Hebron University Research Journal-A (Natural Sciences) - (مجلة جامعة الخليل للبحوث- أ (العلوم الطبيعيه)

Volume 9 | Issue 1 Article 4

2020

A REVIEW ON CORONA VIRUS DISEASE (COVID-19)

hatem hejaz
Hebron University, hhejaz@hebron.edu

Dalia abo arqoup
Hebron University, r.journal@hebron.edu

Rezq Basheer
Hebron university, rezqbasheer@hebron.edu

Hiba Abu znaid
Hebron University, HibAbuZnaid@hebron.edu

Hiba Swaity
Hebron University, HibSwaity@hebron.edu

See next page for additional authors

A REVIEW ON CORONA VIRUS DISEASE (COVID-19)

Authors

hatem hejaz, Dalia abo arqoup, Rezq Basheer, Hiba Abu znaid, Hiba Swaity, and Thara'a Thara'a Rabai

Hebron University Research Journal(A)
Vol.(9), pp.(45-87), 2020

H.U.R.J. is available online at
http://www.hebron.edu/journal

A REVIEW ON CORONA VIRUS DISEASE (COVID-19)

[1] Hatem A. Hejaz, [1] Dalia Abo Arqoup, [1] Hiba Abu Znaid, [1] Hiba Swaity, [1]Thara'a Rabai, and [2] Rezq Basheer-Salimia

[1]College of Pharmacy and Medical Sciences, [2]College of Agriculture, Hebron University

Corresponding author: hhejaz@hebron.edu

Received: (29/5/2020), Accepted: (24/8/2020)

Abstract

Novel Coronavirus (COVID-19) is a new strain of coronavirus that may cause illness in animals or humans. SARS-CoV-2 was first identified in late December 2019, in Wuhan, China. The coronavirus infected patients 'who suffering from Immundeficient or chronic inflammation are at higher risk of getting a severe infection from COVID-19. The symptoms such as proinflammatory and hypercoagulable, non-cardiac pneumonia, multi-organ failure, and ARDS resulting in sudden death have been seen in those patients. Supportive treatment is still the main strategy in treating this disease since there is no evidence that current medicine can prevent or cure the infection resulting from coronavirus. However, more investigations are needed to illustrate their biochemical and hematological disorders, complications, prevention, and treatments. In conclusion, this review provides the most recent information on the current global pandemic coronavirus infection (COVID-19), which may help the health workers and researchers to pursue their studies.

Keywords: SARS-CoV-2, COVID-19, Pneumonia, Coronavirus, Treatment, Prevention

الملخّص:

فيروس كورونا المستجد (COVID-19) هو سلالة جديدة من الفيروسات التّاجيّة التي قد تُسبّب المرض في الحيوانات أو البشر. تـمّ تحديد (SARS-CoV-2) لأوّل مرّةٍ في أواخر ديسمبر 2019. وتجدر الإشارة إلى أنّ المرضى الذين يعانون من نقص المناعة،أو الالتهاب المزمن هم ألأكثر عرضةً للإصابة الشّديدة بهذا الفيروس COVID-19. وعادة ما تظهر عليهم أعراض مثل (Pro-inflammatory) ، و هي أعـراضُ تفاقمِ الالتهاب، وفرط في تخثّر الدم، والتهابٍ رئويّ غير قلبيّ المَنشأ، و فشلٍ متعدّدِ الأعـضاء، و ((ARDS ومتلازمة الفشل التّنفسيّ الحادّ، ممّا يؤدّي إلى الموت المفاجئ .تُـعـدُّ التّدابير الوقائيّة هي الإستراتيجيّة الرّئيسيّة لمنع انتشار هذا الفيروس؛ حيث لا يوجد ـ في الوقت الحالي ـ دليلٌ طبّيّ لمنع العدوى النّاتجة عن فيروس كورونا أو معالجتها؛ لذلك، ثَـمّـةً حاجةٌ إلى مزيد من البحوث والدّراسات لفهم آليّة الاضطرابات الكيميائيّة الحيويّة والدّمويّة النّاجمة عن الإصابة بهذا الفيروس، ومضاعفاته والوقاية منه وكيفيّة علاجه. وفي الختام، تُـقـدّم وتُـوفّـر هذه المراجعة أحدث المعلومات والبيانات المنشوره حول هذا الفيروس الوبائيّ (COVID-19) ، والتي قد تساعد العاملين في المجال الصّحّيّ والباحثين على متابعة دراساتهم وأبحاثهم لتحقيق الأهداف المرجـوّة.

الكلمات المفتاحية: الفيروسات التّاجيّة، فيروس كوروونا المستجد، الوقاية ، العلاج

Introduction

By the end of 2019, several patients were diagnosed with pneumonia of unknown reasons, epidemiologically associated with the same seafood market in Wuhan, Hubei province, central China. This condition caught the attention of the Chinese Center for Disease Control and Prevention (CDC), and the WHO launched an emergency response immediately, and later the CDC experts identified that the pneumonia was caused by a novel coronavirus (NCV). The Chinese government had taken great and extraordinary measures to control the outbreak. On January 30, 2020, the World Health Organization (WHO) designated an outbreak of a novel coronavirus not seen before in humans to be a "public health emergency of international concern" (PHEIC); this was followed by the declaration of a pandemic on March 11, 2020 (WHO, 2020c, Lai *et al*., 2020).

The novel virus was named Wuhan coronavirus or 2019 novel coronavirus (2019-nCov) by the Chinese researchers. The International Committee on Taxonomy of Viruses (ICTV) named the virus as SARS-CoV-2 and the disease as COVID-19. WHO officially named the disease COVID-19. By May 28th, 2020, the pandemic cases were 5,868,922 and 360,476 deaths worldwide with a 6.14% mortality rate estimated by WHO on May 28th, 2020. In Palestine, the pandemic confirmed cases were 570 with 4 deaths only. The diseases spread extremely very fast as by the end of June within only one month, the cases have been nearly doubled as the coronavirus cases by this time were 10,286,435, deaths 505,252 (8%), and recovered were 5,583,314. The high incidence rate and cases were in the USA (2,638,386), then Brazil (1,345,470), Russia (641,156), India, UK, Spain, Peru, Chile, Italy, and Iran respectively. In Palestine by this time, at the end of June, the reported cases were increased very sharply by about four times, more than 2,200 cases reported. The outbreak of the disease globally was continued raising very sharp as by 11th July 2020, the coronaviruses cases reported was 12,872,339 and the death cases were 568,312, the increase rate of the new cases was ~8% and the rate of death increased by 1.125%; within about two weeks period only, which considered high rates. The highest incidences by this time in the USA was 3,356,242 reported cases, then Brazil (1,840,812), India (854,480), Russia (727,162), and Peru (322,710), etc. as shown in Table-1. In terms of the outbreak of the disease, the rank of the countries is changing every day, but the USA and Brazil remain and still rank first and second respectively for a while. In Palestine by 11th July 2020, the confirmed cases were 6688, and the death cases were 36, with an increased rate of 304%, which extremely very high and considered the highest worldwide. The highest cases were in Hebron Governorate (4620 cases), with about 70% of the total reported cases, as shown in the geographical location of confirmed cases (Figure 1). The high outbreak of the disease in this region (Hebron Governorate), as 90% of infections have been caused by people meeting up with their families or attending wedding parties or

funerals and failing to follow health recommendations and maintain social distancing according to the Palestinian Ministry of Health officials.

Figure 1 shown Coronavirus disease 2019 (COVID-19) occupied Palestinian territory by 11th July 2020, Cumulative confirmed, recovered and death cases, confirmed cases per day (from April to July 2020), confirmed cases by gender (5th March to 11th July 2020), and confirmed cases by age in Palestine. Some data reported were included and some excluded East Jerusalem. (http://www.emro.who.int/pse/palestine-news/top-story.html). Table-1 shows cases for the top 30 countries including, other information such as daily new cases, total death, totally recovered, a total test of each country, etc. While the actual and accurate causes and effective treatment of COVID-19 are still unknown or unavailable and the number of active cases of the infection is rising every day as mentioned, which raises panic and concern on public health worldwide. Prevention is still the best strategy to face this pandemic. In this review, we summarized the available up to date studies by global researchers about COVID-19. Besides, we highlighted the virology, pathology and cell targeting, genomic structure and variation, clinical manifestations, transmission, epidemiology, ABO blood groups, and pregnancy-relation of COVID-19, animal hosts, diagnosis, treatment, and prevention about this virus and the pandemic.

The disease spread extremely very fast as by 17th November, 2020 (11:15 GMT) there were 55,446,791 cases diagnosed; with 4.3 times increase in 4 months only, the recovered cases were 38,606,024, and the death cases were 1,334,297, with an increase of ~2.35 times in 4 moths too. The highest incidences by this time were in the USA with 11,538,280 (~3.44 times increase) reported cases, then India (8,874,290, ~104 times increase, which is extremely very high), Brazil (5,876,740), France (1,991,233), Russia (1,971,013), Spain (1,521,899), UK (1,390,681), Argentina (1,318,384) and Italy (1,205,881). The rank of the countries is changing every day, but the USA remain and still rank first for a while. While Palestine on 16th November, 2020 (15 GMT) the confirmed cases

were 76162, with ~11.4 times increase with in 4 months, which is extremely very high. The death cases were 647, and recovered cases in Palestine were 66553 (~87.5%). With these confirmed cases Palestine ranked 69 among 215 countries that have coronavirus. It is worth to mention that Palestine on 13th July 2020 and 1st July, ranked 85 and 97 respectively; among 215 countries that have coronavirus; with one of the highest outbreak rate in the world; compare to population number. Within only 4 months period the Palestine rank changed from 97 to 69; however, if the outbreak in Palestine remains rising in the same rate, Palestine after a short period will be one of the top countries having the disease, if real and serious precautions did not apply especially the health recommendations, isolation and maintain social distance. The high outbreak of the disease in this region (Hebron Governorate) with 12277 confirmed cases (~25%), as 90% of infections have been caused by people meeting up with their families or attending wedding parties or funerals and failing to follow health recommendations and maintain social distancing according to Palestinian Ministry of Health officials. While the actual and accurate causes and effective treatment of COVID-19 are still unknown or unavailable and the number of active cases of the infection is rising every day as mentioned, which rising panic and concern on public health worldwide. Prevention is still the best strategy to face this pandemic. In addition, these numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing.

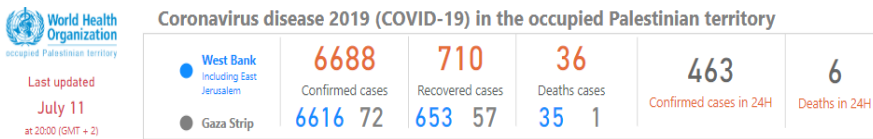
While the vaccines may potentially prevent infection, they cannot cure the disease, but researchers worldwide are working around the clock to find a vaccine against SARS-CoV-2. Vaccines typically require years of research and testing before reaching the clinic, but scientists are racing to produce a safe and effective coronavirus vaccine by next year. Researchers are testing 54 vaccines in clinical trials on humans, and at least 87 preclinical vaccines are under active investigation in animals. Work began in January with the deciphering of the SARS-CoV-2 genome. The first vaccine safety trials in humans started in March, and now 12 have reached the final stages of testing. Some of these trials will fail,

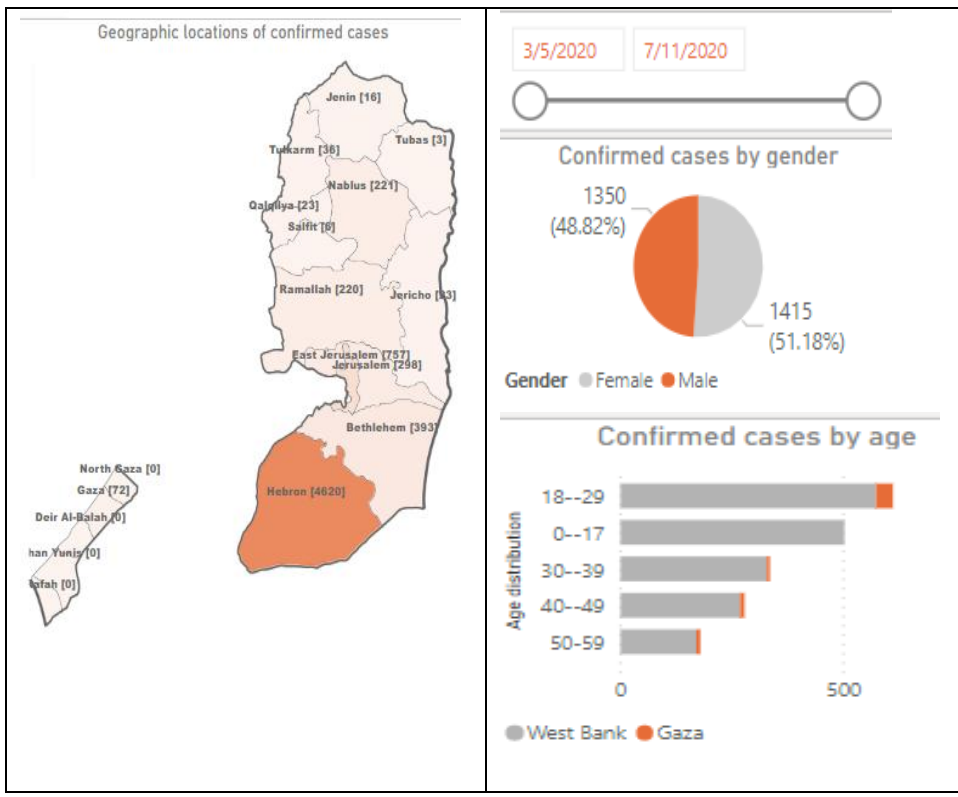
and others may end without a clear result. But a few vaccines may succeed in stimulating the immune system to produce effective antibodies against the virus. Moderna develops vaccines based on messenger RNA (mRNA) to produce viral proteins in the body. They have yet to bring one to the market. In January, they began developing a vaccine for the coronavirus. The vaccine contains genetic instructions for building a coronavirus protein, known as spike. When injected into cells, the vaccine causes them to make spike proteins, which then get released into the body and provoke a response from the immune system. On November 9, 2020 New York-based Pfizer and the German company BioNTech made history by presenting preliminary data indicating that their coronavirus vaccine was over 90 percent effective. It was the first time anyone had found such evidence. A week later, Moderna reported similar findings with a similar vaccine. On November 16, 2020 Moderna announced that a preliminary analysis of the trial indicated that the vaccine was 94.5 percent effective. Out of 95 participants who got Covid-19, 90 had the placebo and only 5 had the vaccine. The results came just a week after Pfizer made a similar announcement about their own vaccine, which is also based on an mRNA molecule encoding the spike protein. Another promising result from Moderna's trial was the finding that the vaccine appears to protect people from severe disease. Of the 11 volunteers who developed severe disease, none were vaccinated. The trial will continue to gather more results; Moderna says it plans to submit an application for an Emergency Use Authorization in the next few weeks. There are different vaccines are under testing by several companies worldwide, either they are in clinical trials or at preclinical investigation as mentioned. (The New York times, 2020).

Methodology

Literature and guidelines in different databases were collected and summarized. Preciously, a literature review using Google Scholar, Medline, PubMed, Web of Science, and Science Direct was conducted to identify peer-reviewed published articles on SARS-CoV, MERS-CoV, and 2019-nCoV. The initial terms "words"

that match with the title or abstract or with the topic including 2019-nCoV, 2019 novel coronavirus, SARS, CoV-2, COVID-19, coronavirus disease 2019, NCP, Novel coronavirus pneumonia were used in searching the databases. Further search using the keywords mentioned above, SARS, SARS-CoV, severe acute respiratory syndrome, MERS, MERS-CoV, Middle East respiratory syndrome, in combinations of with "pike protein, genome, reproductive number, incubation period, fatality rate, clinical characteristics, pathology, autopsy, treatment, and prevention. Moreover, official documents that have been released by the World Health Organization (WHO) were accessed for up to date data on COVID-19.





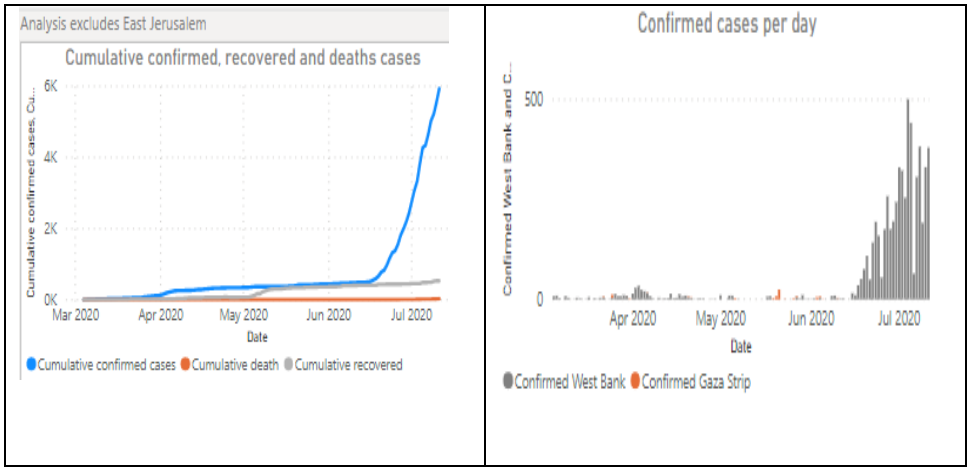


Figure 1: Coronavirus disease 2019 in Palestine (http://www.emro.who.int/pse/palestine-news/landing-page-for-covid19.html)

Table-1: Reported Cases and Deaths by Country (https://www.worldometers.info/coronavirus/)

Country, Other	Total Cases	Total Deaths	Total Recovered	Active Cases	Serious, Critical	Total Cases/ 1M pop	Deaths /1M pop	Total Tests	Population
World	12,872,339	568,312	7,502,157	4,801,870	58,807	1,651	72.9		
USA	3,356,242	137,414	1,490,702	1,728,126	15,819	10,138	415	41,773,190	331,060,504
Brazil	1,840,812	71,492	1,213,512	555,808	8,318	8,658	336	4,572,796	212,603,520
India	854,480	22,718	537,599	294,163	8,944	619	16	11,587,153	1,380,381,949
Russia	727,162	11,335	501,061	214,766	2,300	4,983	78	23,031,056	145,936,493
Peru	322,710	11,682	214,152	96,876	1,315	9,784	354	1,904,242	32,983,682
Chile	312,029	6,881	281,114	24,034	1,999	16,319	360	1,273,627	19,120,870
Spain	300,988	28,403	N/A	N/A	617	6,438	607	5,734,599	46,755,366
Mexico	295,268	34,730	180,852	79,686	378	2,289	269	723,668	128,969,990
UK	288,953	44,798	N/A	N/A	185	4,256	660	11,782,192	67,896,748
South Africa	264,184	3,971	127,715	132,498	539	4,453	67	2,108,570	59,328,450
Iran	257,303	12,829	219,993	24,481	3,359	3,062	153	1,972,207	84,021,254
Pakistan	248,872	5,197	156,700	86,975	2,118	1,126	24	1,562,638	220,990,656
Italy	242,827	34,945	194,579	13,303	67	4,016	578	5,900,552	60,458,858
Saudi Arabia	229,480	2,181	165,396	61,903	2,230	6,589	63	2,226,290	34,827,377
Turkey	211,981	5,344	193,217	13,420	1,194	2,513	63	3,930,223	84,363,898
Germany	199,812	9,134	184,500	6,178	278	2,385	109	6,376,054	83,792,278
Bangladesh	183,795	2,352	93,614	87,829	1	1,116	14	943,524	164,734,934
France	170,752	30,004	78,388	62,360	496	2,616	460	1,384,633	65,278,075
Colombia	145,362	5,119	61,186	79,057	875	2,856	101	1,006,093	50,897,758
Canada	107,347	8,773	71,266	27,308	2,156	2,844	232	3,183,516	37,751,539
Qatar	103,128	146	98,934	4,048	141	36,729	52	409,199	2,807,805
Argentina	97,509	1,810	41,408	54,291	688	2,157	40	456,042	45,207,451
China	83,594	4,634	78,634	326	3	58	3	90,410,000	1,439,323,776
Egypt	81,158	3,769	23,876	53,513	41	793	37	135,000	102,379,206
Indonesia	75,699	3,606	35,638	36,455		277	13	1,061,367	273,603,023
Iraq	75,194	3,055	43,079	29,060	400	1,869	76	671,478	40,241,752
Sweden	74,898	5,526	N/A	N/A	85	7,415	547	600,019	10,101,130
Ecuador	67,209	5,031	30,107	32,071	308	3,808	285	181,564	17,649,781
Belarus	64,932	464	55,380	9,088	89	6,872	49	1,134,653	9,449,221
Belgium	62,606	9,782	17,196	35,628	32	5,401	844	1,361,830	11,591,164

Result and Discussion

Virology

Coronaviruses (CoVs) are named for the crown-like spikes on their surface protruding to the periphery with a diameter of 60-160nm under electron microscopy (Shereen *et al*., 2020, Singhal, 2020, Chavez *et al*., 2020). They belong to the Nidovirales order, which contains Coronaviridae, Arteriviridae, and Roniviridae families (Xie and Chen, 2020, Kang *et al*., 2020). The Coronaviridae is composed of a large, single, positive-sense RNA (+ssRNA) genome of 27-32 kb with a 5'-cap structure and 3'poly-A tail

which interacts with the nucleoprotein (Shereen *et al*., 2020, Kang *et al*., 2020). The Coronavirinae is one of two subfamilies in the Coronaviridae family, and the other one is the Torovirinae (Kang *et al*., 2020). The Coronairinae is further subdivided into four groups, the alpha, beta, gamma, and delta coronaviruses. The groups were labeled by

phylogenetic clustering (Shereen *et al*., 2020, Kang *et al*., 2020). Coronavirus is a beta virus that infects vertebrates including humans and is known to cause gastrointestinal (GI) and respiratory diseases and sometimes involving important organs such as the liver, kidney, heart, and brain (Kang *et al*., 2020, Chavez *et al*., 2020).

Before 2019 six CoVs only were identified to cause a human respiratory infection; HKU1, HCoV-NL63, HCoV-OC43, and HCoV-229E only induce mild upper respiratory disease or sometimes contributed to common clod (Kang *et al*., 2020, Yang *et al*., 2020b), SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and MERS-CoV (the Middle East Respiratory Syndrome Coronavirus) attack lower respiratory tract and always induce severe respiratory syndrome (Kang *et al*., 2020). Genome sequence analysis shows that the 2019 novel coronavirus (2019-nCoV) has a typical beta coronavirus genome structure that includes SARS-CoV and MERS-CoV, it is 82% identical to human SARS-

CoV and 50% to MERS-CoV (Kang *et al*., 2020, Xie and Chen, 2020). See figure 3. It has been the seventh member of coronaviruses that infect humans.

Moreover, phylogenetic analysis of the viral genome reveals that the coronavirus is 89.1% (nucleotide similarity) identical to a group of bat SARS-like coronaviruses bat-SL-CoVZXC21 (NCBI accession number MG772934) (Yang *et al*., 2020b, Xie and Chen, 2020). Also, the genome sequence homology of 2019-nCoV and SARS is about 79%, the 2019-nCoV is closer to the SARS-like bat CoVs bat-SL-CoVZC45 (NCBI accession number MG772933) than the SARS-CoV by 96% (Wang *et al*., 2020b, Yang *et al*., 2020b).

The genome of coronaviruses is the largest among all RNA viruses; all coronaviruses have similar organization and expression of the genome (Kang *et al*., 2020, Shereen *et al*., 2020). 2019-nCoV has 14 open reading frames (ORFs) that encode 27 proteins. ORF1ab and ORF1a are located at the 5' end, both encode 15 non-structural proteins (nsps) from nsp1 to nsp10 and from nsp12 to nsp16 respectively (Shereen *et al*., 2020, Kang *et al*., 2020, Yang *et al*., 2020b). They are followed by four structural proteins, Nucleocapsid (N), Spike (S), Envelope (E), and Membrane (M), which are encoded by four other ORFs at the 3'end (Kang *et al*., 2020) and eight accessory proteins (3a,3b,p6, 7a, 7b, 8b, 9b and orf14) (Yang *et al*., 2020b) Figure 2 & Figure 3.

Pathology and Cell Targeting

The envelope of the virus includes three proteins: M protein binds nucleocapsids and enhances viral assembly and budding, E protein is involved in viral morphogenesis, release as well as pathogenesis, and S protein contributes to homotrimer spikes which recognize the receptor of the cell, thus helping virus invade target cell (Kang *et al*., 2020). See figure 1. They also express other polyproteins, nucleoproteins, and membrane proteins, such as RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and accessory proteins (Shereen *et al*., 2020).

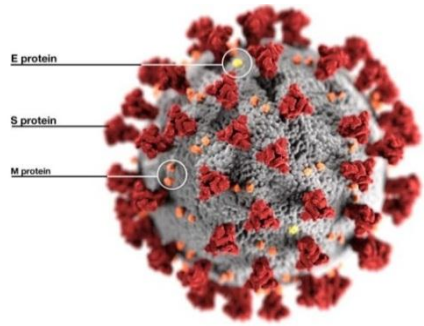


Figure 2. The electron microscope image depicts the spikes on the outer surface of the coronavirus-2 in addition to several protein particles. Eckert A, Higgins D, Centers for Disease Control and Prevention. ID# 23313; 2020. https://phil.cdc.gov/Details.aspx?pid=23313. Accessed April 6th, 2020. (Eckert A, 2020).

The entry mechanism of a coronavirus depends upon cellular proteases which include, human airway trypsin-like protease (HAT), cathepsins, and transmembrane protease serine 2 (TMPRSS2) that split the spike protein and establish further penetration changes, it has been reported that the cellular protease MPRSS2 blocks entry of the virus by cleaving the spike protein and may constitute a treatment option (Hoffmann *et al*., 2020). SARS-CoV and MERS-CoV recognize exopeptidases while other coronaviruses mostly recognize aminopeptidases or carbohydrates as a key receptor for entry to human cells (Bertram *et al*., 2011, Glowacka *et al*., 2011).

The spike S protein of 2019-nCov binds to angiotensin-converting enzyme 2 (ACE2) on target cells, which express ACE2 on their surface, the same mechanism as SARS-CoV. See figure 2. In a recent fluorescent study, it was confirmed that the 2019-nCoV also uses the same ACE2 cell receptor and mechanism for the entry to host cell which is previously used by the SARS-CoV (Xu *et al*., 2020, Gralinski and Menachery, 2020). Zhou et al. confirmed that 2019-nCoV binds to all ACE2 expressing cells except mice ACE2 cells (Zhou *et al*., 2020).

Whereas MERS-CoV uses dipeptidyl peptidase 4 (DPP4) as the primary receptor (Xie and Chen, 2020, Wu *et al*., 2020a). 2019-nCoV binds ACE2 with above 10 folds higher affinity than SARS-CoV, but higher than the threshold required for virus infection (Wrapp *et al*., 2020). Xu et al. concluded that despite the sequence diversity between 2019-CoV and SARS-CoV, they share the same 3-D structure in the Receptor Binding Domaine (RBD), thus they have similar van der Waals and electrostatic properties in the interaction interface of human ACE2 receptors (Xu *et al*., 2020).

The S protein at metastable prefusion conformation undergoes several structural arrangements to combine with the viral membrane of host cells (Su *et al*., 2016, Bosch *et al*., 2003). The S1 subunit binds to the cell receptor, triggers the prefusion trimer's instability, and sheds the S1 subunit, this results in a highly stable post-fusion conformation of the S2 subunit (Walls *et al*., 2017). The S1 subunit has two different states a "down" conformation and an "up" conformation state, which corresponds to a receptor inaccessible state and an unstable receptor-accessible state, respectively (Gui *et al*., 2017, Pallesen *et al*., 2017, Walls *et al*., 2019) Figure 3.

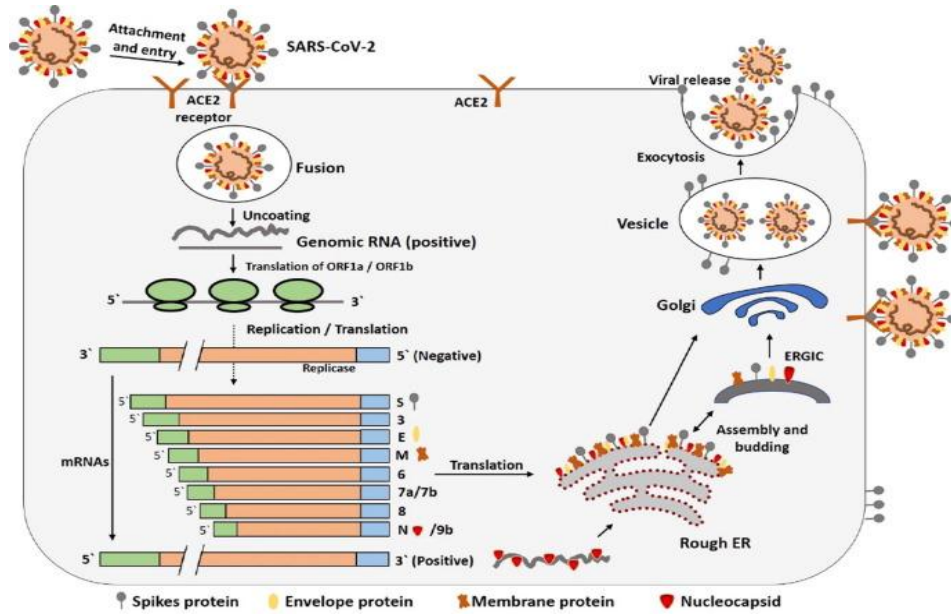


Figure 3. The life cycle of SARS-CoV 2. It starts by binding S protein to the ACE2 receptor, changing the conformation of S protein facilitating the fusion of viral envelope. Then SARS-CoV2 releases its RNA into the host cell, Genome RNA is translated into viral replicase polyproteins pp1a and 1ab, which are then cleaved into small products by viral proteinases. By discontinuous transcription, the polymerase produces a series of sub-genomic mRNA which are translated into viral proteins. Viral proteins and genome RNA are assembled into virions in the ER and Golgi and then transported outside the cell via vesicles (Shereen *et al*., 2020).

The respiratory system is the primary target of 2019-nCoV but bioinformatic analysis of single-cell transcriptomes datasets of lung, esophagus, gastric, ileum, and colon reveal that the digestive system is also a potential route of entry of 2019-nCoV as ACE2 is highly expressed in absorptive enterocytes from the ileum and colon (Zhang *et al*., 2020).

The S protein has two regions the S1 and S2, the former has a stronger affinity with the receptor binding RBD to bind ACE2 to enter the target cell, but since there are changes in the residue in S1 and S2 there are differences in the binding

process and the conformation between 2019-nCoV and SARS-CoV, thus available monoclonal antibodies do not react with 2019-nCoV (Dong *et al*., 2020, Ren *et al*., 2020, Wrapp *et al*., 2020).

The residues at positions 442, 472, 479, 487, and 491 in S-protein are reported to be at receptor complex interface with ACE2, but only TYR491 out of the five are preserved in 2019-nCoV (Xie and Chen, 2020). Arg426 is replaced by Asn426 in 2019-nCoV, so hydrogen bonds are lost which leads to the increased binding free energy of 2019-nCoV compared to SARS-CoV (-50.6kcal mol^{-1} vs. -78.6kcal mol–1) (Xu *et al*., 2020, Xie and Chen, 2020).

It is reported a furin-like cleavage site in the S-protein of 2019-nCoV, which is absent in other beta-coronaviruses (Coutard *et al*., 2020, Wrapp *et al*., 2020). Also, another research team discovered an "RRAR" furin recognition site by an insertion in the S1/S2 protease cleavage site in 2019-nCoV, instead of a single arginine compared to SARS-CoV (Xie and Chen, 2020, Wrapp *et al*., 2020).

Based on current data 2019-nCoV is likely to cause cell pyroptosis in lymphocytes through the activation of NLRP3 inflammasome (Yang, 2020). Pyroptosis is a novel inflammatory form of programmed cell death. In 2019, it was found that SARS-CoV Viroporin 3a triggers the activation of the NLRP3 inflammasome and the secretion of IL-1β in bone marrow-derived macrophages, suggesting SARS-CoV induced cell pyroptosis (Chen *et al*., 2019). Studies reported that patients with 2019-nCoV have increased IL-1β in the serum (Huang *et al*., 2020a). As the increase in IL-1β is an indicator of cell pyroptosis, it is suggested that cell pyroptosis is the pathogenesis of 2019-nCoV. Both classical and non-classical cell pyroptosis can induce an increase in IL-1β, so it is unclear which pathway is involved in 2019-nCoV.

Genomic Structure and Variation

The genomic structure of CoVs is 5′-leader-UTR-replicase-S (Spike)–E (Envelope)-M (Membrane)-N (Nucleocapsid)-3′UTRpoly (A) tail (Yang *et al*.,

2020b). In GenBank, there is only one complete 2019-nCoV genome (29870-bp, excluding the poly (A) tail) (accession number MN908947) (Phan, 2020). Five typical ORFs on the same coding strand were identified, including ORF1ab polyprotein (7096-aa), spike glycoprotein (1273-aa), an envelope protein (75-aa), membrane protein (222-aa), and nucleocapsid protein (419aa) (Phan, 2020) Figure 4.

Spike glycoprotein (S) consists of S1 and S2 subunits. The S1 subunit contains a signal peptide, an N-terminal domain (NTD), and RBD, while the S2 subunit includes the conserved fusion peptide (FP), heptad repeat 1 and 2 (HR1 and HR2), transmembrane domain (TM), and a cytoplasmic domain (CP) (Dong *et al*., 2020, Delmas and Laude, 1990, Xia *et al*., 2020). Furthermore, the S2 subunit of 2019-nCoV is highly conserved and shares 99% similarity with those of Bat-SL-CoVZC45, Bat-SL-CoVZC21, and human SARS-CoV (Dong *et al*., 2020, Ceraolo and Giorgi, 2020). The E protein helps in virus assembly and release (DeDiego *et al*., 2007, Nieto-Torres *et al*., 2014). The N protein consists of two domains; they bind to the virus RNA genome via different mechanisms (Fehr and Perlman, 2015, Chang *et al*., 2006).

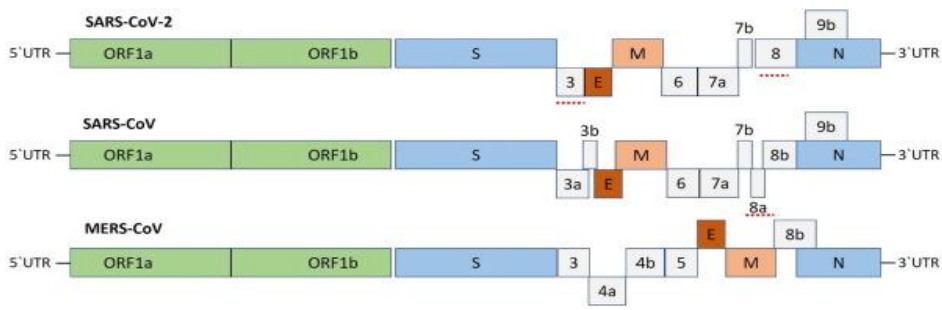


Figure 4. Beta coronaviruses genome organization. The open reading frame (ORF) (green box), structural proteins including spike (blue box), envelope (maroon box0, membrane (pink box), and nucleocapsid (cyan box). Accessory proteins (light gray boxes). The dotted red underlines are the key variations between SARS-CoV and SARS-CoV2 (Shereen *et al*., 2020).

Recent studies declared a bat CoVs sequence, RaTG13, with a 92–96% sequence identity with the novel virus, confirming that RaTG13 is the closest relative of the 2019-nCoV and forms distinct lineage from other SARS-CoVs (Paraskevis *et al*., 2020, Zhou *et al*., 2020). This rejects the hypothesis of emergence as a result of a recombination event which a previous study suggested (Paraskevis *et al*., 2020). Despite the high similarities between 2019-nCoV and RaTG13 S, there are two distinct differences: one is an "RRAR" furin recognition site formed by an insertion residue in the S1/S2 protease cleavage site in SARS-CoV-2, rather than the single Arginine in SARS-CoV (Wrapp *et al*., 2020, Xie and Chen, 2020, Li *et al*., 2003b) the other difference is the presence of 29 variant residues between 2019-nCoV and RaTG13 S, 17 of which mapped to the (RBD) (Wrapp *et al*., 2020).

Coronaviruses of animal origin undergo mutations by evolution and genetic recombination either within the same host species or by transmitting from species to other, thus resulting in highly pathogenic and deadly viruses to humans (Sabir *et al*., 2016, Su *et al*., 2016). In 2019-nCoV two mutations were identified and may explain the zoonotic transmission. Genomic alignment of 54 SARS-CoV-2 genomes identified two hotspots of hypervariability at positions 8789 (synonymous variant) and 28,151 (Ser/Leu change), located in the polyprotein and ORF8 genes respectively (Ceraolo and Giorgi, 2020). There is a single N501T mutation in SARS-CoV-2's Spike protein that may have significantly enhanced its binding affinity for ACE2 (Wan *et al*., 2020).

Clinical Manifestation

Clinical features of COVID-19 are ranging from an asymptomatic state to acute respiratory distress syndrome and multi-organ dysfunction (Singhal, 2020). It is difficult to distinguish COVID-19 from other viral upper respiratory illnesses due to similar symptoms (Wu and McGoogan, 2020). Fever (78.75%) that does not alleviate by traditional anti-infective drugs (Huang *et al*., 2020a), cough

(63.75%), dyspnea (37.50%), tiredness, sore throat, myalgia (22.50%), and headache (16.25%) are the most common clinical findings (Wu *et al*., 2020b, Jernigan, 2020). In addition to conjunctivitis in some cases (Singhal, 2020). Many other symptoms have been reported such as loss of tasting and smelling, increased heart rate (more than 100 bpm), and dehydration (Yang *et al*., 2020b).

Most patients are asymptomatic or have these mild upper respiratory symptoms or non-severe pneumonia (Heymann and Shindo, 2020), and have a good prognosis (Kang *et al*., 2020). Sever cases (13.8%) have dyspnea, oxygen saturation less than 93% in ambient air, RR greater than 30 times/min, and PaO2/FiO2 less than 300 mm Hg (Wu *et al*., 2020b). Critical cases (4.7%) have severe complicated pneumonia with acute respiratory distress syndrome (17-29% of patients) (Huang *et al*., 2020a), septic shock, and/or multiple organ failure (5% of cases) (Cascella *et al*., 2020) and are with poor prognosis (Kang *et al*., 2020). A recent study showed that SARS-CoV-2 might cause liver damage, renal damage, and testicular tissue damage (Fan *et al*., 2020, Chai *et al*., 2020). While the overall case fatality rate is estimated to be 6% (WHO, 2020b).

Moreover, lymphocytopenia occurs in 72.3 % of cases (Liu *et al*., 2020) and leukopenia in 25% of cases (Sun *et al*., 2020). Some patients may also experience confusion, nausea, vomiting, rhinorrhea, and pleurisy (Chen *et al*., 2020c), and other complications include acute kidney injury, secondary bacterial infection, and cardiac injury (Surveillances, 2020). These atypical symptoms are more likely in the elderly and immunocompromised (WHO, 2020b). Disease in neonates, infants, and children have been also reported to be significantly milder than adult (Chavez *et al*., 2020).

Incubation Period (how long it takes for symptoms to appear)

Symptoms of COVID-19 may appear in as few as 2 days or as long as 14 (estimated ranges vary from 2-10 days, 2-14 days, and 10-14 days, during which the virus is contagious but the patient does not display any symptom (*asymptomatic transmission*). 2-14 days represents the current official estimated

range for the novel coronavirus COVID-19. However, a case with an incubation period of 27 days has been reported by Hubei Province local government on Feb. 22 (Reuters, Feb. 22, 2020). Also, a case with an incubation period of 19 days was observed in a JAMA study of 5 cases published on Feb. 21. (JAMA, Bai Y, Yao L, Wei T, *et al*., 2020) An outlier of a 24 days incubation period had been for the first time observed in a Feb. 9 study (Guan WJ, Ni ZY, Hu Y, *et al*., 2020) WHO said at the time that this could reflect a second exposure rather than a long incubation period and that it wasn't going to change its recommendations. The period can vary greatly among patients. Mean incubation period observed: 3.0 days (0-24 days range, a study based on 1,324 cases) 5.2 days (4.1-7.0 days range, based on 425 cases). Mean incubation period observed in travelers from Wuhan: 6.4 days (range from 2.1 to 11.1 days). The interval from the initiation of mild symptoms to significant symptom aggravation like breathlessness or ARDS ranges from one to twenty days, with a median of seven days (Huang *et al*., 2020a). However, this interval can extend to forty days depending on the age of the patient and immune system status (Wang *et al*., 2020c).

Since the presence of different symptoms that varies among the patients in addition to the continuous discovery of new clinical features, WHO is continuously monitoring patients and reporting any new symptoms for a full understanding of this novel coronavirus (WHO, 2020b). Understanding the incubation period is very important for health authorities as it allows them to introduce more effective quarantine systems for people suspected of carrying the virus, as a way of controlling and hopefully preventing the spread of the virus.

Transmission

α and β types of coronaviruses can infect mammals, while γ and δ types tend to infect birds (Lau *et al*., 2010, Yin and Wunderink, 2018). Genome sequencing of the novel coronavirus has revealed that bats from the Hipposideridae family are the natural origin of the virus. Palm civets have been suspected to be the

intermediate that disseminates the infection to humans (Yang *et al*., 2020b). Some of the earliest infected patients with COVID-19 in Wuhan had a history of contact with a seafood market that suggests animal-to-person viral transmission (Lu *et al*., 2020), then person to person transmission was suggested after the infection of a new set of patients who did not have a history of exposure to the mentioned market (Nishiura *et al*., 2020).

Person To person contact, transmission by touch, and transmission by aerosols are the major three ways of transmission of COVID-19 coronaviruses in general (WHO, 2020b). Thus, coronaviruses can be transmitted during coughing or sneezing by respiratory droplets when propelled up to 3 feet through the air followed by the droplets deposition on the mucous membranes of the nose, mouth, or eyes of a close person (Malik *et al*., 2020) also, the virus can be transmitted by handshaking and touch of infected surfaces /object (Lu *et al*., 2020). Another transmission method is by the transmission of the virus from an asymptomatic infected person to other contacts which can be referred to as "hidden transmission" (Chan *et al*., 2020).

Fecal-oral transmission is suggested as a potential route of transmission after several studies that reported gastrointestinal symptoms (2-10% of cases) in infected patients and live virus or viral RNA in feces of some patients (Hindson, 2020, Chen *et al*., 2020c). The mechanisms by which SARS-CoV-2 affects the gastrointestinal tract is still unknown, it's expected to be by use ACE2 as a receptor for the virus since ACE2 is highly expressed in the GIT (Hindson, 2020). Environmental and enteric studies should be done to inform this route of transmission and to check the viability of the virus in the feces and viral concentration in the feces and it correlated with the severity of the infection (Yeo *et al*., 2020). Conclusions based on this information, there is evidence that human-to-human transmission has occurred among close contacts since the middle of December 2019. Considerable efforts to reduce transmission will be

required to control outbreaks if similar dynamics apply elsewhere. Measures to prevent or reduce transmission should be implemented in populations at risk.

Epidemiology

As reported by the WHO Health Emergency Dashboard (April 12, 10 pm GMT), 1,775,206 confirmed cases of COVID-19 (SARS-CoV-2) worldwide and 108,544 (6.18%) confirmed deaths since the beginning of the epidemic, in 213 Countries, areas or territories (WHO, 2020b). In comparison with the previous outbreak of coronaviruses SARS (2002) infected 8422 people in China and 31 other countries and leads to the death of 919 cases (11%), the number of the infected persons is very small compared to COVID-19 while the percent of deaths is still higher (WHO, 2003). By May 28^{th,} 2020, the pandemic cases were 5,868,922 and 360,476 deaths worldwide with a 6.14% mortality rate estimated by WHO on May 28th, 2020 in 216 Countries. The diseases spread extremely very fast as by the end of June within only one month, the cases have been nearly doubled as the coronavirus cases by this time were 10,286,435, deaths 505,252 (8%), and recovered were 5,583,314. The high incidence rate and cases were in the USA (2,638,386), then Brazil (1,345,470), Russia (641,156), India, UK, Spain, Peru, Chile, Italy, and Iran respectively. In Palestine by this time, at the end of June, the reported cases were increased very sharply by about four times, more than 2,200 cases reported.

A study on 425 infected patients with COVID-19 in china (Feb 2020) showed that of which 56% of patients were males and the median age was 59 years (Sun *et al*., 2020, Li *et al*., 2020). Another large Chinese study reported that 86.6% of 72,000 patients are of ages ranging from 30-79 with, 81% of them were mild cases while 2.3% died (Surveillances, 2020) 2.1% of all cases were pediatric cases (0-19 years old). (Khot and Nadkar, 2020) sever and critical cases represent only 14.6% (Surveillances, 2020). Severe COVID-19 risk factors are immunocompromised cases, advanced age, cancer, and chronic illnesses (Khot and Nadkar, 2020). Patients older than 80 years old presented the highest rate of

fatality (14.8%). Patients with comorbidities such as cardiovascular illnesses had a fatality rate of 10.5% while those without comorbid conditions had a rate of fatality less than 1% (Huang *et al*., 2020a).

The outbreak of the disease globally was continued raising very sharp as by 11th July 2020, the coronaviruses cases reported was 12,872,339 and the death cases were 568,312, the increase rate of the new cases were ~8% and the rate of death increased by 1.125%; within about two weeks period only, which considered high rates. The highest incidences were in the USA with 3,356,242 reported cases; by this time, then Brazil (1,840,812), India (854,480), Russia (727,162), and Peru (322,710), respectively, as shown in Table-1. In terms of the outbreak of the disease, the rank of the countries is changing every day, but the USA and Brazil remain and still rank first and second respectively for some time. In Palestine by 11th July 2020, the confirmed cases were 6688, and the death cases were 36, with an increased rate of 304%, which extremely very high and considered the highest worldwide. The highest cases were in Hebron Governorate (4620 cases), with about 70% of the total reported cases, as shown in the geographical location of confirmed cases (Figure 1). The high outbreak of the disease in this region (Hebron Governorate), as 90% of infections have been caused by people meeting up with their families or attending wedding parties or funerals and failing to follow health recommendations and maintain social distancing according to the Palestinian Ministry of Health officials. The greatest number of new cases and deaths of COVID-19 being reported by 11th July was in the USA, Brazil, India, Russia, Peru, Chile, Spain, Mexico, UK, South Africa, Iran, Pakistan, Italy, and (WHO, 2020b). These growing numbers of cases were due to the person-to-person transmission that has been reported both in and outside of China where most initial cases were reported particularly in Hubei Province (Wang *et al*., 2020b) Figure 5 & Table-1.

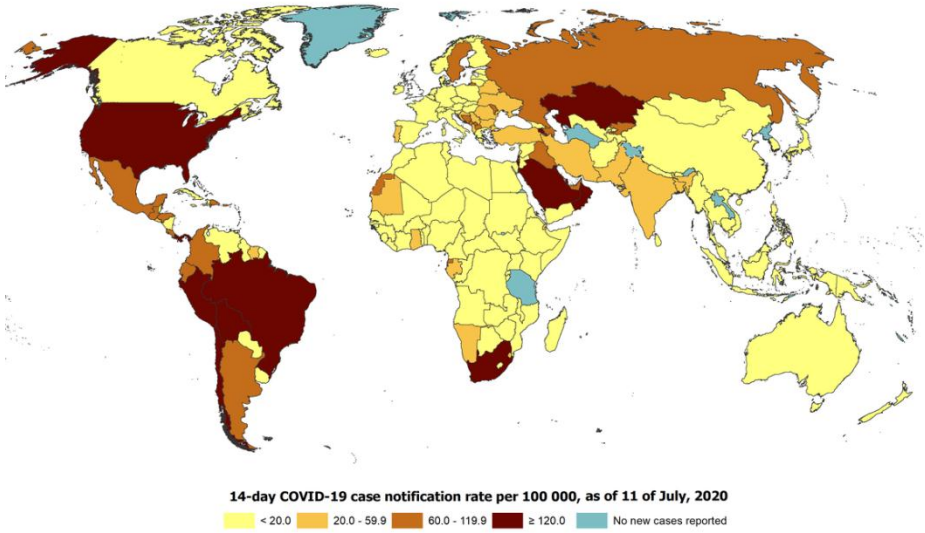


Figure 5: COVID-19 situation update worldwide, as of 11th July 2020

Association between the ABO Blood Type and COVID-19

Interestingly, a small study conducted on 2,173 patients infected with SARS-CoV-2, 206 of them are dead cases, at three hospitals in Wuhan, China, showed that blood group A was associated with a higher risk for acquiring the COVID-19 compared with non-A blood groups, while blood group O was associated with a lower risk (Zhao *et al*., 2020). Previous studies on coronaviruses have shown results that are consistent with the findings of this study (Cheng *et al*., 2005a). This justifies the use of the ABO blood type as a biomarker for differential susceptibility of COVID-19 (Zhao *et al*., 2020).

Although the mechanism behind these findings is still unclear, it's expected that the lack of anti-A antibodies is the reason behind the increased risk of infection in persons with A blood group (Trégouët *et al*., 2009). Thus, the presence of the anti-A antibodies can protect non-A blood groups by the inhibition of the interaction between the virus and angiotensin-converting enzyme 2 (ACE2) receptor, which was found to be the receptor for SARS-CoV-2 (Guillon *et al*., 2008, Zhao *et al*., 2020). This inhibition specifically occurs for the adhesion of S protein-expressing cells of SARS-CoV to ACE2-expressing cell lines (Guillon *et*

al., 2008). By the researcher's predictions, SARS-Cov-2 uses ACE2 not only as its host receptor but also uses ACE2 more efficiently than the SARS-CoV strain in 2003 (Wan *et al*., 2020). However, further research and studies are needed to prove this hypothesis or to explore other mechanisms.

COVID-19 in Pregnancy

Data about pregnancy and neonatal infections are limited, although it's expected that pregnant women have a higher risk of severe disease if infected with the virus due to the pregnancy-related decreased immunity (Schmid *et al*., 2020), there is no evidence that pregnancy increases the susceptibility to COVID-19 infection or causes the development of severe pneumonia (Yang *et al*., 2020a).

Fortunately, unlike the other viruses (except herpes virus) that have hematogenous transmission from mother to fetus when the virus enters the placenta from the maternal blood, coronavirus does not follow this mechanism (Schwartz, 2020). There are a few reported cases of infection of newborn babies infected by person-to-person contact (Qiao, 2020). Moreover, in a recent study on six pregnant patients of COVID-19, the study tested samples from cord blood, amniotic fluid in addition to breastmilk, and neonatal throat swab, all the samples were negative for SARS-CoV-2 (Chen *et al*., 2020a). In the same study, the clinical features of the nine pregnant women with COVID-19 infection were like the symptoms of non-pregnant infected adults (Huang *et al*., 2020a).

Animal Hosts of COVID-19

Although researchers are still learning about the novel coronavirus, it's now known that it is zoonotic and, in some situations, can spread from people to animals (Peeri *et al*., 2020). Scientists are working to establish a potential animal reservoir for SARS-CoV-2. A recent study in which the susceptibility of animals in close contact with humans to SARS-CoV-2 had been investigated found that SARS-CoV-2 replicates poorly in chickens, dogs, ducks, and pigs while cats in addition to ferrets are permissive to infection (Shi *et al* 2020). The study

experimentally confirmed the susceptibility of cats to airborne infections (Shi *et al*., 2020). According to reported cases and studies cats can infect each other with COVID-19 by respiratory droplets. Moreover, the first human-cat transmission has been reported in Belgium (WHO, 2020b). Besides, two cases of dogs in Hong Kong tested positive for COVID-19, one of them died. And a tiger tested positive for the virus after encountering an infected asymptomatic caretaker (WHO, 2020b).

Diagnosis

Anyone who deals directly with a person who is confirmed to be infected with the virus must isolate himself from others until the tests are performed. Most patients with mild cases of COVID-19 have had a fever with and/or symptoms of acute respiratory illness like cough and difficulty in breathing (CDC, 2020 -d). Patients with these symptoms must ask the nearest health center specialized for the examination of COVID-19 to make the test. Patients must wear facemask and gloves before any interaction with anyone and place in a private room isolated from another person which is an airborne infection isolated room (CDC, 2020b, Wax and Christian, 2020). Only health care professionals can enter this room with fully protected and isolated clothes.

Reverse transcription-polymerase chain reaction (RT-PCR) was used for the determination of COVID-19. Specific diagnosis is by specific molecular tests on respiratory samples (throat swab, nasopharyngeal swab, sputum, endotracheal aspirates, and bronchoalveolar lavage). Also, it can be detected in the stool and from blood in severe cases (CDC, 2020a). Specimens for virus detection should reach the laboratory as soon as possible after collection with Correct handling during transportation. And storage in the lab at 2-8°C (WHO, 2020b). There are low data available about the sensitivity and specificity for the test, but false negatives results may be seen in asymptomatic patients and on the patients in the early stage of the illness so they must be continued in isolation until confirmed the positive and negative results (CDC, 2020e). Others may have the symptoms

of this virus but with negative results so they don't have the disease (CDC, 2020c).

Inflammatory factors are often increased in severe and critical patients. Patients in the early stage of the disease have normal or decreased in the total number of leukocytes in peripheral blood and peripheral blood lymphocytes due to weakness in the immune system. Some patients show increases in muscle enzymes, liver enzymes, and myoglobin. Like Troponin which may be elevated in patients with cardiac involvement so it must be in high consideration for patients with suspected myocardial infarction or heart failure (Zaman *et al*., 2020). Other signs are C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are increased in most patients. In severe cases, patients have higher plasma levels of IL-2, IL-7, IL-10, G-SCF, IP-10, MCP-1, MIP-1α, TNFα, D-dimer level, and Prothrombin time. In Guan's study, severe cases had more prominent laboratory abnormalities so 82.1%, 36.2%, and 33.7% of the patients had lymphopenia, thrombocytopenia, and leukopenia, respectively Compared with non-severe cases (Guan *et al*., 2020) Lymphocytopenia can occur in up to 80% of patients, a lymphocyte count <1000 has (Wang *et al*., 2020a).

Ultrasound may help diagnose coronavirus because it is cheap and reliable and can be used more than once, but it does not help to see the deeper lesions present in the lung. However, Patients with COVID-19 have an irregular/thickened pleural line, scattered/confluent B lines, and consolidation of various sizes and other abnormalities on the lung in various zones especially in the middle and outer zones (Zhang *et al*., 2020). A study of 99 COVID-19 patients found 14% had mottling and ground-glass opacities, 25% had unilateral pneumonia and 75% of patients had bilateral pneumonia, on chest X-ray and CT imaging (Chen *et al*., 2020c). In another study in Wuhan for a case series of patients with COVID-19, 100% had chest CT findings consistent with pneumonia (Huang *et al*., 2020a). Many suspected cases with negative results of COVID-19 have abnormal CT scans; many of them had positive tests on repeat testing (Huang *et al*., 2020b).

Treatment

As the coronavirus disease 2019 (COVID-19) spreads, efforts are being made to reduce transmission *via* standard public health interventions based on isolation of cases and tracing of contacts. This contributes to reducing the size of the outbreak but cannot control the outbreak (Hellewell *et al*., 2020). Other interventions that were recommended to reduce the outbreak include strengthening emergency departments, application of strict hygiene measures for the prevention and control of infection, and avoidance of close contact with patients suffering from respiratory tract infections (Wu and McGoogan, 2020).

Efforts are being made to find drugs and vaccines that act against SARS-CoV-2 to control the outbreak of the virus. Supportive care is the main strategy for treatment, preferably with paracetamol for fever. Maintenance of hydration and nutrition is also required. Up to 76% of patients with COVID-19 require oxygen therapy. Some patients require endotracheal intubation such as patients with hypoxemic respiratory patients (Alhazzani *et al*., 2020). Other patients require oxygen supplementation to maintain oxygen saturation between 90%-96% (WHO, 2020a). For patients who do not improve with oxygen therapy, a high-flow nasal cannula (HFNC) is recommended (Alhazzani *et al*., 2020).

Many antivirals are being under clinical trials to find drugs that are effective against the virus. According to the National Health Commission (NHC) of the People's Republic of China for tentative treatment of COVID-19, several antivirals are recommended including, IFN-α, lopinavir/ritonavir, and ribavirin treatment of COVID-19. Chloroquine phosphate and arbidol are also recommended (NHC, 2020).

INF-α is a broad-spectrum antiviral that is usually used to treat hepatitis. It inhibits the replication of SARS-CoV and MERS-CoV (Falzarano *et al*., 2013a). It is also used in combination therapy with other antivirals such as Ribavirin and lopinavir/ritonavir (Arabi *et al*., 2020). Lopinavir/ritonavir is a protease inhibitor that is used for the treatment of HIV (Meynard *et al*., 2018). Lopinavir works by

inhibiting the decomposition of gag-pol protein, while ritonavir works by inhibiting the decomposition of gag-pol protein precursor and inhibiting lopinavir metabolism, thus increasing its concentration (van der Laan *et al*., 2018). It was found that lopinavir/ritonavir has anti-SARS-CoV and MERS-CoV activity in vitro (Chan *et al*., 2015). In South Korea, an infected patient with COVID-19 received lopinavir/ritonavir. After eight days of admission, symptoms improved and coronavirus load began to decrease until no longer it's detectable (Lim *et al*., 2020).

Ribavirin is a nucleoside analog with broad-spectrum antiviral activity. It works by inhibiting the RNA synthesis of viruses. It has been used to treat HCV and RSV (Brown *et al*., 2019). Ribavirin is usually used in combination therapy to treat MERS-CoV and HCoV-OC43. Ribavirin and INF-α combination therapy are efficient in treating MERS-CoV (Shen *et al*., 2016). However, ribavirin side effects like anemia limited its use (Falzarano *et al*., 2013b). A study compared ribavirin and lopinavir/ritonavir in treating severe acute respiratory syndrome (SARS). Patients treated with lopinavir/ritonavir had a lower risk of acute respiratory distress syndrome and death (Chu *et al*., 2004). Ribavirin still needs more studies to determine whether it is effective in treating COVID-19 or not.

Remdesivir is another nucleoside analog with antiviral activity. It has activity against RNA viruses such as Ebola, Marburg, and Nipa viruses (Lo *et al*., 2017). Remdesivir showed activity against MERS-CoV in animal experiments. Remdesivir reduced the viral load in lung tissue in mice affected with MERS-CoV and improved lung function (Sheahan *et al*., 2020). A randomized, placebo-controlled, double-blind, multicenter, phase III clinical trial is now being made to study the efficacy and safety of Remdesivir in patients with COVID-19. This clinical study was launched on February 5, 2020, in China and it's supposed to conclude by the end of April. Patients received an initial dose of 200 mg of Remdesivir and 100 mg subsequent dose for 9 days via IV infusions. The control group patients received the same dose of placebo. It was found that this dose

regimen of intravenous remdesivir was adequately tolerated but did not provide significant clinical or antiviral effects in seriously ill patients with COVID-19. Studies with larger sample sizes will continue to understand the effect of remdesivir on COVID-19. Furthermore, strategies to enhance the antiviral potency of remdesivir (eg, higher-dose regimens, combination with other antivirals, or SARS-CoV-2 neutralizing antibodies) and to mitigate immunopathological host responses contributing to COVID-19 severity (eg, inhibitors of IL-6, IL-1, or TNFα) require rigorous study in patients with severe COVID-19.

Hydroxychloroquine is a drug used to treat malaria and autoimmune diseases such as lupus and rheumatoid arthritis. Hydroxychloroquine has been demonstrated to affect SARS-CoV-2 (Yao *et al*., 2020). A recent study showed the efficacy of hydroxychloroquine in reducing viral nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients in an average of three to six days only (Gautret *et al*., 2020). Azithromycin has been recommended to use with hydroxychloroquine to give a synergistic effect in treating COVID-19. Azithromycin has been shown to prevent severe respiratory tract infections and has activity against Ebola and Zika viruses (Bosseboeuf *et al*., 2018).

Arbidol is an antiviral used to treat the influenza virus. A study found that Arbidol can inhibit SARS-CoV-2 in vitro. Another antiviral that may have anti-SARS-CoV-2 activity is Favipiravir. Favipiravir is an RNA-dependent RNA polymerase (RdRP) inhibitor. It has anti-influenza activity and it can block the replication of filo-, alpha-, arena-, and other RNA viruses (Delang *et al*., 2018). When entering the cells, Favipiravir is converted to its active form Favipiravir-RTP and it is recognized as a substrate by viral RNA polymerase, thus inhibiting its activity (Furuta *et al*., 2017). Therefore, Favipiravir may be effective against SARS-CoV-2 (Table 2).

Table 1. Antivirals included in the NHC guidelines (version 6)			
Drug	**Dosage**	**Method of Administration**	**Duration of Treatment**
IFN-α	5 million U or equivalent dose each time, 2 times/day	Vapor inhalation	No more than 10 days
Lopinavir/ Ritonavir	200 mg/50 mg/capsule, 2 capsules each time, 2 times/day	Oral	No more than 10 days
Ribavirin	500 mg each time, 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir	Intravenous infusion	No more than 10 days
Chloroquine phosphate	500 mg (300 mg for chloroquine) each time, 2 times/day	Oral	No more than 10 days
Arbidol	200 mg each time, 3 times/day	Oral	No more than 10 days

Convalescent plasma therapy is another treatment that is now under investigation for its efficacy against the SARS-CoV-2 virus. The use of convalescent plasma was recommended as an empirical therapy during the outbreak of the Ebola virus. It was also recommended as a protocol for the treatment of MERS-CoV in 2015 (Chen *et al*., 2020b). Viremia usually peaks in the first week and a potential immune response is likely to be developed in the second weak where serum cytokines increase above the normal range (Cheng *et al*., 2005a). Some studies found that convalescent plasma might suppress viremia (Schoofs *et al*., 2016). Another study found that convalescent plasma could reduce serum cytokine response (Hung *et al*., 2011). This indicates that convalescent therapy is only effective in the early stages of the disease (Cheng *et al*., 2005b). The therapeutic effect of convalescent plasma is dependent upon the level of SARS-CoV-2 neutralizing antibody titer (NAT). IgG immunoglobulin began to increase in the third week of onset, and peaks at the twelfth weak (Li *et al*., 2003a). One study found that convalescent plasma with NAT $\geq$ 1:16 reduced the mortality of influenza (Hung *et al*., 2011). Thus, it is better to take plasma from patients who have recovered and are at week 12 of onset with a NAT level of $\geq$ 1:16. Furthermore, it also needs more studies to prove its effectiveness.

Prevention

There is no proven treatment for coronavirus, so prevention is very important. Because of the characteristics of this virus, as it has a long incubation period, the infection can be transmitted to many people before symptoms appear, so preventive measures are very necessary.

The greatest danger is the transmission of the virus to a healthcare worker as the virus has passed on to many of them, however, it is very important to follow a basic protocol to protect them and prevent the transmission of the disease to them and others by them (Chang *et al*., 2020). Those who deal with patients directly are isolated from others and do not deal with ordinary patients. The rooms and surfaces and equipment should undergo regular decontamination.

To reduce the spread of the disease in geographical areas, each country quarantines travelers and people who dealt with the injured for 14 days to ensure that they are free of the virus and prevent its spread (Gostic *et al*., 2015).

As for society, the best ways to prevent coronavirus and other viruses are necessary to move away from crowded places, leave a safe distance between others and follow a healthy lifestyle that is mainly based on maintaining personal hygiene, eating healthy foods, good ventilation, sunlight penetration on all surfaces, adequate rest, using health masks and using sterilizers on an ongoing every 15-20min (Gostic *et al*., 2015, Simpson *et al*., 2015, Yoshikawa and High, 2001). People who already have a vitamin C deficiency are more likely and at risk to become infected with the virus (Nonnecke *et al*., 2014). So vitamin C supplementation is very important for prevention according to many studies (Hemilä, 1997). Every year an estimated 290,000 to 650,000 people die in the world due to complications from seasonal influenza (flu) viruses. There are about 795 to 1,781 deaths per day due to the seasonal flu. SARS (November 2002 to July 2003). The coronavirus that originated from Beijing, China, spread to different countries and resulted in more than ten and a half million people infected with more than half-million deaths (fatality rate of 8%, by end of June

2020). Considering that SARS ended up infecting 5,237 people in mainland China, Wuhan Coronavirus surpassed SARS on January 29, 2020, when Chinese officials confirmed 5,974 cases of the novel coronavirus (2019-nCoV). One day later, on January 30, 2020, the novel coronavirus cases surpassed even the 8,096 cases worldwide which were the final SARS count in 2003, and now by the end of June 2020 coronavirus exceed SARS by millions as mentioned.

Conclusion

Coronavirus disease 2019 (COVID-19) has affected more than twelve million people worldwide until today in 216 countries. Symptoms of this virus may vary from mild symptoms such as fever and cough to severe symptoms in some patients such as a proinflammatory and hypercoagulable state, in addition to non-cardiac pneumonia, multi-organ failure, and ARDS. Supportive treatment is still the main strategy in treating this disease since there is no evidence that current medicine can prevent or cure the infection resulting from coronavirus. Isolating patients and other preventive measures are now the way in reducing the outbreak of this virus infection.

References

Alhazzani, W., Møller, M. H., Arabi, Y. M., Loeb, M., Gong, M. N., Fan, E., Oczkowski, S., Levy, M. M., Derde, L. & Dzierba, A. (2020). Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive care medicine***,** 1-34.

Arabi, Y. M., Shalhoub, S., Mandourah, Y., Al-Hameed, F., Al-Omari, A., Al Qasim, E., Jose, J., Alraddadi, B., Almotairi, A. & Al Khatib, K. (2020). Ribavirin and interferon therapy for critically ill patients with middle east respiratory syndrome: a multicenter observational study. *Clinical infectious diseases,* 70**,** 1837-1844.

Bertram, S., Glowacka, I., Muller, M. A., Lavender, H., Gnirss, K., Nehlmeier, I., Niemeyer, D., He, Y., Simmons, G. & Drosten, C. (2011). Cleavage and activation of the severe acute respiratory syndrome coronavirus spike protein by human airway trypsin-like protease. *Journal of virology,* 85**,** 13363-13372.

Bosch, B. J., Van Der Zee, R., De Haan, C. A. & Rottier, P. J. (2003). The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. *Journal of virology*, 77**,** 8801-8811.

Bosseboeuf, E., Aubry, M., Nhan, T., Pina, J., Rolain, J., Raoult, D. & Musso, D. (2018). Azithromycin Inhibits the Replication of Zika Virus. *J. Antivir. Antiretrovir*, 10**,** 6-11.

Brown, A. J., Won, J. J., Graham, R. L., Dinnon III, K. H., Sims, A. C., Feng, J. Y., Cihlar, T., Denison, M. R., Baric, R. S. & Sheahan, T. P. (2019). Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. *Antiviral research*, 169**,** 104541.

Cascella, M., Rajnik, M., Cuomo, A., *et al*. (2020). Features, Evaluation, and Treatment of Coronavirus. [Updated 2020 Oct 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/

CDC. (2020a). *2019 Novel Coronavirus (2019-nCoV) Testing* [Online]. Centers for Disease Control and Prevention. [Accessed 19/3/2020 2020].

CDC. (2020b). *CDC. 2019 Novel Coronavirus (2019-nCoV) infection control* [Online]. Centers for Disease Control and Prevention. [Accessed 25/3/2020].

CDC. (2020c). *CDC. 2019 Novel Coronavirus (2019-nCoV) frequently asked questions and answers* [Online]. Centers for Disease Control and Prevention. [Accessed 18/3/2020 2020].

CDC. (2020 -d). *Coronavirus Disease 2019 (COVID-19): evaluating and testing persons for Co-ronavirus Disease 2019 (COVID-19)* [Online]. [Accessed 21/3/2020].

CDC. (2020 -e). *Coronavirus Disease 2019 Transcript for CDC Media Telebriefing* [Online]. Centers for Disease Control and Prevention. [Accessed 19/3/2020 2020].

Ceraolo, C. & Giorgi, F. M. (2020). Genomic variance of the 2019- nCoV coronavirus. *Journal of medical virology*, Volume 92, Issue5 522-528.

Chai, X., Hu, L., Zhang, Y., Han, W., Lu, Z., Ke, A., Zhou, J., Shi, G., Fang, N. & Fan, J. (2020). Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. *bioRxiv*. doi: https://doi.org/10.1101/2020.02.03.931766

Chan, J. F.-W., Yao, Y., Yeung, M.-L., Deng, W., Bao, L., Jia, L., Li, F., Xiao, C., Gao, H. & Yu, P. (2015). Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. *The Journal of infectious diseases*, 212**,** 1904-1913.

Chan, J. F.-W., Yuan, S., Kok, K.-H., To, K. K.-W., Chu, H., Yang, J., Xing, F., Liu, J., Yip, C. C.-Y. & Poon, R. W.-S. (2020). A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *The Lancet,* 395**,** 514-523.

Chang, C.-K., Sue, S.-C., Yu, T.-H., Hsieh, C.-M., Tsai, C.-K., Chiang, Y.-C., Lee, S.-J., Hsiao, H.-H., Wu, W.-J. & Chang, W.-L. (2006). Modular organization of SARS coronavirus nucleocapsid protein. *Journal of biomedical science,* 13**,** 59-72.

Chang, D., Xu, H., Rebaza, A., Sharma, L. & Dela Cruz, C. S. (2020). Protecting health-care workers from subclinical coronavirus infection. *The Lancet. Respiratory medicine,* 8**,** e13.

Chavez, S., Long, B., Koyfman, A. & Liang, S. Y. (2020). Coronavirus Disease (COVID-19): A primer for emergency physicians. *The American Journal of Emergency Medicine*, 24:S0735-6757(20)30178-9. doi: 10.1016/j.ajem.2020.03.036.

Bai, Y., Yao, L., Wei. T., *et al*. (2020). Presumed Asymptomatic Carrier Transmission of COVID-19. JAMA, 323 (14):1406–1407. doi:10.1001/jama.2020.2565

Guan, WJ., Ni, ZY., Hu, Y., *et al*. (2020). Clinical characteristics of 2019 novel coronavirus infection in China, medRxiv and bioRxiv doi: https://doi.org/10.1101/2020.02.06.20020974

Chen, H., Guo, J., Wang, C., Luo, F., Yu, X., Zhang, W., Li, J., Zhao, D., Xu, D. & Gong, Q. (2020a). Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *The Lancet,* 395**,** 809-815.

Chen, I.-Y., Moriyama, M., Chang, M.-F. & Ichinohe, T. (2019). Severe acute respiratory syndrome coronavirus viroporin 3a activates the NLRP3 inflammasome. *Frontiers in microbiology,* 10:50. doi: 10.3389/fmicb.2019.00050

Chen, L., Xiong, J., Bao, L. & Shi, Y. (2020b). Convalescent plasma as a potential therapy for COVID-19. *The Lancet Infectious Diseases,* 20**,** 398-400.

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y. & Wei, Y. (2020c). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet,* 395**,** 507-513.

Cheng, Y., Cheng, G., Chui, C., Lau, F., Chan, P. K., Ng, M. H., Sung, J. J. & Wong, R. S. (2005a). ABO blood group and susceptibility to severe acute respiratory syndrome. *Jama,* 293**,** 1447-1451.

Cheng, Y., Wong, R., Soo, Y., Wong, W., Lee, C., Ng, M., Chan, P., Wong, K., Leung, C. & Cheng, G. (2005b). Use of convalescent plasma therapy in

SARS patients in Hong Kong. *European Journal of Clinical Microbiology and Infectious Diseases,* 24**,** 44-46.

Chu, C., Cheng, V., Hung, I., Wong, M., Chan, K., Chan, K., Kao, R., Poon, L., Wong, C. & Guan, Y. (2004). Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax,* 59**,** 252-256.

Coutard, B., Valle, C., De Lamballerie, X., Canard, B., Seidah, N. & Decroly, E. (2020). The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. *Antiviral Research,* 176**,** 104742.

Dediego, M. L., Álvarez, E., Almazán, F., Rejas, M. T., Lamirande, E., Roberts, A., Shieh, W.-J., Zaki, S. R., Subbarao, K. & Enjuanes, L. (2007). A severe acute respiratory syndrome coronavirus that lacks the E gene is attenuated in vitro and in vivo. *Journal of virology,* 81**,** 1701-1713.

Delang, L., Abdelnabi, R. & Neyts, J. (2018). Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. *Antiviral research,* 153**,** 85-94.

Delmas, B. & Laude, H. (1990). Assembly of coronavirus spike protein into trimers and its role in epitope expression. *Journal of Virology,* 64**,** 5367-5375.

Dong, N., Yang, X., Ye, L., Chen, K., Chan, E. W.-C., Yang, M. & Chen, S. (2020). Genomic and protein structure modelling analysis depicts the origin and infectivity of 2019-nCoV, a new coronavirus which caused a pneumonia outbreak in Wuhan, China. *bioRxiv*, 9:121. doi: https://doi.org/10.1101/2020.01.20.913368

Eckert A, H. D. (2020). *Centers for Disease Control and Prevention* [Online]. Centers for Disease Control and Prevention. [Accessed 6/4/2020 2020].

Falzarano, D., De Wit, E., Martellaro, C., Callison, J., Munster, V. J. & Feldmann, H. (2013a). Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin. *Scientific reports,* 3**,** 1686.

Falzarano, D., De Wit, E., RAsmussen, A. L., Feldmann, F., Okumura, A., Scott, D. P., Brining, D., Bushmaker, T., Martellaro, C. & Baseler, L. (2013b). Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV–infected rhesus macaques. *Nature medicine,* 19**,** 1313-1317.

Fan, C., Li, K., Ding, Y., Lu, W. L. & Wang, J. (2020). ACE2 expression in kidney and testis may cause kidney and testis damage after 2019-nCoV infection. *MedRxiv*. doi: https://doi.org/10.1101/2020.02.12.20022418.

Fehr, A.R., & Perlman, S. (2015) Coronaviruses: An Overview of Their Replication and Pathogenesis. In: Maier H., Bickerton E., Britton P. (eds) Coronaviruses. Methods in Molecular Biology, vol 1282. Humana Press, New York, NY. https://doi.org/10.1007/978-1-4939-2438-7_1

Furuta, Y., Komeno, T. & Nakamura, T. (2017). Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proceedings of the Japan Academy, Series B,* 93**,** 449-463.

Gautret, P., Lagier, J.-C., Parola, P., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., GIordanengo, V., Vieira, V. E. & Dupont, H. T. (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International journal of antimicrobial agents***,** 56(1):105949. doi: 10.1016/j.ijantimicag.2020.105949.

Glowacka, I., Bertram, S., Muller, M. A., Allen, P., Soilleux, E., Pfefferle, S., Steffen, I., Tsegaye, T. S., He, Y. & Gnirss, K. (2011). Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. *Journal of virology,* 85**,** 4122-4134.

GOOGLE. (2020) *coronavirus map* [Online]. google news: Google [Accessed 11/4/2020].

Gostic, K. M., Kucharski, A. J. & Lloyd-Smith, J. O. (2015). Effectiveness of traveller screening for emerging pathogens is shaped by epidemiology and natural history of infection. *Elife,* 4**,** e05564.

Gralinski, L. & Menachery, V. (2020). Return of the coronavirus: 2019-nCoV. Viruses; 12 (2). *J Popul Ther Clin Pharmacol,* 27**,** e1-e4.

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. (2020). Clinical characteristics of 2019 novel coronavirus infection in China. *The New England Journal of Medicine, 382:1708-1720. DOI: 10.1056/NEJMoa2002032*

Gui, M., Song, W., Zhou, H., Xu, J., Chen, S., Xiang, Y. & Wang, X. (2017). Cryo-electron microscopy structures of the SARS-CoV spike glycoprotein reveal a prerequisite conformational state for receptor binding. *Cell research,* 27**,** 119-129.

Guillon, P., Clement, M., Sebille, V., Rivain, J.-G., Chou, C.-F., Ruvoen-Clouet, N. & Le Pendu, J. (2008). Inhibition of the interaction between the SARS-CoV spike protein and its cellular receptor by anti-histo-blood group antibodies. *Glycobiology,* 18**,** 1085-1093.

Hellewell, J., Abbott, S., Gimma, A., Bosse, N. I., Jarvis, C. I., Russell, T. W., Munday, J. D., Kucharski, A. J., Edmunds, W. J. & Sun, F. (2020). Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. *The Lancet Global Health*, Volume 8, Issue 4, E488-E496. DOI:https://doi.org/10.1016/S2214-109X(20)30074-7

Hemilä, H. (1997). Vitamin C intake and susceptibility to pneumonia. *The Pediatric infectious disease journal,* 16**,** 836-837.

Heymann, D. L. & Shindo, N. (2020). COVID-19: what is next for public health? *The Lancet,* 395**,** 542-545.

Hindson, J. (2020). COVID-19: faecal–oral transmission? *Nature Reviews Gastroenterology & Hepatology***,** 17, 259. https://doi.org/10.1038/s41575-020-0295-7

Hoffmann, M., Kleine-Weber, H., Kruger, N., Mueller, M. A., Drosten, C. & Pöhlmann, S. (2020). The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. *BioRxiv*. doi: https://doi.org/10.1101/2020.01.31.929042

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J. & Gu, X. (2020a). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet,* 395**,** 497-506.

Huang, P., Liu, T., Huang, L., Liu, H., Lei, M., Xu, W., Hu, X., Chen, J. & Liu, B. (2020b). Use of chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion. *Radiology,* 295**,** 22-23.

Hung, I. F., To, K. K., Lee, C.-K., Lee, K.-L., Chan, K., Yan, W.-W., Liu, R., Watt, C.-L., Chan, W.-M. & Lai, K.-Y. (2011). Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clinical Infectious Diseases,* 52**,** 447-456.

Jernigan, D. B. (2020). Update: public health response to the coronavirus disease 2019 outbreak—United States, February 24, 2020. *Morbidity and mortality weekly report (MMWR),* 69(8);216–219

Kang, S., Peng, W., Zhu, Y., Lu, S., Zhou, M., Lin, W., Wu, W., Huang, S., Jiang, L., Luo, X., & Deng, M. (2020). Recent progress in understanding 2019 novel coronavirus (SARS-CoV-2) associated with human respiratory disease: detection, mechanisms and treatment. *International journal of antimicrobial agents*, 55(5), 105950. https://doi.org/10.1016/j.ijantimicag.2020.105950Khot, W. Y. & Nadkar, M. Y. (2020). The 2019 Novel Coronavirus Outbreak-A Global Threat. *J Assoc Physicians India,* 68**,** 67-71.

Lai, C.-C., Shih, T.-P., Ko, W.-C., Tang, H.-J. & Hsueh, P.-R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges. *International journal of antimicrobial agents***,** 55(3):105924. doi: 10.1016/j.ijantimicag.2020.105924.

Lau, S. K., Li, K. S., Huang, Y., Shek, C.-T., Tse, H., Wang, M., Choi, G. K., Xu, H., Lam, C. S. & Guo, R. (2010). Ecoepidemiology and complete genome comparison of different strains of severe acute respiratory syndrome-related Rhinolophus bat coronavirus in China reveal bats as a reservoir for acute, self-limiting infection that allows recombination events. *Journal of virology,* 84**,** 2808-2819.

Li, G., Chen, X. & Xu, A. (2003a). Profile of specific antibodies to the SARS-associated coronavirus. *The New England journal of medicine,* 349**,** 508-509.

Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., Ren, R., Leung, K. S., Lau, E. H. & Wong, J. Y. (2020). Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *New England Journal of Medicine*, 382(13):1199-1207. doi: 10.1056/NEJMoa2001316.

Li, W., Moore, M. J., Vasilieva, N., Sui, J., Wong, S. K., Berne, M. A., Somasundaran, M., Sullivan, J. L., Luzuriaga, K. & Greenough, T. C. (2003b). Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature,* 426**,** 450-454.

Lim, J., Jeon, S., Shin, H. Y., Kim, M. J., Seong, Y. M., Lee, W. J., Choe, K. W., Kang, Y. M., Lee, B., & Park, S. J. (2020). Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. *Journal of Korean medical science*, 35(6), e79. https://doi.org/10.3346/jkms.2020.35.e79

Liu, K., Fang, Y.-Y., Deng, Y., Liu, W., Wang, M.-F., MA, J.-P., Xiao, W., Wang, Y.-N., Zhong, M.-H. & LI, C.-H. (2020). Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chinese medical journal*, Volume 133 - Issue 9 - p 1025-1031. doi: 10.1097/CM9.0000000000000744

Lo, M. K., Jordan, R., Arvey, A., Sudhamsu, J., Shrivastava-Ranjan, P., Hotard, A. L., Flint, M., Mcmullan, L. K., Siegel, D. & Clarke, M. O. (2017). GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. *Scientific reports,* 7**,** 43395. doi: 10.1038/srep43395.

Lu, C.-W., Liu, X.-F. & Jia, Z.-F. (2020). 2019-nCoV transmission through the ocular surface must not be ignored. *Lancet, 395(10224):e39. doi: 10.1016/S0140-6736(20)30313-5.*

Malik, Y. S., Sircar, S., Bhat, S., Sharun, K., Dhama, K., Dadar, M., Tiwari, R. & Chaicumpa, W. (2020). Emerging novel coronavirus (2019-nCoV)—current scenario, evolutionary perspective based on genome analysis and recent developments. *Veterinary Quarterly,* 40**,** 68-76.

Meynard, J.-L., Moinot, L., Landman, R., Morand-Joubert, L., Besseghir, A., Kolta, S., Spire, B., Todesco, E., Bouchaud, O. & Fagard, C. (2018). Week 96 efficacy of lopinavir/ritonavir monotherapy in virologically suppressed patients with HIV: a randomized non-inferiority trial (ANRS 140 DREAM). *Journal of Antimicrobial Chemotherapy,* 73**,** 1672-1676.

NHC. (2020). Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia, The 5th ed. *In:* COMMISSION, N. H. (ed.).

Nieto-Torres, J. L., Dediego, M. L., Verdia-baguena, C., Jimenez-Guardeno, J. M., Regla-Nava, J. A., Fernandez-Delgado, R., Castano-Rodriguez, C., Alcaraz, A., Torres, J. & Aguilella, V. M. (2014). Severe acute respiratory syndrome coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis. *PLoS pathogens*, 10(5):e1004077. doi: 10.1371/journal.ppat.1004077. eCollection 2014 May..

Nishiura, H., Linton, N. M., & Akhmetzhanov, A. R. (2020). Initial Cluster of Novel Coronavirus (2019-nCoV) Infections in Wuhan, China Is Consistent with Substantial Human-to-Human Transmission. *Journal of clinical medicine*, 9(2), 488. https://doi.org/10.3390/jcm9020488

Nonnecke, B., Mcgill, J., Ridpath, J., Sacco, R., Lippolis, J. & Reinhardt, T. (2014). Acute phase response elicited by experimental bovine diarrhea virus (BVDV) infection is associated with decreased vitamin D and E status of vitamin-replete preruminant calves. *Journal of dairy science*, 97**,** 5566-5579.

Pallesen, J., Wang, N., Corbett, K. S., Wrapp, D., Kirchdoerfer, R. N., Turner, H. L., Cottrell, C. A., Becker, M. M., Wang, L. & Shi, W. (2017). Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen. *Proceedings of the National Academy of Sciences*, 114**,** E7348-E7357.

Paraskevis, D., Kostaki, E. G., Magiorkinis, G., Panayiotakopoulos, G., Sourvinos, G. & Tsiodras, S. (2020). Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. *Infection, Genetics and Evolution*, 79**,** 104212.

Peeri, N. C., Shrestha, N., Rahman, M. S., Zaki, R., Tan, Z., Bibi, S., Baghbanzadeh, M., Aghamohammadi, N., Zhang, W. & Haque, U. (2020). The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? *International journal of epidemiology*, 49(3):717-726. doi: 10.1093/ije/dyaa033.

Phan, T. (2020). Novel coronavirus: From discovery to clinical diagnostics. *Infection, Genetics and Evolution*, 79**,** 104211. doi: 10.1016/j.meegid.2020.104211.

Qiao, J. (2020). What are the risks of COVID-19 infection in pregnant women? *The Lancet*, 395**,** 760-762.

Ren, L.-L., Wang, Y.-M., Wu, Z.-Q., Xiang, Z.-C., Guo, L., Xu, T., Jiang, Y.-Z., Xiong, Y., Li, Y.-J. & Li, H. (2020). Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. *Chinese medical journal*, 133(9), 1015-1024. doi: 10.1097/CM9.0000000000000722

Sabir, J. S., Lam, T. T.-Y., Ahmed, M. M., Li, L., Shen, Y., Abo-Aba, S. E., Qureshi, M. I., Abu-Zeid, M., Zhang, Y. & Khiyami, M. A. (2016). Co-circulation of three camel coronavirus species and recombination of MERS-CoVs in Saudi Arabia. *Science,* 351**,** 81-84.

Schmid, M. B., Fontijn, J., Ochsenbein-Kölble, N., Berger, C. & Bassler, D. (2020). COVID-19 in pregnant women. *The Lancet Infectious Diseases*, 20(6):653. doi: 10.1016/S1473-3099(20)30175-4.

Schoofs, T., Klein, F., Braunschweig, M., Kreider, E. F., Feldmann, A., Nogueira, L., Oliveira, T., Lorenzi, J. C., Parrish, E. H. & Learn, G. H. (2016). HIV-1 therapy with monoclonal antibody 3BNC117 elicits host immune responses against HIV-1. *Science,* 352**,** 997-1001.

Schwartz, D. A. (2020). An analysis of 38 pregnant women with COVID-19, their newborn infants, and maternal-fetal transmission of SARS-CoV-2: maternal coronavirus infections and pregnancy outcomes. *Archives of Pathology & Laboratory Medicine*, doi: 10.5858/arpa.2020-0901-SA

Sheahan, T. P., Sims, A. C., Leist, S. R., Schäfer, A., Won, J., Brown, A. J., Montgomery, S. A., Hogg, A., Babusis, D. & Clarke, M. O. (2020). Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nature Communications,* 11**,** 1-14.

Shen, L., Yang, Y., Ye, F., Liu, G., Desforges, M., Talbot, P. J. & Tan, W. (2016). Safe and sensitive antiviral screening platform based on recombinant human coronavirus OC43 expressing the luciferase reporter gene. *Antimicrobial agents and chemotherapy,* 60**,** 5492-5503.

Shereen, M. A., Khan, S., Kazmi, A., Bashir, N. & Siddique, R. (2020). COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. *Journal of Advanced Research*, Volume 24, 91-98. https://doi.org/10.1016/j.jare.2020.03.005

Shi, J., Wen, Z., Zhong, G., Yang, H., Wang, C., Huang, B., Liu, R., He, X., Shuai, L. & Sun, Z. (2020). Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS–coronavirus 2. *Science*, 368(6494): 1016–1020. doi: 10.1126/science.abb7015

Simpson, R. J., Kunz, H., Agha, N. & Graff, R. (2015). Exercise and the regulation of immune functions. *Progress in molecular biology and translational science,* 135:355-80. doi: 10.1016/bs.pmbts.2015.08.001.

Singhal, T. (2020). A review of coronavirus disease-2019 (COVID-19). *The Indian Journal of Pediatrics***,** 87, 281–286. https://doi.org/10.1007/s12098-020-03263-6

Su, S., Wong, G., Shi, W., Liu, J., Lai, A. C., Zhou, J., Liu, W., Bi, Y. & Gao, G. F. (2016). Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends in microbiology,* 24**,** 490-502.

Sun, P., Lu, X., Xu, C., Sun, W. & Pan, B. (2020). Understanding of COVID- 19 based on current evidence. *Journal of medical virology*, 92(6):548-551. doi: 10.1002/jmv.25722.

Surveillances, V. (2020). The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020. *China CDC Weekly*, 2**,** 113-122.

The New York times. (2020). The Road to a Coronavirus Vaccine. https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

Tregouet, D.-A., Heath, S., Saut, N., Biron-Andreani, C., Schved, J.-F., Pernod, G., Galan, P., Drouet, L., Zelenika, D. & Juhan-Vague, I. (2009). Common susceptibility alleles are unlikely to contribute as strongly as the FV and ABO loci to VTE risk: results from a GWAS approach. *Blood, The Journal of the American Society of Hematology*, 113**,** 5298-5303.

Van Der Laan, L. E., Garcia-Prats, A. J., Schaaf, H. S., Tikiso, T., Wiesner, L., De Kock, M., Winckler, J., Norman, J., Mcilleron, H. & Denti, P. (2018). Pharmacokinetics and drug-drug interactions of lopinavir-ritonavir administered with first-and second-line antituberculosis drugs in HIV-infected children treated for multidrug-resistant tuberculosis. *Antimicrobial agents and chemotherapy*, 62**,** e00420-17.

Walls, A. C., Tortorici, M. A., Snijder, J., Xiong, X., Bosch, B.-J., Rey, F. A. & Veesler, D. (2017). Tectonic conformational changes of a coronavirus spike glycoprotein promote membrane fusion. *Proceedings of the National Academy of Sciences*, 114**,** 11157-11162.

Walls, A. C., Xiong, X., Park, Y.-J., Tortorici, M. A., Snijder, J., Quispe, J., Cameroni, E., Gopal, R., Dai, M. & Lanzavecchia, A. (2019). Unexpected receptor functional mimicry elucidates activation of coronavirus fusion. *Cell*, 176**,** 1026-1039. e15.

Wan, Y., Shang, J., Graham, R., Baric, R. S. & Li, F. (2020). Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *Journal of virology*, 94(7):e00127-20. doi: 10.1128/JVI.00127-20.

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z. & Xiong, Y. (2020a). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama*, 323**,** 1061-1069.

Wang, L.-S., Wang, Y.-R., Ye, D.-W. & Liu, Q.-Q. (2020b). A review of the 2019 Novel Coronavirus (COVID-19) based on current evidence. *International Journal of Antimicrobial Agents***,** 55(6):105948. doi: 10.1016/j.ijantimicag.2020.105948.

Wang, W., Tang, J. & Wei, F. (2020c). Updated understanding of the outbreak of 2019 novel coronavirus (2019- nCoV) in Wuhan, China. *Journal of medical virology*, 92**,** 441-447.

Wax, R. S. & Christian, M. D. (2020). Practical recommendations for critical care and anesthesiology teams caring for novel coronavirus (2019-nCoV) patients. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie***,** 67, 568–576 (2020). https://doi.org/10.1007/s12630-020-01591-x

WHO (2003). Summary table of SARS cases by country, November 1, 2002–August 7, 2003. *World Health Tourism*, 15.

WHO (2020a). Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. Published January 28, 2020.

WHO (2020b). Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. *Internet] World Health Organization*.

WHO (2020c). Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance, 2 March 2020. World Health Organization.

WHO. (2020a). *Coronavirus disease (COVID-19) Pandemic* [Online]. world health organization [Accessed 17/4/2020 2020].

WHO (2020b). Laboratory biosafety guidance related to the novel coronavirus (2019-nCoV): interim guidance.

Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Hsieh, C.-L., Abiona, O., Graham, B. S. & Mclellan, J. S. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*, 367**,** 1260-1263.

Wu, A., Peng, Y., Huang, B., Ding, X., Wang, X., Niu, P., Meng, J., Zhu, Z., Zhang, Z., Wang, J., Sheng, J., Quan, L., Xia, Z., Tan, W., Cheng, G. & Jiang, T. (2020a). Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. *Cell Host & Microbe*, 27**,** 325-328.

Wu, J., Liu, J., Zhao, X., Liu, C., Wang, W., Wang, D., Xu, W., Zhang, C., Yu, J. & Jiang, B. (2020b). Clinical Characteristics of Imported Cases of COVID-19 in Jiangsu Province: A Multicenter Descriptive Study. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, 71(15):706-712. DOI: 10.1093/cid/ciaa199.

Wu, Z. & Mcgoogan, J. M. (2020). Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*, 323(13):1239–1242. doi:10.1001/jama.2020.2648

Xia, S., Zhu, Y., Liu, M., Lan, Q., Xu, W., Wu, Y., Ying, T., Liu, S., Shi, Z. & Jiang, S. (2020). Fusion mechanism of 2019-nCoV and fusion inhibitors

targeting HR1 domain in spike protein. *Cellular & Molecular Immunology***,** 17(7). https://doi.org/10.1038/s41423-020-0374-2

Xie, M. & Chen, Q. (2020). Insight into 2019 novel coronavirus—an updated intrim review and lessons from SARS-CoV and MERS-CoV. *International Journal of Infectious Diseases*, Volume 94, 119-124. DOI:https://doi.org/10.1016/j.ijid.2020.03.071

Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., Zhong, W. & Hao, P. (2020). Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Science China Life Sciences*, 63**,** 457-460.

YANG, H., WANG, C. & POON, L. (2020a). Novel coronavirus infection and pregnancy. *Ultrasound Obstet Gynecol*, 55**,** 435-437.

Yang, M. (2020) Cell Pyroptosis, a Potential Pathogenic Mechanism of 2019-nCoV Infection. Available at SSRN: https://ssrn.com/abstract=3527420 or http://dx.doi.org/10.2139/ssrn.3527420

Yang, Y., Peng, F., Wang, R., Guan, K., Jiang, T., Xu, G., Sun, J. & Chang, C. (2020b). The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. *Journal of autoimmunity***,** 109:102434. doi: 10.1016/j.jaut.2020.102434.

Yao, X., Ye, F., Zhang, M., Cui, C., Huang, B., Niu, P., Liu, X., Zhao, L., Dong, E. & Song, C. (2020). In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clinical Infectious Diseases*, 71(15):732-739. doi: 10.1093/cid/ciaa237.

Yeo, C., Kaushal, S. & Yeo, D. (2020). Enteric involvement of coronaviruses: is faecal–oral transmission of SARS-CoV-2 possible? *The Lancet Gastroenterology & Hepatology*, 5**,** 335-337.

Yin, Y. & Wunderink, R. G. (2018). MERS, SARS and other coronaviruses as causes of pneumonia. *Respirology*, 23**,** 130-137.

Yoshikawa, T. T. & High, K. P. (2001). Nutritional strategies to boost immunity and prevent infection in elderly individuals. *Clinical infectious diseases*, 33**,** 1892-1900.

Zaman, S., Macisaac, A. I., Jennings, G. L., Schlaich, M., Inglis, C. S., Arnold, R., Chew, D. P., Kumar, S., Thomas, L. & Wahi, S. (2020). Cardiovascular disease and COVID-19: Australian/New Zealand consensus statement. *The Medical Journal of Australia***,** 213 (4): 182-187. || doi: 10.5694/mja2.50714

Zhang, H., Kang, Z., Gong, H., Xu, D., Wang, J., Li, Z., Cui, X., Xiao, J., Meng, T. & Zhou, W. (2020). The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. *BioRxiv*. doi: https://doi.org/10.1101/2020.01.30.927806.

Zhao, J., Yang, Y., Huang, H.-P., Li, D., Gu, D.-F., Lu, X.-F., Zhang, Z., Liu, L., Liu, T. & Liu, Y.-K. (2020). Relationship between the ABO Blood Group and the COVID-19 Susceptibility. *medRxiv*. doi: https://doi.org/10.1101/2020.03.11.20031096

Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., Si, H.-R., Zhu, Y., Li, B. & Huang, C.-L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 579**,** 270-273.