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COVID-19: The Story of a Modern Pandemic

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ABSTRACT

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The world has seen the onset of the seventh Coronavirus SARS CoV-2, in the winter of 2019, that spread from a local animal market in the city of Wuhan, in Hubei province to all of China in 30 days. At this time the novel Coronavirus (COVID) disease has spread worldwide by droplets and contact transmission. It can affect people of all ages, though it has the most severe impact in the elderly and those with multiple medical co-morbidities, by affecting the respiratory system leading to high morbidity and mortality. RT-PCR testing of respiratory specimens allows diagnosis. No curative therapy has been approved, while vaccine trials are undergoing. Wearing facial masks, hand hygiene and social distancing can work to prevent community spread. Measures to reduce nosocomial spread and protecting the health of health care workers is crucial as this infection is combatted

Keywords: SARS CoV-2, COVID, RT-PCR test, Facial mask use, Hand hygiene, Social distancing

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MICROBIOLOGY

Coronaviruses are large, enveloped, 80–120 nm long, positive-strand RNA viruses ranging from 26 to 32 kilobases in length that can be divided into 4 genera: alpha, beta, delta, and gamma, of which alpha and beta Corona virus (CoVs) are known to infect humans.[1] The name is derived from Latin *corona*, meaning crown. The viral envelope under electron microscopy appears crown-like due to small bulbar projections formed by the viral spike (S) peplomers. The spike (S) glycoprotein is critical for binding of host cell receptors.[1]

Coronaviruses are broadly distributed among humans, other mammals including bats in whom it has shown the greatest diversity, and birds and causes respiratory, enteric, hepatic, and neurologic diseases. Six coronavirus species are known to cause human disease.[2-5] Four Human coronaviruses (HCoV) 229E, NL63, OC43, and HKU1 are endemic globally and cause 10% to 30% of upper respiratory tract infections in adults. In the early 21st century, two highly pathogenic HCoVs were reported, from animal reservoirs. The Severe acute respiratory syndrome coronavirus (SARS-CoV) emerged in southern China, in November, 2002, and was associated with 10% mortality while the Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in Saudi Arabia in 2012 and had a 30% mortality.[6,7]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a previously unknown *betacoronavirus*.[8] SARS-CoV-2 is the seventh coronavirus to infect humans. SARS-CoV-2 has been found to be similar to SARS-like coronaviruses from bats, and shares only 82% and 50% genome sequence homology to SARS-CoV and MERS-CoV respectly.[57,9]

CLINICAL FEATURES

Epidemiology: **COVID-19** (novel coronavirus disease-2019) is the disease, and **SARS-CoV-2** is the virus. The World Health Organization (WHO) was informed of 44 cases of pneumonia of unknown microbial etiology associated with Wuhan City, in Hubei Province of China on 31 December 2019. Most of the patients reported a link to a large seafood and live animal market, the Huanan South China Seafood Market. The WHO announced that a novel Coronavirus was detected in these patients.[10-12] COVID-19 spread from Wuhan to the entirety of China in just 30 days.[39]

The global spread has been rapid with 3,181,642 confirmed cases and 224,301 deaths as of May 1, 2020. China has reported 84,385 cases, with 4,643 deaths. The vast majority are now from Europe and Americas where a total of 2,753,321 cases were reported. The US, had 1,062,446 cases, with 62,406 deaths, during this time with New York state having almost 300,000 cases and over 23,000 deaths. On May 2, 2020 the Indian Ministry of health and family welfare announced 26,167 cases and 1,218 deaths for all of India. Maharashtra, Gujarat and Delhi had the highest number of cases reported while Madhya Pradesh emerged as the state with the third leading cause of death.[13]

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Transmission: The first communique on COVID-19 by the WHO, on 5 January 2020 mentioned "no evidence of significant human-to-human transmission and no health care worker infections have been reported." Much has changed since then, with person-to-person spread confirmed in the community and healthcare settings. Current evidence indicates that human transmission occurs via close contact with respiratory droplets that are produced when a person exhales, sneezes, or coughs; via direct contact with infected people; or via contact with fomites. Per WHO airborne transmission does not occur in the community but can happen during Aerosol-generating procedures (AGP) performed in clinical care.[14 - 16]

vanDoremalen et al, published a study in the New England Journal of Medicine showing SARS-CoV-2 remains stable on plastic and stainless steel (up to 72 hours),on cardboard (up to 24 hours) and on copper (up to 4 hours). Though this study also found that the virus was viable in aerosol particles for up to 3 hours, it is crucial to note that the aerosols were generated using a high-powered apparatus that does not reflect normal human cough or a clinical setting where aerosol-generating procedures are performed.[17]

Though SARS-CoV-2 has been found in blood, cerebrospinal fluid, urine, semen, stool, saliva, tears, and conjunctival secretions, its role in transmission is unclear. Transmission of Human coronaviruses from contaminated dry surfaces has been postulated including self-inoculation of mucous membranes of the nose, eyes or mouth.[18,19] Widespread transmission has been reported in crowded areas such as nursing homes, homeless shelters, prisons, cruise ships and from family and mass gatherings.[21 - 25]

Presymptomatic spread of SARS-CoV-2:
Presymptomatic transmission is defined as the transmission of SARS-CoV-2 from an infected person to a secondary patient before the infected person developed symptoms, with no evidence that the secondary patient was exposed to anyone else with SARS-CoV-2. Patients may thus be infectious 1 to 3 days before symptom onset with an estimated 44% of secondary cases being infected during the presymptomatic stage.[29,30]

Incubation period: The term incubation period usually means the time between catching the virus and the onset of the disease. According to the US Centers for Disease Control (CDC), symptoms may appear 2-14 days after exposure to the virus.[26] A study published in the Annals of Internal Medicine by Lauer et al reported that the median incubation period was estimated to be 5.1 days and 97.5% of those who develop symptoms did so within 11.5 days of infection.[27] For people who are quarantined, a 14 day observation period has been recommended to exclude infection.

Table 1. Symptoms of COVID-19

Fever	83 – 99 %
Cough	59 – 82 %
Fatigue	44 – 70 %
Anorexia	40 – 84 %
Dyspnea	31 – 40 %
Sputum production	28 – 33 %
Myalgia	11 – 35 %

Symptoms: The signs and symptoms of COVID-19 illness onset vary widely, with children having a milder course. Over the course of the disease, the CDC estimates most persons with COVID-19 will experience the following[31-33] **(Table 1).**

In one study of hospitalized patients, in China, fever was present in only 44% at admission but developed later in 89%.[34] Headache, confusion, rhinorrhea, sore throat, hemoptysis, vomiting, and diarrhea have been reported less commonly (< 10%).[14,34,35,37] Some patients have experienced diarrhea and nausea prior to developing fever and lower respiratory tract signs and symptoms. [38] Anosmia preceding the onset of respiratory symptoms has been anecdotally reported. Cutaneous manifestations of COVID-19 in about 375 cases from Spain has been described recently and range from painful Pseudo chilblain, in milder disease to livedo or skin necrosis in more severe.[59]

Morbidity & Mortality: The Chinese Center for Disease Control and Prevention published the largest case series to date of COVID-19 with over 44,000 confirmed cases.[39] Most patients were 30 to 79 years of age (87%) with 3% aged 80 years or older, with infected healthcare workers contributing 3.8% of the total.

Among patients who developed severe disease, the medium time to dyspnea was 5 to 8 days, while the median time to acute respiratory distress syndrome (ARDS) was 8 to 12 days, and the median time to ICU admission was 10 to 12 days. The median length of hospitalization among survivors was 10 to 13 days.[14,36,39-41] Clinicians should be aware that some patients rapidly deteriorate one week after illness onset. The spectrum disease presentation and case fatality rate are explained below **(Table 2 & Table 3).**

Among all hospitalized patients, a range of 26% to 32% of patients were admitted to the ICU.[36,40,41] ARDS was more likely to develop in ICU patients.[14,34,36,40,41] Early US COVID-19 data by the CDC COVID-19 Response Team showed that about 45% of hospitalizations, 53% of ICU admissions, and 80% of deaths occurred among adults aged ≥ 65 years with the highest percentage of severe outcomes among persons aged ≥ 85 years.[56]

Table 2. Spectrum of disease (N = 44,415)[39]	
MILD	81 %
SEVERE	14 %
CRITICAL	5 %

Table 3. Case fatality rates[39]	
OVERALL	2.3 %
Critical cases	49 %
Age > 80 years	14.8 %
Age 70 – 79 years	8 %
Cardiovascular disease	10.5 %
Diabetes Mellitus	7.3 %
Chronic respiratory disease	6.3 %
Hypertension	6 %
Cancer	5.6 %

COVID-19 testing:

Molecular tests: Diagnosis of COVID-19 requires detection of SARS-CoV-2 RNA by reverse transcription polymerase chain reaction (RT-PCR). Detection of SARS-CoV-2 viral RNA is better in the nasopharynx than the throat. Lower respiratory samples have better yield than upper respiratory samples but risk aerosol generation[42,43] A useful clinical review on how to obtain an appropriate nasopharyngeal swab was recently published in the New England Journal of Medicine.[44]

In view of the difficulty to access test kits, the CDC has allowed Clinicians to use their judgment to determine if a patient should be tested. This can lead to confusion on whom to test.[52] SARS-CoV-2 RNA has been detected in stool and blood, with the latter being a marker of severe illness.[32,45-47] Viral RNA shedding declines with resolution of symptoms, and may continue for days to weeks.[40,42,45] Viral RNA shedding may be longer among elderly and those with severe illness.[28,40,42,45] However, the detection of Viral RNA during convalescence does not necessarily indicate the presence of viable infectious virus. Clinical recovery has been correlated with the detection of IgM and IgG antibodies which signal the development of immunity. [46,49-51]

Clinicians are encouraged to also test for other causes of respiratory illness. Co-infection with both SARS-CoV-2 and other respiratory viruses has been reported, and the detection of another respiratory pathogen does not rule out COVID-19![48] There is no current data concerning re-infection with SARS-CoV-2.

Serologic tests: Serology tests look for antibodies in blood and if present usually indicates a previous infection especially in persons with few or no symptoms.[53] The CDC has developed a serological test using ELISA against SARS-CoV-2 spike protein with a reported sensitivity of 96%, and a specificity of 99%.[54] CDC's serologic test has been designed and validated for surveillance and research purposes but is not for individual use. Commercially manufactured antibody tests are being produced, with over 120 tests available, with unclear quality.[55] The CDC is evaluating the performance of these tests in collaboration with several US federal organizations, such as the U.S. Food and Drug Administration (FDA) and National Institutes of Health (NIH).[54]

It typically takes 1 to 3 weeks after someone becomes infected with SARS-CoV-2 for their body to produce antibodies. The scientists at the CDC are conducting studies to understand if antibodies provide immunity to future infection, what titer or amount of antibodies would be protective and the duration of the protection.[54]

Other viral tests: Viral antigen tests are rapid. While, these tests are not yet on the market, researchers do not expect it to be as accurate as the PCR. This may mean that a positive antigen test requires confirmation by PCR to make a medical diagnosis.[55] Viral cultures have no role in the commercial setting.

Non-viral tests: Lymphopenia is the most common lab finding in COVID-19 and is found in as many as 83% of hospitalized patients.[14,34] Lymphopenia, neutrophilia, elevated serum alanine aminotransferase and aspartate aminotransferase levels, elevated LDH, high CRP, and high ferritin levels may be associated with increased severity. Procalcitonin is typically normal on admission, but may increase among those admitted to the ICU.[14,34,36,40,41,57] The neutrophil – lymphocyte ratio, has been used as a marker of systemic inflammation and infection. Higher serum levels of proinflammatory cytokines (TNF-α, IL-1, and IL-6) and chemokines (IL-8) were found in patients with severe COVID-19.[58]

Radiographic findings: Chest radiographs of patients with COVID-19 typically demonstrate bilateral air-space consolidation. Early on, patients can have unremarkable chest radiographs.[14,34,69] Chest CT images from patients typically demonstrate bilateral, peripheral ground glass opacities.[35,38,41,69-73] As this imaging pattern is non-specific, the diagnostic value of chest CT imaging for COVID-19 may be low and dependent on individual interpretations.[70,74] The American College of Radiology does not recommend CT for screening or as a first-line test for diagnosis of COVID-19 due to lack of specificity and logistical issues with transportation, the need for environmental cleaning and decontamination of rooms.[75] One study found that 56% of patients who presented within 2 days of diagnosis had a normal CT [71] while other studies have identified chest CT abnormalities prior to the detection of SARS-CoV-2 RNA.[69,76]

TREATMENT OF COVID-19

Mild to Moderate Disease: The CDC recommends that patients with a mild clinical presentation (absence of viral pneumonia and hypoxia) may not require hospitalization, and that many patients will be able to manage their illness at home. The decision to monitor a patient in the inpatient or outpatient setting using the tools of telehealth can be made on a case-by-case basis.[31] Patients who are monitored in the outpatient setting will be less likely to utilize precious hospital resources. Patients with risk factors for severe illness should be closely monitored given the risk of disease progression in the second week after symptom onset.[14,36,39,40] The CDC advices that older adults should maintain adequate supplies of nonperishable foods and at least a 30-day supply of necessary medications, practice social distancing, avoid those who are sick, being in crowds, avoid cruise and air travel, and stay home as much as possible.[56]

Severe disease: Patients with severe disease require hospitalization.[31] Corticosteroids have been widely used in hospitalized patients with severe illness in China [36,39-41] The CDC recommends avoiding the use of corticosteroids unless indicated for other reasons, such as management of COPD exacerbation or septic shock.[31] Inpatient management revolves around the supportive care of the most common complications of severe COVID-19: pneumonia, hypoxemic respiratory failure/ARDS, sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalization including secondary bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy.[14,34-36,38-40,60,61] Comprehensive guidelines for the inpatient management of patients with COVID-19, have been released by several professional societies including the Infectious Diseases Society of America (IDSA), NIH (National Institute of Health), the BMJ (British Medical Journal) best practice measures, the WHO and the Surviving Sepsis Campaign.[62-68]

Antivirals against SARS-CoV-2:

Remdesivir: (GS-5734,) by Gilead Sciences Inc. is a broad-spectrum antiviral adenosine nucleotide prodrug with potent in vitro activity against a range of RNA viruses including Ebola virus, Marburg, MERS-CoV, SARS-CoV, Respiratory Syncytial Virus, Nipah and Hendra virus.[77-80] The mechanism of action of remdesivir is premature termination of viral RNA transcription by binding to the RNA dependent RNA polymerase.[80] Remdesivir can only be administered intravenously. Its use improved disease outcomes and reduced viral loads in SARS-CoV-infected mice.[79] The efficacy of prophylactic and therapeutic remdesivir was tested in a rhesus macaque model of MERS-CoV infection.[81] A recent small case series of 53 patients worldwide with severe COVID-19 pneumonia who received remdesivir under a compassionate-use protocol reported clinical improvement in 68% after a median follow-up of 18 days, with 13% mortality and a generally acceptable toxicity profile.[82]

On May 1, 2020 the U.S. Food and Drug Administration (FDA) granted emergency use authorization(EUA) for remdesivir to treat COVID-19 on the basis of the completion of two Phase 3 trials in severely ill patients.[83] The full results of this trial are pending, however preliminary results indicate that patients who received remdesivir had a 31% faster time to recovery than those who received placebo ($p < 0.001$). The median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for placebo. The results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group ($p = 0.059$).[84] The optimal dosing and duration of Remdesivir for the treatment of COVID-19 is still unknown, but under the FDA approved EUA, the 10-day dosing duration is suggested for patients requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO), and the 5-day dosing duration is suggested for less ill patients.[83]

The enthusiasm generated by the NIH trial results must be balanced by the sobering information released a few days prior from a randomized, placebo-controlled, double-blind trial in China.[85] No statistically significant benefits were observed for patients on Remdesivir. Additionally, Remdesivir did not result in significant reductions in viral loads in this study. A drawback of this study was that it did not achieve its predetermined sample size due to being terminated early, from the COVID-19 epidemic being brought under control in China.[85]

Other antivirals: Oseltamivir is a neuraminidase inhibitor used for prophylaxis and treatment of influenza. It has been used only in combinations of antiviral therapy in China[86] and continues to be explored. Lopinavir-ritonavir is a combination protease inhibitor used for the treatment of HIV infection, that has shown in-vitro antiviral activity against Coronaviruses.[87-90] Though lopinavir-ritonavir with ribavirin reduced the mortality and ICU stay of SARS patients, the results of a randomized, open-label 14 day trial of Lopinavir-ritonavir in Chinese COVID-19 patients was disappointing.[89,91] There are only in vitro data available on the activity of ribavirin on SARS-CoV-2 currently. Studies in SARS, and MERS were unimpressive.[92,93]

Immunomodulators: Tocilizumab is an interleukin-6 (IL-6) receptor antagonist approved for use in Rheumatoid Arthritis, Giant Cell Arteritis, Juvenile Idiopathic Arthritis and for Cytokine Release Syndrome (CRS).[94] As a recombinant monoclonal antibody, tocilizumab can bind to the IL-6 receptors and inhibit signal transduction.[95] In patients with COVID-19, a large number of

T-lymphocytes and macrophages are activated, leading to the production of pro-inflammatory cytokines such as IL-6. The IL-6 binds to the IL-6 receptor on the target cells, causing a cytokine storm and severe inflammatory responses in visceral organs. Tocilizumab, can bind with high affinity to the IL-6 receptor, preventing the IL-6 from binding and thus alleviate the inflammatory response.

A small trial conducted by Xu et al in China during the ongoing COVID-19 outbreak showed that tocilizumab effectively improved clinical symptoms and repressed the deterioration of severe COVID-19 patients.[95] However, Tocilizumab can cause serious infections such as Tuberculosis, Cryptococcus, Aspergillosis, Candidiasis, Herpes zoster, Hepatitis B reactivation and Pneumocystosis. Serious cases of hepatic injury and gastrointestinal perforation have been observed.[94] The IDSA guideline panel recommends tocilizumab use only in the context of a clinical trial.[62]

Hydroxycholoroquine: Both Chloroquine and hydroxychloroquine(HCQ) are oral drugs that have been used for decades in the prophylaxis and treatment of malaria, and the treatment of certain autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosus. Both have in vitro activity against SARS-CoV-2. HCQ is similar to chloroquine in therapeutic efficacy, but with a relatively higher potency, fewer adverse effects, and is considered safe in pregnancy.[96-98] Both drugs must be used with caution in patients with pre-existing cardiovascular disease due to the risk of precipitating arrhythmias.[99] Caution is also recommended with the dosing regimen used for chloroquine due to the risk of chloroquine poisoning.[100] Also, higher doses of chloroquine as compared with lower doses, have been associated with an increased risk of QT interval prolongation, especially when used in combination with other drugs that prolong the QT interval.[101]

In France, during early March 2020, Didier Raoult and his group began enrolling confirmed COVID-19 patients into a small study to evaluate the role of hydroxychloroquine on respiratory viral loads. Patients received 600 mg of hydroxychloroquine daily and had their viral load in nasopharyngeal swabs tested daily. Depending on their clinical presentation, azithromycin was added to the treatment. Untreated patients from another center and cases refusing the protocol were included as negative controls. Presence and absence of virus at Day 6 post inclusion was considered the end point. A total of 26 patients received hydroxychloroquine and 16 were control patients. Six hydroxychloroquine-treated patients were lost in follow-up during the survey because of early cessation of treatment. At day 6 post-inclusion, 70% of hydroxychloroquine-treated patients were virologically cured compared with 12.5% in the control group (p= 0.001). Among hydroxychloroquine-treated patients six patients received azithromycin (500mg on day1 followed by 250mg per day, the next four days) to prevent bacterial super-infection, with daily EKG monitoring.[102]

While these results appear extremely promising it has been criticized for its small sample size and study design. Instead of excluding patients who declined treatment, the researchers assigned them to the control group.[103] The other criticism was how it handled patients who were lost to follow-up. Only 20 of 26 patients in the treatment group were included in the analysis. Six patients were excluded because the day 6 PCR data was missing. These patients should have been considered as having had treatment failure and been included in the analysis.[103]

Results from a similar trial in France and China could not replicate these findings.[104,105] At this time, the IDSA guideline panel recommends that hydroxychloroquine/ chloroquine or hydroxychloroquine/chloroquine plus azithromycin be used only in the context of a clinical trial among hospitalized patients.[62] The Surviving Sepsis Campaign and National Institutes of Health guidelines concluded that there is insufficient evidence to offer any recommendation on use of these drugs.[67,68] In a newsletter dated April 1, 2020 the European Medicines Agency (EMA) stressed that these drugs should only be used in the context of clinical trials or emergency-use programmes.[106]

Intravenous immunoglobulin (IVIG): IVIG has been used as an adjuvant to treat a wide variety of pathogens. It is unclear, what the utility of IVIG for the treatment of SARS-CoV-2 is though a small case series showed possible benefit.[107]

Convalescent plasma or serum: There is a long history of using convalescent plasma starting in 1893 for the treatment of infectious diseases,[111] including severe viral lower respiratory tract infections.[108] Individuals who have recovered from SARS-CoV-2 infection may generate neutralizing antibodies[109,110] that could have application in the prevention of infection. An editorial in The Journal of Clinical Investigation on March 13, 2020 by Arturo Casadevall and Liise-anne Pirofski, argued strongly in favor of the use of COVID-19 convalescent sera for either prophylaxis or treatment of disease.[112] That review lead to the foundation of the National COVID-19 Convalescent Plasma Project.[113]

Almost immediately, a case series was published in the JAMA of 5 critically ill patients with laboratory-confirmed COVID-19 and ARDS from Shenzhen, China.[114] They received convalescent plasma from donors who had been previously diagnosed with laboratory confirmed COVID-19 and subsequently tested negative for SARS-CoV-2. 400 mL of convalescent plasma was immediately transfused to the recipients on the same day it was obtained. The results of this study were very encouraging with body temperature normalizing within 3

days in 4 of 5 patients, while the SOFA score decreased. Viral loads decreased and became negative within 12 days after transfusion, while patient's SARS-CoV-2 antibody titers increased. ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment.[114] Based on this trial and a second one by Duan et al,[115] the IDSA guideline panel recommends the use of COVID-19 convalescent plasma in the context of a clinical trial.[62] A large US trial on the use of convalescent plasma for severely ill adults or those thought to become severely ill is ongoing.[116]

PREVENTION

Given the role of respiratory droplets in person-to-person transmission and widespread communal spread of the SARS-CoV-2 virus, the following communal measures of prevention are recommended.[117]

Face masks: The WHO recommends that medical masks should be reserved for healthcare workers. Masks can be worn by people with symptoms, and those caring for a sick person at home when in the same room. There is currently no evidence that wearing a mask in the community setting can prevent infection with respiratory viruses, in a healthy person.[118] Given the presence of asymptomatic and presymptomatic SARS-CoV-2 infections in communities, the CDC recommends wearing cloth masks in public settings where other social distancing measures are difficult to maintain such as in crowded stores.[120] The use of a mask alone is insufficient, and they should be used along with other infection prevention and control measures.[118]

Hand Hygiene: Though hand hygiene has become an important part of the CDC response to COVID-19, the exact contribution of hand hygiene to the reduction of spread is currently unknown. However, practicing hand hygiene, which includes the use of an alcohol-based hand rub or handwashing with soap and water, is a simple and effective way to stop spreading pathogens.[20] The CDC recommends using alcohol-based hand rub with greater than 60% ethanol or 70% isopropanol in the healthcare settings. Unless hands are visibly soiled, an alcohol-based hand rub is preferred over soap and water due to better compliance. Hands should be washed with soap and water for at least 20 seconds to be successful.[20]

Social distancing and Quarantine: CDC describes Social distancing as keeping space between oneself and other people outside of home. To practice social distancing:

- Stay at least 6 feet (about 2 arms' length) from other people
- Do not gather in groups
- Stay out of crowded places and avoid mass gatherings.

Social distancing is recommended for all ages to slow the spread of the virus, protect the health care system, and vulnerable older adults.[56] Many countries have implemented various types of mandatory social distancing measures in order to reduce and delay SARS-CoV-2 transmission such as - lockdowns, stay-at-home orders, curfews, closures of non-essential business, bans on social gatherings, school and university closures, travel restrictions, encourage remote working, and quarantine exposed people/ travellers.[64] Researchers in Singapore found that social distancing measures significantly decreased the number of infections in simulation models.[121] Self quarantine helps limit spread of COVID-19.[122] A Cochrane review found enforced quarantine to be an important measure in reducing the number of people infected and deaths.[123]

Preventing nosocomial spread: The CDC recommends that in the health care facility, measures to minimize exposures to respiratory pathogens should be implemented before patient arrival, at arrival, throughout the duration of the patient's visit, and until the patient's room is cleaned and disinfected.[117] These key core measures have been put together in the table shown below **(Table 4)**. Limiting visitors to the hospital, and actively assessing all visitors for fever and COVID-19 symptoms upon entry is encouraged. If fever or COVID-19 symptoms are present, the visitor should not be allowed entry into the facility.[117] Health Care Providers (HCP) should wear a medical facemask at all times while in the healthcare facility. HCP should perform hand hygiene before and after all patient contact, contact with potentially infectious material, and before putting on and after removing PPE, including gloves.[117] HCP should not wear cotton cloth masks as these have increased risk of infection.[119]

HCP should be asked to regularly monitor themselves for fever and symptoms of COVID-19. Screen all HCP at the beginning of their shift and if a HCP develops fever or symptoms consistent with COVID-19 while at work they should keep their facemask on, inform their supervisor, and leave the workplace.[117] HCP should be reminded

Table 4. Key Concepts in Infection control from the CDC[117]

REDUCE FACILITY RISK	Cancel elective procedures. Use telemedicine resources. Limit points of hospital entry. Manage visitors. Screen everyone for COVID-19 symptoms.
ISOLATE SYMPTOMATIC PATIENTS	Set up separate, well ventilated triage areas. Place suspected/confirmed COVID-19 in private rooms with door closed.
PROTECT HEALTHCARE PERSONNEL(HCP)	Emphasize hand hygiene. Install barriers to limit contact at triage. Cohort patients with COVID-19. Limit staff providing care. Prioritize respirators for aerosol generating procedures. Monitor HCP for illness

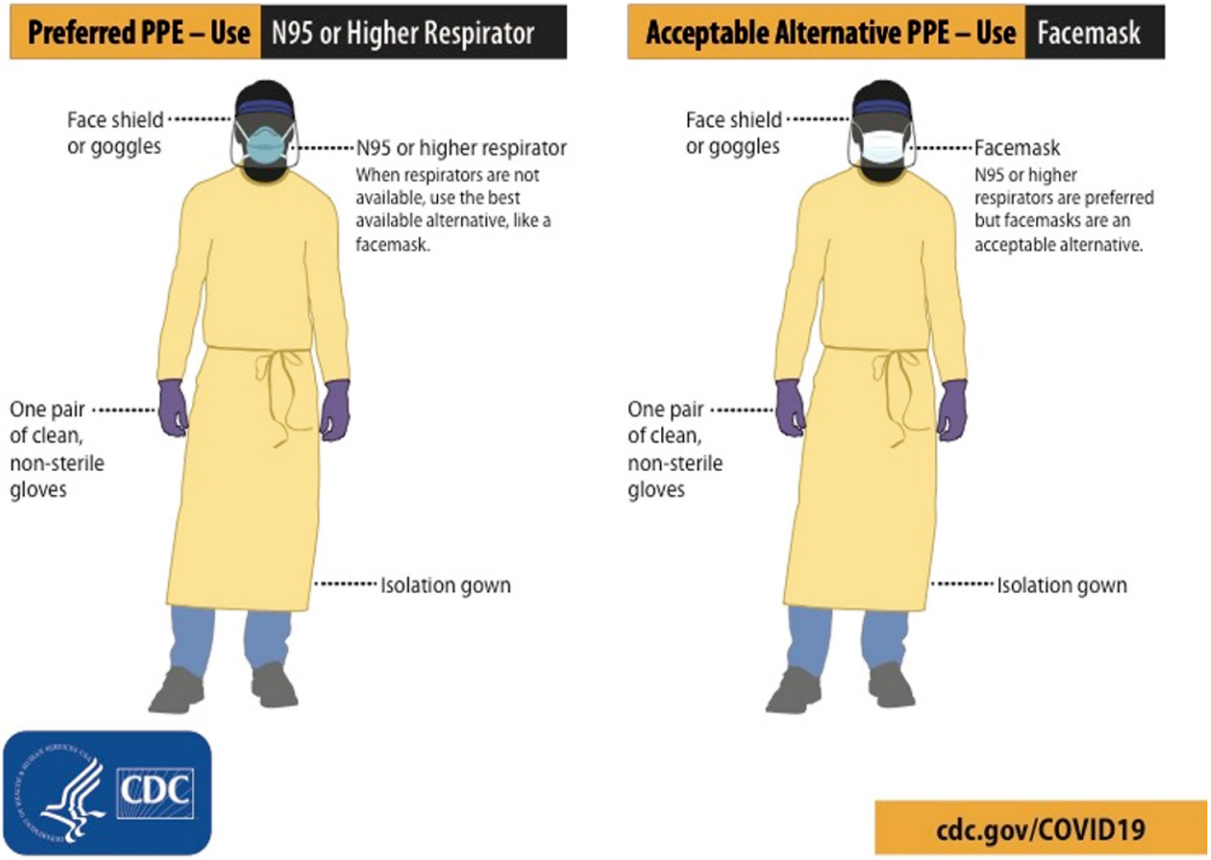

Figure 1. **CDC definition of COVID-19 Preferred and alternative PPE for Health care providers.**[117]

to stay home when they are ill. The CDC definition of acceptable PPE for a HCP is provided in the figure below **(Figure 1),** with an emphasis on airway protection. Any reusable PPE must be properly cleaned, decontaminated, and maintained after and between uses.[117]

VACCINE FOR SARS-CoV-2: There is currently no vaccine for SARS-CoV-2. Vaccines are in development, and may take at least 12 to 18 months before becoming available. Seven vaccine candidates are currently approved for human testing through clinical trials, including mRNA and DNA platform vaccines, adenovirus vector vaccines, and an inactivated virus vaccine. [124] Vaccines are being fast-tracked and skipping the animal testing stage.[64] It is not known at this time whether the immunity provided by vaccines is going to be long lasting.

END NOTE

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REFERENCES

1. de Wilde AH, Snijder EJ, Kikkert M, van Hemert MJ. Host Factors in Coronavirus Replication. Curr Top Microbiol Immunol. 2018;419:1–42.
2. Weiss SR, Leibowitz JL. Coronavirus pathogenesis. Adv Virus Res. 2011;81:85–164.
3. Masters PS, Perlman S. Coronaviridae. In: Fields Virology, 6th ed, Knipe DM, Howley PM, Cohen JI, et al (Eds), Lippincott Williams & Wilkins, a Wolters Kluwer business, Philadelphia 2013. Vol 2, p.825.
4. Su S, Wong G, Shi W, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Micro biol 2016;24:490-502.
5. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14(8):523–34.
6. Chan-Yeung M, Xu R-H. SARS: epidemiology. Respirology. 2003 Nov;8 Suppl:S9-14.
7. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus ADME, Fouchier RAM. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012 Nov 8;367(19):1814–20.
8. Ren L-L, Wang Y-M, Wu Z-Q, Xiang Z-C, Guo L, Xu T, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J. 2020 May 5;133(9):1015–24.

9. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 20;382(8):727–33.
10. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 22;395(10224):565–74.
11. World Health Organization. Pneumonia of unknown cause China. 5 January 2020
12. World Health Organization. Novel coronavirus China. 12 January 2020.
13. Ministry of health and family welfare, India. [Internet]. [cited 2020 May 18].
14. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 15;395(10223):497–506.
15. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020 26;382(13):1199–207.
16. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020 15;395(10223):514–23.
17. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med. 2020 16;382(16):1564–7.
18. Otter JA, Donskey C, Yezli S, Douthwaite S, Goldenberg SD, Weber DJ. Transmission of SARS and MERS coronaviruses and influenza virus in healthcare settings: the possible role of dry surface contamination. J Hosp Infect. 2016 Mar;92(3):235–50.
19. Dowell SF, Simmerman JM, Erdman DD, Wu J-SJ, Chaovavanich A, Javadi M, et al. Severe acute respiratory syndrome coronavirus on hospital surfaces. Clin Infect Dis. 2004 Sep 1;39(5):652–7.
20. CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2020 May 18].
21. McMichael TM, Clark S, Pogosjans S,etal. COVID-19inalongtermcarefacility:King County, Washington, February 27 – March 9, 2020. MMWR Morb Mortal Wkly Rep. 2020 Mar 27;69(12):339-42.
22. Yang H, Thompson JR. Fighting covid-19 outbreaks in prisons. BMJ. 2020 02;369:m1362.
23. Moriarty LF, Plucinski MM, Marston BJ, Kurbatova EV, Knust B, Murray EL, et al. Public Health Responses to COVID-19 Outbreaks on Cruise Ships - Worldwide, February-March 2020. MMWR Morb Mortal Wkly Rep. 2020 27;69(12):347–52.
24. Ghinai I, Woods S, Ritger KA, McPherson TD, Black SR, Sparrow L, et al. Community Transmission of SARS-CoV-2 at Two Family Gatherings - Chicago, Illinois, February-March 2020. MMWR Morb Mortal Wkly Rep. 2020 Apr 17;69(15):446–50.
25. Mat NFC, Edinur HA, Razab MKAA, Safuan S. A Single Mass Gathering Resulted in Massive Transmission of COVID-19 Infections in Malaysia with Further International Spread. J Travel Med [Internet]. 2020 Apr 18
26. CDC. Coronavirus Disease 2019 (COVID-19) – Symptoms [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2020 May 18].
27. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med. 2020 May 5;172(9):577–82.
28. Liu Y, Yan L-M, Wan L, Xiang T-X, Le A, Liu J-M, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis. 2020 Mar 19;
29. Wei WE. Presymptomatic Transmission of SARS-CoV-2 — Singapore, January 23–March 16, 2020. MMWR Morb Mortal Wkly Rep [Internet]. April 10, 2020; 69(14): 411-5.
30. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nature Medicine. 2020 May;26(5):672–5.
31. CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2020 May 18].
32. Cai J, Xu J, Lin D, Yang Z, Xu L, Qu Z, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clin Infect Dis. 2020 Feb 28;
33. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children. N Engl J Med. 2020 23;382(17):1663–5.
34. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine. 2020 Apr 30;382(18):1708–20.
35. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 15;395(10223):507–13.
36. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb 7; 323(11):1061-1069.
37. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. Am J Gastroenterol. 2020;115(5):766–73.
38. Wu Z, McGoogan JM. 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. 2020 Feb 24; 323(13):1239-1242
39. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475–81.
40. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 28;395(10229):1054–62.
41. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020 Mar 13
42. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. N Engl J Med. 2020 19;382(12):1177–9.
43. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA. 2020 Mar 11
44. Marty FM, Chen K, Verrill KA. How to Obtain a Nasopharyngeal Swab Specimen. N Engl J Med. 2020 Apr 17
45. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA. 2020 Mar 3;323(15):1488-1494
46. Zhang W, Du R-H, Li B, Zheng X-S, Yang X-L, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected

patients: implication of multiple shedding routes. Emerg Microbes Infect. 2020;9(1):386–9.

47. Chen W, Lan Y, Yuan X, et al. Detectable 2019-nCoV viral RNA in blood is a strong indicator for the further clinical severity. *Emerging microbes & infections.* 2020;9(1):469-473.
48. Ding Q, Lu P, Fan Y, Xia Y, Liu M. The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. J Med Virol. 2020;1–7 2020 Mar 20.
49. To KK-W, Tsang OT-Y, Leung W-S, Tam AR, Wu T-C, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020;20(5):565–74.
50. Zhao J, Yuan Q, Wang H, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. *Clinical Infectious Diseases*, Published:28 March 2020
51. Guo L, Ren L, Yang S, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). *Clinical Infectious Diseases*, Published:21 March 2020
52. CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2020 May 18].
53. CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2020 May 18].
54. Freeman B, Lester S, Mills L, Rasheed MAU, Moye S, Abiona O, et al. Validation of a SARS-CoV-2 spike protein ELISA for use in contact investigations and sero-surveillance. bioRxiv. 2020 Apr 25;2020.04.24.057323.
55. How Reliable Are COVID-19 Tests? Depends Which One You Mean [Internet]. NPR.org. [cited 2020 May 18].
56. CDC COVID-19 Response Team. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020 Mar 27;69(12):343–6.
57. Zhang C, Shi L, Wang F-S. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5(5):428–30.
58. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 12, March 2020
59. Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández Nieto D, Rodríguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020 Apr 29
60. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 Mar 27
61. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094–9.
62. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC-C, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Clin Infect Dis. 2020 Apr 27
63. Infectious Diseases Society of America Guidelines on Infection Prevention in Patients with Suspected or Known COVID-19 [Internet]. [cited 2020 May 18].
64. BMJ Best Practice [Internet]. [cited 2020 May 18].
65. WHO. Laboratory testing strategy recommendations for COVID-19.
66. WHO. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected.
67. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Critical Care Medicine [Internet]. 2020 May 13 [cited 2020 May 18
68. Information on COVID-19 Treatment, Prevention and Research [Internet]. COVID-19 Treatment Guidelines. [cited 2020 May 18].
69. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. The Lancet Infectious Diseases. 2020 Apr 1;20(4):425–34.
70. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology. 2020 Feb 26;200642.
71. Bernheim A, Mei X, Huang M, et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. *Radiology.* February 20,2020:200463.
72. Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study. AJR Am J Roentgenol. 2020;214(5):1072–7.
73. Xu X, Yu C, Qu J, et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. Eur J Nucl Med Mol Imaging. 2020 May;47(5):1275-1280
74. Bai HX, Hsieh B, Xiong Z, Halsey K, Choi JW, Tran TML, et al. Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT. Radiology. 2020 Mar 10;200823.
75. ACR Recommendations for the use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection [Internet]. [cited 2020 May 18].
76. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical 2019-nCoV Pneumonia: Relationship to Negative RT-PCR Testing. Radiology. 2020 Feb 12;200343.
77. PubChem. Remdesivir [Internet]. [cited 2020 May 18].
78. Lo MK, Jordan R, Arvey A, et al. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. Sci Rep **2017;** 7: 43395.
79. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med **2017;** 9(396).
80. Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature **2016;** 531(7594): 381-5.
81. de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci USA **2020**; 117(12): 6771-6
82. Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe COVID-19. N Engl J Med **2020.**
83. Gilead's Investigational Antiviral Remdesivir Receives U.S. Food and Drug Administration Emergency Use Authorization for the Treatment of COVID-19 [Internet]. [cited 2020 May 18].
84. NIH clinical trial shows Remdesivir accelerates recovery from advanced COVID-19 [Internet]. National Institutes of Health (NIH). 2020 [cited 2020 May 18].
85. Wang Y, Zhang D, Du G, Du R et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. Published online April 29, 2020

86. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet **2020**; 395(10223): 507-13.
87. Chen F, Chan KH, Jiang Y, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 2004; 31(1): 69-75.
88. Chan JF, Chan KH, Kao RY, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Infect 2013; 67(6): 606-16
89. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004; 59(3): 252-6
90. Chan JF, Yao Y, Yeung ML, et al. Treatment with Lopinavir/Ritonavir or Interferon-beta1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. J Infect Dis 2015; 212(12): 1904-13
91. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 07;382(19):1787–99.
92. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med **2006;** 3(9): e343.
93. Arabi YM, Shalhoub S, Mandourah Y, Al-Hameed F, Al-Omari A, Al Qasim E, et al. Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. Clin Infect Dis. 2020 Apr 15;70(9):1837–44.
94. Tocilizumab. Manufacturer's prescribing information. Last accessed May 4, 2020.
95. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. PNAS [Internet]. 2020 Apr 29 [cited 2020 May 18]
96. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020 Mar;30(3):269-71.
97. Cortegiani A, Ingoglia G, Ippolito M, et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care. 2020 Mar 10
98. Zhou D, Dai S-M, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. J Antimicrob Chemother. 2020 Mar 20
99. Roden DM, Harrington RA, Poppas A, Russo AM. Considerations for Drug Interactions on QTc in Exploratory COVID-19 (Coronavirus Disease 2019) Treatment. Circulation. 2020 Apr 8
100. Wong YK, Yang J, He Y. Caution and clarity required in the use of chloroquine for COVID-19. Lancet Rheum. 2020 Apr 2
101. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. JAMA Netw Open. 2020 24;3(4):e208857.
102. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 Mar 20:105949.
103. Kim AHJ, Sparks JA, Liew JW, Putman MS, Berenbaum F, Duarte-García A, et al. A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19. Ann Intern Med. 2020 Mar 30
104. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect. 2020 Mar 30
105. J. Chen, D. Liu, L. Lui, *et al.* A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 COVID-19) J Zhejiang Univ Sci, 03 (2020)
106. European Medicines Agency. COVID-19: chloroquine and hydroxychloroquine only to be used in clinical trials or emergency use programmes. 2020 [internet publication]
107. Cao W, Liu X, Bai T, et al. High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Patients With Coronavirus Disease 2019. Open Forum Infect Dis March **2020**; 7(3): ofaa102. 21 March 2020.
108. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis **2015**; 211(1): 80-90.
109. Ou X, Liu Y, Lei X, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun **2020;** 11(1): 1620
110. Nie J, Li Q, Wu J, et al. Establishment and validation of a pseudovirus neutralization assay for SARS-CoV-2. Emerg Microbes Infect **2020;** 9(1): 680-6.
111. R.Rubin. Testing an Old Therapy Against a New Disease: Convalescent Plasma for COVID-19. JAMA. Published online April 30, 2020
112. Arturo Casadevall, Liise-anne Pirofski.J Clin Invest 2020;130(4):1545-1548
113. National COVID-19 Convalescent Plasma Project.
114. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA. 2020 Mar 27
115. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. medRxiv. 2020 Mar 23;2020.03.16.20036145.
116. Expanded access to Convalescent Plasma for the treatment of patients with COVID-19. ClinicalTrials.gov Identifier: NCT04338360.
117. CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2020 May 18].
118. WHO. World Health Organization. Advice on the use of masks in the context of COVID-19. 2020.
119. MacIntyre CR, Seale H, Dung TC, Hien NT, Nga PT, Chughtai AA, et al. A cluster randomised trial of cloth masks compared with medical masks in healthcare workers. BMJ Open. 2015 Apr 1;5(4):e006577.
120. CDC. Recommendation regarding the use of cloth face coverings, especially in areas of significant community-based transmission.
121. Koo JR, Cook AR, Park M, Sun Y, Sun H, Lim JT, et al. Interventions to mitigate early spread of SARS-CoV-2 in Singapore: a modelling study. The Lancet Infectious Diseases [Internet]. 2020 Mar 23 [cited 2020 May 18];0(0).
122. CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2020 May 18].
123. Nussbaumer-Streit B, Mayr V, Dobrescu AI, Chapman A, Persad E, Klerings I, et al. Quarantine alone or in combination with other public health measures to control COVID-19: a rapid review. Cochrane Database Syst Rev. 2020 08;4:CD013574.
124. Mahase E. Covid-19: What do we know so far about a vaccine? BMJ. 2020 Apr 27;369:m1679.