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## EMERGING RESPIRATORY DISEASE - CORONAVIRUSES

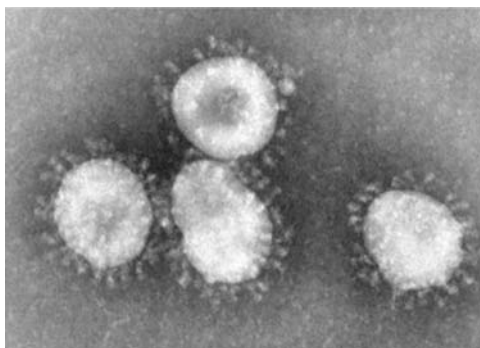
### CORONAVIRUSES – AN OVERVIEW

Coronaviruses (CoV) are a diverse group of viruses capable of infecting humans, and a wide range of animals. CoV affect multiple systems, and can cause respiratory, gastrointestinal, hepatic, and neurological illnesses, ranging from mild sickness to death. CoV are classified into multiple genera, including Alpha, Beta, Gamma and Delta coronaviruses. [1–10]. Of note, CoV seem to be able to adapt to new hosts and changing environments; this may be related to CoV ability to mutate and recombine [1,3,5,7], perhaps contributing to novel viruses with varying human pathogenicity.

Coronaviruses (order Nidovirales, family *Coronaviridae*, genus *Coronavirus*) are large, enveloped, single stranded, positive-sense RNA viruses, capable of infecting a variety of animals, including bats, mice, birds, dogs, pigs, cattle, and humans.

Identified many decades ago, Coronavirus (Figure 7 [9] – from the Latin *corona* (translation “crown” or “halo”) represents the appearance of CoV virions as they are viewed through an electron microscope [2,7–10]. The virus appearance is created by viral spikes (S), peplomers that populate the surface and determine host tropism (Figure 7) [8–10].

Fig. 7 Coronavirus. Centers for Disease Control and Prevention (CDC)/Dr. Fred Murphy [9].



Typically CoV are considered to be highly species-specific. In immunocompetent hosts, infection elicits the immune response of neutralizing antibodies and cell-mediated immune responses that attempt to kill infected cells [1,10,11].

Coronaviruses, members of the Coronaviridae family were identified and grouped based upon their serological cross-reactivity, and genomic sequence homology. Host ranges are diverse, and can include canines, felines, swine, mice, camels, bats, birds, and humans. [1,2,7,10–14]

Across the four genera of coronaviruses are Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus [2,5,10,11] there is a high frequency of recombination and rate of mutation which are believed to allow CoVs to adapt to new hosts and environments [3,11–16]. SARS CoV [2,5,6,17–34] is a good illustration of this; studies revealed it originated from animals – bats as the natural reservoir [5–8,10,11,25–27], and palm civet as the intermediate host [11–13]. This underscores the infection risk in human animal interactions – occupational, or adventure or travel, as well as environmental incursion and changing habits expected with climate change, which can pose significant risks to human, as well as animal health.

As an animal pathogen, coronaviruses can lead to highly virulent respiratory, enteric, and neurological diseases, in addition to hepatitis, resulting in epizootics of respiratory diseases and/or gastroenteritis. As a human virus the range of disease is broad, from cold like to severe multisystem involvement (These CoV infections are associated with short incubation periods (2–7 days), such as those found in SARS [2,5,6,17,18,24,25]. Several coronaviruses are capable of causing fatal systemic diseases in animals, including feline infectious peritonitis virus (FIPV), swine hemagglutinating encephalomyelitis virus (HEV), some strains of avian infectious bronchitis virus (IBV) and mouse hepatitis virus (MHV). These particular CoV can replicate in liver, lung, kidney, gut, spleen, brain, spinal cord, retina, as well as other tissues [2,7,13].

### SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS (SARS CoV, SARS)

According to the CDC, the first case of SARS CoV was reported in Asia in early 2003 [35]. Further investigation notes November 2002 the first case of an atypical pneumonia emerged in China (Guangdong Province) where ultimately the causative agent was determined to be a newly discovered coronavirus. By 2003 an epidemic of similarly severe, atypical pneumonias, was emerging from Hong Kong, Guangdong, and Toronto, Ontario. The following is the timeline of initial events that transpired referable to SARS CoV. On 11 February 2003 China reported to the World Health Organization (WHO) that 305 cases of atypical pneumonia of unknown etiology had been identified in Guangdong Province since 16 November 2002; five people had died. As of 21 February 2003 a physician from Guangdong Province, who was ill with an atypical pneumonia, travelled to Hong Kong, staying overnight in a hotel. The etiology causing his illness was identified as severe acute respiratory syndrome coronavirus (SARS CoV); it was likely transmitted to at least 10 additional persons. These transmissions/infections subsequently initiated outbreaks in Hong Kong, Singapore, Viet Nam, and Canada [20–24,35,36]

Symptoms characteristic of this aggressive atypical pneumonia included an onset of illness associated with high fever (temperature greater than 100.4°F [ $>38.0^{\circ}\text{C}$ ]), headache – often severe, an overall feeling of discomfort, and body aches, again often severe. Some persons may have had respiratory symptoms at the outset. Approximately 10% to 20% percent experienced diarrhea. After 2 to 7 days, SARS patients may develop a dry cough. Most patients develop pneumonia.

Given the prior outbreaks of highly pathogenic avian influenza in that same region of China, it was first considered to be an emerging flu virus. Other pathogens, including members of the *Paramyxoviridae* family, and human metapneumovirus (hMPV) were considered as causative of this new clinical illness which became known as Severe Acute Respiratory Syndrome or SARS. After international collaboration among multiple research facilities, a previously unknown pathogen was ultimately determined to be causative of SARS – a new coronavirus – SARS CoV [20–29].

While SARS CoV is a significant pathogen capable of causing profound illness, even death, historically coronaviruses were one cause of ‘the common cold.’ Known as endemic human betacoronaviruses HCoV-OC43 and HCoV-HKU1. Coronaviruses affecting humans (HCoVs) historically were associated with mild illness. Found in group 1 (HCoV-229E) and group 2 (HCoV-OC43) they are a widespread cause of **mild** respiratory illnesses [12], although occasionally these CoV cause serious infections of the lower respiratory tract in children and adults, including necrotizing enterocolitis in newborns [12–16].

Early research into the SARS Co-V genomic sequence demonstrated that this new CoV does not belong to any of the known groups of coronaviruses, previously described human coronaviruses HCoV-OC43 and HCoV-229E [20–24]. In fact it appears SARS CoV is only somewhat related to these HCoV. The SARS-CoV genome appears to be equidistant from those of all known coronaviruses. Moreover, SARS CoV closest relatives appear to be the murine, bovine, porcine, and human coronaviruses in group 2 and avian coronavirus IBV in group 1.

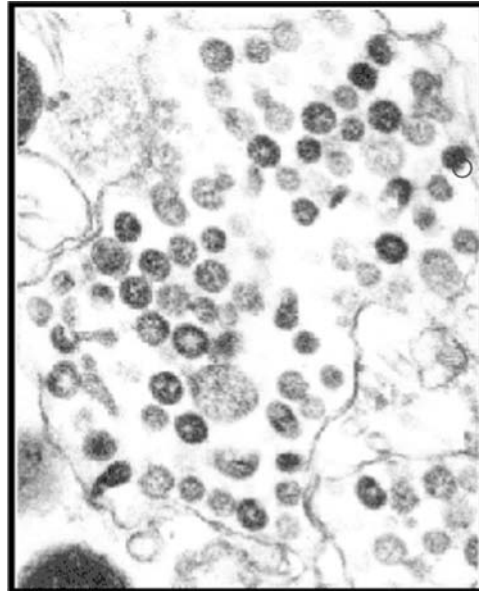
Research on the SARS CoV suggests this new virus represents a fourth group or lineage of coronavirus – Group 4 [23]. Genomic sequence analysis seems to support the hypothesis that of SARS-CoV is an animal virus for which the normal host is still unknown and that developed the ability to productively infect humans or has the ability to cross species barriers [25]. The genome shows that SARS-CoV is neither a mutant of a known coronavirus, nor a recombinant between known coronaviruses. As the virus passes through human beings, SARS-CoV maintains genotype, and is adapted to the human host [26]. Testing allows genetic analysis to distinguish different strains of SARS-CoV, allowing epidemiological studies [28].

Not surprisingly there are also economic, as well as health implications – coronaviruses cause important diseases in domestic animals, as well as in human populations. Toronto during and in the aftermath of their SARS outbreak saw a significant, albeit temporary decline in tourism and business related visits, as well as lost conference and trade show related

commerce. Recognizing the importance of animal – human pathogen crossover, opportunities to reduce the spread of contagion, and to identify potential risks is critical to prevent or at least reduce the likelihood of SARS, MERS, and influenza outbreaks such as the avian influenza outbreaks of the 1990's and early 2000's and the swine flu outbreak in 2009.

SARS Co-V (Figure 8) [37] can be detected in extracts of lung and kidney tissue by virus isolation or PCR; bronchoalveolar lavage specimens by virus isolation, electron microscopy and PCR; and sputum or upper respiratory tract swab, aspirate, or wash specimens by PCR [20,21,29]. SARS-associated coronavirus RNA was detected in nasopharyngeal aspirates by RT-PCR in 32% at initial presentation (mean 3.2 days after onset of illness) and in 68% at day 14 [30]. In stool samples, viral RNA was detected in 97% of patients two weeks after the onset of illness. 42% of urine samples were positive for viral RNA [30]. Viral RNA was also detected at extremely low concentrations in plasma during the acute phase and in feces during the late convalescent phase, suggesting that the virus may be shed in feces for prolonged periods of time [20,21].

Fig. 8 – SARS CoV – CDC National Center for Immunization and Respiratory Disease. Division of Viral Diseases [37].



The timelines of events as noted by CDC concluded towards the end of 2003 with removal of travel warnings to China and Ontario. By the end of 2003, according to the CDC report of WHO data, reports of SARS infections from 29 countries and regions revealed 8,096 persons with probable SARS resulting in 774 deaths – with an estimated case fatality rate just below 10% (higher in elderly, infirm patients). In the United States, eight SARS infections were documented by laboratory testing and an additional 19 probable SARS infections were reported. By 2004 the CDC issued a “Notice of Embargo of Civets” as a SARS-like virus had been isolated from civets (captured in areas of China where the SARS outbreak originated). CDC also banned the importation of civets. The civet is a mammal with a catlike body, long legs, a long tail, and a masked face resembling a raccoon or weasel. SARS CoV was detected in animal handlers of civets. The ban on civets is currently still in effect. By 2012 The National Select Agent Registry Program declared SARS-coronavirus a select agent. A select agent is a bacterium, virus or toxin that has the potential to pose a severe threat to public health and safety [32,35].

## TREATMENT

In spite of significant effort to develop countermeasures for coronaviruses, there are as of yet no licensed therapeutics that have shown consistent effectiveness against MERS CoV or SARS CoV. [38]. Intensive care – providing ventilator, circulatory and other organ system support to preserve renal, hepatic and neurological function, as well as prevention of secondary infection is critical. During the SARS CoV pandemic of 2003 immune based therapies have been tried, with equivocal results.

Ribavirin and interferon combinations showed some clinical improvements in non human primate studies, but unlike actual clinical experiences with MERS and SARS, where the illness, let alone treatment are rarely initiated rapidly after infection, the trials provided interventions soon after viral challenge [38–42]. During SARS CoV epidemics, various combinations of therapies were trialed [38–49], but no scaled, controlled approaches were conducted, making recommendations on current antivirals with or without interferon combination therapy, of concern, and questionable [38–47].

Ribavirin is a potent nucleoside analogue used with varying degrees of success against RNA viruses, but there is the potential for adverse side effects including hemolytic anemia, metabolic derangements. Interferon can also elicit adverse effects, although they have demonstrated value against viral infection [38–41].

Corticosteroids have been tried in SARS CoV infection – they resulted in increased viral load, admissions to intensive care unit, and mortality [43,44].

During SARS CoV, convalescent plasma, hyperimmune globulin were shown to be relatively safe, and possibly effective for reducing mortality [45–48]. Convalescent plasma, when administered within 14 days of illness, did decrease mortality in SARS CoV patients, according to one study [46]. They found this was a time critical issue – administration had to be given within a 2 week period. The challenge of course is in identifying cases and contacts rapidly and immediate utilization of such therapies for a chance at optimal effect. Donor supply, technical capacity in regions where SARS, MERS or other emerging threats are likely to occur, safety of end product and other challenges can limit the potential of this therapeutic option.

Monoclonal antibodies (mAbs) offer promise, and have demonstrated efficacy in the treatment of cancer and autoimmune diseases, as well as respiratory syncytial virus (RSV) [38,47,48]. Trials are ongoing to determine the use of mAbs for Ebola virus disease, HIV - primary and secondary prevention [38]. Unfortunately the costs, as well as research and development timelines are longer than for polyclonal antibody preparations. Nevertheless, in spite of rigorous testing, regulatory and cost issues associated with mAbs, their potential as therapies for MERS and other potentially deadly diseases continue to drive research in this area.

Antiviral research into adenine analogues that can disrupt viral RNA replication [50] are being developed as well as a nucleoside analogues with the potential to work against filoviruses, coronaviruses, and other RNA viruses [51].

Ideally an antiviral that covers a broad range of coronaviruses will be developed based upon the genetic sequence of these viruses and their life cycle. But the development of such an antimicrobial and other interventions still remains in the future.

Of note, extensive research is also being conducted towards developing vaccines. Towards that end, not unlike vaccines directed towards other pathogens, research has focused on viral structure [51,52], and replication mechanisms (Figure 9 [52])/(Table 1) [38].

Fig. 9 [52].

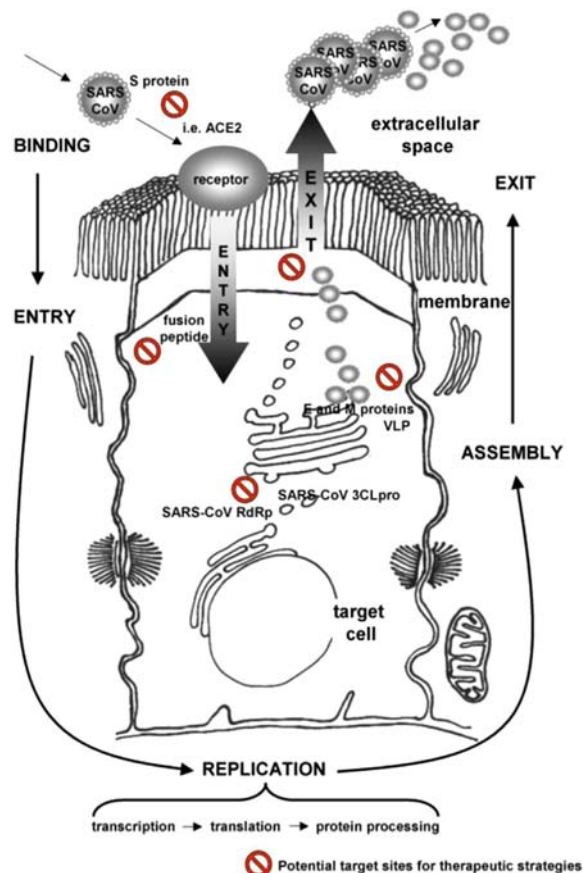




Table 1 Examples Of Anti CoV Therapeutic Strategies (Adapted 38, 51,52).

Mode of action	Drug
Virus entry blockers	Anti-S protein monoclonal antibodies Peptides that bind to the heptad repeat on the S (spike) protein Peptides that bind to other regions of S and block oligomerisation, etc.
Virus replication blockers	3C-like protease inhibitors Other viral protease inhibitors, e.g. papain-like cysteine protease nsp1–16 Viral polymerase inhibitors Nelfinavir, lopinavir/ritonavir, ribavirin, RNAi, glycyrrhizin, niclosamide
Immune modulators	Type 1 interferons Lopinavir/ritonavir

Table 2 Examples Of Vaccine Strategies For SARS CoV Adapted from Enjuanes et al. [34], Gillim-Ross et al. [54], Lin et al. [55] and Martin et al. [56].

Vaccine type	Animal studies	Induction of neutralizing antibodies/protection	Human trials
Inactivated virus	Mice	+	+
Subunit or expressed protein	Mice	+	–
Viral or bacterial expression vectors (S or N protein)	Mice, ferrets, primates	+	–
DNA vaccine (S, N, M protein)	Mice, primates	+	+
Live attenuated virus	Hamsters	+	–

Not surprisingly, as with other pathogens, such as Dengue [57–61] where there remain unknowns, such as protective immunity, cross protection against a variety of strains, and other technical difficulties, there are a variety of challenges to overcome in developing an effective vaccine against SARS or other coronaviruses. For example, in developing a live SARS CoV vaccine, it will be necessary to address the various coronavirus strains to recombine with each other, with the potential of attenuated parts of the genome being replaced with non-attenuated components of the genome, resulting in a pathogenic virus. One approach being considered is the use of reverse genetics; it may eliminate the risk of recombination between coronavirus strains [38,53–56,58,60,62].

As suddenly as SARS CoV emerged, it has seemingly gone quiescent. However another significant, and previously unknown or not described coronavirus respiratory disease has emerged.

In the next section the newest member of CoV discovered that causes human illness will be discussed. It is the Middle East Respiratory Syndrome Coronavirus (MERS-CoV, MERS), which is part of the beta group of coronaviruses.

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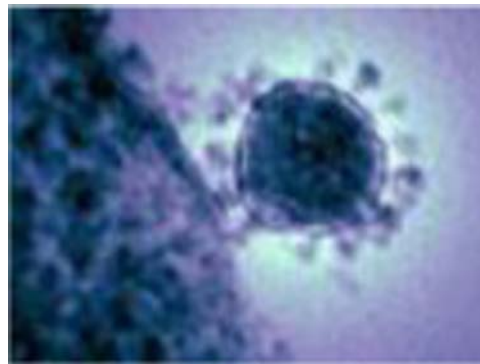
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## MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS – MERS, MERS CoV

Fig. 10 MERS CoV [1]. The National Institute of Allergy and Infectious Diseases (NIAID), this highly-magnified, digitally-colored transmission electron microscopic (TEM) image reveals ultrastructural details exhibited by a single, spherical-shaped Middle East Respiratory Syndrome Coronavirus (MERS-CoV) virion.



### BACKGROUND

In June 2012 a new CoV (Figure 10) [1] was isolated from a patient who died from severe pneumonia and multi-organ failure in Saudi Arabia [2,3]. This newly identified respiratory viral illness was caused by a novel coronavirus, which was initially designated as human betacoronavirus [2–5], but was eventually named Middle East Respiratory Syndrome Coronavirus (MERS CoV).

Reminiscent of, and worth considering as a caution for greater vigilance towards emerging pathogens, the suddenness that SARS CoV emerged as a new cause of severe pulmonary illness, has been replicated in this new aggressive respiratory illness MERS CoV. Unlike SARS CoV, it has not caused the thousands of cases over a short period of time. But it also differs from SARS CoV in that it carries a much higher case fatality rate, and causes more severe illness [6,7].

According to the World Health Organization (WHO) as of 12/05/16 there have been 1917 laboratory confirmed cases of MERS CoV since 09/12, reported from 27 countries (Maps 1 and 2), resulting in 677 deaths, yielding a significant case fatality rate (~35%) [6]; a fatality rate for a coronavirus that is significantly greater than that associated with SARS CoV Delta (~9%), at least among confirmed cases [6–8]. As with other CoV, including SARS CoV, the exact epidemiology, including whether there are larger numbers of mild illness, remains unknown. Males over 60 yrs of age seem to be at higher risk of severe disease symptoms and death among those infected. While the greatest spike in cases occurred near 2014, new cases continue to be reported. To date, since September 2012 there have been cases reported in 27 countries across 4 continents, with most human cases occurring in Saudi Arabia (Map 1 and 2) [6].