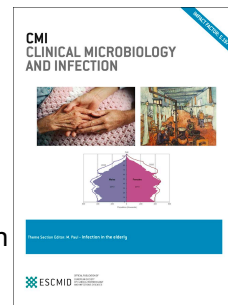


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COVID-19, SARS and MERS: are they closely related?

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1 **COVID-19, SARS and MERS: are they closely related?**

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12

13 **ABSTRACT**

14 **Background:** The 2019 novel coronavirus (SARS-CoV-2) is a new human coronavirus which is
15 spreading with epidemic features in China and other Asian countries with cases reported
16 worldwide. This novel Coronavirus Disease (COVID-19) is associated with a respiratory illness that
17 may cause severe pneumonia and acute respiratory distress syndrome (ARDS). Although related to
18 the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS),
19 COVID-19 shows some peculiar pathogenetic, epidemiological and clinical features which have not
20 been completely understood to date.

21 **Objectives:** We provide a review of the differences in terms of pathogenesis, epidemiology and
22 clinical features between COVID-19, SARS and MERS.

23 **Sources:** The most recent literature in English language regarding COVID-19 has been reviewed
24 and extracted data have been compared with the current scientific evidence about SARS and
25 MERS epidemics.

26 **Content:** COVID-19 seems not to be very different from SARS regarding its clinical features.
27 However, it has a fatality rate of 2.3%, lower than SARS (9.5%) and much lower than MERS
28 (34.4%). It cannot be excluded that because of the COVID-19 less severe clinical picture it can
29 spread in the community more easily than MERS and SARS. The actual basic reproductive number
30 (R_0) of COVID-19 (2-2.5) is still controversial. It is probably slightly higher than the R_0 of SARS (1.7-
31 1.9) and higher than MERS (<1). The gastrointestinal route of transmission of SARS-CoV-2, which
32 has been also assumed for SARS-CoV and MERS-CoV, cannot be ruled out and needs to be further
33 investigated.

34 **Implications:** There is still much more to know about COVID-19, especially as concerns mortality
35 and capacity of spreading on a pandemic level. Nonetheless, all of the lessons we learned in the
36 past from SARS and MERS epidemics are the best cultural weapons to face this new global threat.

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40 INTRODUCTION

41 The 2019 novel coronavirus (SARS-CoV-2) is a new human coronavirus which emerged at the end
42 of December 2019 in Wuhan, China. It is currently spreading with epidemic features in China and
43 other Asian countries, with cases reported in Europe, Australia and North America. Currently, at
44 the date of 8th of March 2020, 105 586 confirmed cases have been reported in 101 countries with
45 a total number of 3584 deaths.¹

46 COVID-19 (Coronavirus Disease) is the clinical syndrome associated with SARS-CoV-2 infection,
47 which is characterized by a respiratory syndrome with a variable degree of severity, ranging from a
48 mild upper respiratory illness to severe interstitial pneumonia and acute respiratory distress
49 syndrome (ARDS).²⁻⁴

50 Although SARS-CoV-2 belongs to the same *betacoronavirus* genus of the coronaviruses responsible
51 for the severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS)
52 (i.e SARS-CoV and MERS-CoV, respectively), this novel virus seems to be related to milder
53 infections. Moreover, SARS and MERS were mainly associated with nosocomial spread, whereas
54 SARS-CoV-2 is much widely transmitted in the community.⁵

55 In this review we aim to analyze the differences in terms of pathogenesis, epidemiology and
56 clinical features between COVID-19, SARS and MERS.

57 PHYLOGENY

58 Genome sequence analysis has shown that SARS-CoV-2 belongs to *betacoronavirus* genus, that
59 includes Bat SARS-like coronavirus, SARS-CoV, and MERS-CoV.⁶

60 SARS-CoV-2 possesses a genomic structure which is typical of other *betacoronaviruses*. Similarly to
61 other coronaviruses, its genome contains 14 open reading frames (ORFs), encoding for 27
62 proteins: the ORF1 and ORF2 at the 5'-terminal region of the genome encode for 15 non-structural
63 proteins important for virus replication.^{7,8} The 3'-terminal region of the genome encodes for

64 structural proteins, namely spike (S), envelope protein (E), membrane protein (M) and
65 nucleocapsid (N), plus 8 accessory proteins.^{7,8}

66 Phylogenetic tree analysis of the novel coronavirus showed that SARS-CoV-2 belongs, together
67 with SARS-CoV and Bat SARS-like coronavirus, to a different clade from MERS-CoV and it is more
68 phylogenetically related to Bat SARS-like coronaviruses isolated in China from horseshoe bats
69 between 2015 and 2018 than to the SARS-CoV (**Table 1**). This suggests a different viral evolution
70 from SARS and MERS, involving bats as wild reservoir.⁹⁻¹⁴ Genomic comparison between SARS and
71 SARS-CoV2 has shown that there are only 380 amino acid substitutions between SARS-CoV-2 and
72 SARS-like coronaviruses, mostly concentrated in the nonstructural protein genes, while 27
73 mutations have been found on genes encoding for viral spike protein S responsible of receptor
74 binding and cell entry.⁸ This mutations might explain the apparent lower pathogenicity of SARS-
75 CoV-2 than SARS-CoV, but further studies are required.⁹

76 **PATHOGENICITY**

77 Accumulating evidence based on genomic analysis suggest that SARS-CoV-2 shares the same
78 human cell receptor with SARS-CoV, the angiotensin-converting enzyme 2 (ACE2), while MERS-CoV
79 uses dipeptidyl peptidase 4 (DPP4) to enter in host's cells (**Table 1**).¹⁵ It is well established that
80 SARS-CoV emerged as human pathogen thanks to favorable mutations on the receptor binding
81 domain (RBD) of the S protein, that increased its pathogenicity by strengthening its affinity to the
82 receptor; it is therefore assumed that SARS-CoV-2 has behaved in a similar way.¹⁵ However, in
83 SARS-CoV-2 no amino acid substitutions were present in the RBD that directly interact with human
84 receptor ACE2 compared with SARS-CoV, but six mutations occurred in the other regions of the
85 RBD.⁸ The role of such substitutions on the pathogenicity of SARS-CoV-2 must be further
86 investigated. Analysis of receptor affinity shows that SARS-CoV-2 binds ACE2 more efficiently than
87 the 2003 strain of SARS-CoV, although less efficiently than the 2002 strain.¹⁵ Moreover, it has

88 been predicted that a single nucleotide mutation on RBD of SARS-CoV-2, if occurs, could further
89 increase its pathogenicity.¹⁵
90 ACE2 is an ectoenzyme anchored to the plasma membrane of the cells of several tissues,
91 especially lower respiratory tract, heart, kidney and gastrointestinal tract.¹⁶ Inoculation of the
92 2019-nCoV onto surface layers of human airway epithelial cells in vitro causes cytopathic effects
93 and cessation of the cilia movements.¹⁷ SARS-CoV highly replicates in the type I and II
94 pneumocytes and in enterocytes, and the SARS-induced down-regulation of ACE2 receptors in
95 lung epithelium contributes to the pathogenesis of acute lung injury and subsequent ARDS.^{16,18} It
96 must be further investigated if the higher receptor affinity of SARS-CoV-2 than SARS-CoV for ACE2
97 could lead to a more severe lung involvement in COVID-19 than in SARS.

98 **TRANSMISSIBILITY**

99 The reproductive number (R_0) of the novel infection is estimated by World Health Organization
100 (WHO) to range between 2 and 2.5, which is higher than SARS (1.7-1.9) and MERS (<1), suggesting
101 that SARS-CoV-2 has a higher pandemic potential.¹⁹⁻²³ However, it must be noted that some
102 published studies have estimated a R_0 for SARS reaching the value of 4.²⁴ Interestingly, a recent
103 review by Liu and colleagues has shown that the average reproductive number of SARS-CoV-2 is
104 estimated to be 3.28, with a median value of 2.79, thus exceeding the WHO estimates.²⁵

105 Nonetheless, in **Table 1** we only report the WHO data, since the estimation of R_0 depends on the
106 estimation method used and the current estimate can be biased by insufficient data and short
107 onset time of the diseases, as Liu and colleagues also state.

108 According to a recent large descriptive study carried out by the Chinese Center for Disease Control
109 and Prevention (CCDC) on 44 672 individuals diagnosed with COVID-19 in China, the fatality rate of
110 novel coronavirus infection is estimated to be 2.3²⁶, lower than SARS (9.5%) and much lower than
111 MERS (34.4%).^{5,27} Interestingly, according to CCDC, the case fatality rate in the Hubei province,

112 where the epidemic has started, is 7-fold higher than other provinces.²⁶ This could be related to
113 the fact that, among the 44 672 cases reported by CCDC, 10 567 (14.6%) cases were diagnosed
114 only clinically and exclusively in the Hubei province. Therefore, it cannot be excluded that clinically
115 diagnosed cases presented with a more severe clinical picture, thus increasing the case fatality
116 rate.²⁶ After the change of case definition, the number of cases increased due to the inclusion of
117 cases cumulated over the past weeks. The question is: were mild cases registered at all? It is not a
118 minor matter, because including mild cases will reduce the mortality rate. Indeed, the number of
119 infected outside of China is currently 24 727 with 484 fatal outcomes, and a mortality rate of
120 1.9%.¹ Of interest, the fatality rate of the novel coronavirus infection increases to an estimated
121 14% when considering only the hospitalized cases, reaching the overall SARS case-fatality rate that
122 was estimated to be around 15%.^{28,29}

123 **CLINICAL FEATURES**

124 Up to date, complete clinical data concerning COVID-19 have been reported for 458 cases in the
125 English-language literature, of which 415 from Hubei province in China^{2-4,30}, 17 in other Chinese
126 provinces^{31,32}, 25 in Korea^{33,34} and 1 in USA³⁵. In **Table 2** the main clinical characteristics from the
127 three most significant case series of COVID-19 cases are listed and compared with the most
128 recently available data about SARS and MERS. The median age of the COVID-19 cases ranges from
129 49 to 57 years, similar to SARS and MERS, higher in those admitted to ICU; up to 50% of patients
130 reported a chronic comorbid illness in a slightly lower percentage compared to patients diagnosed
131 with MERS. The most common presenting symptoms is fever, followed by cough, sore throat and
132 dyspnea; all of the infected patients had at least one symptom. However, according to the CCDC
133 report, 81% of the cases had mild symptoms and 1.2% were asymptomatic.²⁶

134 Laboratory findings in patients diagnosed with COVID-19 are not remarkably different from those
135 diagnosed with the other coronavirus infections, with lymphopenia as the most common finding,

136 together with low platelet count, decreased albumin levels and increased aminotransferases,
137 lactic dehydrogenase, creatine kinase and C-reactive protein levels. No data are available on
138 lymphocyte subpopulations levels, but it can be interesting to know if the virus associated
139 lymphopenia affects in a different way CD4+ and CD8+ subpopulations, to predict the possible
140 development of superimposed bacterial or opportunistic infections, which have currently been
141 reported in a small amount of cases to date.²

142 Radiological presentation of COVID-19 is not much different from the other two coronavirus-
143 associated pneumonia, even though the proportion of cases with bilateral findings seems to be
144 higher in COVID-19 cases. The most common CT findings in COVID-19 is bilateral pulmonary
145 parenchymal ground-glass, consolidative or “crazy paving” pulmonary lesions, often with a
146 rounded shape and a peripheral distribution.³⁶ Interestingly, in a recent study on 167 patients
147 from Hubei province with suspected COVID-19 who underwent chest CT scan and respiratory swab
148 for detection of SARS-CoV-2, five subject (3%) had a CT scan that was strongly suggestive of
149 COVID-19, but an initially negative real-time polymerase reaction (RT-PCR). These patients were
150 isolated for presumed COVID-19 pneumonia and the respiratory swab repeated between 2 and 8
151 days later turned positive.³⁷

152 Patient diagnosed with COVID-19 may have an unfavorable clinical course with the onset of
153 dyspnea within 5 days, ARDS within 8 days in 30% of cases and need for invasive mechanical
154 ventilation and extracorporeal membrane oxygenation (ECMO) in 17% and 4% of cases,
155 respectively.³ These findings are in line with SARS percentages, while clinical course of MERS
156 seems to be characterized by a more frequent development of ARDS and needing of invasive life
157 support, especially in elderlies and smokers.³⁸ In particular, acute kidney injury (AKI), which rarely
158 occurs in SARS and COVID-19, seems to be a peculiar complication of MERS. Although this could be
159 explained by a direct renal cytopathic effect induced by the virus, since DDP4 receptors are largely

160 represented in tubules and glomeruli, it seems more probable that the high percentage of AKI
161 reported is due to multi-organ failure, which occurs more frequently in MERS than in the other
162 coronavirus infections.³⁹

163 **CONCLUSIONS**

164 COVID-19 seems no to be very different from SARS regarding the clinical features; it seems to be
165 less lethal than MERS, which is less related with the other two coronavirus both in terms of
166 phylogenetic and pathogenesis features.

167 COVID-19 generally has a less severe clinical pictures, and thus it can spread in the community
168 more easily than MERS and SARS, which have been frequently reported in the nosocomial setting.

169 The previous knowledge learned from SARS and MERS lessons might have contributed to the
170 institution of more efficient preventive measures in the healthcare settings.

171 Which are the causes of such different ability to spread among these three viruses? A first
172 hypothesis is a different viral tropism for the respiratory tract, resulting in a milder but highly
173 transmittable disease when the virus replicates in the upper respiratory tract and a severe
174 pneumonia with lower spreading potential when the viral tropism is higher for the lower
175 respiratory tract. This hypothesis derives from the example of the influenza viruses, namely
176 seasonal influenza viruses H1N1 and H3N2. They preferably bind alpha 2,6-linked sialic acid
177 receptors of the upper respiratory tract, usually causing a less severe but more transmissible
178 disease than avian influenza H5N1 or H7N9, which preferably bind alpha 2,3-linked sialic acid in
179 the lung alveoli, causing severe pneumonia.⁴⁰ On the other hand, SARS-CoV-2, SARS-CoV and
180 MERS-CoV use receptors that have been found both in the upper and in the lower respiratory
181 tract. Moreover, other human coronaviruses, such as NL63-CoV, cause a mild illness even if they
182 bind to the same receptor of SARS-CoV-2 and SARS-CoV⁵. So, in our opinion, it is likely that the
183 different inoculum dose at the time of infection makes the difference in terms of severity of the

184 disease; heavy inoculum exposures seem to be linked to an higher penetration in the lower
185 respiratory tract, giving severe pneumonia, whereas lower inoculum exposures allow viruses to
186 only reach the upper airway, causing a milder infection.

187 Viral loads are higher at the time of symptoms onset and higher in nose than in throat
188 specimens.^{41,42} Furthermore, in patients affected by COVID-19, viral load progressively decreases
189 within days, following a different pattern than SARS, in which the highest shedding is recorded
190 after 10 days from the symptoms' onset.⁴¹⁻⁴³ These findings suggest that SARS-CoV-2 may spread
191 more easily in the community than SARS even when initial mild symptoms or no symptoms are
192 present.

193 The differences in the intrinsic virulence of the viruses themselves can explain the different
194 capacity of spreading. MERS-CoV has a higher mortality but a lower transmissibility probably
195 because it causes a more severe clinical picture than COVID-19 and SARS, requiring hospitalization
196 more frequently, thus reducing the community spreading of the infection and increasing the
197 nosocomial transmission.^{5,21} On the other hand, the higher mortality of MERS could be biased by
198 the fact that the largest data available on MERS were derived from hospitalized patients, thus
199 implicating a more severe clinical picture than community acquired cases.⁴⁴ This hypothesis is
200 strengthened by the observation that, when the cohort of patients with MERS was derived from
201 the community and not from hospital outbreaks, the mortality rate decreased to 10%, as it has
202 been observed in a cohort study carried out in 2015 in Saudi Arabia.⁴⁴

203 Interestingly, despite the high virological similarity between the SARS-CoV-2 and SARS-CoV,
204 gastrointestinal (GI) symptoms and diarrhea seem to be much more common in SARS, although
205 the proportion of SARS patients with GI symptoms varies among different studies, from 23% to
206 70% in the Toronto outbreak and in the Hong Kong community outbreak, respectively.^{43,45} Such
207 difference could be related to the fact that the Hong Kong outbreak seemed to originate from a

208 fecal contamination of a residence complex due to a faulty sewage system, while the Toronto
209 outbreak was mainly caused by nosocomial hospital droplet transmission.^{43,45} The GI route of
210 transmission has been also hypothesized for MERS-CoV, through the consumption of infected
211 camel milk; moreover, GI transmission has been demonstrated in the animal model through
212 intestinal DPP4 receptors.⁴⁶ According to this findings, the reported detection of SARS-CoV-2 RNA
213 in the loose stools of the first US patient with COVID-19 is not surprising.³⁵ SARS-CoV replicates in
214 the enteric epithelium by binding to the ACE2 receptor and it cannot be excluded that SARS-CoV-2
215 would behave in the same way.¹⁸ This may contribute to the hypothesis that SARS-CoV-2 could
216 also be transmitted via this route, together with the evidence that SARS-CoV and MERS-CoV
217 remain viable in environmental conditions that could facilitate faecal–oral transmission.⁴⁷ In **Table**
218 **3** we provide a synthesis of what is certain to date about COVID-19 and what needs to be further
219 addressed.

220 In conclusion, there is still much more to know about COVID-19, especially its epidemiological
221 features, such as mortality and capacity of spreading on a pandemic level. The lessons we have
222 learned in the past from the SARS and MERS epidemics are the best cultural weapons to face this
223 new global threat.

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225

	<i>Phylogenetic origin</i>	<i>Animal reservoir</i>	<i>Intermediate host</i>	<i>Receptor</i>	<i>Case fatality rate</i>	<i>R₀</i>
<i>SARS-CoV-2</i>	Clade I, cluster IIa	Bats	Unknown	angiotensin-converting enzyme 2 (ACE2)	2.3% ²⁶	2-2.5 ¹⁹
<i>SARS-CoV</i>	Clade I, cluster IIb	Bats	Palm civets	angiotensin-converting enzyme 2 (ACE2)	9.5%	1.7-1.9
<i>MERS-CoV</i>	Clade II	Bats	Camels	dipeptidyl peptidase 4 (DPP4)	34.4%	0.7

226 *Table 1 - Phylogenetic, pathogenetic and epidemiologic characteristics*

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	COVID-19¹⁻³	SARS^{45,48-50}	MERS^{38,51,52}
	Date of emergence in human population		
	2019	2002	2012
	Absolute number of cases		
	80 239	8096	2,260
	Demographic and general characteristics, % of cases		
Male	40-60	38-42	59.5-64
Female	40-55	64-68	35-40
Cardiovascular diseases	10-46	8	9.1
Chronic lung disease	1-2	1-2	10.2
Diabetes	10	16	18.8
Malignancy	2-4	6	15.5
	Signs and symptoms, % of cases		
Fever	81-91	99-100	81.7-98
Cough	48-68	57-75	56.9-83
Dyspnea	19-31	40-42	22-72
Sore throat	29	13-25	9.1-14
Dizziness and confusion	22	4-43	5.4
Diarrhea	16	23-70	19.4-26
Nausea and vomiting	6	20-35	14-21
	Laboratory findings on admission, % of cases		
Leukopenia	35	33.9	14
Lymphopenia	35-72	54-70	32
Thrombocytopenia	12	44.8	36
Elevated aminotransferases	28-35	23	11-40
	Radiological chest findings on admission, % of cases		
Unilateral infiltrate	10	46-54	14.3-62.6
Bilateral infiltrate	84-90	29-45	37.4-75
No findings	14	13-25	4.3-30
	Complications, % of cases		
Intensive Care Unit admission	24	23-34	53-89
Acute Respiratory Distress Syndrome	18-30	20	20-30
Acute Kidney Injury	3	6.7	41-50
Deaths in hospitalized	10-11	3.6-15.7	30-40

231 *Table 2 - Clinical characteristics*

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Facts about COVID-19	Questions needing to be further assessed
<ul style="list-style-type: none"> • SARS-CoV-2 is more phylogenetically related to SARS-CoV than to MERS-CoV. • Only minor differences have been found in the genome sequences of SARS-CoV-2 comparing with SARS-CoV. • SARS-CoV-2 affinity for angiotensin-converting enzyme 2 (ACE2) receptor is higher than in SARS-CoV. • COVID-19 fatality rate is lower than that found in SARS and MERS. • SARS-CoV-2 RNA has been detected in the stools of infected patients, similarly to SARS-CoV and MERS-CoV. • 1.2% of COVID-19 cases are asymptomatic. • COVID-19 is not very different from SARS and MERS regarding demographic characteristics, laboratory and radiological findings. • Clinical complications in COVID-19 are as frequent as in SARS, but less frequent than in MERS. • Viral loads in COVID-19 patients are higher at the time of symptoms onset and progressively decrease during the clinical course of the disease. 	<ul style="list-style-type: none"> • Which is the role of aminoacid substitutions on the SARS-CoV-2 receptor binding domain in terms of pathogenesis? • Does the higher affinity of SARS-CoV-2 than SARS-CoV for angiotensin-converting enzyme 2 (ACE2) receptor have an implication in respiratory complications? • Is the fecal-oral route of transmission possible for COVID-19? • Which is the role of asymptomatic COVID-19 cases in the epidemiology of the disease? • Which is the actual COVID-19 basic reproductive number (R_0)? • Are differences in viral kinetics in respiratory tract responsible of the different spreading potential of COVID-19, SARS and MERS?

235 *Table 3 - Facts and open issues about COVID-19*

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241

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247 revised the manuscript and gave their final opinion for its intellectual content.

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