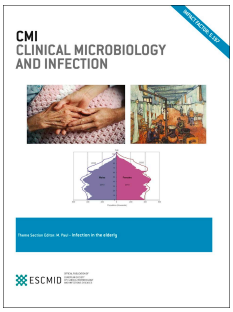
Journal Pre-proof



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

Nicola Petrosillo, Giulio Viceconte, Onder Ergonul, Giuseppe Ippolito, Eskild Petersen

PII: S1198-743X(20)30171-3

DOI: https://doi.org/10.1016/j.cmi.2020.03.026

Reference: CMI 1988

To appear in: *Clinical Microbiology and Infection*

Received Date: 16 February 2020

Revised Date: 9 March 2020

Accepted Date: 21 March 2020

Please cite this article as: Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E, COVID-19, SARS and MERS: are they closely related?, *Clinical Microbiology and Infection*, https://doi.org/10.1016/j.cmi.2020.03.026.

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

Nicola Petrosillo[1], Giulio Viceconte[2], Onder Ergonul[3,4], Giuseppe Ippolito[1], Eskild Petersen.[5,6,7]

[1]National Institute for Infectious Diseases "L. Spallanzani", IRCCS, Rome, Italy

[2]University "Federico II", Department of Clinical Medicine and Surgery, Naples, Italy

[3]Koc University, School of Medicine, Istanbul, Turkey

[4]ESCMID Executive Committee

[5]Directorate General for Disease Surveillance and Control, Min of Health, Muscat, Oman

[6]ESCMID Emerging Infections Task Force, ESCMID, Basel

[7]Institute for Clinical Medicine, Faculty of Health Sciences, University of Aarhus, Denmark

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 with cases reported worldwide. This novel Coronavirus Disease (COVID-19) is associated with a respiratory illness that may cause 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 have not been completely understood to date.

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

Sources: The most recent literature in 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 SARS (9.5%) and much lower than MERS (34.4%). It cannot be excluded that because of the COVID-19 less severe clinical picture it can spread in the community more easily than MERS and SARS. The actual basic reproductive number (R_0) of COVID-19 (2-2.5) is still controversial. It is probably slightly higher than the R_0 of SARS (1.7-1.9) and higher than MERS (<1),. The gastrointestinal route of transmission of SARS-CoV-2, which has been also assumed for SARS-CoV and MERS-CoV, cannot be ruled out and needs to be further investigated.

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

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, with cases reported in Europe, Australia and North America. Currently, at the date of 8th of March 2020, 105 586 confirmed cases have been reported in 101 countries with a total number of 3584 deaths.[1]

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

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

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

PHYLOGENY

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

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

structural proteins, namely spike (S), envelope protein (E), membrane protein (M) and nucleocapsid (N), plus 8 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 the SARS-CoV (**Table 1**). This suggests a different viral evolution from SARS and MERS, involving bats as wild reservoir. [9–14] Genomic comparison between SARS and SARS-CoV2 has shown that there are only 380 amino acid substitutions between SARS-CoV-2 and SARS-like coronaviruses, mostly concentrated in the nonstructural protein genes, while 27 mutations have been found on genes encoding for viral spike protein S responsible of receptor binding and cell entry.[8] This mutations might explain the apparent lower pathogenicity of SARS-CoV-2 than SARS-CoV, but further studies are required. [9]

PATHOGENICITY

Accumulating evidence based on genomic analysis suggest that SARS-CoV-2 shares the same human cell receptor with SARS-CoV, the angiotensin-converting enzyme 2 (ACE2), while MERS-CoV uses dipeptidyl peptidase 4 (DPP4) to enter in host's cells (**Table 1**).[15] It is well established that SARS-CoV emerged as human pathogen thanks to favorable mutations on the receptor binding domain (RBD) of the S protein, that increased its pathogenicity by strengthening its affinity to the receptor; it is therefore assumed that SARS-CoV-2 has behaved in a similar way.[15] However, in SARS-CoV-2 no amino acid substitutions were present in the RBD that directly interact with human receptor ACE2 compared with SARS-CoV, but six mutations occurred in the 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. [15] Moreover, it has

been predicted that a single nucleotide mutation on RBD of SARS-CoV-2, if occurs, could further increase its pathogenicity.[15]

ACE2 is an ectoenzyme anchored to the plasma membrane of the cells of several tissues, especially lower respiratory tract, heart, kidney and gastrointestinal tract.[16] Inoculation of the 2019-nCoV onto surface layers of human airway epithelial cells in vitro causes cytopathic effects and cessation of the cilia movements.[17] 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.[16,18] It must be further investigated if the higher receptor affinity of SARS-CoV-2 than SARS-CoV for ACE2 could lead to a more severe lung involvement in COVID-19 than in SARS.

TRANSMISSIBILITY

The reproductive number (R_0) of the novel infection is estimated by World Health Organization (WHO) to range between 2 and 2.5, which is higher than SARS (1.7-1.9) and MERS (<1), suggesting that SARS-CoV-2 has a higher pandemic potential.[19–23] However, it must be noted that some published studies have estimated a R_0 for SARS reaching the value of 4.[24] 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.[25] Nonetheless, in **Table 1** we only report the WHO data, since the estimation of R0 depends on the estimation method used and the current estimate can be biased by insufficient data and short onset time of the diseases, as Liu and colleagues also state.

According to a recent large descriptive study carried out by the Chinese Center for Disease Control and Prevention (CCDC) on 44 672 individuals diagnosed with COVID-19 in China, the fatality rate of novel coronavirus infection is estimated to be 2.3[26], lower than SARS (9.5%) and much lower than MERS (34.4%).[5,27] Interestingly, according to CCDC, the case fatality rate in the Hubei province,

where the epidemic has started, is 7-fold higher than other provinces.[26] This could be related to the fact that, among the 44 672 cases reported by CCDC, 10 567 (14.6%) cases were diagnosed only clinically and exclusively in the Hubei province. Therefore, it cannot be excluded that clinically diagnosed cased presented with a more severe clinical picture, thus increasing the case fatality rate.[26] After the change of case definition, the number of cases increased due to the inclusion of cases cumulated over the past 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 outside of China is currently 24 727 with 484 fatal outcomes, and 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%.[28,29]

CLINICAL FEATURES

Up to date, complete clinical data concerning COVID-19 have been reported for 458 cases in the English-language literature, of which 415 from Hubei province in China[2–4,30], 17 in other Chinese provinces[31,32], 25 in Korea[33,34] and 1 in USA[35]. 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 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 symptoms is fever, followed by cough, sore throat and dyspnea; all of the infected patients had at least one symptom. However, according to the CCDC report, 81% of the cases had mild symptoms and 1.2% were asymptomatic.[26]

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 can be interesting to know if the virus associated lymphopenia affects in a different way CD4+ and CD8+ subpopulations, to predict the possible development of superimposed bacterial or opportunistic infections, which have currently been reported in a small amount of cases to date.[2]

Radiological presentation of COVID-19 is not much different from the other two coronavirus-associated pneumonia, 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.[36] 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 subject (3%) had a CT scan that was strongly suggestive of COVID-19, but an initially negative real-time polymerase 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.[37]

Patient diagnosed with COVID-19 may have an unfavorable clinical course with the onset of dyspnea within 5 days, ARDS within 8 days in 30% of cases and 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 clinical course of MERS seems to be characterized by a more frequent development of ARDS and needing of invasive life support, especially in elderlies and smokers.[38] 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 multi-organ failure, which occurs more frequently in MERS than in the other coronavirus infections.[39]

CONCLUSIONS

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

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

Which are the causes of such different ability to spread among these three viruses? A first hypothesis is a different viral tropism for the respiratory tract, resulting in a milder but highly transmittable 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 alpha 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 alpha 2,3-linked sialic acid in the lung alveoli, causing severe pneumonia.[40] On the other hand, SARS-CoV-2, SARS-CoV and MERS-CoV use receptors that have been found both in the upper and in the lower respiratory tract. Moreover, other human coronaviruses, such as NL63-CoV, cause a mild illness even if they bind to the same receptor of 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 an higher penetration in the lower respiratory tract, giving 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 symptoms onset and higher in nose than in throat specimens.[41,42] Furthermore, in patients affected by COVID-19, viral load progressively decreases within days, following a different pattern than SARS, in which the highest shedding is recorded after 10 days from the symptoms' onset.[41–43] 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 of 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 spreading of the infection and increasing the nosocomial transmission.[5,21] On the other hand, the higher mortality of MERS could be biased by the fact that the largest data available on MERS were derived from hospitalized patients, thus implicating a more severe clinical picture than community acquired cases.[44] 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 it has been observed in a cohort study carried out in 2015 in Saudi Arabia.[44]

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

fecal contamination of a residence complex due to a faulty sewage system, while the Toronto outbreak was mainly caused by nosocomial hospital droplet transmission.[43,45] The GI route of transmission has been also hypothesized for MERS-CoV, through the consumption of infected camel milk; moreover, GI transmission has been demonstrated in the animal model through intestinal DPP4 receptors.[46] According to this findings, the reported detection of SARS-CoV-2 RNA in the loose stools of the first US patient with COVID-19 is not surprising.[35] 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.[18] This may contribute to the hypothesis that SARS-CoV-2 could also be transmitted via this route, together with the evidence that SARS-CoV and MERS-CoV remain viable in environmental conditions that could facilitate faecal–oral transmission.[47] In **Table 3** we provide a synthesis of what is certain to date about COVID-19 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 of spreading on a pandemic level. The lessons we have learned in the past from the SARS and MERS epidemics are the best cultural weapons to face this new global threat.

224

225

	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%[26]	2-2.5[19]
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

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

227

228

	COVID-19[1–3]	*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

Table 2 - Clinical characteristics

234

Facts about COVID-19	Questions needing to be further assessed
• 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.	• 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*

236

TRANSPARENCY DECLARATION

• Conflict of interest disclosure: authors have no conflict of interest to disclose.

• Funding: no external funding was received.

• Acknowledgments: work supported by Ricerca Corrente, IRCCS.

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

REFERENCES

1. World Health Organization. Coronavirus Disease 2019 (COVID-19) Situation Report-48, 08th March 2020. Availabe from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200308-sitrep-48-covid-19.pdf?sfvrsn=16f7ccef_4
2. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet (London, England)*. 2020;0(0). doi:10.1016/S0140-6736(20)30211-7
3. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. February 2020. doi:10.1001/jama.2020.1585
4. Liu K, Fang Y-Y, Deng Y et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)*. 2020. doi:10.1097/CM9.0000000000000744
5. Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E. A Novel Coronavirus Emerging in China — Key Questions for Impact Assessment. *N Engl J Med*. January 2020:NEJMp2000929. doi:10.1056/NEJMp2000929
6. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. *J Med Virol*. February 2020:jmv.25681. doi:10.1002/jmv.25681
7. Malik YS, Sircar S, Bhat S, et al. Emerging novel Coronavirus (2019-nCoV) - Current scenario, evolutionary perspective based on genome analysis and recent developments. *Vet Q*. February 2020:1-12. doi:10.1080/01652176.2020.1727993

8. Wu A, Peng Y, Huang B, et al. Commentary Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. *Cell Host Microbe*. February 2020:1-4. doi:10.1016/j.chom.2020.02.001

9. Benvenuto D, Giovanetti M, Ciccozzi A, Spoto S, Angeletti S, Ciccozzi M. The 2019-new coronavirus epidemic: Evidence for virus evolution. *J Med Virol*. February 2020:jmv.25688. doi:10.1002/jmv.25688

10. Fuk-Woo Chan J, Yuan S, Kok K-H, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020;0(0). doi:10.1016/S0140-6736(20)30154-9

11. Chan JF-W, Kok K-H, Zhu Z, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect*. 2020;9(1):221-236. doi:10.1080/22221751.2020.1719902

12. Wu A, Peng Y, Huang B, et al. Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. *Cell Host Microbe*. February 2020. doi:10.1016/j.chom.2020.02.001

13. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet (London, England)*. 2020;0(0). doi:10.1016/S0140-6736(20)30251-8

14. Paraskevis D, Kostaki EG, Magiorkinis G, Panayiotakopoulos G, Sourvinos G, Tsiodras S. Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. *Infect Genet Evol*. 2020;79:104212. doi:10.1016/j.meegid.2020.104212

15. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. *J Virol*. January 2020.

doi:10.1128/JVI.00127-20

16. Imai Y, Kuba K, Ohto-Nakanishi T, Penninger JM. Angiotensin-Converting Enzyme 2 (ACE2) in Disease Pathogenesis. *Circ J*. 2010;74(3):405-410. doi:10.1253/circj.CJ-10-0045

17. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. January 2020. doi:10.1056/nejmoa2001017

18. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203(2):631-637. doi:10.1002/path.1570

19. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), 16-24 February 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf. Accessed March 09, 2020.

20. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *N Engl J Med*. January 2020:NEJMoa2001316. doi:10.1056/NEJMoa2001316

21. Chen J. Pathogenicity and Transmissibility of 2019-nCoV-A Quick Overview and Comparison with Other Emerging Viruses. *Microbes Infect*. February 2020. doi:10.1016/j.micinf.2020.01.004

22. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *Lancet (London, England)*. January 2020. doi:10.1016/S0140-6736(20)30260-9

23. Liu T, Hu J, Kang M, et al. Transmission dynamics of 2019 novel coronavirus (2019-nCoV). *bioRxiv*. January 2020:2020.01.25.919787. doi:10.1101/2020.01.25.919787

24. Bauch CT, Lloyd-Smith JO, Coffee MP, Galvani AP. Dynamically Modeling SARS and Other

Newly Emerging Respiratory Illnesses. *Epidemiology*. 2005;16(6):791-801. doi:10.1097/01.ede.0000181633.80269.4c

25. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med*. February 2020. doi:10.1093/jtm/taaa021

26. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. *China CDC Wkly*. 2020;8(2):113-122. http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51. Accessed February 20, 2020.

27. Chen J. Pathogenicity and Transmissibility of 2019-nCoV-A Quick Overview and Comparison with Other Emerging Viruses. *Microbes Infect*. February 2020. doi:10.1016/j.micinf.2020.01.004

28. Wu P, Hao X, Lau EHY, et al. Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020. *Eurosurveillance*. 2020;25(3):2000044. doi:10.2807/1560-7917.ES.2020.25.3.2000044

29. World Health Organization, Department of Communicable Disease Surveillance and Response. Consensus Document on the Epidemiology of Severe Acute Respiratory Syndrome (SARS), 16-17th May 2003.

30. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan , China. *Lancet*. 2020;6736(20):1-10. doi:10.1016/S0140-6736(20)30183-5

31. Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. doi:10.5582/bst.2020.01030

32. Chang D, Lin M, Wei L, et al. Epidemiologic and Clinical Characteristics of Novel Coronavirus

Infections Involving 13 Patients Outside Wuhan, China. *JAMA*. February 2020. doi:10.1001/jama.2020.1623

33. Kim JY, Choe PG, Oh Y, et al. The First Case of 2019 Novel Coronavirus Pneumonia Imported into Korea from Wuhan, China: Implication for Infection Prevention and Control Measures. *J Korean Med Sci*. 2020;35(5):e61. doi:10.3346/jkms.2020.35.e61

34. Ki M, -nCoV TFF. Epidemiologic characteristics of early cases with 2019 novel coronavirus (2019-nCoV) disease in Republic of Korea. *Epidemiol Health*. 2020:e2020007. doi:10.4178/epih.e2020007

35. Holshue ML, DeBolt C, Lindquist S, et al. First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med*. January 2020:NEJMoa2001191. doi:10.1056/NEJMoa2001191

36. Chung M, Bernheim A, Mei X, et al. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). *Radiology*. February 2020:200230. doi:10.1148/radiol.2020200230

37. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical 2019-nCoV Pneumonia: Relationship to Negative RT-PCR Testing. *Radiology*. February 2020:200343. doi:10.1148/radiol.2020200343

38. Azhar EI, Hui DSC, Memish ZA, Drosten C, Zumla A. The Middle East Respiratory Syndrome (MERS). *Infect Dis Clin North Am*. 2019;33(4):891-905. doi:10.1016/j.idc.2019.08.001

39. Cha RH, Joh JS, Jeong I, et al. Renal Complications and Their Prognosis in Korean Patients with Middle East Respiratory Syndrome-Coronavirus from the Central MERS-CoV Designated Hospital. *J Korean Med Sci*. 2015;30(12):1807-1814. doi:10.3346/jkms.2015.30.12.1807

40. Yang W, Punyadarsaniya D, Lambertz RLO, et al. Mutations during the Adaptation of H9N2 Avian Influenza Virus to the Respiratory Epithelium of Pigs Enhance Sialic Acid Binding Activity and Virulence in Mice. *J Virol*. 2017;91(8). doi:10.1128/jvi.02125-16

41. Kim JY, Ko J-H, Kim Y, et al. Viral Load Kinetics of SARS-CoV-2 Infection in First Two Patients in Korea. *J Korean Med Sci*. 2020;35(7). doi:10.3346/jkms.2020.35.e86

42. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med*. February 2020:NEJMc2001737. doi:10.1056/NEJMc2001737

43. Peiris JSM, Chu CM, Cheng VCC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: A prospective study. *Lancet*. 2003;361(9371):1767-1772. doi:10.1016/S0140-6736(03)13412-5

44. Bleibtreu A, Bertine M, Bertin C, Houhou-Fidouh N, Visseaux B. Focus on Middle East respiratory syndrome coronavirus (MERS-CoV). *Médecine Mal Infect*. November 2019. doi:10.1016/j.medmal.2019.10.004

45. Booth CM. Clinical Features and Short-term Outcomes of 144 Patients With SARS in the Greater Toronto Area. *JAMA*. 2003;289(21):2801. doi:10.1001/jama.289.21.JOC30885

46. Zhou J, Li C, Zhao G, et al. Human intestinal tract serves as an alternative infection route for Middle East respiratory syndrome coronavirus. *Sci Adv*. 2017;3(11):eaao4966. doi:10.1126/sciadv.aao4966

47. Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal–oral transmission of SARS-CoV-2 possible? *Lancet Gastroenterol Hepatol*. 2020;0(0). doi:10.1016/S2468-1253(20)30048-0

48. Hui DSC, Zumla A. Severe Acute Respiratory Syndrome. *Infect Dis Clin North Am*. 2019;33(4):869-889. doi:10.1016/j.idc.2019.07.001

49. Lee N, Hui D, Wu A, et al. A Major Outbreak of Severe Acute Respiratory Syndrome in Hong Kong. *N Engl J Med*. 2003;348(20):1986-1994. doi:10.1056/NEJMoa030685

50. Chu KH, Tsang WK, Tang CS, et al. Acute renal impairment in coronavirus-associated severe

acute respiratory syndrome. *Kidney Int*. 2005;67(2):698-705. doi:10.1111/j.1523-1755.2005.67130.x

51. Choi WS, Kang C-I, Kim Y, et al. Clinical Presentation and Outcomes of Middle East Respiratory Syndrome in the Republic of Korea. *Infect Chemother*. 2016;48(2):118. doi:10.3947/ic.2016.48.2.118

52. Saad M, Omrani AS, Baig K, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: A single-center experience in Saudi Arabia. *Int J Infect Dis*. 2014;29:301-306. doi:10.1016/j.ijid.2014.09.003