

## REVIEW ARTICLE

### COVID-19, MERS and SARS; Understanding Similarities and Differences

Kinza Waqar, Maham Zahid

#### ABSTRACT

Severe acute respiratory syndrome corona virus (SARS-CoV), Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are members of the corona virus family that have been implicated for epidemics and deaths globally. These viruses have similar structural features and pathogenesis, yet are different in terms of genome sequence, coat protein and infectivity. There are no proven treatments or vaccines for previous epidemics caused by MERS COV and SARS CoV and the infection spread by SARS COV-2 has been more pronounced as compared to the other two. So far, the spread of SARS CoV 2 can be prevented by social distancing and treated with supportive therapies. This article reviews the three corona viruses and draws comparison between their features to better understand the disease process.

**Key Words:** COVID-19, MERS CoV and SARS CoV, SARS CoV-2.

**How to cite this:** Waqar K, Zahid M. COVID-19, MERS and SARS; Understanding Similarities and Differences. *Life and Science*. 2020; 1(suppl): 107-113. doi: <http://doi.org/10.37185/LnS.1.1.139>

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#### Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a member of Coronaviridae family of the order Nidovirales. It is a positive sense, single stranded RNA virus. This family is further subdivided into alpha, beta, gamma and delta corona viruses.<sup>1</sup> These are large RNA viruses and genome ranges from 26-32 kilobases. These viruses have wide distribution which enables them with widespread infectivity. They occur naturally in livestock, birds and mammals such as cats, mice, dogs, civets, bat and camels.<sup>2</sup> The human pathogenic types of the virus cause only mild disease but there are a few exceptions such as outbreak caused by Middle East respiratory syndrome corona virus (MERS CoV) in 2012. The respiratory illness, first emerged in Saudi Arabia resulted in 2,494 cases and 858 deaths. The other notorious corona virus is the severe acute respiratory syndrome corona virus (SARS-CoV) that caused the severe acute respiratory syndrome

(SARS) outbreak in Guangdong, China in 2002-2003. The disease escalated quickly, spreading to 37 countries and caused 8,000 infections, and 774 mortalities.<sup>3</sup>

The initial cases of the latest outbreak by the novel corona virus, SARS CoV-2 were reported in Wuhan, China in late December 2019 where large number of patients presented with pneumonia of unknown cause. On March 11, 2020, World Health Organization (WHO) declared the novel coronavirus outbreak a pandemic.<sup>4</sup> The sequencing of the virus revealed it to be new kind of corona virus which was named 2019-nCoV (3) however the committee on taxonomy of viruses later named it SARS CoV-2.<sup>5</sup> WHO named it coronavirus disease (COVID 19) pertaining to its massive infectivity across the globe a potential public health threat. As of April 14th 2020, 11,500,302 confirmed cases, and 535,759 deaths from 216 countries, areas or territories have been reported.<sup>6</sup> The highest number of cases appeared in the Americas accounting to 5,915,551 confirmed cases and 266,736 deaths.<sup>7</sup>

#### Morphology, structure and replication

Coronaviruses are the largest RNA viruses. They occur naturally in many animal species. They cause infection of the respiratory, gastrointestinal, nervous and hepatic system. The spike glycoproteins on the enveloped structure of the virus gives them a crown

Department of Department of Clinical Trial Unit  
National University of Medical Sciences, Rawalpindi  
Correspondence:

Ms. Kinza Waqar

Department of Clinical Trial Unit  
National University of Medical Sciences, Rawalpindi  
E-mail: [kinzawaqar@gmail.com](mailto:kinzawaqar@gmail.com)

Funding Source: NIL; Conflict of Interest: NIL

Received: Aug 19, 2020; Revised: Nov 04, 2020

Accepted: Nov 10, 2020

like appearance. Among the four genera of the virus, gene source of alpha and beta CoV are rodents and bats while avian species are sources of gamma and delta CoVs. The coronaviruses cause 5-10% of human respiratory infections. In immune competent individuals, the virus poses mild respiratory infections and common cold, whereas in older and immunocompromised individuals, these viruses invade the lower respiratory tracts. The CoVs; SARS CoV-2, MERS and SARS CoV can also cause extra pulmonary infections. The animal reservoir of the corona viruses are bats whereas intermediate host varies; for MERS intermediate host is camel, and for SARS it is palm civet. Although the intermediate host of SARSCoV-2 is still debatable but phylogenetic analysis shows strong possibility that pangolins are the intermediate host of SARS CoV-2.<sup>11</sup>

The structure of corona viruses is pleomorphic or spherical with the envelope encasing the genetic material and spike projections on the outside of the virus. These viruses are classified based on the shape on the envelope glycoproteins. The virus enters the cells with the help of receptor binding un-coats, transcribes and translates its RNA. The manufactured surface proteins assemble onto the cell membrane and new particles containing the replicated set of the genetic material exit the host cell.<sup>5</sup>

**Incubation Period**

The estimated mean incubation period of SARS CoV-2 is 1-14 days while data of 425 patients from Wuhan indicates the period of 3-7 days.<sup>8</sup> As more literature is reported from different regions of the world, there is a variability in incubation period ranging from 3 days to 24 days in some cases. For MERS CoV, the incubation period ranges from 7 to 14 days.<sup>9</sup> Health authorities therefore recommend a quarantine time of 14 days to individuals who are exposed by the virus. SARS CoV has incubation period of 2-7 days and in some cases can take up to 14 days.<sup>10</sup>

COVID 19, MERS and SARS; Comparison

**Transmission**

SARS CoV-2 was epidemiologically linked to the seafood market in Wuhan, China. It strongly indicated the animal to human transmission of the virus. The virus sequence homology is also identical to bat SARS-like CoVZXC21.<sup>3</sup> The disease presented with massive community spread, indicating human

**Table 1: Comparison of phylogenetic, pathogenic and epidemiologic characteristics of SARS CoV 2, MERS and SARS CoV**

	SARS CoV 2	MERS	SARS CoV
<b>Year</b>	2019- present	2012	2002 -2003
<b>Location</b>	Wuhan, China	Saudi Arabia	Guangdong, China
<b>Cases</b>	11,500,302	2494	8000
<b>Deaths</b>	535,759	858	774
<b>Fatality rate (%)</b>	3.6	32	10
<b>Animal reservoir</b>	Bat	Bat	Bat
<b>Intermediate host</b>	Unknown (suspected intermediate host: Pangolins)	Camel	Palm civet
<b>Mode of transmission</b>	<ul style="list-style-type: none"> <li>• Human-to-human through fomites, physical contact, aerosol droplets</li> <li>• Nosocomial transmission</li> </ul>	<ul style="list-style-type: none"> <li>• Human-to-human through fomites, physical contact, aerosol droplets</li> <li>• Nosocomial transmission</li> <li>• Fecal-oral transmission</li> </ul>	<ul style="list-style-type: none"> <li>• Human-to-human through fomites, physical contact, aerosol droplets</li> <li>• Nosocomial transmission</li> </ul>
<b>Incubation period</b>	1-14 days	14 days	3-7 days
<b>Reproduction number (R0)</b>	3.28	<1	2-5
<b>Receptor</b>	Angiotensin Converting Enzyme 2 (ACE2)	Dipeptidyl Peptidase 4 (DPP4)	Angiotensin Converting Enzyme 2 (ACE2)

to human transmission. The virus spreads through cough and sneeze droplets of an infected individual. Individuals can be asymptomatic and still transmit the virus. SARS CoV-2 has the basic reproduction number (R0) of 3.28 which means that an infected individual can infect three or more people. The primary route of transmission for SARS-CoV 2 is contact of the mucous membranes with respiratory droplets or fomites. While diarrhea is common in people with SARS, the fecal-oral route does not appear to be a common mode of transmission for SARS CoV-2. Most transmission has occurred in the circumstances of close contact with severely ill persons in healthcare or household setting<sup>13</sup> and there is evidence of transmission from asymptomatic cases, much less likely as compared to symptomatic individuals<sup>44</sup>. The R0 of MERS CoV is <1 (12) and R0 of SARS ranges from 2-5.<sup>4</sup>

**Host Cell Infection**

The process of infection starts with the binding of

virus to host receptor. Previous findings of SARS CoV showed that it targets angiotensin converting enzyme 2 (ACE 2) receptor which are expressed in airway, vascular endothelial cells, epithelial and alveolar epithelial cells and macrophages.<sup>14</sup> Same entry mechanism is used by SARS CoV2 and potentially involves the same subsets in the airway.<sup>15</sup> The spike glycoprotein of MERS CoV binds to the host cells by targeting the dipeptidyl peptidase 4 (DPP4) cellular receptor expressed in human airway.<sup>16</sup>

### Pathophysiology

The pathophysiology of SARS CoV-2 resembles that of SARS CoV, both viruses inflict an aggressive inflammatory response that damages the airways. The clinical manifestations of SARS CoV2 can be divided into mild, severe and critically ill based upon the following symptoms:

- **Mild disease:** Absence of pneumonia or mild pneumonia; occurs in 81% of cases
- **Severe disease:** Characterized by blood oxygen saturation  $\leq$  93%, lung infiltrates  $>$  50%, respiratory frequency  $\geq$  30/min, and/or dyspnea within 24 to 48 hours; occurs in 14% of cases.
- **Critical disease:** Characterized by septic shock, multiple organ dysfunction or failure and/or respiratory failure; occurs in 5% of cases.<sup>17</sup>

The disease severity of the patient is not only due to the viral response but also due to the host immune response. Other feature of increased severity with advanced age is also consistent with MERS and SARS.<sup>18</sup>

COVID-19 causes acute respiratory distress syndrome (ARDS) that is characterized by difficulty in breathing and low levels of oxygen in blood. ARDS may lead to respiratory failure which is the cause of 70% deaths in severe cases.<sup>19</sup> SARS CoV 2 causes release of vast quantity of cytokines that cause cytokine storm followed by multi organ damage, similar response is also seen in MERS CoV and SARS CoV infection.<sup>20</sup>

### Infectivity and Fatality Rate

Fatality rate (in percentage) of COVID-19 is 3.6, MERS is 32 and SARS is 10.<sup>21</sup> Male and female have shown different fatality rates in COVID 19, with 2.8% in males and 1.7% in females.<sup>22</sup> The ACE 2 receptors gene being present on the X chromosomes, it might confer resistance by some alleles, this effect being absent in males, makes them more prone to the

infection. Similarly, estrogen and testosterone are specific to the sex of the patient and both involve different immunomodulatory mechanisms thus provides variable immune protection and disease severity.<sup>23</sup>

The magnitude of infectivity in SARS CoV-2 is far greater as seen in MERS CoV and SARS CoV. SARS CoV-2 shares 79% sequence homology with SARS CoV. The spike (S) protein has two subunits, S1 and S2. The S1 subunit has receptor binding domain and amino terminal domain. The virus targets the receptor ACE 2. The binding initiates the endocytosis and SARS CoV-2 gets exposed to endosomal proteases. The S2 subunit contains two heptads repeat regions; HR1 and HR2 and fusion peptide. Once the S1 subunit is cleaved in the endosome, it exposes the fusion peptide and insets it into the host cell membrane. The S2 subunit then folds upon itself and brings HR1 and HR2 together which results in membrane fusion and viral particle is released in the cytoplasm.

The amino acid sequence of receptor binding domain in SARS CoV and SARS CoV 2 share 89.8% sequence homology. Biophysical and computational modeling have shown that the SARS CoV-2 has higher affinity of binding to the receptor binding domain (RBD) and ACE 2 as compared to SARS CoV.<sup>24</sup> The increase in binding affinity of SARS CoV-2 pertains to the ACE 2 binding affinity in the RBD of the S1 subunit of the S protein. This results in 10 to 20-fold higher binding affinity of SARS CoV 2 as compared to SARS CoV.<sup>25</sup>

One other factor responsible for higher infectivity of SARS CoV-2 is the plasma membrane-associated type II transmembrane serine protease, TMPRSS2. Both ACE 2 and TMPRSS 2 are highly expressed in gastrointestinal tract, particularly the intestinal epithelial cells which are the targets of SARS CoV-2. The membrane bound protease, TMPRSS 2 promotes the viral entry by enabling the cleavage of S protein, thereby enhancing viral entry into the host cell.<sup>26</sup>

In addition to that the SARS CoV 2 S proteins also contains a furin like cleavage site which is also found in MERS CoV. These features result in stronger infectivity of SARS CoV-2 as compared to MERS CoV and SARS CoV.<sup>27</sup>

## Symptoms

The first major symptom of COVID 19 is fever which occurs in 98.6% cases, it may or may not be accompanied by other symptoms such as nausea, and vomiting, dry cough, sore throat, shortness of breath, headache, chest pain, dizziness, rhinorrhea, muscle ache and diarrhea. While in severe case patients quickly develops acute respiratory syndrome, metabolic acidosis, coagulopathy and septic shock. The majority of patients develop bilateral pneumonia as seen on the chest CT images. According to center for disease control and prevention (CDC) China, the asymptomatic and mild cases are around 81%. COVID-19 manifests a wide clinical spectrum ranging from asymptomatic patients to septic shock and multiorgan dysfunction [4]. COVID-19 is classified based on the severity of the presentation. The disease may be classified into mild, moderate, severe, and critical. The most common symptoms of patients include fever (98.6%), fatigue (69.6%), dry cough, and diarrhea.<sup>28</sup>

MERS causes fever, cough, expectoration, and shortness of breath [8]. One review of 47 laboratory confirmed cases in Saudi Arabia gave the most common presenting symptoms as fever in 98%, cough in 83%, shortness of breath in 72% and myalgia in 32% of people (29). Similarly, SARS causes fever, dry cough and can eventually leads to shortness of breath and pneumonia; either direct viral pneumonia or secondary bacterial pneumonia.<sup>30</sup>

## Laboratory Diagnosis

For SARS CoV-2 the WHO recommends collecting samples from both the upper and lower respiratory tracts. This can be achieved through expectorated sputum, bronchoalveolar lavage, or endotracheal aspirate.<sup>4</sup> These samples are then assessed for viral RNA using quantitative polymerase chain reaction (PCR). If a positive test result is achieved, it is recommended to repeat the test for verification purposes. A negative test with a strong clinical suspicion also warrants repeat testing.<sup>31</sup>

MERS presents with history of acute febrile and respiratory illness. A positive MERS-CoV laboratory test or a direct epidemiologic link confirms MERS-CoV case.<sup>32</sup>

SARS COV is diagnosed by the symptoms, including a fever of 38 °C (100 °F) or higher, and either a history

of contact with someone with a diagnosis of SARS within the last 10 days or travel to any of the regions with recent local transmission of SARS and positive chest X-ray for atypical pneumonia or respiratory distress syndrome. Samples can also be assessed for viral RNA on ELISA, immunofluorescence or PCR.<sup>33</sup>

## Management

Isolation remains the most effective measure for containment of COVID-19. No specific antiviral medication or vaccine is currently available. Therefore, the treatment of COVID-19 includes symptomatic treatment.<sup>31</sup>

Remdesivir is an inhibitor of viral RNA polymerase reaction. It proved beneficial during pervious outbreaks of MERS and SARS and is a candidate drug for treatment of COVID 19. This drug has shown inhibitory activity against SARS CoV-2 in in-vitro studies (34) and was given emergency use authorization by the U.S. Food and Drug Administration (FDA).<sup>35</sup> Currently this drug is used to treat severely ill patients and is undergoing clinical trials. Similarly, another emergency drug, Lopinavir, a protease inhibitor which is approved for treatment of HIV has shown in vitro activity against SARS CoV and MERS CoV and is a potential treatment option for SARS CoV 2.<sup>36</sup>

SARS CoV-2 infection is characterized by cytokine storm, as discussed earlier, by release of large amount of proinflammatory cytokines that result in damage to lungs and results ARDS. In view of cytokine storm there are a few therapeutic options. Interleukin – 6 (IL-6) inhibitor, Tocilizumab is an IL-6 receptor blocker which blocks the signal transduction cascade and thereby prevent the damage due to the cytokine storm. Another option is the use of steroids to prevent the impact of cytokine storm in SARS CoV-2 infection. Although not yet proven, but use of steroids have shown some beneficial results when administered early in treatment of critically ill patients.<sup>37</sup>

Convalescent plasma therapy is another therapeutic avenue that is still under investigation but has shown beneficial results in severely ill patients. A person who recovers from SARS CoV-2 infection has certain number of neutralizing antibodies. The convalescent plasma, containing neutralizing antibodies is drawn from the recovered person and administered to ill person, the neutralizing antibodies reduce



symptoms and mortality.<sup>38</sup>

One other candidate drug for treatment of SARSCoV-2 is Arbidol. It targets the spike glycoprotein thereby interfering the viral entry process. Arbidol has the potential to hamper the trimerization of the spike glycoproteins and therefore can impact viral attachment and entry to the host cell. In absence of successful adherence and host cell entry, the naked viral structure is immature and therefore less infectious. Although this drug seems promising but is still under investigation.<sup>39</sup>

For MERS, there has been no specific treatment, but extra-corporeal membrane oxygenation (ECMO) significantly improved the clinical outcomes.<sup>40</sup> Similarly for SARS, antibiotics do not have direct effect but may be used against secondary bacterial infection. Treatment of SARS is mainly supportive with antipyretics, supplemental oxygen and mechanical ventilation as needed. Antiviral medications are used as well as high doses of steroids to reduce swelling in the lungs.<sup>41</sup>

### Prevention

Preventive measures must focus on optimizing infection control protocols, self-isolation, and patient isolation during the provision of clinical care. WHO has released advisory for prevention of spread of disease Patients and the general public must cover coughs and sneezes to help prevent aerosol transmission. Frequent hand washing, for at least 20 seconds, with soap and water is also required. As an alternative measure, hand sanitizers (70% alcohol) can also be used. Immunocompromised individuals are advised to avoid public gatherings. Emergency medicine departments must apply strict hygiene measures for the control of infections. Healthcare personnel must use personal protective equipment such as N95 masks, FFP3 masks, gowns eye protection, gloves, and gowns.<sup>31</sup>

Prevention against MERS included use of medical mask, eye protection (i.e. goggles or a face shield), clean, non-sterile, long sleeved gown; and gloves (some procedures may require sterile gloves) and hand hygiene before and after contact with the person and his or her surroundings and immediately after removal of personal protective equipment (PPE). These specifications are specifically for the hospital staff dealing the MERS patients since it is more commonly spread to the individuals in direct

contact with the infected person.<sup>42</sup>

There is no vaccine for SARS, therefore clinical isolation and quarantine remain the most effective means to prevent the spread of SARS. Other preventive measures include handwashing with soap and water, or use of alcohol-based hand sanitizer. Disinfection of surfaces of fomites to remove viruses and isolating oneself as much as possible is vital to minimize the chances of transmission of the virus.<sup>43</sup>

### Conclusion

The corona viruses have caused widespread infections and epidemics over different times in the past, . SARS CoV-2 has an enormous spread affecting humans across the globe. These viruses share structural homology, clinical features and mode of transmission. One could speculate the widespread infection of the novel coronavirus since it has a community spread and can also be transmitted via the asymptomatic carriers. So far, precautions like good hygiene, handwashing and social distancing are providing good means to contain the disease, in the hope of reaching the cure before it takes more lives.

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