DOI: 10.4149/BLL_2020_120

Bratisl Med J 2020; 121 (10)
733 – 741

EPIDEMIOLOGY STUDY

Coronaviruses as the emerging threats for human health: should we be prepared for the future outbreaks of new coronaviruses?

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ABSTRACT
Recent emergence of SARS-CoV-2 in human communities as the first major zoonotic pandemics of the new millennium following the emergence of SARS-CoV and MERS-CoV has increased our awareness about the future threat of viral zoonosis. Although, several studies have been conducted for better understanding of these viruses` evolution, and designing the effective anti-viral drugs and vaccines, the impact of human beings on occurrence of zoonotic diseases has been less considered and discussed. Improvement in global health resulted in human population growth, increasing demand for animal proteins, more exposures to wildlife, zoonotic and degradation of environment, which have facilitated interspecies transmissions. Since world population is increasing proportionately, the protection of public health against zoonotic diseases is a challenging task. It seems that intensified revision of human lifestyle is the best strategy to prevent the potential devastating future zoonotic pandemics. Herein, the characteristics of SARS-CoV, MERS-CoV, SARS-CoV-2, their transmission routs, their pathogenicity, the therapeutic and prevention approaches including of attempts for designing of effective prophylactic vaccines, anti-viral drugs, and the animal models that have been used for these studies have been reviewed *(Ref. 134)*. Text in PDF *www.elis.sk*
KEY WORDS: SARS-CoV-2, COVID-19, pandemic, zoonosis, SARS, MERS.

Introduction

Coronaviruses belonging to *Nidoviral* order, and *Coronaviridae* family, are enveloped viruses with a single stranded positive sense RNA genome with 26-32kb, which makes them the largest RNA viruses (1, 2). *Orthocoronavirinae* is one of the two sub-family of *Coronaviridae* which, composed of 4 genera; *Alphacoronavirus, Betacoronovirus, Deltacoronavirus,* and *Gammacoronavirus* (1, 2) Human coronavirus NL63 (HCoV-NL63), HCoV-229E, porcine respiratory coronavirus (PRCV), porcine transmissible gastroenteritis coronavirus (TGEV), and PEDV are members of alpha-coronaviruses. Beta-coronaviruses are as well divided into 4 lineages; A, B, C, and D. β-coronaviruses lineage A consists of HCoV-OC43, HCoV-HKU1, while SARS-CoV and SARS-CoV-2 are in the β-coronaviruses lineage B (β-B coronaviruses), and MERS-CoV is in the β-coronaviruses lineage C. Avian infectious bronchitis coronavirus (IBV) and porcine deltacoronavirus (PdCV) are representative of gamma and deltacoronaviruses respectively (2). Members of this family share structural proteins, the envelop protein (E), the membrane (M), the nucleocapsid protein (N), and spike (S) protein, while some *Betacoronaviruses (Betacoronavirus 1)* encode a different envelope-associated hemagglutinin-esterase protein (HE) (2–5) . Coronaviruses infect respiratory, gastrointestinal, hepatic, and central nervous system of vertebrates ranging from human, birds, bat, mouse, and many other wild animals (3, 4). Alpha-and betacoronaviruses infect mammals, gammacoronaviruses infect avian species, and deltacoronaviruses infect both mammalian and avian species (3, 4) . Zoonotic viral diseases such as: Rabies, Ebola, West Nile fever, Crimean-Congo haemorrhagic fever, Dengue fever, Lassa fever, Marburg viral haemorrhagic fever, and Rift Valley fever, which are caused by different viruses` families have been identified for many years (6, 7). Four CoVs had been known until 2002: HCoV-229E, HCoV-OC43, HCoV-NL63, HKU1 to infect humans causing mostly a mild upper respiratory disease and leading to extreme conditions in infants and old patients in some unusual situations. For the first time, animal-to-human and human-to-human transmission was confirmed in an outbreak of severe acute respiratory syndrome (SARS) caused by SARS-Cov in 2002/2003 which was followed by Middle East respiratory syndrome (MERS) caused by MERS-CoV outbreak in 2012 that both viruses infect lower respiratory tract in humans (4, 8, 9). First report of SARS was an infected human in the Guangdong province of southern China in 2002 (10). It has been found that

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horseshoe bats are the natural source of SARS-CoV and civets are their amplification hosts (11, 12). In 2003, an epidemic of SARS affected 26 countries and a total of 8,098 people worldwide were infected. After 2003, the outbreak has been vanished. Only small number of cases have been reported due to laboratory accidents or, in some very rare situations through animal-to-human transmission especially in China (10). Close contact of person to person, which increases the risk of virus spreading through droplets produced from patients' coughs, sneeze and stool, was known as the main transmission rout of SARS-CoV. In addition, SARS-CoV could spread through touching eyes, nose or mouth with contaminated fingers, which touched the contaminated surfaces by infectious droplets (10, 13). According to the CDC fact sheets, SARS-CoV might be considered as airborne virus, which could spread more broadly through the air (13). Finally, in 2004, implementation of proper infection control practices resulted in a successful ending of that global outbreak (10, 13).

In 2012, MERS-CoV outbreak was reported the first case from Saudi Arabia, but further investigations revealed that the first known cases of MERS occurred in Jordan (14, 15). Although the exact route(s) of transmission of the MERS-CoV and the role of camels in its transmission remained unknown it has been proposed that dromedary camels are the major source or intermediate host of MERS-CoV (14, 15).

In 2019, the World Health Organization (WHO) has recorded 2,428 cases of MERS from 27 countries suffering from this outbreak, resulting in about 43% mortality (16, 17). Most outbreaks (>80 percent) were geographically linked to Saudi Arabia, although travel-related cases occurred in Europe, Asia and Africa (18–20). After detection of SARS-CoV, at least 63 coronaviruses from many animal species were isolated. Recently, a related SARS-CoV and MERS-CoV virus; SARS-CoV-2 (farmer name was 2019-nCoV) emerged and was reported for the first time from patients with mystery pneumonia in Wuhan city in China (3, 4). First phylogenetic analysis revealed that, SARS-CoV, MERS-CoV and SRARS-CoV-2 belong to the same genus; betacoronaviruses with the same rout of transmission in human communities albeit, with little differences in their natural origin (11, 12). Surprisingly, further analysis of SARS-CoV-2 showed the more distant relation to SARS-CoV and the close sequence relation between bat-SL-CoV ZC45 and bat-SL-CoV ZXC21 with this new coronavirus (4). Like its precedents, this new coronavirus invades low respiratory tract and leads to pneumonia as well, causing multi organ failure like kidney, liver, and central nervous system. So, the related disease was named Coronavirus Disease 2019 (COVID-19), which spreads from person to person through a close contact and droplets via the same routs that were described for SARS and MERS (20, 21).

Up to date, there were no confirmed documents about the risk of transfusion transmission of SARS-CoV, MERS-CoV and SARS-CoV-2. However, the safety approaches have been recommended such as deferral of blood donation from confirmed COVID-19 recovered patients for at least 28 days after a complete recovery (22–25). The estimation of an average number of people, who could be infected by an active case is called basic reproduction number; R_0 which could be variable over time because it depends on age, crowdedness, cultural behaviors and location so, there are different estimations of R_0 for SARS-CoV-2 ranging from 1.4 to 6.49 with the Mean of 3.28 (26). The number of infections/deaths due to SARS-CoV-2 increased rapidly, therefore restricted containment efforts were urgently needed (20, 27, 28). Despite of those containments, virus was spread worldwide and finally, in March 2020 World Health Organization declared the COVID-19 as pandemic (29).

This review describes the most famous coronaviruses; SARS-CoV, MERS, and SARS-CoV-2 that used to be only in wildlife, but they could overcome the species barriers and caused the severe human health and economic problems threat as well.

Cellular receptors and Cell Entry

SARS-CoV is an enveloped, single and positive-stranded RNA virus. Its genome RNA encodes 28 proteins, 4 structural proteins, including spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins, and sixteen non-structural proteins (named nsp1-nsp16) involved in replication such as: RNA dependent RNA polymerase (RdRp), coronavirus main protease (3CLpro), and papain-like protease (PLpro), and the rest are "group-specific" or "accessory proteins" that might have a very important role in the survival of the virus (30, 31). The S protein is a surface glycoprotein precursor with about 1,255 amino acids in length, composed of two subunits; the S1, which is a receptor-binding domain (RBD) and the S2 that mediates fusion between the virus and cell membrane (32). The S protein should be primed to be functional and this priming is done by a host cellular serine protease TMPRSS211, and also, by other proteases like trypsin, and cathepsin L (32). It has been shown that S protein is important in induction of neutralizing antibody and cellular immunity (32, 33). The main cellular receptor for SARS-CoV is angiotensin-converting enzyme 2 (ACE2) that is recognized and attached by S1 subunit (33, 34). However, it can also use alternative receptors, such as DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin) and/or L-SIGN (liver/lymph node-SIGN) (35, 36). After binding of the RBD of S1 to the receptor ACE2, the fusion process is initiated due to the acidic environment of the endosomes (not on the cell surface) through a conformational change of the pre fusion form of S2 to a post-fusion form occurred, leading insertion of the fusion peptide (amino acids 770–788) into the cell membrane (32, 37). Two residues at positions 479 and 487 in RBD of S1 protein, determine SARS-CoV tropism and the severity of SARS disease (37). SARS-CoV genome was identified in lung, trachea/bronchus, stomach, small intestine, distal convoluted renal tubule, sweat gland, parathyroid, pituitary, pancreas, adrenal gland, liver and cerebrum; indicating of its ability for infecting multiple organs (32, 37). In addition, to understand the routes of virus entry and its pathogenesis, distribution of ACE2 protein was investigated. It was found that ACE2 protein is expressed in many organs such as: lung, liver, kidney, spleen, oral and nasal mucosa, nasopharynx, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, and brain as well as in arterial and venous endothelial cells (32, 38). The most remarkable finding was the

surface expression of ACE2 protein on lung alveolar epithelial cells and enterocytes of the small intestine (38, 39). Like other coronaviruses, the MERS-CoV contains a surface spike glycoprotein (S) that interacts with its cellular receptor dipeptidyl peptidase 4 (DPP4 also called CD26) (40, 41). Although, the receptor binding domains of the S protein from MERS-CoV and SARS-CoV show a high degree of structural similarity, they are notably divergent in the receptor-binding subdomain, which results in utilization of totally different cellular receptors; as SARS-CoV utilizes ACE2 while MERS-CoV attaches to DPP4 (40, 42).

The attachment to DPP4 is followed by proteolytic cleavage of receptor-bound S protein and mediates virus-cell membrane fusion, while this binding also induces the immunosuppression signals, which facilitates viral replication and spread (42, 43). More studies showed that the tetraspanin CD9, formed cell-surface complexes of dipeptidyl peptidase 4 (DPP4) and a MERS-CoV-activating type II transmembrane serine protease named (TTSP) to facilitate an early, and efficient entry of virus (43–44).

In 2019, SARS-CoV-2 has been emerged and computer modelling revealed the identical 3-D structures in receptor binging domain of the spike proteins of SARS-CoV-2 and SARS-CoV (46–48). Also, the spike protein of these two viruses share 76.5 % identity in amino acid sequences (38, 48, 49). However, the studies demonstrated that SARS-CoV-2 S protein could recognize human ACE2 more efficiently and bind to it with a strong affinity (48). This characteristic could explain the higher ability of SARS-CoV-2 for transmission from human to human (49). According to further studies, SARS-CoV-2 does not utilize other coronavirus receptors such as aminopeptidase N and dipeptidyl peptidase 4 (45, 46).

Symptoms

Generally, all these viruses have similar incubation period between 2 to 14 days and symptoms such as: influenza-like symptoms that usually begin 2 to 7 days after infection (46). In addition, all three viruses attack the lower respiratory system to cause viral pneumonia, but they also affect kidney, heart, the gastrointestinal system, even central nervous system leading to multiple organ failure (10, 13, 32). The symptoms range from asymptomatic, paucisymptomatic to severe acute respiratory disease and death and are not specific for a diagnosis of infection with SARS-CoV, MERS-Cov, means SARS-CoV-2 including fever, malaise, myalgia, headache, cough (initially dry), shortness of breath, and diarrhoea are present in the first and/or second week of infection (10, 13). Older people or people with medical conditions such as: asthma, diabetes, or heart disease, immunocompromised patients, cancer, renal disease, and chronic lung disease are considered as high risk groups that make severe cases, which often evolve rapidly, progressing to respiratory distress and requiring an intensive care (10, 13, 50–51). After the virus enters the lung bubbles, macrophages in this area are unable to prevent the spread of infection and in response to the cell's immune response results in the release of cytokines, which causes lung fluid to accumulate and cause severe inflammation. Symptoms such as: abdominal obstruction, hypovolemic shock are very common (50–51). However, there are some little differences in the severity of symptoms between SARS, MERS and COVID-19, for example pneumonia is common in MERS, but not always present (52). Published data about the clinical manifestations of COVID-19 describe the different categories from mild, severe and critical disease. Severe disease cases could be distinguished by dyspnoea, respiratory frequency ≥ 30/min, blood oxygen saturation (SpO^2) ≤ 93 %, PaO_2/FiO_2 ratio, and the percentage of oxygen supplied (fraction of inspired oxygen, FiO_2) < 300, and/or lung infiltrates > 50 % within 24 to 48 hours, while in the critical situations other complications such as respiratory failure, septic shock, multiple organ dysfunction (MOD) or failure (MOF) have been reported (53, 54). Severe dyspnoea and hypoxemia, renal impairment with a reduced urine output, tachycardia, altered mental status are the main clinical manifestations of sepsis while, acidosis, high lactate, coagulopathy, thrombocytopenia, and hyperbilirubinemia could be considered as the laboratory confirmation of functional alterations of organs (54, 55). Also, there are different studies indicating that there might be gender-dependent differences in SARS, MERS, and COVID-19 outcomes (54, 55). One study on 2004 showed that males had significantly ($p < 0.0001$) higher case fatality rate than females did in Hong Kong (55). It has been proposed that estrogen receptor signalling should be considered critical for the protection in females from SARS and MERS, while there are other factors such as copy number of immune response X-linked genes have their own impact on outcomes (56–59). There are some reports of severity of COVID-19 in males compared to females, but more studies are needed (60, 61).

Animal models, therapeutic agents and treatment approaches

Generally, an ideal animal model should support the viral replication and a correlation between virus titer and disease severity. Also, the selected animal should reflect the clinical manifestations such as: the route of infection, and pathology seen in humans (62–64). Several inbred strains of mice have been used as SARS-CoV replication models. BALB/c, C57BL6 and 129S were infected via intranasal route and the results showed that 129S mice were more susceptible in comparison with BALB/c but, older BALB/c mice showed similar age-dependent susceptibility like human (65, 66). Studying on MERS-CoV is more challenging because of the difference between the critical virus spike interaction areas of the human receptor (hDPP4) and mice receptor (DPP4), which makes them resistant to infection by MERS-CoV. This problem has been resolved by a transduction of BALB/c and B6 mice with Ad5-hDPP4 (adenoviral vector expressing hDDP4) so; they could be used for the study on MERS-CoV replication and its clinical manifestations such as: interstitial pneumonia (67, 68). Recent pandemic of COVID-19 pushed researchers to develop animal models like mouse models. For example, hACE2 transgenic mouse model is under developing. Rhesus macaques, African green monkeys and cynomolgus macaques have been used in many studies on viral replication, clinical signs and pathology of SARS-CoV and MERS-CoV and they could induce pneumonitis in each species (69–71). However, there were some differences in the outcomes using non-

human primates as infection with MERS-CoV resulted in a transient pulmonary infection in Rhesus macaques (63, 72). Rhesus macaques have been suggested as non-human primates for studying on SARS-CoV-2 infection, but no published data is available yet.

Up to date, there is actually no antiviral treatment with a proven efficacy in humans. There are reports of using interferon alfa-2a in combination with ribavirin and also, remdesivir (GS5734)- an inhibitor of RNA polymerase in multiple RNA viruses-, which showed the effectivity for both prophylaxis and therapy of SARS, MERS. Also recently has been suggested for therapy of COVID-19 the same combination (73–76). Passive immunity suggested to cure these viruses` infections in animal models (77). One study showed that passive immunity by using human monoclonal antibodies could reduce the disease severity of SARS-CoV in golden Syrian hamsters (78). Some investigators suggest that using human monoclonal antibodies could be promising. However, further research is needed also there are some obstacles such as being expensive for massive production (79–89).

Oxygen therapy through mechanical ventilation represents the major treatment for patients with severe respiratory failure caused by SARS-CoV, MERS-CoV and SARS-CoV-2, whereas hemodynamic support is necessary for managing septic shock. It is important that unselective or inappropriate administration of antibiotics should be avoided. However, recent data showed that Azithromycin could reduce the respiratory complications (81–84, 89). There have been many clinical trials testing different agents against MERS-CoV such as: interferon (INF), ribavirin and inhibitors of HIV protease and combination of lopinavir/ritonavir and interferon-β1b (MIRACLE trial) (85, 89, 90).

In 2013, in Saudi Arabia, the first use of antiviral agents for treating MERS-CoV infection was observed in 5 patients. Unfortunately, all patients died at 1–2 months of respiratory and multiorgan failure and four patients had adverse drug reactions such as: thrombocytopenia, anaemia and pancreatitis. All the patients obtained oral and subcutaneous interferon alfa-2b ribavirin (85, 89). In 2015, two patients with MERS-Cov infection in Kuwait underwent subcutaneous and oral ribavirin therapy with pegylated interferon alfa-2b. Within 42 days after starting antiviral therapy, one patient was sent home, and ribavirin was stopped due to anaemia within one week of treatment. The second patient survived from MERS-CoV, and died with multidrug-resistant organism two months later (85, 90).

Another small study used ribavirin and interferon-alfa 2b in three patients receiving care within 1–2 days of admission and was matched with three other patients receiving treatment 12–19 days after admission. The first group survived and the second group passed away (85, 87). Lopinavir / ritonavir has been used in conjunction with ribavirin and IFN-α2a and resulted in virus clearance, and survival in treatment of MERS patients in Korea while the similar treatment in Greece was not effective; viral RNA remained detectable and the patients died (90, 91). Although, the HIV protease inhibitors, Nelfinavir and lopinavir, were criteria for inhibiting SARS-CoV and MERS-CoV based on SARS results, there are some controversies on using this combination for the treatment of COVID-19 as Cao et al. reported that WHO researchers did not find any clinical improvement or mortality rate or even reduction of viral RNA in patients` specimens by treatment with lopinavir-ritonavir (91, 92).

Chloroquine, and its derivatives including hydroxychloroquine and chloroquine phosphate are the most effective drugs for the treatment of severe acute respiratory syndrome. However, cardiotoxicity with prolonged use has been reported in patients with immunosuppression, hepatic or renal dysfunction (93-97). Up to date there is no FDA-approved and specific antiviral drug for the treatment of patients infected with SARS-COV-2 so, the clinical management such as infection prevention and control measures and supportive care, including supplementary oxygen and mechanical ventilation are the best curative things that could be done. Several investigational drugs are under evaluation and different treatment protocols are being revised based on the clinical trial results. Remdesivir, developed by Gilead Sciences Inc., is one of the investigational antiviral drugs that causes premature termination of RNA transcription and its combination with Chloroquine showed the promising inhibitory effects in-vitro on SARS-CoV-2 replication (98). Also, it shows the same effect on other beta-coronaviruses such as SARS-CoV and Mers-CoV in-vitro and in-vivo (99). Favipiravir (known as T-705), is a purine nucleoside, which leads to an inaccurate viral RNA synthesis in many RNA viruses and was originally developed by Toyama Chemical of Japan (99-103). This anti-virus RNA dependent RNA polymerase is currently being studied in phase III clinical trials in both China and the USA (105). There are reports that using Favipiravir could be the most available and effective treatment for COVID-19 (100, 106).

Very recently, human recombinant soluble ACE2 (hrsACE2) was designed and evaluated on Vero cells, engineered human blood vessel, and human kidney organoids (107). The results showed that this recombinant soluble ACE2 could inhibit the replication of SARS-CoV-2 at early stage by a factor of 1000–5000 in Vero cells and also, in engineered human blood vessel and kidney organoids (107). However, it did not show the same effect on mouse rsACE2. The similar compound; GSK2586881, and APN01 was used in a randomized, double-blind, placebo-controlled investigation for the treatment of SARS, but it did not show significant changes in the clinical outcome (108, 109).

Vaccine candidates

Efforts towards developing a vaccine for SARS, and MERS have led to patent different types of viral vaccines like: inactive or live-attenuated viruses, virus-like particle (VLP), viral vectors, protein-based, DNA-based, and mRNA-based vaccines. Up to date, 15 patents disclose information about inactive and live-attenuated virus vaccines, 13 patents disclose information on VLP vaccines, DNA vaccines have been disclosed in 28 patent, 21 patents described information on viral vector vaccines, and three patents are focused on mRNA vaccines (110, 111). The results of vaccine trials showed that viral S protein subunit vaccines produced higher neutralizing antibody titers and were more effective than DNA-based S protein vaccines, full-length S protein, and live-attenuated SARS-CoV (111–115).

Inactivated SARS-CoV–based vaccines, S protein–based vaccines, and vaccines based on fragments containing neutralizing epitopes are the most in progress vaccine candidates for SARS-CoV (111–115).

Vaccine candidates for MERS include DNA vaccine albeit with a low effectiveness human MERS vaccines for long-term protection of people at high exposure risk and for reactive use in outbreak (116–119). Although multiple attempts are in progress to develop a vaccine against COVID-19, up to date no vaccine has completed clinical trials. There are some reports of Clinical trials of vaccine candidates such as an RNA vaccine (mRNA-1273) from the USA and other countries (120, 121).

Discussion

Viruses consist of only genetic materials (DNA or RNA) which, means that with some differences, they have a very high capacity for different kinds of genomic mutations (transition, transversion, insertion, deletion, recombination, reassortment, etc), and adaptation to variety of hosts and conditions. Also, they could transfer genes between different hosts from different species that makes them the most effective creatures in evolution. Breaking the "species barriers" and compromise with a new host due to the genomic mutations is the main key of their survival. Zoonotic viral diseases like Rabies, Spanish flu, swine flu, Yellow fever, Hantavirus, HIV, and Ebola have spread from animals to humans (1, 3, 125, 126). Development of human civilization resulted in human population growth, increase in life expectancy and need for more expansion of villages, cities, farms, concomitant with special nutrition cultures that caused more contact between human and animals; therefore, increasing interactions facilitated a perpetuated transmission of animal viruses to human (6–9, 125–127). The Spanish flu pandemic with 500,000,000 infected people and at least 50,000,000 deaths worldwide was the first pandemic of a viral disease (128). The causative virus was an H1N1 virus with genes of avian origin (130). The second pandemic of a new strain of H1N1 virus (pdm09 virus) named swine flu was in 2009 (128). It caused about 700,000,000 to 1.4 billion infections with 150,000 to 575,000 fatalities (132). Despite of SARS, MERS, and COVID-19 we have lots of knowledge about influenza virus, its effective vaccine has been up- dated annually, and specific drugs for treatment are available. The most serious health problems caused by coronaviruses occurred at the early phase of SARS epidemic in the 2002 and 2003, the prototype group consisting of three viral genome sequences of animal origin was identified as the evolutionary starting point as they showed a low-pathogenicity due to six amino acid substitutions of the S protein, and in the second epidemic (2003–2004), more amino acid alterations (about 11) again in S protein resulting in a high-pathogenicity virus group (55, 96, 106, 112, 133). Since then scientists have been interested in following the coronaviruses and several studies were conducted to understand their evolutionary trend. Bioinformatics' analysis revealed that spike protein (S) acts as the cellular receptor binding, fusion protein, and is the most immunogenic viral protein, which induces the production of neutralizing antibodies, So, this protein is under the host immune system pressure and has to be evolved rapidly. Recently, a sequence analysis revealed 89.8 % sequence identity between SARS-CoV and SARS-CoV-2 S2 subunit of their spike (S) proteins, while both of their S1 subunits utilize the same cellular receptor (ACE2) (133). However, it has been shown that the higher infectivity and transmissibility of SARS-CoV-2 compared to SARS-CoV is because of the higher ACE2-binding affinity (about 10- to 20-fold) of the receptor binding domain (RBD) in S1 subunit of SARS-COV-2 (127, 128). These findings resulted in introducing SARS-CoV-2 as an emerging virus, which caused severe health problems in the world (96, 133).

Emerging of SARS and MERS with mortality rates of about 10 and 43% respectively, with no cure or vaccine to combat with, impressed the human health strategy makers with contact precautions such as: travel restrictions, and patient isolation were recommended to limit transmission of those viruses (63, 64, 96, 133). Since in late of 2019, we are dealing with the similar situation again, keeping social/physical distance, "staying at home" or in some more restricted conditions "quarantine" accompanied with a frequent hand washing, disinfection of hands and surfaces by using disinfectants such as alcohol, and wearing the mask are strongly recommended to reduce COVID-19 (63, 64, 133). Although we are used to encounter with epidemics or even pandemics due to re-emerging of some mutant viruses like HIV or influenza virus with new characteristics in their virulence, tropisms, and genomic information, recent outbreaks of emerging viruses from other viral families such as: SARS, MERS, Ebola, and COVID-19 in a time rang of about 20 years might be the warning of potential viral diseases outbreaks in the next future. Zoonoses with the ability of interspecies transmission are responsible for most emerging infectious diseases. Therefore, the ideal approach for preventing from future outbreaks could be the intensified monitoring of zoonosis and antiviral strategies involving small molecules and biologics targeting complex molecular interactions in viral infections also recent pandemic of SARS-CoV-2 highlights the necessity for the rapid development of effective interventions against these highly pathogenic coronaviruses.

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Received April 30, 2020.
Accepted May 2, 2020.