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# SARS-CoV-2, SARS and MERS: Three formidable coronaviruses which have originated from bats

## SARS-CoV-2, SARS-CoV i MERS-CoV: Trzy groźne koronawirusy pochodzące od nietoperzy

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### Summary

The recent continuously emerging rampancy of novel coronavirus (SARS-CoV-2) that started in Wuhan in late December 2019 has become an international public health emergency and is still spreading rapidly in the world. Up to October 11, 2020, 37.109.6851 confirmed cases of COVID-19 have been announced with 2.8 percent death, which means 1.070.355 confirmed death cases. At the moment, a specific vaccine or drug for the new coronavirus is not available; thus, the development of a drug with far-reaching HCoV inhibitory activity is an urgent medical need. It is, however, vital to first comprehend the nature of this family and other coronaviruses that have caused the outbreak. Here, we relate the epidemiological and virological characteristics of the COVID-19, SARS, and MERS rampancy.

**Keywords:** COVID19, SARS-CoV-2, SARS, MERS, Coronavirus

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**Abbreviations:** **ACE-2** – angiotensin-converting enzyme-2, **ALI** – acute lung injury, **ARDS** – acute respiratory distress syndrome, **CoVs** – Coronavirus, **DPP4** – dipeptidyl 4, **MERS** – Middle East respiratory syndrome, **RBD** – Receptor binding domain, **RBM** – receptor-binding motif, **SARS** – severe acute respiratory syndrome.

### INTRODUCTION

In the last two decades, new coronaviruses have emerged globally. For instance, severe acute respiratory syndrome (SARS-CoV) in 2002 and the Middle East respiratory syndrome (MERS) in 2012 were both devastating new human coronaviruses (HCoVs), which that greatly affect the respiratory tract. Recently, the unprecedented emergence of HCoV has caused unexplained pneumonia in Wuhan, Hubei province, China. In Feb. 2020, the virus was officially called

SARS-CoV-2 by the WHO, and the disease was designated COVID-19, which stands for coronavirus disease 2019 [19].

This review emphasizes the pandemic and epidemic potential of the emerging coronaviruses and discusses the current state of knowledge on the biology, genome and protein characteristics, animal reservoirs, the pathogenesis of SARS-CoV-2 and tries to furnish a reference for drug development based on the researcher's current knowledge of SARS-CoV, MERS-CoV.



Fig. 1. History of SARS-CoV (a), MERS-CoV (b), and COVID-19 epidemic consequence

## HISTORY

In November 2002, the first case of severe acute respiratory syndrome (SARS) erupted in Foshan, China. In March 2003, clusters of atypical pneumonia were reported in several countries [32, 34, 46], and soon after, SARS crossed 26 countries, causing 8,096 reported cases and 774 deaths (9.6%) [13, 34, 46]. The World Health Organization (WHO) appointed a network of labs to characterize the disease's causative agent. In March 2003, global efforts led to the identification of a novel CoV, SARS coronavirus (SARS-CoV). The outbreak was partly controlled using quarantining, and the disease was finally controlled in June 2003. Some SARS-CoV-like viruses were discovered in bats, which presented as being able to contaminate human cells without former coincidence, which indicated that SARS could reappear [16].

Ten years later, in June 2012, a man with acute pneumonia and renal failure died in Saudi Arabia. A novel coronavirus, named Middle East respiratory syndrome coronavirus (MERS-CoV), was isolated from his sputum [9]. After that, some cases of MERS were diagnosed in Jordan, the UK, and

outside the Arabian Peninsula [10, 58]. In 2015, MERS-CoV spread across 15 countries, starting the second pandemic in South Korea. In November 2019, the WHO reported 2,494 laboratory-confirmed cases of MERS-CoV infection, including 858 deaths (35%) in 27 countries ([www.who.int/emergencies/mers-cov/en/](http://www.who.int/emergencies/mers-cov/en/)).

In late December 2019, a group of patients with unknown pneumonia were reported in Wuhan, Hubei Province, China [59]. A novel CoV was isolated from the epithelial cells of the respiratory tract of a patient. The Wuhan Municipal Health Commission at the end of December 2019 reported the new outbreak of viral pneumonia with an idiopathic pathogen in Wuhan, China, in four employees of South China Seafood Wholesale Market [53].

Today, the number of infected people with this virus around the world is increasing, which requires more attention and work [20]. By 11 October 2020, 37,109,851 confirmed cases and 1,070,355 (2.8%) deaths were reported from more than 200 countries worldwide. The overall perspective of SARS, MERS, and SARS-CoV-2 epidemic development is presented in Fig. 1a-c, sequentially.

## CLASSIFICATION

Coronaviruses (CoVs) are enveloped positive-stranded RNA viruses that are generally distributed among humans, other mammals, and birds, causing acute and persistent infections. Coronaviruses are the largest group among the *Nidovirales*. From the four identified genera (Alpha-, Beta-, Gamma-, and Delta), human coronaviruses (HCoVs) were classified in alpha- (HCoV-229E and NL63) and beta- (SARS-CoV, HCoV-OC43, HCoV-HKU1, and MERS-CoV) coronavirus genera [16]. People around the world are frequently confronted and infected in their life with four HCoVs (OC43, HKU1, NL43, 229E), which typically leads to an upper respiratory tract infection manifested by typical cold symptoms [24]. The most harmful CoVs, such as severe acute respiratory syndrome (SARS-CoV) in 2002, Middle East respiratory syndrome (MERS) in 2012, and these new SARS-CoV-2, transmit from animals to humans and spread further from human to human [19]. Although generally associated with mild, upper respiratory tract infections, the currently existing human CoVs can also cause lower respiratory infections and have the most severe complications in the young, elderly, and immunocompromised individuals. This novel CoV, SARS-CoV-2, belongs to the beta coronavirus genus based on phylogenetic clustering [57].

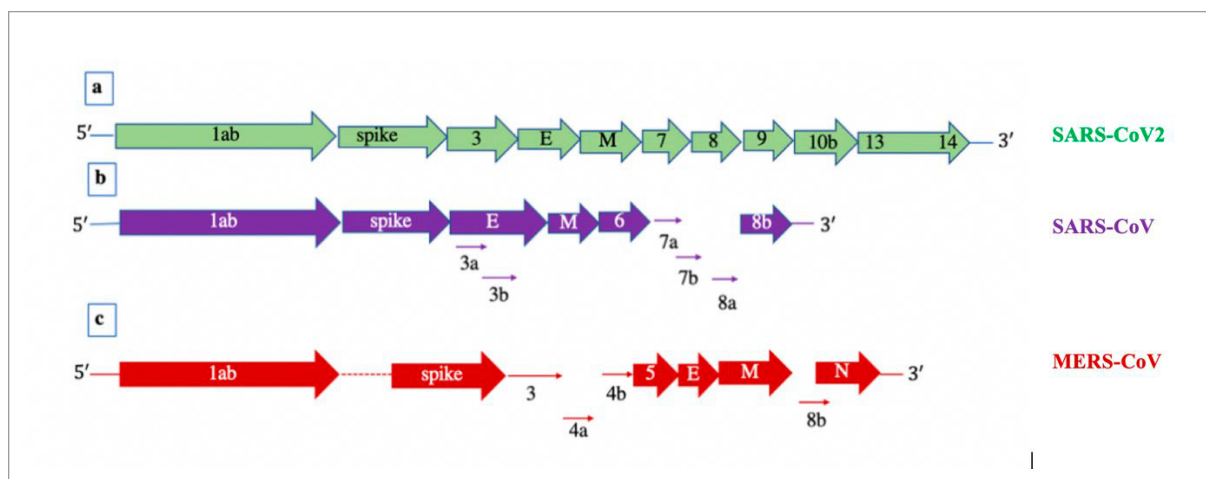
## GENOME ORGANIZATION

The coronavirus has the largest genome among RNA viruses, including RNA viruses that have segmented genomes. The genome sizes SARS-CoV, MERS-CoV, and SARS-CoV-2, are 27.9, 30.1 kb, and 29.9 kb, respectively. Likewise, all viruses in the order *Nidovirales*, SARS-CoV, MERS-CoV and SARS-CoV-2 have a singular coding scheme: viral genomic RNA translates to two large polyproteins (pp1a and pp1ab that nonstructural code proteins), and the rest of the viral genome is transcribed into subgenomic mRNA from transcribed negative-sense RNA [42, 43]. SARS- and MERS-CoV transcribe 12 and 9 subgenomic RNAs, respectively. Coronaviruses contain a set of four major structural

proteins: the spike (S), envelope (E), membrane (M) proteins, which are located in the envelope, and nucleocapsid (N), found in the ribonucleoprotein helical core. Also, several accessory proteins that are not involved in viral replication but interfere with the host innate immune response or with unknown or poorly understood function are produced in infected cells [15] (Fig. 2). The genome comparison between SARS-CoV and SARS-CoV-2 demonstrates that they have more than 85% similarity in their genomes at the level of nucleotides. There are six regions of difference (RD) between the SARS-CoV and SARS-CoV-2 genome, and three of them (RD1, RD2, RD3) code partial sequence of ORF1ab gene, two of RDs (RD4, RD5) are partial coding sequence of the spike genome. Also, RD6 is part of ORFs 7b and 8. These are probably new targets to help us develop new drugs against SARS-CoV-2 [62]. Phylogenetic analysis showed that SARS-CoV-2 exhibited about 50% of the sequence of MERS-CoV. Therefore, this virus is closer to SARS-CoV strains than to MERS-CoV [39].

## RESERVOIRS AND TRANSMISSION

SARS-CoV, MERS-CoV, and SARS-CoV-2 most probably have a zoonotic origin. Sequence analysis has revealed that bats are the potential animal reservoirs [42]. The SARS-CoV outbreak demonstrated that the ability of CoVs to cross species, as the virus, naturally a bat virus, was able to infect humans and small mammals such as Himalayan palm civets (*Paguma larvata*), raccoon dogs (*Nyctereutes procyonoides*), and a Chinese ferret badger (*Melogale moschata*) in the Guangdong Province [21]. The search for the source of MERS-CoV was initially focused on bats. The serological investigation by the Food and Agriculture Organization in 2011 declared that the primary causes of MERS-CoV in Jordan, Saudi Arabia, and the United Arab Emirates might be the meat and milk of cows, goats, sheep, and dromedary camels [24, 47, 49]. Full genomic sequence analysis from the Shanghai Public Health Clinical Center argued for a bat origin for the SARS-CoV-2. By investigating the virome composition of pangolin, multiple ancestors of pangolin



**Fig. 2.** Genomic comparison among SARS-CoV, MERS-CoV, and SARS-CoV-2. A schematic of the complete genome of SARS-CoV-2 (a), SARS-CoV (b), and MERS-CoV (c) are shown

coronavirus have been discovered, and their similarity to SARS-CoV-2 suggests that pangolins should be considered as possible hosts in the emergence of novel coronaviruses and should be removed from wet markets to prevent zoonotic transmission [62]. Furthermore, vertical transmission of SARS-CoV-2 is possible and increasingly reported [64]. In addition to the ability to cross species, CoVs readily undergo recombination. This potential has raised concerns about the use of live attenuated coronavirus vaccines and the likelihood of an emerging virus via contact with infected animals in wet markets.

## ENTRY AND UNCOATING

The entry of virions into cells results from the fusion of viral and cellular membranes [17].

Coronaviruses use S (spike) glycoprotein to bind to the host cell receptor. The known receptor for SARS-CoV is angiotensin-converting enzyme-2 (ACE2). Furthermore, an alternative receptor, CD209L, with lower affinity, is considered. ACE2 is broadly expressed in the respiratory tract and on alveolar epithelial cells, tracheae, bronchi, bronchi serosa glands, alveolar monocytes, and macrophages [43]. The receptor role of ACE2 seems to be independent of its enzymatic activity. An analysis of the SARS-CoV receptor-binding domain (RBD)-ACE2 interface demonstrated a mutation of only two key RBD residues, which was sufficient to cross the species barrier [16]. Spike receptor binding domain (RBD) of SARS-CoV-2 accurately identifies the ACE2 receptor of the host. The structure of RBD demonstrates that the SARS-CoV-2 RBD domain contains a core-like structure and one receptor-binding motif (RBM). RBM attaches to the outer paw-like structure of the ACE2 receptor. Furthermore, such specific amino acids in some positions enhanced the affinity of SARS-CoV-2 spike protein to human ACE2 [15].

The S proteins of many CoVs are uncleaved in mature virions and require a cellular protease at the entry step to separate the receptor binding (S1) from the fusion domain (S2) of the spike. SARS-CoV can use the endosomal cysteine proteases cathepsin B and L (CatB/L) for S protein priming. Alternatively, cell-bound SARS-CoV can be activated by TMPRSS2. This transmembrane serine protease, which is expressed in pneumocytes, co-localizes with and binds to ACE-2. This route of activation greatly enhances the infectivity of SARS-CoV and allows the virus to enter from the cell surface. A more recent study demonstrated that SARS-CoV-2 uses TMPRSS2 for priming. TMPRSS2 inhibitors might be considered a treatment option. The S1 domain is hugely variable. By contrast, the S2 domain is highly conserved [8]. This spike stalk in SARS-CoV-2 is highly conserved and shares 99% identity with bats SARS-like CoVs and SARS-CoV [9]. Thus, broad-spectrum antiviral peptides against S2 has treatment potency [30]. The coronavirus S protein is a class I viral fusion protein with domains functionally similar to other viral fusion proteins such as the influenza virus, HIV, and Ebola virus. Like those other viral fusion proteins, the CoVs S2 domain contains two

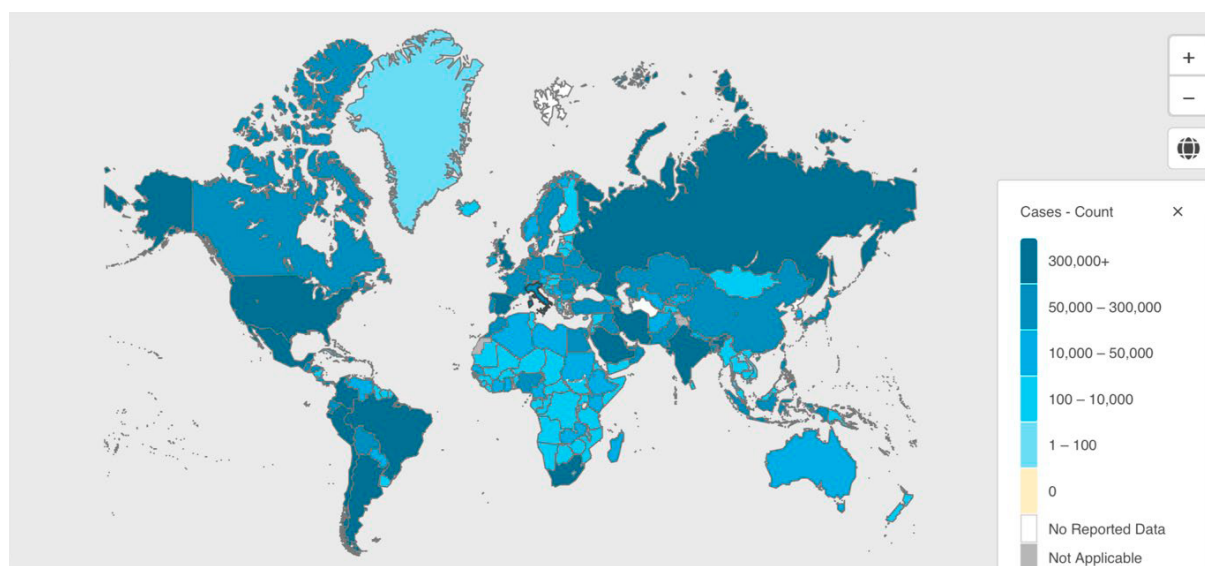
separated heptad repeats, HR1 and HR2, with a fusion peptide upstream HR1 and the transmembrane area immediately downstream of HR2. Soon after priming, the two HR1 and HR2 are brought together to form a six-helix bundle. The outcome is sufficient to allow fusion of the virus envelope with cellular membranes. Therefore, it is rational to consider HR1 also to be the right candidate for the development of fusion inhibitors against highly pathogenic HCoVs. Enfuvirtide is a synthetic peptide of 36 amino acids that mimics an HR2 fragment of HIV fusion protein, gp41. Its binding to the HR1 region blocks the formation of the six-helix bundle structure, which is critical for the fusion process [5]. Such approved and available fusion inhibitor drugs might be considered in the treatment of COVID-19. The MERS-CoV's primary receptor is DPP4 (dipeptidyl 4, also known as CD26) that is broadly expressed in epithelial cells of the kidney, intestine, liver, alveoli, prostate, and activated leukocytes. Therefore, MERS-CoV could infect multi-human cell lines, including the lower respiratory tract, kidney, intestine, histocytes, and liver cells. Tissue tropism in MERS is broader than in other coronaviruses. Also, it can cause high lethal acute pneumonia and kidney dysfunction [48]. DPP4 receptor MERS-CoV receptor is proved not to be a receptor of SARS-CoV-2 [27].

## PATHOGENESIS AND PATHOLOGY MECHANISM

Human-to-human transmission of SARS-CoV, MERS-CoV, and SARS-CoV-2 occurred through the nosocomial transmission. Effectual human-to-human includes multiple transmission routes, such as secretions from respiratory tracts, direct and indirect contact. About 43.5% to 100% of MERS-CoV cases in individual outbreaks are correlated with hospital and are very similar to some clusters of SARS-CoV. Transfer among family members occurred 13–21% and 2–39% of MERS-CoV and SARS-CoV cases, respectively [30]. Moreover, so far, respiratory droplets are the most significant route of transmission in the new emerging coronavirus. There are some routes that are still not confirmed but must also be noticed; the fecal-oral path is one that must be considered and later will be confirmed with the detection of SARS-CoV-2 nucleic acids in the stool samples of pneumonia patients with abdominal symptoms [67]. Another one is transmission via the ocular surface, which could be contaminated easily with droplets and secretions that contain the virus [38].

## HUMAN CORONAVIRUS INFECTIONS

All three CoVs cause the most severe disease of any human CoV [37]. The virus infects upper and alveolar epithelial cells, resulting in mild to severe lung injury [15]. SARS-CoVs are also detected in the kidney, liver, small intestine, and in the stool. Although the lung is recognized as the most severely affected organ, the exact mechanism of lung injury is controversial. The spike protein (S) may contribute to the severity of the disease. The S protein facilitates the entrance of CoVs into the host cell via primary attachment to the ACE2 and virus infusion with the host membrane. Following attachment, the S protein



**Fig. 3.** Distribution of SARS-CoV-2 in the world

downregulates ACE2, and this may exacerbate the disease during SARS-CoV [69]. Cells in the upper respiratory airway are initially infected, resulting in little epithelial cell damage. However, the virus rapidly spreads to the alveoli, causing diffuse alveolar damage.

Overtime, alveolar damage has progressed, resulting in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). ARDS is the a joint immunopathological event for SARS-CoV-2, SARS-CoV, and MERS-CoV infections [63]. ARDS is the leading cause of death in COVID-19 patients. There are two-phased immune responses (innate and adaptive immune response) inferred by SARS-CoV-2 infection during the incubation and non-severe phases. As mentioned, the entrance of the virus occurs with the interaction of ACE2 and toll-like receptor 7 (TLR7), and then TLR7 activation leads to the production of an interleukin cascade such as alpha-interferon, TNF-alpha, IL12, and IL6, which lead to the formation of CD8+ -specific cytotoxic T cells and, via the CD4+ T helper cell, lead to the production of B-cells and antibody. Specific adaptive immunity is needed to remove the virus and to prevent the disease from developing to severe stages. Hence, strategies to enhance immune responses (anti-sera or pegylated IFN- $\alpha$ ) at this phase are undoubtedly important [50, 63]. When the body cannot produce enough adaptive immune response against the virus, unremitting innate-inferred inflammation could result in a cytokine storm [1, 18]. One of ARDS's primary mechanisms is the cytokine storm, the deadly uncontrolled systemic inflammatory response [28]. The cytokine storm will trigger a violent attack by the immune system to the body, cause ARDS and multiple organ failure, and finally lead to death in severe cases of SARS-CoV-2 infection, which is exactly what occurs in SARS-CoV and MERS-CoV infection [63].

MERS-CoV infection in humans, the primary receptor, is a multi-functional cell surface protein, which is DPP4 or the same CD26, broadly expressed in the epithelial cells of the

kidney, intestine, liver, alveoli, prostate, and activated leukocytes. Therefore, MERS-CoV could infect multi-human cell lines, including the lower respiratory tract, kidney, intestine, histocytes, and liver cells. Tissue tropism in MERS is broader than in other coronaviruses. Also, it can cause high lethal acute pneumonia and kidney dysfunction. DPP4 receptor for MERS-CoV entrance highly expressed in the kidney and, for this reason, results in kidney dysfunctional either by hypoxia damage or epithelial infecting [48, 54].

### CLINICAL FEATURES

The average age and man to woman ratio for SARS-CoV infection were 39.9 (1–91 years) and 1:1.3, respectively [2]. SARS-CoV has caused more disease in the healthcare setting [46], has the incubation time is 4.6 days, and it has a case fatality ratio (CFR) about 11% [3, 34]. The primary clinical manifestation of SARS-CoV was fever (100%), cough (61.8%), myalgia (48.7%), dyspnea (40.8%), and diarrhea (31.6%) [55]. The average age in MERS-CoV infection was 56 (14–94), but with higher mortality than in SARS-CoV due to the infection severity and the extreme need for mechanical ventilators. Generally, 35% of patients with MERS died. The clinical manifestations of MERS-CoV infection differ from asymptomatic infections to severe pneumonia; MERS patients present after an incubation period of 2 to 14 days with fever, chills, myalgia, cough, and dyspnea. Some patients have gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Fever may be absent in up to 15% of hospitalized cases [31, 65]. The exact incubation period for COVID-19 is not known. It is presumed to be between 2 to 14 days after exposure, with most cases occurring within three to five days after exposure [21]. It is estimated that the case fatality rate in COVID-19 is 2.4%. As put forward by Tindale et al., Zhanwei Du et al., and H. Nishiura et al., the serial interval for COVID-19 is estimated at about four days, with approximately 40 to 80% of transmission occurring two to four days before the onset of symptoms in infected patients, which is dramatically lower than in



**Table 1.** Comparison among SARS-CoV, MERS-CoV and SARS-CoV-2 in respect to their virology, epidemiology, and clinical manifestation

	MERS-CoV	SARS-CoV	SARS-CoV-2
Virology	Betacoronavirus lineage 2C	Betacoronavirus lineage 2B	Betacoronavirus lineage B
Receptor	hDPP4	ACE2	Angiotensin-converting enzyme 2 (ACE2)
Genome Size	30.1kb	27.9kb	29.9kb
Source	Evolutionary origin: bats Intermediate host: Not yet confirmed camel is the likely host Limited	Evolutionary origin: horseshoe bats Intermediate host: palm civets, raccoon dogs, and Chinese ferret badger	Evolutionary origin: horseshoe bat Intermediate host: Pangolin, cats
Epidemiology	Zoonotic, human to human transmission, the disease is mostly localized in the Middle East, Eastern Africa, and Northern Africa	Human to human transmission is well-recognized, affected many countries	Human-to-human transmission respiratory droplets is the major route of transmission, fecal-oral route of transmission is considered but unconfirmed, Vertical transmission
Respiratory failure	More common	Less common	More common
Travel association	Limited travel-associated exposure	Recognized travel-associated exposure	Recognized travel-associated exposure
Incubation period	0–16 days	2–8 days	4–8 days
Male to Female Ratio	3.3:1	1:1.3	2.7:1
Clinical presentation	Unpredictable and erratic clinical course ranging from asymptomatic illness to severe pneumonia	A typical biphasic clinical course	Fever, dry cough, and shortness of breath, and most patients (80%) experienced mild illness.
Laboratory Features	Leukopenia (42.6%), thrombocytopenia (46.6%), and elevation of aspartate aminotransferase (42.7%)	Lymphopenia, features of low grade disseminated intravascular coagulation (thrombocytopenia, prolonged activated partial thromboplastin time, elevated D-Dimer), elevated alanine transaminases (ALT), lactate dehydrogenase (LDH) and creatinine kinase (CPK)	Higher levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GT) and $\alpha$ -hydroxybutyric dehydrogenase ( $\alpha$ -HBDH)

SARS-CoV and MERS-CoV 40, [40, 53]. Pre-symptomatic transmissions have occurred more than symptomatic ones, because the serial interval is shorter than the incubation period. A significant ratio of secondary transmission occurred before the disease inception, which indicates that many contagious influences cannot be prevented only by the isolation of symptomatic cases. They may have already become infectious themselves and produced secondary cases [35].

SARS-CoV-2 spreads more rapidly than SARS and MERS. The basic reproduction number (R0) is a sign of a virus's transmissibility, demonstrating the average number of new infections begotten. R0 estimates for SARS and MERS-CoV of approximately 3 and <1 have been reported respectively, within the range of the mean R0 for COVID-19 which is the reason that COVID-19 is already more widespread than SARS-CoV and MERS-CoV, indicating it may be more transmissible [36]. Also, the lag between the entrance of the virus until the onset of the disease is broader than other infections in this family virus [50]. COVID-19 has similarities with SARS patients, but the principal manifestation of this disease are fever, fatigue, and dry cough [10] (Fig. 3 and Table 1).

## DIAGNOSIS

The laboratory diagnostic tests and imaging modality are used to detect COVID-19. The laboratory diagnostic tests are divided into molecular assays for the detection of SARS-CoV-2 viral RNA, which use polymerase chain reaction (PCR)-based techniques or nucleic acid hybridization-related methods, and serological and immunological assays, which are based to a large extent on detecting antibodies generated as a result of exposure to the virus or on detecting antigenic proteins in infected organisms. Tests used for detecting SARS-CoV-2 viral RNA identify SARS-CoV-2 during the acute phase of the infection; afterwards, the serological tests identify individuals who have extended antibodies to the virus and could be convalescent plasma donors. Molecular assays for the detection of viral nucleic acids contain several methods such as reverse transcription-polymerase chain reaction (RT-PCR), Isothermal Nucleic Acid Amplification, Nucleic Acid Hybridization Using Microarray, Amplicon-Based Metagenomic Sequencing, High-Level Overview of Current Molecular Genetic Assays on SARS-CoV-2 Detection. Another serological and

immunological assay is the enzyme-linked immunosorbent assay (ELISA), lateral flow immunoassay, neutralization assay, luminescent immunoassay, biosensor test and rapid antigen test. In the light of the above mentioned tests in molecular assays, isothermal nucleic acid amplification is categorized into reverse transcription loop-mediated isothermal amplification (RT-LAMP), transcription-mediated amplification (TMA), CRISPR based assays and rolling circle amplification [6, 7, 44, 65, 67]. Nucleic acid-based diagnosis contains deep sequencing molecular methods such as next generation sequencing and metagenomic, along with the most practical method, which is real-time reverse transcription-polymerase chain reaction (rRT-PCR). COVID-19 infection is currently diagnosed by rRT-PCR analysis of nasopharyngeal swab specimens, which have high specificity and low sensitivity (60–70%). IgM and IgG antibody play a pivotal role in COVID-19; generally, IgM response is non-specific and needs weeks to develop, but IgG response could remain for a long time after the infection, offering a protective role. The first IgM becomes detectable in serum after a few days and remains a couple of weeks during the infection and is followed by a switch to IgG. Thus, IgM can be an indicator of early stage infection, and IgG can be an indicator of current or prior infection. IgG may also be used to suggest the presence of post-infection immunity. For surveying serological tests, a nucleocapsid protein from bat SARS-CoV RP3 was used as an IgG and IgM ELISA antigen [69]. The tests based on the detection of polyclonal antibodies against SARS-CoV-2 are developing faster other than detection tests. The different detection methods that have developed are combinational serological tests combined with immunochromatography, colloidal gold, and other technologies [28]. Also, point of care test (POC) immunoassays has been developed for the rapid detection of SARS-CoV-2 antibodies (IgG and IgM). To detect SARS-CoV-2 early and manage the disease in time, a faster and more comfortable method for SARS-CoV-2 nucleic acid detecting has been developed: RT-LAMP technique (reverse transcription loop-mediated isothermal amplification) [60]. Aptamers are virus markers that can detect any viral infection markers, such as viral genes, proteins, and antibodies. By applying some attitudes, aptasensors can differentiate infected and active form cells from uninfected and inactive ones [55]. Chest computed tomography (CT), particularly high-resolution CT (HRCT), is the method of choice for detecting pneumonia caused by COVID-19, even in the initial stages. Several non-specific HRCT findings and patterns can be found; despite that nearly 50% of patients imaged in the first two days after the symptom onset had regular chest CT, serial CT imaging is valuable in assessing the progression of lung abnormalities [31]. These tests will be essential for real-time patient handling, screening, and infection control decisions, especially when other, less infectious forms of pneumonia are present, and respiratory isolate resources are rare [51].

The instantaneous requirement for precise and rapid diagnosis of SARS-CoV-2 infection remains critical. Particularly, serological and immunological testing of infected asymptomatic and symptomatic people, and their close contacts,

is anticipated to be in strong demand. Molecular genetic tests, in addition to confirming suspected infections, would provide noteworthy data about the course and degree of immune response, as well as the longevity of immunity in infected individuals and participants in vaccine clinical trials.

## CONCLUSION

With re-estimated mortality rates achieved by dividing the death number on patients being divided by the confirmed COVID-19 cases on a given day, using WHO data until March 1, 2020, the mortality rate would be 5.6% for China and 15.2% for another country, which represents the higher potential of this virus for dissemination [4].

The development of genetic diversity among coronaviruses and their consequent potency to make the disease in individuals result from infected peridomestic animals, which are intermediate hosts and could be saved, facilitating recombination and mutation events. The spike glycoprotein (S glycoprotein), which attaches the virion to the host cell membrane, is hypothesized to play a significant role in host range restriction. There are multiple kinds of treatments for SARS and MERS in animal models *in vitro*, including small-molecule protease inhibitors, neutralizing antibodies, and inhibitors of the host immune response. Nevertheless, there is no specific treatment for coronaviruses, as the treatment protocol is just supportive and symptomatic [40]. Up-to-date treatment recommendations for clinicians who are caring for patients with COVID-19 are classified to four groups based on disease severity including: 1. Patients with COVID-19 who are not hospitalized or who are hospitalized with moderate disease but do not require supplemental oxygen, 2. Hospitalized patients with COVID-19 who require supplemental oxygen but who do not require delivery of oxygen through a high-flow device, non-invasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation, 3. Hospitalized patients with COVID-19 who require delivery of oxygen through a high-flow device or non-invasive ventilation but not invasive mechanical ventilation or extracorporeal membrane oxygenation and 4. Hospitalized patients with COVID-19 who require invasive mechanical ventilation or extracorporeal membrane oxygenation, which for the first group suggests the use of dexamethasone (or other corticosteroids for the treatment of COVID-19 (unless a patient has another clinical indication for corticosteroid therapy. And for the rest of groups use of Remdesivir intravenously (IV) until hospital discharge, or A combination of Remdesivir plus dexamethasone IV or orally for up to 10 days or until hospital discharge or if Remdesivir cannot be used, dexamethasone may be used instead: <https://www.covid19treatmentguidelines.nih.gov>.

There is an urgent need for global surveillance of humans infected with COVID-19. To halt the spread of the COVID-19 outbreak, affected countries should look back and notice the successes and failures of the beta-coronavirus range. Lessons learned from the MERS and SARS outbreaks can provide tremendous insight into how to behave

and deal with the current epidemic. These include proper hand hygiene, isolation of infected individuals in properly ventilated hospitals (negative pressure rooms), isolation of individuals with suspected symptoms or fever, and the prevention of direct contact with alleged animal reservoir hosts.

One of the most important effects found in our study is a significant induction of the expression of the *DEFB4A* gene by the T4 phage. This gene encodes for  $\beta$ -defensin-2 (BD2), a potent antimicrobial peptide produced by epithelial cells, which has a very important role in inducing innate immune responses against bacteria and other microbes [28]. Recently, it was shown that recombinant BD2 ameliorated an inflammatory reaction in three different animal models of inflammatory bowel disease (IBD) [12]. In another study, transfection of Caco-2 cells with a gene encoding for BD2 resulted in down-regulated expression of pro-inflammatory cytokines in response to infection by *Salmonella typhimurium* [7]. Thus, our findings may suggest a novel mechanism of anti-inflammatory activity of phages. Such activity might be exhibited by endogenous phages from the microbiota as well as exogenous phages administered during phage therapy. Moreover, our results may provide a starting point for further studies to evaluate potential anti-inflammatory effects of phages in animal models of IBD.

We also found that the T4 phage displayed a tendency to increase the expression of the *TNF* gene. This result deserves further research because the product of this gene – TNF- $\alpha$  – is a key cytokine implicated in the pathogenesis of IBD [30]. However, it needs to be stressed that while T4 increased the expression of *TNF* more than twofold compared with control cultures, this effect fell short of statistical significance.

Moreover, we found that neither of the examined phage preparation significantly induced the expression of the *IL15* gene. While the role of IL-15 in the pathogenesis of IBD has not been fully elucidated yet, most studies have shown that this cytokine can display pro-inflammatory activity in this context [34].

A number of studies published over recent years showed substantial differences in the composition of the gut virome, including bacteriophages, between patients with IBD and healthy individuals [4, 22, 36]. Some authors suggested that phages might contribute to inflammatory reactions in the gut not only by inducing dysbiosis of the microbiota, but also by exerting direct pro-inflammatory effects [22]. However, our results show that some bacterial viruses could in fact exert contrary (anti-inflammatory) effects. Further studies are necessary to elucidate the actual role of bacteriophages in the pathogenesis of IBD.

We also found that A5/80, but not T4 phage, significantly induced the expression of the *PIGR* gene. This gene encodes for the polymeric immunoglobulin receptor (pIgR), a key protein involved in the transport of dimeric immunoglobulin A and polymeric immunoglobulin M from the lamina propria across the epithelial barrier to mucosal surfaces. Secretion of polymeric Igs is one of the main mechanisms mediating antimicrobial immune responses in the gut [35]. Thus, it is possible that some phages might contribute to the elimination of pathogenic bacteria and viruses in the gut by facilitating the transport of polymeric Igs across the epithelial barrier.

An important question is what mechanism(s) underlie phage-mediated modulation of gene expression in Caco-2 cells. The results of other studies showed that some bacteriophages could penetrate the cell membranes of different cell lines (including Caco-2) as a result of transcytosis [25]. Thus phages can interact with both extra- and intracellular receptors. However, it remains to be elucidated what class of receptors mediated the effects observed in this study.

In conclusion, both examined phages significantly induced the expression of genes with potentially beneficial activities, especially *DEFB4A* and *PIGR*. These findings imply a possibility for the immunomodulatory role of phages from the gut microbiota, and may provide a starting point for novel applications of phages (phage repurposing), especially in the treatment of IBD.

## REFERENCES

- [1] Ahmadpoor P., Rostaing L.: Why the immune system fails to mount an adaptive immune response to a COVID-19 infection. *Transpl. Int.*, 2020; 33: 824–825
- [2] Al-Tawfiq J.A., Zumla A., Memish Z.A.: Travel implications of emerging coronaviruses: SARS and MERS-CoV. *Travel Med. Infect. Dis.*, 2014; 12: 422–428
- [3] Assiri A., McGeer A., Perl T.M., Price C.S., Al Rabeeah A.A., Cummings D.A., Alabdullatif Z.N., Assad M., Almulhim A., Makhdoom H., Madani H., Alhakeem R., Al-Tawfiq J.A., Cotton M., Watson S.J.: Hospital outbreak of Middle East respiratory syndrome coronavirus. *N. Engl. J. Med.*, 2013; 369: 407–416
- [4] Baud D., Qi X., Nielsen-Saines K., Musso D., Pomar L., Favre G.: Real estimates of mortality following COVID-19 infection. *Lancet Infect. Dis.*, 2020; 20: 773
- [5] Bosch B.J., van der Zee R., de Haan C.A., Rottier P.J.: The coronavirus spike protein is a class I virus fusion protein: Structural and functional characterization of the fusion core complex. *J. Virol.*, 2003; 77: 8801–8811
- [6] Cai X.F., Chen J., Hu J.L., Long Q.X., Deng H.J., Liu P., Fan K., Liao P., Liu B.Z., Wu G.C., Chen Y.K., Li Z.J., Wang K., Zhang X.L., Tian W.G., et al.: A peptide-based magnetic chemiluminescence enzyme immunoassay for serological diagnosis of corona virus disease 2019. *J. Infect. Dis.*, 2020; 222: 189–193
- [7] Carter L.J., Garner L.V., Smoot J.W., Li Y., Zhou Q., Saveson C.J., Sasso J.M., Gregg A.C., Soares D.J., Beskid T.R., Jervey S.R., Liu C.: Assay techniques and test development for COVID-19 diagnosis. *ACS Cent. Sci.*, 2020; 6: 591–605
- [8] Cascella M., Rajnik M., Cuomo A., Dulebohn S.C., Di Napoli R.: Features, evaluation and treatment coronavirus (COVID-19). *StatPearls Publishing*, 2020



- [9] Chan J.F., Kok K.H., Zhu Z., Chu H., To K.K., Yuan S., Yuen K.Y.: Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg. Microbes Infect.*, 2020; 9: 221–236
- [10] Chen Z.M., Fu J.F., Shu Q., Chen Y.H., Hua C.Z., Li F.B., Lin R., Tang L.F., Wang T.L., Wang W., Wang Y.S., Xu W.Z., Yang Z.H., Ye S., Yuan T.M., Zhang C.M., Zhang Y.Y.: Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. *World J. Pediatr.*, 2020; 16: 240–246
- [11] de Wit E., van Doremalen N., Falzarano D., Munster V.J.: SARS and MERS: Recent insights into emerging coronaviruses. *Nat. Rev. Microbiol.*, 2016; 14: 523–534
- [12] Donnelly C.A., Ghani A.C., Leung G.M., Hedley A.J., Fraser C., Riley S., Abu-Raddad L.J., Ho L.M., Thach T.Q., Chau P., Chan K.P., Lam T.H., Tse L.Y., Tsang T., Liu S.H., Kong J.H., Lau E.M., Ferguson N.M., Anderson R.M.: Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. *Lancet*, 2003; 361: 1761–1766
- [13] Drosten C., Günther S., Preiser W., van der Werf S., Brodt H.R., Becker S., Rabenau H., Panning M., Kolesnikova L., Fouchier R.A., Berger A., Burguière A.M., Cinatl J., Eickmann M., Escriou N., et al.: Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N. Engl. J. Med.*, 2003; 348: 1967–1976
- [14] Du Z., Xu X., Wu Y., Wang L., Cowling B.J., Meyers L.A.: Serial interval of COVID-19 among publicly reported confirmed cases. *Emerg. Infect. Dis.*, 2020; 26: 1341–1343
- [15] Fehr A.R., Perlman S.: Coronaviruses: an overview of their replication and pathogenesis. In: *Coronaviruses. Methods and Protocols*, eds.: H.J. Maier, E. Bickerton, P. Britton. Springer, 2015: 1–23
- [16] Fields B.N., Knipe D.M., Howley P.M.: *Fundamental Virology*. Lippincott-Raven Philadelphia; 1996
- [17] Gallagher T.M., Buchmeier M.J.: Coronavirus spike proteins in viral entry and pathogenesis. *Virology*, 2001; 279: 371–374
- [18] García L.F.: Immune response, inflammation, and the clinical spectrum of COVID-19. *Front. Immunol.*, 2020; 11: 1441
- [19] Gorbalenya A.E., Baker S.C., Baric R.S., de Groot R.J., Drosten C., Gulyaeva A.A., Haagmans B.L., Lauber C., Leontovich A.M., Neuman B.W., Penzar D., Perlman S., Poon L.L., Samborskiy D., Sidorov I.A., et al.: Severe acute respiratory syndrome-related coronavirus: The species and its viruses – a statement of the Coronavirus Study Group. *BioRxiv*, 2020. doi: <https://doi.org/10.1101/2020.02.07.937862>
- [20] Gralinski L.E., Menachery V.D.: Return of the Coronavirus: 2019-nCoV. *Viruses*, 2020; 12: 135
- [21] Guan W.J., Ni Z.Y., Hu Y., Liang W.H., Ou C.Q., He J.X., Liu L., Shan H., Lei C.L., Hui D.S., Du B., Li L.J., Zeng G., Yuen K.Y., Chen R.C., et al.: Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med.*, 2020; 382: 1708–1720
- [22] Guan Y., Zheng B.J., He Y.Q., Liu X.L., Zhuang Z.X., Cheung C.L., Luo S.W., Li P.H., Zhang L.J., Guan Y.J., Butt K.M., Wong K.L., Chan K.W., Lim W., Shortridge K.F., Yuen K.Y., Peiris J.S.M., Poon L.L.: Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science*, 2003; 302: 276–278
- [23] Haagmans B.L., Al Dhahiry S.H., Reusken C.B., Raj V.S., Galiano M., Myers R., Godeke G.J., Jonges M., Farag E., Diab A., Ghobashy H., Alhajri F., Al-Thani M., Al-Marri S.A., Al Romaihi H.E., et al.: Middle East respiratory syndrome coronavirus in dromedary camels: An outbreak investigation. *Lancet Infect. Dis.*, 2014; 14: 140–145
- [24] Habibzadeh P., Stoneman E.K.: The novel coronavirus: A bird's eye view. *Int. J. Occup. Environ. Med.*, 2020; 11: 65–71
- [25] Han Q., Lin Q., Jin S., You L.: Recent insights into 2019-nCoV: A brief but comprehensive review. *J. Infect.*, 2020; 80: 373–377
- [26] Hijawi B., Abdallat M., Sayaydeh A., Alqasrawi S., Haddadin A., Jaarour N., Alsheikh S., Alsanouri T.: Novel coronavirus infections in Jordan, April 2012: Epidemiological findings from a retrospective investigation. *East. Mediterr. Health J.*, 2013; 19: S12–S18
- [27] Hoffmann M., Kleine-Weber H., Schroeder S., Krüger N., Herrler T., Erichsen S., Schiergens T.S., Herrler G., Wu N.H., Nitsche A., Müller M.A., Drosten C., Pöhlmann S.: SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*, 2020; 181: 271–280
- [28] Huang C., Wang Y., Li X., Ren L., Zhao J., Hu Y., Zhang L., Fan G., Xu J., Gu X., Cheng Z., Yu T., Xia J., Wei Y., Wu W., et al.: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, 2020; 395: 497–506
- [29] Huang C., Wen T., Shi F.J., Zeng X.Y., Jiao Y.J.: Rapid detection of IgM antibodies against the SARS-CoV-2 virus via colloidal gold nanoparticle-based lateral-flow assay. *ACS Omega*, 2020; 5: 12550–12556
- [30] Hunter J.C., Nguyen D., Aden B., Al Bandar Z., Al Dhaheri W., Abu Elkheir K., Khudair A., Al Mulla M., El Saleh F., Imambaccus H., Al Kaabi N., Sheikh F.A., Sasse J., Turner A., Abdel Wareth L., et al.: Transmission of Middle East respiratory syndrome coronavirus infections in healthcare settings, Abu Dhabi. *Emerg. Infect. Dis.*, 2016; 22: 647–656
- [31] Kanne J.P.: Chest CT findings in 2019 novel coronavirus (2019-nCoV) infections from Wuhan, China: Key points for the radiologist. *Radiology*, 2020; 295: 16–17
- [32] Lee N., Hui D., Wu A., Chan P., Cameron P., Joynt G.M., Ahuja A., Yung M.Y., Leung C.B., To K.F., Lui S.F., Szeto C.C., Chung S., Sung J.J.: A major outbreak of severe acute respiratory syndrome in Hong Kong. *N. Engl. J. Med.*, 2003; 348: 1986–1994
- [33] Lee P.I., Hsueh P.R.: Emerging threats from zoonotic coronaviruses—from SARS and MERS to 2019-nCoV. *J. Microbiol. Immunol. Infect.*, 2020; 53: 365–367
- [34] Leo Y.S., Chen M., Heng B.H., Lee C.C.: Severe acute respiratory syndrome—Singapore, 2003. *MMWR Morb. Mortal. Wkly. Rep.*, 2003; 52: 405–411
- [35] Leung G.M., Hedley A.J., Ho L.M., Chau P., Wong I.O., Thach T.Q., Ghani A.C., Donnelly C.A., Fraser C., Riley S., Ferguson N.M., Anderson R.M., Tsang T., Leung P.Y., Wong V., Chan J.C., Tsui E., Lo S.V., Lam T.H.: The epidemiology of severe acute respiratory syndrome in the 2003 Hong Kong epidemic: An analysis of all 1755 patients. *Ann. Intern. Med.*, 2004; 141: 662–673
- [36] Li P., Fu J.B., Li K.F., Liu J.N., Wang H.L., Liu L.J., Chen Y., Zhang Y.L., Liu S.L., Tang A., Tong Z.D., Yan J.B.: Transmission of COVID-19 in the terminal stages of the incubation period: A familial cluster. *Int. J. Infect. Dis.*, 2020; 96: 452–453
- [37] Liu Y., Gayle A.A., Wilder-Smith A., Rocklöv J.: The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J. Travel Med.*, 2020; 27: taaa021
- [38] Lu C.W., Liu X.F., Jia Z.F.: 2019-nCoV transmission through the ocular surface must not be ignored. *Lancet*, 2020; 395: e39
- [39] Lu R., Zhao X., Li J., Niu P., Yang B., Wu H., Wang W., Song H., Huang B., Zhu N., Bi Y., Ma X., Zhan F., Wang L., Hu T., et al.: Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet*, 2020; 395: 565–574

- [40] Mirzaie A., Halaji M., Dehkordi F.S., Ranjbar R., Noorbazargan H.: A narrative literature review on traditional medicine options for treatment of corona virus disease 2019 (COVID-19). *Complement. Ther. Clin. Pract.*, 2020; 40: 101214
- [41] Nishiura H., Kobayashi T., Yang Y., Hayashi K., Miyama T., Kinoshita R., Linton N.M., Jung S.M., Yuan B., Suzuki A., Akhmetzhanov A.R.: The rate of underascertainment of novel coronavirus (2019-nCoV) infection: Estimation using Japanese passengers data on evacuation flights. *J. Clin. Med.*, 2020; 9: 419
- [42] Pasternak A.O., Spaan W.J., Snijder E.J.: Nidovirus transcription: How to make sense...? *J. Gen. Virol.*, 2006; 87: 1403–1421
- [43] Perlman S., Netland J.: Coronaviruses post-SARS: Update on replication and pathogenesis. *Nat. Rev. Microbiol.*, 2009; 7: 439–450
- [44] Phan T.: Novel coronavirus: From discovery to clinical diagnostics. *Infect. Genet. Evol.*, 2020; 79: 104211
- [45] Postnikova E.N., Pettitt J., Van Ryn C.J., Holbrook M.R., Bollinger L., Yú S., Cai Y., Liang J., Sneller M.C., Jahrling P.B., Hensley L.E., Kuhn J.H., Fallah M.P., Bennett R.S., Reilly C.: Scalable, semi-automated fluorescence reduction neutralization assay for qualitative assessment of Ebola virus-neutralizing antibodies in human clinical samples. *PLoS One*, 2019; 14: e0221407
- [46] Poutanen S.M., Low D.E., Henry B., Finkelstein S., Rose D., Green K., Tellier R., Draker R., Adachi D., Ayers M., Chan A.K., Skowronski D.M., Salit I., Simor A.E., Slutsky A.S., et al: Identification of severe acute respiratory syndrome in Canada. *N. Engl. J. Med.*, 2003; 348: 1995–2005
- [47] Raj V.S., Farag E.A., Reusken C.B., Lamers M.M., Pas S.D., Voermans J., Smits S.L., Osterhaus A.D., Al-Mawlawi N., Al-Romaihi H.E., Al. Hajri M.M., El-Sayed A.M., Mohran K.A., Ghobashy H., Alhajri F., et al.: Isolation of MERS coronavirus from a dromedary camel, Qatar, 2014. *Emerg. Infect. Dis.*, 2014; 20: 1339–1342
- [48] Raj V.S., Mou H., Smits S.L., Dekkers D.H., Müller M.A., Dijkman R., Muth D., Demmers J.A., Zaki A., Fouchier R.A., Thiel V., Drosten C., Rottier P.J., Osterhaus A.D., Bosch B.J., et al.: Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature*, 2013; 495: 251–254
- [49] Reusken C.B., Haagmans B.L., Müller M.A., Gutierrez C., Godeke G.J., Meyer B., Muth D., Raj V.S., Smits-De Vries L., Corman V.M., Drexler J.F., Smits S.L., El Tahir Y.E., De Sousa R., van Beek J., et al.: Middle East respiratory syndrome coronavirus neutralising serum antibodies in dromedary camels: A comparative serological study. *Lancet Infect. Dis.*, 2013; 13: 859–866
- [50] Shi Y., Wang Y., Shao C., Huang J., Gan J., Huang X., Bucci E., Piccentini M., Ippolito G., Melino G.: COVID-19 infection: The perspectives on immune responses. *Cell Death Differ.*, 2020; 27: 1451–1454
- [51] Tang Y.W., Schmitz J.E., Persing D.H., Stratton C.W.: Laboratory diagnosis of COVID-19: Current issues and challenges. *J. Clin. Microbiol.*, 2020; 58: e00512–20
- [52] Tindale L., Coombe M., Stockdale J.E., Garlock E.S., Lau W.Y., Saraswat M., Lee Y.H., Zhang L., Chen D., Wallinga J., Colijn C.: Transmission interval estimates suggest pre-symptomatic spread of COVID-19. *MedRxiv*, 2020; <https://doi.org/10.1101/2020.03.03.20029983>
- [53] Tu W., Tang H., Chen F., Wei Y., Xu T., Liao K., Xiang N., Shi G., Li Q., Feng Z.: Epidemic update and risk assessment of 2019 novel coronavirus – China, January 28, 2020. *China CDC Wkly.*, 2020; 2: 83–86
- [54] Wan Y., Shang J., Graham R., Baric R.S., Li F.: Receptor recognition by the novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS coronavirus. *J. Virol.*, 2020; 94: e00127–20
- [55] Wandtke T., Woźniak J., Kopiński P.: Aptamers in diagnostics and treatment of viral infections. *Viruses*, 2015; 7: 751–780
- [56] Wang J.T., Sheng W.H., Fang C.T., Chen Y.C., Wang J.L., Yu C.J., Chang S.C., Yang P.C.: Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients. *Emerg. Infect. Dis.*, 2004; 10: 818–824
- [57] Wertheim J.O.: A glimpse into the origins of genetic diversity in the severe acute respiratory syndrome coronavirus 2. *Clin. Infect. Dis.*, 2020; 71: 721–722
- [58] Wise J.: Patient with new strain of coronavirus is treated in intensive care at London hospital. *Br. Med. J.*, 2012; 345: e6455
- [59] Wu F., Zhao S., Yu B., Chen Y.M., Wang W., Song Z.G., Hu Y., Tao Z.W., Tian J.H., Pei Y.Y., Yuan M.L., Zhang Y.L., Dai F.H., Liu Y., Wang O.M., et al.: A new coronavirus associated with human respiratory disease in China. *Nature*, 2020; 579: 265–269
- [60] Wu J.L., Tseng W.P., Lin C.H., Lee T.F., Chung M.Y., Huang C.H., Chen S.Y., Hsueh P.R., Chen S.C.: Four point-of-care lateral flow immunoassays for diagnosis of COVID-19 and for assessing dynamics of antibody responses to SARS-CoV-2. *J. Infect.*, 2020; 81: 435–442
- [61] Xia S., Yan L., Xu W., Agrawal A.S., Algaissi A., Tseng C.T., Wang Q., Du L., Tan W., Wilson I.A., Jiang S., Yang B., Lu L.: A pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike. *Sci. Adv.*, 2019; 5: eaav4580
- [62] Xu J., Zhao S., Teng T., Abdalla A.E., Zhu W., Xie L., Wang Y., Guo X.: Systematic comparison of two animal-to-human transmitted human coronaviruses: SARS-CoV-2 and SARS-CoV. *Viruses*, 2020; 12: 244
- [63] Xu Z., Shi L., Wang Y., Zhang J., Huang L., Zhang C., Liu S., Zhao P., Liu H., Zhu L., Tai Y., Bai C., Gao T., Song J., Xia P., Dong J., Zhao J., Wang F.S.: Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir. Med.*, 2020; 8: 420–422
- [64] Zaigham M., Andersson O.: Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. *Acta Obstet. Gynecol. Scand.*, 2020; 99: 823–829
- [65] Zaki A.M., van Boheemen S., Bestebroer T.M., Osterhaus A.D., Fouchier R.A.: Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N. Engl. J. Med.*, 2012; 367: 1814–1820
- [66] Zhang F., Abudayyeh O.O., Gootenberg J.S.: A protocol for detection of COVID-19 using CRISPR diagnostics. [https://www.broadinstitute.org/files/publications/special/COVID-19%20detection%20\(updated\).pdf](https://www.broadinstitute.org/files/publications/special/COVID-19%20detection%20(updated).pdf)
- [67] Zhang H., Kang Z., Gong H., Xu D., Wang J., Li Z., Li Z., Cui X., Xiao J., Zhan J., Meng T., Zhou W., Liu J., Xu H.: Digestive system is a potential route of COVID-19 infection: An analysis of single-cell coexpression pattern of key proteins in viral entry process. *Gut*, 2020; 69: 1010–1018
- [68] Zhang W., Du R.H., Li B., Zheng X.S., Yang X.L., Hu B., Wang Y.Y., Xiao G.F., Yan B., Shi Z.L., Zhou P.: Molecular and serological investigation of 2019-nCoV infected patients: Implication of multiple shedding routes. *Emerg. Microbes Infect.*, 2020; 9: 386–389
- [69] Zhou P., Yang X.L., Wang X.G., Hu B., Zhang L., Zhang W., Si H.R., Zhu Y., Li B., Huang C.L., Chen H.D., Chen J., Luo Y., Guo H., Jiang R.D., et al.: Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. *BioRxiv*, 2020. <https://doi.org/10.1101/2020.01.22.914952>
- [70] Zhou P., Yang X.L., Wang X.G., Hu B., Zhang L., Zhang W., Si H.R., Zhu Y., Li B., Huang C.L., Chen H.D., Chen J., Luo Y., Guo H., Jiang R.D., et al.: A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 2020; 579: 270–273

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The authors have no potential conflicts of interest to declare.