Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Severe Acute Respiratory Syndrome Coronavirus (SARS, SARS CoV)

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As discussed in an earlier section, coronaviruses are a diverse group of viruses capable of causing animal, as well as human disease; from mild illness (low pathogenicity coronaviruses), consistent with what is often referred to as "the common cold[1–14]," all the way to severe illness and death (highly pathogenic coronaviruses) from more recently identified SARS, MERS, and now COVID-19[15-34]. (Fig. 1).

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 °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.

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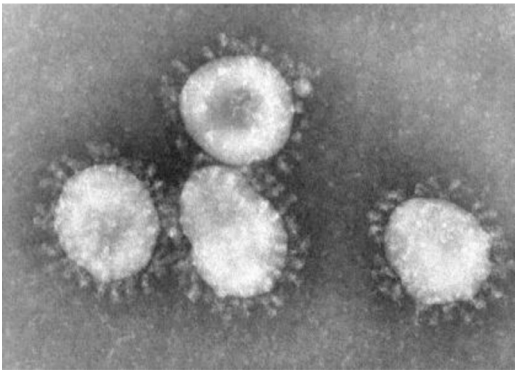

Fig. 1. Coronavirus. Centers for Disease Control and Prevention (CDC)/Dr. Fred Murphy[9].

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].

Whiles 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 beta-coronaviruses HCoV-OC43 and HCoV-HKU1. Coronaviruses affecting humans (HCoVs) historically were associated with mild illness. HCoV-229E and HCoV-OC43 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]. Human coronavirus OC43 (HCoV-OC43) seems to be more predominant than other HCoVs, at least until COVID-19, especially in children and the elderly. An interesting insight into coronavirus persistence, OC43 exhibits high nucleotide substitution rates. It has a capacity for genotype shift based on recombination of HCoV-OC43, which may be an adaptive mechanism allowing to remain a perennial background infection (36b). This level of genetic adaptation potentially poses an additional level of difficulty in vaccine development.

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

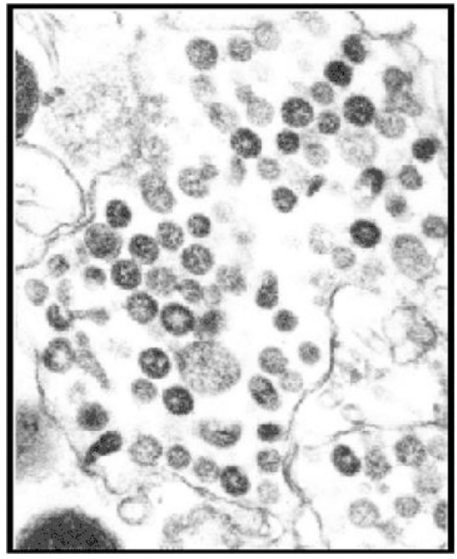

Fig. 2. SARS CoV – CDC National Center for Immunization and Respiratory Disease. Division of Viral Diseases[37].

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 early2000's and the swine flu outbreak in 2009.

SARS Co-V (Fig. 2)[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% of persons infected, 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].

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 8096 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].

Radiographic features SARS

SARS infection can result in rapidly progressive respiratory illness as Figs. 3–6 reveal[38–42]. Initial radiographic studies on chest XRays (CXR) (Figs. 3 and 4) often show small effusions, uni-

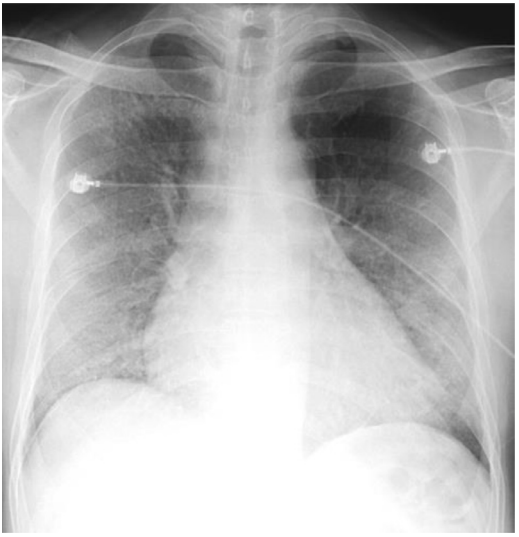

Fig. 3. (Left) CXR SARS Patient – Consider the extensive bilateral ground-glass opacities and poorly defined nodular pattern. In this case diffuse involvement Rt lung, Lt apical sparing. There is mild air-space consolidation is seen in retro-cardiac region of RLL. Mild cardiomegaly present[38,39].

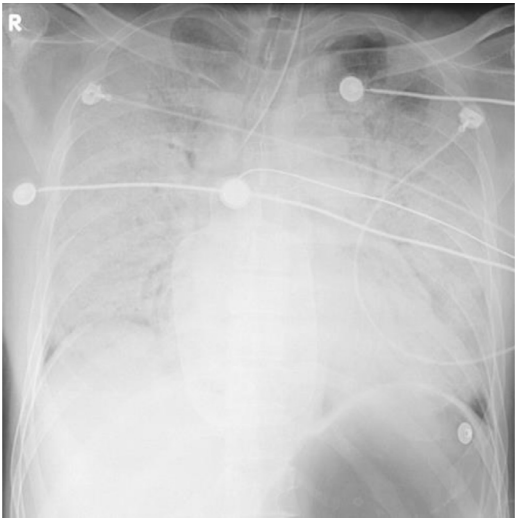

Fig. 4. (Right) Bedside supine AP CXR – same patient in Fig. 3, radiograph taken **12 hr after initial radiograph** – Note progressive disease in SARS patient, consistent with rapidly declining ARDS. Findings: diffuse bilateral air-space consolidation, prominent air bronchograms. **Clinical caveat**: note the low position of the endotracheal tube (ETT), and gaseous distention of stomach.[38,39].

lateral or bilateral patchy or confluent areas of consolidation, or ground glass opacities. Similar to other etiologies of ARDS, SARS can cause rapid progression of findings with both CXR and Chest CT (Figs. 5– 6) are common, and reflective of deteriorating lung function[38,39].

Of note, from the SARS, MERS, and especially early COVID-19 experience, chest CT scanning is an important modality to help characterize the extent of pulmonary disease. Typical findings include ground glass opacities, consolidation; in COVID-19 expect bilateral lung involvement.

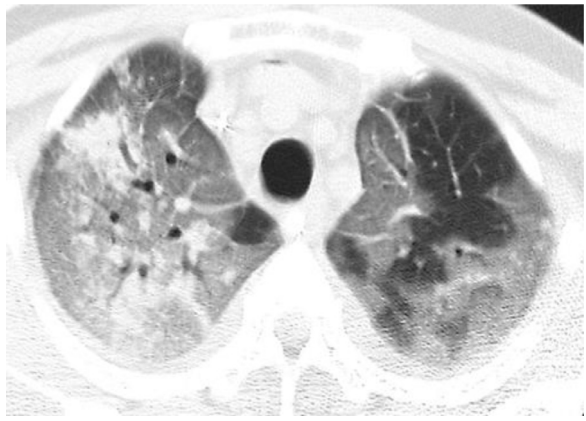

Fig. 5. CT Scan Transverse unenhanced image obtained at level of apical segments of upper lobes shows extensive bilateral areas of ground-glass attenuation, more severe on right, and focal areas of consolidation in right upper lobe. Note lobular areas of sparing particularly in left upper lobe[38,39].

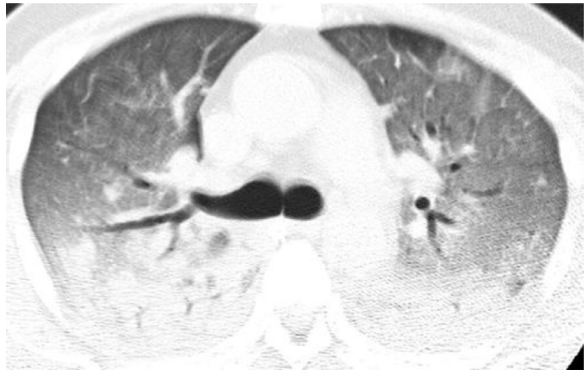

Fig. 6. CT image obtained at level of right upper lobe bronchus shows diffuse bilateral areas of ground-glass attenuation and dependent areas of consolidation (37b – 37e).

The imaging features of SARS and MERS, as well as COVID-19 not surprisingly overlap, but there are some differences (Table 1)[38–40]. According to various reports the initial chest XRays (CXR) will be abnormal in up to 80% patients infected and symptomatic with SARS[38-42]. Although it is demonstrated that COVID-19 has bilateral involvement in a significant proportion of patients, with SARS, initial imaging usually reveals abnormalities in one lung, with peripheral distribution and ill-defined areas of airspace opacity in the lower lung zones[38-42]. Focal findings on initial studies are found in ~50% patients, with multifocal findings in ~50%. Less than 10% of these studies reveal early diffuse involvement[38-42]. Subsequent imaging reveals in the majority of patients progressive multifocal consolidation over a course of 6–12 days, which may at that point involve one or both lungs. It has been noted that in ~25% of patients, visualized opacity will remain focal and unilateral[38-42].

CT studies often reveal patchy areas of ground glass opacity (GGO) and consolidation. Of note, centrilobular nodules and tree-in-bud opacities are not characteristic of the highly pathogenic coronavirus illnesses, possibly suggesting other atypical or opportunistic causes of pneumonia[38-42]. Radiologic improvement after recovery is expected in most patients. Poor outcomes are noted in patients with bilateral confluent diffuse airspace opacities, similar to the findings of acute respiratory distress syndrome, involvement of four or more lung zones, bilateral lung

Table 1
Comparison of clinical and radiologic features of SARS, MERS, and COVID-19[40].

Feature	SARS	MERS	COVID-19
Clinical sign Or symptom			
Fever or chills	Yes	Yes	Yes
Dyspnea	Yes	Yes	Yes
Malaise	Yes	Yes	Yes
Myalgia	Yes	Yes	Yes
Headache	Yes	Yes	Yes
Cough	Dry	Dry or productive	Dry
Diarrhea	Yes	Yes	Uncommon
Nausea or vomiting	Yes	Yes	Uncommon
Sore throat	Yes	Uncommon	Uncommon
Arthralgia	Yes	Uncommo	
Imaging finding			
Acute phase			
Initial imaging			
Normal	15–20% of patients	17% of patients	15–20% of patients
Abnormalities			
Common	Peripheral multifocal airspace opacities (GGO, consolidation, or both) on chest radiography and CT	Peripheral multifocal airspace opacities1660, consolidation, or both) on chest radiography and CT	Peripheral multifocal airspace opacities 1660, consolidation, or both) on chest radiography and CT
Rare	Pneurmothorex	Pneurmothorex	Pneurmothorex
Not seen	Cavitation or lymphadenopathy	Cavitation or lymphadenopathy	Cavitation or lymphadenopathy
Appearance	Unilateral, focal (50%)l; multifocal (40%); diffuse (10%)	Bilateral, multifocal basal airspace on chest radiography or CT (80%); isolated unilateral (20%)	Bilateral, multifocal, basal airspace; normal chest radiography findings (15%)
Follow-up imaging appearance	Unilateral, focal (25%); progressive (most common, can be unilateral *and* multifocal or bilateral with multifocal consolidation)	Extension into upper lobes or perihilar areas, pleural effusion (33%) interlobular septet thickening (26%)	Persistent or progressive airspace opacities
Indications of poor prognosis	Bilateral (like ARDS), four or more lung zones, progressive involvement after12 d	Greater involvement of the lungs, pleural effusion, pneumothorax	Consolidation (vs GGO)
Chronic phase			Unknown, but pleural effusion and interlobar septal thickening have not yet been reported
Transient reticular opacities[a]	Yes	Yes	
Airtrapping	Common I us u a I ly persistent)		
Fibrosis	Rare	One-third of patients	Not yet reported

Note—SARS = severe acute respiratory syndrome, MERS = Middle East respiratory syndrome, COVID,19 = coronavirus disease 2019. GG0 = ground-glass opacity, ARDS acute respiratory distress syndrome.
[a] Over a period Of weeks or months.

involvement, and progressive worsening of airspace consolidation on chest imaging more than 12 days after symptom onset despite treatment[38-42].

With MERS imaging, ~ 83% of patients have abnormal initial chest radiography studies. Multifocal airspace opacities in the lower lung fields are the most commonly reported findings in this patient population[38-42]. Abnormalities are noted to extend into other areas, notably the perihilar and upper lobes, associated with disease progression.

CT studies in MERS patients often involve bilateral lungs, where predominantly ground-glass opacities notably in the basilar and peripheral lung regions are seen. Be aware there can be isolated consolidation, interlobular septal thickening, and pleural effusion in MERS as well. Some studies suggest upwards of 20–33% of MERS infected individuals may have these findings. Tree-in-bud opacities and cavitation rarely have been reported. Lymphadenopathy does not seem to be characteristic of MERS infection on radiographic findings. Not surprisingly, pleural effusion, pneumothorax, and greater involvement of the lungs are associated with a poorer prognosis[38-42].

Information gained from SARS and MERS suggests that follow-up imaging should also be obtained in patients recovering from COVID-19[40]. There remains the potential for chronic involvement of the lungs; examples of which include interlobular thickening, air trapping, or fibrosis[38,40].

In terms of COVID-19, early evidence suggests that initial chest imaging will show abnormality in at least 85% of patients, with 75% of patients having bilateral lung involvement initially that most often manifests as subpleural and peripheral areas of ground-glass opacity and consolidation. Older age and progressive consolidation might suggest poorer prognosis. Besides the acute phase, CT is recommended for follow-up in individuals who are recovering from COVID-19 to evaluate long-term or permanent lung damage including fibrosis, as is seen with SARS and MERS infection[38,40].

It is worth noting in SARS, even with post infection recovery CT study may still show transient interlobular septal thickening and reticulation for several weeks to months[38-42]. Data suggest the reticulation observed usually appears ~ week 2, with peaking expected ~ week 4.[38-42]. Of concern, 1/3 of those patients who have persistent respiratory symptoms will have imaging findings of fibrosis, including interlobular and intralobular reticulation, as well as traction bronchiectasis. Although uncommon “honeycombing” has been seen. Air trapping, which is considered the result of damage to the ciliated respiratory epithelium, has been reported as a finding in ~92% of patients who have recovered from pneumonia. It portends chronic pulmonary involvement; these patients are less likely to have complete resolution of their infection[38-42].

Clinical experience with MERS suggests the majority of patients recover fully. However radiographic studies suggest ~33% of MERS survivors will have some evidence of lung fibrosis on follow-up imaging. Demographically, these patients were likely to be older, experienced prolonged ICU care, as well as more significant lung involvement in the acute phase of their illness[38–40].

Discussion

In spite of significant effort to develop countermeasures for coronaviruses, during the SARS and MERS outbreaks there were no specific licensed therapeutics, nor any identified that demonstrated consistent effectiveness against either of these[43]. The mainstay of medical care was symptomatic and supportive, often involving intensive critical care – providing ventilator, circulatory and other organ system support to preserve renal, hepatic and neurological function, as well as prevention of secondary infection. Newer approaches being trialed against SARS2 COVID-19 will be discussed in that section.

That said, among the available options, including the limited number of medications with potential antiviral capability, various combinations of therapies were trialed[43-54], but no scaled, controlled approaches were conducted, making recommendations on antivirals employed during the SARS outbreak, with or without interferon combination therapy, of concern, and questionable[43-52].

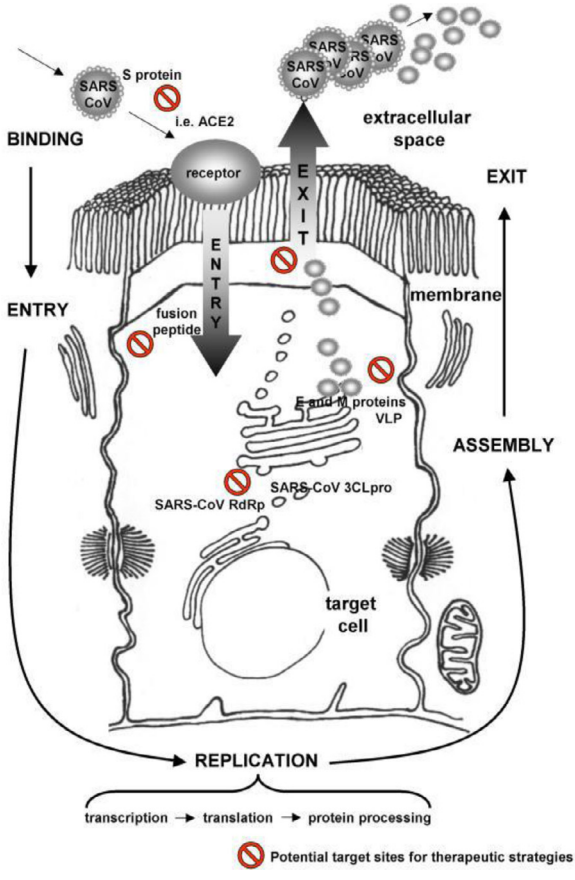

Fig. 7. Vaccine research focused on viral structure[56,57]

Immune based therapies were also administered, with equivocal results.

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 it has demonstrated value against viral infection[43-46].

One intervention that held promise however during the SARS CoV outbreak was the use of convalescent plasma; hyperimmune globulin was shown to be relatively safe, and possibly effective for reducing mortality[50-53]. 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.

Convalescent plasma is showing similar benefit with SARS-2 COVID – 19 patients. The challenges with convalescent plasma are several. First there is the need to identify cases and contacts rapidly, and second, the immediate utilization of such therapies for a chance at optimal effect. Donor supply, technical capacity to obtain and deliver convalescent plasma in regions where SARS, MERS, SARS2-COVID-19 or other emerging threats are likely to occur, safety of end product and other challenges can limit the potential of this therapeutic option.

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[56,57], and replication mechanisms (Fig. 7)[57]/(Table 2)[43].

Table 2
Examples Of Anti CoV Therapeutic Strategies (Adapted[43,56,57]).

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 3
Examples Of Vaccine Strategies For SARS CoV Adapted from Enjuanes et al., Gillim-Ross et al., Lin et al.[60] and Martin et al.[61]

Vaccine type	Animal studies	Induction of neutralizing anti-bodies/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[62-66] where there remain unknowns, such as protective immunity (Table 3)[34,59–61], 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[43,59–61,63,65,67]

The timelines of events as noted by CDC concluded towards the end of 2003 with removal of travel warnings to China and Ontario. 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].

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 early2000's and the swine flu outbreak in 2009.

As suddenly as SARS CoV emerged, it has seemingly gone quiescent. However, there are two new, highly pathogenic, and previously unknown or not described coronaviruses that have emerged.

Treatment

There are as of yet no FDA approved or licensed therapeutics that have shown consistent effectiveness against MERS CoV or SARS CoV[38]. The emergence of COVID-19 has led to a renewed interest in discovering antiviral treatments – either de novo medications created for this purpose, or repurposing existing medications with potential anti-coronavirus properties are being investigated. These will be discussed in the COVID-19 Therapeutics Section of this article.

To date, whether for SARS, MERS, or COVID-19, Intensive care – providing ventilator, circulatory and other organ system support to preserve renal, hepatic and neurological function, as well as prevention of secondary infection remain the mainstay of care, with early aggressive intervention being critical.

Other interventions, including repurposing currently available therapies were tried. Here are some examples:

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]. It has become apparent clinically, especially with certain potential antiviral treatments that this is a time critical step in the life cycle of the virus, as a consideration in medical intervention. This is true for other viruses, as there is often a narrow window of opportunity to interrupt the illness, such in the case with influenza and neuraminidase based therapies such as oseltamivir.

During SARS CoV epidemics, various combinations of therapies were trialed[43-54], but no scaled, controlled approaches were conducted, making recommendations on current antivirals with or without interferon combination therapy, of concern, and questionable[43-52].

Ribaviran 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[43-46].

Corticosteroids have been tried in SARS CoV infection – they resulted in increased viral load, admissions to intensive care unit, and mortality[48,49].

During SARS CoV, convalescent plasma, hyperimmune globulin were shown to be relatively safe, and possibly effective for reducing mortality[49–53]. Convalescent plasma, when administered within 14 days of illness, did decrease mortality in SARS CoV patients, according to one study[46,51]. 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 being able to initiate immediate utilization of such therapies for a chance at optimal effect. Some challenges exist with this approach, depending upon the region. These include donor supply, technical capacity in regions where SARS, MERS or other emerging threats are likely to occur, safety of the end product and other challenges can limit the potential of this therapeutic option. The World Health Organization, and Centers for Disease Control maintain consulting expertise and guidance to assist with these challenges.

Table 4
Examples Of Anti CoV Therapeutic Strategies (Adapted[43, 55–57]).

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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

Monoclonal antibodies (mAbs) offer promise, and have demonstrated efficacy in the treatment of cancer and autoimmune diseases, as well as respiratory synctial virus (RSV)[43,52,53]. Trials are ongoing to determine the use of mAbs for Ebola virus disease, HIV - primary and secondary prevention[43]. 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[56].

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[56,57], and replication mechanisms (Fig. 7)[57]/(Table 4)[43].

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[43,59–61,63,66,67].

Also the question of immune response with SARS, MERS, and COVID-19 remain to be answered, including the sustainability of protection – either through surviving infection, or via vaccination[63,68,69].

Unlike influenza which is an annual, recurring virus, or the low pathogenic coronaviruses, which are among several pathogens associated with “the common cold” and which seems to linger as a background infectious agent, 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 another highly pathogenic CoV was discovered that causes human illnes the Middle East Respiratory Syndrome Coronavirus (MERS-CoV, MERS), which is part of the beta group of coronaviruses, and carries a more significant case fatality rate than any coronavirus before it (~30%) . The last sections of this edition will discuss various aspects of the newest highly pathogenic coronavirus – one that shares clinical similarities with the first SARS coronavirus, but

seems to cause a more diverse range of sickness, including extrapulmonary disease, and noted as SARS CoV2, or COVID-19[68].

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