General characteristics of the Human Coronavirus (HCoVs) and the new coronavirus (SARS-CoV-2) that produces COVID-19 illness.

Dora Rosete[1], Gabriel Cortez[1], and Carlos Gutiérrez[2]

[1]National Institute of Respiratory Diseases
[2]Affiliation not available

September 11, 2020

Abstract

The new coronavirus has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible of the COVID-19 illness, it is a virus that belongs to the Coronavirus family, it is the third virus in this family that causes an epidemic. It originated in China and has spread throughout the world. It is highly pathogenic and transmissible that mainly affects the respiratory tract and can cause death. There is not antiviral drug or vaccines against COVID-19 illness, infected person only have supportive treatments. Recently, some antiviral drugs and vaccines are being valued. In this review, we described the general characteristics of HCoVs and latest research of the transmission, prevention and clinical characteristics of SARS-CoV-2 and some treatments and vaccines more development for to combat COVID-19 illness.

General characteristics of the Human Coronavirus (HCoVs) and the new coronavirus (SARS-CoV-2) that produces COVID-19 illness.

Dora Patricia Rosete-Olvera, Gabriel Palma-Cortés, Carlos Cabello-Gutiérrez.

Department of Research in Virology and Mycology, National Institute of Respiratory Diseases. Ismael Cosío Villegas (INER), Calzada de Tlalpan No. 4502, Colonia Sección XVI. Tlalpan 14080, México CDMX.

Correspondence

M en C Dora Patricia Rosete Olvera

Department of Research in Virology and Mycology

National Institute of Respiratory Diseases, Ismael Cosío Villegas, CDMX.

Email: dorosete67@yahoo.com.mx

Phone: 55 54 87 17 00. Ext: 5123

Co-Autors

Gabriel Palma Cortés. Email: gabpal52@yahoo.com.mx

Carlos Cabello Gutiérrez. Email: carloscginer@gmail.com

Abstracs

The new coronavirus has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible of the COVID-19 illness, it is a virus that belongs to the Coronavirus family, it is the third virus in

this family that causes an epidemic. It originated in China and has spread throughout the world. It is highly pathogenic and transmissible that mainly affects the respiratory tract and can cause death. There is not antiviral drug or vaccines against COVID-19 illness, infected person only have supportive treatments. Recently, some antiviral drugs and vaccines are being valued. In this review, we described the general characteristics of HCoVs and latest research of the transmission, prevention and clinical characteristics of SARS-CoV-2 and some treatments and vaccines more development for to combat COVID-19 illness.

KEYS WORDS: HCoVs, SARS-CoV-2, COVID-19

1 INTRODUCCION

The Human Coronaviruses (HCoVs) are a family of enveloped positive-sense RNA viruses that principally cause respiratory diseases and infect numerous mammals including humans. Family has 4 genera: alpha, beta, gamma and delta-coronavirus (α-β-γ and δ-CoVs), of which α and β-CoVs infect the human.[1] The first CoV was detected in 1930 and in 1960 was isolated the first human CoV.[2] Since then 7 types of CoVs have been detected in humans: 229E, OC43 (α-CoVs) and NL63, HKU1H, SARS (Severe acute respiratory syndrome), MERS (East Middle respiratory syndrome) (β-CoVs) and the most recent SAR-CoV-2 that causes COVID-19 illness (β-CoV). The first four viruses are low in pathogenicity and cause mild respiratory symptoms, similar to a common cold.[3,4] However, SARS-CoV[5] and MERS-CoV[6] are highly pathogenic and cause severe respiratory diseases with fatal outcomes. These types of CoVs have caused epidemics with high mortality and morbidity rate.[7]

In December 2019, a new virus SARS-CoV-2 is originated in Wuhan, China causing COVID-19 illness.[8] The Chinese government taken emergency measures to control the outbreak, but the virus spread in various provinces of China and in some countries.[9,10] The World Health Organization (WHO) officially designated this event as a pandemic. COVID-19 is a highly contagious disease that spread from person-to-person via close contact, resulting high morbidity and mortality.[11] In this moment, China and Europe have contained their epidemic with some outbreaks, however Latin America is found in highest peak of the epidemic. [12] There is no specific treatment or vaccine against the SARS-CoV-2, but there are some candidates and clinic tests that are under investigation.[13-15] An effective vaccine or antiviral drug against SARS-CoV-2 is necessary to combat this disease. In this review, we described the general characteristics of HCoVs and latest research of the transmission, prevention and clinical characteristics of SARS-CoV-2 and some treatments and vaccines more development for to combat COVID-19 illness.

2 HISTORY OF CORONAVIRUS

In 1930 the description of CoVs was made for the first time, the infection was detected in chickens, it was not given much importance and in 1960 the first case of coronavirus was discovered in humans, the virus was isolated from a patient with the common cold.[2] The virus were classified into a new family called *CORONAVIRUS* for its appearance of a crown on its viral surface, when viewed in the electron microscope.[1,16]The first two human coronaviruses were identified as 229E and OC43, they cause respiratory infections in the upper respiratory tract, symptoms similar to a common cold.[3,4] Later another member of this family caused the first pandemic of the 21st century, it was called severe acute respiratory syndrome (SARS-CoV), and it's originated in China in 2002. It was more aggressive than the previous types mainly causing lung diseases and it rapidly spread in some countries of Southeast Asia, North America, Europe, and South Africa with a mortality rate of 9.5%.[5,17] Since then, the study of this family regains great interest due to its pathogenicity and the need to identify therapeutic targets. In 2004-2005 other two viruses that infect humans are discovered (NL63 and HKU1), they cause upper and lower respiratory tract infections such as bronchiolitis, pneumonia especially in children, older adults, and immunocompromised.[3,4]In 2012 in Saudi Arabia another CoV was isolated from a patient with pneumonia called East Middle respiratory syndrome (MERS), some cases was exported to other countries through travel and the mortality rate was of 35%.[4,6,17] Recently, a new CoV (SAR-CoV-2) that caused COVID-19 illness, it was originated in China, has spread throughout the world and is causing high rates of morbidity and mortality.[9-11] Actually, China already contained her epidemic with some outbreaks. Many countries of Europe also, however, Latin America is at

the highest peak of the epidemic.[12]

3 CLASSIFICATION OF CORONAVIRUS

CoVs belong to the family *Coronaviridae* , subfamily*Coronarivinae* , and order *Nidovirales* and depending on the serotype they are divided in 4 genera: α, β, γ and δ-CoVs. α and β-CoVs infect human and γ and δ-CoVs infect birds.[16,18,19]Furthermore, β-CoVs have 4 lineages (A, B, C, D). CoV-A cause asymptomatic and mild symptomatic respiratory infections, CoV-B can cause asymptomatic, mild, and severe respiratory diseases that can lead to death. Seven serotypes infect the human: 229E, NL63 (α-CoVs); OC43, HKU1 (β-CoVs, lineage A); SARS (β-CoV, lineage B); MERS (β-CoV, lineage C) and the most recent SARS-CoV-2 (β-CoV, lineage B).[16,19] (Figure 1).

4 STRUCTURAL CHARACTERISTICS OF CORONAVIRUS

The CoV are enveloped positive single-stranded RNA viruses with spikes on the surface giving the appearance of a crown. CoVs genome encodes 4 structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (NP). In some types of CoVs, another protein hemagglutinin esterase (HE) (0C43 and HKU1) is present. In addition to structural proteins, the genome also codes for accessory proteins: 3a, 3b, 6, 7a, 7b, 8a, 8b, and 9b, these have functions related with viral pathogenesis.[1,19,20] (Figure 2) The structural proteins are required by CoVs to produce a structurally complete viral particle:

The S protein is a protein forms trimeric spicules on the surface of the virion, it is cut by a cellular protease and results in separation into two S1 and S2 subunits. The S1 subunit is responsible for binding to the cell receptor and forms the globular head of the structure, the S2 subunit is involved in fusion with the cell membrane and forms the stem.[1] S1 has cell receptor binding domains (RBDs), these sites are highly conserved and are related to interspecific transmission and viral pathogenesis.[16] Protein S mediate cell-cell fusion between infected and adjacent, uninfected cells resulting in formation of syncytia or multinucleated giant cells, a strategy that viruses use to spread.[21,22] It also induces the production of neutralizing antibodies and is therefore an important target for the development of vaccines.[2,23]

The M protein is the most abundant structural protein and it exists as a dimer and can take two different conformations that defines the shape of viral envelope.[1,20,21] Also is responsible for assembly virus components and incorporate in the new virions. It interacts with other structural proteins, interaction with protein S is necessary to retain it in the RE-Golgi compartment and to mature. The interaction with protein N is to give stability to the nucleocapsid and promote the termination of the viral assembly. The interaction of M and E is sufficient for the production and release of virus-like particles (VPLs).[20,21,23]

The E protein is found in small quantities within the virion and during the virus replication cycle is highly abundant in the cytoplasm of infected cells. Also facilitates assembly, release of the virus and increases the apoptosis.[1,20,24] E protein acting as a viroporin that forms ion channels in the lipid bilayer, causing more permeability to monovalent cations. In addition, E protein has PDZ domain that activates the pathology and triggering the overexpression of inflammatory cytokines.[25,26]

The N protein is a protein that encapsidates the RNA viral genome to form ribonucleoprotein complex with helical symmetry and it is produced abundantly in infected cells. Also protected the genome from degradation and is important during viral assembly and release of virions.[20,21,24] N protein is involved in the host's immune response and inhibits the production of interferon.[27]

The HE protein is forms a disulfide-linked homodimer and forms the short spicules on the virion surface. HE allows the initial adsorption of the virus to the cell membrane, but requires the subsequent interaction of the S protein. Also has esterase activity allows viral particles to be released from the infected cell by removing acetyl groups of membrane.[1,20,28]

5 ORIGEN AND SPREAD OF COVID-19

In December 30 2019, the city of Wuhan, the capital Hubei province of China with 11 million of habitants, cases with pneumonia of unknown etiology were identified. Most cases were associated with a food market

where a variety of shellfish, cuts of meat, live and dead animals are sold. China notifies the outbreak to WHO and a week later, January 7, the Chinese scientists isolated and sequenced a new virus from these infected patient, analyzes showed that the virus belonged to the *Coronavirus* family.[17] The genome of the new CoV presented 95% homology with bat coronaviruses and 70% similarity with SARS-CoV.[29] The new virus was initially referred as SARS-CoV-2 and was given the official name of COVID-19 by WHO.[30] The number of cases began to increase exponentially, some had not been exposed to the market, suggesting that human-human transmission was occurring and was due to direct contact or by aerosols from infected people. The first fatal case was reported on January 11, 2020, the infection spread in other provinces of China and several cases began to appear in Thailand, Japan, Korea, Taiwan, and USA. At this time, the R0 was calculated with results between 2 and 3.5, indicating that one patient could transmit the disease to 2 or 3 people. The infected patients with SARS-CoV-2 exhibit high fever, dry cough, shortness of breath, and severe cases presented pneumonia, the fatality rate was of 2%. On February 9, the WHO reported 37,251cases confirmed in China and 812 deaths, surpassing the number of deaths than in the SARS-CoV epidemic. March 2020, a total of 79,968 cases were confirmed with 2873 death. The Chinese authorities took the global threat very seriously and initiated containment measures (closing airports, train stations, and highways) and sanitary measures for health workers, government, and general public, all cooperating to try to prevent the spread of SARS-CoV-2.[17,18] Actually, China already contained her pandemic with some outbreaks.

6 TRANSMISSION ROUTE OF SARS-COV-2.

SARS-CoV-2 is transmits for direct contact from person to person through the respiratory droplets that are produced by an infected person while coughing, talking or sneezing and staying in the short distance from another person. Also the indirect contact is very common, it occurs through virus-contaminated surfaces and subsequent contact with mucous membranes of the eyes, mouth and nose.[31] The virus can remain viable on surfaces in favorable atmospheric conditions. Van Doremalen et al reported that SARS-CoV-2 can remain viable in aerosols for 3 hours and on surfaces such as plastic and stainless steel for more than 72 hours, in copper for 4 hours and in cardboard for 24 hours.[32] Some gastrointestinal symptoms such as diarrhea, nausea and vomiting have been reported in patients infected with SARS-CoV-2 and is associated with the expression of enterocytes that express the ACE2 receptor, suggesting that the digestive system may be a potential transmission route.[33] There is increasing evidence that many patients are asymptomatic, they have not clinical symptoms but they are able to transmit the virus to others. A recent research found that the viral load detected in asymptomatic patients were similar that in symptomatic patients, indicating that asymptomatic infections have the high potential for transmission.[34]

Patients elderly has clinic manifest more severe when had one or more comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease and cardiovascular disorders and they have a higher mortality principally men. However, there are few cases in children below 15 years of age.[35,36] The woman pregnant are also a vulnerable population for COVID-19 and reports of maternal deaths with SARS-CoV-2 has been confirmed.[37,38] Vertically mother-to-child transmission occurs, the newborn presents mild disease with faster recovery, viral shedding time is shorted and the baby has a good prognosis, the mortality is extremely low.[39]

The incubation time from SARS-CoV-2 is of 14 days, however most patients develop the disease between 2-7 days after infection. The virus remains contagious throughout the latency period and they can transfer the virus to other people before developing symptoms. Samples from patients with medium or moderate disease more rapidly become negative than samples with severe disease.[31]

7 CLINICAL MANIFESTATIONS

A wide range of clinical manifestations is seen in patients with SARS-CoV-2 from asymptomatic to symptomatic: mild, moderate, severe and critical cases. The asymptomatic patients have no typical clinical symptoms, but virus is detected. Other patients have mild flu-like symptoms and patients with moderate symptoms the disease begins in the upper respiratory tract and subsequently infects the lower respiratory tract causing pneumonia. Patients with severe disease after one week present with dyspnea, hypoxemia,

shortness of breath and significant lung injuries. Later the disease progresses rapidly caused respiratory failure, and need mechanical ventilation, septic shock, difficult to correct metabolic acidosis, coagulation dysfunction, acute respiratory distress syndrome and the patient dead for multiorgan failure.[34,35] The older patients has clinic manifest more severe when had one or more coexisting medical conditions such as hypertension, diabetes, chronic obstructive pulmonary disease and cardiovascular disorders and they have a higher mortality.[35,36]

The most common symptoms are fever, dry cough, shortness of breath, muscle pain, the least common are confusion, sore throat, headache, runny nose, chest pain. A smaller percentage manifest gastrointestinal symptoms, diarrhea, vomiting, or conjunctivitis.[34,40]Some authors have described loss of taste and olfactory sensation.[31,41-43] Others have describe what patients with SARSCoV-2 can presented cardiac dysfunction during the course of the illness[44] or dysfunction in the nervous system.[45,46] Recently, reports of patients with COVID-19 can presents abnormal coagulation parameters and thrombosis.[47,48]

The laboratory results of patients with severe disease for COVID-19 show a strong immune response, triggering a cytokine storm and severe lung damage. The cytokine storm is characterized by uncontrolled production of pro-inflammatory cytokines and is the main cause of acute respiratory distress syndrome (ARDS) and multiorgan failure. The patients has high plasma cytokines and chemokines levels (IL-2, IL-6, IL-7, IL10, GCSF, IFN-γ, MCP-1, MIP1-α, and TNF-α).[35,49] Also presents leucopenia and lymphopenia, total number of CD4 and CD8 T cells, hemoglobin, and platelets are decreased. In contrast, neutrophils count, D-dimers, blood urea, lactate dehydrogenase and creatinine levels are higher significantly. Other patients have abnormal liver function, with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST).[18,35]

Computed tomography (CT) examination is plays an important role in the diagnosis of SARS-CoV-2 pneumonia, the most common manifestations are the ground-glass opacities (GGO) and can identified four stages of disease: Early: GGO is distributed in the lower lobes unilaterally or bilaterally. Progressive: GGO is diffuse, bilateral and it consolidated in more than two lobes. In the critical stages: GGO is diffuse with dense consolidation and the absorption stage: GGO is extensive and the consolidation is gradually absorbed.[35,50]

8 PREVENTION AND TREATMENT

Recently, there are not antiviral treatment or vaccines against SARS-CoV-2, prevention, management and support healhcare are crucial. The best means of protection is to stay away from the virus exposure. The preventive measure are: washing hands with water and soap for more than 2s or sanitizer with 70% alcohol, ventilate work or home spaces, disinfecting common spaces, avoid public places, avoiding travel, maintain a social distance of approximately 1 m, suspected or confirmed cases must remain at home in quarantine. People who are in contact with infected patients/individuals wear face masks and tissue while sneezing/coughing and avoid touching, face, nose, eyes or mouth.[10,29,51]

Supportive care are: hydration with serum, cough and fever management. Patients with shortness of breath should be hospitalized for oxygen supply or mechanical ventilation. Patients with diabetes mellitus, hypertension, chronic diseases or kidney problems should be carefully monitored for any organic deterioration and have care that patients do not acquire opportunistic infections.[16,52]

There is not specific antiviral drugs against COVID-19, however some treatment with antivirals and adjunctive therapies as convalescent plasma, tocilizumab, azithromycin and corticosteroids are used as supportive care for COVID-19 patients with promising results as described below:

9 Antivirals:

Remdesivir (R) . Is an adenosine analogue that incorporates into nascent viral RNA chains resulting in pre-mature termination. In vitro studies have shown that R inhibits the replication of SARS-CoV-2 and in the non-human primates R penetrated efficiently in different organs of body.[53,54] In In the US, the first patient infected with SARS-CoV-2 was administered R, the patient's clinical symptoms improved and no adverse effects were observed.[55] In another study with hospitalized patients with severe COVID-19, they were treated with R, clinical improvement was observed in 36 of 53 (68%) of the patients, mainly in oxygen

support, they did not need to be intubated.[56] Remdesivir (GS-5734) is in phase 3 clinical trials for the treatment of COVID-19 and this drug has shown very promising activity.[57]

Lopinavir/ritonavir (L/R). L is an aspartic acid protease inhibitor and it is co-formulated with R to boost the pharmacokinetic activity and half-life of L through inhibition of CYP450 cytochrome, the effect is block viral replication.[57] In Korea, a patient of 54 years old years infected with SARS-CoV-2 had mild respiratory symptoms was administered L/R and clinical symptoms and viral load decreased.[58] However, in China, another study with 99 adult hospitalized patients with severe COVID19 received treatment with L /R and benefit was no observed,[59]other studies have similar results.[60,61]

Favipiravir (Avigan). Is a guanine analogue that inhibits the viral RNA polymerase, first enters the infected cells through endocytosis and is then transformed into in an active phosphoribosylated form and its interrupts the nucleotide incorporation process during viral replication.[13,62] In vitro studies shows inhibition of SARSCoV-2 replication.[63] COVID-19 patients treated with favipiravir showed that have superior recovery rate than that treated with umifenovir[64] or lopinavir/ritonavir.[53] Favipiravir was approved for the treatment of COVID-19 in China in March, 2020.[57]

Chloroquine (CQ). CQ blocks viral infection by increasing endosomal pH required for virus/cell fusion, also has immune-modulating activity, suppressing the production/release of TNF-α and IL-6. Studies demonstrated that CQ has anti-SARS-CoV-2 activity *in vitro*[18, 65] and clinical trials confirmed that CQ is efficacious in treating caused COVID-19 pneumonia, it is improved pulmonary lesions and shorter disease course. Given the efficiency CQ has been included in the Guidelines for the Diagnosis and Treatment of COVID-19 in China.[66,67]

10 Supporting Agents

Convalescent plasma (CP). Is an immunotherapy of neutralizing antibody of patients who have recovered from COVID-19. Two studies with patients diagnosed with critical and severe COVID-19 have reported clinical improvement and without serious side effects.[68, 69] Given the clinical effectiveness of CP, the FDA has approved their use.[15]

Tocilizumab (TCZ). Is a monoclonal antibody targeted against IL-6 receptors, it blocks the signal transduction pathway of IL-6, thereby reducing the inflammatory response. IL-6 plays an important role in cytokine storm.[70,71] Process induced for SARS-CoV-2 infection and that can leading to rapid disease progression. China, recommends TCZ as an immunotherapy drug for critical patients with COVID-19, patients showed the signs of improvement.[71,72]

Azythromycinm (AZ). Is a broad-spectrum macrolide antibiotic with immunomodulation and antiviral properties. AZ regulate the inflammatory response, attenuating the production of anti-inflammatory cytokines and promoting the production of immunoglobulins. Also, has the ability to induce pattern recognition receptors and IFNs.[73,74] *In vitro* studies shows that AZ has activity against SARS-CoV-2 and studies with patients shows that hydroxychloroquine combined with azithromycin is observed an improvement in the cases and viral load reduction and mortality for COVID-19.[75,76]

Dexamethasone (D). Is a synthetic glucocorticoid with anti-inflammatory and immunosuppressive properties. Studies has been showed that dexamethasone reduces mortality among COVID-19 patients with severe respiratory complications. Only it is recommended for severe cases.[77-79]

10 Current Status of COVID-19 Vaccine Development

Recently, several companies, institutions and research groups worldwide have been working on the development of nearly 200 vaccines for the novel coronavirus SARS-CoV-2. These companies include, BioNtech, Pfizer, GlaxoSmithKline, Johnson & Johnson, and many others. However, these trials are still in their early stages and require more time for finished their clinic trials and verified safety and immunogenicity of vaccine.[80] Three countries are producing vaccines, they are in the most advanced stages of development (phase 3) and they are the main candidates for to finish with this pandemic. United State (Scientists of

National Institute of Allergy and Infectious Disease and Biotechnology Company Moderna). They used an mRNA vaccine, mRNA-1273 that encodes the S protein of SARS-CoV-2 encapsulated in lipid nanoparticles, to produce specific neutralizing antibodies and a potent immune responses.[14,81-83] Oxford, UK (Oxford University and AstraZeneca Company) and China (CanSino Biologics), both groups used an adenoviral vector (Ad5) that expressing the S glycoprotein of SARS-CoV-2 and both report that the vaccine is safety and can produce a robust immune response.[80,82,84]

CONCLUSION

Infection with the novel SARSCoV-2 virus that causes COVID-19 disease has originate severe respiratory diseases with a high degree of morbidity and mortality worldwide. Measures for stop this pandemic is through the vaccine or discovering and identifying effective treatment. Although, several agents shows significant efficacy and safety, others remains controversial, this is because their investigations are case reports or preliminary data from clinical trials with small sample sizes and results have to be confirmed. The clinical manifestations of severe illness is complex and difficult of treated, the healthcare professionals should take great caution, because each patient behaves differently. This virus will remain and it will become a seasonal virus and we have to learn to live with it. For the moment the social distancing, hygiene, use of masks, quarantine and principally social consciousness are basic for prevent or control the infection. The vaccine is already in advanced stages with encouraging results, all the world see with great hope the purchase of the vaccine in the coming months to combat this deadly virus and to pass very soon a new normality in this world.

ACKNOWLEDGEMENTS

The authors like to thank the financial support from National Institute of Respiratory Diseases "Ismael Cosío Villegas, México and including those colleagues who assisted with this review.

CONFLICT OF INTEREST

The authors declare no conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

DPRO, GPC and CCG contributed in the writing-review the paper. DPRO also contributed in the traduction and editing. CCG in the final supervision.

ORCID

Dora Patricia Rosete Olvera

https://orcid.org/0000-0001-6021-9950

REFERENCES

1. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1-23.
2. Peiris JSM. 2012. Coronaviruses. Medical Microbiology. Eighteenth Edition. 2012; 12:587-593.
3. Ogimi C, Kim YJ, Martin MT, Huh HJ, Chiu CH, and Englund JA. What's New with the old Coronaviruses? J Pediatr Infec Dis Soc. 2020:1-8.
4. Su S, Wong G, Shi W et al. Epidemiology, Genetic, Recombination, and Pathogenesis of Coronaviruses. Trends Microbiol. 2016;24:490-502.
5. Drosten C, Günther S, Preiser W et al. Identification of a Novel Coronavirus in Patients with Severe Acute Respiratory Syndrome. N Engl J Med. 2003;348:1967-1976.
6. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, and Fouchier RA. Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia. N Engl J Med 2012; 367:1814-1820.
7. Cui J, Li F and Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019:17:181-192.

8. Zhu N, Zhang D, Wang W et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382:727.
9. Bogoch II, Watts A, Thomas-BA, Huber MS, Kraemer UG and Khan K. Potential for global spread of a novel coronavirus from China. J Travel Med. 2020:1-3.
10. Islam A, Ahmed A, Naqvi IH, Parveen S. Emergence of deadly severe acute respiratory syndrome coronavirus-2 during 2019–2020. Virus Dis. 2020. https://doi.org/10.1007/s13337-020-00575-1
11. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmunity. 2020.*https://doi.org/10.1016/j.jaut.2020.102433*
12. Burki T. COVID-19 in Latin America. Lancet Infec Dis. 2020. https://doi.org/10.1016/S1473-3099(20)30303-0
13. Wu R, Wang L, Dina KHC et al. An Update on Current Therapeutic Drugs Treating COVID-19. Curr Pharmacol Rep. 2020. https://doi.org/10.1007/s40495-020-00216-7
14. Ahn DG, Shin HJ, Kim MH et al. Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19). J Microbiol Biotechnol. 2020;30(3):313-324.
15. El-Aziz TMA and Stockand JD. Recent progress and challenges in drug development against COVID-19 coronavirus (SARS-CoV-2) – an update on the status. Infect Genet Evol. 2020. https://doi.org/10.1016/j.meegid.2020.104327
16. Chan JFW, Kok KH, Zhuc Z et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerging Microbes & Infections. 2020;9:221-236.
17. Guarner J. Three emerging Coronaviruses in two decades the story of SARS, MERS, and now COVID-19. Am J Clin Pathol. 2020;153:420-421.
18. Guo YR, Cao QD, Hong ZS et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak-an update on the status. Mil Med Res. 2020;7:11.*https://doi.org/10.1186/s40779-020-00240-0*
19. Fung TS and Liu DX. Human Coronavirus: Host-Pathogen Interaction. Annu Rev Microbiol. 2019;73:529-557.
20. Ashour HM, Elkhatib WF, Rahman M and Elshabrawy HA. Insights into the Recent 2019 Novel Coronavirus (SARS-CoV-2) in Light of Past Human Coronavirus Outbreaks. Pathogens. 2020;9:186. DOI:10.3390/pathogens9030186
21. Malik YA. Properties of Coronavirus and SARS-CoV-2. Malaysian J Pathol. 2020; 42(1): 3-11.
22. Schoeman D and Fielding BC. Coronavirus envelope protein: current knowledge. Virol J. 2019;16:69. https://doi.org/10.1186/s12985-019-1182-0
23. Li H, Liu SM, Yu XH, Tang SL, Tang CK. Coronavirus disease 2019 (COVID-19): current status and future perspectives. Int J Antimicrob Agents. 2020;20:54. https://doi.org/10.1016/j.ijantimicag.2020.105951
24. Hasöksüz M, Kili S, Sasac F. Coronaviruses and SARS-COV-2. Turk J Med Sci. 2020;50:549-556.
25. DeDiego ML, Nieto TJL, Jimenez GJM et al. Coronavirus virulence genes with main focus on SARS-CoV envelope gene. Virus Res. 2014;194:124-137.
26. Jimenez GJM, Nieto TJL, DeDiego ML et al. The PDZ-binding motif of severe acute respiratory syndrome Coronavirus envelope protein is a determinant of viral pathogenesis. PLoS Pathog. 2014;10(8):e1004320. DOI:10.1371/journal.ppat.1004320
27. Hu Y, Li W, Gao T et al. The Severe Acute Respiratory Syndrome Coronavirus Nucleocapsid Inhibits Type I Interferon Production by Interfering with TRIM25-Mediated RIG-I Ubiquitination. J Virol. 2017;91:e02143-16. https://doi.org/10.1128/JVI.02143-16.
28. Weiss SR and Leibowitz JL. Coronavirus Pathogenesis. Adv Virus Res. 2011;81:85-164.
29. Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). Indian J Pediatr. 2020;87(4):281-286.
30. Gorbalenya AE, Baker SC, Baric RS et al. The species severe acute respiratory syndrome related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020;5:536-544.
31. Krajewska J, Krajewski W, Zub K, Zatoński1 T. COVID-19 in otolaryngologist practice: a review of current knowledge. Eur Arch Oto-Rhino-L. 2020. https://doi.org/10.1007/s00405-020-05968-y

32. Van Doremalen N, Bushmaker T, Morris DH et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med. 2020. DOI: 10.1056/NEJMc2004973
33. Li JY, You Z, Wang Q et al. The epidemic of 2019-novel-coronavirus (2019-nCoV) pneumonia and insights for emerging infectious diseases in the future. Microb Infect. 2020;22:80-85.
34. Gao Z, Xu Y, Sun C, Wang S, Guo Y, Qiu S, Ma K. A systematic review of asymptomatic infections with COVID-19. J Microbiol Immunol Infect. 2020. https://doi.org/10.1016/j.jmii.2020.05.001
35. He F, Deng Y, Li W. Coronavirus disease 2019: What we know?. Med Virol. 2020:1-7. DOI: 10.1002/jmv.25766
36. Zhang Y, Xu J, Li H, Cao B. A novel Coronavirus (COVID-19) outbreak a call for action. Chest. 2020. DOI: https://doi.org/10.1016/j.chest.2020.02.014
37. Karami P, Naghavi M, Feyzi A et al. Mortality of a pregnant patient diagnosed with COVID-19: A case report with clinical, radiological, and histopathological findings. Travel Med Infect Dis.2020. https://doi.org/10.1016/j.tmaid.2020.101665
38. Juan J, Gil MM , Rong Z, Zhang Z, Yang H and Poon L. Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review. Ultrasound Obstet Gynecol. 2020;56:15-27.
39. Yang P, Wang X, Liu P et al. Clinical characteristics and risk assessment of newborns born to mothers with COVID-19. J Clin Virol. 2020;127. https://doi.org/10.1016/j.jcv.2020.104356
40. Colavita F, Lapa D, Carletti F et al. SARS-CoV-2 isolation from ocular secretions of a patient with COVID-19 in Italy with prolonged viral RNA Detection. Ann Intern Med. 2020. DOI: 10.7326/M20-1176
41. Gautier JF and Ravussin Y. A New Symptom of COVID-19: Loss of Taste and Smell. Obesity. 2019. DOI:10.1002/oby.22809
42. Mullol J, Alobid I, Mariño-SF et al. The Loss of Smell and Taste in the COVID-19 Outbreak: a Tale of Many Countries. Curr Allergy Asthma Rep. 2020;20:61. https://doi.org/10.1007/s11882-020-00961-1
43. Pallanti S. Importance of SARs-Cov-2 anosmia: From phenomenology to neurobiology. Compr Psychiatry. 2020;100. https://doi.org/10.1016/j.comppsych.2020.152184
44. Bansal M. Cardiovascular disease and COVID-19. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14:247e250. https://doi.org/10.1016/j.dsx.2020.03.013
45. Huang J, Zheng M, Tang X, Chen Y, Tong A. and Zhou LX. Potential of SARS-CoV-2 to Cause CNS Infection: Biologic Fundamental and Clinical Experience. Front. Neurol. 11:659. DOI: 10.3389/fneur.2020.00659 2020;11:659
46. Manji H, Carr AS, Brownlee WJ, Lunn MP. Neurology in the time of COVID-19. Neurol Neurosurg Psychiatry. 2020;91:568-570.
47. Connors J, Levy J. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020. https://ashpublications.org/blood/articlepdf/doi/10.1182
48. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. J Thromb Thrombolys. 2020. https://doi.org/10.1007/s11239-020-02105-8
49. Liu J, Zheng X, Tong Q et al. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. J Med Virol. 2020;92:491-494.
50. Wu D, Wu T, Liu Q, Yang Z. The SARS-CoV-2 outbreak: What we know. Int J Infect Dis. 2020;94:44-48.
51. Ali I, Alharbi OML. COVID-19: Disease, management, treatment, and social impact. Sci Total Environ. 2020;728. https://doi.org/10.1016/j.scitotenv.2020.138861
52. McArthur L, Sakthivel D, Ataide R, Chan F, Richards JS, and Narh CA. Review of Burden, Clinical Definitions, and Management of COVID-19 Cases. Am J Trop Med Hyg. 2020;103(2):625-638.
53. Jan H, Faisal S, Khan A et al. COVID-19: Review of Epidemiology and Potential Treatments Against 2019 Novel Coronavirus. Discoveries. 2020;8(2):e108. DOI: 10.15190/d.2020.5
54. Yan Y, Shin WI, Pang YX et al. The First 75 Days of Novel Coronavirus (SARS-CoV-2) Out-

break: Recent Advances, Prevention, and Treatment. Int J Environ Res Public Health. 2020;17:2323. DOI:10.3390/ijerph17072323
55. Holshue ML, DeBolt C, Lindquist S et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020;382:929-936.
56. Grein J, Ohmagari N, Shin D et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med.2020. DOI: 10.1056/NEJMoa2007016
57. Barlow A, Landolf KM, Barlow B et al. Review of Emerging Pharmacotherapy for the Treatment of Coronavirus Disease 2019. Pharmacotherapy. 2020;40(5):416-437.
58. Lim J , Jeon S , Shin HY et al. Case of the index patient who caused tertiary transmission of Coronavirus disease 2019 in Korea: the application of Lopinavir/Ritonavir for the treatment of COVID-19 pneumonia monitored by quantitative RT-PCR. J Korean Med Sci. 2020;35(6):e79. https://doi.org/10.3346/jkms.2020.35.e79
59. Cao B, Wang Y, Wen D et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. NEJM. 2020. DOI: 10.1056/NEJMoa2001282
60. Ford N, Vitoria N, Rangaraj A, Norris SL, Calmy A, and Doherty M. Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS or COVID-19: initial assessment. J Int AIDS Soc. 2020;23:e25489. https://doi.org/10.1002/jia2.25489
61. Baden LR and Rubin EJ Covid-19 -The Search for Effective Therapy. N Engl J Med. 2020;382;19. DOI: 10.1056/NEJMe2005477
62. Jean SS, Lee PI, Hsueh PR. Treatment options for COVID-19: The reality and challenges. J Microbiol Immunol Infect. 2020. https://doi.org/10.1016/j.jmii.2020.03.034
63. Du YX, and Chen XP. Response to "Dose Rationale for Favipiravir Use in Patients Infected With SARS-CoV-2. Clin Pharmacol Ther. 2020. DOI: 10.1002/cpt.1878
64. Chen C, Zhang Y, Huang J et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial.2020. DOI: https://doi.org/10.1101/2020.03.17.20037432
65. Wang M, Cao R, Zhang L et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30:269-271.
66. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020;14:72-73.
67. Gao J, Hu S. Update on use of chloroquine/hydroxychloroquine to treat coronavirus disease 2019 (COVID-19). BioSci Trends. 2020. DOI: 10.5582/bst.2020.03072
68. Shen C,Wang Z, Zhao F et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020;323(16):1582-1589.
69. Duan K, Liu B, Li C et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. PNAS. 2020;117(17):9490-9696.
70. Zhao M. Cytokine storm and immunomodulatory therapy in COVID-19: Role of chloroquine and anti-IL-6 monoclonal antibodies. Int J Antimicrob Agents. 2020:55. https://doi.org/10.1016/j.ijantimicag.2020.105982
71. Zhang S, Li L, Shen A, Chen Y, Qi Z. Rational Use of Tocilizumab in the Treatment of Novel Coronavirus Pneumonia. Clin Drug Invest. 2020. https://doi.org/10.1007/s40261-020-00917-3
72. Wang L, Peng X, Wang Z, Cai J, Zhou FC. Tocilizumab in the treatment of a criticalCOVID-19 patient: a case report. Eur Rev Med Pharmacol Sci. 2020;24:5783-5787.
73. Damle B, Vourvahis M, Wang E, Leaney J and Corrigan B. Clinical Pharmacology Perspectives on the Antiviral Activity of Azithromycin and Use in COVID-19. Clin Pharmacol Ther. 2020. DOI:10.1002/cpt.1857
74. Pani A, Lauriola M, Romandini A, Scaglione F. Macrolides and viral infections: focus on azithromycin in COVID-19 pathology. Int J Antimicrob Agents. 2020;56. https://doi.org/10.1016/j.ijantimicag.2020.106053
75. Arshad S, Kilgore P, Chaudhry ZS et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Infect Dis. 2020;97:396-403.
76. Gautret P, Lagier JC, Parola P et al. Clinical and microbiological effect of a combination of hydrox-

ychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. Travel Med Infect Dis. 2020;34. https://doi.org/10.1016/j.tmaid.2020.101663
77. Selvaraj V, Dapaah AK, Finn A, Flanigan TP. Short-Term Dexamethasone in Sars-CoV-2 Patients. RIMJ Archives.2020.
78. Rizk JG, KalantarZK, Mehra MR, Lavie CJ, Rizk Y, Forthal DN. Pharmaco-Immunomodulatory Therapy in COVID-19. Drugs. 2020. https://doi.org/10.1007/s40265-020-01367-z
79. Singh AK, Majumdar S, Singh R, Misra A. Role of corticosteroid in the management of COVID-19: A systemic review and a Clinician's perspective. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020:14:971e978. https://doi.org/10.1016/j.dsx.2020.06.054
80. Bar-Zeev N, Moss WJ. Encouraging results from phase 1/2 COVID-19 vaccine trials. Lancet. 2020. https://doi.org/10.1016/S0140-6736(20)31611-1
81. Liu C, Zhou Q, Li Y et al. Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases. ACS Cent. Sci. 2020;6:315-331.
82. Tu YF, Chien CS, Yarmishyn AA et al. A Review of SARS-CoV-2 and the Ongoing Clinical Trials. Int J Mol Sci. 2020;21:2657. DOI:10.3390/ijms21072657
83. Zhang J, Xie B, Hashimoto K. Current status of potential therapeutic candidates for the COVID-19 crisis. Brain, Behav Immun. 2020. https://doi.org/10.1016/j.bbi.2020.04.046
84. Zhu FC, Li YH, Guan XH et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Lancet. 2020;395:1845-1854.

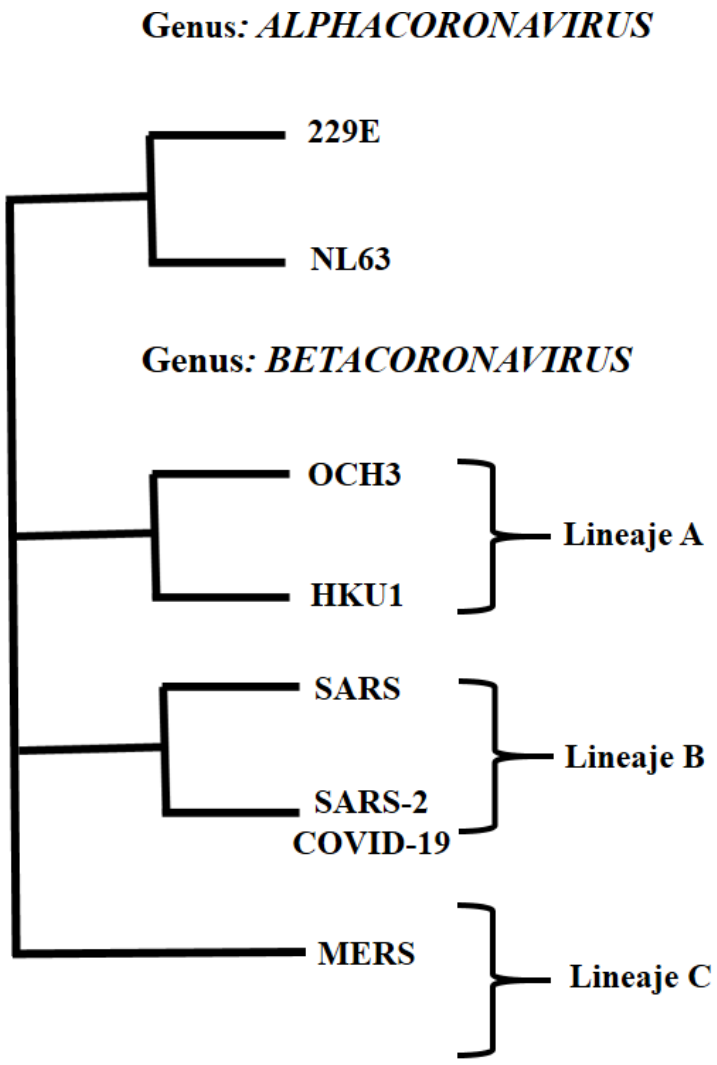

FIGURE 1. Classification of the seven types of *Coronavirus* that infected humans and the new virus SARS-CoV-2 that produces COVID-19 Illness.

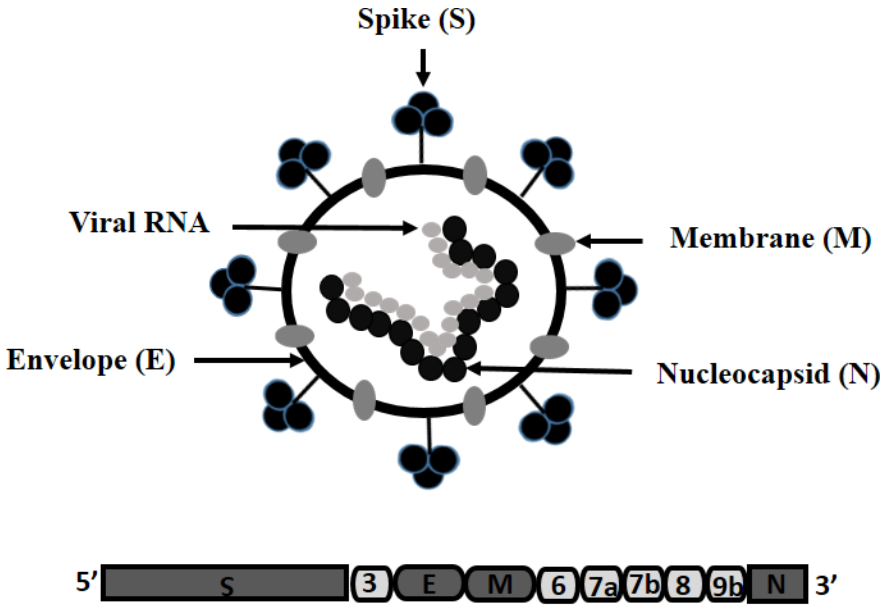

Figure 2. Structure and genome organization of new *Coronavirus* SARS-CoV-2. Structural proteins: S, E, M and N (black boxes) and accessory proteins (grey boxes) (reproduced from Chan FWJ et al, 2020).