

## Chapter

# Severe Acute Respiratory Syndromes and Coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV-2)

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## Abstract

The current SARS-CoV-2 (coronavirus) outbreak has reached pandemic proportions with a large global imprint. In December 2019, COVID-19 was first reported in Wuhan, Hubei Province, China and has continued largely unabated. The SARS-CoV-2 (coronavirus) is much talked about currently; however, it is worth noting that there are several different coronaviruses known to man, with most of them being responsible for causing illness in animals. Seven (7) types of coronaviruses are identified as causing illnesses in humans. Of the seven human coronavirus infections, four involve mild upper respiratory tract complaints that produce slight symptoms of the common cold. Conversely, the other three human coronavirus infections present more severe consequences as recently demonstrated by the SARS-CoV-2. These deadly outbreaks of pneumonia can have consequences that are far-reaching and are global in nature. SARS-CoV was the first new viral pandemic of the 21st century. It had its beginnings in southern China during November 2002 having started mysteriously; It was contained in 2004 after having spread to five continents and thirty-three countries, infecting approximately 8000 people. MERS-CoV the virus that causes Middle East respiratory syndrome (MERS) was first identified in 2012 in Saudi Arabia and Jordan and has since registered roughly 2,220 confirmed cases and 790 deaths.

**Keywords:** Coronavirus, SARS-CoV, CoVid-19, SARS-CoV-2, MERS-CoV, Pandemic

## 1. Introduction

Coronavirus (CoV) is one of the leading pathogens primarily targeting that the human respiratory system [1]. Earlier outbreaks of coronaviruses include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which have been formerly considered as a serious threat to public health [2]. The first iteration of coronavirus was identified in the mid-1960s and categorized into four separate subfamilies:  $\alpha$ - $\beta$ - $\gamma$ - $\delta$ -Coronavirus. Alpha and beta-coronaviruses predominantly causes infection in mammals, whereas gamma and delta-coronaviruses primarily infect birds [3]. A new contagious coronavirus is presently holding much of the worldwide population hostage. This virus,

SARS-CoV-2, which causes the COVID-19 disease, emerged in Hubei, China and has spread to most countries with ongoing devastating effects [4].

Since the era of the pneumonic plague, emergent respiratory infections have enthralled the scientific and Public communities' and more recently have manifested in popular films depicting airborne viral outbreaks [5]. This has led to deliberations pertaining to the possibility for respiratory spread of these infections [6]. Although numerous emerging agents can exhibit respiratory involvement, this chapter will focus on emerging pathogens that involve the respiratory system and focus on 3 agents that exhibit a range of characteristics of emerging diseases: SARS-CoV, MERS, and SARS-CoV-2.

## **2. SARS-CoV**

### **2.1 Etiology, epidemiology, and clinical presentation**

Severe acute respiratory virus (SARS) is a deadly pulmonary infection caused by the SARS coronavirus (SARS-CoV), first reported in Guangdong Province, China, in November 2002 [7]. The emergence of SARS-CoV signaled the first time the public, as well as numerous scientists, observed this cluster of viruses, and its potential to cause severe infections and death in humans [8]. By July 3, 2003, SARS global infections were 8439 cases of which 812 were fatal [9]. This prompted a full-bodied international response estimated at roughly 40 billion dollars which aided in containing the outbreak [10]. By the close 2004 there were no new reported cases [9, 10]. Genetic classification indicates that the introduction into the human population took place from civets or other mammals found in live-animal markets of China [9]. Furthermore, it is prevailingly considered that SARS-CoV originated in a colony of horseshoe bats in southern China, with civets acting as the intermediate amplifying and transmitting host to humans [11].

## **3. SARS-CoV infection in humans**

**SARS-CoV** is an airborne virus transmissible between humans through small respiratory droplets, in a similar manner to influenza [6]. SARS-CoV can also be spread indirectly via surfaces that have been touched by someone who is infected with the virus, and by close interactions with infected individuals acting as so-called "super spreaders" [6]. The incubation period of SARS-CoV is generally 2–7 days, but infected persons may present symptoms as long as 10 days after infection [6]. Several epidemiological studies conducted during the outbreak identified numerous deaths occurring disproportionately among the elderly, and individuals who were immunosuppressed. At the onset of SARS-CoV illness, patients present with flu-like symptoms typically non-specific, with mild respiratory symptoms identified as most common in some cases, while other symptoms included rash, malaise, fever, and myalgia [12, 13]. Approximately 70% of the SARS-CoV patients experience shortness of breath and lingering or persistent fever, while clinical improvements were observed in 30% patients after the first week [14]. Intensive care treatments such mechanical ventilation was required by about 20 to 30% of SARS-CoV patients [14, 15]. Individuals 12 years of age and younger displayed limited severe disease manifestations [6, 13, 16]. Prognostic studies indicate greater risk of severe outcomes associated with increased age, high pulse, and lactate dehydrogenase (LDH) levels [7, 17, 18].

#### 4. Pathological changes and clinical diagnosis in SARS-COV infection

Histopathologic data existing on SARS-CoV patients have been mostly determined from autopsy cases. Pathological lesions in certain organs of SARS-CoV victims, such as the lungs and intestines, have been extensively studied [1, 4]. The primary pathological change in SARS-CoV patients occurs in the lungs [4, 6]. Gross examination of the lungs revealed edematous, heavy lungs weighing up to 2100 g with several areas of extensive consolidation (**Figure 1**) [1, 4].

Histopathologic data for SARS-CoV of infected lungs characteristically displayed diffuse alveolar damage [DAD] [19, 20]. Through the initial period of the disease (7 to 10 days), SARS lungs exhibited the following characteristics of acute exudative DAD: 1) Widespread edema, 2) desquamation of alveolar epithelial cells, 3) formation of hyaline membrane, 4) collapse of alveoli, and 5) fibrous tissue in alveolar spaces (**Figure 2**) [6, 12, 19, 21, 22].

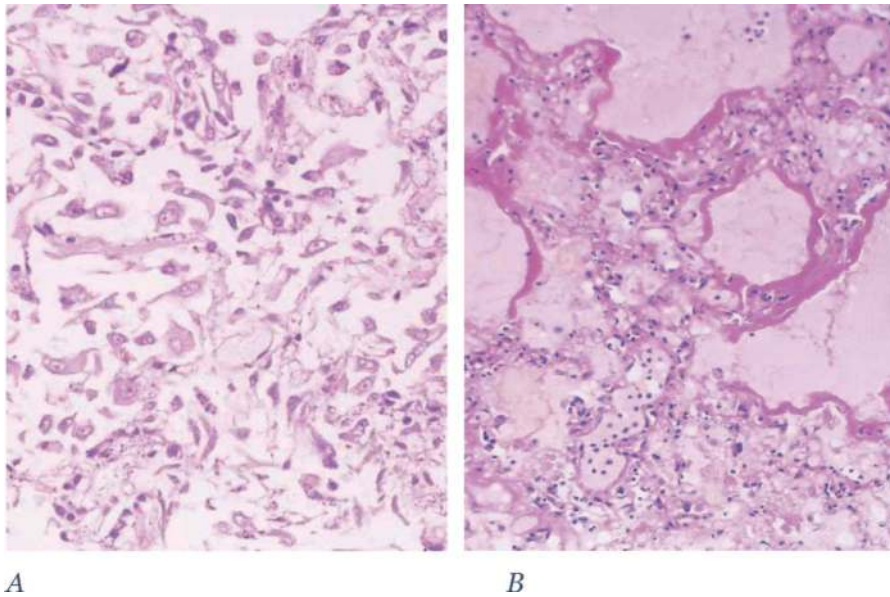
In SARS cases of lengthier disease duration, fibrous organization features of DAD were visible after approximately 10–14 days. These features included interstitial and airspace fibrosis and pneumocytic hyperplasia [12, 23, 24]. The more extensive the disease period, the more widespread the fibrous organization of the lung tissue [14, 25, 26]. Dense septal and alveolar fibrosis were exhibited in SARS cases with duration of more than 2 to 3 weeks [12, 19, 23, 24]. The overall histological data presentation of SARS lung infection is non-specific and dependent on symptom onset; Acute DAD is most frequently associated with early phase disease (<10 days) [6, 27]. Furthermore, there is limited documentation on the pathologic demonstration of SARS-CoV in living patients, since the bulk of patient tissue samples were taken from autopsy [1, 4, 6].

The predominant changes involving SARS-CoV cases have been visceral and involve severe pulmonary changes [1, 19]. Accurate and easily implementable diagnostics formed an essential part of SARS-CoV disease control, due to the non-specific nature of the infection and its rapid spread. Following the initial disease outbreak, many laboratories rapidly developed SARS-CoV reverse transcription polymerase chain reaction test (RT-PCR) analyzes, to detect viral RNA. These tests have numerous advantages over traditional RT-PCR tests [28].

Real-time RT-PCR assays use amplification primers and internal probes as a result, can be designed to be extremely precise for SARS-CoV RNA [6]. Real-time



**Figure 1.**  
SARS gross morphology of the lung [19]. Images ©John Wiley and Sons Ltd. as cited.



**Figure 2.**  
(A) Alveoli filled with desquamated epithelial cells. (B) Formation of hyaline membrane (H&E, original magnification  $\times 200$ ).

RT-PCR analyzes can be extremely sensitive, with steady detection limits of between 1 and 10 SARS-CoV RNA copies per reaction [6, 29]. They can be completed quicker than traditional RT-PCR analyzes with reduced risk of contamination in the laboratory. Real-time RT-PCR assays often times give a very accurate estimate of the viral load present in a sample [29].

## 5. MERS-CoV

### 5.1 Etiology, epidemiology and clinical presentation

The Middle East respiratory syndrome coronavirus (MERS-CoV or MERS) was first identified in September 2012 in a fatal case of severe respiratory failure in a Saudi Arabian patient [30, 31]. Previous cases were retrospectively acknowledged from an outbreak of severe respiratory illness in Jordan in 2012 [32]. In contrast to the rapid spread and subsequent latency of SARS-CoV, MERS-CoV has moved continuously through the Arabian Peninsula and generated sporadic outbreaks in countries where infected persons have traveled [6]. As of January 2020, there have been 2519 laboratory-confirmed cases of MERS, and 866 associated deaths (case-fatality rate: 34.3%) reported globally [32].

A significant number of cases has been identified in Saudi Arabia and to a lesser extent the United Arab Emirates (UAE), Qatar and Jordan [33]. While the close relationship to numerous bat coronaviruses suggests a bat-related origin, overwhelming molecular and serological evidence points to the involvement of dromedary camels in the transmission of MERS-CoV to a human host [34]. While transmission from ancestral bats to camels cannot be excluded, and camels may have introduced the virus into human populations, the majority of reported MERS-CoV cases have ensued from human-to-human nosocomial transmission [6, 33].

A hospital outbreak was reported in Saudi Arabia with a cluster of six cases; Three of the cases were healthcare workers, two were patients (one of whom died) and one was a visitor. Another instance involved an ill patient admitted to a Korean

hospital which led to an outbreak of 186 infections including 36 fatal cases [35]. Person-to-person transmission has also been identified within households, where the highest risk of transmission involves patient respiratory secretions and individuals being within close proximity with each other. Individuals exhibiting signs and symptoms or other epidemiological characteristics suggestive of MERS should be promptly quarantined and tested for viral infection [32, 35].

## **6. MERS-CoV infection in humans**

The clinical manifestation for MERS-CoV infection varies from asymptomatic/mild to severe disease. Generally, individuals with chronic comorbid conditions (diabetes, heart disease) and elderly patients are at increased risk for development of respiratory failure [35]. Although infection is commonly associated with respiratory disease, in some rare cases viral RNA has been discovered in blood, stool and urine signifying a systemic infection [33, 35].

Notwithstanding the increased mortality related to symptomatic cases, research studies have shown that roughly 25% of patients infected with MERS-CoV are asymptomatic [36]. A seroepidemiological analysis of over 10,000 infected samples from Saudi Arabia revealed positive antibodies in approximately 0.15% of patients. Individuals with some level of camel-exposure had an increased likelihood of positive serology [33, 35]. Clinical symptoms are non-specific, and patients have reported an expansive range of diverse indicators including chest pain, fever, cough, myalgia, sore throat, shortness of breath, vomiting and diarrhea [32]. In more severe cases, mechanical ventilation is required for patients who are presented with acute hypoxic respiratory failure [15, 31]. Fatal outcome of MERS-CoV infection have been associated with underlying comorbidities such as hypertension, diabetes mellitus type II, obesity, and cardiac disease [37]. MERS-CoV infection has an incubation period that ranges from 2 to 14 days [30]. Signs and symptoms usually appear well before the patient reaches a detectable viremia i.e. the virus is present in the patients' bloodstream [30, 37]. Neurological sequelae, and gastrointestinal distress have also been documented in addition to these respiratory symptoms [37].

## **7. Pathological changes and clinical diagnosis in MERS-COV infection**

The understanding of the pathological findings related to MERS-CoV infection have relied on a paucity of autopsy cases. Notwithstanding the limited number of autopsy cases, several studies have assessed the pathological features of MERS-CoV infection in human tissue. The pathogenesis of MERS-CoV infection in human tissue *ex vivo* revealed exudative diffuse alveolar damage (DAD) with hyaline membranes, interstitial pneumonia (which was primarily lymphocytic), pulmonary edema, multinucleate syncytial cells, and type II pneumocyte hyperplasia [38]. Researchers also observed bronchial submucosal gland necrosis in diseased lung tissue, where these bronchial lesions make up the pathologic origin for respiratory failure and radiologic anomalies of MERS-CoV infection [38]. Some of the cells in the lungs targeted by the MERS-CoV infection include: pneumocytes, multinucleated epithelial cells, and bronchial submucosal gland cells [39]. Microstructurally, viral particles were discovered in the pulmonary macrophages, pneumocytes, renal proximal tubular epithelial cells and macrophages infiltrating the skeletal muscles [38, 40]. Consistent with the microstructural results in the kidney, renal biopsies revealed acute tubulointerstitial nephritis and acute tubular sclerosis with proteinaceous cast formation [40].

Researchers discovered comparable replication of kinetics and cellular tropism in a study comparing the replication of camel-isolated MERS-CoV strains to human-isolated MERS-CoV strains. Non-ciliated bronchial epithelium and alveolar epithelial cells including type II pneumocytes were infected by all strains. It is important to note that no infection of the pulmonary macrophages was present [39]. Infection of several cell types including vascular endothelial cells, renal tubular cells, and podocytes was established in studies examining kidney explants [41]. Exploratory infection of small intestine tissue samples with MERS-CoV confirmed that infection was restricted to the surface enterocytes and formation of syncytial cells [6]. It has been observed that infected patients shed virus in their urine and stool, which is consistent with these findings.

RT-PCR has functioned as the main clinical laboratory diagnostic test throughout transmission events. Critical to the success of these tests is an understanding of the viral kinetics and tissue tropism discovered in MERS-CoV cases. Numerous studies have acknowledged that lower respiratory tract samples contain the highest viral loads, while upper respiratory swabs, whole blood or serum, feces, and urine may also contain significant viral load [35]. Samples from the upper respiratory tract, urine and blood may offer further diagnostic usefulness by delivering a convenient sample type, notwithstanding 10 to 100 times lower virus levels. Measurable viremia at the point of diagnosis has been linked with an increase in patient death due to the necessity for mechanical ventilation, despite blood only being positive in approximately one-half to one-third of cases [42]. The reduced viremia rate in MERS-CoV samples in comparison to SARS-CoV is significantly different, where RT-PCR on blood can be beneficial for preliminary diagnosis and is normally the primary positive site identified. Analyses of upper and lower respiratory samples as well as blood samples for MERS-CoV patients, has shown that it may benefit in maximizing the sensitivity while also stratifying risk [34]. Two RT-PCR testing approaches were approved for emergency use authorization by the FDA during the MERS-CoV outbreak: both targeted a region upstream of the envelope gene (principal target of the humoral immune response). Of these two tests, one additionally targets a specific region of the ORF1a gene, while the other targets two regions inside the nucleocapsid gene [6].

MERS-CoV serology tests share comparable kinetics to that of SARS-CoV infections. About 2–3 weeks following the onset of symptoms, a significant number of patients develop measurable levels of IgM and IgG antibodies. However, in many cases the detection of IgG has superior diagnostic value when compared to IgM [34]. Some researchers posit that if serologic testing is used to detect current infection, “a neutralization assay and 4-fold increase in titer after 14 days should be used to confirm a specific immune response” [6, 42]. Disease severity may affect antibody responses as numerous studies have established; PCR-positive patients exhibiting only mild disease symptoms often do not generate measurable quantities of antibodies, especially when monitored during the post-acute phase of disease [34].

## **8. SARS-CoV-2**

### **8.1 Etiology, epidemiology, and clinical presentation**

The coronavirus (SARS-CoV-2) (also known as the novel coronavirus) outbreak has reached pandemic proportions with a large global footprint [43, 44]. In late December 2019, SARS-CoV-2 was first reported in Wuhan, Hubei Province, China among clusters of patients with pneumonia of unknown etiology [43, 44]. In early

January 2020, the National Health Commission of People's Republic of China released information regarding the causative agent of an enigmatic pneumonia identified as a novel coronavirus (SARS-CoV-2). The novel coronavirus (SARS-CoV-2) was verified by several independent laboratories located in China [45, 46]. The World Health Organization (WHO) provisionally named the causative virus as 2019 novel coronavirus [2019-nCoV/SARS-CoV-2] [46]. Coronaviruses are known to cause respiratory, hepatic, and neurologic diseases and are generally spread among humans and animals [3]. The SARS-Cov-2 virus is illustrated by a spherical shape, and a characteristic "crown" appearance, and they belong to the family of coronaviruses of positive-stranded RNA viruses [47].

Genetically, SARS-CoV-2 has a closer resemblance to SARS-CoV than the Middle East respiratory syndrome coronavirus [MERS-CoV] [48]. Nevertheless, the span of the incubation period, clinical severity, and transmissibility of SARS-CoV-2 differs from SARS-CoV [49]. Public health and government efforts aimed at curbing the spread by implementing social practices through social distancing, mask wearing, isolating/quarantining and non-pharmacological and preventive treatments for psychophysical wellbeing, has been relatively successful in part, but SARS-CoV-2 has continued to increase globally [50, 51]. By the end of January 2021, SARS-CoV-2 accounted for more than two million deaths and more than 100 million confirmed cases of the disease [52]. Radiologically, SARS-CoV-2 has distinctive imaging features that constitute a visual identity. Besides, SARS-CoV-2 negatively impacts other organs in addition to the lungs. As a result of these developments, SARS-CoV-2 has grown exponentially with nearly 2000 articles being published per week [50].

## **9. SARS-CoV-2 infection in humans**

SARS-CoV-2 infections are variable in nature, with some infections being asymptomatic with others causing minor to moderate illness with respiratory and flu-like symptoms, including sore throat, fever, chills, and cough [53]. Injury, inflammation and ensuing respiratory distress in SARS-CoV-2 patients occurs as a result of the SARS-CoV-2 spike protein binding to human angiotensin I-converting enzyme 2 (hACE2) predominantly targeting the virus to type II pneumocytes inside the lung [54, 55]. A substantial number (approximately 20%) of patients also develop severe infection and multi-organ failure which necessitates intensive care with mechanical ventilation or extracorporeal membrane oxygenation [50, 53]. In some cases, SARS-Cov-2 infection can be deadly, with a case fatality rate of ~5%. The incubation period of SARS-CoV-2 is generally 5–7 days, but the symptoms of infection may present itself well after that period [56]. The phase from the onset of symptoms to fatality usually varies from 7 to 40 days with a median of 14 days [57]. This phase is dependent on the patients' age, and the status of their immune system.

Similarities in the symptoms between SARS-CoV-2 and earlier beta-coronavirus such as fever, dry cough, and dyspnea are distinctive [50]. However, there are distinctive features presented by SARS-CoV-2 which involves affecting of the lower airway as evident by upper respiratory tract indicators like sneezing, rhinorrhoea, and sore throat [58]. Additionally, chest radiograph results taken upon admission, show an infiltrate in the upper lobe of the infected lungs, associated with increased difficulty breathing (dyspnea) resulting in low levels of oxygen in the blood (hypoxemia) [58]. Notably, while most SARS-CoV-2 patients exhibit gastrointestinal symptoms like diarrhea, very few MERS-CoV or SARS-CoV patients show similar gastrointestinal concerns. Thus, testing fecal and urine samples to exclude a potential alternative route of transmission among patients and healthcare workers [57].

## **10. Pathological changes and clinical diagnosis in SARS-CoV-2 infection**

Nasal droplets and saliva from infected patients function as the leading route of SARS-CoV-2 virus communicability [59]. According to Heydarloo et al., the virus accesses the alveolar-type 2 cells (AT2 cells) by attaching its viral spike (S1 and S2) proteins to the angiotensin-converting enzyme 2 (ACE2) receptor [60]. Researchers found that previous iterations of coronaviruses specifically SARS-CoV, replicated more aggressively in alveolar-type 2 cells than in alveolar type 1 cells in the lung [38]. This is significant since it has been reported that there is an 80% genetic similarity between the SARS-CoV and SARS-CoV-2 viruses [61]. SARS-CoV-2 has an extraordinary potential for binding with AT2 cells in the lungs as shown via molecular pathways [62].

The SARS-CoV-2 pandemic continues to affect much of the world and understanding its clinical diagnosis is important. Data on diagnostic testing for SARS-CoV-2 is still in its infancy, as such, understanding these tests and interpreting their results is imperative. The most frequently administered and dependable test for SARS-CoV-2 diagnosis thus far, has been the RT-PCR test completed using nasopharyngeal swabs. In some cases, alternative upper respiratory tract samples, comprising throat swabs and/or saliva have been used. Individual companies focus on a variety of RNA genes, with a significant number of tests affecting 1 or more of the envelope, RNA-dependent RNA polymerase (RdRp), and ORF1 genes [63].

In most SARS-CoV-2 patients with symptomatic infection, viral RNA in the nasopharyngeal swab becomes detectable as early as day 1 of symptoms and peaks within the first week of symptom onset. The cycle threshold (Ct) that is used to measure viral RNA, can be defined as “the number of replication cycles required to produce a fluorescent signal, with lower cycle threshold values representing higher viral RNA loads” [63]. A PCR positive is typically clinically reported as a Ct value of less than 40. By week three of infection, there is usually a decline in this positivity and subsequently becomes unnoticeable. In severely ill hospitalized SARS-CoV-2 patients, the cycle threshold values are lower than the cycle threshold values recorded in less severe cases. It is important to note, a “positive” PCR result reveals only the recognition of viral RNA and does not automatically suggest presence of viable virus [62]. It has been reported in a minority of positive test cases that viral RNA was detected by RT-PCR past week six. There have also been instances of a positive result being reported after consecutive negative PCR tests completed two days apart. Currently, it is unclear whether this is a testing error, reinfection, or recurrence.

SARSCoV-2 infection can also be identified indirectly by assessing the patients' immune response to infection. In patients who exhibit mild to moderate symptoms, serological diagnosis becomes extremely important past the first two weeks of illness onset. Serological diagnosis is an essential means of understanding the scope of SARSCoV-2 infection in the community and may assist in identifying individuals who are immune/protected from infection.

## **11. Conclusion**

Wide-ranging efforts to decrease transmission of SARSCoV-2 infection are crucial to controlling the present epidemic. Lessons learned from the SARS-CoV and MERS-CoV outbreaks offer, valuable experiences and insights into how to fight the SARSCoV-2. Specific consideration aimed at decreasing spread must be applied in vulnerable populations specifically health care workers, and the elderly. Additionally, research into the pathogenesis of human coronavirus infection is crucial for finding suitable therapeutic objectives. Presently, no specific antiviral drug is available for SARS-CoV, MERS, and SARSCoV-2.



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