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Narrative review

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

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ABSTRACT

Background: The 2019 novel coronavirus (SARS-CoV-2) is a new human coronavirus which is spreading with epidemic features in China and other Asian countries; cases have also been reported worldwide. This novel coronavirus disease (COVID-19) is associated with a respiratory illness that may lead to severe pneumonia and acute respiratory distress syndrome (ARDS). Although related to the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), COVID-19 shows some peculiar pathogenetic, epidemiological and clinical features which to date are not completely understood.
Aims: To provide a review of the differences in pathogenesis, epidemiology and clinical features of COVID-19, SARS and MERS.
Sources: The most recent literature in the English language regarding COVID-19 has been reviewed, and extracted data have been compared with the current scientific evidence about SARS and MERS epidemics.
Content: COVID-19 seems not to be very different from SARS regarding its clinical features. However, it has a fatality rate of 2.3%, lower than that of SARS (9.5%) and much lower than that of MERS (34.4%). The possibility cannot be excluded that because of the less severe clinical picture of COVID-19 it can spread in the community more easily than MERS and SARS. The actual basic reproductive number (R_0) of COVID-19 (2.0—2.5) is still controversial. It is probably slightly higher than the R_0 of SARS (1.7—1.9) and higher than that of MERS (<1). A gastrointestinal route of transmission for SARS-CoV-2, which has been assumed for SARS-CoV and MERS-CoV, cannot be ruled out and needs further investigation.
Implications: There is still much more to know about COVID-19, especially as concerns mortality and its capacity to spread on a pandemic level. Nonetheless, all of the lessons we learned in the past from the SARS and MERS epidemics are the best cultural weapons with which to face this new global threat.
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Introduction

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

Coronavirus disease (COVID-19) is the clinical syndrome associated with SARS-CoV-2 infection; it is characterized by a respiratory syndrome with a variable degree of severity, ranging from a mild upper respiratory tract illness to severe interstitial pneumonia and acute respiratory distress syndrome (ARDS) [2—4].

Although SARS-CoV-2 belongs to the same *Betacoronavirus* genus as the coronaviruses responsible for the severe acute

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respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (SARS-CoV and MERS-CoV, respectively), this novel virus seems to be associated with milder infections. Moreover, SARS and MERS were associated mainly with nosocomial spread, whereas SARS-CoV-2 is much more widely transmitted in the community [5].

In this review we aim to analyse the differences in pathogenesis, epidemiology and clinical features among COVID-19, SARS and MERS.

Phylogeny

Genome sequence analysis has shown that SARS-CoV-2 belongs to the *Betacoronavirus* genus, which includes Bat SARS-like coronavirus, SARS-CoV, and MERS-CoV [6].

SARS-CoV-2 possesses a genomic structure which is typical of other betacoronaviruses. Like other coronaviruses, its genome contains 14 open reading frames (ORFs) encoding 27 proteins. The ORF1 and ORF2 at the 5′-terminal region of the genome encode 15 non-structural proteins important for virus replication [7,8]. The 3′-terminal region of the genome encodes structural proteins—namely spike protein (S), envelope protein (E), membrane protein (M), and nucleocapsid (N)—plus eight accessory proteins [7,8].

Phylogenetic tree analysis of the novel coronavirus showed that SARS-CoV-2 belongs, together with SARS-CoV and Bat SARS-like coronavirus, to a different clade from MERS-CoV, and it is more phylogenetically related to Bat SARS-like coronaviruses (isolated in China from horseshoe bats between 2015 and 2018) than to SARS-CoV (Table 1). This suggests a different viral evolution from SARS and MERS, involving bats as a wild reservoir [8–13]. Genomic comparison between SARS and SARS-CoV-2 has shown that there are only 380 amino acid substitutions between SARS-CoV-2 and SARS-like coronaviruses, mostly concentrated in the non-structural protein genes, while 27 mutations have been found in genes encoding the viral spike protein S responsible for receptor binding and cell entry [8]. These mutations might explain the apparent lower pathogenicity of SARS-CoV-2 compared with SARS-CoV, but further studies are required [9].

Pathogenicity

Accumulating evidence based on genomic analysis suggests that SARS-CoV-2 shares with SARS-CoV the same human cell receptor, the angiotensin-converting enzyme 2 (ACE2), while MERS-CoV uses dipeptidyl peptidase 4 (DPP4) to enter host cells (Table 1) [14]. It is well established that SARS-CoV emerged as a human pathogen thanks to favourable mutations in the receptor binding domain (RBD) of the S protein which increased its pathogenicity by strengthening its affinity with the receptor; it is therefore assumed that SARS-CoV-2 has behaved in a similar way [14]. However, in SARS-CoV-2 no amino acid substitutions were present in the RBD that directly interacts with human receptor ACE2 compared with SARS-CoV, but six mutations occurred in other regions of the RBD [8]. The role of such substitutions on the pathogenicity of SARS-CoV-2 must be further investigated. Analysis of receptor affinity shows that SARS-CoV-2 binds ACE2 more efficiently than the 2003 strain of SARS-CoV, although less efficiently than the 2002 strain [14]. Moreover, it has been predicted that a single nucleotide mutation on the RBD of SARS-CoV-2, if it occurs, could further increase its pathogenicity [14].

ACE2 is an ectoenzyme anchored to the plasma membrane of the cells of several tissues, especially those of the lower respiratory tract, heart, kidney and gastrointestinal tract [15]. Inoculation of the 2019 nCoV onto surface layers of human airway epithelial cells *in vitro* causes cytopathic effects and cessation of the cilia movements [16]. SARS-CoV highly replicates in the type I and II pneumocytes and in enterocytes, and the SARS-induced down-regulation of ACE2 receptors in lung epithelium contributes to the pathogenesis of acute lung injury and subsequent ARDS [15,17]. Whether the higher receptor affinity for ACE2 of SARS-CoV-2 than SARS-CoV could lead to a more severe lung involvement in COVID-19 than in SARS requires further investigation.

Transmissibility

The reproductive number (R_0) of the novel infection is estimated by the World Health Organization (WHO) to range between 2 and 2.5, which is higher than that for SARS (1.7–1.9) and MERS (<1), suggesting that SARS-CoV-2 has a higher pandemic potential [18–22]. However, it must be noted that some published studies have estimated an R_0 for SARS reaching the value of 4 [23]. Interestingly, a recent review by Liu and colleagues has shown that the average reproductive number of SARS-CoV-2 is estimated to be 3.28, with a median value of 2.79, thus exceeding the WHO estimates [24]. Nonetheless, in Table 1 we report only the WHO data, since the estimation of R_0 depends on the estimation method used, and the current estimate can be biased by insufficient data and the short onset times of the diseases, as Liu and colleagues also state.

According to a recent large descriptive study carried out by the Chinese Centre for Disease Control and Prevention (CCDC) on 44 672 individuals diagnosed with COVID-19 in China, the fatality rate of the novel coronavirus infection is estimated to be 2.3% [25], lower than that of SARS (9.5%) and much lower than that of MERS (34.4%) [5,20]. Interestingly, according to the CCDC, the case fatality rate in the Hubei province, where the epidemic started, is seven-fold higher than in other provinces [25]. This could be related to the fact that, among the 44 672 cases reported by the CCDC, 10 567 cases (14.6%) were diagnosed only clinically and exclusively in the Hubei province. Therefore, it cannot be excluded that clinically diagnosed cases presented with a more severe clinical picture, thus increasing the case fatality rate [25]. After the change of the case definition, the number of cases increased due to the inclusion of cases cumulated over the previous weeks. The question is: were mild cases registered at all? It is not a minor matter, because including mild cases will reduce the mortality rate. Indeed, the number of infected cases outside of China is currently 24 727, with 484 fatal outcomes, a mortality rate of 1.9% [1]. Of interest, the fatality rate of the novel coronavirus infection increases to an estimated 14% when considering only the hospitalized cases, reaching the overall SARS case-fatality rate that was estimated to be around 15% [26,27].

Table 1
Phylogenetic, pathogenetic and epidemiological characteristics of SARS-CoV-2, SARS-CoV and MERS-CoV

	Phylogenetic origin	Animal reservoir	Intermediate host	Receptor	Case fatality rate	R_0
SARS-CoV-2	Clade I, cluster IIa	Bats	Unknown	Angiotensin-converting enzyme 2 (ACE2)	2.3% [25]	2–2.5 [18]
SARS-CoV	Clade I, cluster IIb	Bats	Palm civets	Angiotensin-converting enzyme 2 (ACE2)	9.5%	1.7–1.9
MERS-CoV	Clade II	Bats	Camels	Dipeptidyl peptidase 4 (DPP4)	34.4%	0.7

Clinical features

To date, complete clinical data concerning COVID-19 have been reported for 458 cases in the English language literature, of which 415 are from the Hubei province in China [2—4,28], 17 are from other Chinese provinces [29,30], 25 are from Korea [31,32] and one is from USA [33]. In Table 2 the main clinical characteristics from the three most significant case series of COVID-19 cases are listed and compared with the most recently available data about SARS and MERS. The median age of the COVID-19 cases ranges from 49 to 57 years (similar to SARS and MERS), higher in those admitted to the ICU; up to 50% of patients reported a chronic comorbid illness in a slightly lower percentage compared to patients diagnosed with MERS. The most common presenting symptom is fever, followed by cough, sore throat and dyspnoea; all of the infected patients had at least one of these symptoms. However, according to the CCDC report, 81% of the cases had mild symptoms and 1.2% were asymptomatic [25].

Laboratory findings in patients diagnosed with COVID-19 are not remarkably different from those diagnosed with the other coronavirus infections, with lymphopenia as the most common finding, together with low platelet count, decreased albumin levels and increased aminotransferases, lactic dehydrogenase, creatine kinase and C-reactive protein levels. No data are available on lymphocyte subpopulations levels, but it would be interesting to know whether the virus-associated lymphopenia affects CD4+ and CD8+ subpopulations differently, to predict the possible development of superimposed bacterial or opportunistic infections which have so far been reported in a small number of cases [2].

Radiological presentation of COVID-19 is not much different from pneumonia associated with the other two coronaviruses, even though the proportion of cases with bilateral findings seems to be higher in COVID-19 cases. The most common CT findings in COVID-19 is bilateral pulmonary parenchymal ground-glass, consolidative or 'crazy paving' pulmonary lesions, often with a rounded shape and a peripheral distribution [34]. Interestingly, in a recent study on 167 patients from Hubei province with suspected COVID-19 who underwent chest CT scan and respiratory swab for detection of SARS-CoV-2, five subjects (3%) had a CT scan that was strongly suggestive of COVID-19, but an initially negative real-time polymerase chain reaction (RT-PCR). These patients were isolated for presumed COVID-19 pneumonia, and the respiratory swab repeated between 2 and 8 days later turned positive [35].

Patients diagnosed with COVID-19 may have an unfavourable clinical course with the onset of dyspnoea within 5 days, ARDS within 8 days in 30% of cases, and the need for invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO) in 17% and 4% of cases, respectively [3]. These findings are in line with SARS percentages, while the clinical course of MERS seems to be characterized by a more frequent development of ARDS and the need for invasive life support, especially in elderly patients and smokers [36]. In particular, acute kidney injury (AKI), which rarely occurs in SARS and COVID-19, seems to be a peculiar complication of MERS. Although this could be explained by a direct renal cytopathic effect induced by the virus, since DDP4 receptors are largely represented in tubules and glomeruli, it seems more probable that the high percentage of AKI reported is due to multiorgan failure, which occurs more frequently in MERS than in the other coronavirus infections [37].

Conclusions

COVID-19 seems not to be very different from SARS regarding its clinical features; it seems to be less lethal than MERS, which is less

Table 2
Clinical characteristics of COVID-19, SARS and MERS

	COVID-19 [1—3]	SARS [43,46—48]	MERS [36,49,50]
Date of emergence in human population			
	2019	2002	2012
Absolute number of cases			
	80 239	8096	2260
Demographic and general characteristics, % of cases			
Male	40—60	38—42	59.5—64
Female	40—55	64—68	35—40
Cardiovascular disease	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
Dyspnoea	19—31	40—42	22—72
Sore throat	29	13—25	9.1—14
Dizziness and confusion	22	4—43	5.4
Diarrhoea	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 patients	10—11	3.6—15.7	30—40

Table 3
Facts and open issues about COVID-19

Facts about COVID-19	Questions needing further assessment
• SARS-CoV-2 is more phylogenetically related to SARS-CoV than to MERS-CoV • Only minor differences have been found between the genome sequences of SARS-CoV-2 and SARS-CoV • SARS-CoV-2 affinity for angiotensin-converting enzyme 2 (ACE2) receptor is higher than that of 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 symptom onset and progressively decrease during the clinical course of the disease	• What is the role of amino acid 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 faecal—oral route of transmission possible for COVID-19? • What is the role of asymptomatic COVID-19 cases in the epidemiology of the disease? • What is the actual COVID-19 basic reproductive number (R_0)? • Are differences in viral kinetics in the respiratory tract responsible for the different spreading potential of COVID-19, SARS and MERS?

closely related to the other two coronavirus in terms of both phylogenetic and pathogenetic features.

COVID-19 generally has a less severe clinical picture, and thus it can spread in the community more easily than MERS and SARS, which have frequently been reported in the nosocomial setting. The lessons learned from SARS and MERS might have contributed to the institution of more efficient preventive measures in healthcare settings.

What are the causes of such different abilities to spread among these three viruses? A first hypothesis is a different viral tropism for the respiratory tract, resulting in a milder but highly transmissible disease when the virus replicates in the upper respiratory tract, and a severe pneumonia with lower spreading potential when the viral tropism is higher for the lower respiratory tract. This hypothesis derives from the example of the influenza viruses, namely seasonal influenza viruses H1N1 and H3N2. They preferably bind α-2,6-linked sialic acid receptors of the upper respiratory tract, usually causing a less severe but more transmissible disease than avian influenza H5N1 or H7N9, which preferably bind α-2,3-linked sialic acid in the lung alveoli, causing severe pneumonia [38]. On the other hand, SARS-CoV-2, SARS-CoV and MERS-CoV use receptors that have been found in both the upper and the lower respiratory tract. Moreover, other human coronaviruses, such as NL63-CoV, cause a mild illness even if they bind to the same receptor as SARS-CoV-2 and SARS-CoV [5]. So, in our opinion, it is likely that the different inoculum dose at the time of infection makes the difference in terms of severity of the disease; heavy inoculum exposures seem to be linked to a greater penetration into the lower respiratory tract, causing severe pneumonia, whereas lower inoculum exposures allow viruses to only reach the upper airway, causing a milder infection.

Viral loads are higher at the time of symptom onset and are higher in nose than in throat specimens [39,40]. Furthermore, in patients affected by COVID-19, viral load progressively decreases within days, following a different pattern from SARS in which the highest shedding is recorded after 10 days from symptom onset [39—41]. These findings suggest that SARS-CoV-2 may spread more easily in the community than SARS even when initial mild symptoms or no symptoms are present.

The differences in the intrinsic virulence of the viruses themselves can explain the different capacity for spreading. MERS-CoV has a higher mortality but a lower transmissibility, probably because it causes a more severe clinical picture than COVID-19 and SARS, requiring hospitalization more frequently, thus reducing the community spread of the infection and increasing the nosocomial

transmission [5,20]. On the other hand, the apparent higher mortality of MERS could be biased by the fact that most of the data available on MERS were derived from hospitalized patients, thus implicating a more severe clinical picture than community-acquired cases [42]. This hypothesis is strengthened by the observation that, when the cohort of patients with MERS was derived from the community and not from hospital outbreaks, the mortality rate decreased to 10%, as was observed in a cohort study carried out in 2015 in Saudi Arabia [42].

Interestingly, despite the high virological similarity between the SARS-CoV-2 and SARS-CoV, gastrointestinal symptoms and diarrhoea seem to be much more common in SARS, although the proportion of SARS patients with gastrointestinal symptoms varies among different studies, from 23% to 70% in the Toronto outbreak and in the Hong Kong community outbreak, respectively [41,43]. Such a difference could be related to the fact that the Hong Kong outbreak seemed to originate from a faecal contamination of a residential complex due to a faulty sewage system, while the Toronto outbreak was caused mainly by nosocomial hospital droplet transmission [41,43]. The gastrointestinal route of transmission has also been hypothesized for MERS-CoV through the consumption of infected camel milk; moreover, gastrointestinal transmission has been demonstrated in the animal model through intestinal DPP4 receptors [44]. From this finding, the reported detection of SARS-CoV-2 RNA in the loose stools of the first US patient with COVID-19 is not surprising [33]. SARS-CoV replicates in the enteric epithelium by binding to the ACE2 receptor, and it cannot be excluded that SARS-CoV-2 would behave in the same way [17]. This may contribute to the hypothesis that SARS-CoV-2 could also be transmitted via this route; there is also evidence that SARS-CoV and MERS-CoV remain viable in environmental conditions that could facilitate faecal—oral transmission [45]. In Table 3 we provide a synthesis of what is certain about COVID-19 to date and what needs to be further addressed.

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

Author contributions

NP and GV contributed to literature search and writing the paper. EP, OE and GI revised the manuscript and gave their final opinion on its intellectual content.

Transparency declaration

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