animal models of cytokine storm, ADX-629 and structural analogue reproxalap, which is now in phase III clinical testing for certain inflammatory ocular diseases, have demonstrated reduction in the levels of a variety of proinflammatory cytokines, including TNF-alpha, IFN-gamma, IL-1 and IL-17, while upregulating the principal anti-inflammatory cytokine, IL-10. By potentially mitigating aberrant cytokine responses, it is believed that ADX-629 may delay or prevent progression of acute respiratory distress syndrome and other forms of respiratory compromise that generally require mechanical ventilation. Aldeyra plans to facilitate the clinical testing of ADX-629 in patients with COVID-19-associated respiratory compromise by requesting a pre-IND meeting with the Infectious Disease Division of the FDA. Additionally, the company has filed ADX-629 under the FDA's Coronavirus Treatment Acceleration Program (CTAP). Contingent on clinical research facility availability, which is currently limited due to COVID-19 precautions, Aldeyra also plans to test ADX-629 in phase II clinical trials of respiratory

and dermal conditions associated with elevated levels of RASP, potentially including atopic asthma, chronic cough, psoriasis and atopic dermatitis (Aldeyra Therapeutics News Release).

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15-Apr-2020

Sanofi and GSK collaborate to develop an adjuvanted vaccine for COVID-19

Sanofi and GlaxoSmithKline (GSK) have signed a letter of intent to develop an adjuvanted vaccine for COVID-19 to help address the ongoing pandemic. The adjuvanted vaccine would be developed using innovative technology from both companies. Sanofi will contribute its S-protein COVID-19 antigen, which is based on recombinant DNA technology that has produced an exact genetic match to proteins found on the surface of the virus. The DNA sequence encoding this antigen has been combined into the DNA of the baculovirus expression platform, the basis of Sanofi's licensed recombinant influenza product in the U.S. GSK will contribute its proven pandemic adjuvant technology. An adjuvant is added to some vaccines to enhance the immune response and has been shown to create a stronger and longer-lasting immunity against infections than the vaccine alone. It can also improve the likelihood of delivering an effective vaccine that can be manufactured at scale. The use of an adjuvant can be of particular importance in a pandemic situation since it may reduce the amount of vaccine protein required per dose, allowing more vaccine doses to be produced and therefore contributing to protect more people. The combination of a protein-based antigen together with an adjuvant is well-established and used in a number of vaccines available today. Sanofi and GSK plan to initiate phase I trials in the second half of 2020. If these studies are successful (subject to regulatory considerations) the companies aim to complete the development required for availability by the second half of 2021. As previously announced by Sanofi, development of the recombinant-based COVID-19 vaccine candidate is being supported through funding and a collaboration with the Biomedical Advanced Research and Development Authority (BARDA), part of the office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services. The companies plan to discuss funding support with other governments and global institutions prioritising global access. The companies have set up a joint taskforce, which will seek to mobilize resources from both companies to look for every opportunity to accelerate the development of the candidate vaccine. Both Sanofi and GSK believe that global access to COVID-19 vaccines is a priority and are committed to making any vaccine that is developed through the collaboration affordable to the public and through mechanisms that offer fair access for people in all countries. The companies have entered into a material transfer agreement to enable them to start working together immediately. Definitive terms of the collaboration are expected to be finalised over the next few weeks (Sanofi News Release).

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15-Apr-2020

Tocilizumab shows promise in single-center study in patients with COVID-19

Researchers from Tongji Medical College of Huazhong University of Science and Technology have published results from a clinical trial of the monoclonal antibody against IL-6 tocilizumab in COVID-19 patients. A total of 15 patients with COVID-19 were enrolled in the single-center study, designed to evaluate demographic, treatment, laboratory parameters of C-reactive protein (CRP) and IL-6 before and after therapy, as well as clinical outcome of tocilizumab therapy in this patient group. Two of the 15 enrolled subjects were moderately ill, 6 were seriously ill and 7 were critically ill. In 8 patients, tocilizumab was administered in combination with methylprednisolone, and 5 patients were administered tocilizumab twice or more. Tocilizumab treatment rapidly ameliorated the increased CRP in all patients. However, of the 4 critically ill patients who received only a single dose of tocilizumab, 3 died and in the remaining patient, the CRP level failed to return to normal range, resulting in a clinical outcome of disease aggravation. Serum levels of IL-6 showed the tendency to initially increase, with decreases seen in 10 patients after tocilizumab therapy. A persistent and dramatic increase of IL-6 was observed in the 4 patients who failed treatment. Overall, tocilizumab appeared to be an effective treatment option in patients with COVID-19 who are at risk of cytokine storm. Repeated dosing

of tocilizumab is recommended for the critically ill patients with elevated IL-6 (Luo, P. et al. J Med Virol 2020, Advanced publication).

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14-Apr-2020

Ridgeback Biotherapeutics initiates phase I study of EIDD-2801 for COVID-19

Ridgeback Biotherapeutics has commenced a phase I study in the U.K. of an orally available antiviral compound, EIDD-2801, following clearance by the U.K. Medicines and Healthcare products Regulatory Agency (MHRA). EIDD-2801 is an orally bioavailable form of a highly potent ribonucleoside analogue that inhibits the replication of multiple RNA viruses including SARS-CoV-2, the causative agent of COVID-19. In animal studies of two distinct coronaviruses (SARS-CoV-1 and MERS), EIDD-2801 demonstrated the ability to improve pulmonary function, decrease body weight loss, and reduce the amount of virus in the lung. When given prophylactically, EIDD-2801 was able to prevent significant manifestations of disease in animals challenged with these two coronaviruses. In addition to activity against coronaviruses, laboratory testing of EIDD-2801 demonstrated that the candidate also has activity against seasonal and bird influenza, respiratory syncytial virus, chikungunya virus, Ebola virus, Venezuelan equine encephalitis virus and Eastern equine encephalitis virus. In March 2020, Ridgeback and DRIVE signed a partnership with the focused mission of advancing EIDD-2801 through clinical development and optimizing availability during the current COVID-19 pandemic (BioWorld Science, March 20, 2020) (Ridgeback Biotherapeutics News Release). The company also recently obtained clearance from the FDA to begin clinical testing in the U.S. (BioWorld Science, April 7, 2020).

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14-Apr-2020

Bausch Health initiates clinical trial of Virazole in patients with COVID-19

Bausch Health announced that it has initiated a clinical trial program in Canada evaluating Virazole (ribavirin for inhalation solution, USP) in combination with standard-of-care therapy for the treatment of hospitalized adult patients with respiratory distress resulting from COVID-19 infection. Due to its activity of ribavirin as a synthetic nucleoside that works to stop viral replication, Virazole may be effective in reducing the severity of COVID-19. The initial clinical study has been approved by Health Canada and is expected to be initiated within the next few weeks. The company is also in discussions with the FDA and health authorities in multiple countries regarding additional studies to evaluate Virazole as a treatment for COVID-19 infection. Additionally, the Bausch Foundation is continuing to work directly with health authorities in Italy to make Virazole for inhalation available free of charge in compassionate use in Italian hospitals. The initial study protocol is designed as an open-label, interventional trial, with will evaluate the safety and efficacy of Virazole in hospitalized adult patients (aged 18 years or older) who have tested positive for COVID-19, and as a result of their infection, have significant respiratory distress. Two active study arms will compare different dosing regimens of Virazole in combination with standard-of-care therapy. Virazole is currently approved in several countries around the world, including the U.S. and Canada, for the treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV) (Bausch Health News Release).

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14-Apr-2020

Lilly advances plans to evaluate baricitinib and LY-3127804 for COVID-19

Eli Lilly has entered into an agreement with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), to study baricitinib as an arm in NIAID's Adaptive COVID-19 Treatment Trial (ClinicalTrials.gov Identifier NCT04280705). The study will investigate the efficacy and safety of baricitinib as a potential treatment for hospitalized patients diagnosed with COVID-19, beginning this month in the U.S., with a planned expansion to additional sites, including Europe and Asia. Results are expected within

the next 2 months. Baricitinib is an oral JAK1/JAK2 inhibitor marketed as Olumiant and approved in more than 65 countries for adults with moderate to severely active rheumatoid arthritis. Given the inflammatory cascade seen in COVID-19, baricitinib's anti-inflammatory activity has been hypothesized to have a potential beneficial effect in COVID-19. Lilly has also announced that it will advance LY-3127804, an investigational selective monoclonal antibody against angiopoietin 2 (Ang2), to phase II testing in hospitalized patients with COVID-19 and pneumonia who are at a higher risk of progressing to acute respiratory distress syndrome (ARDS) (ClinicalTrials.gov Identifier NCT04342897). Ang2 is known to be elevated in ARDS patients and Lilly will test whether inhibiting the effects of Ang2 with a monoclonal antibody can reduce the progression to ARDS or the need for mechanical ventilation in patients with COVID-19. This trial will begin later this month at several U.S. centers. Lilly currently does not anticipate shortages for any of its medicines, including baricitinib, which remains widely available in countries where it is approved (Eli Lilly News Release).

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09-Apr-2020

Active compound of WP-1122 reduces coronavirus replication in vitro

Moleculin Biotech announced that independent research found 2-deoxy-D-glucose (2-DG) to reduce replication of the SARS-CoV-2 virus by 100% in in vitro testing. Researchers at the University of Frankfurt reported that inhibiting glycolysis with nontoxic concentrations of 2-DG completely prevented SARS-CoV-2 replication in Caco-2 cells. Moleculin's drug candidate WP-1122 is a prodrug of 2-DG, whereby chemical elements are added to 2-DG to improve its delivery in vivo. 2-DG is metabolized too quickly to enable enough concentration in human tissues and organs to be therapeutic. WP-1122 can achieve much higher tissue/organ concentrations than 2-DG alone. The drug has demonstrated a good safety profile in mice and the company is in the process of demonstrating safety in additional species before submitting an IND application for clinical testing (Moleculin Biotech News Release).

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09-Apr-2020

OncoImmune cleared to begin phase III study of CD24Fc for hospitalized patients with COVID-19

OncoImmune has received clearance from the FDA for a phase III trial testing the safety and efficacy of CD24Fc for the treatment of patients hospitalized with COVID-19 (ClinicalTrials.gov Identifier NCT04317040). A cohort of 230 subjects with severe clinical symptoms will be randomized and administered a single dose of CD24Fc (480 mg intravenous infusion) or placebo and followed for a 14-day period to assess safety and efficacy in clinical improvement. CD24Fc will be tested in combination with the best available therapy, and patients receiving other experimental therapies may also join the trial. The double-blind, randomized, multicenter trial consists of two interim analyses, respectively, for safety and therapeutic activity, and for therapeutic efficacy. CD24Fc is a first-in-class biologic that fortifies an innate immune checkpoint against excessive inflammation caused by tissue injuries (OncoImmune News Release).

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09-Apr-2020

CSL Behring and SAB partner on development of COVID-19 therapeutic candidate SAB-185

CSL Behring and SAB Biotherapeutics (SAB) have partnered to develop SAB-185, a COVID-19 therapeutic candidate set to enter the clinic by early summer. SAB-185 is generated from SAB's proprietary DiversitAb platform producing large volumes of human polyclonal antibodies targeted specifically to SARS-CoV-2, the virus that causes COVID-19. SAB's novel approach, leveraging genetically engineered cattle to produce fully human antibodies, enables a scalable and reliable production of targeted, higher potency neutralizing antibody product than has been previously possible. CSL Behring has provided seed funding to offset some initial development costs that were funded by SAB in good faith. SAB has already secured approximately USD 7.2

million in funding through an interagency agreement with the Joint Program Executive Office for Chemical, Biological, Radiological, and Nuclear Defense (JPEO - CBRND) and Biomedical Advanced Research and Development Authority (BARDA) to support SAB to complete manufacturing and preclinical studies. CSL Behring will then commit its clinical, regulatory, manufacturing and supply chain expertise and resources to deliver the therapeutic to the market as soon as possible, on terms to be agreed with SAB. Earlier this year, the companies entered into a collaboration to investigate SAB's platform technology as a new source for human immunoglobulin G (IgG) and the potential for new therapies to treat autoimmune, infectious and idiopathic diseases by leveraging the DiversitAb platform (CSL Behring News Release).

Suggested reading

Related websites

- Centers for Disease Control and Prevention (CDC) -- Coronavirus (Covid-19)
- Centers for Disease Control and Prevention (CDC) -- SARS information
- Coalition for Epidemic Preparedness Innovation (CEPI)
- Coronavirus Global Health Emergency (United Nations)
- European Centre for Disease Prevention and Control -- Novel coronavirus
- European Commission - Public health - COVID-19 resources
- 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.)

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

Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected - Interim guidance (World Health Organization, January 12, 2020)

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

Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: Experts 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, January 25, 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)

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

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

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

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