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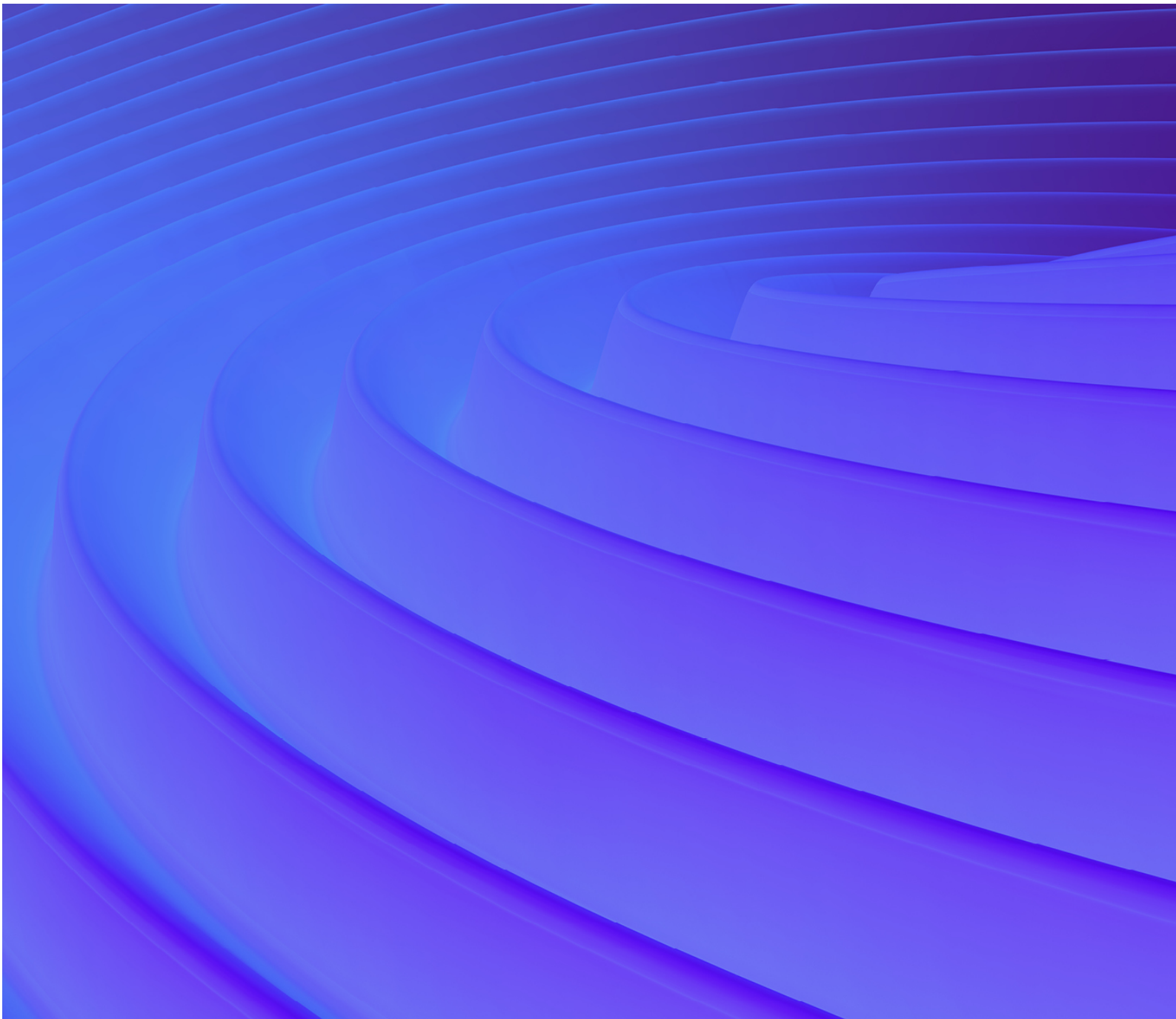
Disease Briefing: Coronaviruses



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Coronavirus: Disease Briefings

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 (Chan, P.K. et al (2013); Berry, M. et al (2015)).

Coronaviruses have long been recognized as important veterinary pathogens, causing respiratory and enteric diseases in mammals as well as in birds. Before 2019, only six coronaviruses had been 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)). The first four are endemic locally; they have been associated mainly with mild, self-limiting disease, whereas the latter two can cause severe illness (Song, Z. et al (2019); Paules, C.I. et al (2020)). SARS-CoV and MERS-CoV are betacoronaviruses (Chen, Y. et al (2020)), and 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 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	Parainfluenza 1-3 virus	Upper respiratory infection,

(Paramyxoviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; nonsegmented genome)	Respiratory syncytial virus Measles virus Mumps	croup Upper respiratory infection, croup Measles Aseptic meningitis
Coronaviruses (Coronaviridae) Single-stranded RNA,enveloped (No DNA step in replication; positive-sense genome)	Human coronaviruses	Upper respiratory infection
Rhabdoviruses (Rhabdoviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; nonsegmented genome)	Rabies virus	Rabies
Picornaviruses (Picornaviridae) Single-stranded RNA, nonenveloped	Rhinoviruses Hepatitis A virus Enteroviruses: - Polioviruses - Coxsackie A24 viruses - Coxsackie B viruses - Coxsackie B1-5 viruses - Coxsackie A9 viruses - Echoviruses	Common cold Hepatitis Paralysis Acute hemorrhagic conjunctivitis Myocarditis, pericarditis Aseptic meningitis Aseptic meningitis Aseptic meningitis, encephalitis
Caliciviruses (Calciviridae) Single-stranded RNA, nonenveloped	Norwalk virus	Gastroenteritis
Hepeviruses (Hepeviridae) Single-stranded RNA, nonenveloped	Hepatitis E	Hepatitis
Togaviruses (Togaviridae) Single-stranded RNA, enveloped (No DNA step in replication; positive-sense genome)	Alphaviruses (Group A arboviruses) 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)	Meningitis
	Lassa virus	Hemorrhagic fever
Retroviruses (Retroviridae) Single-stranded RNA, enveloped (DNA step in replication)	HTLV-I, HTLV-II	T cell leukemia, lymphoma, paresis
	HIV-1, HIV-2	AIDS
Filoviruses (Filoviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; nonsegmented genome)	Marburg virus	Marburg disease
	Ebola virus	Ebola hemorrhagic fever

Morphology, Structure and Replication

Coronaviruses are so named because of their characteristic solar corona (crown-like) appearance when observed under an electron microscope. This appearance is produced by the peplomers of the spike [S] glycoprotein radiating from the virus lipid envelope (Chan, J.F. et al (2015); Chen, Y. et al (2020)).

There are two major envelope proteins. The S glycoprotein is a major antigen responsible for both receptor binding and cell fusion (Song, Z. et al (2019)) and the transmembrane glycoprotein [M] is involved in budding and envelope formation; the M protein has also been found to play a pivotal role in virion assembly (Tseng, Y.T. et al (2010)). A few coronavirus species have a third glycoprotein, the haemagglutinin-esterase [HE]. The viral genome is associated with the basic phosphoprotein [N] within the capsid. 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' (Kilianski, A. et al (2014); Song, Z. et al (2019); Chen, Y. 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 COVID-19 (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 (Chan, J.F. et al (2015)) and Pneumonia. Coronaviruses are responsible for 15-30% of all cold cases. Coronaviruses can also

cause gastroenteritis in humans as well as a plethora of diseases in other animals (To, K.K. et al (2013); Berry, M. et al (2015)). Unlike other coronaviruses pathogenic in humans, SARS and MERS can cause severe acute respiratory disease and multi-organ failure (Zumla, A. et al (2016)).

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)).

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)).

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

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

Facts about SARS-CoV

Severe acute respiratory syndrome (SARS) was a viral illness caused by a novel coronavirus and affecting the respiratory system. It originated in the Chinese province of Guandong in November 2002, and was first reported at the beginning of 2003 in Asia, followed by reports of a similar disease in North America and Europe (Heymann, D.L. et al (2013)). Worldwide, 33 countries and regions on five continents reported SARS cases, but the most severely affected were China and Hong Kong. In spring 2003, SARS became a global health threat. The rapid spread of the virus to different continents after the initial outbreak underscored the ease with which infectious diseases can be spread internationally among members of our highly mobile global population (Cleri, D.J. et al (2010); Heymann, D.L. et al (2013)).

Although the disease has been absent since 2003, the rapid global spread of SARS demonstrated 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 need for international coordination of response (McCloskey, B. et al (2020)). In the post-SARS era, the Chinese government 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 (Cheng, V.C. et al (2013); Al-Tawfiq, J.A. et al (2014); Zumla, A. et al (2015)). These lessons were again put to test in 2020 with the emergence and explosive spread of COVID-19 in China and globally (Perlman, S. (2020)).

Causative Agent: SARS Coronavirus

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 (Falsey, A.R. et al (2003); Berry, M. et al (2015)).

The new coronavirus was named "Urbani SARS-associated coronavirus" in honor of Dr. Carlo Urbani, a WHO scientist who first reported the disease and subsequently died from SARS on March 29, 2003 (Cleri, D.J. et al (2010); Felkai, P. (2018)). Evidence based on many different methods, such as cell culture, microscopy, microarray data, serologic tests and PCR, supported the hypothesis that this new coronavirus was the causative agent of SARS (Gerberding, J.L. (2003)).

The absence of antibodies against the SARS virus in healthy people indicated that the virus had not previously circulated in the human population, providing additional supporting data for the possibility that SARS was caused by a new virus. The SARS virus was likely to have originated in animals, followed by either mutation or recombination events that facilitated infection of humans (Zumla, A. et al (2016)).

Investigators in both the U.S. and the Netherlands developed a model system of infection in monkeys in order to fulfill Koch's postulates. Experiments conducted at the Erasmus Medical Center of the University of Rotterdam gave the ultimate evidence that the SARS-CoV was the causative agent of SARS (Fouchier, R.A.M. et al (2003); Kuiken, T. et al (2003)).

SARS-CoV Morphology, Structure and Replication

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.

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 37ºC 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 (Perlman, S. et al (2009); Berry, M. et al (2015); Abdel-Moneim, A.S. (2014)).

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)).

The complete nucleotide sequence varied at only a few positions among different isolates of SARS-CoV (Rota, P.A. et al (2003)). Sequence analysis of isolates from Singapore, Canada, Hong Kong, Hanoi, Guangzhou annd Beijing revealed two distinct strains that were related to the geographic origin of the virus (Ruan, Y.J. et al (2003)).

Origin of SARS-CoV

The fact that different animal coronaviruses are able to recombine their RNA to originate new viruses led to the hypothesis that SARS-CoV may have arisen as a result of a recombination event between an animal and a human virus (Hajiema, B.J. et al (2003); Chan, P.K. et al (2013)).

Early data suggested that SARS-CoV was related to bovine and murine hepatitis coronaviruses. However sequence studies of the entire genome did not reveal a bovine-murine origin. The SARS-CoV was determined to be a new, previously unknown pathogen that did not originate from already known strains (Ruan, Y.J. et al (2003)). It probably derived from an ancestor of the coronaviruses that naturally infected wild animals before crossing the species barrier to humans and causing SARS (Chan, P.K. et al (2013)).

How the virus became infectious for humans is unknown. The lack of sequence homology with any of the known human coronavirus strains makes a recombination event among human pathogens a remote possibility. By using methods such as Bayesan phylogenetic interference, it has been shown that the SARS-CoV genome has a recombination breakpoint within the RNA polymerase gene, and that the 5' region is related to mammalian and the 3' region to avian coronaviruses (Rest, J.S. et al (2003)).

In May 2003, scientists in Hong Kong reported the discovery of a virus virtually identical to the virus causing SARS in a rare species of civet (Civettictis civetta), a tree-dwelling cat. Yuen Kwok-Yung, a microbiologist at Hong Kong University, reported that the coronavirus had been found in the feces of masked palm civets, a nocturnal species found from Pakistan to Indonesia. The masked palm civet is considered to be a delicacy in southern China. Some of the first known cases of SARS occurred in November 2002 among food handlers who handled, killed and sold animals for food and chefs in Guangdong Province who were involved in the preparation of wild game for banquets. Infected civets are asymptomatic. The Hong Kong University team was able to culture a coronavirus almost identical to the SARS coronavirus from all 25 of the masked palm civets, representing eight different species that were tested (Enserink, M. (2003)).

Another team detected SARS-CoV-like viruses in live animals sold for food in the Guandong province. The presence of the virus was confirmed in the Himalayan palm civet (Paguma larvata) and was found in a raccoon dog (Nytereutes procyonoides) (Chan, P.K. et al (2013)). Sequence analysis showed a phylogenetic distinction between animal and human viruses, making passage from humans to the analyzed animals unlikely. This finding points to the possibility of interspecies transmission route within animals held in the market, making the identification of the natural reservoir even more difficult. Subsequent studies suggested that the SARS-CoV had not been circulating in civets for long, and thus that some other species may be acting as a natural reservoir (Hui, D.S. et al (2010)); later investigations identified bats as the reservoir species for SARS-CoV as well as closely related coronaviruses (Song, Z. et al (2019)).

By serological analysis about 40% of wild animal traders and 20% of people employed in the slaughter of animals for market in the affected region had SARS-CoV antibodies, although none had SARS-like symptoms (Berry, M. et al (2015)). Therefore a SARS-like coronavirus had been present in the area at least two years before the SARS-outbreak. The virus, initially not infectious in the human population, may have evolved and adapted to humans to give rise to the SARS-CoV.

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. First, the international population is highly mobile as a result of air travel. Second, high urban population densities, especially on the Asian continent, make person-to-person contact frequent (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 (Loeb, M. et al (2004); Cleri, D.J. et al (2010); Chen, W.Q. et al (2009)). Nocosomial spread was reduced through use of surgical masks, gloves and gowns (Seto, W.H. et al (2003)).

Virus load and shedding peak at approximately 10 days from the appearance of clinical symptoms, when the patient's status worsens and requires medical attention. Thus patients are most infectious at the time of seeking health care (McDonald, L.C. et al (2004); Cleri, D.J. et al (2010)). Viral shedding continues for at least 13 more days (range 2-60 days) (Cleri, D.J. et al (2010)). Patients are 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. A superspreading event was believed to be involved in the rapid propagation of the virus in the Amoy Gardens apartment building outbreak, where more than 300 residents were infected, presumably by a single patient (Cleri,

D.J. et al (2010)). Other superspreading events were reported in the Hotel Metropole in Hong Kong, among passengers on Air China flight 112 from Hong Kong to Beijing, and in an acute care hospital in Toronto, Canada (Braden, C.R. et al (2013)). 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 includes high fever (>38°C) or history of fever in the previous 48 hours; new infiltrates on chest x-ray suggestive of pneumonia; flu-like symptoms (chills, cough, malaise, myalgia) or history of exposure to SARS-CoV; and one or more positive diagnostic tests for SARS (Cleri, D.J. et al (2010)). Unfortunately, the initial symptoms and clinical appearance are not easily distinguishable from other common respiratory infections, and fever may be 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)). In tissues SARS-CoV commonly causes diffuse alveolar damage, bronchial epithelial denudation, loss of cilia and squamous metaplasia. Giant-cell infiltration, hemophagocytosis and cytomegalic alveolar pneumocytes were also observed in some cases (Nicholls, J.M. et al (2003)). 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 has been reported (Lau, K.K. et al (2004); Zhang, D.M. et al (2008)). Symptomatically, SARS generally followed a triphasic pattern that accompanies each of the phases in tissues. 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)).

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 stimulation, persistent chemokine responses and dysregulated adaptive immune response (Schäfer, A. et al (2014)).

Independent correlates of adverse clinical outcome included known history of diabetes/hyperglycemia (Yang, J.K. et al (2006)), 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

The WHO reported a total of 8,096 SARS cases and 774 resulting deaths worldwide during the period of the major outbreak between November 1, 2002 and August 7, 2003 (see Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003 (World Health Organization)). China was hardest hit, with at least 5,327 cases and 349 deaths (66% and 45% of the total, respectively) (Zhang, Y. et al (2013)). 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 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 (Lau, E.H. et al (2010); Berry, M. et al (2015)).

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 now 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 (Perlman, S. et al (2013)) and to use a different host-cell receptor, identified as dipeptidyl peptidase 4 (DPP4, also known as CD26) (Raj, V.S. et al (2013); 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)).

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 the first member of the betacoronavirus genus known to infect humans, and is more closely related to bat coronaviruses such as HKU4 and HKU5 than it is to SARS-CoV (Banik, G.R. et al (2015); Chan, J.F. et al (2015)). 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 is a new virus (Chan, J.F. et al (2015)).

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

The virus gains entry into the host cell by binding to DPP4 receptors expressed in the lower airway as well as in the kidney and other organs (Paules, C.I. et al (2020)). It uses host proteases to gain entry into lung cells. The protease furin activates the S protein on the viral envelope, mediating membrane fusion and enabling virus entry into the host cell (Banik, G.R. et al (2015)). Like the SARS-CoV, the Middle East respiratory virus is able to overcome the host innate immune response until high virus titres have been achieved, and induces cytokine dysregulation

(Gralinski, L.E. et al (2015); Skariyachan, S. et al (2019)).

Transmission

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

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

Symptoms and Disease

The incubation period is approximately 5 days (range 2-15 days), with 94% of patients showing signs of disease by day 12 (Chan, J.F. et al (2015)). Typical presenting symptoms are nonspecific and include fever, chills, nonproductive cough, dyspnea, rigor, headache, myalgia and malaise. Some patients present with gastrointestinal symptoms, including diarrhea, nausea and vomiting, and abdominal pain. Acute renal impairment is a unique feature of MERS and occurs with significantly greater frequency than was seen in patients with SARS (Song, Z. et al (2019); Paules, C.I. et al (2020)).

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 April 10, 2019). Initial cases were restricted to the Middle East as well as two cases in the U.K. among family members of an infected individual who had recently traveled from Saudi Arabia. Several cases later occurred in clusters, including a hospital outbreak in Saudia Arabia, and confirmed that the virus can be

transmitted between humans during close contact (Assiri, A. et al (2013); Zumla, A. et al (2015)). As of November 2019, the World Health Organization had been notified of 2,494 laboratory-confirmed human cases of infection with the virus and 780 related deaths (case-fatality rate 37.1%) (Middle East respiratory syndrome coronavirus (MERS-CoV) (World Health Organization), consulted January 28, 2020).

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

On May 20, 2015, the index case in what became the largest outbreak of MERS-CoV outside the 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. As of September 11, WHO had been notified of the existence of 185 laboratory-confirmed cases, including 36 fatalities, in Korea, as well as an additional case in China (Middle East respiratory syndrome coronavirus (MERS-CoV) (World Health Organization)).

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

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

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

Facts about SARS-CoV-2 and COVID-19

In late 2019, a new coronavirus began causing febrile respiratory illness in China; two months later, the rapidly spreading disease was officially christened COVID-19 (coronavirus disease 2019) by WHO. Earliest reports of the illness were communicated 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 a population with no preexisting immunity (Chen, J., 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 involved exposure to the Huanan market (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 75-80% similarity in genetic sequence to SARS-CoV (Hui, D.S. et al., 2020; Zhu, N. et al., 2020; Perlman, S., 2020). Like SARS-CoV, the new virus is believed to use ACE2 as its binding receptor (Wan, Y. et al., 2020). Due to these similarities, the Coronavirus Study Group of the International Committee on Taxonomy of Viruses (ICTV) named the new virus SARS-CoV-2. The as-yet-unidentified animal

host of SARS-CoV-2 is presumed to be a bat; an intermediate host may also have been involved (Perlman, S., 2020).

Following an incubation ranging from 2-14 days, COVID-19 manifests as respiratory illness ranging from mild to severe, with symptoms that include fever, cough and dyspnea. Chest CT scan reveals the presence of bilateral ground-glass opacities (Huang, C. et al., 2020; Centers for Disease Control and Prevention (CDC) -- 2019 novel coronavirus, Wuhan, China). In an early description of 41 clinical cases, patients had serious, sometimes fatal, pneumonia. Clinical presentations were very similar to those of SARS. The most severely ill patients developed acute respiratory distress, requiring ICU admission and oxygen therapy. The mortality rate in this early patient set was approximately 15% (Huang, C. et al., 2020), and primarily involved patients with serious underlying diseases or conditions. A diagnostic challenge for COVID-19 is that those who are infected with subclinical or mild disease might not present to health care centers, which means these cases are not counted. Moreover, these individuals can spread the virus to their contacts at home and at work as well as during travel (Munster, V.J. et al., 2020). A study of the transmission dynamics in the first 425 confirmed cases in Wuhan concluded that SARS-CoV-2 is extremely contagious, and estimated a basic reproduction number (R0) of 2.2 (Li, Q. et al., 2020). For contrast, the R0 for both SARS-CoV and MERS-CoV is less than 1 (Wu, J.T. et al., 2020). Whether or not asymptomatic individuals are capable of transmitting the disease remains unknown (Chen, J., 2020).

According to WHO, as of February 12, 2020, a total of 45,171 confirmed cases of COVID-19 had been detected worldwide, although the vast majority (44,730) continued to be from China. Also as of February 12, WHO confirmed 1,114 deaths from COVID-19 in China and the first death outside that country. The risk assessment of this event was deemed by WHO to be very high in China, and high at both the regional and global level (Emergencies: Novel coronavirus 2019 (World Health Organization), consulted February 13, 2020; First travel-related case of 2019 novel coronavirus detected in United States (CDC press release, January 21, 2020)). As of February 13, China CDC reported 59,804 confirmed and 13,435 suspected cases, resulting in 1,367 deaths (Tracking the epidemic (China CDC), consulted February 13, 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) (Anonymous, 2020).

Although the early case-fatality rate appeared to be low, the rapid spread and ease of transmission of the virus are causing global alarm: experts point out that although a virus may pose a low health threat at the individual level, if easily transmissible, it can nonetheless pose a significant risk at the population level. Given its pandemic potential, careful surveillance of the COVID-19-causing virus is critical to monitor its future host adaption, viral evolution, infectivity, transmissibility and pathogenicity (Huang, C. et al., 2020).

To track the outbreak in real time, click here: Coronavirus COVID-19 global cases dashboard (Johns Hopkins University Center for Systems Science and Engineering).

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

Diagnosis

Until standardized reagents for detection of both virus and antibody became available, SARS diagnosis was based on the basis of clinical symptoms together with a positive epidemiological history (Cleri, D.J. et al (2010)). Symptoms associated with SARS are high fever (>100.4°F/38°C), cough and difficulty breathing.

Diagnosis may be confirmed by chest radiography if there is evidence of infiltration consistent with pneumonia or respiratory distress syndrome.

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)). Some patients develop detectable anti-SARS virus antibodies within two weeks after symptoms, but a definitive negative diagnosis could not be obtained until three weeks after the onset of fever.

The diagnostic tests for detection of the SARS-CoV all had limitations. ELISA detects SARS-CoV antibodies but only about 20 days after the onset of symptoms and is only useful for confirmation of SARS but not for rapid diagnosis. The immunofluorescence assay (IFA) can detect antibodies after 10 days from the onset of symptoms in serum of infected patients. However serologic testing is the only available laboratory test for excluding a diagnosis of SARS. If sera are negative for antibody four weeks after onset of symptoms, the disease is not SARS (Jernigan, J.A. et al (2004)). Neither virus isolation in cell cultures nor electron microscopy are sensitive enough for general diagnostic use and both methods are inconvenient.

The availability of RNA sequence information on a number of strains of SARS viruses facilitated the development of rapid diagnostic tests. Molecular tests based on reverse transcription polymerase chain reaction (RT-PCR) specifically detect viral RNA. RT-PCR is the only early detection test available, but its sensitivity is low, identifying only 37.5-50% of probable SARS cases (Suresh, M.R. et al (2008)). Detection of viral RNA increases and peaks after about 10 days from the onset of the disease. The virus remains detectable in respiratory secretions for more than one month in some patients, but after three weeks cannot be recovered for culture. In the initial phase that occurs in the first week postinfection, the virus may be detected in nasopharyngeal aspirates, throat swabs and sputum samples, while in later phases viral RNA may be more easily detected in stool samples (Chan, K.H. et al (2004)).

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 outbreak (Peiris, J.S. et al (2008)). A report from the CDC indicated that real-time RT-PCR may be more sensitive than conventional RT-PCR, potentially providing a useful technique for detecting virus in the early phases of the diseases, when virus titer is low (Emery, S.L. et al (2004)). ELISA detection of anti-nucleocapsid protein (NP) antibodies, which peak early in infection, has been 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)). In June 2013, the U.S. FDA granted emergency use authorization for the CDC Novel Coronavirus 2012 Real-time RT-PCR Assay, which can be used by qualified laboratories to detect MERS-CoV in respiratory, blood and stool specimens. 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 (COVID-19) was first identified in samples taken three patients with acute respiratory disease in Wuhan, China. The virus was isolated from bronchoalveolar lavage fluid; however, viral RNA has also been detected in blood samples. The genetic sequence of COVID-19 was made available to the WHO on January 12, 2020, facilitating the production of specific diagnostic PCR tests to detect the infection (Hui, D.S. et al (2020); Zhu, N. 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 (Shanghai Geneodx Biotech, Daan Gene, Shanghai ZJ Bio-tech, Huada Biotechnology and Sansure Biotech) have developed such 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, has developed test kits with an isothermal amplification instrument that automatically interpreted the results in minutes, with both sensitivity and specificity values of 100%.

In Wuhan (December 2019), hospitalized patients with suspected COVID-19 were screened by RT-PCR and next-generation sequencing. Among those identified with COVID-19 infection, 32% had underlying diseases including diabetes, hypertension and cardiovascular disease. Up to 66% had been exposed to the Huanan seafood market, including one family cluster. Other diagnosing criteria were fever (98%), cough (76%) and myalgia or fatigue (44%). All patients had pneumonia with abnormal findings on chest CT. Critically ill patients admitted to intensive care unit showed high plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNF alpha, all corresponding with disease severity (Huang, C. et al (2020)).

On February 5, 2020, the U.S. FDA issued an emergency use authorization that will allow emergency use of the CDC's 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 that provided detection of COVID-19 from respiratory secretions, such as nasal or oral swabs. Novacyt has also launched a quantitative PCR assay, targeting the unique COVID-19 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, Ares Genetics is collaborating with BGI Group to make real-time fluorescence PCR tests for the new coronavirus, producing results in several hours.

Differential Diagnosis

Pneumonia of other viral or bacterial origin --especially *Streptococcus pneumonia, Haemophilus influenzae, Moraxella catarrhalis*, methicillin-resistant *Staphylococcus aureus* and *Legionella* spp.-- must be included in the differential diagnosis of SARS. Other febrile viral diseases that should also be included in the differential diagnosis include seasonal and avian **Influenza**, **Respiratory Syncytial Virus**, **Varicella Zoster Virus**, human metapneumovirus and hantavirus. When appropriate, other epidemic or population-wide diseases may also need to be taken into consideration, e.g. smallpox (see **Poxviruses**), tularemia, **Anthrax**, viral hemorrhagic fever or plague (Cleri, D.J. et al (2010)).

Prevention

Without effective drugs or vaccines against the infectious agent, physical interventions such as isolation and quarantine are the most effective means of controlling a coronaviral infections with epidemic potential; however, patients are typically asymptomatic during the incubation period, which ranges from 2-14 days (mean 4 days) in the case of SARS (Cleri, D.J. et al (2010)) and COVID-19 (**Centers for Disease Control and Prevention (CDC) – 2019 novel coronavirus, Wuhan, China**), and from 2-15 days (mean 5 days) in the case of MERS (Banik, G.R. et al (2015)). 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 R0 (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 airborn infection isolation procedures in the care of all confirmed MERS infections in that country (Al-Tawfiq, J.A. et al (2014)). Soon after the outbreak of COVID-19 began to expand, Chinese authorities imposed restrictions on movement in and around Wuhan, the major air and train transportation hub of central mainland China. Based on assumptions of exponential growth of the outbreak (R0 = 2.68) beyond the original focus, WHO-linked epidemiology experts recommended even more 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, hygienic 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 30ªC (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 trasported 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 (Enserink, M. (2003)). 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)).

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 anti-MERS-CoV vaccines (Ma, C. et al (2014); Zhang, N. et al (2015)), including mucosal vaccine for intranasal administration (Ma, C. et al (2014)). This research 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)).

Research by scientists at the University of Pittsburgh School of Medicine and the Graduate School of Public Health in collaboration with CDC showed that an adenoviral-based vaccine could induce both SARS-CoV-specific T cell and virus-neutralizing antibody responses (Gao, W. et al (2003)). Both responses have been found important for lasting protection. In long-term studies of recovered SARS patients, antibody responses waned after approximately six years,

while T-cell responses persisted, suggesting that the latter is required for long-lasting immunity (Zumla, A. et al (2015)).

In the case of the MERS-CoV outbreak in the Middle East, the development of a vaccine for use in camels has also been prioritized, in order to interrupt the ongoing zoonotic transmission of the disease (Zumla, A. et al (2016); Wirblich, C. et al (2017)).

The following table presents an up-to-date overview of the development of potential coronavirus vaccines.

Drug name	Organisations	Description	Phase
GLS-5300	Inovio Pharmaceuticals; GeneOne Life Science	Middle East Respiratory Syndrome DNA vaccine using the SynCon (TM) technology, encoding MERS spike protein	Phase I/II
ChAdOx1 MERS	Vaccitech Ltd.; University of Oxford	Middle East respiratory syndrome recombinant (MERS) vaccine consisting of replication - deficient simian adenovirus vector ChAdOx1 carrying full - length spike gene of MERS - CoV camel isolate; under the control of human cytomegalovirus major immediate early promoter (IE CMV)	Phase I
MVA-MERS-S	Ludwig-Maximilians-Univ. Muenchen	Middle East respiratory syndrome coronavirus (MERS - CoV) vaccine comprising modified vaccinia virus encoding full - length S protein of MERS - CoV, under the control of early/late promoter PmH5	Phase I
GREVAX/MERS	Greffex	Recombinant adenoviral vector developed using GREVAX Universal Platform (GREVAX	Preclinical

		vector) encoding Middle East respiratory syndrome coronavirus (MERS - CoV) antigens	
INO-4800	Inovio Pharmaceuticals	Novel coronavirus strain 2019 (2019 - nCov) vaccine	Preclinical
IR-101C	Immune Response BioPharma	Coronavirus vaccine consisting of depleted coronavirus spike glycoprotein without outter envelope inactivated with beta propiolactone and gamma irradiation; propagated in HUT78 cells	Preclinical
MVA-MERS-S_DF1	Universitaetsklinikum Hamburg-Eppendorf	Middle east respiratory syndrome (MERS) vaccine consisting of a modified vaccinia ankara (MVA) virus encoding MERS - CoV spike (S) protein antigens	Preclinical

Treatment

There is no approved drug therapy for SARS, MERS or any other coronavirus infection at this time, and there is a paucity of clinical trial data upon which to base treatment decisions. Supportive care is the mainstay of treatment for patients with severe disease (To, K.K. et al (2013); Arabi, Y.M. et al (2016); Momattin, H. et al (2019)).

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); Tai, D.Y. (2007)). 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)).

In response to a request by the World Health Organization, a systematic review was made of all published reports of treatments that were used during the 2002-2003 SARS epidemic, as a tool to guide future treatment decisions and identify research priorities. The drugs reviewed included ribavirin, corticosteroids, lopinavir/ritonavir, type I interferon (IFN), intravenous immunoglobulin (IVIG) and SARS convalescent-phase plasma. A total of 54 SARS treatment studies, 15 in vitro

studies and three acute respiratory distress syndrome (ARDS) studies were identified for inclusion. Although some of the in vitro studies indicated potential antiviral efficacy for ribavirin, lopinavir and type I IFN in tissue culture, none of the clinical studies supported these findings. In the case of ribavirin, 26 trials were inconclusive and four suggested potential harm. In the case of steroids, 25 studies were inconclusive and four indicated possible harm. Studies on convalescent plasma, IVIG, type I IFN and lopinavir/ritonavir were also inconclusive. The researchers concluded that in spite of an intensive literature review, no conclusive evidence was obtained to support the efficacy of any drug used in the treatment of patients with SARS. They emphasized that clinical trials should be designed to validate a standard treatment protocol for possible future outbreaks, in order to standardize doses and timing of treatment and to facilitate data accrual and the monitoring of specific adverse effects and potential benefits of specific therapies (Stockman, L.J. et al (2006)). Should the virus reemerge, patients with recognized SARS infection should be isolated in negative-pressure single rooms and appropriate, well-fitting face masks should be used to minimize potential for transmission of the virus through respiratory secretions (Cleri, D.J. et al (2010)).

Repurposing of known drugs with proven safety records is a faster and more efficient way of developing drugs in an outbreak situation, when time is of the essence. In light 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. Further evaluation of these agents in animal models is 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)).

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, a retrospective study of data on treatment of SARS patients during the epidemic shows that corticosteroid use was associated with worse outcomes (Stockman, L.J. et al (2006)), and as such they should be used only with caution in the treatment of patients with MERS (Zumla, A. et al (2015)). Based on this experience, routine use of corticosteroids is not recommended in patients with COVID-19 (Huang, C. et al (2020)).

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 used for the treatment of SARS patients, with variable results (Cleri, D.J. et al (2010)). Ribavirin has also been tested in the rhesus macaque model of MERS-CoV, which is a model of mild to moderate human disease. The results obtained--IFN-a2b plus ribavirin reduced virus replication, moderated the host response and improved clinical outcome--support use of the combination to treat patients with MERS (Falzarano, D. et al (2013)). However, a retrospective study of 20 patients in Saudi Arabia who received the combination therapy between October 2012 and May 2014 revealed that while 14-day survival improved significantly with ribavirin/IFN alfa-2a combination therapy as compared to standard of care, the difference no longer existed at 28 days (Omrani, A.S. et al (2014)). Adverse events, including dose-dependent anemia, arrhythmia, chest pain and dizziness, are a significant concern with ribavirin (Cleri, D.J. et al (2010)).

With the possible exception of ribavirin, there is a lack of broad-spectrum antiviral agents. Unlike other infections agents (bacteria, fungi and parasites), viruses share extremely few common features that could be targeted by broad-spectrum agents. The development of broad-range agents requires a better understanding of pivotal virus-host interactions and the identification of targetable host cell proteins involved. German researchers have reported that the calcineurin/NF-AT pathway plays an important role in immune cell activation in CoV-infected hosts, and that non-immunosuppressive derivatives of ciclosporin may be capable of interrupting this process, thereby acting as broad-spectrum pan-CoV inhibitors (Pfefferle, S. et al (2011)).

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)); 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-beta1b, in which significant reductions in mortality were obtained in a marmoset model, clinical evaluation of the combination was recommended (Chan, J.F. et al (2015)). The ongoing MIRACLE trial is evaluating the efficacy and safety of lopinavir/ritonavir plus recombinant interferon-beta1b compared to placebo--both given in combination with optimal supportive care--in patients with laboratory-confirmed MERS-CoV infection requiring hospital admission (Arabi, Y.M. et al (2018)).

Since the combination of lopinavir and ritonavir was already available in the Wuhan, China hospital where early COVID-19-infected patients were treated, a randomized controlled trial was quickly initiated to assess the efficacy and safety of the combination to treat this emerging coronavirus infection (Huang, C. et al (2020)).

The nucleobindin-1 (NUCB1) 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, Gilead began supplying remdesivir for experimental use to treat hospitalized adult patients with COVID-19 illness.

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)).

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 interferon alfa (Abdel-Moneim, A.S. (2014)).

Canadian researchers described the use of combination therapy incorporating interferon alfacon-1 plus corticosteroids to treat a small group of patients diagnosed with probable SARS at a Toronto hospital between April 11 and May 30, 2003. Nine patients were given the combination therapy, while 13 patients were treated with corticosteroids alone. Both treatment strategies had similar effects on fever and leukopenia. However, the incidence of transfers to the intensive care unit and need for intubation and mechanical ventilation were lower in the interferon/corticosteroid combination group (33.3% and 11.1%, respectively) than in the corticosteroid monotherapy group (38.5% and 23.1%, respectively). Most significantly, the incidence of mortality in the corticosteroid therapy group was 7.7%, whereas there were no deaths in the combination therapy group. Furthermore, chest x-rays were normal within four days of initiating combination therapy, versus nine days in the corticosteroid monotherapy group (Loutfy, M.R. et al (2003)).

During the SARS outbreak, Amarillo Bioscience announced that it would distribute its low-dose oral interferon alfa lozenges for the potential treatment and prevention of SARS in China and Taiwan. Low-dose oral interferon alfa significantly reduces mortality in piglets infected by the transmissible gastroenteritis coronavirus (TGEV) when administered once daily for four days, suggesting a possible benefit in SARS-infected humans.

A study demonstrated that Alferon N (interferon alfa-n3) had the most potent antiviral activity against the SARS-CoV among 19 clinically approved antiviral drugs of the major antiviral pharmacologic classes (Tan, E.L. et al (2004)).

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 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 infection. Although there is no conclusive data available regarding the product's efficacy in the

SARS indication, it is regarded by some as a promising therapy for this and other infectious disorders (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)).

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)).

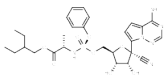
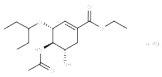
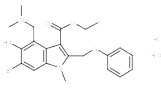
Scientists at the Dana-Farber Cancer Institute reported the isolation of an antibody from a human library capable of blocking infection of the SARS-CoV. The 80R antibody is targeted to the spike glycoprotein, and blocks the virus from binding to ACE2 receptors. The antibody was tested in animal models, in which it protected against acute lung injury. Such an antibody is envisioned for use in passive immunization for the early treatment of the SARS-CoV infection (Sui, J. et al (2004); Cleri, D.J. et al (2010)). However, subsequent studies showed that the antibody was not broadly protective, as it was ineffective against a distinct strain of SARS-CoV associated with the 2003/2004 outbreak (Cleri, D.J. et al (2010)).

Researchers from the National Cancer Institute later reported two new antibodies with improved affinity for the ACE2 receptor as compared to 80R. These MAbs, designated m396 and S230.15, were shown in modeling studies to be capable of neutralizing all SARS-CoV isolates from the two outbreaks in humans as well as strains isolated from palm civets; they may therefore be applicable to use in the diagnosis, prevention and/or treatment of future SARS infections (Zhu, Z. et al (2007)).

Neutralization of Middle East respiratory syndrome coronavirus has also been achieved using monoclonal antibodies. In a collaborative study by U.S. and Chinese researchers, three MAbs targeting the receptor (CD26/DPP4) binding domain of the MERS-CoV spike glycoprotein were identified from a large library of candidate antibodies and were evaluated in vitro. The MAb 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)).

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.

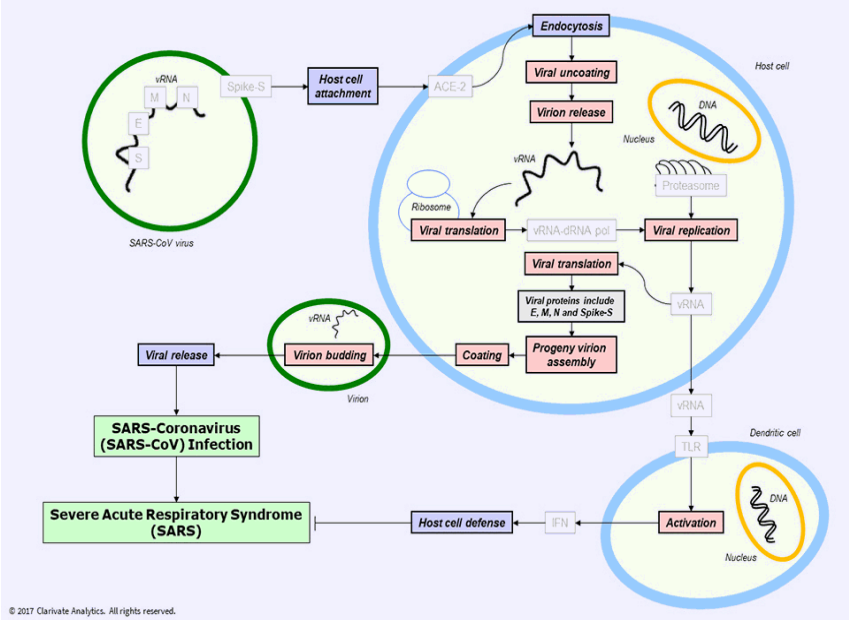
Drug	Organization	Description	Phase	Structure
Remdesivir	Gilead	Nucleobindin-1 (NUCB1) Inhibitors	Phase III	
Lopinavir/ritonavir	King Abdullah International Med Res Cent	HIV Protease Inhibitors; HIV-1 Protease Inhibitors; Tumor Necrosis Factor Receptor Superfamily Member 6 (CD95)/PLC-gamma-1 Interaction Inhibitors	Phase II/III	
GLS-5300	Inovio Pharmaceuticals; GeneOne Life Science	Spike Glycoprotein (S) (MERS-CoV)-Directed Immunity Inducers	Phase I/II	
ChAdOx1 MERS	Vaccitech Ltd.; University of Oxford	Spike Glycoprotein (S) (MERS-CoV)-Directed Immunity Inducers	Phase I	
MVA-MERS-S	Ludwig-Maximilians-Univ. Muenchen	Spike Glycoprotein (S) (MERS-CoV)-Directed Immunity Inducers	Phase I	
REGN-3048	Regeneron	Anti-Spike Glycoprotein (MERS-CoV Coronavirus)	Phase I	
REGN-3051	Regeneron	Anti-Spike Glycoprotein (MERS-CoV Coronavirus)	Phase I	
SAB-301	SAB Biotherapeutics	Anti-Spike Glycoprotein (MERS-CoV Coronavirus)	Phase I	
Darunavir/cobicistat	Shanghai Public Health Clinical Center	Cytochrome P450 CYP3A4 Inhibitors; HIV Protease Inhibitors	Clinical	
Oseltamivir phosphate	Wuhan Tongji Hospital	Neuraminidase (Sialidase) (Influenza Virus) Inhibitors	Clinical	
Umifenovir hydrochloride	Wuhan Tongji Hospital	Capsid Assembly (Hepatitis B Virus) Modulators; Viral Entry Inhibitors	Clinical	
IFX-1	Staidson (Beijing) Biopharmaceuticals	Anti-C5 (Complement 5)	IND Filed	
GREVAX/MERS	Greffex		Preclinical	

Human leukocyte interferon alpha	AIM ImmunoTech		Preclinical
INO-4800	Inovio Pharmaceuticals		Preclinical
IR-101C	Immune Response BioPharma		Preclinical
LCA-60	Vir Biotechnology	Anti-Spike Glycoprotein (MERS-CoV Coronavirus)	Preclinical
MVA-MERS-S_DF1	Universitaetsklinikum Hamburg-Eppendorf	Spike Glycoprotein (S) (MERS-CoV)-Directed Immunity Inducers	Preclinical

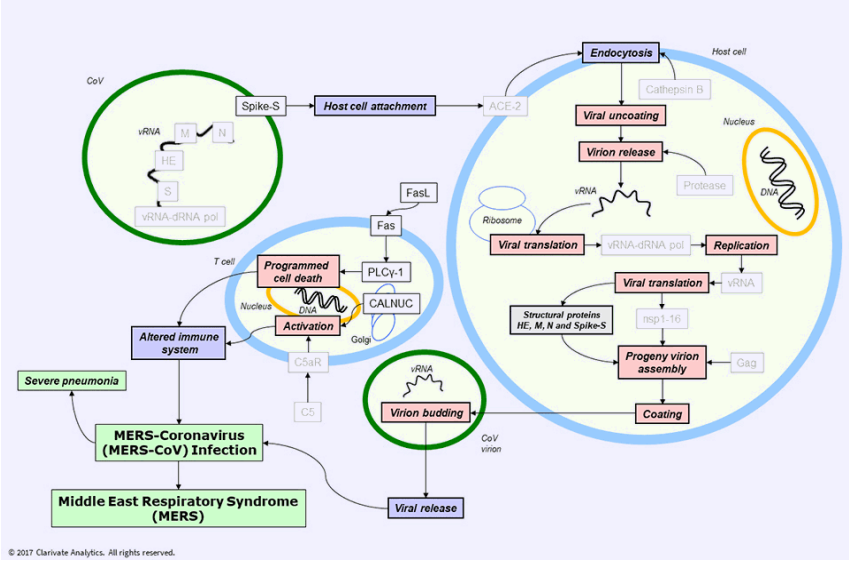
Targets for therapeutic intervention.

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.

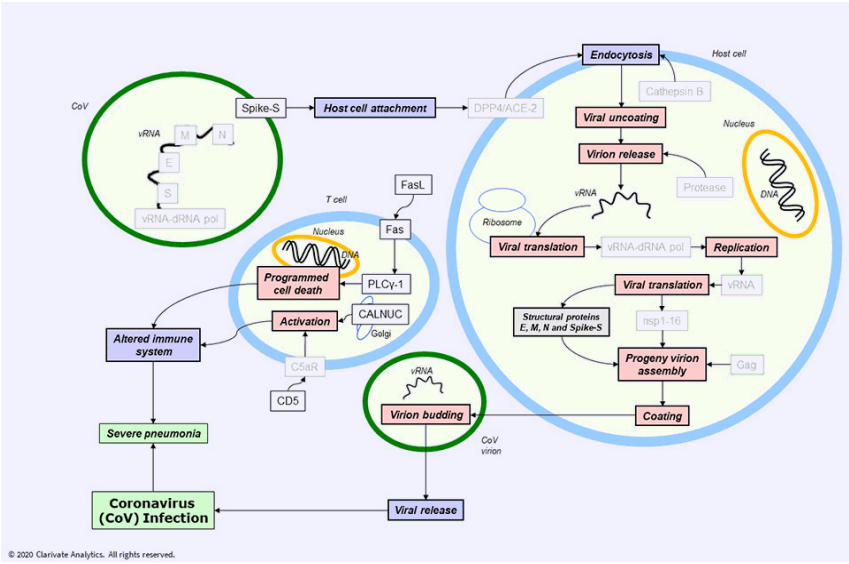
Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV) Targetscape



Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Targetscape



Coronavirus (CoV) Infection Targetscape



Latest Headlines

05-Feb-2020

Regeneron expands agreement with HHS to develop treatments for 2019-nCoV

Regeneron Pharmaceuticals has entered into an expanded agreement with the U.S. Department of Health and Human Services (HHS) to develop new treatments combating the novel coronavirus, 2019-nCoV, which was recently declared a global public health emergency by the World Health Organization. The HHS and Regeneron Other Transaction Agreement (OTA), established in 2017, focuses on discovery, research, development and manufacturing of a portfolio of antibodies targeting up to 10 pathogens that pose significant risk to public health, now including the influenza virus and 2019-nCoV. The use of Regeneron's proprietary VelociSuite technologies enables swift identification, preclinical validation and development of antibody candidates and includes the VelocImmune platform utilizing a unique genetically engineered mouse with a humanized immune system that can be challenged with all or parts of a virus (Regeneron Pharmaceuticals News Release).

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05-Feb-2020

FDA issues EUA for CDC's 2019-nCoV Real-Time RT-PCR Diagnostic Panel

The FDA has issued an emergency use authorization (EUA) to enable emergency use of the Centers for Disease Control and Prevention's (CDC) 2019-nCoV Real-Time RT-PCR Diagnostic Panel. To date, this test has been limited to use at CDC laboratories, but the new authorization allows the use of the test at any CDC-qualified laboratory in the U.S. The diagnostic is a reverse transcriptase PCR test that provides presumptive detection of 2019-nCoV from respiratory secretions, such as nasal or oral swabs. A positive test result indicates likely infection with 2019-nCoV, although negative results do not preclude 2019-nCoV infection and must be combined with clinical observations, patient history and epidemiological information. Last month, a public health emergency was declared in the U.S., recognizing the potential threat that 2019-nCoV poses. There are no commercially available diagnostic tests cleared or approved by the FDA for the detection of 2019-nCoV (FDA News Release)

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03-Feb-2020

CureVac and CEPI collaborate to develop vaccine against coronavirus nCoV-2019

CureVac and the Coalition for Epidemic Preparedness Innovations (CEPI) announced a collaboration to develop a vaccine against the new coronavirus nCoV-2019. The aim of the cooperation is to safely advance vaccine candidates into clinical testing as quickly as possible, with the agreement building on the existing partnership between CureVac and CEPI to develop a rapid-response vaccine platform and including additional initial funding of up to USD 8.3 million by CEPI for accelerated vaccine development, manufacturing and clinical tests. CureVac is also working on the development of The RNA Printer, which is a mobile, automated production unit for rapid mRNA supply. In February, 2019, CEPI agreed to provide up to USD 34 million in support of this innovative technology platform, which will provide a rapid supply of lipid-nanoparticle (LNP)-formulated mRNA vaccine candidates that can target known pathogens and prepare for rapid response to new and previously unknown pathogens. The Federal Ministry of Education and Research (BMBF) in Germany is one of the founding members of the CEPI and has committed a total of 90 million euros to its work. CEPI brings together a range of diverse stakeholders to develop much-needed vaccines for the prevention of future pandemics (CureVac News Release)

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03-Feb-2020

Gilead provides remdesivir for use in response to novel coronavirus

In response to the novel coronavirus (2019-nCoV) outbreak in China, Gilead Sciences has provided remdesivir for use in a small number of patients with 2019-nCoV for emergency treatment in the absence of any approved treatment options. This was at the request of treating physicians, and with the support of local regulatory agencies. Gilead is working with health authorities in China to establish a randomized, controlled trial to determine whether remdesivir can be used safely and effectively to treat 2019-nCoV. It is also expediting appropriate laboratory testing of remdesivir against 2019-nCoV samples. Although there are no antiviral data for remdesivir that show activity against 2019-nCoV at this time, there are promising data available in other coronaviruses. Remdesivir has demonstrated in vitro and in vivo activity in animal models against the viral pathogens Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), coronaviruses that are structurally similar to 2019-nCoV. There are also limited clinical data available from the emergency use of remdesivir in the treatment of patients with Ebola virus infection. Remdesivir is not yet licensed or approved anywhere globally (Gilead Sciences News Release).

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31-Jan-2020

Immune Response BioPharma plans IND filing for new SARS/coronavirus vaccine

Immune Response BioPharma has completed a new severe acute respiratory syndrome (SARS)/coronavirus vaccine, IR-101C (RespiResponse), and plans to file an IND with the FDA. RespiResponse is a novel first-in-class two-dose vaccine consisting of depleted coronavirus spike glycoprotein without an outer envelope inactivated with beta propiolactone and gamma irradiation, and propagated in HUT78 cells. The second dose involves a novel peptide VB V Beta sequenced gene type in IFA adjuvant. The company intends to seek U.S. breakthrough therapy designation for RespiResponse as a universal coronavirus vaccine (Immune Response BioPharma News Release).

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29-Jan-2020

Clover begins development of recombinant subunit vaccine for 2019-nCoV

Clover Biopharmaceuticals has initiated development of a recombinant subunit vaccine for 2019-nCoV, the newly identified coronavirus that is believed to have originated from Wuhan, China. Similar to other enveloped RNA viruses such as HIV, respiratory syncytial virus (RSV) and influenza, 2019-nCoV is also an RNA virus that has a trimeric spike (S) protein on its viral envelope. The trimeric S protein of 2019-nCoV is responsible for binding to host cell surface receptor ACE2 and subsequent viral entry. Clover is using its patented Trimer-Tag technology to construct a recombinant 2019-nCoV S protein subunit-trimer vaccine (S-Trimer) and will produce it via a rapid mammalian cell-culture based expression system. Clover expects to obtain highly purified S-Trimer vaccine for further preclinical safety and analysis within the next 6-8 weeks. Clover has previously developed recombinant subunit-trimer vaccines for HIV, RSV and influenza viruses utilizing its Trimer-Tag technology and has demonstrated that they are able to evoke protective neutralizing antibody responses in multiple animal models. The company invites collaboration to accelerate development of a successful vaccine (Clover Biopharmaceuticals News Release).

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29-Jan-2020

CytoDyn explores use of leronlimab for novel coronavirus

CytoDyn is exploring leronlimab (PRO-140), a CCR5 antagonist, as a potential treatment for patients infected with the 2019 novel coronavirus (2019-nCoV), the cause of an outbreak of respiratory illness first detected in Wuhan, China. 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 with 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 the specific strain of the 2019-nCoV. CytoDyn and IncellDx, a diagnostic partner and an advisor to CytoDyn, anticipate advancing discussions with potential partners to study leronlimab as a treatment option for this virus. CytoDyn is already exploring the utility of leronlimab in cancer, HIV/AIDS and graft-versus-host disease (CytoDyn News Release).

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28-Jan-2020

GeoVax and BravoVax sign letter of intent to codevelop 2019-nCoV coronavirus vaccine

GeoVax Labs and BravoVax have signed a letter of intent to jointly develop a vaccine against the new coronavirus, 2019-nCoV. Under the collaboration, GeoVax will use its MVA-VLP vaccine platform and expertise to design and construct the vaccine candidate using genetic sequences from the ongoing coronavirus outbreak originating in Wuhan, China. BravoVax, which is based in Wuhan, will provide further development, including testing and manufacturing support, as well as direct interactions with Chinese public health and regulatory authorities. GeoVax's Modified Vaccinia Ankara (MVA) platform technology is built on a fifth generation MVA vector system. MVA vaccines elicit protective T-cell as well as antibody responses in animals and humans. The GeoVax MVA platform can be combined with the potent immunogenicity of virus-like particles (VLPs) or be used to express proteins in their native conformations, enabling construction of vaccine candidates that induce full protection after a single dose (GeoVax Labs News Release).

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27-Jan-2020

CEPI awards funding to support development of vaccines against coronavirus 2019-nCoV

The Coalition for Epidemic Preparedness Innovations (CEPI) has awarded funding to a number of companies to develop a vaccine against the novel coronavirus 2019-nCoV. This month, 2019-nCoV was identified as the cause of pneumonia cases in Wuhan City, China, and additional cases have been found in a growing number of countries. Under an agreement between CEPI and Moderna, the company will manufacture an mRNA vaccine against 2019-nCoV, which will be funded by CEPI. Moderna will leverage its mRNA vaccine technology to potentially develop a vaccine against coronavirus 2019-nCoV. The Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID), part of National Institutes of Health (NIH), is collaborating with Moderna to design the vaccine. NIAID will conduct IND-enabling studies and a phase I study in the U.S. CEPI has also awarded Inovio Pharmaceuticals a

grant of up to USD 9 million to develop a vaccine against 2019-nCoV. This initial CEPI funding will support Inovio's preclinical and clinical development through phase I testing of INO-4800, its new coronavirus vaccine matched to the outbreak strain. Inovio's participation is based on the ideal suitability of its DNA medicine platform to rapidly develop a vaccine against an emerging virus with pandemic potential. Inovio was the first to advance its vaccine (INO-4700) against MERS-CoV, a related coronavirus, into evaluation in humans. In a phase I trial, its MERS-CoV vaccine demonstrated it was well tolerated and induced high levels of antibody responses in roughly 95% of subjects, while also generating broad-based T cell responses in nearly 90% of study participants. Durable antibody responses to INO-4700 were also maintained through 60 weeks following dosing. Inovio is currently preparing to initiate a phase II vaccine trial for INO-4700 in the Middle East where most MERS viral outbreaks have occurred. Inovio's collaborators in this coronavirus vaccine development include the Wistar Institute, VGXI, a fully owned subsidiary of GeneOne Life Science, and Twist Bioscience (Moderna News Release; Inovio Pharmaceuticals News Release).

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12-Aug-2019

Phase I safety and immunogenicity data for GLS-5300 MERS vaccine

Researchers from the Walter Reed Army Institute for Research and GeneOne Life Science presented results from a phase I study of the GLS-5300 Middle East respiratory syndrome (MERS) coronavirus DNA vaccine (ClinicalTrials.gov Identifier NCT02670187). At the time of data analysis, 75 healthy adult volunteers (aged 18 to 50 years) were enrolled in the open-label, single-arm, dose-escalation, phase I study, designed to evaluate the safety, tolerability and immunogenicity of the GLS-5300 MERS coronavirus DNA vaccine in healthy adults. Eligible participants were enrolled sequentially using a dose-escalation protocol to receive 0.67, 2 or 6 mg GLS-5300 administered by trained clinical site staff via a single intramuscular 1-mL injection at each vaccination at baseline, week 4 and week 12, followed immediately by colocalized intramuscular electroporation. Enrollment into the higher dose groups occurred after a safety monitoring committee reviewed the data following vaccination of the first 5 participants at the previous lower dose in each group. At the time of data cutoff, 25 subjects were enrolled in each of the 3 dose cohorts. No vaccine-associated serious adverse events (SAEs) were reported, with the most commonly reported AEs being injection-site reactions. Overall, 73 of 75 participants (97%) reported at least one solicited AE, with the most common systemic symptoms being headache and malaise or fatigue. The most commonly reported local solicited symptoms were administration site pain and tenderness, with most of these solicited symptoms being reported as mild and were self-limiting. Unsolicited symptoms were reported for 56 of the 75 participants (75%) and were deemed treatment-related for 26 participants (35%). The most common unsolicited AEs were infections, which occurred in 27 participants (36%), and 6 (8%) of these were deemed possibly related to study treatment. There were no laboratory abnormalities of grade 3 or higher that were related to study treatment. Laboratory abnormalities were generally uncommon, except for 15 increases in creatine phosphokinase, reported in 14 participants. Of these 15 increases, 5 (33%) were deemed possibly related to study treatment. Seroconversion measured by S1-ELISA occurred in 59 of 69 participants (86%) and 61 of 65 participants (94%) after two and three vaccinations, respectively, and neutralizing antibodies were detected in 34 of 68 participants (50%). T-cell responses were detected in 47 of 66 participants (71%) after two vaccinations and in 44 of 58 participants (76%) after three vaccinations. No differences in immune responses were seen between dose groups after 6 weeks. At week 60, vaccine-induced humoral and cellular responses were detected in 51 of 66 participants (77%) and 42 of 66 participants (64%), respectively. Taken together, these results support further development of the GLS-5300 vaccine, including additional studies to test the efficacy of GLS-5300 in a region endemic for MERS coronavirus (Modjarrad, K. et al. Lancet Infect Dis 2019, Advanced publication).

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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
- 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

- 2019 novel coronavirus (2019-nCoV) (New England Journal of Medicine)
- 2019-nCoV resource centre (The Lancet)
- Coronavirus (The BMJ)
- SARS Reference by B.S. Kamps and C. Hoffman (Eds.)
- The 2019 novel coronavirus (2019-nCoV) (JAMA Network)

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 guidance document: Clinical management of severe acute respiratory infections when novel coronavirus is suspected: What to do and what not to do (World Health Organization, 2013)

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

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

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

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

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