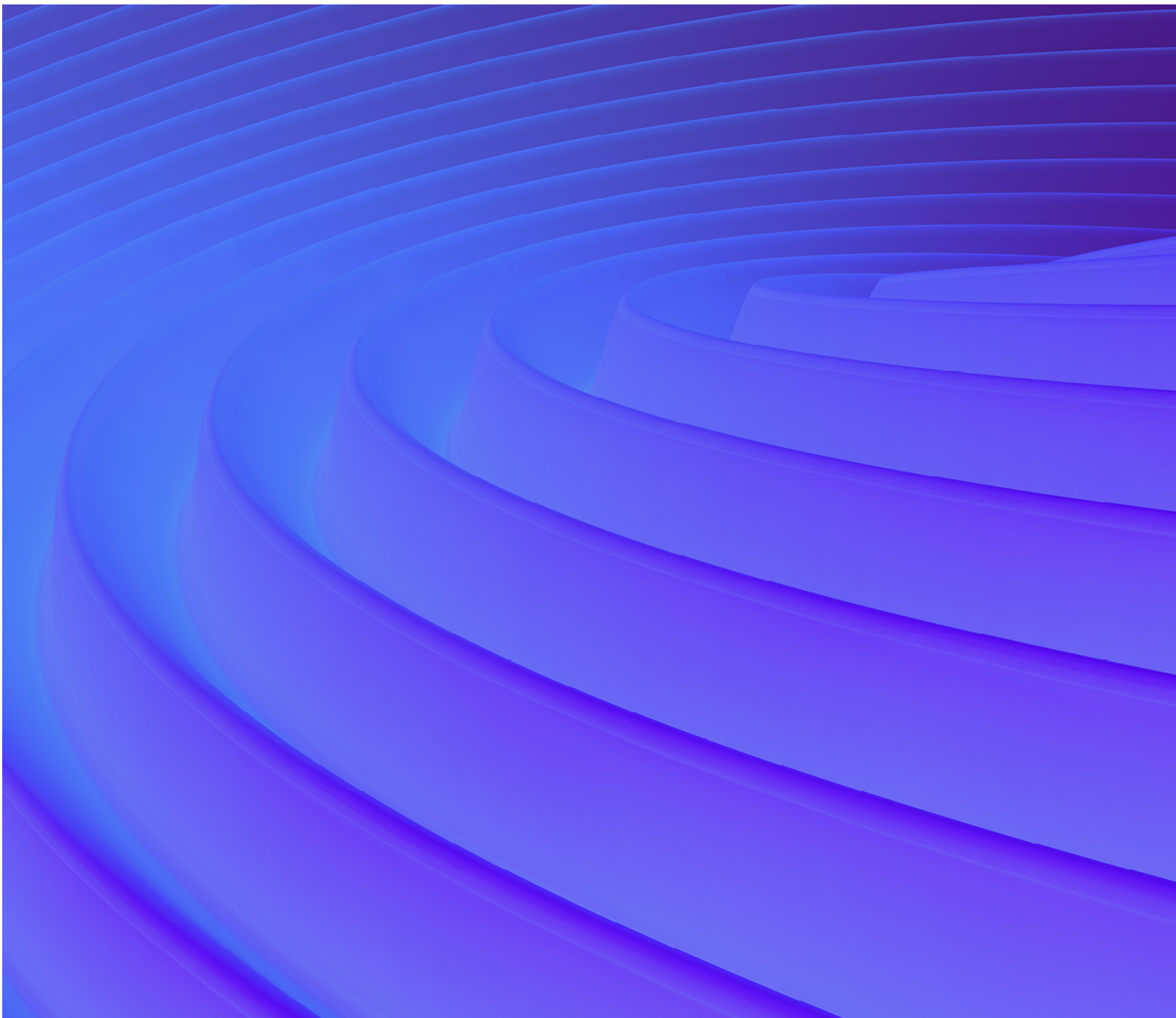


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Disease Briefing: Coronaviruses



Contents

CONTENTS	1
CORONAVIRUS: DISEASE BRIEFING	2
LATEST HEADLINES	35
SUGGESTED READING	39
GUIDELINES	40
SOURCES	41

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 chicken. 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 represent an ongoing threat to human health (Hui, D.S. et al (2020); Zhu, N. et al (2020)). This fact again became 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 respiratory disease, including potentially fatal pneumonia, in Wuhan, China (**WHO statement regarding cluster of pneumonia cases in Wuhan, China (World Health Organization, January 9, 2020); Emergencies: Novel coronavirus 2019 (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
	Rhinoviruses	Common cold
	Hepatitis A virus	Hepatitis
Picornaviruses (Picornaviridae) Single-stranded RNA, nonenveloped	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 (Caliciviridae) 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) Rubivirus	Encephalitis, hemorrhagic fever, chikungunya Rubella
Flaviviruses (Flaviviridae) Single-stranded RNA, enveloped (No DNA step in replication; positive-sense genome)	Group B arboviruses Hepatitis C virus Dengue virus Zika virus	Encephalitis, hemorrhagic fever Hepatitis Dengue fever Zika
Bunyaviruses (Bunyaviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; segmented genome)	Some arboviruses Hantavirus	Encephalitis, hemorrhagic fevers Fever, renal involvement
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) Lassa virus	Meningitis Hemorrhagic fever
Retroviruses (Retroviridae) Single-stranded RNA, enveloped (DNA step in replication)	HTLV-I, HTLV-II HIV-1, HIV-2	T cell leukemia, lymphoma, paresis AIDS
Filoviruses (Filoviridae) Single- stranded RNA, enveloped (No DNA step in replication; negative-sense genome; nonsegmented genome)	Marburg virus Ebola virus	Marburg disease 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 nucleocapsid (N) within the capsid. The envelope (E) protein is a highly hydrophobic protein encasing the entire structure of the coronavirus. The genome is nonsegmented, positive single-stranded RNA of about 26-32 kb, making it the longest RNA viral genome known, and contains at least six different open reading frames. The RNA molecule has a methylated cap in 5' and a poly-A tail in 3' (Schoeman, D. et al (2019); Chen, Y. et al (2020); Pillaiyar, T. et al (2020)).

Coronaviruses are capable of adapting quickly to new hosts through the processes of genetic recombination and mutation *in vivo*. As RNA viruses, coronaviruses rely on RNA-dependent RNA polymerase (RdRp) to replicate the virus genome. The intrinsic error rate of RdRp is approximately 1,000,000 mutation/site/replication, resulting in continuous point mutations. Point mutations alone are not sufficient to create a new virus, however; this can only occur when the same host is simultaneously infected with two coronavirus strains, enabling recombination. One coronavirus can gain a genomic fragment of hundreds or thousands base-pair long from another CoV strain when the two co-infect the same host, enabling the virus to increase its ecological niche or to make the leap to a new species (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 Guangdong in November 2002 and soon spread throughout Asia, North America and Europe. Worldwide, 33 countries and regions on five continents reported SARS cases, although the most severely affected were mainland China and Hong Kong. By spring 2003, SARS became recognized as a global health threat. The rapid spread of the virus to different continents following the initial outbreak underscored the ease with which infectious diseases can be spread internationally within a highly mobile global population (Heymann, D.L. et al (2013); Yang, Y. et al (2020)).

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

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

SARS-CoV Morphology, Structure and Replication

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

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

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

The genome contains a total of 11 predicted open reading frames that potentially encode as many as 23 mature proteins (Ruan, Y.J. et al (2003)). The two principal ORFs, occupying about two-thirds of the genome, code for two major polyproteins, ORF1a and ORF1b. The polyproteins are cleaved by proteolysis to produce nonstructural proteins, the most important of which are the RNA-dependent RNA polymerase (Rep) and an ATPase helicase (Hel). The SARS-CoV has some genetic characteristics that are slightly different from other coronaviruses. There is a short anchor in the S protein, the number and location of the small ORFs are different, there is only one PLP-protease, and a unique, short lysine-rich region exists in the nucleocapsid

protein. The biologic significance of these variations is unknown (Rota, P.A. et al (2003); Marra, M.A. et al (2003)).

Coronaviruses enter cells via binding to a host receptor followed by membrane fusion. ACE2 was identified as the cell receptor for SARS-CoV (Wan, Y. et al (2020)). 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)). Nosocomial 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 ($>38^{\circ}\text{C}$) 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)).

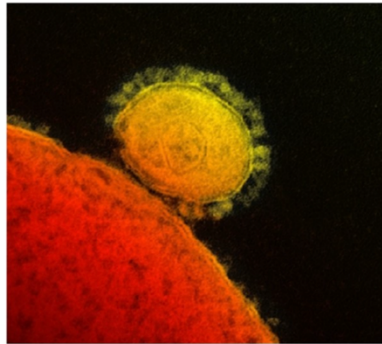
The SARS epidemic had important economic implications. It has been estimated that the worldwide economic cost of the SARS epidemic was about USD 30 billion. The 6% annual economic growth of East Asia in 2003 was reduced to 5% during the epidemic (Kondro, W. (2003)). The total economic impact of SARS 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)). Globally, the economic cost of the epidemic was estimated at up to 100 billion (Paules, C.I. et al (2020)).

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)).

MIDDLE EAST RESPIRATORY SYNDROME
CORONAVIRUS (MERS-COV)



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); Skaryachan, 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); Skaryachan, 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 Saudi Arabia, and confirmed that the virus can be transmitted between humans during close contact (Assiri, A. et al (2013); Zumla, A. et al (2015)). As of 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 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 (R_0) 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)).

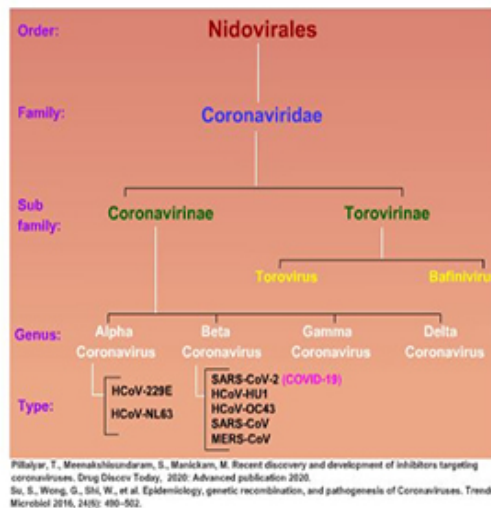
For more epidemiology information, consult the Incidence and Prevalence Database (IPD): **IPD: Middle East respiratory syndrome coronavirus (MERS-CoV).**

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



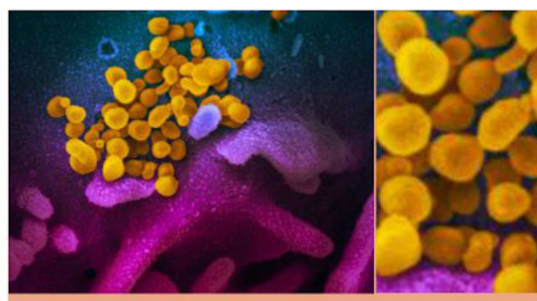
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SARS-CoV-2 Morphology, Structure and Replication

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 uses ACE2 as its binding receptor (Wan, Y. et al (2020)), deploying the S protein for virus-cell receptor interaction during viral entry (Li, G. 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 rapid spread through human populations (He, F. et al (2020)). The virus uses the host cellular protease 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)).

Coronavirus (2019-nCoV; SARS-CoV-2)



Source: NIAID-RML NIAID had produced images of the novel coronavirus (SARS-CoV-2, previously known as 2019-nCoV) on its scanning and transmission electron 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 during the viremic stage of disease is primarily via inhalation of airborne respiratory secretions (droplets) or direct contact with infected patients (Lai, C.C. et al (2020)). Infectious droplets and body fluids can also contaminate the human conjunctival epithelium, producing ocular complications in infected patients, which 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)). However, there is no evidence of vertical transmission, as evidenced by lack of virus detection in amniotic fluid, cord blood, neonatal throat swab and breastmilk samples obtained from six confirmed SARS-CoV-2 pregnant women (Yang, Y. et al (2020)). Transmission via fomites is also possible. The virus 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)).

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 (R_0) of 2.2 (Li, Q. et al (2020)); later studies with more data suggested a higher R_0 of 2.24-3.58 (Lai, C.C. et al (2020)). In contrast, the R_0 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 infected individuals might be capable of transmitting the disease during the prodromal period (Heymann, D.L. et al (2020)), as well as 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

Following an incubation period ranging from 2-14 days (median 5.1 days) (Lauer, S.A. et al (2020)), Covid-19 manifests as respiratory illness ranging 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)).

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 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)).

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 March 20, 2020, a total of 234,073 laboratory-confirmed cases of Covid-19 had been diagnosed and reported 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 March 20, WHO confirmed 9,840 deaths from Covid-19 worldwide, with the epicenter of the outbreak now in Europe. The risk assessment of this event, as determined by WHO, was very high at the global level (**Emergencies: Novel coronavirus 2019 (World Health Organization)**, consulted March 21, 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 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.

The rapid spread and ease of transmission of the virus are causing global alarm. Experts point out that although the virus may pose a 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)).

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) specifically detect viral RNA. RT-PCR was the only 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 RT-PCR is currently the only rapid diagnostic test that can give the necessary sensitivity and specificity that are required for a routine clinical diagnostic tool; 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**). 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 results. 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.

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)).

Differential Diagnosis

Pneumonia of other viral or bacterial origin –especially *Streptococcus pneumoniae*, *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 (see Poxviruses), 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, quarantine and community containment are the most effective means of controlling a coronavirus outbreak with epidemic potential (Wilder-Smith, A. et al (2020)). Authorities are often reluctant to impose these measures because of their economic and social impact; however, without other means of control of the epidemic spread of SARS, there was no alternative. The success of these measures was demonstrated in Singapore, where application of infection control measures resulted in a decrease in R_0 (secondary infection rate) from 7 at week 1 to <1 after week 2 (Cleri, D.J. et al (2010)). In Taiwan, the application of Level A quarantine (that of potentially exposed contacts of suspected SARS patients) resulted in the prevention of approximately 461 additional cases and 62 additional deaths; the use of Level B quarantine (that of travelers arriving from affected areas), in contrast, reduced the number of new cases and deaths by only about 5% (Hsieh, Y.H. et al (2007)). CDC recommends use of airborne infection isolation procedures in the care of all confirmed MERS infections in that country (Al-Tawfiq, J.A. et al (2014)). 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 $R_0 = 2.68$), WHO-linked epidemiology experts recommend stringent controls in order to prevent independent, self-sustaining outbreaks in major cities around the world (Wu, J.T. et al (2020)).

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 handrubs is effective for interrupting virus transmission. SARS and other 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 for up to 48 hours at 20°C and for 24 hours at 30°C (Chan, J.F. et al (2015)). Personal protective equipment, including eye protection, is 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, based on either killed or attenuated virus, points to the potential success of vaccine programs.

The S protein is currently considered to be one of the most promising targets for coronavirus vaccine development (Song, Z. et al (2019)), and is being targeted for the development of both anti-MERS-CoV and anti-SARS-CoV-2 vaccines. Development of the former 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)). Human MERS-CoV vaccines are also now in development, including DNA vaccines, vector-based, live attenuated and protein subunit vaccines (Cho, H. et al (2018); Schindewolf, C. et al (2019)); many of these vaccines target the S protein (Li, F. et al (2019); Song, Z. et al (2019)).

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 \(Nature News, March 9, 2020\)](#)). Upon emergence of SARS-CoV-2, 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)). The most rapidly developed vaccines against Covid-19 have been mRNA vaccines. These include Moderna's mRNA-1273, which encodes for a prefusion stabilized form of the S protein, and which entered phase I testing in the U.S. in March 2020. This study, being conducted by the National Institutes of Health, is evaluating the safety and immunogenicity of three dose levels of mRNA-1273 administered on a two-dose vaccination schedule, given 28 days apart. A total of 45 healthy adults will be enrolled in the study. Participants will be followed through 12 months after the second vaccination. The primary objective is to evaluate the safety and reactogenicity of the two-dose vaccination schedule. The secondary objective is to evaluate the immunogenicity to the SARS-CoV-2 S protein.

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	Organisations	Description	Phase
<u>LV-SMENP-DC</u>	Shenzhen Genoimmune Medical Institute	Human COVID - 19 coronavirus (SARS - CoV - 2) 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 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)	Phase I/II
<u>mRNA-1273</u>	National Institutes of Health (NIH); Moderna	Human COVID - 19 coronavirus (SARS - CoV - 2) mRNA vaccine	Phase I
<u>1084319</u>	Shenzhen Genoimmune Medical Institute	COVID - 19 coronavirus (SARS - CoV - 2) vaccine consisting of artificial antigen presenting cells (aAPC) carrying SARS - CoV - 2 antigens	Phase I
<u>Ad5-nCoV</u>	CanSino Biologics	Human COVID - 19 coronavirus (SARS - CoV - 2) vaccine consisting of a replication - defective adenovirus type 5 vector encoding SARS - CoV - 2 spike (S) gene	IND Filed
<u>INO-4800</u>	Inovio Pharmaceuticals	Human COVID - 19 coronavirus (SARS - CoV - 2) DNA vaccine	Preclinical

<u>LUNAR-COV19</u>	Duke University; Arcturus Therapeutics	Human COVID - 19 coronavirus (SARS - CoV - 2) mRNA vaccine comprising a self - replicating RNA based on STARR technology platform delivered using Lipid - enabled and Unlocked Nucleomonomer Agent modified RNA (LUNAR(R)) platform	Preclinical
<u>TNX-1800</u>	Tonix Pharmaceuticals	Human COVID - 19 coronavirus (SARS - CoV - 2) vaccine comprising an engineered, live replicating strain of horsepox virus (HPXV) encoding a protein of COVID - 19 virus	Preclinical
<u>1082107</u>	Novavax	Human COVID - 19 coronavirus (SARS - CoV - 2) vaccine comprising recombinant COVID - 19 spike glycoprotein; encapsulated in nanoparticles	Preclinical
<u>1083739</u>	Mitsubishi Tanabe Pharma	Human COVID - 19 coronavirus (SARS - CoV - 2) virus - like particle (VLP) vaccine	Preclinical
<u>1080103</u>	CureVac	Human COVID - 19 coronavirus (SARS - CoV - 2) mRNA vaccine	Preclinical
<u>1080229</u>	Jenner Vaccine Foundation	Human COVID - 19 coronavirus (SARS - CoV - 2) vaccine comprising replication - deficient simian adenovirus vector ChAdOx1 encoding spike glycoprotein of COVID - 19 virus	Preclinical

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

Drug name	Organisations	Description	Phase
<u>BVRS-GamVac-Combi</u>	Ministry Healthcare Russian Federation	Middle East respiratory syndrome coronavirus (MERS - CoV) vaccine comprising a combined heterologous adenoviral vector	Phase I/II
<u>GLS-5300</u>	Inovio Pharmaceuticals; GeneOne Life Science	Middle East Respiratory Syndrome DNA vaccine using the SynCon (TM) technology, encoding MERS spike protein	Phase I/II
<u>ChAdOx1 MERS</u>	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
<u>MVA-MERS-S</u>	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

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 atorvastatin 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)).

Interim guidelines for the appropriate care of patients in whom Covid-19 is suspected have been issued by WHO, CDC and other organizations (see Links to Guidelines).

Broad-Spectrum Antiviral Agents

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- α 2b 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- α 2a, rIFN- α 2b or rIFN- β 1a), 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 are cited as one factor against its use in patients with Covid-19 (Li, G. et al (2020)).

The antimalarial agents chloroquine and hydroxychloroquine have broad-spectrum antiviral activity, including anti-SARS-CoV-2 activity in vitro, as well as antiinflammatory effects. Chloroquine acts by increasing endosomal pH required for fusion of the virus with the host cell, as well as by interfering with glycosylation of SARS-CoV-2 cellular receptors. Based on this promising profile, low cost and easy availability of the drug, a clinical trial evaluating chloroquine for the treatment of Covid-19 pneumonia has been initiated (Gao, J. et al (2020); Colson, P. et al (2020)). Chinese experts have issued a consensus statement regarding the use and appropriate dosing of chloroquine (Unknown Author (2020)).

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 polypeptides 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)). A number of host proteases have been shown to proteolytically process the S protein, which determines viral entry. These include cathepsin, furin and trypsin (Millet, J.K. et al (2015); Kilianski, A. et al (2014)). The S protein can also be activated by other host proteases including type II transmembrane serine protease (TMPRSS2), which is considered a promising antiviral drug target (Kilianski, A. et al (2014); Li, F. et al (2019)).

The protease inhibitor combination lopinavir/ritonavir has progressed furthest in development for treatment of MERS-CoV. Following successful preclinical evaluation of lopinavir/ritonavir plus interferon- β 1b, 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- β 1b 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 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.

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) often represent the first line of investigation and defense against emerging diseases. Neutralizing MAbs, including murine, chimeric and fully human antibodies have been tested; the latter are preferred due to their reduced immunogenicity (Jin, Y. et al (2017)).

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 have 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)).

The anti-CCR-5 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.

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/ritonavir in combination with IFN-alfa-2b in hospitalized patients with SARS-CoV-2 infection.

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)). Because ribavirin decreases the release of proinflammatory cytokines in mice infected with the mouse hepatitis coronaviruses, it may also act as an immunomodulator (Peiris, J.S. et al (2003)). In vitro studies indicate that ribavirin concentrations that inhibit other viruses are not sufficient to inhibit the replication of the SARS-CoV (Normile, D. (2003)). Therefore some of its benefits may be due to its immunomodulatory activity (Mazzulli, T. et al (2004)). Other treatment options with immunomodulating properties were also used during the SARS epidemic, including i.v. immunoglobulins and convalescent-phase plasma (Tai, D.Y. (2007); Mair-Jenkins, J. et al (2015)).

During the MERS-CoV outbreak in 2015, some Korean patients were treated with convalescent plasma, i.e. passive immunotherapy entailing the infusion of blood plasma from patients who had overcome the infection. 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 antibody titers (Arabi, Y. et al (2016)).

In March 2020, Takeda announced that it was initiating the development of an anti-SARS-CoV-2 polyclonal hyperimmune globulin (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. These convalescent donors have developed antibodies to the virus that could potentially mitigate severity of illness in COVID-19 patients and possibly prevent it.

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)).

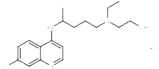
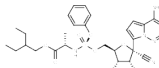
Data obtained in a Hong Kong hospital support use of pulsed methylprednisolone as rescue therapy only during the later stages of SARS; administration during the earlier phases of disease appeared to actually prolong viremia (Hui, D.S. et al (2010)). In fact, later analysis showed that prolonged methylprednisolone 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 with Covid-19 (Huang, C. et al (2020)). However, 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)).

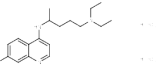
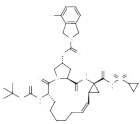
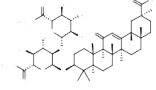
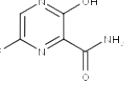
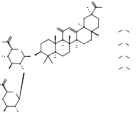
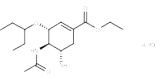
Current Coronavirus Pipeline

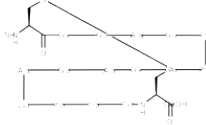
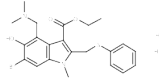

Consult the tables below for an overview of all products mentioned in this review, including drugs, biologics and diagnostic agents that have been marketed or are under active development for this indication. Tables may also include drugs not covered in the preceding sections because their mechanism 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
<u>ASC-09/ritonavir</u>	Ascleptis	HIV Protease Inhibitors; HIV-1 Protease Inhibitors; Tumor Necrosis Factor Receptor Superfamily Member 6 (CD95)/PLC-gamma-1 Interaction Inhibitors	Phase III	
<u>Darunavir/cobicistat</u>	Shanghai Public Health Clinical Center	Cytochrome P450 CYP3A4 Inhibitors; HIV Protease Inhibitors	Phase III	
<u>Hydroxychloroquine sulfate</u>	Shanghai Public Health Clinical Center	Autophagy Inhibitors; Palmitoyl-Protein Thioesterase 1 (PPT1) Inhibitors	Phase III	
<u>Remdesivir</u>	Gilead	RNA-Directed RNA Polymerase (Viral) Inhibitors; Viral Replication Inhibitors	Phase III	
<u>Lopinavir/ritonavir</u>	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	
<u>Sarilumab</u>	Regeneron	Anti-Interleukin-6 Receptor Subunit Alpha (CD126; IL-6R); Signal Transduction Modulators	Phase II/III	
<u>Interferon-beta</u>	Synairgen		Phase II	
<u>BVR5-GamVac-Combi</u>	Ministry Healthcare Russian Federation		Phase I/II	

<u>GLS-5300</u>	Inovio Pharmaceuticals; GeneOne Life Science	Spike Glycoprotein (S) (MERS-CoV)-Directed Immunity Inducers	Phase I/II
<u>LV-SMENP-DC</u>	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
<u>[131I]-Metuximab injection</u>	Fourth Military Medical University	Anti-CD147; Signal Transduction Modulators	Phase I/II
<u>AmnioBoost</u>	Lattice Biologics		Phase I
<u>ChAdOx1 MERS</u>	Vaccitech Ltd.; University of Oxford	Spike Glycoprotein (S) (MERS-CoV)-Directed Immunity Inducers	Phase I
<u>MVA-MERS-S</u>	Ludwig-Maximilians-Univ. Muenchen	Spike Glycoprotein (S) (MERS-CoV)-Directed Immunity Inducers	Phase I
<u>REGN-3048</u>	Regeneron	Anti-Spike Glycoprotein (MERS-CoV Coronavirus)	Phase I
<u>REGN-3051</u>	Regeneron	Anti-Spike Glycoprotein (MERS-CoV Coronavirus)	Phase I
<u>SAB-301</u>	SAB Biotherapeutics	Anti-Spike Glycoprotein (MERS-CoV Coronavirus)	Phase I
<u>mRNA-1273</u>	National Institutes of Health (NIH); Moderna	Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins-Directed Immunity Inducers	Phase I

<u>1084319</u>	Shenzhen Genoimmune Medical Institute	Drugs Targeting Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins	Phase I	
<u>APN-01</u>	Apeiron Biologics		Clinical	
<u>CB-MSCs</u>	Wuhan University of Science Technology		Clinical	
<u>Chloroquine phosphate</u>	Guangdong Zhongsheng Pharmaceutical	Apoptosis Inducers; Histamine N- methyltransferase (HNMT) Inhibitors	Clinical	
<u>Danoprevir</u>	Ascleitis	Serine Protease NS3/Non- Structural Protein 4A (NS3/NS4A) (HCV) Inhibitors	Clinical	
<u>Diammonium glycyrrhizinate</u>	Sino Biopharmaceutical	Microbiome Modulators	Clinical	
<u>Favipiravir</u>	Hisun Pharmaceutical (Hangzhou); Sihuan Pharmaceutical	RNA-Directed RNA Polymerase (Influenza A Virus H1N1) Inhibitors; RNA- Directed RNA Polymerase (NS5B) (HCV) Inhibitors	Clinical	
<u>Leronlimab</u>	CytoDyn	Anti-CD195 (CCR5); Signal Transduction Modulators; Viral Entry Inhibitors	Clinical	
<u>Magnesium isoglycyrrhizinate</u>	Sino Biopharmaceutical		Clinical	
<u>Oseltamivir phosphate</u>	Wuhan Tongji Hospital	Neuraminidase (Sialidase) (Influenza Virus) Inhibitors	Clinical	
<u>Siltuximab</u>	EUSA Pharma	Anti-IL-6; Signal Transduction Modulators	Clinical	

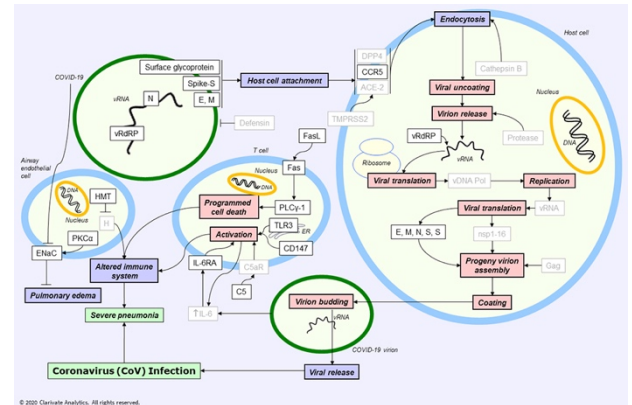
<u>Solnatide</u>	APEPTICO	Epithelial Sodium Channel (ENaC) Activators; Protein Kinase PKC alpha Inhibitors; Signal Transduction Modulators	Clinical	
<u>Umifenovir hydrochloride</u>	Wuhan Tongji Hospital	Capsid Assembly (Hepatitis B Virus) Modulators; Viral Entry Inhibitors	Clinical	
<u>Ad5-nCoV</u>	CanSino Biologics	Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers	IND Filed	
<u>IFX-1</u>	Staidson (Beijing) Biopharmaceuticals	Anti-C5 (Complement 5)	IND Filed	
<u>CK-0802</u>	Cellenkos		Preclinical	
<u>EIDD-2801</u>	Ridgeback Biotherapeutics		Preclinical	
<u>FM-201</u>	Future Medicine		Preclinical	
<u>GREVAX/MERS</u>	Greffex		Preclinical	
<u>Human leukocyte interferon alpha</u>	AIM ImmunoTech		Preclinical	
<u>INO-4800</u>	Inovio Pharmaceuticals	Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins-Directed Immunity Inducers	Preclinical	
<u>IR-101C</u>	Immune Response BioPharma		Preclinical	

<u>LCA-60</u>	Vir Biotechnology	Anti-Spike Glycoprotein (MERS-CoV Coronavirus)	Preclinical
<u>LUNAR-COV19</u>	Duke University; Arcturus Therapeutics	Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins-Directed Immunity Inducers	Preclinical
<u>MVA-MERS-S DF1</u>	Universitaetsklinikum Hamburg-Eppendorf	Spike Glycoprotein (S) (MERS-CoV)-Directed Immunity Inducers	Preclinical
<u>Rintatolimod</u>	AIM ImmunoTech	Signal Transduction Modulators; Toll-Like Receptor 3 (TLR3) Agonists	Preclinical
<u>Sp2CBMTD</u>	Pneumagen		Preclinical
<u>TNX-1800</u>	Tonix Pharmaceuticals	Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins-Directed Immunity Inducers	Preclinical
<u>1080103</u>	CureVac	Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins-Directed Immunity Inducers	Preclinical
<u>1080229</u>	Jenner Vaccine Foundation	Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers; Viral Entry Inhibitors	Preclinical
<u>1082107</u>	Novavax	Spike Glycoprotein (S) (SARS-CoV-2; COVID-19 Virus)-Directed Immunity Inducers; Viral Entry Inhibitors	Preclinical
<u>1083739</u>	Mitsubishi Tanabe Pharma	Drugs Targeting Human Coronavirus (SARS-CoV-2; COVID-19 Virus) Proteins	Preclinical

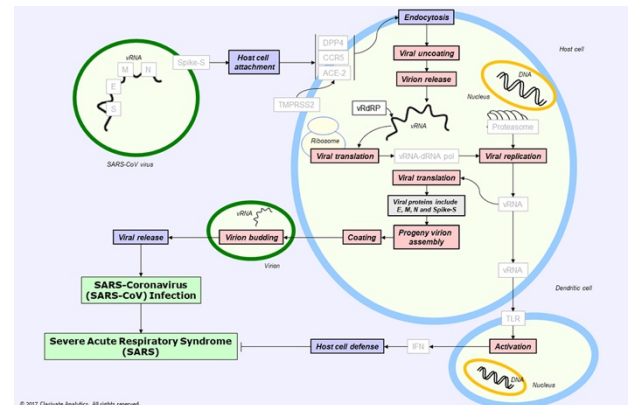
Targets for Therapeutic Intervention

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.

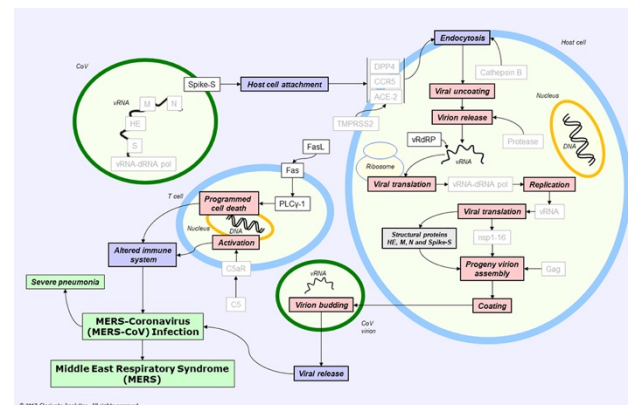
Coronavirus (CoV) Infection Targetscape



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

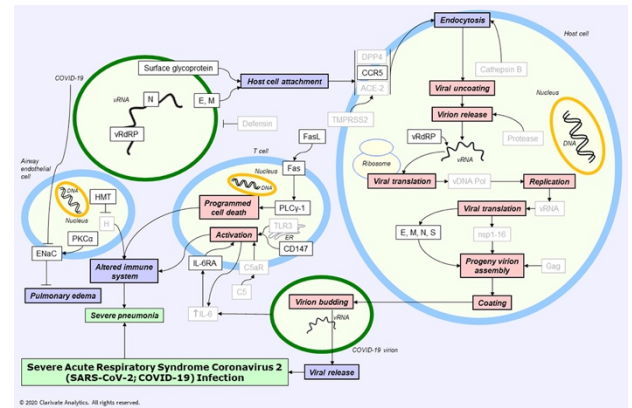


Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection Targetscape



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

Targetscape



Latest Headlines

20-Mar-2020

Algernon supports phase II study of ifenprodil for coronavirus infection

Algernon Pharmaceuticals announced that Novotech has identified physicians in South Korea who have agreed to conduct an investigator-initiated phase II study of ifenprodil (NP-120) for patients with coronavirus infection. Ifenprodil is an N-methyl-D-aspartate (NMDA) receptor glutamate receptor antagonist specifically targeting the NMDA-type subunit 2B (Glu2NB). The investigators were identified after Algernon retained Novotech to conduct a feasibility study in South Korea, with Novotech being asked to advise on the most efficient regulatory approach to initiating a phase II clinical trial for ifenprodil for COVID-19 as well as to help identify potential investigators. The decision to retain Novotech to conduct a feasibility study was made after a recent independent study found that ifenprodil significantly reduced acute lung injury (ALI) and improved survivability in an animal study with Asian H5N1 infected mice by 40%. In a separate study, the drug has also shown the ability to prolong survival under anoxic conditions, as might occur in patients with severely impaired lung function. Ifenprodil is an already approved drug in South Korea and Japan for certain neurological conditions with a known safety profile. Algernon has been investigating ifenprodil under its repurposed drug program and has appointed Novotech as the lead CRO for its upcoming idiopathic pulmonary fibrosis (IPF) and chronic cough phase II clinical trial to be conducted in Australia. Algernon is in the process of refining the protocol for the phase II coronavirus study after receiving input from the investigators. The company working with Novotech to provide the necessary information and support in order to assist with the study's approval, which may be expedited due to the current global health crisis (Algernon Pharmaceuticals News Release)

20-Mar-2020

Roivant seeks to advance development of gimsilumab for COVID-19-related ARDS

Roivant Sciences has engaged with regulators in the U.S., Europe and Asia to rapidly advance the clinical development of gimsilumab for the treatment of acute respiratory distress syndrome (ARDS) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Clinical trials of gimsilumab in patients with COVID-19 will commence upon approval by relevant regulatory authorities. Roivant will prioritize these trials instead of a phase II trial in a separate disease area which had been previously planned. Gimsilumab is a clinical-stage, fully human monoclonal antibody targeting granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF, a proinflammatory cytokine, is found to be upregulated in the serum of COVID-19 patients according to recent data from patients in China. The percentages of GM-CSF-expressing CD4+ T cells (Th1), CD8+ T cells, NK cells, and B cells have been observed to be significantly higher in the blood of ICU-admitted COVID-19 patients when compared with healthy controls. These reported immunological changes also appear to be more pronounced in ICU-admitted COVID-19 patients versus non-ICU patients. GM-CSF boosts the expression of proinflammatory cytokines such as TNF, IL-6 and IL-23 in addition to promoting the differentiation of Th1/17 cells and the polarization of macrophages to a M1-like phenotype. Increased levels of GM-CSF result in positive feedback which further elevates these inflammatory mediators. In patients with severe COVID-19, GM-CSF may be the key link between the pulmonary syndrome-initiating capacity of pathogenic Th1 cells and the feedback loop of inflammatory monocytes, which in turn secrete additional GM-CSF and IL-62. Gimsilumab has been tested in two clinical studies, including a 4-week phase I study of a subcutaneous formulation in healthy volunteers, which completed dosing last month. It has demonstrated a favorable safety and tolerability profile based on data collected to date, with no serious adverse events (Roivant Sciences News Release).

20-Mar-2020

Aqualung Therapeutics advances development of ALT-100 for ARDS and VILI

Aqualung Therapeutics has announced that it is advancing ALT-100 (enampcumab), a therapeutic monoclonal antibody, into IND-enabling studies to combat serious unchecked inflammation, with the initial application aiming to reduce the mortality of acute respiratory distress syndrome (ARDS) and ventilator-induced lung injury (VILI). This could offer a potential treatment option for patients with COVID-19, which causes severe pneumonia and respiratory failure and can be compounded by mechanical ventilation, resulting in multiorgan failure and death. There are currently no FDA-approved treatments for ARDS or for ARDS-inducing stimuli such as COVID-19 (Aqualung Therapeutics News Release).

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20-Mar-2020

Promising data reported on favipiravir for COVID-19 in China

Preliminary results have been released from a clinical study led by the Third People's Hospital of Shenzhen in China that evaluated the safety and efficacy of favipiravir in patients with COVID-19 (Chinese Clinical Trial Registry Number ChiCTR2000030113). In this study, favipiravir alleviated pneumonia symptoms in patients with COVID-19, with high tolerance and few adverse reactions, potentially through a mechanism that can quickly eliminate the coronavirus from patients' bodies. Significant clinical differences were observed between the 35-patient experimental group treated with favipiravir and the 45-patient control group treated with lopinavir/ritonavir. The medians of the virus clearance time were 4 days (2.5-9 days) and 11 days (8-13 days), respectively. The post-treatment fever-allaying rates within 2 days were 72.41% versus 26.30%. Chest-imaging improvement rates were 91.43% versus 62.22%. The adverse reaction rate of favipiravir-treated patients was 11.43%, compared to 55.56% in the control group. Another clinical trial led by the Zhongnan Hospital (Wuhan, China), with 120 COVID-19 patients recruited in an experimental group (favipiravir) and control group (abidole) also showed improved effectiveness in the favipiravir group (71.43%) compared with the control group (55.86%). The same significant advantage was shown in average antipyretic and cough remission time. Favipiravir, which comes in oral tablet form, is included in the antiviral national strategic stockpile in Japan. In 2016, the patent for favipiravir was exclusively franchised by Toyama Chemical to Zhejiang Hisun Pharmaceutical, which partnered with the Academy of Military Medical Sciences of China to develop favipiravir tablets. The medication was approved for marketing last month and designated as important goods for fighting against the epidemic by the Chinese government (Zhejiang Hisun Pharmaceutical News Release).

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20-Mar-2020

Ridgeback and DRIVE partner to develop EIDD-2801 for COVID-19

Ridgeback Biotherapeutics and Drug Innovations at Emory (DRIVE), a not-for-profit biotechnology company wholly owned by Emory University, have established a collaboration to rapidly advance DRIVE's EIDD-2801, a potential oral treatment for COVID-19, into human testing. Under the collaboration, Ridgeback has exclusively licensed DRIVE's EIDD-2801, an orally bioavailable form of a highly potent ribonucleoside analogue that inhibits the replication of multiple RNA viruses, including SARS-CoV2. It has broad-spectrum activity against a number of diseases of extreme public health concern, including influenza, SARS, MERS, chikungunya and equine encephalitis (VEE and EEE). In laboratory and animal studies of two distinct coronaviruses (SARS-CoV1 and Middle East respiratory syndrome [MERS]), the bioactive form of EIDD-2801 has been shown to improve pulmonary function, decrease body weight loss and reduce the amount of virus in the lung. EIDD-2801 is expected to begin clinical testing for SARS-CoV2 and influenza in the second quarter of this year. Ridgeback Biotherapeutics will be responsible for advancing it through clinical development and ensuring that EIDD-2801 is available during the current pandemic. The development of EIDD-2801 has received funding from the National Institute of Allergy and Infectious Diseases (NIAID) and from the Defense Threat Reduction Agency (DTRA) for the treatment of influenza, coronavirus, chikungunya and

Venezuelan equine encephalitis virus. Ridgeback's experience of developing novel drug treatments during an ongoing disease outbreak includes the development of ansumimab, which it licensed from the NIAID's Vaccine Research Center to target Ebola. The company is currently completing its BLA submission for ansumimab, which demonstrated a highly statistically significant survival benefit (as measured by a reduction in 28-day mortality) in the PALM trial conducted during the 2018-2020 Ebola outbreak in the Democratic Republic of Congo (Ridgeback Biotherapeutics News Release).

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19-Mar-2020

Enrollment begins in phase I study of AmnioBoost for treatment of COVID-19

Lattice Biologics announced the initiation of patient enrollment in a phase I study designed to address safety and efficacy of its novel stem cell technology, AmnioBoost, for the treatment of severe acute respiratory syndrome (SARS) related to COVID-19. AmnioBoost is derived from amniotic fluid taken from nonrelated, healthy, living donors during a Cesarean delivery, with no harm caused to the baby in any way. The eligible individuals must have laboratory-confirmed infection with COVID-19 and evidence of lung involvement requiring supplemental oxygen or mechanical ventilation, while individuals with mild symptoms or individuals who are asymptomatic will not be eligible for enrollment. All potential patients will undergo a physical exam, and the participants will then be randomized into the investigational group or the placebo group. Individuals enrolled into the investigational group will receive approximately 5 million stem cells of AmnioBoost on the first day of enrollment and another 5 million stem cells on the second day of enrollment. Clinicians will monitor the patients' temperature, blood pressure, need for supplemental oxygen, and other factors daily to determine daily scores based on a scale of clinical outcomes. In the initial stage of the investigation, the clinicians will compare participant outcomes on day 7 in both groups to evaluate if AmnioBoost treatment has produced any clinical benefit, and the study will be halted if there is no evidence of a treatment difference between AmnioBoost and placebo. Initial patient enrollment in this U.S. trial will be limited to 10 patients. The study will be conducted in the Seattle area, as it is one of the most concentrated areas of COVID -19 in the U.S (Lattice Biologics News Release)

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19-Mar-2020

CanSino receives clearance in China for phase I trials with Ad5-nCoV candidate vaccine for COVID-19

CanSino Biologics has received approval to begin a phase I trial with its recombinant novel coronavirus vaccine (adenovirus type 5 vector) candidate, Ad5-nCoV, codeveloped with the Beijing Institute of Biotechnology (BIB). It is the first novel coronavirus vaccine for COVID-19 that has made it to this stage in China. GMP clinical batches have passed quality testing and are ready for phase I testing. Ad5-nCoV is a genetically engineered vaccine candidate with the replication-defective adenovirus type 5 as the vector to express SARS-CoV-2 spike protein. It is designed to be used to prevent the disease caused by the novel coronavirus infection. Results from preclinical animal studies of Ad5-nCoV show that the vaccine candidate can induce a promising immune response in animal models and has an encouraging safety profile. The vaccine candidate is built upon CanSino Biologics' adenovirus-based viral vector vaccine technology platform, which has also been successfully applied to develop a vaccine against Ebola virus infection (CanSino Biologics News Release).

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19-Mar-2020

Mateon to develop OT-101 against COVID-19

Mateon Therapeutics provided an update on its rapid antiviral response program against coronaviruses, initially against the COVID-19 virus, SARS-CoV-2. Mateon has made significant progress in deploying its phase III clinical asset, the TGF-beta antisense drug OT-101, against coronavirus. In vitro, OT-101 demonstrated EC50 of 7.6 mcg/mL while showing no toxicity at

the highest dose of 1000 mcg/mL, giving a safety index value of > 130, which is considered highly active. Mateon intends to work with the FDA to allow OT-101 to enter into clinical evaluation against COVID-19 as soon as preclinical testing is completed. The proposed mechanism and actions for OT-101 against COVID-19 include the inhibition of cellular binding, inhibition of viral replication, as well as suppression of viral-induced pneumonia. OT-101 is currently also being developed as a broad-spectrum anticancer drug, to be used in combination with other standard cancer therapies to establish an effective multi-modality treatment strategy for difficult-to-treat cancers, including high-grade gliomas and pancreatic cancer. Mateon also plans to initiate phase III clinical trials for OT-101 in both high-grade glioma and pancreatic cancer. In addition to therapeutic approaches for inhibiting virus replication and treating the consequences of infection, Mateon is also evaluating the potential of its AI Vision technology to be deployed to help monitor patients infected with the current COVID-19 virus, or any future viruses, while simultaneously reducing the need for direct contact with hospital personnel, which poses a risk to the caregivers (Mateon Therapeutics)

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19-Mar-2020

Pneumagen announces new program to target COVID-19 infections

Pneumagen has initiated a new program to prevent and treat SARS-CoV-2 coronavirus infection (COVID-19) using its first-in-class carbohydrate binding modules (mCBMs), generated using its proprietary GlycoTarge platform. Pneumagen's lead mCBM, Neumifil, is already being developed for the universal treatment of respiratory tract infections (RTIs), including influenza virus (IFV) and respiratory syncytial virus (RSV), and now coronaviruses. Neumifil's novel mechanism of action, which consists of masking glycan receptors in patients' airways and thereby preventing the entry of the virus, has the potential to revolutionize the treatment of RTIs by providing clinicians with the opportunity to offer patients total protection against all viral strains. This approach would overcome current vaccine limitations caused by viruses mutating and allow the treatment to be stockpiled in advance for pandemic use. Pneumagen has already demonstrated significant preclinical efficacy in several other RTIs caused by viruses, including RSV and IFV, providing the potential for a pan-viral respiratory product. The new program now seeks to extend this efficacy to COVID-19 (Pneumagen News Release).

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19-Mar-2020

Global phase III trial to evaluate Actemra for severe COVID-19 pneumonia

Genentech, a member of the Roche group, is working with the FDA to initiate a phase III trial (COVACTA), in collaboration with the Biomedical Advanced Research and Development Authority (BARDA), to evaluate Actemra (tocilizumab, RoActemra) in hospitalized adult patients with severe COVID-19 pneumonia. The randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of intravenous Actemra added to standard of care in adult patients hospitalized with severe COVID-19 pneumonia compared to placebo plus standard of care. The 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. This first global study of Actemra in this setting is expected to begin enrolling as early as possible next month, with a target of approximately 330 patients globally, including the U.S. To date, there are several independent clinical trials exploring the efficacy and safety of Actemra for the treatment of patients with COVID-19 pneumonia. Actemra was included in the seventh updated diagnosis and treatment plan for COVID-19 issued by China's National Health Commission (NHC). Roche has also received FDA emergency use authorization for the cobas SARS-CoV-2 test to detect the novel virus that causes COVID-19 disease (Roche News Release; Genentech News Release).

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Suggested reading

Related websites

- [Centers for Disease Control and Prevention \(CDC\) – 2019 novel coronavirus, Wuhan, China](#)
- [Centers for Disease Control and Prevention \(CDC\) – SARS information](#)
- [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 \(SARS\) \(World Health Organization\)](#)

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 \(The Lancet\)](#)
- [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, clinicians, and public health authorities - January 2015 \(Centers for Disease Control and Prevention, January 30, 2015\)](#)

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