Disease Briefing: Coronaviruses
Contents

CONTENTS 1
CORONAVIRUS: DISEASE BRIEFINGS 2
LATEST HEADLINES 29
SUGGESTED READING 34
GUIDELINES 35
SOURCES 36
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.

<table>
<thead>
<tr>
<th>Family/Characteristics</th>
<th>Viruses</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthomyxoviruses (Orthomyxoviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; segmented genome)</td>
<td>Influenza A and B virus</td>
<td>Upper respiratory infection, croup</td>
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<tr>
<td>Paramyxoviruses (Paramyxoviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; segmented genome)</td>
<td>Parainfluenza 1-3 virus Respiratory syncytial virus</td>
<td>Upper respiratory infection, croup</td>
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<td>Virus Family</td>
<td>Virus Name</td>
<td>Disease</td>
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<td>stranded RNA, enveloped (No DNA step in replication; negative-sense genome; nonsegmented genome)</td>
<td>Measles virus</td>
<td>Upper respiratory infection, croup</td>
</tr>
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<td></td>
<td>Mumps</td>
<td>Measles</td>
</tr>
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<td></td>
<td></td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td>Coronaviruses (Coronaviridae) Single-stranded RNA, enveloped (No DNA step in replication; positive-sense genome)</td>
<td>Human coronaviruses</td>
<td>Upper respiratory infection</td>
</tr>
<tr>
<td>Rhabdoviruses (Rhabdoviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; nonsegmented genome)</td>
<td>Rabies virus</td>
<td>Rabies</td>
</tr>
<tr>
<td>Picornaviruses (Picornaviridae) Single-stranded RNA, nonenveloped</td>
<td>Rhinoviruses</td>
<td>Common cold</td>
</tr>
<tr>
<td></td>
<td>Hepatitis A virus</td>
<td>Hepatitis</td>
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<td></td>
<td>Enteroviruses:</td>
<td></td>
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<tr>
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<td>- Polioviruses</td>
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<td>- Coxsackie A24 viruses</td>
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<td>- Coxsackie B viruses</td>
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<td>- Coxsackie B1-5 viruses</td>
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<td>- Coxsackie A9 viruses</td>
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<td>- Echoviruses</td>
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</tr>
<tr>
<td>Caliciviruses (Calciviridae) Single-stranded RNA, nonenveloped</td>
<td>Norwalk virus</td>
<td>Gastroenteritis</td>
</tr>
<tr>
<td>Hepeviruses (Hepeviridae) Single-stranded RNA, nonenveloped</td>
<td>Hepatitis E</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Togaviruses (Togaviridae) Single-stranded RNA, enveloped (No DNA step in replication; positive-sense genome)</td>
<td>Alphaviruses (Group A arboviruses)</td>
<td>Encephalitis, hemorrhagic fever, chikungunya</td>
</tr>
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<td>Rubivirus</td>
<td>Rubella</td>
</tr>
<tr>
<td>Flaviviruses (Flaviviridae) Single-stranded RNA, enveloped (No DNA step in replication; positive-sense genome)</td>
<td>Group B arboviruses</td>
<td>Encephalitis, hemorrhagic fever</td>
</tr>
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<td></td>
<td>Hepatitis C virus</td>
<td>Hepatitis</td>
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<td>Dengue virus</td>
<td>Dengue fever</td>
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<td>Zika virus</td>
<td>Zika</td>
</tr>
<tr>
<td>Bunyaviruses (Bunyaviridae) Single-stranded RNA, enveloped (No DNA step in replication; negative-sense genome; segmented genome)</td>
<td>Some arboviruses</td>
<td>Encephalitis, hemorrhagic fevers</td>
</tr>
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<td></td>
<td>Hantavirus</td>
<td>Fever, renal involvement</td>
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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 AIDS
HIV-1, HIV-2

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 four major structural proteins. The S glycoprotein is a major antigen responsible for both receptor binding and cell fusion (Song, Z. et al (2019)) and the membrane glycoprotein (M) is involved in budding and envelope formation; the M protein has also been found to play a pivotal role in virion assembly (Tseng, Y.T. et al (2010)). The viral genome is associated with the basic phosphoprotein nucleocapside (N) within the capsid. The envelope (E) protein is a highly hydrophobic protein encasing the entire structure of the coronavirus. The genome is nonsegmented, positive single-stranded RNA of about 26-32 kb, making it the longest RNA viral genome known, and contains at least six different open reading frames. The RNA molecule has a methylated cap in 5' and a poly-A tail in 3' (Schoeman, D. et al (2019); Chen, Y. et al (2020); Pillaiyar, T. et al (2020)).

Coronaviruses are capable of adapting quickly to new hosts through the processes of genetic recombination and mutation in vivo. As RNA viruses, coronaviruses rely on RNA-dependent RNA polymerase (RdRp) to replicate the virus genome. The intrinsic error rate of RdRp is approximately 1,000,000 mutation/site/replication, resulting in continuous point mutations. Point mutations alone are not sufficient to create a new virus, however; this can only occur when the same host is simultaneously infected with two coronavirus strains, enabling recombination. One coronavirus can gain a genomic fragment of hundreds or thousands base-pair long from another CoV strain when the two co-infect the same host, enabling the virus to increase its ecological niche or to make the leap to a new species (Raj, V.S. et al (2014); Gralinski, L.E. et al (2015)). This susceptibility enabled the emergence in approximately two decades of three new human coronavirus species with epidemic potential: SARS-CoV, MERS-CoV and 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 (Pillaiyar, T. et al (2020)) and pneumonia. Coronaviruses are responsible for one third of cold cases. Coronaviruses can also cause gastroenteritis in humans as well as a plethora of diseases in other animals (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 37°C in contrast to other coronaviruses that grow at lower temperature, and can infect the lower respiratory tract (Vicenzi, E. et al (2004)). The SARS coronavirus genome is between 29705 and 29751 nucleotides (NCBI Sequence Viewer: SARS coronavirus). The SARS virus genome did not match any of the three previously known groups of coronaviruses, and had only a weak antigenic relationship to coronaviruses 229E and OC43. The polymerase gene is closely related to the bovine and murine coronaviruses in group 2, but also has some characteristics of avian coronaviruses in group 3. The SARS-CoV does not have a hemagglutinin-esterase present in group 2 and some group 3 coronaviruses, but it has a single papain-like proteinase that is present in group 3 coronaviruses (Holmes, K.V. et al (2003)). The differences between SARS-CoV and other coronaviruses pointed to a new group (Marra, M.A. et al (2003); Rota, P.A. et al (2003)) that was phylogenetically equidistant from the three known groups at that time. A new coronaviruses group 4 was proposed, of which the SARS-CoV is the only member. The discovery of SARS-CoV drove the search for other, previously unknown, human coronaviruses. Two such viruses were identified shortly thereafter: HCoV-NL63 (2004) and HCoV-HKU1 (2005). Both appear to be distributed worldwide, and at least the former has been circulating in human populations for centuries (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 and 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 (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 Bayesian 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)). Nosocomial 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
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Older patients had greater morbidity and mortality, the result of an aging-related attenuation in the adaptive immune response (Frieman, M. et al (2008); Schäfer, A. et al (2014)).

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

Independent correlates of adverse clinical outcome included known history of diabetes/hyperglycemia (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)).

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

WHO has released interim guidelines for the appropriate care of patients in whom this infection is suspected (see Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected - Interim
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)). Pathological features of MERS-CoV infection include exudative pulmonary edema, diffuse alveolar damage with hyaline membranes, type II pneumocyte hyperplasia, interstitial pneumonia, and necrosis of the bronchial submucosal glands (Liu, J. et al (2020)).

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.
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)). At the end of December 2019, the World Health Organization had been notified of 2,499 laboratory-confirmed human cases of infection with the virus and 861 related deaths (Middle East respiratory syndrome coronavirus (MERS-CoV) (World Health Organization), consulted February 18, 2020). The case-fatality rate remains extremely high: in excess of 30% (Salamatbakhsh, M. et al (2019)).

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

On May 20, 2015, the index case in what became the largest outbreak of MERS-CoV outside the the kingdom of Saudi Arabia was reported in the Republic of Korea. The index patient had recently traveled to four countries in the Middle East, and returned to Korea while still asymptomatic. Between May 2015 and June 2016, there were 185 laboratory-confirmed cases, including 38 fatalities, in Korea, as well as an additional case in China. The outbreak cost the central government of the Republic of Korea USD 860 million in concept of quarantine system reform, emergency support for hospitals and other MERS response activities, and loans for affected medical institutions. Direct medical costs of the outbreak were approximately USD 12 million (Joo, H. et al (2019)).
The epidemiology of new MERS infections appears to follow a seasonal pattern, with outbreaks in the spring of 2013, 2014 and 2015 coinciding with the months when camels give birth (Al-Tawfiq, J.A. et al (2014)).

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

For more epidemiology information, consult the Incidence and Prevalence Database (IPD): 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 issued by doctors in the densely populated city of Wuhan, Hubei province. Index cases were linked to the Huanan wholesale seafood market, which was immediately closed. Although the initial cases were traced to zoonotic transmission, human-to-human transmission was soon documented, both in healthcare settings and in familial clusters (Chan, J.F. et al (2020); Li, Q. et al (2020)). In fact, following the initial leap across the species barrier, human-to-human transmission quickly became responsible for widespread and rapid dissemination of the virus across populations with no preexisting immunity (Chen, J. (2020)); the disease spread from a single focal point across the entire country of China in just 30 days (Wu, Z. et al (2020)). In January, the Chinese Center for Disease Control and Prevention (China CDC) acknowledged that only 22% of the 198 confirmed COVID-19 cases included in its outbreak analysis could be traced to a Huanan market-related exposure (Wu, J.T. et al (2020)).

The causative virus—originally termed 2019-nCoV—was sequenced and identified as a betacoronavirus belonging to the sarbecovirus subgenus, with approximately 80% similarity in genetic sequence to SARS-CoV (Hui, D.S. et al (2020); Zhu, N. et al (2020); Perlman, S. (2020)). The viral genome is a single-stranded, positive-sense RNA encoding for structural (especially spike [S]) and nonstructural (3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase) proteins as well as accessory proteins (Li, G. et al (2020); Zhang, L. et al (2020)). Like SARS-CoV, the new virus is believed to use ACE2 as its binding receptor (Wan, Y. et al (2020)), deploying the S protein for virus-cell receptor interaction during viral entry (Li, G. et al (2020)). 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)).
Transmission of the virus during the viremic stage of disease is primarily via respiratory secretions (droplets), and infection can be detected in oral swabs. At later stages of infection, however, viral persistence has been detected in anal swabs, blood and serum, suggesting additional shedding mechanisms and the potential for transmission via the oral-fecal or body fluid routes (Zhang, W. et al (2020)).

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); Wu, Z. et al (2020)). 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 older patients with serious underlying diseases or conditions. A later analysis of a larger group of patients (N = 44,672) found an overall mortality rate of 2.3%, which increased with age, from zero in children under 9 to 14.8% in those over 80 (Unknown Author (2020); Wu, Z. et al (2020)). A challenge for scientists studying COVID-19 is that those who are infected with subclinical or mild disease might not present to health care centers, impacting the accuracy of total case counts and calculation of case-fatality rates. Moreover, asymptomatic, seemingly healthy individuals can spread the virus to their contacts at home and at work as during travel (Munster, V.J. et al (2020)). Infected individuals appear to be capable of transmitting the disease during the prodromal period (Heymann, D.L. et al (2020)). A study of the transmission dynamics in the first 425 confirmed cases in Wuhan concluded that SARS-CoV-2 is extremely contagious, and estimated a basic reproduction number (R0) of 2.2 (Li, Q. et al (2020)). For contrast, the R0 for both SARS-CoV and MERS-CoV is less than 1 (Wu, J.T. et al (2020)).

According to WHO, as of February 25, 2020, a total of 81,109 laboratory-confirmed cases of COVID-19 had been detected worldwide. Although the vast majority (78,191) continued to be from China, the outbreak in that country appeared to be slowing as of late February -- at the same time that it began picking up in other countries. In fact, February 25 was the first day on which more new cases of COVID-19 were reported from February 25, WHO confirmed 2,718 deaths from COVID-19 in China and 44 more outside that country. The risk assessment of this event, as determined by WHO, continued to be very high in China, and high at both the regional and global level (Emergencies; Novel coronavirus 2019 (World Health Organization), consulted February 26, 2020). As of February 27, China CDC reported 78,497 confirmed and 2,358 suspected cases, resulting in 2,744 deaths in that country (Tracking the epidemic (China CDC), consulted February 27, 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 in China a Public Health Emergency of International Concern (PHEIC) (Unknown Author (2020)). In subsequent weeks, significant outbreaks were reported in Italy, South Korea, Iran and on a cruise ship in Japan; dozens of other countries have also reported cases, albeit smaller numbers. To track the outbreak in real time, click here: Coronavirus COVID-19 global cases dashboard (Johns Hopkins University Center for Systems Science and Engineering).

Although the early case-fatality rate appeared to be low--2.3%, according to a study of the first 44,000 cases (Unknown Author (2020)), 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)).

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)). 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 antinucleocapsid 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, later identified as SARS-CoV-2, was first identified in samples taken from 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 SARS-CoV-2 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 Geneotech 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 interprets the results in minutes, with both sensitivity and specificity values of 100%.

Patients hospitalized in Wuhan with suspected SARS-CoV-2 infection were screened by RT-PCR and next-generation sequencing. Among those identified with SARS-CoV-2 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 IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, and TNF-alpha—a so-called "cytokine storm"—corresponding with disease severity (Huang, C. et al (2020); Zumla, A. 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 (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 SARS-CoV-2 from respiratory secretions, such as nasal or oral swabs. Novacyt has also launched a quantitative PCR assay, targeting the unique SARS-CoV-2 genome sequences without the need for cold chain shipping. In addition, Co-Diagnostics is using the Coprimer multiplexing technology to differentiate between similar genetic sequences, thereby reducing false positive diagnosis. Also, at Meridian Bioscience, the molecular diagnostic test (Meridian Lyo-Ready 1-Step RT-qPCR Mix) can be prepared and freeze-dried, making it highly stable and only requiring the addition of the patient sample to run the assay. In Europe, 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 agents (Li, G. et al (2020)), social distancing strategies 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 airborne infection isolation procedures in the care of all confirmed MERS infections in that country (Al-Tawfiq, J.A. et al (2014)). Soon after the COVID-19 outbreak began to expand, Chinese authorities imposed restrictions on movement in and around Wuhan, the major air and train transportation hub of central mainland China. Transportation and activities throughout the country were subsequently limited (Wu, Z. et al (2020)). Based on assumptions of exponential growth of the outbreak (R0 = 2.68), WHO-linked epidemiology experts recommend stringent controls in order to prevent independent, self-sustaining outbreaks in major cities around the world (Wu, J.T. et al (2020)).

On the personal level, hygiene measures are recommended to prevent the spread of disease in situations where individuals are in contact with patients or contaminated fomites (Chen, Y. et al (2020)). Washing hands with soap and water or with alcohol-based handrubs is effective for interrupting virus transmission. SARS and other coronaviruses are able to survive on metal, glass and plastic surfaces at room temperature for up to nine days, but can be inactivated by disinfection with ethanol (62-71%), hydrogen peroxide (0.5%) or sodium hypochlorite (0.1%) (Kampf, G. et al (2020)). The MERS virus is capable of surviving for up to 48 hours at 20ºC and for 24 hours at 30ºC (Chan, J.F. et al (2015)). Personal protective equipment, including eye protection, is recommended for health care personnel, as well as surgical masks or N95 disposable filtering respirators (Huang, C. et al (2020)). Airborne precautions should be applied especially when performing aerosol-generating procedures such as intubation (Paules, C.I. et al (2020)). All potentially infectious specimens should be handled and transported with caution, and must be tested in laboratories meeting WHO BSL3 standards (Chan, J.F. et al (2015)).

As a result of the SARS outbreak, WHO revised the rules for reporting infectious diseases by its member states. The previous reporting requirements, formulated in 1951, required reporting for plague, cholera and yellow fever only, and the resulting delay in reporting cases early in the outbreak was likely to have contributed to its rapid spread (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.

**Experimental coronavirus vaccines in active preclinical and clinical development**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Organisations</th>
<th>Description</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>BVRS-GamVac-Combi</td>
<td>Ministry Healthcare Russian Federation</td>
<td>Middle East respiratory syndrome coronavirus (MERS-CoV) vaccine comprising a combined heterologous adenviral vector</td>
<td>I/II</td>
</tr>
<tr>
<td>GLS-5300</td>
<td>Inovio Pharmaceuticals; GeneOne Life Science</td>
<td>Middle East Respiratory Syndrome DNA vaccine using the SynCon (TM) technology, encoding MERS spike protein</td>
<td>I/II</td>
</tr>
<tr>
<td>ChAdOx1 MERS</td>
<td>Vaccitech Ltd.; University of Oxford</td>
<td>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)</td>
<td>I</td>
</tr>
<tr>
<td>MVA-MERS-S</td>
<td>Ludwig-Maximilians-Univ. Muenchen</td>
<td>Middle East respiratory syndrome coronavirus (MERS-CoV) vaccine comprising modified</td>
<td>I</td>
</tr>
<tr>
<td><strong>vaccinia virus encoding full-length S protein of MERS-CoV, under the control of early/late promoter PmH5</strong></td>
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<td><strong>GREVAX/MERS</strong></td>
<td>Greffex</td>
<td>Preclinical</td>
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<tr>
<td><strong>INO-4800</strong></td>
<td>Inovio Pharmaceuticals</td>
<td>Human COVID-19 coronavirus (SARS-CoV-2) vaccine</td>
<td></td>
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<tr>
<td><strong>IR-101C</strong></td>
<td>Immune Response BioPharma</td>
<td>Coronavirus vaccine consisting of depleted coronavirus spike glycoprotein without outer envelope inactivated with beta propiolactone and gamma irradiation; propagated in HUT78 cells</td>
<td></td>
</tr>
<tr>
<td><strong>MVA-MERS-S_DF1</strong></td>
<td>Universitätsklinikum Hamburg-Eppendorf</td>
<td>Middle East respiratory syndrome (MERS) vaccine consisting of modified vaccinia ankara (MVA) virus encoding MERS-CoV spike (S) protein antigens</td>
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</tr>
<tr>
<td><strong>TNX-1800</strong></td>
<td>Tonix Pharmaceuticals</td>
<td>Human COVID-19 coronavirus (SARS-CoV-2) vaccine comprising an engineered, live replicating strain of horsepox virus (HPXV) encoding a protein of COVID-19 virus</td>
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</tbody>
</table>
There is no approved drug therapy for SARS, MERS or any other coronavirus infection at this time (Li, G. et al (2020)). Supportive care is the mainstay of treatment for patients with severe disease (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)). Some physicians preferred to delay administration of corticosteroids until the second week of infection in order to reduce side effects. The HIV protease inhibitor Kaletra (lopinavir/ritonavir), which inhibits the major CoV protease 3CLpro, was the most effective treatment for SARS (Zumla, A. et al (2016)). Twenty-one day ARDS and death rates were lowest in subjects treated with a combination of ribavirin, lopinavir/ritonavir and a corticosteroid (Pillaiyar, T. et al (2020)).

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, and further evaluation of these compounds was recommended. In MERS-CoV-infected patients, administration of drugs such as these—even if not 100% effective in blocking viral replication—could provide a window of opportunity during which the patient’s immune system might begin to respond to the infection (de Wilde, A.H. et al (2014)). A systematic review of drugs evaluated in preclinical and clinical studies against MERS-CoV found that the combination of lopinavir/ritonavir and interferon-beta-1b gave excellent results in common marmosets, and has progressed to testing in a randomized control trial setting. Ribavirin and interferon were the most widely used combination in observational studies, and may warrant further investigation (Momattin, H. et al (2019)).
In early 2020, as the number of people affected by COVID-19 outbreak steadily multiplied and with a lack of virus-specific therapies, an international group of thought leaders proposed the repurposing of host-directed therapies with demonstrated safety to treat the most seriously ill patients. Candidate drugs included metformin, glitazones, fibrates, sartans and atorvastatin for boosting the immune response; zinc and other metal-containing supplements with antiviral activity; cyclosporine, lopinavir/ritonavir, interferon beta-1b, ribavirin and remdesivir, also for their antiviral activity; various cellular therapies; and the anti-IL-6 monoclonal antibody (MAb) tocilizumab (Zumla, A. et al (2020)). Others have similarly proposed repurposing available therapeutic options, based on previous lines of investigation into SARS-CoV and MERS-CoV. These include a range of host-directed approaches: nutritional interventions (vitamins A, C, D and E, B vitamins, omega-3 polyunsaturated fatty acids, selenium, zinc and iron), immuno-enhancing agents (interferons, IVIG, thymosin alpha-1, thymopentin, levamisole and ciclosporin), convalescent plasma and traditional Chinese medicine. Suggested virus-directed approaches include the antimalarial agent chloroquine; flavonoids, for their antiviral and antioxidant activity; the virucidal anthraquinone emodin and the antipsychotic agent chlorpromazine, both of which block the interaction of the viral S glycoprotein with the ACE2 binding receptor; and MAbs directed against S glycoprotein (Zhang, L. et al (2020); Pillaiyar, T. et al (2020)).

Corticosteroids

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

Data obtained in a Hong Kong hospital support use of pulsed methylprednisolone as rescue therapy only during the later stages of SARS; administration during the earlier phases of disease appeared to actually prolong viremia (Hui, D.S. et al (2010)). In fact, later analysis showed that prolonged methylprednisolone use was associated with worse outcomes, including disseminated fungal infection and avascular osteonecrosis, and increased 30-day mortality (Pillaiyar, T. et al (2020)); as such corticosteroids should be used only with caution in the treatment of patients with MERS (Zumla, A. et al (2015)). Based on 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, in an observational study of 349 critically ill MERS patients, of whom 144 received ribavirin/IFN (ribavirin and/or IFN-alfa2a, IFN-alfa2b or IFN-beta1a), the treatment was not associated with any reduction in 90-day mortality or in faster MERS-CoV RNA clearance (Arabi, Y.M. et al (2019)). Adverse events, including dose-dependent anemia, are a significant concern with ribavirin, and are cited as one factor against its use in patients with COVID-19 (Li, G. et al (2020)).

Favipiravir, another nucleoside analogue that is approved for use in treating influenza A and B, has been identified as a potential broad-spectrum antiviral for use in the COVID-19 outbreak. Favipiravir inhibits RNA-dependent RNA polymerase of various RNA viruses including influenza,
yellow fever virus, Ebola virus, norovirus and chikungunya virus (Li, G. et al (2020)).

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

Viral Enzyme Inhibitors

The process of coronavirus replication is well understood. Several unique steps have been identified as potential targets for antiviral drugs. Viral fusion with the host cell could potentially be blocked by entry inhibitors or membrane fusion inhibitors, similar to antivirals used for HIV infection. Viral protease inhibitors may block cleavage of the polymerase protein to inhibit viral RNA synthesis. Nucleoside inhibitors might specifically inhibit viral replication without causing damage to the host cell. Targeted inhibitors of the serine proteases, which are required to activate the viral infectivity of some coronaviruses, may block the later stages of the viral life cycle (Kilianski, A. et al (2014); Zhou, Y. et al (2015)); 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 RNA-directed RNA polymerase inhibitor remdesivir showed broad-spectrum antiviral activity against coronaviruses in vitro and in vivo, inhibiting the replication of both endemic and zoonotic strains in cell culture. In a relevant murine model of SARS-CoV infection, prophylactic administration of remdesivir prevented development of symptomatic disease; postexposure administration was also effective in mitigating the immunopathological phase of disease, improving respiratory function and reducing viral load (Sheahan, T.P. et al (2017)). In 2020, based on these and other studies suggesting its anti-CoV activity (Sheahan, T.P. et al (2020); Wang, M. et al (2020)) and at the request of treating physicians, remdesivir was supplied by the manufacturer for experimental use in China, to treat hospitalized adult patients with COVID-19 illness. In late February, the U.S. NIH announced that a randomized, controlled clinical trial to evaluate the safety and efficacy of remdesivir in hospitalized adults diagnosed with COVID-19 has begun at the University of Nebraska Medical Center in Omaha.

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.
**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)).

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.

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Organization</th>
<th>Mechanism</th>
<th>Phase</th>
<th>Structure</th>
</tr>
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<tr>
<td>Remdesivir</td>
<td>Gilead</td>
<td>RNA-Directed RNA Polymerase (Viral) Inhibitors</td>
<td>Phase III</td>
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<tr>
<td>Drug Name</td>
<td>Developer/Institution</td>
<td>Description</td>
<td>Phase</td>
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<tr>
<td>Lopinavir/ritonavir</td>
<td>King Abdullah International Med Res Cent</td>
<td>HIV Protease Inhibitors; HIV-1 Protease Inhibitors; Tumor Necrosis Factor Receptor Superfamily Member 6 (CD95)/PLC-gamma-1 Interaction Inhibitors</td>
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<td>Ministry Healthcare Russian Federation</td>
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<td>I/II</td>
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<td>GLS-5300</td>
<td>Inovio Pharmaceuticals; GeneOne Life Science</td>
<td>Spike Glycoprotein (S) (MERS-CoV)-Directed Immunity Inducers</td>
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<tr>
<td>ChAdOx1 MERS</td>
<td>Vaccitech Ltd.; University of Oxford</td>
<td>Spike Glycoprotein (S) (MERS-CoV)-Directed Immunity Inducers</td>
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<td>MVA-MERS-S</td>
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<td>Chloroquine</td>
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<td>Apoptosis Inducers; Histamine N-methyltransferase (HNMT) Inhibitors</td>
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<td>Darunavir/cobicistat</td>
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<td>Oseltamivir</td>
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<td>Neuraminidase (Sialidase) (Influenza Virus) Inhibitors</td>
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<td><strong>Human leukocyte interferon alpha</strong></td>
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</table>

**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.
Latest Headlines

27-Feb-2020

Pilot study of APN-01 for the treatment of coronavirus disease COVID-19 in China

Apeiron Biologics announced the launch of a pilot investigator-initiated clinical trial (IIT) with the recombinant human angiotensin-converting enzyme 2 (rhACE2), APN-01, to treat patients with severe coronavirus infection in the People’s Republic of China. A total of 24 patients are to be treated for 7 days in the randomized, unblinded study, with the aim of obtaining preliminary data on the impact of rhACE2 on biological, physiologic, and clinical outcomes, as well as safety in patients with severe SARS-CoV-2 infection. These data will be assessed to determine whether a phase Ib clinical trial in a larger number of patients is warranted. The study is being supported by a global team of leading experts. APN-01 was developed by Apeiron for the treatment of acute lung injury (ALI), acute respiratory distress syndrome (ARDS) and pulmonary arterial hypertension (PAH). After licensing from Apeiron in February 2010, GlaxoSmithKline (GSK) conducted trials from 2014 to 2017 to treat ALI and PAH and ARDS, the latter being the major source of COVID-2019 mortalities. In 2019, Apeiron obtained the APN-01 licenses back from GSK for further clinical development, after a strategic refocusing of GSK to oncology. Apeiron currently has the full licenses, clinical data and protocol from GSK, GMP production technology and stored GMP grade rhACE2 available for immediate use in trials in China. The drug candidate is administered intravenously as an infusion and has shown safety and tolerability in 89 patients and volunteers (Apeiron Biologics News Release).

27-Feb-2020

Novavax produces nanoparticle COVID-19 vaccine candidates

Novavax announced progress in its efforts to develop a novel vaccine to protect against coronavirus disease COVID-19, as the company has produced and is currently assessing multiple nanoparticle vaccine candidates in animal models prior to identifying an optimal candidate for human testing, which is expected to begin by the end of spring 2020. Novavax created the COVID-19 vaccine candidates using its proprietary recombinant protein nanoparticle technology platform to generate antigens derived from the coronavirus spike protein. The company expects to utilize its proprietary Matrix-M adjuvant with its COVID-19 vaccine candidate to enhance immune responses (Novavax News Release).

27-Feb-2020

Tonix collaborates with Southern Research on vaccine TNX-1800 for COVID-19

Tonix Pharmaceuticals has entered into a strategic collaboration with Southern Research to support the development of a vaccine, TNX-1800 (live modified horsepox virus vaccine for percutaneous administration) to protect against the new coronavirus disease, COVID-19. Tonix is developing TNX-801 (live horsepox virus vaccine for percutaneous administration) as a potential smallpox preventing vaccine for the U.S. strategic national stockpile and as a monkeypox preventing vaccine. Under the research collaboration, Southern Research will test one or more vaccine constructs in the Tonix horsepox vector that express one or more proteins or protein fragments from the virus (SARS-CoV-2) that causes COVID-19. The first such potential vaccine is TNX-1800. The collaboration seeks to leverage Tonix’s horsepox vaccine technology that was originally developed to protect against smallpox but has capabilities as a vector for other infectious diseases. Tonix has previously reported that horsepox has efficacy as a vaccine and good tolerability in mice and cynomolgus macaques (Tonix Pharmaceuticals News Release).
Study of CoV-OC43 dissemination in mouse CNS and drug testing using non-invasive bioluminescence

Six coronaviruses (CoVs) predominantly causing respiratory and central nervous system (CNS) pathologies have been identified in humans. However, little is known about the replication and the dissemination of these CoVs in the CNS, and no therapeutic options are currently available. In a recent publication, researchers from the National Institute for Viral Disease Control and Prevention from China and colleagues used a reporter HCoV-OC43 strain expressing Renilla luciferase (Rluc; rOC43-ns2DelRluc) to understand its replication ability and pathogenicity in two mouse models (C57BL/6 and BALB/c). Intranasal inoculation of rOC43-ns2DelRluc was fatal to suckling mice. They detected viral titers and Rluc expression in the brains and spinal cords of mice infected with rOC43-ns2DelRluc. Using non-invasive bioluminescence, the researchers observed viral replication before the infection spread to the spinal cord of BALB/c mice after intranasal or intracerebral inoculation with rOC43-ns2DelRluc, consistent with its tropism in the CNS. The Rluc readout correlated with the CoV replication ability and protein expression, allowing quantification of antiviral activity in live mice. Moreover, using chloroquine, they validated the utility of rOC43-ns2DelRluc-infected mice as an in vivo tool for testing the efficiency of antiviral drugs against human CoVs. Chloroquine phosphate (30 mg/kg, administered 2 h before viral inoculation) strongly inhibited rOC43-ns2DelRluc replication in vivo. In summary, these results help to understand the temporal and spatial dissemination of CoV-OC43 in the CNS, while providing an extremely sensitive platform for evaluating the efficacy of antiviral therapies in live mice (Niu, J.W. et al. Antiviral Res 2020, 173: 104646).

It was recently reported that chloroquine phosphate showed efficacy in treating COVID-19-associated pneumonia in patients in China (BioWorld Science, February 21, 2020).

COVID-19 spreading but not yet pandemic disease, says WHO

By Nuala Moran, Staff Writer

The COVID-19 outbreak appears to be sliding toward pandemic status, with the virus spreading to four more countries and confirmed cases and deaths mounting in infection hotspots in Italy, Iran and South Korea.

Parts of northern Italy are in lockdown, with 200-plus cases and 7 deaths. Austria and Switzerland are reported to be considering closing their borders with Italy, and the E.U. has responded with a EUR 232 million (USD 252 million) package of aid, including EUR 90 million for development of a vaccine and EUR 10 million for therapeutics and diagnostics.

After confirming its first case as recently as February 19, by February 24 Iran had reported 61 cases and 12 deaths. That number seems likely to increase as diagnostic testing gets into full swing. Neighboring countries have closed their borders, after the infection was spread by pilgrims returning home from holy sites in Qom, Iran.

Meanwhile, the number of cases in South Korea rose by 256 to 602 over the weekend, with 5 deaths recorded in total.

"Are we there yet? No."

Tedros Adhanom Ghebreyesus, World Health Organization (WHO) director general, agreed the sudden increase in cases in Italy, Iran and South Korea is “deeply concerning” and acknowledged he understands why there is so much speculation about whether that means COVID-19 is now a pandemic disease. But he said, at present, there is no international uncontained spread.

"Does it have pandemic potential? Absolutely it does. Are we there yet? No," Ghebreyesus said in his daily update on the state of play. The focus for now should remain on containment, whilst also preparing for if COVID-19 does become a pandemic disease, he said.
The latest figures from China are 77,362 cases and 2,618 deaths. In the 24 hours to 6 am CET on February 24, there were 460 new cases and 150 deaths. Ghebreyesus said he is encouraged by the continued decline in cases in China.

Earlier on February 24, the WHO joint expert mission to China presented its findings after 2 weeks traveling the country, talking to clinicians, tracking the epidemiology and assessing containment measures.

Bruce Aylward, leader of the mission, said the evidence is the epidemic peaked and plateaued in the country between January 23 and February 2, and has been steadily declining since then. The strict control measures that were put in place have saved hundreds of thousands of people from contracting the pathogen in China. There is no question that the "bold response" has changed the course of a rapidly escalating and deadly epidemic, said Aylward.

Two weeks ago when Aylward arrived in China, there were 2,500 new cases every day. Two weeks later, the number of new reported cases is 460. "That's an 80% decline, and the decline we're seeing is real," he said.

The country rolled out the "most agile and aggressive disease containment exercise in history," initially deploying old-fashioned measures such as handwashing and temperature monitoring. "But then very quickly, as the epidemic evolved, the response started to change. It moved from a one-size-fits-all, to a science and risk-based approach," Aylward said, presenting the mission's findings at a briefing in Beijing.

Some relief in sight

Among their conclusions, the WHO team found there has been no significant change in the DNA of the virus since the first genome sequence was released on January 11.

Between 2% and 4% of people who contracted COVID-19 in Wuhan, the city at the epicenter of epidemic, died. Patients with mild disease recovered in around 2 weeks, while those with severe infections took 3-6 weeks to get better.

Aylward was in Wuhan on February 22, where he said, "for the first time in weeks" hospitals have free beds. As another indicator the epidemic is waning, the principal investigator in one of the clinical trials running in the city told Aylward there are difficulties in recruiting new patients.

China is now looking at easing restrictions on travel and association, which the WHO mission agrees is appropriate. However, Aylward said, that does not mean a return to the status quo ante, but a "new normal" that recognizes the virus is likely to be around for months.

"The country should be getting back onto a regular footing, even though it is still dealing with a significant number of cases," said Aylward. "The key to doing this will be in phasing the lifting of control measures."

China's success in "blunting" the outbreak holds lessons for other countries, as they respond to COVID-19. But, said Aylward, the global community "is not ready in mindset or materials" to contain the virus in the same way as China has done.

In its 45-page report, the WHO expert mission acknowledges there remain gaps in understanding of COVID-19 transmission. Michael Ryan, WHO's executive director of health emergencies, said there are different dynamics in every country. In Singapore, a cluster of cases occurred in people attending the same conference; in Iran, it was a religious gathering; taken overall, most clusters have been in families. "Transmission is driven by the context," said Ryan.

The relatively high number of deaths among confirmed cases in Iran is probably due to the fact that only the most severe infections are being diagnosed at this point. "We need to understand the exact dynamics of what is happening in Iran," Ryan said.

It is important to put in place and maintain control measures, even if the result is only to delay the peak of an epidemic. That would help, even in advanced healthcare systems, which are likely to be running at full capacity currently in the northern hemisphere flu season. "Even slowing down by 1 month would be a benefit," Ryan said.
However, he questioned the rationale for closing borders within Europe, saying what is needed is good communication between states to stage a comprehensive and coherent public health response.

"We cannot shut down the world," said Ryan. "We need to focus on risk management and understand the virus may cause an outbreak or epidemics in any number of countries, but they can be managed." (Bai, Y. et al. JAMA 2020, Advanced publication).

25-Feb-2020

**Moderna releases novel coronavirus vaccine mRNA-1273 to NIAID for phase I trial**

Moderna has released the first batch of mRNA-1273, the company’s vaccine against the novel coronavirus, for human use. Vials of mRNA-1273 have been shipped to the National Institute of Allergy and Infectious Diseases (NIAID), a part of the National Institutes of Health (NIH), to be used in the planned phase I study in the U.S. mRNA-1273 is an mRNA vaccine against the novel coronavirus encoding for a prefusion stabilized form of the Spike (S) protein, which was selected by Moderna in collaboration with investigators at the NIAID Vaccine Research Center. Manufacture of this batch was funded by the Coalition for Epidemic Preparedness Innovations (CEPI) (Moderna News Release).

21-Feb-2020

**Chloroquine phosphate improves COVID-19-associated pneumonia in patients**

Efficacy against pneumonia associated with the coronavirus disease COVID-19, caused by the SARS-CoV-2 virus, has been demonstrated in patients by the malaria treatment chloroquine phosphate in clinical trials in China. Chloroquine blocked COVID-19 infection at low-micromolar concentrations in vitro (EC50 = 1.13 mcM, CC50 > 100 mcM). Chloroquine and hydroxychloroquine have since been evaluated for treating COVID-19-associated pneumonia in more than 10 hospitals in rapidly organized clinical trials in Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chongqing and Ningbo. In a news briefing, experts from the government and regulatory authorities and organizers of the clinical trials described results from over 100 patients showing that chloroquine phosphate was superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion and shortening the disease course. The patients did not have severe adverse reactions to chloroquine phosphate. The drug was recommended for inclusion in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People’s Republic of China (Gao, J. et al. BioSci Trends 2020, Advanced publication).

Further information on the clinical trials can be found at the Chinese Clinical Trials Registry.

Open access to a variety of news, tools and resources on the coronavirus outbreak from Clarivate Analytics can be found here.

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).

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).

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).
Suggested reading

Related websites

- Centers for Disease Control and Prevention (CDC) -- 2019 novel coronavirus, Wuhan, China
- Centers for Disease Control and Prevention (CDC) -- SARS information
- European Centre for Disease Prevention and Control -- Novel coronavirus
- European Commission - Public health - COVID-19 resources
- MEDLINEplus: Coronavirus infections
- Middle East respiratory syndrome coronavirus (MERS-CoV) (World Health Organization)
- National Institute of Allergy and Infectious Diseases
- NCBI web resource: Severe Acute Respiratory Syndrome (SARS)
- SARS information - Health Canada
- Severe acute respiratory syndrome (SARS) (World Health Organization)

Related articles

- 2019-nCoV resource centre (The Lancet)
- Coronavirus (The BMJ)
- Novel coronavirus (COVID-19) resource center (Center for Infectious Disease Research and Policy, University of Minnesota)
- SARS Reference by B.S. Kamps and C. Hoffman (Eds.)
- 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)


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)


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

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

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

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


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