AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

Coronavirus (COVID-19)

Last Updated: March 29, 2021
Prior versions: April 8, 2020; April 24, 2020; May 8, 2020; June 12, 2020; June 17, 2020; August 19, 2020; December 14, 2020.

The March 29, 2021 update includes the following major changes:

- New guidance on rehabilitation (pulmonary, cardiac, cognitive, musculoskeletal, debility) for severe and/or chronic COVID-19 cases
- Vaccination information, including travel advice for vaccinated individuals, success against common virus variants, and adverse effects
- New recommendation on the Johnson & Johnson COVID-19 vaccine
- Upgraded recommendation for baricitinib from insufficient evidence (I) to evidence (B)
- Upgraded recommendation for bamlanivimab from insufficient evidence (I) to evidence (C)
- Upgraded recommendation for interferon beta-1b from insufficient evidence (I) to evidence (B)
- Upgraded recommendation for low-molecular-weight heparin from insufficient evidence (I) to evidence (C)
- Downgraded recommendation for convalescent antibodies to No Recommendation (I)
- Review of evidence for ivermectin (insufficient evidence, with no recommendation)
- Review of masking efficacy
- Updates from the CDC on physical distance in K-12 classrooms

Contents

Contributors

Editor-in-Chief
Kurt T. Hegmann, MD, MPH, FACOEM, FACP

Evidence-based Practice COVID-19 Panel Members
Clayton T. Cowl, MD, MS, FACOEM
Philip Harber, MD, MPH, FACOEM, FCCP, ATSF
Mark H. Hyman, MD, FACP, FIAIME
Karin A. Pacheco, MD, MSPH, FAAAAI
Thomas Winters, MD, FACOEM, FACPM, FACP
Eric M. Wood, MD, MPH, FACOEM

Evidence-based Practice COVID-19 Consultants
Steven Mandel, MD, FACOEM
William Niehaus, MD
Greg S. Vanichkachorn, MD, MPH, FACOEM

These panel members and consultants represent expertise in occupational medicine, internal medicine, family medicine, pulmonary medicine, infectious disease, physical medicine and rehabilitation and neurology. As required for quality guidelines – Institute of Medicine's (IOM's) Standards for Developing Trustworthy Clinical Practice Guidelines and Appraisal of Guidelines for Research and Evaluation (AGREE) – a detailed application process captured conflicts of interest. The above Panel has none to declare relevant to this guideline.

Research Team

Kurt T. Hegmann, MD, MPH, FACOEM, FACP
Matthew S. Thiese, PhD, MSPH
Emilee Eden, MPH
Kristine Hegmann, MSPH, CIC
Jenna L. Praggastis, BS
Alison Mancuso, BA
Braydon R. Black
Madison N. Tallman
Madeleine Smith, BS
Elise D. Chan
Andrew S. Barbee
Michael R. Langston, BS
Christina P. Pick, BS
Chapman B. Cox, BS
Derrick K. Wong
Jenny L. Echeverria
Uchenna C. Ogbonnnaya MS, CSCS
Katherine C. Castro, MPH

Specialty Society and Society Representative Listing

ACOEM acknowledges the following organizations and their representatives who served as reviewers of the Coronavirus (COVID-19) Guideline. Their contributions are greatly appreciated. By listing the following individuals or organizations, it does not infer that these individuals or organizations support or endorse the Coronavirus (COVID-19) Guideline developed by ACOEM. Reviewers from three additional societies wished to remain anonymous.

American College of Chest Physicians
Holly Keyt, MD
Steven Q. Simpson, MD

Society for Healthcare Epidemiology of America
Meghan A. Baker, MD, ScD
David J. Weber, MD, MPH

Other Reviewers:
James W. Butler, MD, MPH, MRO, FAADEP, CIME, FACOEM
Victoria A. Cassano, MD, MPH, MPhil, FACPM, FACOEM
Glenn S. Pransky, MD, MOCCH, FACOEM
Kenji Saito, MD, JD, FACOEM
Tanisha K. Taylor, MD, MPH, FACP, CIME, FACOEM

Strength of Evidence Ratings

Strength of Evidence ratings are used to designate the quality and amount of evidence that supports a specific guideline recommendation, when taking into account the entire body of relevant evidence found in the literature search. The body of evidence on a topic consists of all studies found that were relevant to the specific clinical question and of acceptable quality. In general, the highest quality of evidence found should be used by the Panel as the basis for the guideline recommendation, unless other factors, such as the potential for harm, are an overriding consideration. When multiple studies of similar quality and relevance are found on a topic, these studies should be evaluated as a group; if results are generally consistent, they would be considered either Strong Evidence (for high-quality studies) or Moderate Evidence (for moderate-quality studies). In all cases, the rationale for each recommendation and scientific studies used as evidence should be documented by the Panel.

A	**Strong evidence-base**: Two or more high-quality studies.[*]
B	**Moderate evidence-base**: At least one high-quality study or multiple moderate-quality studies[†] relevant to the topic and the working population.
C	**Limited evidence-base**: At least one study of moderate quality.
I	**Insufficient Evidence**: Evidence is insufficient or irreconcilable.

For treatment, the criteria used by evidence reviewers to categorize the quality of individual randomized controlled trials as high, moderate, or low quality are: adequate randomization, concealed treatment allocation, baseline cohort comparability, patient blinded, provider blinded, assessor blinded, controlled for co-interventions, compliance acceptable, dropout rate acceptable, timing of assessments equivalent, data analyzed by intention to treat, and lack of bias.[‡] Each criterion receives a score of 0, 0.5, or 1. See Table B in the Methodology for a definition of each criterion and scoring level. Studies are considered of low quality if they are rated 3.5 or less, moderate quality if they are rated 4-7.5, and high quality if they are rated 8-11.

Please see https://info.mdguidelines.com/wp-content/uploads/2019/08/Methodology-2017-Update.pdf for our full methodology.

[*] For therapy and prevention, randomized controlled trials (RCTs) with narrow confidence intervals and minimal heterogeneity. For diagnosis and screening, cross-sectional studies using independent gold standards. For prognosis, etiology or harms, prospective cohort studies with minimal heterogeneity.

[†] For therapy and prevention, a well-conducted review of cohort studies. For prognosis, etiology or harms, a well-conducted review of retrospective cohort studies or untreated control arms of RCTs.

[‡] van Tulder M, Furlan A, Bombardier C, Bouter L. Updated method guidelines for systematic reviews in the Cochrane Collaboration back review group. *Spine*. 2003;28(12):1290-9.

Introduction

Note: *This guideline and its recommendations were last reviewed and updated on* ***March 29, 2021.***

This guideline has previously undergone extensive peer reviews. However, the total depth and breadth of quality literature for the treatment of COVID-19, although growing, remains fairly limited. Some of the studies underlying this guideline are particularly fluid due to the pace of change in knowledge. Research data, especially those associated with treatments, continue to be published prior to peer review. Some vaccination phase 3 trials have not been published; thus, reliance for those is necessarily on press releases and other non-peer-reviewed sources. Under normal circumstances, such data would not be considered for an evidence-based guideline. However, the severity, urgency, and mortality associated with this pandemic do not allow the luxury of time to await the publication of randomized controlled trial data and/or the completion of peer review. The literature will continue to be monitored and this guideline will be updated as needed in response to new research reports, changes in prior reports caused by peer review, and any retractions.

Novel coronavirus 2019 (COVID-19) is an acute respiratory infection caused by a new strain of coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been variously named "coronavirus disease 2019" (abbreviated "COVID-19") [1].

The pandemic began in Wuhan, China in November 2019, then expanded markedly throughout the Wuhan region. Based on prior research and experience with coronavirus infections, the origin of this pandemic is thought to be traced to bats near Wuhan, China; speculation is that pangolins may have been an intermediate species between bats and humans [2, 3]. COVID-19's SARS-CoV-2 virus can now be found in humans on all continents around the world [4, 5]. There is indirect and strongly disputed evidence suggesting that the epidemic may have begun earlier than November, including increased hospital traffic, web searches for potential COVID-related symptoms in Wuhan beginning in August 2019, and other information that suggested a potential laboratory shutdown in October 2019 [6-10]. Regardless, the Chinese New Year likely accelerated the spread of the virus through global travel and hastened the development of a pandemic.

Quarantines were implemented early in pandemic. However, they were likely ineffective at preventing the pandemic [11] for several reasons, including delayed global implementation of quarantining, travel bans, droplet/aerosol precautions, and other public health measures; early emphasis on contact instead of respiratory spread; the number of undiagnosed, mild, or asymptomatic patients spreading the virus [12, 13]; and the spread of cases in a region prior to the recognition of COVID-19 within that area [14]. An added complication in preventing the elimination of the virus from the global human population is the susceptibility of animals,

although the importance of this potential factor is still poorly documented; it is not believed to be a significant contributor to the pandemic spread beyond China.

Public health management of this pandemic has varied across countries, states, and jurisdictions. Because there was no quality evidence to support any of these measures early in the pandemic, expert opinion was used for their implementation. The initial guidance focused on handwashing and restricting travel to China (January 2020, which subsequently expanded to include other countries), varying degrees of closure for businesses and schools (March 2020), recommendations for personal masking (March-April 2020), and public masking orders (April-July 2020). Some states began to reopen most, if not all businesses, starting in May-June 2020. Typically, a combination of approaches has been used, including the quarantine of affected individuals, contact tracing, isolation, stay-at-home orders, physical distancing, mask use, and the closure of non-essential businesses [15].

The pandemic subsided markedly in the summer of 2020 in northern latitudes. However, as fall/winter 2020–21 began, the pandemic predictably surged in northern, cold climates where conditions of lower temperatures, lower humidity, less intense ultraviolet (UV) irradiation, and higher indoor population densities combined to cause record levels of cases in nearly all jurisdictions [16-18]. Additionally, controversy regarding the efficacy and sustainability of various public health measures, especially the (re)closure of businesses and schools, has intensified as the case rates plummeted in 2021. Quality data are weak; some countries (e.g., Japan, South Korea) have instituted less stringent measures with seemingly somewhat comparable or better results [19-29]. Worldwide, the pandemic continues to provide numerous challenges, especially in countries with lagging immunization rates, including surges, hotspot outbreaks, surge prevention, and mitigation; healthcare and first-responder personal protective equipment availability; COVID-19 diagnostic testing availability, capacities, and limitations; unique treatment challenges and sparse evidence of efficacy; growing public restlessness with restrictions; resurgences of cases with loosening of restrictions; and increasing business/economic concerns.

Termination of the COVID-19 pandemic (or at least this phase of it) is now in sight in the United States. Termination is primarily credited to the rapidly increasing rates of vaccination, residual immunity due to prior infections in the population, and falling infection rates. Attention is now turning to issues such as vaccine hesitancy, whether to immunize children, the duration of vaccine-related immunity, and virus variants.

Other coronavirus outbreaks have occurred in the past, such as severe acute respiratory syndrome (SARS) in 2003-04 and Middle East respiratory syndrome (MERS) in 2012-15 [30, 31]. When a virus mutates or changes, studies must be performed to determine the new strain's virulence (i.e., its ability to infect humans).

Virus Characteristics

Contagiousness

COVID-19's SARS-CoV-2 virus appears to be more contagious than the prior coronaviruses. Initially, the virus was thought to be primarily spread through direct contact. That belief has changed markedly and the virus is now thought to be spread by respiratory droplets (defined as >100 µm in size), with weaker but increasing evidence for microdroplets/aerosols (defined as <0.5 µm), and less so via direct hand-to-mucous membrane contact. Consensus now is that droplets are the primary method of spread [32]. Although respiratory aerosol spread was initially controversial, a committee of the National Academy of Sciences and others found limited evidence that the virus is also spread by respiratory aerosols [33-41]; other evidence of at least some spread by aerosols is rapidly accruing [42]. Currently, droplet spread continues to be viewed as the major mode of transmission [38, 41, 43-51]. Aerosols can remain suspended in the air for a longer time and well beyond the commonly quoted 6-foot (or 1-meter, per the World Health Organization) physical distancing guideline [51]. Whether, and to what extent, an infectious dose can be generated and present beyond 6-foot distances has yet to be clearly demonstrated [52-58].

The contagiousness and virulence of the SARS-CoV-2 virus appear to be about 3-fold greater than that of influenza. Estimates of the contagiousness or transmission rate without interventions (e.g., physical distancing) range from 2.0 to 3.9—that is, 2 to 3.9 new cases arise from each known case [59], which is far higher than typical influenza transmission rate of ~1.3 [60]. While the prior Centers for Disease Control and Prevention (CDC) estimate for the United States was 2.5 [13], recent estimates for the 50 US states range from 0.91 to 1.54 [61]. From a population standpoint, however, each case does not appear to be equally infectious. One analysis of 1,038 confirmed SARS CoV-2 infections in Hong Kong between January and April 2020 revealed that 80% of the infections were caused by just 19% of the initial cases; the majority of patients failed to infect anyone else. Most transmission occurred from household contacts, followed closely by external social events [62]. Beyond the transmission rates, the CDC previously estimated that >10 times more cases are missed than are recorded based on seroprevalence studies [63], suggesting a far higher degree of contagiousness; this underestimate may be even greater depending on the rate of false-negative results from seroprevalence tests. Serial seroprevalence studies across all states have shown evidence of prior infection ranging from 1% to 23% [64]. The most recent CDC estimates from February-December 2020 indicate that only 52.6% of hospitalized cases, 23.8% of symptomatic cases, and 21.7% of all COVID-19 infections are reported [65], in which case there have been 83.1 million total infections. Estimates for reaching herd immunity may have large degrees of error if they do not incorporate these underestimates of infections.

More precise estimates of transmission rates will become known with time, particularly as testing rates escalate, although false-negative rates are reportedly 20-67% [32]. Collectively, although global next-generation sequencing results indicate that SARS-CoV-2 genomes are relatively stable (mutating on average 2 times per month), dynamic mutations can be selected in symptomatic individuals [66]. There have been documented changes in the SARS-CoV-2 spike protein D614G due to recombination between locally circulating strains, which is now the

dominant pandemic form in many countries. This new version is associated with higher viral loads and suggests that it is more transmissible, although there was no significant correlation found between D614G status and hospitalization status (i.e., severity of disease) [67].

It is now estimated that 40–45% of infections develop due to exposure to asymptomatic or presymptomatic cases [68]. Yet, the proportion who remain persistently asymptomatic is unclear [69-88]. Among 59,073 contacts of 5,706 COVID-19 index patients, 11.8% had COVID-19 compared with 1.9% of non-household contacts [89], showing the importance of close contacts. The viral load needed to infect a contact remains unclear.

The virus's survivability on surfaces varies depending on the material; it has been estimated with experimental methods to survive up to 9 days [90], although those experimental methods are limited by not including environmental settling rates, inactivation by UV light, or diffusion. Furthermore, a thin nanofilm of liquid from droplets has been reported to extend the viral survival on surfaces [91]. The total viable viral counts decline with time [51]. The survival time of the virus was reported to differ by surface type, with approximate upper limits of detection being 4 hours on copper, 24 hours on cardboard, 48 hours on stainless steel, and 72 hours on plastic [90]. Survival on human skin has been measured at 9.04 hours, which is much longer than the measured survival of influenza virus on skin (1.82 hours) [92]. Survival of the virus in aerosols is thought to be at least 3 hours. However, it is still unclear how much virus is needed to infect a human from either surfaces or aerosols. Many studies show detection of viral RNA that is likely inadequate for and/or incapable of transmitting an infection.

Preliminary experimental and epidemiological-ecological data suggest spread may be optimal in indoor and/or cooler climate conditions [16, 93-96], and prior data on the SARS coronavirus are corroborative [97]. Experimental evidence suggests that simulated sunlight rapidly inactivates the virus. At a simulated sunlight intensity of the summer solstice at 40 degrees of latitude, the inactivation rate was 90% inactivated every 6.8 minutes [98]. The ecological data indicate that there were slower rates of infection with higher temperatures in Delhi, India, and Pakistan [16, 96], although there was no correlation with humidity [16]. The data from Pakistan also suggest an inverse relationship between COVID infection rates and UV light, although the UV data appear to be highly correlated with the heat indices [96]. Other data suggest lower infections with higher humidity [18]. This suggests highly variable disease transmission risks based on seasonality and in indoor compared with outdoor environments. Taken together, these data were projected by this guideline in spring 2020 to project a surge in COVID cases in northern latitudes in fall 2020 [94]; further, it could be predicted that even in the absence of vaccination, the pandemic would taper down by summer 2021. Similarly, disease surges in Florida and Texas in August 2020 are explicable by these conditions, avoidance of time in the humid outdoors, and the use of air conditioning. Less dramatic epidemic surges were predicted to occur during winter 2020-21 in the deep South, assuming that the viral epidemic did not tail off and/or sufficient numbers of individuals did not become immune (i.e., herd immunity) through infection or vaccination in the meantime.

Incubation and Period of Infectious Viral Shedding

The incubation period is the amount of time that occurs between exposure and the onset of symptoms. The incubation period of the SARS-CoV-2 virus is estimated to be approximately 5–6 days [13, 99, 100], with 97.5% of cases occurring by 11.5 days after exposure and infrequent cases of up to 14 days [5, 32, 101]. The time between symptom onset in an individual and symptom onset in a second person infected by that individual also averages 6 days [13]. Viral shedding may antedate symptoms by 1–2 days, and viral titers are highest in the earliest phases of infection.

The duration of infectious viral shedding is controversial, primarily due to the ability to measure virus and/or virus particles in body fluids for long periods after the acute infection with sensitive techniques, such as polymerase chain reaction (PCR) [102, 103]. Yet, it is less clear whether these particles are infectious, and there are far fewer studies of viral shedding that relied on viral culture suggesting active virus. Even those few studies with viral culture results may not yield enough virus particles that are sufficient to provide an infectious dose [103].

A pooled study of 79 studies with 1,858 patients reported that pharyngeal virus shedding peaks prior to the onset of symptoms, averages 17 days, and lasts up to 83 days [104, 105]. The mean durations of viral shedding were 14 days in the lower respiratory tract, 16 days in stool, and 16 days in serum. Although replication-competent virus has not been isolated 3 weeks after symptom onset, recovered patients can continue to have SARS-CoV-2 RNA detected in their upper respiratory specimens for up to 12 weeks [106-108]. Further study of 285 “persistently positive” persons, which included 126 persons who had developed recurrent symptoms, found no secondary infections among 790 contacts attributable to contact with these case patients. Efforts to isolate replication-competent virus from 108 of these case patients were unsuccessful, suggesting a lack of viable virus [106]. No study detected live virus beyond the ninth day [104]. These findings contrast with those of MERS and SARS, which peaked after symptom onset and lasted for shorter durations.

There are some case reports of re-infections [109-111], which include a few cases with a different genomic COVID-19 strain [112-114]. However, whether these cases represent true reinfection or reactivation is unclear [109, 115, 116]. In a few cases, the purported second apparent infection was more severe [117]; in others, it was less severe or even asymptomatic [118].

Clinical Presentation

There are at least six distinct types or clinical presentations of COVID-19’s SARS-CoV-2 virus infections, the first and third of which incur no healthcare visits; pre-symptomatic individuals may or may not incur healthcare visits [13]:

1. Asymptomatic
2. Pre-symptomatic
3. Mild, subclinical infection (e.g., mild rhinorrhea)

4. Upper respiratory tract infection (URI), which also may include gastrointestinal symptoms
5. Lower respiratory tract infection, including pneumonia
6. Acute respiratory distress syndrome (ARDS)

Treatments differ for each presentation (see Treatment section for more details).

Symptoms and Signs

The symptoms of COVID-19 vary but are generally typical of respiratory infections, such as fever and cough. COVID-19 symptoms may include the following [32, 119-122]:

- Fever (low or high grade; 80–88%)
- Dry cough (63–69%) [5, 123]
- Loss of appetite (39–84%) [124]
- Fatigue (38–46%)
- Sputum production (33–42%)
- Chest pain or pressure (28–36%)
- Dyspnea (shortness of breath) (19–35%)
- Myalgia and/or arthralgia (muscle and joint pain; 15–33%)
- Sore throat (12–14%)
- Headache (11–15%)
- Chills (6–11%)
- Nausea or vomiting (5–10%)
- Diarrhea (4–29%) [124]
- Nasal congestion (4–5%)
- Abdominal pain (4%)
- Conjunctivitis (pink eye; 1%) [125]
- Hemoptysis (1%)
- Rhinorrhea (runny nose)
- Anosmia and dysgeusia (loss of smell and taste; 85% moderate/severe or anosmic) [126]

Severity of disease may be related to the inoculation dose [127]. The wearing of masks has been theorized to increase the proportion of asymptomatic cases by lowering that inoculation dose [127, 128].

Cardiovascular symptoms and signs may also be noted on initial presentation [129-134]. Immunothrombotic dysregulation associated with COVID-19 pneumonia has been described [135]. Coagulopathy associated with antiphospholipid antibodies and multiple infarcts have been reported [136, 137]. Seizures have been reported as a presenting disorder [138]. Young and old patients have presented with large-vessel strokes as an initial manifestation of COVID-19 infection [138, 139]. Among ICU patients, 31–59% of patients incurred venous or arterial thromboembolic event(s) [140, 141], compared with 10–25% of patients hospitalized for other

reasons [141, 142]. Recovering competitive athletes also have been found to have cardiac abnormalities on magnetic resonance imaging (MRI) [143].

Dermatological abnormalities such as urticaria, vasculitides, and pityriasis rosea have been described [144-147]. The most common dermatological presentations have been polymorphic and erythematous, chilblain-like, and urticarial lesions [148]. Various neurological and psychiatric presentations including stroke-like symptoms, altered mental status, dementia-like syndromes, and new or recurrent affective disorders have been reported [149-156]. Although the prevalence of direct kidney involvement in COVID-19 disease ranges from 3 to 15%, it is a marker for multiple organ failure and severe disease [157]. Acute kidney injury is thought to be triggered by a cytokine storm. In addition, the ACE2 receptor, essential for viral uptake, is highly expressed on podocytes and tubule epithelial cells. Albuminuria and hematuria have been detected in COVID-19 infection [158], along with the isolation of viral RNA from urine [159]. Most (71%) of those who die from COVID-19 have findings consistent with disseminated intravascular coagulation [160].

Because the symptoms for most patients are typical of nonspecific respiratory tract infections, they can be difficult to distinguish from other diseases [161, 162]. The disease commonly begins with mild symptoms for several days, which may readily facilitate its spread to other individuals. A minority of patients then develop more severe symptoms and may require ICU care [163]. This appears to be most common at days 4–7 after symptom onset. These more severe cases of COVID-19 involve additional symptoms that typically accompany pneumonia, such as shortness of breath. Respiratory problems may further progress to severe dyspnea, require oxygen supplementation, and develop into acute respiratory distress syndrome (ARDS). Patients with pneumonia may have tissue hypoxia, tachypnea, tachycardia, and crackles on chest examination. Severe cases may present with shock and respiratory failure. The hallmarks of COVID-19 infection on thoracic imaging have been bilateral and peripheral ground-glass and consolidative pulmonary opacities [164].

The virus infection may also cause no symptoms; however, asymptomatic and pre-symptomatic individuals may still pass the virus to others, who may then develop symptoms [12, 163, 165]. The CDC estimates that 40–45% of transmission occurs prior to symptom onset and that the infectiousness is comparable between asymptomatic and symptomatic individuals [12, 13]. Children tend to be asymptomatic or have milder symptoms, which suggests a mechanism that may accelerate disease transmission throughout the population [163], although this is not proven. It is also possible that the immune system of most children effectively detects the virus with resultant lower average viral loads and thus contagion; however, nasopharyngeal viral loads are not well correlated, whereas saliva viral loads have been correlated with severity [166, 167]. Regardless, one-third of hospitalized children require ICU stays [168]. A pediatric multisystem inflammatory syndrome also has been reported in children who presented with persistent fever and features of Kawasaki disease or toxic shock. Most of those patients tested positive for the COVID-19 virus or for antibodies to the virus, suggesting a post-infection immune response. None of the children have died, but several have required mechanical ventilation [169].

Mortality

The mortality rate for COVID-19 has changed considerably over the course of the epidemic, being much lower more recently [170]. The mortality of COVID-19 was estimated to be approximately 10-fold higher than that of typical seasonal influenza [171]. Subsequently, severity estimates have been reported as low enough to be comparable with prior influenza epidemics [87, 172-174], with a range of infection fatality rates of 0.03–0.5% and corrected rates of 0.02–0.4% [175]. More recently, the CDC estimated the overall *symptomatic* case fatality ratio is 0.004, or 1 in 250 [13]. Using the CDC estimate of 83.1 million infections and the overall COVID mortality of 503,587 [176], the overall case fatality rate over the duration of the pandemic in the United States would be approximately 1 in 165. Mortality can be predicted based on risk factors and clinical findings on presentation [177].

Mortality risks increase sharply with age, with a symptomatic case fatality ratio of 1 in 2000 among those 0–49 years of age, 1 in 500 among those 50–64 years of age, and 1 in 77 among those 65+ years of age [13]. The mortality rate for males is 57–64% higher than that for females. Nursing home residence is a particularly potent fatality risk [178-182]. The risk of severe disease and/or death is also correlated with other underlying conditions, such as heart disease, hypertension, diabetes mellitus, chronic renal disease, dialysis, liver disease, chronic obstructive pulmonary disease (COPD), smoking, and obesity [41, 183-188]; however, approximately 1% of fatalities occur in previously healthy patients [189]. Genetic susceptibility (i.e., 3p21.31 gene cluster) has been reported in a large genome-wide association study, along with a 45% increased risk among those with type A blood [190]. Past outbreaks of coronavirus infections had considerably higher mortality rates: 34% for MERS and 10% for SARS. However, the mortality rate is not the only factor in determining the seriousness of a disease; a high rate of infectivity and/or easy transmissibility could result in many more total deaths despite a lower case fatality rate.

Business Considerations

The actions an employer can take to mitigate the risk of COVID-19 infection center primarily on the virus's potential airborne respiratory and secondarily on contact spread. There are multiple domains for an employer's actions. Please see the following sections on:

1. Employee issues (e.g., education and medical surveillance)
2. Travel issues
3. Physical distancing methods
4. Personal protective equipment (e.g., respirators, masks, gloves, face shields)
5. Ventilation issues
6. Disinfection practices and contact spread measures
7. Policies and procedures
8. Industry-specific recommendations

The education of workers in each of these areas is advised as appropriate.

A business with broad geographic interests may also wish to incorporate geographic-specific risks. This is particularly true given that the current vaccination rates vary more than 100-fold

across the globe [191], and it can be anticipated that differences by northern/southern hemisphere and other environmental issues (i.e., heat, humidity, UV, use of air conditioning) will persist. McKinsey suggested risks for a given jurisdiction should be related to four metrics assessing the strength of test, trace, and quarantine efforts (adapted from [192]):

1. *Test positivity rate*, a measure of testing systems' abilities to capture all cases. The World Health Organization recommends a target of <10% positivity.
2. *Tests per million population,* a measure of the depth of testing.
3. *Average number of contacts identified per case,* a measure of how effective contact-tracing systems are at identifying and isolating the likely next generation of cases. The figures are expected to trend lower in lockdown settings than when people are moving and interacting freely.
4. *Fraction of cases arising from contact lists,* a measure of the portion of cases arising from known sources versus undetected community transmission.

(*Note*: It is recommended to check for current guidance from the Centers for Disease Control and Prevention.)

Employee Issues

COVID-19 Vaccination

Employers are recommended to strongly encourage vaccination of their entire workforce at the earliest date (see also Vaccination recommendations). The CDC has produced many publications to support these efforts [193, 194]. States are implementing markedly different vaccination prioritizations (e.g., CDC/ACIP prioritizations based on susceptibilities and select workforces [195] vs. age-based only) with different administration strategies (mass vaccination sites vs. pharmacy-based vs. healthcare-based vs. combinations), and at considerably different success rates (which range by more than 2-fold) [196]. Communication to employees regarding their eligibility is recommended. Encouraging household member vaccination also is recommended, as it helps protect the workforce. Other considerations include facilitation of vaccination appointments for workers (e.g., computers at the worksite to access scheduling platforms) and hosting on-site vaccination clinics.

Until there is evidence herd immunity has been achieved, the CDC recommends that masking be continued [197]. If there is a possible or confirmed COVID exposure to a fully vaccinated worker who is between 2 weeks after and not more than 90 days after their second immunization, quarantining is no longer required [198].

COVID-19 surveillance

Employers are recommended to have implemented a surveillance system that continues to include education and screening to avoid having workers with potential asymptomatic, early,

and/or symptomatic but subclinical COVID symptoms enter the workplace premises. Options for larger employers and/or jobs with greater risks (e.g., mission-critical jobs; a workforce where one ill worker could infect an essential group of workers, which would shut down the workplace at least until herd immunity is largely achieved) include daily/periodic electronic questionnaires with or without temperature measurements. Electronic questionnaires are likely to be more effective than temperature measurements because 69% of seriously ill individuals are afebrile [199]; temperature measurements are also likely to miss all subclinical and many symptomatic cases [13]. Diagnostic testing should be performed on those with symptoms, most commonly through the local healthcare or public health systems. Diagnostic testing may also be performed to ascertain asymptomatic spread, especially among essential workers. Testing daily or every few days has been increasingly used in some workplaces and among mission-critical workers. However, testing without experienced medical judgment is ill-advised because the false-negative rates are reportedly 20–67% [32]; thus, cases with high indices of clinical suspicion should typically be treated as presumptive cases [32]. Considerations also include providing communications and expectations to subcontractors, suppliers, and others who may have significant interactions with the employer (e.g., assurance of policies to address symptomatic employees, surveillance).

Employees with possible COVID symptoms

Sick employees (including those with minimal symptoms) should stay home from work, as it is important to eliminate all contact between the healthy workers in the workplace and anyone with potentially infectious symptoms [200]. If there is believed to be SARS-CoV-2 virus transmission in the area (currently true of essentially all US urban and many rural areas, although the rates are now decreasing markedly), then anyone with even mild symptoms of a respiratory tract infection (e.g., cough, fever, fatigue) should stay home to be sure they do not progress to a clear, and potentially severe, COVID-19 infection [163], as well as to prevent transmission to others. Sick employees should also be encouraged to undergo testing if available. They should be instructed to call a provider or healthcare organization in advance, discuss the symptoms, seek testing if available (especially at outdoor tents), and wear a mask in public settings.

Any questions about potential COVID-19 infections should be directed to the local health department, which has the expertise and personnel to investigate outbreaks and perform contact tracings (provided they are not overwhelmed by the current epidemic). It is important to recognize that return-to-work recommendations for essential workers, especially healthcare workers including volunteers, may need to be modified during the course of the epidemic for practical reasons in response to acute workforce shortages in key jobs and sectors.

CDC recommendations for healthcare workers have been revised to address the removal of exposed workers who had relatively low risks for conversion during potential incubation periods, as it affected the capacity for patient care [201]. Current guidance includes the following [201, 202]:

- A symptom-based strategy should be used for PCR or antigen-confirmed symptomatic workers, who are recommended to be excluded from work until there has been at least 1 day since resolution of fever (without use of medication), other symptoms have improved, and at least 10 days since the symptoms first appeared. For those with severe illness and/or immunocompromised state, there should be at least 20 days since symptom onset, and consultation with an infectious disease expert is advised.
- A time-based strategy should be used for PCR- or antigen-confirmed but asymptomatic employees, who are recommended to be excluded from work for 10 days following the positive test result.
- A test-based strategy is no longer recommended as the basis of a return to the workplace, other than to discontinue isolation or other precautions earlier than would occur under the symptom-based strategy above. This strategy requires negative PCR or antigen tests on at least 2 consecutive respiratory specimens collected at least 24 hours apart.

Readers are advised to refer to current CDC guidance, as this changes frequently [203]. It is also advisable for a healthcare employer to consider factors including staffing needs, infection rates, and individualized assessment of the degree of that person's contact with susceptible patients (especially those with comorbidities). Furthermore, it is advisable that the other CDC guidance be followed [201, 202]. Depending on those factors, more conservative or more liberal return-to-work timeframes may be advisable to balance the risks of infecting patients with the ability to staff and care for patients.

What to do if an employee tests positive for COVID-19

The sick employee should follow current CDC guidelines in conjunction with local health department guidance, including isolating at home (if able). A symptom-based approach recommends recording temperatures twice daily until at least 24 hours have passed without fever or treatment with any fever-reducing medications. In order to leave isolation, it is advised that a minimum of 10 days have passed since the onset of symptoms, with then at least 1 day of no fever and improvement in other symptoms. A testing-based approach requires two negative PCR (or antigen) viral tests obtained at least 24 hours apart if there is a need for a shorter waiting time. Otherwise, testing to return to work is not recommended as viral particles (which may not be infectious) can persist for 90 days after acute infection. The areas where the sick employee worked, including conference rooms and common areas, should undergo deep cleaning and decontamination to prevent spread to other employees. Coordination with the local health department's contact tracing efforts is generally essential, and the employer is frequently able to augment and assist with those efforts.

Employees in contact with an infected coworker

If a fully vaccinated worker who is between 2 weeks after the second immunization and 90 days after immunization is exposed to a known/suspected case, quarantine is no longer advised by the CDC [198]. Otherwise, employees in contact with an infected coworker should continue to

undergo medical screening. Close contacts are defined as any individual who was within 6 feet for 15 cumulative minutes over 24 hours starting from 2 days before symptoms onset [204, 205]. Risk assessment should include the duration of contact with the sick employee, whether they were using any personal protective equipment, and the type of personal protective equipment used (e.g., cloth face covering vs. respirator) [206]. The employer should attempt to maintain confidentiality regarding an ill employee's identity. Employers may wish to apply more or less restrictive policies depending on their individual business requirements, organizational characteristics (e.g., closeness and numbers of other workers), and risk tolerances. For higher-risk exposures with greater business considerations (e.g., mission-critical workers), the most conservative approach is to have employees who could be in the incubation stage self-quarantine and work from home for at least 10 days; they may then be released with monitoring of symptoms until day 14 after the possible exposure. If there is an absence of symptoms, another option is to quarantine for 7 days; with a negative test on day 5 or later, the person may be released on day 8 with ongoing monitoring until day 14 [207, 208]. The CDC has changed their quarantine recommendations for exposed but asymptomatic workers to 10 days, or 7 days with a negative PCR test after a minimum of 5 days.

In certain manpower shortage situations, medical centers, and critical services, COVID-19 exposed workers are being allowed to work while asymptomatic with self-surveillance for symptoms, physical distancing, disinfection of workspaces, and consistent mask-wearing instead of being quarantined [209]. This option is controversial and not without considerable risks because pre-symptomatic spread is believed to be a primary source of epidemic spread. This option should be carefully weighed between the industry sector, criticality of the job, job requirements, and risks of an infectious individual in that particular workplace. This option is likely unduly risky if the workforce or work group is mission critical.

High-Risk Employee Issues

For the purposes of these recommendations, high-risk individuals have any of the following conditions [199, 210]:

- Age 65 years and older
- Chronic lung disease, including moderate to severe asthma
- Serious heart condition (e.g., history of heart attack or heart failure)
- Immunocompromised (e.g., having had bone marrow or organ transplantation, immune deficiencies, poorly controlled HIV or AIDS; using corticosteroids or other immune-modulating medications; undergoing cancer treatment)
- Smoking, current or former
- Obesity, especially severe [183]
- Diabetes mellitus
- Chronic kidney disease, especially those undergoing dialysis
- Liver disease
- Hypertension
- Current cancer
- Neurological diseases, including stroke and dementia

Generally, the risks of severe illness associated with the above conditions are greater as the severity of the conditions increase. The presence of multiple conditions increases the risk of severe disease [211].

Employers should attempt to reduce exposures to higher-risk situations for workers who self-identify as high-risk, while being cognizant of the implications of the Americans with Disabilities Act and amendments. A full- or part-time medical director and medical department may help to interface between the worker and management to effect these risk assessments and potential risk reductions. Examples of reductions in exposure (beyond electronic questionnaires with or without temperature checks) include the following:

- Emphasize distance-based work methods, including telecommuting where feasible.
- Place all, but especially high-risk, individuals behind barriers.
- Institute physical distancing [212].
- Reduce public-facing work.
- Use personal protective equipment (PPE) to protect from exposure.
- Use masks; evidence that masks prevent transmission is accruing [212-221]. Randomized controlled trials have not shown differences between the effectiveness of masks and respirators for preventing influenza [222-225]; however, some studies have been critiqued for power and unclear effects of outside influenza vaccination. A longitudinal pre/post interventional study reported 67% lower COVID tests among healthcare workers after masking compared with before masking [226].
- Use respirators, especially for higher exposure risks and for those with higher risks of severe disease. Evidence has suggested a surgical mask is equally effective as an N95 respirator for prevention of influenza.
- Consider placing high-risk individuals closer to ventilation that provides fresh air.
- Regularly disinfect surfaces.

Some educational videos help to demonstrate significant reductions in droplets with the use of a mask [227]. Other training videos help illustrate potential transmission by contact spread and donning/doffing masks [228]. A recent study compared face mask efficacy for filtering expelled droplets during speech. A fitted N95 respirator was the most efficient, but 3-layer surgical masks, cotton-polypropylene-cotton 3-layer masks, 2-layer polypropylene apron masks, and 2-layer cotton pleated-style masks were nearly as effective at reducing relative droplet transmission through the mask [229]. A low-cost, low-tech method to assess facemask efficacy has been reported [229].

Travel Issues

Travel risks include those associated with travel to and from a site, as well as business conducted at those sites [230]. Risks differ considerably by mode of transportation, geographic locations, current state of the epidemic in any given locale, and vaccination rates. Businesses need to weigh the value of the travel against the risks associated with that travel.

Fully vaccinated employees may reasonably travel. For non-vaccinated employees, travel valuations should include costs associated with any potential illness and any post-trip quarantine period. Caution is advised for non-essential travel by non-vaccinated employees to locales with outbreaks or community spread in progress [230], which currently includes much of the United States (see map to help with other risk considerations: https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6) [231]. International trips are currently significantly affected as many countries are limiting travel from countries with outbreaks, although this is anticipated to change rapidly with the acquisition of herd immunity. Air travel may be safer than some other forms of travel [232], although the primary risks of air travel are more likely to be exposure risks at the destination, which may be challenging to control in non-vaccinated individuals by methods other than masking. As risks are now subsiding, travel to lower-risk locales is increasingly acceptable, although the destination country or region may not permit visits from countries or regions with high rates of viral transmission and/or may be slow to adapt to the rapidly changing risks. Mask or respirator use during air travel is advised, at least until herd immunity and lack of high community spread has been shown.

Employees returning from, or having traveled through, areas known to have COVID-19 infections

For non-vaccinated employees returning from personal or work-related travel to areas with community-based COVID-19 spread, the safest course of action is to self-quarantine while working from home for 2 weeks[§] and avoiding direct contact with other workers [101], especially for travel from higher-risk areas compared with travel by personal automobile to an unaffected rural area. If that worker becomes ill, he or she should promptly call a healthcare provider before appearing in a clinic or hospital (i.e., to arrange which entrance to use, wear a mask in public, and/or when needed, to be given an appropriate type of mask before entering the building). The person should also avoid all contact with other people.

Physical Distancing Methods

Physical distancing is believed to be one of the most effective control measures, particularly because it does not rely on training and compliance (e.g., as effective masking requires) [233]. The following are some physical distancing options to consider, especially for non-vaccinated personnel when there is ongoing community spread:

- Work from home when feasible to help improve physical distancing.
- Consider rotating workers between home and work settings to reduce workplace population densities while facilitating functions that are best performed at work.
- Improve physical distancing at work (e.g., increase distances between workers and workstations to a minimum of 6 feet, install temporary barriers, mark 6-foot distances on the floor between co-workers).

[§] See data above regarding outlier cases of >14 days for incubation. A company must weigh the risks vs. their risk tolerance. Four weeks is a safer course of action.

- Consider either physical spacing in cafeterias, closing cafeterias and offering individual prepackaged meals, using disposable packaging and utensils to avoid the potential for contamination before cleaning, and/or having workers eat their own food at their workstations.
- Where there are two options for walking through a workplace, set up one-way walkways.
- Reorganize shifts to spatially and temporally spread workers.
- Route shifts of workers to enter through one entrance and exit through a different one.
- Provide protection for those who interact with the general public (e.g., install temporary barriers to prevent respiratory transmission, install barriers to ensure physical distancing of 6+ feet).
- Consider discouraging carpooling and mass transit; encourage the use of masks if using either of those options (although a face mask in public places is now a requirement in many cities and states).
- Minimize reasons for external individuals and the public to enter a workplace (e.g., curbside deliveries, web-based meetings). If there are multiple options for meetings onsite, attempt to limit which rooms are used and have them cleaned after every use.

Personal Protective Equipment

PPE measures (respirators, masks, gloves, and eye protection/face shields [212, 234-238]) have been recommended to be used until there is further evidence that herd immunity has been achieved, but they are lower on the list of controls. Detailed tables are available from the World Health Organization [234, 235]. Currently, at least 16 states either never had or no longer have a statewide masking mandate [239] and thus far are without evidence of a resurgence of COVID cases. Regardless, resurgence is still possible, if not likely, at some point with a virus variant. Evidence suggests that PPE helped to slow the spread of the COVID-19 virus. The following options continue to be recommended, at least until herd immunity is shown:

- Healthy individuals should wear a face covering or mask when interacting with the public or other workers, as evidence suggests efficacy in preventing viral transmission [215]. Results from a natural experiment on the effects of state government mandates for face mask use in public places were accrued between April 8 and May 15, 2020. Mandating public face mask use was associated with declining daily COVID-19 infection rates, which decreased by 0.9% in the first 1–5 days after the mandate, and by 2% at 21 or more days after the mandate [240]. See also the section on Masking, below.
- There is strong evidence that the SARS-CoV-2 virus may be spread by asymptomatic and presymptomatic individuals [241, 242]. Infection risk from these individuals is also reduced by wearing masks.
- In terms of the kinds of masks/respirators recommended, the fitted N95 respirator is the most efficient at reducing relative droplet transmission through the mask. However, a 3-layer surgical mask, a cotton-polypropylene-cotton 3-layer mask, a 2-layer polypropylene apron mask, and a 2-layer cotton pleated style mask were nearly as effective [229]. Single-layer, non-cotton clothing (e.g., gaiters and some bandanas) are least effective and should be discouraged if better options for masking are available. A

randomized controlled trial (RCT) in Denmark suggested minimal efficacy of a mask added to other public health measures [243].

- Use of N95 respirators with exhalation valves is generally not recommended due to theoretical exposure to other individuals.
- Use face shields, especially where there is potential for human-related splashes or droplet exposures, and with aerosol-generating procedures. However, a face shield should be combined with a mask as a face shield has not been shown to be sufficiently protective.
- Follow OSHA guidance regarding requirements for fit testing of respirators and to assure proper use, donning, and doffing [244, 245].
- Appropriate PPE for cleaning and disinfecting a workspace contaminated by the virus is thought to normally be a face mask and gloves. If there are increased concerns about aerosols (e.g., an infected worker was in the room, especially with bronchoscopy, suctioning, sputum induction), an option may be to leave the room overnight before cleaning and disinfecting it; otherwise, an N95 respirator would ideally be recommended (P100 is not an appropriate mask for these purposes).

Reuse, Extended Use, and Reprocessing of Respirators

The pandemic initially caused demands on all types of PPE far beyond manufacturing capacities, which has been subsequently alleviated. Differences in management by sector (i.e., healthcare vs. general) was proposed. Accordingly, protocols were developed for reuse, extended use, and reprocessing of respirators [246, 247], including the following:

- It has been recommended that reuse, extended use, and reprocessing of respirators be reserved for situations where their use is indispensable.
- Nevertheless, respirators should be discarded after procedures at high risk of contamination (e.g., aerosol-generating), when contaminated, when defective, or when no longer functioning properly.
- Extended use of respirators typically involves up to 6–8 hours of use time. The respirator should still be able to make a tight seal and the mask should not be wet or damaged [246].
- Extended use has been advised over reuse as reuse also involves handling of a potentially contaminated respirator. This is facilitated by co-location of COVID-19 patients.
    - Extended-use risks include contamination by touching the respirator, dermatitis, respiratory fatigue, impaired work capacity, increased O_2 debt, earlier exhaustion at light workloads, elevated CO_2 levels, and increased non-compliance with best practices [246].
- The CDC's reuse protocol involves supplying each worker with the number of N95 respirators that they need for an upcoming week's work, then reusing a respirator up to 7 days later [247].
    - A face shield is recommended to reduce the probability of respirator contamination.
    - Storage in a paper bag is advised.

    - Paper bags should be clearly marked.
    - Handwashing and handling should be done with care to avoid contamination, especially during doffing.
- Reprocessing systems involve sterilization with the following: saturated steam, UV light, gas plasma, and vaporized hydrogen peroxide. Reprocessing should follow protocols, be carefully monitored, and be matched to the type of respirator, which can differ due to factors such as the process degrading the efficiency of the respirator.

Ventilation Issues

Ventilation issues (general and local supply of fresh air) have been markedly underutilized as potential COVID controls [248-252]. This issue also has potentially major implications for the future reduction in other epidemics, such as influenza or resurgences of COVID-19. Consultation with an HVAC expert may be helpful. Area ventilation can provide a relatively safe zone for workers. The following general ventilation measures can be used to dilute viral concentrations:

- Identify the number of air exchanges per hour (ACH) in the room.
- Increase ACH in work areas. The number of necessary ACH depends upon occupancy of the area and the purposes for which the area is used (e.g., more ACH in healthcare or crowded areas than in sparsely populated warehouses).
- Assure homogeneity of airflow to avoid "dead spots" and short-circuiting from air supply to exhaust.
- Run the ventilation system as many hours as possible.
- Increase the proportion of fresh (rather than recirculated) air.
- Filter and/or disinfect the air.
- Use effective filters in the HVAC system. HEPA filters are optimal, but some ventilation systems cannot effectively overcome their added resistance. A minimum filtration efficiency rated at least MERV 13 should be used [253, 254].
- Air disinfection, such as ultraviolet germicidal irradiation, can be placed within the central HVAC system [251, 254]. Use portable air cleaners and local exhaust.
- Local standalone HEPA filtration in high-risk areas may be potentially helpful for risk mitigation.
- Fans and other airflow and/or filtration devices may be used to control the direction of airflow from clean to potentially contaminated areas. Where possible, consider using portable air purification systems for small work areas.

Disinfection Practices and Contact Spread Measures

Ventilation and other control measures addressing droplets and microdroplets are far more important than disinfection of surfaces for COVID-19 [255]. Disinfection of surfaces may have some limited role in reducing spread. The following disinfection practices may be helpful:

- Train staff on how to disinfect workplaces.

- Disinfect commonly touched worksite surfaces daily. Consider cleaning commonly used select surfaces handled by non-gloved workers between shifts (e.g., machine controls).
- Consider propping open bathroom and other doors to reduce handling or touching.
- Avoid shared equipment when possible (e.g., keyboards), and clean common surfaces between shifts or between worker usage.
- Disinfect surfaces with an EPA-approved virucidal agent and follow manufacturer's instructions for use. Reports include agents containing 62–71% ethanol, 0.5% hydrogen peroxide, and 0.1% sodium hypochlorite for at least 1 minute [90], although some agents will require longer contact times. It is important to allow sufficient time for disinfecting agents to work, and directions should be carefully followed. The CDC has a list of disinfecting agents and the EPA has a list of products active against human coronavirus, with recommendations for the duration of contact time [256].
- Encourage frequent hand hygiene (handwashing or use of alcohol-based hand disinfectants) with appropriate techniques [257].
- Provide ample hand sanitizer and hand-sanitizer stations throughout the worksite.

Policies and Procedures

The following are potential policies and procedures to consider:

- Inform and seek support and authorization for the plan from the organization's leadership.
- Develop a plan in conjunction with occupational health and safety professionals, government regulations, and public health authorities (including the CDC).
- Ensure affected workers have sufficient paid leave to observe a quarantine period or are able to stay home as indicated.
- Continue to monitor sickness absence, but expand sick leave provisions to allow employees to stay at home if ill and to care for sick family members.
- Educate and place posters throughout workplace to remind employees to avoid touching their eyes, nose, and/or mouth with unwashed hands (e.g., CDC poster).
- Teach workers to use tissues to catch a cough or sneeze, then throw that tissue away and wash their hands.
- Avoid scheduled aggregate meetings and encourage physical distancing within group settings, ideally a distance of at least 6 feet. Encourage use of teleconferences and/or other virtual meeting formats.
- Consider instituting required daily electronic symptom trackers with an automated management system for all employees to report symptoms of COVID-19 infection, including fever, cough, shortness of breath, myalgias, abdominal discomfort, and diarrhea. Responses should be monitored daily by the medical department or health and safety [258-261].
- If daily symptom tracking is not instituted, encourage early reporting of any symptoms consistent with COVID-19 to the medical department, designated employer representative, and/or supervisor, following the company's established policies. It is preferable to preclude all symptomatic workers, including those who are mildly symptomatic, from physically entering all workplaces; electronic questionnaires may be

useful to facilitate this. Place posters prominently to help remind workers of procedures (e.g., CDC posters).

- Have employees who develop symptoms stay away from the workplace until clinically evaluated and/or until the symptoms are resolved and any quarantining period has expired.
- Consider having employees who could be in the incubation stage work from home for at least 2 weeks after the possible exposure.
- In certain manpower shortage situations, medical centers and critical service workers are being allowed to work while asymptomatic with twice-daily temperature checks, self-surveillance for symptoms, and consistent mask-wearing instead of being quarantined for 14 days. However, this has some residual risks of transmission and may not be compatible with mission-critical operations (e.g., dispatch center, air traffic control tower).
- If there is a confirmed case in your workplace, have the worker identify his or her most common contacts in collaboration with public health officials while attempting to maintain confidentiality. Using business risk tolerance procedures, identify whether any further actions are required other than increased monitoring (see above) and increased cleaning and disinfection of commonly used areas.
- Antibody testing is now widely available, but the sensitivity and specificity vary greatly between kits (see Diagnostic Testing). Their usefulness is limited in areas where the prevalence of disease is around 1 to 3%; in this setting and even with 95% specificity, the majority of positive tests will be false positives. With further validation, antibody testing may likely become useful in assessing possible susceptibility to infection versus protective response to prior infection. Currently, however, antibody testing is not able to provide that information and cannot be reliably used for that purpose. In the future, COVID-19 serology can determine infection risk in critical and susceptible populations (under medical direction to ensure proper implementation, interpretation, and management). Examples of these critical populations include employees in health care settings, oil drilling platforms, commercial maritime, food preparation, cruise lines, airlines, and assembly lines with workforces working closely together.
- Provide proactive assistance to support mental health for the workforce.
- Identify and train workplace coordinators who will be responsible for implementing and monitoring the plan.

Industry-Specific Recommendations

Below are select industry guidelines, which are in addition to the general guidance above. These guidelines assume lack of herd immunity and/or ongoing community-based spread. Further guidance is available from the CDC [253].

Restaurants

- Provide physical distancing between tables. Be alert to local ventilation issues that may cause downwind exposures beyond 6 feet.
- Barriers between tables allow for seating closer than 6 feet.

- Outdoor seating may allow distancing that is closer than 6 feet.
- Menus should be either disposable or laminated and sanitized after each customer contact. Other options are electronic access and use of QR codes.
- Clean and disinfect chairs and tables after each customer use (see Disinfection Practices).
- Assign high-risk employees with multiple co-morbidities or concerns to low-exposure areas, such as working in non-customer-facing areas as much as possible.
- Wear protective masks.
- When possible, designate non-high-risk employees to bus tables.
- Housekeeping in public areas should ideally be performed by lower-risk employees.
- Encourage drive-through and carryout options to promote physical distancing.

Retail

- When possible, preferentially assign low-risk employees to cashiering and other customer-facing work.
- Stocking by high-risk individuals should ideally be done when customers are not present.
- Returns that cannot be disinfected should best be handled by low-risk employees.
- Clothing from dressing rooms should ideally be restocked by low-risk employees.
- Housekeeping in public areas should ideally be assigned to lower-risk employees.
- Limit total number of customers within enclosed dwellings or structures at one time to allow for physical distancing.
- Encourage customers to use personal respiratory protection and provide PPE to customers where feasible.

Hospitality

- Eliminate handling of luggage and other customer items.
- Valet services should be provided by lower-risk employees if possible.
- Room keys should be disinfected between employee and customer usage.
- Housekeeping in public areas should ideally be assigned to lower-risk employees.

Personal Services (hair, tattoo, nail salons)

- Use physical barriers where possible.
- Employees should use aprons, gloves, eye, and face protection in addition to protective masks.

Home Repair

- Where clothing may be potentially contaminated from SARS-CoV-2, protective coverings (e.g., Tyvek or disposable smocks) should be worn to protect clothing from surface exposure.

Gyms

- Locker room and gym housekeeping should ideally be performed by low-risk employees.
- Towel service and other laundry should ideally be handled by low-risk employees.
- Disinfect equipment between patrons.
- Housekeeping in public areas should be assigned to lower-risk employees.
- Saunas and steam rooms should be limited in use and ideally cleaned only by low-risk employees.

Construction

- Assure cleanliness and frequent cleaning and disinfection of portable restrooms.
- Face coverings should be used when performing maneuvers that require close contact with co-workers or within confined spaces.
- Avoid sharing tools or disinfect between users.
- Reduce unnecessary shared rides; disinfect heavy equipment cabs between operators.
- Designate a COVID-19 coordinator for large jobsites, with the responsibility to coordinate prevention efforts for all contractors, subcontractors, and crafts on site.
- Provide handwashing or issue hand sanitizer to be used for donning/doffing respiratory PPE.

Manufacturing

- Install physical barriers when physical distancing is not possible.
- Evaluate ventilation measures (see above)

Food Production Facilities

Meat and poultry processing facilities have been hot spots of virus infection due to structural and socioeconomic challenges. Difficulties to overcome include workers speaking many different primary languages, an incentive to work while ill as a result of limited medical leave and disability policies, and attendance bonuses that could encourage working while sick. At home, many workers live in crowded, multigenerational settings and may share transportation to and from work, increasing risk for transmission of disease [262]. Recommended potential changes in facility practice include the following:

- Adjust start and stop times of breaks and shifts; add outdoor breakrooms. Avoid en masse movements of workers.
- Install physical barriers between workers.
- Screen all workers and visitors; isolate workers who become ill at work.
- Require universal face coverings and provide training on donning and doffing PPE.
- Assign additional staff to sanitize high-touch areas.
- Add hand-sanitizer dispensers and handwashing stations.
- Develop culturally informed messaging.
- Include messaging about behaviors to limit spread of virus at home.
- Add additional vehicles to shuttle routes.
- Provide additional medical leave and disability benefits; remove attendance bonuses.

More details regarding business concerns are available from the CDC [253].

Schools

Schools have high human population densities. However, extensive data show that children have the lowest risk of symptomatic, severe, and/or fatal COVID-19 disease across the lifespan, with the risks appearing to be lowest in the youngest school-age children [120, 263, 264]. Data to explain these observations are sparse; theories include that children have relative lymphocytosis, superior immunity to coronaviruses, and an ACE2 receptor (to which the virus binds to gain entry) that is inadequately developed in their airways [265, 266]. Initial reports that children do not become infected appear increasingly dubious [267]; however, that they are resilient to symptomatic and/or severe disease is not in question.

Schools in most countries were at least temporarily closed in spring 2020 in response to the pandemic. However, students' learning by distance-based methods has been reportedly suboptimal and sometimes poor. The burden of the inability to educate students using traditional methods also disproportionately falls on the poor and immigrant populations, which have fewer skills and resources to educate and/or guide their children's learning [268-272]. For example, increases in computer search intensity for school-centered resources in higher socioeconomic US regions were double those of lower socioeconomic status regions in April 2020 compared with 2015–2020 [270]. A 5-month global shutdown of schools has been estimated to have had an adverse worldwide impact, with a loss of $10 trillion of lifecycle earning for the 1 billion affected students because of lower levels of learning, lost months, or dropping out of school [273]. Schools also play important roles in students' social development and mental health [274-276].

Restarting of schools has been controversial and widely divergent strategies have been deployed. Nearly all reports have suggested few problems with most re-openings in Belgium, Denmark, Finland, France, Japan, Norway, Germany, Quebec, Singapore, South Korea, and Sweden; these reports have also included some opening without physical distancing, masking, alternate school schedules, or other mitigations [277]. The main contrary example is Israel, where school-based transmission to teachers was briefly problematic [278, 279]. However, this exception may have been due to very hot weather, which led many to stop wearing masks and close windows. The many successful countries also have had generally lower rates of transmission when the schools (re)opened; thus, the implications and safety of schools reopening may not be readily applied to many US states or other geographic regions with ongoing significant community spread. Alternatively, areas having had sufficient community spread may have attained some degree of herd immunity.

The CDC has developed sets of guidance for schools [280-285], which include decision logic for (re)opening schools [280]. Others have recommended a combination of ventilation and mask use [286, 287]. This ACOEM guideline primarily addresses the protection of teachers/staff (see also Appendix A). Student-related guidance has been recommended by the CDC to be summarized in policies and briefly includes the following: (1) wearing face protection, (2) physical distancing, (3) washing hands and other personal hygiene measures, (4) cohorting of

students, (5) regular cleaning and disinfection, and (6) removing those students infected with COVID [288]. Regardless of community transmission levels, the CDC recommends that all elementary school students can remain 3 feet apart in classrooms where mask use is universal; middle and high school students can also remain at least 3 feet apart in classrooms where mask use is universal and in communities where transmission is low, moderate, or substantial. Where community transmission is high, middle and high school students should be at least 6 feet apart if cohorting is not possible. Face shields have not been recommended for children [288], and face shields without masks have not been shown to be sufficiently preventive. However, in situations where compliance is an issue, face shields may be a reasonable alternative, although use with a mask (especially a clear mask) may be an option. Face shields are suggested for teachers, particularly for teachers of younger age groups where development depends on social queuing.

Cloth face coverings are recommended and are classified as “may be considered” for other more dispersed seating arrangements, as well as for during recess, music classes, physical education (vigorous exercise is not advised if in a confined space), mealtime, among children under 2 years of age, and for students who are deaf, are hard of hearing, and/or use lip-reading in communicating. Universal symptom screening of students is not recommended, although preclusion of attendance if symptoms develop is advised [288]. It is advised to identify an isolation room for those who develop COVID-like symptoms at school [282]. While CDC guidance for teachers is limited, the CDC does not recommend universal testing of students and staff [282]. Yet, many schools have instituted such testing protocols. A universal testing or sampling strategy may be helpful in identifying asymptomatic students and staff with COVID-19, allowing isolation of COVID-19-positive individuals to prevent transmission; such an approach could also guide school administration in monitoring the number of cases to inform decision making.

Teachers may be protected using methods that are somewhat similar to other adults. These methods should be administratively coordinated, and policies and procedures should be developed and enforced. Teachers should undergo daily symptom screening when working (e.g., electronic survey). As with all individuals, those with symptoms consistent with COVID-19 should be tested, although there is risk of false-negative results. Symptomatic, presumptively positive teachers should be isolated for 10 days. Contact tracing of positive cases should be performed, and contacts should be quarantined for up to 14 days. Symptomatic contacts should be tested.

The administrative options for students discussed previously (e.g., cohorting, physical distancing, masking) should reduce teachers’ risk of disease. Other options for protecting teachers include universal masking, N95 respirators for those with comorbidities (if available), face shields, physical distancing between the teacher and students, shielding around the teacher’s desk, and fully remote teaching for those with the highest degrees of risks/comorbidities.

Security and administrative personnel should follow similar protocols to those of the teachers. These include daily electronic symptoms screening, physical distancing, mask use, and glove use for security personnel. As the epidemic waxes and wanes, it is helpful to have pre-planned policies and procedures that may administratively and readily become more or less restrictive as determined by community rates of disease. For example, with greater COVID-19 incidence rates, learning could move to more distance-based teaching methods. Table 1 provides an example matrix for adaptive implementation and relaxation of restrictions in schools for the protection of teachers.

Table 1. Adaptive Matrix for Implementation and Relaxation of Restrictions in Schools*

	Green (no or minimal community spread; <5%)	**Yellow (sporadic or low-level community spread; 5–10%)**	**Red (widespread, uncontrolled community spread; >10%)**
Teacher age			
<40 years, no comorbidities**	No mask	Mask	Mask
40-65 years	No mask	Mask	Mask
>65 years	No mask	Mask	Respirator (N95 respirator if available; mask if unavailable). Consider co-use of face shield for multiple co-morbidities, or a face shield when also remote teaching.
Comorbidities*	No mask	Respirator (N95 respirator if available; mask if unavailable)	Respirator (N95 respirator if available). Consider co-use of face shield for multiple co-morbidities, or a face shield when also remote teaching.

*These categories are expert opinion, as there currently is insufficient evidence for evidence-based guidance.
** Comorbidities include heart disease, hypertension, diabetes mellitus, chronic renal disease, dialysis, liver disease, chronic obstructive pulmonary disease (COPD), smoking, and obesity [185-188].

Disability and Return-to-Work Considerations

Disability from COVID-19 will be better defined with studies over time. Extrapolation using recovery from other conditions, such as pneumonia and ARDS, may provide some preliminary estimates.

Preliminary reports suggest recovery duration is, unsurprisingly, at least partially correlated with measures of case severity. At least one symptom persisting for at least 60 days has been reported among hospitalized survivors, with the most prevalent symptoms being fatigue, dyspnea, joint pain, chest pain, cough, and anosmia [289]. However, persistent symptoms are reported in individuals with mild cases, and long-term symptoms have been reported [290]. There are many cases that require home healthcare after discharge [291].

Permanent disability is determined by the existence of some combination of fixed deficits when a healing plateau has been reached (see the ACOEM Disability Prevention Guideline). One of the greatest factors facilitating recovery is the interest and ability of the employer to reintegrate the employee into their workforce. Such integration often requires accommodations that hopefully can be reduced as time, recovery, and workarounds progress. While not yet demonstrated for COVID-19, employer support for recovery is critical for many other conditions.

Permanent disability is only appropriate for those with fixed, non-improving chronic impairments (see the Rehabilitation section below). Some of these cases have obvious permanent deficits from complications such as myocardial infarction and stroke. There is also increasing literature supporting the development of chronic symptoms associated with COVID, which is elsewhere termed “ongoing symptomatic,” “post-COVID syndrome,” and “long COVID” [292]. The term “post-acute sequalae of COVID” has also been used by the National Institutes of Health.

Factors contributing to disability beyond fixed but remediable deficits can include a lack of full implementation and utilization of evidence-based treatments, and lack of effort and compliance. Other factors may potentially involve advocagenic, psychological, and other influences.

Return-to-work evaluations should consider the worker’s current status as compared with the physical requirements of the job, mental demands of the job, safety-critical work functions, current treatments, use of impairing medication, residual effects of the virus, requirements for personal protective equipment, potential risk to others if returned too early, and protection of other employees if additional risk is identified. Many of these complex cases will need to be addressed by occupational and environmental medicine physicians.

Currently, for patients without hospitalization, there are no quality data on returning to work, short-term disability, or long-term disability. One random sample (n=292) of affected individuals diagnosed as outpatients reported 65% had returned to normal health at a median of 16 days; no or few comorbidities and age statistically impacted those rates, with 74% among

those 18–34 years of age, 68% among those 35–49 years of age, and 53% among those 50 years and older returning to normal health [293]. Regarding short-term disability and return to work, recovery from post-infection fatigue is estimated to take approximately 2–3 weeks and appears to correlate with clinical duration and severity. For patients with mild to moderate pneumonia treated with oxygen supplementation, recovery is estimated to require 4–8 weeks after hospitalization or clinical recovery. Severe pneumonia and ARDS have worse prognoses.

The overall trajectory of recovery from COVID-19 remains unclear. Prior experience with diseases that have similar manifestations, such as ARDS, suggest there is significant risk of delayed return to work and long-term disability, as approximately 50% of individuals surviving ARDS have not returned to work after 1 year [294, 295]. ARDS is also associated with approximately 20% reductions in spirometry and lung volume, which resolve at about 6 months based on prior H7N9 influenza data [296]. Lung diffusion abnormalities can take up to 5 years to resolve in ARDS cases [296, 297]. Cognitive impairments and psychiatric abnormalities related to ARDS may be projected to occur in 30–55% and 40–60% of patients, respectively; the duration of these impairments is unclear, but other causes of ARDS raise considerable concerns about long-term disability [295-301]. Generalized skeletal muscle deconditioning is expected in patients who are intubated for any extended duration; these patients require exercise programs and possibly rehabilitation, which often results in residual incapacity [295, 298, 302, 303]. Cardiac problems are common with COVID-19, with cardiomyopathy, arrhythmia, and direct cardiac muscle injury affecting approximately 30%, 20%, and 10% of patients, respectively [304]; they are contributing causes to fatality [304-306].

In general, for patients who are intubated and survive, recovery of the cardiorespiratory systems and endurance are estimated to take at least several months. Among recent COVID-ARDS survivors, 78% had evidence of cardiac involvement and 60% had evidence of ongoing myocardial inflammation on MRI [307]. It currently appears likely that some hospitalized and severely affected individuals will incur long-term disability with permanent impairments of the cardiac, respiratory, neurological, and/or musculoskeletal systems [295-299, 308]. There is also the potential for a minority of patients to be permanently totally impaired [299].

Cardiac, respiratory, and neurological disability measures include the following:

- 6-minute walk test
- Metabolic stress echocardiogram (including ECG)
- Full pulmonary function testing with impedance booth or washout testing
- High-resolution CT scan of the chest, especially for those with COVID-19 pneumonia
- Functional capacity testing (although there are some limits in interpretation)
- Neuropsychological testing

For individuals with less symptoms but high exertion requirements, a cardiac evaluation may be indicated.

An approach to evaluating COVID-19 worker's compensation claims has been published [309]. There is no specific impairment class for COVID-19 and surrogate diagnoses may be needed and/or used by analogy. Ratings for impairment can be found in the AMA Guides 5th Edition [310] and 6th Edition [311].

Vaccines

Development work has progressed at record speed on more than 270 COVID-19 vaccine candidates [200, 312-314]. These efforts have used at least four types of vaccine classes or approaches against this infection (virus, viral vector, nucleic acid, and protein-based) [313]. Although vaccine development was estimated to require 12–18+ months if successful, it has been achieved in approximately 9–10 months [315]. Several more of these COVID-19 vaccines are in advanced stages of development and have potential for approval (see Table 2). Few relevant efficacy data have been published in peer-reviewed publications. Safety data are largely reported from phase 2 trials; thus, some of the information is based on relatively small sample sizes. Reported rates of vaccine efficacy range from 62% to 95% [316]. After initiating vaccination programs, COVID-19 infections have declined markedly [317].

There is a helpful website (see https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/) updated weekly with multiple COVID-19 vaccine databases, including a vaccine pipeline tracker, clinical trials database, and living review [312, 316]. The CDC has also provided guidance regarding what is recommended for those who have been vaccinated [318].

The vaccines have very good to excellent rates of efficacy both in randomized trials and in early reports from community-based studies and surveillance systems, which underscores support for broad-scale vaccination programs. As the vaccinations are being widely implemented, the following questions require answering going forward, although they should not delay the expeditious and widespread implementation and completion of the vaccination programs:

- Duration of vaccine-induced immunity and whether there are differences between the types of immunizations
- Success of immunity, especially durability
- Whether duration of immunity differs in different subgroups, which may suggest the need for (earlier) re-vaccination
- Whether immunity is shorter-lived in vaccinated patients or in naturally infected patients
- Whether annual immunizations are needed
- The proportion of the population that requires immunization to prevent COVID-19 re-emergence
- Utility and/or adverse effects among those who have been infected with COVID-19
- Long-term adverse effects
- Whether the vaccine is safe in the elderly

- Whether children at risk of severe disease should be immunized
- Whether all children should be immunized

Adverse Effects

Both the Pfizer and Moderna vaccines have been associated with a low frequency of adverse effects. Even though vaccine reactions are rare, it is important to address them because they may generate fear, anxiety, and vaccine avoidance that is out of proportion with the actual prevalence of these outcomes. The earliest reports appeared in the January 6, 2021 *MMWR* [319], which described data collected from the December 14–23, 2020 period of vaccine administration of the Pfizer-BioNTech COVID-19 vaccine. Out of 1,893,360 first doses administered, there were 4,393 (0.2%) adverse events reported. After reviewing all cases, only 175 cases were considered to be consistent with a severe allergic reaction; of these, only 21 cases were deemed to represent anaphylaxis, for a rate of 11.1 per million doses administered. Nonallergic adverse events, mostly vasovagal or anxiety-related, were excluded from analyses. The median age of those with anaphylaxis was 40 years, and 90% were women. Typical symptoms included a diffuse erythematous rash, throat closure, hoarseness, swollen lips, difficulty swallowing, wheezing, cough, and nausea. Most (17/21; 81%) had a prior history of allergic reactions to drugs, medical products, foods, and insect stings, and 9.5% (2/21) had prior reactions to a vaccine. Most (19/21; 90.5%) were treated with epinephrine, and no deaths were reported. There was no geographical clustering of cases or associations with any specific vaccine lot. There were 83 cases of non-anaphylactic allergic reactions, with a similar age and sex distribution, and 56 (67%) also had a prior history of allergies or allergic reactions. Almost all reactions occurred in the first 30 minutes after vaccine administration.

A review subsequently published noted that confirmed allergic reactions to vaccines are usually not to the active ingredients, but rather due to reactions to excipients [320]. Reactions specifically focus on polyethylene glycol (PEG) and polysorbate, which have been added to multiple other vaccines, injected medications, chemotherapeutic agents, and biologicals to increase water solubility. These excipients are also found in multiple creams, ointments, lotions, and personal care products. Multiple existing vaccines contain polysorbate 80, including the AstraZeneca and Johnson & Johnson vaccines, and both the Pfizer and Moderna vaccines contain PEG2000. A recent study of the general population found that 5 to 9% of serum samples were positive for anti-PEG IgG [321]. Skin tests for polyethylene glycol are available, and other medications containing PEG3350 (methylprednisolone acetate), polysorbate 80 (triamcinolone acetonide, Refresh eye drops, Prevnar) or polysorbate 20 (hepatitis A vaccine, Twinrix) can be used for skin testing to document an allergy to one of these excipients. The authors proposed a risk stratification to determine who should undergo pre-vaccination skin testing or extended observation postvaccine, using the following patient-directed questions:

Do you have a history of a severe allergic reaction to any of the following:

1. An injectable medication (IV, IM, or SQ)
2. A prior vaccine
3. Another allergen, such as food, venom, or latex?

4. Polyethylene glycol (PEG), a polysorbate, or a paclitaxel-containing injectable or vaccine?

If the patient answers “yes” to question 4, he or she is higher risk and should be referred to an allergist before receiving the vaccine. Questions 1, 2, and 3 represent medium risk; the patient should be observed for 30 minutes after the vaccine. If the patient answers “no” to all four questions, then he or she is lower risk and should be observed for 15 minutes after the vaccine.

Delayed large local reactions to the Moderna vaccine occurring 8 to 12 days after vaccination have been described in 12 patients [322]. Of these, 10 were women, 8 had a prior history of allergy or allergic reactions, 9 described itching, 9 described pain, and 7 described fatigue or other systemic symptoms. Most were treated with antihistamines and topical steroids, and two received oral steroids. Reactions resolved by day 14 to 19. All then received the second vaccine dose, with only minor rash or itching reported; none were severe.

In addition, there have been reports of 36 cases of immune thrombocytopenic purpura (ITP) following the vaccination of 31 million people as of February 8, 2021, but no cases were associated with any one vaccine or vaccine lot. The majority of patients received platelet transfusions, IVIG, and/or steroids along with hospital care; there was one reported death. Importantly, ITP has been associated with other vaccines, including the MMR, DTaP, varicella, hepatitis B, and pneumonia vaccines [323], as well as following viral infections. For patients with a pre-existing history of ITP, the American Society of Hematology recommends that platelet counts be checked before receiving the vaccine; however, the presence of ITP is not a contraindication to receiving the vaccine.

Variant Concerns

The spike protein of the SARS CoV-2 virus is the focus of all currently available vaccines. This is the primary viral protein responsible for entry into host cells by attaching to the ACE2 cellular receptor present on multiple human tissues, including the lungs, heart and blood vessels, kidney, testis, and brain. The primary antibody response elicited by the virus in natural infections is directed against the spike protein. Hence, as the spike protein appears to be the preferred target of the natural immune response, it was naturally selected as the primary target for the vaccine response.

The first variant of the SARS CoV-2 spike protein, D614G, was detected in early March 2020, substituting a glycine for an aspartic acid in the carboxy terminal region of the S1 domain. Not present in any of the viral sequences in January and February 2020, it constituted 26% of viral sequences in March and 70% in May, attributed to enhanced ACE2 binding affinity and infectivity [324, 325].

The next set of more transmissible variants, all containing adaptations in the spike protein, were identified in the fall of 2020 and include B.1.1.7 (UK), B1.351 (South Africa), and P.1 (Brazil). The B.1.1.7, or UK variant, was first identified on September 20, 2020 In Kent, England.

It is thought to have arisen in a patient with an impaired immune system who was treated with antibodies from a recovered patient, and possibly also with remdesivir [326]. With this patient's specific scenario, the virus would theoretically have the opportunity to replicate multiple times, increasing the odds of random mutations, and under the pressure of antibodies targeted to the spike protein. Hence, those variants that survived could develop slightly different spike proteins that are not (as well) recognized by existing antibodies. This variant carries a N501Y mutation of asparagine to tyrosine in the S protein that increases its binding strength to the ACE2 cellular receptor, as well as a deletion at positions 69 and 70, which are both hypothesized to increase transmissibility. The deletion causes S-gene target failure in one PCR-based assay, the ThermoFisher TaqPath COVID-19 assay, producing a negative result for the S-gene target and still positive results for the other two targets.

By January 12, 2021, the B.1.1.7 variant had been detected in 12 U.S. states. Estimates are that this will become the dominant strain in the United States by the end of March 2021 [327]. There is some concern that this variant is more lethal than previous strains: the mortality hazard ratio associated with infection with B.1.1.7 compared with infection with previous variants was estimated at 1.64 (95% confidence interval 1.32 to 2.04) [328].

B.1.351 is another variant that independently emerged in South Africa; it was first detected in the US at the end of January 2021. It carries eight specific mutations in the spike protein, along with the N501Y variant carried in the UK strain. Preliminary results demonstrated that a higher titer of antibodies generated by the MRNA-1273 (Moderna) vaccine were required to neutralize the B.1.351 variant, although sera were still able to fully neutralize the virus. Specifically, geometric mean titers (GMT) of immunized human sera to neutralize the D614G variant were 1:1852, compared to GMT of 1:290 against the B.1.351 variant. What is not clear, however, is whether this translates to any reduction in protection against infection [329]. Similarly, sera from subjects immunized with the BNT162b2 (Pfizer) vaccine exhibited the same neutralization of a Y501 laboratory variant as the parent N501 version of the virus [330].

P-1 is a variant of SARS-CoV-2 that emerged in Manaus, Brazil, and was detected in the United States at the end of January 2021. This variant carries 20 unique mutations, including three identified in other variants in the receptor binding domain of spike protein (K417T, E484K, and N501Y). A separate study showed that serum samples from subjects immunized with the BNT162b2 (Pfizer) vaccine effectively neutralized engineered CoV-2 viruses carrying all the identified variant spike proteins, most at titers >1:40 [331].

It is important to note that all settings of natural and vaccine-induced immunity will exert selection pressures against the virus and drive the emergence of resistance mutations. One study cultured a SARS-CoV-2 recombinant virus in the presence of 18 different neutralizing monoclonal antibodies that were selected for different RBD mutations. In all cases, the antibody selected for the emergence of a resistant variant. This same study also demonstrated that antibodies elicited by either the Moderna (mRNA-1273) or Pfizer BioNTech (BNT162b2) vaccine were nearly identical and were effective against the dominant variant of SARS CoV-2 (D614G), with only a modest decrease in the ability of these antibodies to neutralize viral

variants [332]. This likely reflects the polyclonal nature of neutralizing antibodies elicited by the vaccines—that is, that the mRNA carried by these vaccines codes for a number of different proteins with many different antigenic epitopes. Antibody responses will correspond to multiple epitopes, including many sites that remain unchanged in different variants of the virus.

Although the intense scrutiny of the SARS CoV-2 virus has resulted in early identification of viral variants, their emergence should be considered a normal process in a pandemic. As host susceptibility to infection changes, the virus, under these selection pressures, will change accordingly. More variants will emerge. This may, or may not, have an effect on host susceptibility. Thus far, vaccine-elicited antibodies have been shown to remain active against spike protein variants. Most SARS CoV-2 specific CD4+ and CD8+ T-cell responses from both naturally infected and vaccinated subjects are equally effective against variant strains [333]. Lastly, it is expected that the vaccines will be altered going forward to address novel variants that have already emerged, as well as those yet to emerge.

Vaccines for the Prevention of COVID-19

Strongly Recommended.

Vaccination is strongly recommended for the prevention of COVID-19.

Strength of Evidence – **Strongly Recommended, Evidence (A)**
Level of Confidence – **High**

Indications:	Indicated for nearly all adults. Particularly indicated for those with increased risk of severe COVID-19 disease (e.g., increased age, obesity, diabetes mellitus, COPD, cardiovascular disease, renal disease, immunosuppressed states). Earlier vaccination is indicated for adults with high numbers of close personal contacts as a means to terminate the pandemic sooner (e.g., healthcare workers, grocery workers, firefighters, police officers, EMS, assembly line workers, teachers). Because the pandemic is primarily affecting middle to older age groups, vaccination of young adults is of unclear benefit compared with natural immunity, particularly early in the vaccination period when vaccines should be reserved for higher-risk groups. Common RCT exclusion criteria include pregnancy, immunodeficiency, immunosuppression, use of glucocorticoids 20+ mg/day in the past 6 months, and prior vaccine allergic reactions. Thus, efficacy and applicability for these populations are technically less clear. However, those with immunosuppressed states would be potentially high-impact populations to receive early vaccination. Safety in pregnancy is unknown and immunization in pregnant women is not generally recommended.
Benefits:	Markedly reduced risk of COVID-19 infection, as well as serious COVID-19 disease. Termination of the pandemic. Two 2-shot series of mRNA vaccines (Pfizer and Moderna) have ~95% efficacy, whereas the single shot (Janssen/Johnson & Johnson has ~67% efficacy [334].

Harms:	Reported rates of adverse effects from a passive but large-scale surveillance system (V-safe) include injection site pain (Pfizer/Moderna; Pfizer dose #2; 73-78% after first dose and 79% after second dose), fatigue (22-25%/25-54%), headache 15-23%/20-43%), myalgia (15-23%/18-47%), chills (6-11%/8-31%), fever (6-11%/8-29%), injection site swelling (6-11%/9-13%), joint pain (5-10%/7-24%), and nausea (4-9%/6-14%) [316, 335, 336]. Anaphylactoid reactions are quite rare (4.5 per million doses administered [335]); those with severe food and/or medicine allergies have been suggested to delay getting the vaccine. Pfizer BioNTech/Fosun Pharma: Grade 3 adverse effects >2% were fatigue 3.8% and headache 2.0% [316].
Indications for Discontinuation:	N/A for single-administration series. A second immunization is not recommended for those with significant and/or serious adverse effects with the first administration of a two-immunization series.
Frequency/Dose/Duration:	N/A
Rationale:	One trial has been reported and found 95.1% efficacy [337]. Other available data are published in press releases and suggest strong efficacy of these vaccines. Adverse effects reported thus far are relatively minor. There are no long-term safety data. COVID-19 immunizations are minimally invasive (IV), thus far have minor reported adverse effects, are usually no-cost, have reported evidence of strong efficacy, and thus are strongly recommended.

Table 2. Advanced COVID-19 Vaccine Candidate Information*

Vaccine / Manufacturer	Type (Platform)	Participant Characteristics	IM Doses	Special Handling	Primary Outcomes	Adverse Events	Efficacy / Interim Analysis
AstraZeneca (University of Oxford)	Weakened adenovirus, non-replicating viral vector (ChAdOx1-S AZD 1222)	40,051 participants aged ≥18 years	2 doses, days 1 and 29	None; store at normal refrigeration temperatures for up to 6 months	• Incidence of COVID-19 cases at days 43 to 365 • Incidence of AEs, SAEs, MAAEs, and AESs at 28 days after doses and up to day 730 • Incidence of solicited and local and systemic AEs up to days 8 and 36	Nonquantified reports of injection site pain, rash, headaches, muscle soreness, and fevers. Nearly half reported neutropenia.	50% (with 95% CI, lower bound >30%)
Jannsen (Johnson & Johnson)	Non-replicating viral vector As26.COV2.S	60,000 participants aged ≥18 years	1 dose	None; safe to store at normal refrigeration temperatures	• Incidence of moderate to severe/critical COVID-19 cases up to day 759	Mild adverse effects similar to those seen with other vaccines, including injection site pain, rash, headaches, muscle soreness, and fevers.	60% (with 95% CI, lower bound >30%)
Moderna/NIAID	LNP-encapsulated mRNA (mRNA-1273)	30,000 participants aged >18 years	2 doses; days 1 and 29	Yes; requires storage at −20°C. May store at normal refrigeration temperatures up to 30 days.	• Incidence of COVID-19 cases at days 43 to 759 • Participants' AEs and MAAEs leading to withdrawal up to day 759 • Participants with solicited local and systemic ARs up to day 8 and 36 and unsolicited AEs up to day 57	Fatigue, 9.7%; myalgia, 8.9%; arthralgia, 5.2%; headache, 4.5%; injection site pain, 2.7%; erythema at injection site, 2.0%; headache, 2.0%; fever, <2.0%	Vaccine efficacy against COVID-19 was 94.1%; vaccine efficacy against severe COVID-19 was 100% (90 vs. 5 COVID cases; 11 vs. 0 severe COVID cases occurred)

Novavax	Recombinant glycoprotein nanoparticle (NVX-CoV2373)	30,000 participants aged ≥18 years	2 doses; days 1 and 29	None; safe to store at normal refrigeration temperatures	• Incidence of COVID-19 cases at days 29 to 750	Reports include injection site pain, rash, headaches, muscle pain, fever, nausea, and vomiting.	Currently unknown
Pfizer (BioNTech / Fosun Pharma	3 LNP-mRNA (mRNA BNT 162)	43,998 participants aged ≥12 years	2 doses, days 1 and 22	Yes; requires storage at −70°C. FDA-approved storage at usual refrigerator temperatures for up to 2 weeks [338].	• Incidence of COVID-19 cases at days 29 to 730 (per 1000 person-years of follow-up) • Incidence of AEs and SAEs after doses and up to day 202	Influenza-like symptoms, injection site pain, rash, fever, headaches, muscle soreness, and nausea. Grade 3 adverse effects >2% were fatigue (3.8%) and headache (2.0%).	95% meeting all primary efficacy endpoints (162 vs. 8 COVID cases; 9 vs. 1 severe COVID cases occurred)

Abbreviations: AE, adverse event; AES, adverse event of special interest; AR, adverse reaction; CI, confidence interval; LNP, lipid nanoparticle; MAAE, medically attended adverse event; SAE, severe adverse event.

*Adapted from Dal-Ré R, Caplan AL, Gluud C, Porcher R. Ethical and scientific considerations regarding the early approval and deployment of a COVID-19 vaccine. *Ann Intern Med.* 2020 Nov 20:M20-7357. doi: 10.7326/M20-7357. Epub ahead of print. PMID: 33216636; PMCID: PMC7713906. Data from clinical trials as of November 20, 2020. Data supplemented from London School of Hygiene & Tropical Medicine's COVID-19 Vaccine Tracker (https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape) [316].

Masks and Respirators

Masks are used to control respiratory exposures, are relatively easy to use, and do not require special fitting. Respirators have much higher performance standards, are more challenging to use, and require fit testing. Masks have been commonly used by the public to control COVID-19 exposure. Respirators have been selectively used to control COVID-19 viral exposures among higher-risk workers or individuals. Masking mandates have been used for control of COVID-19 both in the workplace and in jurisdictions (e.g., statewide) [15].

Masking for the Prevention of COVID-19 Transmission

Sometimes Recommended.

Masking in closed public spaces is recommended for the prevention of COVID-19 transmission when there are significant community-based COVID transmission rates. Masking may be selectively indicated when there are insufficient immunization rates but some ongoing community spread. Individual masking may be advisable for those at higher risk for complications and/or when there is not achievement of herd immunity. Masking may not be indicated when there is a lack of community spread and/or when there is sufficient immunity. In contrast with masks, N95 respirators may be indicated for select populations (e.g., high-exposure workers, workers with high personal risks).

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
(When transmission is moderate or high)
Level of Confidence – **Low**

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
(When transmission is low and herd immunity is inferred to have been achieved)
Level of Confidence – **Low**

Indications:

Masking in closed public spaces is: (1) recommended when there are significant community-based COVID transmission rates; and (2) selectively indicated when there are insufficient immunization rates, yet some ongoing community spread.

Individual masking may be advisable for those at higher risk for complications and/or when there is not yet achievement of herd immunity. Three-ply masking is preferable to 2-ply masking, and ASTM-rated mask standards are available [339]. Single fabric layers are not advised unless there is no alternative [340-342].

Masking may not be indicated when there is a lack of community spread and/or when there is sufficient immunity. Sufficient immunity is challenging to determine as the numbers of cases reported may be underestimated by more than 5-fold, and antibody tests likely miss

	some individuals with sufficient immune system protection yet non-detectable circulating antibodies. N95 respirators may be indicated for either high-exposure workers (e.g., frontline healthcare personnel) and/or workers with high personal risks for a severe outcome [343, 344]. Respirators require at least a health questionnaire, potentially require a medical examination, and necessitate appropriate fit testing. Fit testing should include observation of appropriate donning and, relevant for COVID-19, doffing. For populations using masks, education on how to obtain a good seal during use is believed to be quite important. Training in donning and doffing, as well as assessments for tolerance and appropriate use, may also be helpful. Guidance is available regarding how to obtain a tighter seal by tying a knot in the ear loops, flattening material near the face, and tucking the knot [345].
Benefits:	Reduced community spread and reduced risk of individual patient disease acquisition. However, once fully immunized, benefits are nearly entirely limited to unimmunized patients.
Harms:	Dermatological problems, inconvenience, reduced communication. There is evidence that poor mask hygiene may be associated with increased risk of infections [346, 347].
Indications for Discontinuation:	Masking may not be indicated when there is a lack of community spread and/or when there is sufficient immunity.
Frequency/Dose/Duration:	In closed public spaces. Recent guidance has suggested double-masking, which infers there are increasing concerns about microdroplet and aerosol spread. However, there are few data to suggest the superiority of double-masking. N95 respirator use among those who are high risk and not yet immunized may be the most effective strategy, assuming mask availability (which currently is good). Contamination of masks may be an avoidable problem [348] and should be addressed by proper training (see Indications above).
Rationale:	One community-based moderate-quality trial from Denmark found a lack of benefits from mask wearing in addition to other measures in the COVID epidemic [349]. One trial of mask use for COVID-19 assessing household transmission failed to find at least 50% reduction in risk and reported that most disease acquisition was thought to be community-based [350]. Quality RCTs mostly involve influenza and influenza-like illness [219, 351-356] and show somewhat conflicting results regarding efficacy to reduce risks of infections, particularly with use of respirators; there are more negative [357-361] than positive trial results [362-364]. Equivalency has been reported between surgical mask use and N95 respirators [222, 225], although experimental evidence suggests superiority of respirators to reduce droplet and aerosols [340-342]. Weak evidence suggests masking may be effective and that N95 respirator use may be superior to mask use in healthcare settings [347, 365-367]. All of the epidemiological data have the benefits of being real-world data, but weaknesses include unclear compliance and masking techniques [368]. Respirators performed better than masks in

simulation studies [369]; however, a simulation of SARS-CoV-2 found incomplete protection from masks and N95 respirators [370].

Data on filtering were as follows: N95 respirators, 99%; medical masks, 59%; 3-ply cotton, 51% vs. 47%; double-gaiter, 60%; face shield, 2% [343, 371]. Surgical and cloth mask efficacies vary widely [372].

Although quality data on the efficacy of masking are sparse and conflict, some data suggest efficacy. With few other options for control of a pandemic, the risk-benefit ratio favors masking during the active pandemic phase. Masking in closed public spaces is: (1) recommended when there are significant community-based COVID transmission rates; and (2) selectively indicated when there are insufficient immunization rates and some ongoing community spread. Individual masking may be advisable for those at higher risk for complications and/or when there is not achievement of herd immunity.

Masking may not be indicated when there is a lack of community spread and/or when there is sufficient immunity. Sufficient immunity is challenging to determine as the numbers of cases reported may be underestimated by more than 5-fold; furthermore, antibody tests may miss some individuals with sufficient immune system protection but non-detectable circulating antibodies.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to February 2020 using the following terms: Mask, bandana, scarf, reusable cloth mask, standard surgical mask, N-95, face shield; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 237 articles in PubMed, 70 in Scopus, 71 in CINAHL, 117 in Cochrane Library, 2882 in Google Scholar, and 3 from other sources[†]. We considered for inclusion 29 from PubMed, 4 from Scopus, 2 from CINAHL, 1 from Cochrane Library, 44 from Google Scholar, and 3 from other sources. Of the 82 articles considered for inclusion, 23 randomized trials and 40 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Lockdowns and Shutdowns

Restrictions on businesses, schools, and public gatherings have been used in attempts to control the COVID-19 pandemic, including limitations on travel, large gatherings, in-person schools, restaurants, bars, and non-essential businesses. Even under the strictest shelter-in-place jurisdictions in the United States, however, most individuals could continue to visit grocery stores, which may have provided a means for continuing community spread despite masking requirements.

Studies are beginning to be published concerning the efficacy of lockdowns. Most studies have reported reduced COVID-19 transmission after the implementation of a lockdown [382, 383], although it has been reported that lockdowns were not effective in Europe [382]. An ecological study suggested greater spread where restaurant dining was allowed [384]. One analysis of multiple countries found non-significant small reductions in COVID-19 case rates in most countries, which was not felt to be outweighed by the costs [382]. Reports have questioned the cost-benefit efficacy of lockdowns, including in Israel and the United Kingdom [385, 386]. Adverse mental health effects have been reported [387-391]. The subject of lockdowns requires considerably greater research, especially as future surges attributed to variants seem likely; the re-implementation of such lockdown policies may necessitate a stronger evidence base.

Diagnostic Approach

Laboratory Tests

COVID-19 has a widely varying clinical presentation. Depending on the extent of infection and the organ systems affected, any or all of the following may be found [161, 162]:

- Lymphopenia (a fairly unique and characteristic finding)
- Elevated liver enzymes
- Elevated lactate dehydrogenase (LDH)
- Elevated direct bilirubin
- Elevated pancreatic enzymes
- Elevated prothrombin time (PT)
- Elevated troponin
- Elevated creatine phosphokinase (CPK)
- Elevated inflammatory markers (e.g., C-reactive protein [CRP], ferritin)
- Elevated D-dimer
- Elevated fibrinogen
- Elevated creatinine
- Elevated blood urea nitrogen

- Hypoxemia

A risk prediction model has been developed to predict the development of severe disease [211]. The 10 variables included in the model are: chest radiographic abnormality (odds ratio [OR]: 3.39), age (OR: 1.03), hemoptysis (OR: 4.53), dyspnea (OR: 1.88), unconsciousness (OR: 4.71), number of comorbidities (OR: 1.60), cancer history (OR: 4.07), neutrophil-to-lymphocyte ratio (OR: 1.06), lactate dehydrogenase (OR: 1.002), and direct bilirubin (OR: 1.15). A free online risk calculator is available [392].

Decreases in creatinine kinase (CK) and LDH have been associated with increased COVID-19 viral clearance in a secondary analysis of hospitalized patients treated with varying antiviral and other medications (IFN-α + lopinavir/ritonavir ± ribavirin) [393].

Diagnostic Testing

Three main types of diagnostic tests are used for COVID-19: (1) polymerase chain reaction (PCR)-based testing, typically using swabs [394]; (2) antigen testing, and (3) antibody testing of blood serum. PCR testing is considered to be diagnostic of the infection because it detects the actual virus or viral particles. Antigen tests have been approved by the U.S. Food and Drug Administration (FDA) and are also considered diagnostic [395]. Antibody testing detects prior infection. All types of testing have had limitations in specificity and sensitivity. A difference in performance over time since symptom onset has been reported [396].

Saliva testing for SARS-CoV-2 detection is also available, which is appealing for ease of collection. Pooled saliva testing has been used in employed populations [397]. One study detected higher SARS-CoV-2 titers in saliva compared to nasopharyngeal swabs, with less longitudinal variability [398]. If validated with larger-scale studies, saliva testing could provide near universal sampling coverage for both symptomatic and asymptomatic patients [399].

Test results, when accurate, may only indicate the presence or absence of infection at the time of the test; thus, the frequency of testing, and which methods to use, are debatable. In university settings, routine surveillance testing of representative subpopulations of students is recommended, with more frequent testing of higher-risk groups such as athletes. More frequent testing with less sensitive (and often cheaper) tests that are capable of detecting infectious virus (rather than any virus) will shortly become available and are recommended [400].

PCR Testing

PCR samples and testing techniques amplify viral particles to identify relatively small amounts of virus, with the nucleocapsid antigen test being the most sensitive for detecting early infection [401]. Because they also amplify viral fragments, they can show recent infection among those who are still clearing the viral particles, up to weeks after infection; thus, they may not reflect active viral shedding and/or infectiousness. These tests can indicate the RNA debris of coronavirus and may reflect non-viable virus remnants.

Importantly, the risks of false-negative and false-positive test results change as a pandemic progresses. For example, as disease becomes more common, individuals who present with symptoms but test negative are increasingly more likely to represent false-negatives irrespective of testing accuracy. Thus, once an epidemic disease becomes highly pervasive and there is not a common competing cause of similar symptoms, diagnostic testing is often unnecessary for typical cases because it does not materially alter the post-test probability. At an epidemic's peak, the testing of unusual cases is ideally performed with highly accurate tests, as such cases may represent unusual presentations of COVID-19 infection that should be distinguished from non-COVID-19 causes. Because the SARS-CoV-2 virus causes such a wide spectrum of disease, from asymptomatic illness to life-threatening infection, along with the possibility of other co-circulating respiratory viruses at various times (e.g., influenza), the issue of accurate diagnostics for SARS-CoV-2 becomes one of paramount importance for the foreseeable future. The ability to widely perform COVID-19 testing is of particular importance during times of anticipated epidemic waves (e.g., fall/winter 2020–21).

Most of the limited evidence suggests that nasopharyngeal and oropharyngeal samples are comparable for the first week, but then the nasopharyngeal sample becomes more sensitive [402, 403]:

- From days 0–7, oropharyngeal and nasopharyngeal sensitivities are 61/60% and 72/73% for mild/severe disease, respectively.
- On days 8–14, oropharyngeal and nasopharyngeal sensitivities are approximately 30/50% and 54/72% for mild/severe disease, respectively [404].

PCR testing is recommended for the diagnosis of COVID-19. Testing should be performed either at the time of COVID-19-like symptom onset, or within several days of the onset of symptoms consistent with a COVID-19 infection. Testing without experienced medical judgment [405] is ill-advised given that the risk of false-negative tests are 20–67% [32]. Thus, there is a strong indication to presumptively treat cases who test negative, which requires experienced medical judgment. Repeat testing may be indicated for those with a negative test but a high index of suspicion.

PCR testing is also recommended for inpatient and outpatient preoperative assessments. Preoperative tests must be ordered sufficiently ahead of surgery such that the results are received in time to address/respond to the results (generally 72–96 hours before surgery).

Antigen Testing

Antigen tests detect viral proteins either on or within the virus. These have been FDA-approved and are considered diagnostic [395]. Antigen testing is growing in popularity as its main strength is rapid test results, which are provided in minutes compared with up to several days for PCR tests.

Antigen testing is recommended for the diagnosis of COVID-19. Testing should be performed either at the time of COVID-19-like symptom onset, or within several days of the onset of

symptoms consistent with a COVID-19 infection. Antigen testing has not been validated for asymptomatic persons. However, the sensitivity among symptomatic persons is estimated to be approximately 80%. Thus, testing without experienced medical judgment is ill-advised [405], given the risks of false-negative tests. There is a strong indication to presumptively treat cases who test negative, which requires experienced medical judgment. Repeat testing may be indicated for those with a negative test but a high index of suspicion.

Antigen testing is also recommended for inpatient and outpatient preoperative assessments. Preoperative tests must be ordered sufficiently ahead of surgery such that the results are received in time to address/respond to the results (generally 72–96 hours before surgery). Preoperative tests may be needed both for those without any history of symptoms, as well as for those with prior infections, to assure the person is no longer infectious.

Antibody Testing

Antibody testing detects the body's humoral response to the virus [406-411]. Most antibody tests detect IgG, although some tests attempt to also detect IgM or IgA. The median IgM seroconversion is 11–13 days (or 5–7 days after symptoms onset), while the median seroconversion for IgG is 14 days (or 8 days after symptoms onset), although IgM may wane after 2 to 3 weeks, and IgG persists for a far longer period of time [412]. A positive antibody test does not exclude the potential for the patient being infectious with COVID-19. Antibody tests are in early stages of deployment and reported reliability varies widely [408-410]. Because there is no reference standard and widespread testing of large populations have not been reported, the determination of test accuracy, sensitivity, and specificity remain problematic. In addition, the timing of the antibody testing is critical to accurate detection: testing too soon after infection onset, or too late after infection resolution, can further increase risks of negative results.

It has been aspirational that immune status testing (IgG, IgM) would eventually be the most important test for population-based risk assessments, such as herd immunity. This still requires considerable research, including large-scale determinations of sensitivity, specificity, reliability, timing, persistence of the immunoglobulins, and whether the immunoglobulin status identified by testing will be associated with true immunity [413]. Preliminary evidence includes a large population-based Spanish study suggesting a 87.6–91.8% seroprevalence rate among those who had PCR confirmation of infection; yet, individuals meeting a case definition of anosmia or at least 3 relevant symptoms had a seroprevalence rate of only 15.3–19.3% [414]. A large-scale hospital-based study found a sensitivity of 97.6% and 98.8% specificity when performed 14 days or later after symptoms onset; the immunoglobulins levels were correlated with worse disease, and were detectable in those with negative PCR tests but clinical suspicion of infection [415]. Others have correlated titers with disease severity [409]. An added challenge is that while 1.24% of a community's 5,882 samples showed antibody reactivity to receptor binding domain, 18% of the samples failed to neutralize the SARS-CoV-2 virus [416].

Evidence also suggests immunoglobulins may not be measurable over time [417]. Still, other studies suggest laboratory tests assessing T-cell responses remain robust for some time, even

among those with no detectable immunoglobulins and/or those who had mild disease [418, 419]. Hence, a lack of measurable immunoglobulins may not indicate lack of immunity. If these lines of research remain viable, then it is theoretically possible for immunoglobulin testing, perhaps combined with history, to help designate workers who may more safely interact with the public. If proven, antibody testing may be used to assure a workplace that a previously infected worker is safe to return to work (i.e., that they are not actively infected and unlikely to be shedding virus). Unfortunately, the currently available antibody tests have yet to be sufficiently validated on a widespread basis, and inaccuracies are increasingly reported [420, 421]. Once these problems are addressed, it is anticipated that antibody testing may become widespread in many workplaces and other populations of concern (e.g., nursing homes, mission-critical workers, irreplaceable workers, dispatch centers, C-suite executives).

Immune status determination, if proven, may be of major importance for workplace populations in many, if not all, sectors. It may be complementary with vaccination, particularly if the virus continues to circulate and cause disease. Workforces with the greatest needs for immune status testing include those with isolated populations, increased risk of transmission to vulnerable populations, high worker densities, and/or distance from and lack of access to appropriate healthcare (e.g., oil platform drilling, commercial maritime, cruise lines, overseas workforces, airlines, rail, trucking, mining).

Antibody testing is selectively recommended for assessing immune status regarding the potential for COVID-19. These tests should be interpreted by experienced medical and/or public health professional(s) who are thoroughly knowledgeable about numerous factors, including the specific test, its reported performance (e.g., sensitivity, specificity), the prevalence of COVID-19 in the specific community, principles of testing, Bayes' theorem, and assessment of pre-test probability and post-test odds. In general and at this point, antibody testing should be limited to only mission-critical workers and special populations. As the experience with these tests improves, the populations assessed may markedly expand. As a general statement, a person who has recovered from COVID-19, has a duration of at least 10 days since first symptoms, and has demonstrated antibodies would not be infectious or capable of transmitting infection and scientifically would no longer have to wear a mask or participate in mitigation procedures.

Specific examples where serology might be helpful include the following:

- Patients with symptoms consistent with COVID-19 of more than 1 week in duration, for whom PCR testing has been negative and no alternative diagnosis has been found. For these cases, a positive IgG serology would be diagnostic. A negative serology could be repeated at >2 weeks from symptom onset and repeat negative testing would then effectively rule out COVID-19.
- Patients with initial negative PCR and serology at <2 weeks after symptom onset but who remain symptomatic beyond 2 weeks without an alternative diagnosis. Repeat serology testing documenting seroconversion would be diagnostic, whereas failure to seroconvert would help to rule out COVID-19.

- Symptomatic, febrile, PCR-positive patients with an unknown time since infection where presence of antibodies might help in choice of therapeutic modalities (e.g., antivirals and/or convalescent serum before antibodies arise).

Imaging

Although radiographs are usually abnormal for individuals with pulmonary involvement, radiography in general should not be used as a stand-alone screening tool for COVID-19. X-ray abnormalities peak at 10–12 days after onset of symptoms [161, 422]. One series reported that chest radiographs most commonly show either consolidation (47%) or ground-glass abnormalities (33%). The same series noted that 41% were peripheral, 50% were lower distribution, and 50% were bilateral [422]. **Radiographs are recommended as part of the diagnostic evaluation of COVID-19.**

Computerized tomography (CT) is commonly performed [423, 424] and shows patchy infiltrates and ground-glass opacities [425-429]. One series reported 72% of cases with ground-glass appearance, 12% with consolidation, 12% with crazy paving patterns, 37% with interlobular thickening, 56% with adjacent pleural thickening, and 61% with linear opacities [162]. **CT scans are recommended for the diagnostic evaluation of COVID-19.**

Treatment Recommendations

Overview

Treatment is increasingly guided by RCTs, yet it continues to evolve as data are published. Many additional studies are underway. There are numerous treatment guidelines available; although these guidelines tend to have similar recommendations, there are many differences regarding individual treatments [430-437]. The FDA has provided unprecedented flexibility to accelerate the development of new drugs and testing [438]. No treatment is yet indicated for asymptomatic cases.

The four main classes of interventions with evidence of efficacy for more serious infections are antiviral treatments, cytokine storm-reducing and/or immunomodulating agents, anticoagulants, and ventilatory support (both non-invasive and invasive).

Many medications and agents are being used for treatment, including the following: ACE inhibitors, anticoagulants, bamlanivimab, casirivimab/imdevimab, COVID-19 convalescent plasma, famotidine, monoclonal antibodies, azithromycin, baloxavir, baricitinib, chloroquine, colchicine, favipiravir, glucocorticosteroids, hydroxychloroquine, immunoglobulin, interferons, ivermectin, lopinavir/ritinovir, nitric oxide, remdesivir, sarilumab, siltuximab, statins, thrombolytics, tocilizumab, zinc [439-442], vitamin C [443], and vitamin D [444-447]. Most of these treatments have no quality evidence of efficacy. There is no clear evidence of lower risk of mortality with statin use [448]. Vitamin D levels have been strongly correlated with COVID-19 disease severity [444, 446, 447]; for example, individuals with low vitamin D levels were

reported to have an approximate 8-fold greater risk of a severe outcome and 20-fold greater risk of a critical outcome [444].

Only glucocorticosteroids have thus far been clearly shown in multiple quality trials to reduce mortality [449-451], although data also suggest that low-molecular-weight heparin likely reduces mortality. Remdesivir and low-molecular-weight heparin have proven to be modestly effective at shortening intensive care unit (ICU) stays in a large trial [452].

If individuals develop more severe symptoms or have complications (e.g., ARDS or respiratory failure), they are primarily treated with non-invasive ventilatory support measures, glucocorticosteroids, anti-cytokine storm agents, mechanical ventilation (including prone positioning), other respiratory support measures, and prophylaxis for deep vein thrombosis, including low-molecular-weight heparins [453-455]. Evaluations should include exclusion of other causes (e.g., influenza). The efficacy of glucocorticoids appears to be related to the stage of the COVID-19 infection. Glucocorticosteroids used early in the time course of infection do not appear to improve outcomes, and in theory could potentially allow viral replication to increase and foster the development of other infections.

Multiple agents have been studied to attempt to suppress the purported cytokine storm; most of the trials are centered around interleukin-6 (IL-6) [456]. Yet, most quality data on IL-6 receptor antagonists have been negative. There is ongoing controversy regarding a cytokine storm in relation to ARDS caused by COVID-19 [457]. There are many cytokines believed to be involved in the cytokine release syndrome (IL-2, IL-7, G-CSF, IFN-γ, inducible protein 10, MIP 1-β, TNF-α).

Antiviral medications may have minimal to no role in advanced pneumonia or ARDS [458], particularly as viral replication appears to peak at or about the time of symptoms onset. However, antiviral therapies are showing increasing promise to lessen the severity of the disease among outpatients who are treated early in the disease. Two therapies targeting this window have recently been approved by FDA under emergency use authorization: bamlanivimab and casirivimab/imdevimab. Both of these treatments have preliminary data suggesting strong abilities to reduce the risk of hospitalization among those at high risk. Similarly, data on hydroxychloroquine (HCQ) suggest modest efficacy early in the symptomatic phase, but clear evidence of inefficacy for later stage use [459]. There are few studies assessing the efficacy of antiviral medications within the first 1–2 days of symptom onset [460], despite the parallels with influenza medications.

Potential hierarchical approaches for the treatment of COVID-19 are as follows:

Outpatient	Inpatient moderate	Inpatient severe/critical
Mild: 1. No treatment unless high risk for severe disease Moderate/severe: 1. Bamlanivimab or casirivimab / imdevimab 2. HCQ for 5 days	1. Glucocorticosteroids 2. Low-molecular-weight heparin/unfractionated heparin 3. Remdesivir 4. Oxygen supplementation	1. Glucocorticosteroids 2. Low-molecular-weight heparin/unfractionated heparin 3. Remdesivir 4. Baricitinib 5. Convalescent antibodies 6. Oxygen supplementation 7. Prone positioning (due to shunting) and/or non-invasive ventilation (NIV) 8. Mechanical ventilation, prone 9. Extracorporeal membrane oxygenation (ECMO)

Mental health issues are increasingly recognized as problematic, both among those infected as well as those otherwise impacted by the epidemic but not infected. Several references are available that include evidence of an epidemic of depression (50% increased), suicidal ideation, anxiety, post-traumatic stress disorder (PTSD), substance use, divorce (30% increased), and violence [168, 461-468]. An association between adverse mental health and financial concerns has been noted [469].

Hydroxychloroquine has been used for the treatment of COVID-19 [439, 442, 458, 470-511]. There also are many in vitro studies suggesting antiviral activity [512-520].

Hydroxychloroquine for Treatment of COVID-19

Sometimes Recommended.

Hydroxychloroquine (HCQ) is not recommended for the treatment of patients with COVID-19 after the first 3 days of symptoms [492]. HCQ is recommended for use in the first 3 days of symptoms onset.

Strength of Evidence – **Recommended, Evidence (C)**
(First 3 days of symptoms)
Level of Confidence – **Low**

Strength of Evidence – **Moderately Not Recommended, Evidence (B)**
(Use beyond first 3 days of symptoms)
Level of Confidence – **Moderate**

Indications:	Indicated for early symptom onset, ideally in the first 1–3 days during the COVID-19 phase with viral replication. Not indicated for late symptoms, especially days 5 or later. Generally for moderate to severely affected patients with COVID-19 and would include zinc supplementation. Use in mild cases could be justified, especially for a patient with multiple comorbidities (e.g., pre-diabetes, diabetes, cardiovascular disease, COPD) and thus risk of progression.
Benefits:	Meta-analysis evidence of a 24% reduction in composite risk of COVID-19 infection, hospitalization, and death [459]. Earlier clearance of pneumonia on CT scan [458].
Harms:	Negligible for most patients undergoing short-course use. Gastrointestinal symptoms occur above rates of placebo. Prior concerns about prolonged corrected QT intervals, and thus arrhythmias [490, 500], have been largely resolved among previously healthy patients without risks for arrhythmias who are given HCQ at typical doses. ECG monitoring may be indicated for patients with underlying cardiovascular disease, history of prolonged QT, unexplained syncope, family history of premature sudden cardiac death, electrolyte abnormalities, renal insufficiency, and use of other drugs reported to prolong QT intervals, including when there is planned adjunctive use with azithromycin. Renal insufficiency also may increase toxicity risks. Retinopathy appears highly unlikely with these short courses, as it has been reported at levels of >100-fold greater cumulative doses [521].
Frequency/Dose/Duration:	Multiple regimens have been used. There is both a mechanistic rationale for the concomitant use of zinc to inhibit viral replication and pre-post interventional clinical evidence of efficacy for the adjunctive use of zinc [442]. The following are the most common regimens, the first of which was used in the one quality RCT: • Hydroxychloroquine 400mg BID x 1 day, then 200mg BID for 4 days [513]. • Hydroxychloroquine 400mg BID x 1 day, then 400mg QD for 4 day. • Hydroxychloroquine 200mg BID x 5 days [458] • Hydroxychloroquine 200mg TID x 10 days [477] • Hydroxychloroquine 200mg TID x 10 days plus azithromycin 500mg x 1 day then 250mg QD x 4 days [477] • Hydroxychloroquine 600mg BID x 1 day, then 400mg QD for 4 day. Because the half-life of these medications is long, a loading dose for the first day or two may be preferable.
Rationale:	There are many quality RCTs among hospitalized and/or ICU patients that consistently show late use of HCQ does not improve clinical outcomes, including mortality [492, 493, 522-525]. Because there is consistent moderate-quality evidence that HCQ is ineffective as a solitary intervention in COVID-19 patients treated late after the viral replication phase has largely ceased, the use of HCQ in that timeframe is not recommended. There are multiple RCTs and studies of early use of HCQ that range from pre-diagnosis to within a few days of symptom onset [459]. These trials are naturally individually underpowered for severe

outcomes such as mortality as they tend to include younger, healthier patients. A meta-analysis of 5 RCTs that analyzed 5,577 patients found that all studies trended towards efficacy and the combined data showed a statistically significant 24% reduction in composite risk of infection, hospitalization, and death [459]. A nationwide cohort study in the Netherlands found evidence of efficacy of hydroxychloroquine for reducing risk of transfer to an ICU by 53% compared with no treatment, but there was no similar effect for chloroquine [526]. A study of 1,274 outpatients in a propensity-matched cohort from New Jersey found a 31.2% reduced risk of hospitalization [527].

One early-use trial found non-significant reductions, with 20% being symptomatic at 14 days and a 60% reduced risk of death [528]. Another trial of HCQ used within 4 days of high-risk exposure found a 17% reduced risk of subsequent infection [487]. Another trial of once-weekly or twice-weekly HCQ as pre-exposure prophylaxis among HCWs found a non-significant 26–28% reduced risk of infection [529]. Because there is quality evidence of efficacy for the early use of HCQ, it is recommended for these select patients.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Hydroxychloroquine; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 528 articles in PubMed, 741 in Scopus, 137 in CINAHL, 425 in Cochrane Library, 9,380 in Google Scholar, and 38 from other sources†. We considered for inclusion 24 from PubMed, 6 from Scopus, 1 from CINAHL, 2 from Cochrane Library, 6 from Google Scholar, and 35 from other sources. Of the 74 articles considered for inclusion, 7 randomized trials, 2 non-randomized trials, 5 case series, 11 retrospective studies, and 5 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens, then the remaining articles are not reviewed due to a lack of relevancy.

Chloroquine has been used for the treatment of COVID-19 [526].

Chloroquine for Treatment of COVID-19

Not Recommended.

Chloroquine is not recommended for the treatment of patients with COVID-19 after the first 3 days of symptoms [492]. There is no recommendation for or against the use of chloroquine in the first 3 days of symptoms.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
(First 3 days of symptoms)
Level of Confidence – **Low**

Strength of Evidence – **Not Recommended, Evidence (C)**
(Use beyond first 3 days of symptoms)
Level of Confidence – **Low**

Rationale:

Chloroquine is a closely related compound to hydroxychloroquine. There is no RCT-level evidence that chloroquine has different efficacy. There are sparse trials of chloroquine, especially compared with the evidence base for hydroxychloroquine. One population-based cohort study found evidence of efficacy of hydroxychloroquine but not chloroquine [526]. Thus, by analogy to hydroxychloroquine, chloroquine is not recommended for treatment of hospitalized COVID-19 patients. See the Hydroxychloroquine Rationale for Recommendation for details.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Chloroquine; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 89 articles in PubMed, 3,513 in Scopus, 28 in CINAHL, 0 in Cochrane Library, 11,440 in Google Scholar, and 0 from other sources†. We considered for inclusion 9 from PubMed, 20 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 10 from Google Scholar, and 5 from other sources. Of the 45 articles considered for inclusion, 2 randomized trials, 1 retrospective analysis and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we

review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens, then the remaining articles are not reviewed due to a lack of relevancy.

Hydroxychloroquine has been used for prophylaxis for COVID-19, most typically among healthcare workers [508, 530].

Hydroxychloroquine or Chloroquine for Widespread Prophylaxis Against COVID-19

No Recommendation.

There is no recommendation for or against the use of hydroxychloroquine and chloroquine for widespread prophylaxis against COVID-19.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – **Low**

Rationale: One high-quality trial of hydroxychloroquine (without zinc) for postexposure prophylaxis suggested no statistically significant benefit (11.8% vs. 14.3%, 17.5% reduction, p=0.35), although there was a 17% reduction of risk [487]; thus, underpowering is possible. A cluster-randomized trial found a nonsignificant 8.1% reduction in PCR-confirmed COVID [531]. An RCT found lack of efficacy for prophylaxis among healthcare workers [532]. A meta-analysis was performed with multiple RCTs that included early use of HCQ, ranging from pre-diagnosis to within a few days of symptoms onset [459]. These trials are naturally individually underpowered for severe outcomes such as mortality as they tend to include younger, healthier patients. This meta-analysis of 5 RCTs that analyzed 5,577 patients found that all studies trended towards efficacy and the combined data showed a statistically significant 24% reduction in composite risk of infection, hospitalization, and death [459]. A systematic review found weak and conflicting evidence [533]. As evidence for widespread prophylactic use is weak and conflicting, there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Hydroxychloroquine, Prophylaxis; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 73 articles in PubMed, 180 in Scopus, 25 in CINAHL, 41 in Cochrane Library, 8,280 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 4 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 3 from other sources. Of the 12 articles considered for inclusion, 3

randomized trials and 1 systematic review met the inclusion criteria. There were no exclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Chloroquine Prophylaxis; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 73 articles in PubMed, 18 in Scopus, 4 in CINAHL, 44 in Cochrane Library, 9560 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 0 randomized trials, 0 non-randomized trial, and 2 systematic review met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Azithromycin has been suggested to inhibit the growth of both the Zika and Ebola viruses, as well as prevent severe lower respiratory tract infections [542-545]. Azithromycin has been used for treatment of COVID-19, as both stand-alone and combined therapy [546-548].

Azithromycin for Treatment of COVID-19

Not Recommended.

Azithromycin is not recommended for the adjunctive treatment of selected patients with more severe COVID-19. There is no recommendation for or against the use of azithromycin in the first 3 days of symptoms.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
(First 3 days of symptoms)
Level of Confidence – **Low**

Strength of Evidence – **Not Recommended, Evidence (C)**
(Use beyond first 3 days of symptoms)
Level of Confidence – **Low**

Indications:	A moderate-quality RCT found the addition of azithromycin (AZT) to standard care that included HCQ produced no apparent benefit among hospitalized patients with severe COVID-19 [549]. A moderate-quality RCT found benefits with shortened hospital stay, improved oxygenation, and reduced respiratory rates associated with the addition of AZT to a combination of HCQ and lopinavir/ritonavir [510]. There are no quality RCTs regarding early treatment. Adjunctive use with hydroxychloroquine in severely affected patients with COVID-19. For severely affected patients, AZT has been added [477], but ECG monitoring should be particularly considered when adjunctive therapy with agents prolonging the QT interval is considered, including azithromycin plus HCQ/CQ (see Harms). Low-quality evidence suggests better efficacy if administered earlier in the clinical course when viral replication is occurring. There is no quality evidence of efficacy after ARDS is established [458].
Benefits:	Theoretical reduced need for a ventilator or ICU stay.
Harms:	Negligible for most patients undergoing short-course use. There are concerns about the potential for prolonged corrected QT intervals when used in combination therapy, and thus arrhythmias. ECG monitoring is particularly indicated in those undergoing adjunctive treatment with HCQ/CQ with underlying cardiovascular disease, history of prolonged QT, unexplained syncope, family history of premature sudden cardiac death, electrolyte abnormalities, renal insufficiency, and use of other drugs reported to prolong QT intervals, including when there is planned adjunctive use with hydroxychloroquine/chloroquine.
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect, prolongation of QT interval.
Frequency/Dose/Duration:	The regimen used for treatment of COVID is azithromycin 500mg on day 1 and then 250 mg/day for 4 days [477, 538].
Rationale:	One RCT has suggested no difference between AZT, HCQ, and the combination for treatment of hospitalized patients [493]. Thus, AZQ is not recommended for late treatment of COVID-19. Most non-randomized but controlled studies have suggested some evidence of efficacy, particularly for early adjunctive use when combined with HCQ [476, 477, 481-483, 538], although some other studies have suggested a lack of efficacy [484, 485]. Thus, there is no recommendation for use of AZT in the early phase of COVID-19.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Azithromycin ; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 164 articles in PubMed, 1161 in Scopus, 40 in CINAHL, 77 in Cochrane Library, 5170 in Google Scholar, and 16 from other sources†. We considered for

inclusion 19 from PubMed, 9 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 16 from other sources. Of the 45 articles considered for inclusion, 2 randomized trials, 2 non-randomized trials, 4 case series, 9 retrospective studies, and 0 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Favipiravir, a guanine analogue to inhibit RNA-dependent RNA polymerase, has been used to treat influenza. Favipiravir has also been used to treat severely affected COVID-19 patients [550-557].

Favipiravir for the Treatment of COVID-19

Not Recommended.

Favipiravir is not recommended for the treatment of COVID-19.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – **Low**

Rationale: A moderate-quality RCT found a lack of efficacy for combined favipiravir with interferon beta-1b compared with HCQ for moderate to severe COVID-19 pneumonia patients [558]. A moderate-quality RCT found no evidence of benefit of favipiravir for viral clearance, although there was faster defervescence [559]. One RCT comparing favipiravir with arbidol found no significant differences in the main clinical outcome measure, although fever and cough resolved more quickly in the favipiravir group [560]. A low-quality RCT of baloxavir, marboxil, and favipiravir found no evidence that favipiravir accelerated viral clearance [561]. There is one non-randomized controlled trial suggesting acceleration of viral clearance compared with lopinavir-ritonavir [562]. Although there is no quality evidence of efficacy, these studies suggest there may be potential efficacy; thus, while needing further quality data, this medication may be helpful in the treatment of patients with COVID-19.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Favipiravir; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized

controlled trials as topics. We found and reviewed 26 articles in PubMed, 2,429 in Scopus, 13 in CINAHL, 52 in Cochrane Library, 6,400 in Google Scholar, and 6 from other sources†. We considered for inclusion 5 from PubMed, 7 from Scopus, 0 from CINAHL, 2 from Cochrane Library, 8 from Google Scholar, and 6 from other sources. Of the 28 articles considered for inclusion, 3 randomized trials, 1 non-randomized trial, and 2 systematic review met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Lopinavir-ritonavir has been used for the treatment of COVID-19 [511, 563-571].

Lopinavir-Ritonavir for the Treatment of COVID-19

Sometimes Recommended.

Lopinavir-ritonavir is recommended in combination therapy [572], but is not recommended as a stand-alone treatment for COVID-19.

Strength of Evidence – **Recommended, Evidence (C)**
(Combination therapy)
Level of Confidence – **Low**

Strength of Evidence – **Moderately Not Recommended, Evidence (B)**
(Stand-alone treatment)
Level of Confidence – **Low**

Indications:	Adjunctive use with ribavirin and interferon beta-1b in moderately and severely affected patients with COVID-19 [572]. Evidence suggests better efficacy if administered within 7 days of symptom onset; after 7 days, data suggest no differences between this combination therapy and lopinavir-ritonavir [572] .
Benefits:	Faster symptom resolution, viral clearance, and hospital discharge. Reduced need for a ventilator or ICU stay.
Harms:	Nausea, diarrhea, hepatitis.
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect, prolongation of QT interval.
Frequency/Dose/Duration:	The regimen used for the treatment of COVID-19 is lopinavir 400mg, ritonavir 100mg every 12hrs, ribavirin 400mg every 12hrs, plus 3 doses of 8M IU interferon beta-1b on alternate days [572].
Rationale:	One open-label RCT found combination therapy of lopinavir 400mg, ritonavir 100mg every 12hrs, ribavirin 400mg every 12hrs, plus 3 doses of 8M IU interferon beta-1b on alternate days to be superior to lopinavir-ritonavir [572]. However, another trial found comparable faster clinical improvement (9 vs 11 days), fewer adverse events, and

~67% reduction in mortality (6.1 vs. 18.2%) when comparing treatment with interferon beta-1-b with treatment with the control group (lopinavir-ritonavir/HCQ or atazanavir/ritonavir/HCQ) [573], which could suggest that the only medication effective in the triple therapy is the interferon beta-1b.

Lopinavir-ritonavir as a stand-alone antiviral treatment has been trialed in four RCTs, all of which showed a lack of efficacy compared with standard care [511, 571, 574, 575]. Another double-blind RCT also suggested lack of efficacy, although it may have been underpowered [574]. One RCT treated severe patients and the other treated mild/moderately severe patients at an average of 4–5 days duration. It is unclear if lopinavir-ritonavir would be effective if provided earlier in the clinical course. These medications have also been suggested to be inferior to favipiravir in a non-randomized comparative trial [562].

Based on the one moderate-quality RCT showing evidence of efficacy, the regimen of triple-combination therapy using lopinavir, ritonavir, ribavirin, and interferon beta-1b is recommended [572]. However, the combination of only lopinavir-ritonavir is not recommended for the treatment of COVID-19 patients.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Lopinavir-Ritonavir; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 123 articles in PubMed, 7,275 in Scopus, 68 in CINAHL, 7 in Cochrane Library, 10,610 in Google Scholar, and 11 from other sources†. We considered for inclusion 11 from PubMed, 1 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 11 from other sources. Of the 30 articles considered for inclusion, 4 randomized trials, 3 cohort studies, and 2 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Remdesivir has been used to treat COVID-19 [580-587].

Remdesivir for the Treatment of COVID-19

Recommended.

Remdesivir is recommended for the treatment of selected patients with COVID-19.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
(First 3 days of symptoms)
Level of Confidence – **Low**

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
(Beyond 3 days)
Level of Confidence – **Low**

Indications:	Severe COVID-19 patients, with <94% O_2 saturation or need for O_2 supplementation, mechanical ventilation, or extracorporeal membrane oxygenation [588]. Patients included in trials had creatinine clearance >30 mL/min; ALT and AST <5 times upper limit of normal.
Benefits:	Shortened ICU stay, but minimal to no impact on survival.
Harms:	Increased hepatic enzymes, diarrhea, rash, renal impairment, hypotension. However, the largest RCT did not report significantly increased adverse events in any category [452].
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect.
Frequency/Dose/Duration:	Remdesivir 200 mg IV on day 1, then 100 mg QD for 9 additional days [452, 589].
Rationale:	There is one high-quality RCT of remdesivir suggesting a lack of clinical efficacy, although it also suggests non-significant trends toward earlier clinical improvements [590]. A larger, moderate-quality NIH trial showed modest efficacy, including 31% shorter ICU stays and earlier clinical improvements. A RCT comparing remdesivir with standard care found a trend towards better results with a 5-day course of remdesivir [591]. However, one RCT found a lack of efficacy [511]. None of the RCTs was able to show statistically improved survival, although the NIH trial trended toward improved survival [452]. There is one case series suggesting a fairly low death rate (13%) [589] and another non-randomized study suggesting potential efficacy [592]. A low-quality RCT found no difference between 5 and 10 days of treatment [593]. There is evidence that remdesivir inhibits viral replication in vitro studies [516]. It is possible that remdesivir is more effective if administered in the viral replication stage. Remdesivir is invasive (IV), has minimal adverse effects, is high cost, has evidence of modest efficacy (particularly for the treatment of hospitalized patients requiring oxygen), and thus is selectively recommended. There are other treatments with stronger efficacy at reducing mortality (e.g., glucocorticosteroids, low-molecular-weight heparin).

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Remdesivir; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 161 articles in PubMed, 3268 in Scopus, 16 in CINAHL, 2804 in Cochrane Library, 10300 in Google Scholar, and 6 from other sources†. We considered for inclusion 11 from PubMed, 6 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 6 from Google Scholar, and 6 from other sources. Of the 30 articles considered for inclusion, 6 randomized trials, 1 case series and 0 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Low-molecular-weight heparin has been used for the treatment of hospitalized, severely affected patients with COVID-19; the degree of coagulopathy has been associated with worsened survival [595-607]. Fondaparinux and unfractionated heparin have also been recommended in the *Chest* guidelines [608]. Thrombectomies and other procedures have been performed in COVID-19 patients with known venous thromboembolism [608, 609].

Low-Molecular-Weight Heparin for the Treatment of COVID-19

Recommended.

Low-molecular-weight heparin is recommended for the treatment of select patients with COVID-19 [598, 601-603, 608, 610-625].

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – **Moderate**

Indications:

Severely affected COVID-19 patients, especially those with known evidence or suspicion of having coagulopathy (e.g., small-vessel thromboses, large-vessel arterial and/or venous thromboses [e.g., infarcts, DVTs, pulmonary emboli], thrombocytopenia, increased D-dimer, increased fibrin degradation products, prolonged coagulation times). May also be indicated for those who are hospitalized and either (i) sedentary, as there is some evidence of post-mortem coagulopathy in those without pre-morbid suspicions of coagulopathy

	and/or (ii) on a worsening clinical trajectory that suggests trending towards critical status and/or cytokine storm [626].
Benefits:	Possible improved survival, improved oxygenation, reduced time on ventilator [627], reduced risks of DVT, pulmonary emboli, myocardial infarction, cerebrovascular thromboembolic disease.
Harms:	Usual risks of heparin, particularly bleeding complications.
Indications for Discontinuation:	Recovery from COVID-19 and resolution of findings of coagulopathy with regaining of normal ambulation. Also discontinue for significant adverse effects. May be continued after hospital discharge for a period of time during recovery and while still not as active and ambulatory as pre-morbid.
Frequency/Dose/Duration:	Per manufacturer's recommendations. A stepped approach with more intensive prophylaxis for more severely affected patients has been reportedly successful [628]. Unfractionated heparin is another therapeutic option.
Rationale:	One RCT reported efficacy of enoxaparin over standard anticoagulation (unfractionated heparin, generally 5,000U TID) to significantly increase gas exchange and reduce need for ventilatory support [627]. A trial of sulodexide found reduced need for hospitalization and oxygen therapy [624]. Reductions in mortality have been reported in non-randomized studies [602, 629-633], including an estimated 47–50% reduced risk of mortality among those on therapeutic anticoagulation among 4,389 in a hospital system [626]. Another cohort of patients on mechanical ventilation was found to have a 54% reduction in mortality [631, 634]. An early escalating thromboprophylactic approach has been suggested as preventive among hospitalized patients with less severe disease [635]. Low-molecular-weight heparins are minimally invasive, have potentially significant adverse effects, are moderately costly, and have evidence suggesting associations with lower mortality rates and fewer complications among severely affected COVID-19 patients; thus, they are selectively recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to December 2020 using the following terms: Low Molecular Weight Heparin; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 60 articles in PubMed, 837 in Scopus, 11 in CINAHL, 22 in Cochrane Library, 4,410 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 16 from PubMed, 21 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 13 from Google Scholar, and 0 from other sources. Of the 51 articles considered for inclusion, 2 randomized trials and 13 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Various interleukin-6 receptor antagonists have been used for the treatment of hospitalized patients with COVID-19 [475, 636-671].

Interleukin-6 (IL-6) Receptor Antagonists (Tocilizumab, Sarilumab, and Siltuximab) for the Treatment of COVID-19

Not Recommended.

Interleukin-6 inhibitors (sarilumab, siltuximab, and tocilizumab) are not recommended for the treatment of patients with COVID-19.

Strength of Evidence – **Not Recommended, Evidence (C)**
Level of Confidence – **Low**

Rationale:

One moderate-quality trial suggested a reduced need for mechanical ventilation but no improved survival [672], while three other moderate-quality RCTs found a lack of efficacy of tocilizumab [673-675]. One moderate-quality RCT found trends towards reduced mortality by 2 weeks but not 4 weeks associated with tocilizumab [676]. One controlled study suggested increased adjusted survival rates among the group of patients treated with tocilizumab, although there were baseline differences likely favoring survival among the treated [640]. Another controlled but non-randomized study of tocilizumab added to a standard-care regimen of HCQ, lopinavir, plus ritonavir suggested efficacy if administered earlier in the hospital course [475]. One retrospective study found no benefit of tocilizumab [639]. One case series suggested significant survival and oxygenation benefits [636].

As there is now evidence of a lack of efficacy of the IL-6 receptor antagonists, they are not recommended. There also are currently other treatments with demonstrated efficacy.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Interleukin-6, tocilizumab, sarilumab, siltuximab; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study

clinical trial; non-randomized controlled trials as topics. We found and reviewed 436 articles in PubMed, 5,491 in Scopus, 66 in CINAHL, 116 in Cochrane Library, 12,300 in Google Scholar, and 6 from other sources†. We considered for inclusion 17 from PubMed, 21 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 8 from Google Scholar, and 6 from other sources. Of the 53 articles considered for inclusion, 5 randomized trials, 1 case series and 5 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Baricitinib is an orally bioavailable reversible inhibitor of Janus kinases 1 and 2 (JAK 1/2) typically used to rheumatoid arthritis. It has anti-inflammatory, immunomodulating, and antineoplastic activities, and has an FDA emergency use authorization (EUA) for use in COVID-19 infection due to its antiviral effects. Baricitinib has been used for the treatment of patients with COVID-19 [677-681].

Baricitinib for the Treatment of COVID-19

Recommended.

Baricitinib is moderately recommended for the treatment of select patients with COVID-19 [594].

Strength of Evidence – **Moderately Recommended, Evidence (B)**
Level of Confidence – **Moderate**

Indications:	Severely affected patients with COVID-19 with cytokine storm manifestations, including ARDS. Also indicated for those requiring supplemental oxygen and/or mechanical ventilation. Other treatments may be combined (e.g., glucocorticosteroids). The U.S. FDA issued an Emergency Use Authorization for use in combination with remdesivir [682, 683].
Benefits:	Improved recovery time, clinical outcomes, oxygenation, reduced need for ICU stay. Possible 35% reduced 28-day mortality.
Harms:	Fever, chills, tiredness, muscle pain, increased urination, stomach pain, diarrhea, weight loss, cough, dyspnea.
Indications for Discontinuation:	Completion of a course, intolerance, adverse effects.
Frequency/Dose/Duration:	Doses used have included 4 mg loading then 2 mg/day and 4 mg/day [678].
Rationale:	One high-quality trial found that adding baricitinib to remdesivir compared with remdesivir alone resulted in one less day of ICU stay. The evidence was stronger in the non-mechanical ventilated group

with a 44% reduction in recovery time, and there was a trend in a 35% reduction in 28-day mortality [594, 682, 683]. There are multiple non-randomized studies suggesting efficacy at mitigating the cytokine storm. A non-randomized trial found that the addition of baricitinib to glucocorticosteroids was associated with improved clinical outcomes, including an 82% reduced need for supplemental oxygen at discharge [678]. A comparative consecutive case series suggested significant benefits, such as eliminating ICU transfers and 58% vs. 8% discharge at 2 weeks [681]. Baricitinib is invasive, has some adverse effects, is costly, has some evidence of strong efficacy, and thus is recommended for select patients.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Baricitinib, Olumiant; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 15 articles in PubMed, 1,177 in Scopus, 2 in CINAHL, 14 in Cochrane Library, 2,670 in Google Scholar, and 1 from other sources†. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 8 from Google Scholar, and 1 from other sources. Of the 10 articles considered for inclusion, 1 randomized trial and 2 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Casirivimab plus imdevimab are recombinant human monoclonal antibodies that bind to nonoverlapping epitopes of the SARS-CoV-2 spike protein receptor-binding domain and have been used to treat COVID-19. These have been approved for use by FDA under the emergency use authorization provision [684].

Casirivimab plus Imdevimab for the Treatment of COVID-19

Recommended.

Casirivimab plus imdevimab is recommended for the treatment of patients with mild to moderate COVID-19.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – **Low**

Indications:	Generally only for outpatient treatment of mild to moderate COVID-19 cases and for those at high risk of disease progression. FDA criteria for adults include BMI 35+, chronic renal disease, diabetes mellitus, immunocompromising condition, current receipt of immunosuppressive treatment, age 65+, age 55+ with comorbidity (cardiovascular disease, hypertension, COPD). Oxygen therapy is an exclusion.
Benefits:	Milder case with reduced risk of hospitalization.
Harms:	Unclear
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect.
Frequency/Dose/Duration:	N/A
Rationale:	Data provided to the FDA suggest a reduction of 67% in the risk of hospitalization (9% vs. 3%) [685]. An NIH panel felt more data are needed prior to a recommendation. Casirivimab plus imdevimab have apparent preliminary evidence suggesting efficacy. Because there are so few medications with proven efficacy for this stage of disease to prevent severe outcomes, these medications are recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to December 2020 using the following terms: Casirivimab, Imdevimab; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 0 articles in PubMed, 0 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 32 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Bamlanivimab is a neutralizing monoclonal IgG1 antibody that targets the receptor-binding domain of the spike protein of SARS-CoV-2 and has been used to treat COVID-19. It has been approved for use by the FDA under the emergency use authorization provision [686, 687].

Bamlanivimab for the Treatment of COVID-19

Recommended.

Bamlanivimab is recommended for the treatment of patients with mild to moderate COVID-19 [688].

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – **Low**

Indications:	Generally only for outpatient treatment of patients with mild to moderate COVID-19 cases and those at high risk of disease progression. FDA criteria for adults include BMI 35+, chronic renal disease, diabetes mellitus, immunocompromising condition, current receipt of immunosuppressive treatment, age 65+, age 55+ with comorbidity (cardiovascular disease, hypertension, COPD). Oxygen therapy is an exclusion.
Benefits:	Milder case with reduced risk of hospitalization.
Harms:	Unclear. Reported reactions include anaphylaxis and a serious infusion-related reaction.
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect.
Frequency/Dose/Duration:	N/A
Rationale:	One moderate-quality trial found marked reductions in the need for hospitalization or need for emergency room visits compared with placebo, while also reporting reduced viral loads [689]. Data provided to the FDA suggest a reduction of 68–84% in the risk of combined 28-day hospitalization, emergency department visit, or death [686]. Another study suggested a 72% reduction in the risk of hospitalization among those at high risk [686]. Bamlanivimab has quality evidence of considerable efficacy and is thus recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to December 2020 using the following terms: Bamlanivimab; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 0 articles in PubMed, 5 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 85 in Google Scholar, and 1 from other sources†. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 1 article considered, 1 randomized trial and 0 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Ivermectin has been used for the treatment of COVID-19 [690-697].

Ivermectin for the Treatment of COVID-19

No Recommendation.

There is no recommendation regarding ivermectin for the treatment of patients with mild to moderate COVID-19 [691-708].

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – **Low**

Rationale: There is one moderate-quality RCT comparing usual care to usual care plus ivermectin, which found no benefits when started within 7 days of symptom onset [691]. Another found a lack of benefit when started within 7 days of symptom onset [690]. Two small RCTs showed an association of ivermectin with subsequently lower viral loads, but the studies did not have meaningful clinical outcomes [692, 693]. Thus, the available evidence does not well target the high viral replication stage that occurs at symptom onset. Because the quality literature does not clearly show clinical efficacy, there is no recommendation regarding ivermectin.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to December 2020 using the following terms: Ivermectin, Stromectol; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 18 articles in PubMed, 1095 in Scopus, 6 in CINAHL, 35 in Cochrane Library, 2757 in Google Scholar, and 0 from other sources†. We considered for inclusion 5 from PubMed, 0 from Scopus, 0 from CINAHL, 2 from Cochrane Library, 11 from Google Scholar, and 0 from other sources. Of the 18 articles considered for inclusion, 8 randomized trials and 3 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy.

The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Convalescent COVID-19 antibodies have been used to treat COVID-19 [670, 709-724].

Convalescent COVID-19 Antibodies

No Recommendation.

There is no recommendation for or against the use of convalescent antibodies for the treatment of patients with COVID-19.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – **Low**

Indications:	Generally only for severely affected patients with COVID-19 and after other exhausting other interventions with stronger evidence of efficacy (especially monoclonal antibodies early in the course of disease). Timing of convalescent antibodies is best in the viral replication stage [725]. There are three pathways for administration: 1) clinical trials, 2) expanded use, and 3) single-patient emergency Investigational New Drug. FDA requirements include laboratory confirmation and severe disease (dyspnea, respiratory rate >30, O_2 saturation ≤93%, or lung infiltrates >50% within 24-48 hrs) or life-threatening disease (respiratory failure, septic shock, and/or multiorgan failure or dysfunction) and informed consent [726].
Benefits:	Expected reduced need for a ventilator, ICU stay.
Harms:	Allergic reactions, thrombotic events.
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect.
Frequency/Dose/Duration:	N/A
Rationale:	Multiple moderate-quality trials found lack of efficacy [576, 727-729]. A moderate-quality RCT found significant improvement in dyspnea and fatigue, although no benefits regarding mortality or disease progression at day 28 [730]. One moderate-quality trial suggested potential reduction in the need for mechanical ventilation [731]. There is one low-quality RCT suggesting a lack of efficacy [724]. There are few other studies of convalescent antibodies [732, 733]. However, they were reportedly successful in one case series [734] and have been successfully used for other diagnoses, including Ebola [735, 736]. Convalescent antibodies are invasive, have adverse effects, and are costly; however, the quality data are conflicting and thus there is no recommendation.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: convalescent, antibodies; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial,

controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 15 articles in PubMed, 1 in Scopus, 1 in CINAHL, 1 in Cochrane Library, 1 in Google Scholar, and 13 from other sources†. We considered for inclusion 9 from PubMed, 1 from Scopus, 1 from CINAHL, 1 from Cochrane Library, 3 from Google Scholar, and 13 from other sources. Of the 28 articles considered for inclusion, 7 randomized trials, 1 case series, and 3 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Glucocorticosteroids for the Treatment of COVID-19

Recommended.

Glucocorticosteroids are recommended for the treatment of COVID-19 [738-741]. There are other indications for use that may occur in the context of treatment of COVID-19 (e.g., asthma, COPD) (pending publication of UK trial data [449, 450]).

Strength of Evidence – **Moderately Recommended, Evidence (B)**
Level of Confidence – **Moderate**

Indications:	Hospitalized patients with moderate or severe COVID-19. Especially effective reportedly for those critically ill on ventilators, requiring supplemental oxygen and/or cardiovascular support.
Benefits:	A meta-analysis estimated a 36% reduction in mortality with dexamethasone, 31% reduction with hydrocortisone, and 9% reduction with methylprednisolone [742]. One trial estimated a reduced mortality by 20% if requiring supplemental oxygen and 35% if ventilated. A reduced number of ventilator days has also been reported.
Harms:	Hyperglycemia, risk of secondary infection, higher blood pressure.
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect.
Frequency/Dose/Duration:	Different treatments have been used. There are no comparative trials and optimal dosing is somewhat unclear. Medications and doses used have included: • Dexamethasone 6 mg PO or IV QD x 10 days or until discharge (or equivalent dose)s. • Hydrocortisone 50mg or 100mg every 6 hours [743].

Rationale: There are multiple RCTs, with all larger sized studies suggesting efficacy [743-747]. A meta-analysis estimated a 36% reduction in mortality with dexamethasone, 31% reduction with hydrocortisone, and 9% reduction with methylprednisolone [742]. A large RCT found mortality reductions with dexamethasone [449, 450, 745]. An RCT found a 65% increase in ventilator-free days from 4.0 to 6.6 days over a 28-day period, although there was no difference in mortality [744]. Another RCT found superiority of glucocorticosteroid [743]. Two RCTs of modest size found no significant benefits, but appear underpowered [524, 748]. Another negative study used a low dose of hydrocortisone [748]. As glucocorticosteroids have moderate adverse effects, low costs, and have significant efficacy in reducing mortality based on meta-analyses, they are moderately recommended for treatment of COVID-19.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Glucocorticosteroids; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 137 articles in PubMed, 292 in Scopus, 13 in CINAHL, 6 in Cochrane Library, 4470 in Google Scholar, and 5 from other sources†. We considered for inclusion 22 from PubMed, 3 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 33 from Google Scholar, and 5 from other sources. Of the 63 articles considered for inclusion, 0 randomized trials, 2 cohort studies, and 3 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Interferon beta-1b has been used both as sole therapy and combination therapy for the treatment of patients with COVID-19 [556, 751].

Interferon Beta-1b for the Treatment of COVID-19

Recommended.

Adjunctive use of interferon beta-1b is recommended for the treatment of selected patients with COVID-19.

Strength of Evidence – **Moderately Recommended, Evidence (B)**
(Stand-alone treatment)
Level of Confidence – **Low**

Strength of Evidence – **Recommended, Evidence (C)**
(Combination therapy)
Level of Confidence – **Low**

Indications:	Adjunctive use with lopinavir-ritonavir and ribavirin in moderately and severely affected patients with COVID-19 [572]. Evidence suggests better efficacy if administered within 7 days of symptom onset; after 7 days, data suggest no differences between this combination therapy and lopinavir-ritonavir [572] .
Benefits:	Faster symptom resolution, viral clearance, and hospital discharge. Reduced need for a ventilator or ICU stay.
Harms:	Nausea, diarrhea, hepatitis.
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect, prolongation of QT interval.
	*Frequency/Dose/Duration:*Two successful trials utilized sole therapy with interferon beta-1b 250ug SQ QOD for 2 weeks [573]. The combination regimen used successfully for the treatment of COVID-19 is lopinavir 400mg, ritonavir 100mg every 12hrs, ribavirin 400mg every 12hrs, plus 3 doses of 8M IU interferon beta-1b on alternate days [572].
Rationale:	Two successful moderate-quality trials utilized sole therapy with interferon beta-1b and one study found accelerated clinical improvement and a non-statistically significant reduction in death by 67% at 1-month [573]. The second trial found comparable results to the other RCT with faster clinical improvement (9 vs 11 days), fewer adverse events, and ~67% reduction in mortality (6.1 vs. 18.2%) when compared with treatment with the control group (lopinavir-ritonavir/HCQ or atazanavir/ritonavir/HCQ) [573]. One open-label RCT found combination therapy of lopinavir 400mg, ritonavir 100mg every 12hrs, ribavirin 400mg every 12hrs, plus 3 doses of 8M IU interferon beta-1b on alternate days to be superior to lopinavir-ritonavir [572]. However, one RCT found a lack of efficacy [511]. Based on the two moderate-quality RCTs showing considerable evidence of efficacy, stand-alone treatment with interferon beta-1b is moderately recommended.

A moderate-quality RCT found a lack of efficacy for combined favipavir with interferon beta-1b compared with HCQ for moderate to severe COVID-19 pneumonia patients [558].

Based on one trial with demonstrated efficacy, the regimen of triple-combination therapy using lopinavir, ritonavir, ribavirin, and interferon beta-1b is recommended [572], although it should be noted that it is possible that the only medication effective in the combination therapy is interferon beta-1b.

Other interferons are being investigated. One successful trial used a different interferon in a Phase 2 trial that was nebulized interferon-1a (SNG001) [752]. A trial with interferon beta-1a when added to (lopinavir-ritonavir/HCQ or atazanavir/ritonavir/HCQ) found earlier 14-day hospital discharge rates (67% vs. 44%) [753]. A trial on interferon-kappa plus TFF2 and including many potentially active cointerventions found reduced viral RNA [754].

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Interferon Beta-1b; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 11 articles in PubMed, 814 in Scopus, 7 in CINAHL, 7 in Cochrane Library, 6,630 in Google Scholar, and 6 from other sources†. We considered for inclusion 0 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 6 from other sources. Of the 10 articles considered for inclusion, 7 randomized trials and 0 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Ribavirin has been used to treat patients with COVID-19 [755-758].

Ribavirin for the Treatment of COVID-19

Recommended.

Adjunctive use of ribavirin is recommended for the treatment of selected patients with COVID-19.

Strength of Evidence – **Recommended, Evidence (C)**
(Combination therapy)
Level of Confidence – **Low**

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
(Stand-alone treatment)
Level of Confidence – **Low**

Indications:	Adjunctive use with lopinavir-ritonavir and interferon beta-1b in moderately and severely affected patients with COVID-19 [572]. Evidence suggests better efficacy if administered within 7 days of symptom onset; after 7 days, data suggest no differences between this combination therapy and lopinavir-ritonavir [572].
Benefits:	Faster symptom resolution, viral clearance, and hospital discharge. Reduced need for a ventilator or ICU stay.
Harms:	Nausea, diarrhea, hepatitis.
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect, prolongation of QT interval.
Frequency/Dose/Duration:	The regimen used for the treatment of COVID-19 is lopinavir 400mg, ritonavir 100mg every 12hrs, ribavirin 400mg every 12hrs, plus 3 doses of 8M IU interferon beta-1b on alternate days [572].
Rationale:	One open-label RCT found combination therapy of lopinavir 400mg, ritonavir 100mg every 12hrs, ribavirin 400mg every 12hrs, plus 3 doses of 8M IU interferon beta-1b on alternate days to be superior to lopinavir-ritonavir [572]. Two other RCTs were underpowered for meaningful clinical differences [759, 760]. Based on the one moderate-quality RCT showing evidence of efficacy, the regimen of triple-combination therapy using lopinavir, ritonavir, ribavirin, and interferon beta-1b is recommended [572]. However, there is no quality evidence demonstrating efficacy and thus no recommendation for stand-alone treatment with ribavirin.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: ribavirin; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies;

clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 47 articles in PubMed, 1,529 in Scopus, 11 in CINAHL, 9 in Cochrane Library, 6,580 in Google Scholar, and 1 from other sources†. We considered for inclusion 3 from PubMed, 2 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 1 from other sources. Of the 8 articles considered for inclusion, 1 randomized trial and 1 systematic review met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Zinc serum levels have been found to be low in those with more severe COVID-19 disease [761-763]. Zinc supplementation has been used typically as adjunctive treatment to reduce severity of COVID-19 [442, 764].

Zinc for the Treatment of COVID-19

Recommended.

Zinc is recommended for potential prevention of more severe disease as well as for the treatment of patients with COVID-19.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – **Low**

Indications:	Ongoing use during the epidemic, as well as for mild, moderate, and severe COVID-19 disease. Also especially recommended for those with zinc deficiency.
Benefits:	Potential to reduce disease severity
Harms:	Negligible
Indications for Discontinuation:	After cessation of the epidemic
Frequency/Dose/Duration:	10-15 mg/day (>100% Recommended Daily Allowance)
Rationale:	There are no quality RCTs testing the value of zinc alone [439-442]. There is one low-quality study suggesting lack of efficacy of zinc added to HCQ [765] and another low-quality trial found lack of efficacy of high-dose zinc and ascorbic acid added to usual care [443]. However, one study of HCQ, AZT, and zinc suggested earlier treatment resulted in 84% lower risk of hospitalization and lower risk of death among patients treated by ~day 4 [439]. A large-scale pre/post intervention study showed that adjunctive use of zinc to hydroxychloroquine was

associated with a 44–49% decreased need for ventilation, admission to the ICU, mortality, or transfer to hospice, and increased the frequency of being discharged home [442]. This is supported by evidence that hydroxy/chloroquine are zinc ionophores, which increase intracellular zinc and reduce or prevent viral replication in laboratory studies [472, 473].

Zinc supplementation has negligible adverse effects and has been associated with improved outcomes in non-randomized studies; thus, it is recommended with insufficient evidence.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Zinc; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 4 articles in PubMed, 562 in Scopus, 8 in CINAHL, 5 in Cochrane Library, 40,610 in Google Scholar, and 4 from other sources†. We considered for inclusion 0 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 7 from Google Scholar, and 4 from other sources. Of the 13 articles considered for inclusion, 2 randomized trials, 1 case study, 1 retrospective analysis and 0 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Vitamin D levels have been low in those with more severe COVID-19 disease and supplementation has been used for the treatment of patients with COVID-19 [766-783]. It has also been used in patients with COVID-19 to maintain bone health.

Vitamin D for the Treatment of COVID-19

Recommended.

Vitamin D is recommended for potential prevention of more severe disease as well as for the treatment of patients with COVID-19.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – **Low**

Indications:	Ongoing use during the epidemic, as well as for mild, moderate, and severe COVID-19 disease. High-dose use may be considered for those with onset of COVID-19 disease. Also recommended for those with vitamin D deficiency and/or risks for deficiency.
Benefits:	Potential to reduce disease severity
Harms:	Negligible
Indications for Discontinuation:	After cessation of the epidemic
Frequency/Dose/Duration:	A moderate-quality trial utilized calcifediol 0.532mg on day 1, 0.266mg days 3 and 7 and weekly in addition to HCQ+AZT until hospital discharge [784]. Other daily dosing used among healthy individuals at risk include 600 IU/day for up to 70 years of age and 800 IU/day for those over 70 years of age (>100% Recommended Daily Allowance).
Rationale:	A moderate-quality RCT used calcifediol compared with no calcifediol in addition to HCQ+AZT until hospital discharge and found a 96% reduction in risk of needing an ICU stay [784]. Another RCT for treatment of asymptomatic of mildly symptomatic but vitamin D deficient individuals treated with vitamin D supplementation cleared virus sooner and with reduced fibrinogen levels [785]. One RCT found lack of efficacy using only one administration of 200,000 IU, although the risk of mechanical ventilation trended towards reduction by 51% (p=0.09) [786]. Vitamin D levels have been strongly correlated with COVID-19 disease severity [444, 446, 447], with a reported ~8-fold risk of a severe outcome and ~20-fold risk of a critical outcome among those with low vitamin D levels [444]. Vitamin D supplementation has negligible adverse effects, especially over shorter periods of time, and low vitamin D levels have been strongly associated with worse outcomes in non-randomized studies. Vitamin D levels also fall with illness status affecting bone health. Thus, vitamin D supplementation is recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Vitamin D; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random

allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 29 articles in PubMed, 2706 in Scopus, 11 in CINAHL, 27 in Cochrane Library, 11,210 in Google Scholar, and 3 from other sources†. We considered for inclusion 5 from PubMed, 11 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 7 from Google Scholar, and 3 from other sources. Of the 26 articles considered for inclusion, 3 randomized trials, 3 retrospective studies, and 0 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Rehabilitation

Overview

Although most patients with COVID-19 completely recover, some cases may experience a multitude of disorders [787]. It is beyond the scope of this guideline to address every possible presentation, combination, and permutation. Indeed, it is arguably impossible to do so. Instead, this guideline addresses what currently appear to be the most common conditions needing rehabilitative services after COVID-19. This also may suggest a framework for approaching treatment of less common presentations.

For simplicity, clarity, and consistency with other diagnoses and the general medical literature, this review defines symptoms lasting less than 1 month as *acute*, from 1–3 months as *subacute*, and more than 3 months as *chronic*. Some of the alternate terms for these conditions include “ongoing symptomatic,” “post-COVID syndrome” [292], “post-acute sequalae of COVID,” and “long COVID.”

The severity of the COVID-19 infection has been associated with the risk of long-term symptoms and impairments [788]. For example, approximately two-thirds of outpatients diagnosed with COVID-19 return to normal health by the fourth week [789]. In contrast, of those who were evaluated in an emergency department (66% hospitalized), 50.9% developed chronic COVID-19 symptoms [790]. Yet, a mild case does not preclude development of chronic COVID-19 symptoms. The comparatively large numbers of mildly affected patients likely mean

that most patients with chronic symptoms will be found in this group, despite the higher risk among those who are more severely affected.

Evidence also suggests that symptoms improve over time. Overall, 5–51% of patients have symptoms persisting up to 12 weeks [293, 791-793], whereas 2–15% have symptoms beyond 12 weeks after onset [790, 791, 793-795]. Long-term symptoms have wide-ranging estimates of prevalence and include fatigue (17–98%) [293, 790-793, 796-798], dyspnea (17–93%) [293, 790-793, 796-798], cough (29–43%), chest pain (44–88%) [293, 790-792, 796, 797], back pain, muscle pain, and headache (38–91%) [790]. Cognitive changes, such as impaired memory, concentration, and multitasking ability, are also reportedly common. Risk factors for chronic COVID-19 beyond severity of the initial disease appear to include increased age, having more comorbidities, and psychological disorders [793, 799].

Acute mental health disorders are common and reportedly affect 55% of those having visited an emergency department (75% were hospitalized) in the first month [800]. New-onset psychiatric illness was reported in 5.8% [801]. Of these, 4.7% were anxiety disorders and 2% were depression [801]. One report noted persistence of post-traumatic stress among survivors [802]. Another reported PTSD symptoms related to illness at 4–8 weeks after discharge among 46.9% of ICU survivors and 23.5% of ward survivors [788].

Some rehabilitation protocols are heavily multidisciplinary, reportedly including pulmonologists, physiatrists, neurologists, cardiologists, physical therapists, occupational therapists, psychologists, neuropsychologists, psychiatrists, speech therapists, and nutritionists [803, 804]. Telemedicine has been used for rehabilitation of COVID-19 patients [804, 805]. There are no quality trials to assess the various disciplines on rehabilitation teams, comparative trials of different treatment regimens, and/or efficacy of telemedicine approaches.

Pulmonary Rehabilitation

Dyspnea is typically the presenting complaint for emergency and hospitalized treatment. However, dyspnea has been shown to persist into many chronic COVID-19 case histories [788]. The most common spirometric abnormalities after initial recovery are reduced diffusion capacity and restrictive ventilatory defects [806, 807]. Risk and severity of spirometric abnormalities are correlated with COVID-19 severity [807].

Pulmonary rehabilitation is used for COVID-19 [808] and has been shown to be successful for functional improvements in individuals with non-COVID-related pulmonary deficits [809, 810], including those from pneumonia [811], interstitial lung disease [812], and SARS [813]. It commonly includes behavioral components [814].

Pulmonary Rehabilitation for Treatment of Pulmonary Problems Related to COVID-19

Recommended.

Pulmonary rehabilitation is recommended for the treatment of pulmonary problems related to COVID-19.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – **Moderate**

Indications:	Indicated for COVID-19 affected patients with pulmonary dysfunction and/or dyspnea, especially when combined with activity reductions or exercise intolerances attributed to the infection's pulmonary complications. Earlier institution of exercises, as tolerated, is advised to counter the debility associated with the disease [814]. Careful cardiac evaluation (e.g., 24-hr ECG, echocardiogram, exercise testing, MRI [815]) is also indicated due to the probability of cardiac abnormalities.
Benefits:	Improved pulmonary function, maximum ventilation, health-related quality of life, emotional involvement in everyday life, activity levels, 6-minute walk distance, peak workload, exercise and/or activity endurance.
Harms:	As fatalities in the recovery period have been thought to be due to arrhythmias, a careful assessment of cardiac involvement is advised to help guide the onset and progression of exercises. Those with evidence of thrombotic tendencies and/or multi-system involvement may have greater risk of harm from aggressive exercise regimens.
Indications for Discontinuation:	Completion of a treatment course, noncompliance, reaching a plateau in recovery.
Frequency/Dose/Duration:	An individualized but interdisciplinary treatment regimen is usually formulated based on a comprehensive baseline assessment [812, 816]. Careful cardiac evaluation (e.g., 24-hr ECG, echocardiogram, exercise testing, MRI [815]) is also indicated due to the probability of cardiac abnormalities, which may result in a recommendation to delay onset of exercises and/or slow the rate of progression. While program components include education, exercise training, and behavior change to "promote the long-term adherence to health-enhancing behaviours [816]," exercise training is the central component, and is usually either walking or cycling. One consensus statement recommended beginning at not more than 3 METS, especially when supplemental oxygen is needed [815]. Another review suggested an exercise regimen of 18-60 min at 55–80% of VO_2Max or 60–80% of heart rate maximum, 1–3 times per week [817]. Program duration is typically at least 4 weeks.
Rationale:	There is one low-quality pilot study suggesting efficacy for treatment of COVID-19 patients [818], but no quality trials. There are many trials documenting efficacy for other pulmonary conditions [809-813]. Pulmonary rehabilitation has negligible adverse effects, is moderate to high cost depending on number of treatments and durations required, and is recommended for patients meeting indications.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to February 2021 using the following terms: rehabilitation;

coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 112 articles in PubMed, 4,699 in Scopus, 3 in CINAHL, 13 in Cochrane Library, 34,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 8 from PubMed, 5 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 13 articles considered for inclusion, 1 randomized trial and 8 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Cardiac Rehabilitation

Cardiomyopathy, cardiac muscle damage, and arrhythmias have been reported to affect 30–78% of patients [304], and cardiac problems contribute to COVID-19 fatalities [304-307]. Vascular inflammation, hypotension, and direct muscle damage are all potential mechanisms [819, 820]. The probability of cardiac problems is correlated with the severity of the COVID-19 infection, including cardiac biomarkers (e.g., troponin) and numbers of comorbidities [819, 820], although ongoing, subclinical cardiac problems have been detected among recovered patients [307, 821].

Cardiac rehabilitation is used for COVID-19 [822] and has been shown to be successful for functional improvements in individuals with non-COVID-related cardiac deficits [823-827], including those from myocardial infarction [819], as well as quality-of-life measures.

Cardiac Rehabilitation for Treatment of Cardiac Problems Related to COVID-19

Recommended.

Cardiac rehabilitation is recommended for the treatment of cardiac problems related to COVID-19.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – **Moderate**

Indications: Indicated for COVID-19 affected patients with cardiac dysfunction and/or dyspnea, especially when combined with activity reductions or

	exercise intolerances attributed to the infection's cardiac complications. A consensus statement advises waiting 2–3 weeks after cessation of COVID-related symptoms to start exercise [815], although there is no quality evidence to support the expert consensus.
Benefits:	Improved cardiac function, health-related quality of life, 6-minute walk test, time to perform 10 sit-to-stands, emotional involvement in everyday life, activity levels, exercise and/or activity endurance [828].
Harms:	As fatalities in the recovery period have been thought to be due to arrhythmias, a careful assessment of cardiac involvement is advised to help guide the onset and progression of exercises. Those with evidence of thrombotic tendencies, and/or multi-system involvement may have greater risk of harm from aggressive exercise regimens.
Indications for Discontinuation:	Completion of a treatment course, noncompliance, reaching a plateau in recovery.
Frequency/Dose/Duration:	An individualized but multidisciplinary treatment regimen is usually formulated based on a comprehensive baseline assessment [829, 830]. Careful cardiac evaluation (e.g., 24-hr ECG, echocardiogram, exercise testing, MRI [815]) is indicated due to the probability of cardiac abnormalities, which may result in a recommendation to delay onset of exercises and/or slow the rate of progression. Program components typically include education, aerobic exercise training, strength/resistance training, and psychological factors [831]. Exercise training is the central component. Aerobic exercise is usually either walking or cycling. Strength training is another component thought to be important in cardiac rehabilitation [830]. A slowed and cautious progression may be indicated in COVID patients due to the underlying cardiac disease, and tailoring regarding arrythmias and monitoring for exercise-induced arrythmias has been recommended [830]. Program duration is typically at least 4 weeks. High-demand occupations may be analogized to sports, where a consensus recommendation is for resumption of sports if: (1) left ventricular systolic function is normal, (2) serum biomarkers of cardiac injury are normal, (3) absence of relevant cardiac arrythmias on 24-hr monitoring, and (4) absence of relevant cardiac arrythmias on 24-hr monitoring on exercise testing [815].
Rationale:	There is one low-quality pilot study suggesting efficacy for treatment of COVID-19 patients [832], but no quality trials. There are many trials documenting efficacy for other pulmonary conditions. Cardiac rehabilitation has negligible adverse effects, is moderate to high cost depending on numbers of treatments and durations required, and is recommended for patients meeting indications.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to February 2021 using the following terms: rehabilitation; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 112 articles in PubMed, 4,699 in Scopus, 3 in CINAHL, 13 in Cochrane Library, 34,300

in Google Scholar, and 0 from other sources†. We considered for inclusion 8 from PubMed, 5 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 13 articles considered for inclusion, 1 randomized trial and 8 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Exercise Therapy

Research has supported rehabilitation for hospital-associated deconditioning prior to the COVID pandemic [833-835]. Early mobilization of COVID-19 patients has been encouraged [836], yet others suggest delaying until after the acute COVID-related symptoms have been resolved for 2-3 weeks [815]. Early therapy has also been used in the ICU and pre-discharge for COVID patients [837-839]. A review of physical therapy suggests that there will eventually be efficacy, but currently the available literature is sparse and mostly low quality [840].

For those with fibromyalgia, please refer to the ACOEM Chronic Pain Guideline. Also consider chronic fatigue syndrome and myalgic encephalomyelitis [841].

Exercise Therapy for Physical Debility and/or Chronic Fatigue Associated with COVID-19 **Recommended.**

Exercise therapy is recommended for the treatment of physical debility and/or chronic fatigue associated with COVID-19.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – **Moderate**

Indications:	Indicated for COVID-19 affected patients with debility and/or chronic fatigue attributed to the COVID-19. Baseline testing should indicate the area(s) of deficits (e.g., 6-min walk test; sit to stand; leg strength; grip strength). Rehabilitation should target, measure, and track progress for those specific areas.
Benefits:	Improved distance walked, strength, functional gains, ability to perform ADLs independently, return to work.
Harms:	As fatalities in the recovery period have been thought to be due to arrhythmias, a careful assessment of cardiac involvement is advised to help guide the onset and progression of exercises. Those with evidence of thrombotic tendencies and/or multi-system involvement may have greater risk of harm from aggressive exercise regimens.

Indications for Discontinuation:	Completion of course of treatment, noncompliance, reaching a plateau in recovery.
Frequency/Dose/Duration:	A multidisciplinary approach may be beneficial (e.g., physical therapy, occupational therapy, medical, psychology). Generally, sets of appointments are ordered (e.g., 6-8). Two to three appointments per week plus a home exercise program are normally prescribed. Those with marked deficits may benefit from more intensive regimens (e.g., 5 times/week). Aerobic and strengthening exercises are normally prescribed. Some exercises are ideally repeated exertions that directly target specific deficits (e.g., sit to stand or walking endurance). Objective improvement should be tracked. When there is a lack of further improvement, the course of treatment should be discontinued. Web-based programs are also possible.
Rationale:	There are no quality trials of exercise therapy for the treatment of physical debility and/or chronic fatigue attributed to COVID. Exercise therapy has negligible adverse effects, is moderate to high cost depending on numbers of treatments required and is recommended for patients meeting indications.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to February 2021 using the following terms: rehabilitation; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 112 articles in PubMed, 4,699 in Scopus, 3 in CINAHL, 13 in Cochrane Library, 34,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 8 from PubMed, 5 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 13 articles considered for inclusion, 0 randomized trials and 8 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Memory and Cognition

Memory issues are also potentially problematic for some workers. One report noted new or worsened short-term memory problems at 4–8 weeks after discharge among 18.8% of ICU patients and 17.6% of ward patients [788], yet that same study found strong relationships for some other data such as COVID severity for breathlessness and any PTSD symptoms related to illness. It is recommended that these problems be evaluated and treated. Cognitive

rehabilitation has been successfully used for various infectious disease complications, especially for HIV [842] and severe malaria [843].

Cognitive Rehabilitation for Treatment of Cognitive Problems Related to COVID-19

Recommended.

Cognitive rehabilitation is recommended for the treatment of cognitive problems related to COVID-19.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – **Moderate**

Indications:	Indicated for COVID-19 affected patients with evidence of ongoing cognitive dysfunction attributed to the infection without trending towards rapid resolution. Screening for cognitive function should be performed. Testing should indicate the area(s) of deficits and the rehabilitation should target, measure, and track progress for those specific areas.
Benefits:	Improved memory and executive functions.
Harms:	Negligible
Indications for Discontinuation:	Completion of course of treatment, noncompliance, reaching a plateau in recovery.
Frequency/Dose/Duration:	Generally, sets of appointments are ordered (e.g., 6-8), most commonly with psychology, neuropsychology and potentially speech pathology. Depending on the severity, more intensive regimens may be indicated, e.g., in acute inpatient stroke patients, daily regimens of 30min/day for 4 weeks have been used, but likely would only be indicated for the most severely affected COVID patients. Objective improvement should be tracked. When there is a lack of further improvement, the course of treatment should be discontinued and/or re-evaluated and changed to a more effective approach (e.g., addressing a different aspect of cognitive function). Web-based programs and virtual reality [844-846] are also possible. There is some evidence in stroke patients that combining cognitive rehabilitation with aerobic exercise results in superior outcomes [847].
Rationale:	There are no quality trials of cognitive rehabilitation for the treatment of memory and executive problems attributed to COVID. Cognitive rehabilitation has negligible adverse effects, is moderate to high cost depending on numbers of treatments required and is recommended for patients meeting indications.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to February 2021 using the following terms: rehabilitation; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 112 articles in

PubMed, 4,699 in Scopus, 3 in CINAHL, 13 in Cochrane Library, 34,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 8 from PubMed, 5 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 13 articles considered for inclusion, 2 randomized trials and 8 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Joint Pain

Joint pain is common in subacute and chronic COVID [289, 831, 848], with 27.3% reporting joint pain at 2 months after COVID onset [289]. Detailed guidance is available by body part in other ACOEM guidelines (see, e.g., Ankle and Foot Disorders, Elbow Disorders, Chronic Pain, Hand/Wrist/Forearm Disorders, Hip and Groin Disorders, Knee Disorders, Low Back Disorders, Neck Disorders, Shoulder Disorders).

Mental Health Disorders

Treatments for mental health disorders that result from COVID-19 have not undergone rigorous trials for efficacy. Only low-quality trials have thus far been reported. One combined anxiety, depression, and stress, reporting that cognitive behavioral therapy (CBT) was effective [849]. Another trial found progressive muscle relaxation helpful for anxiety and sleep quality [818]. Another trial found an internet-based intervention on depression and anxiety to be effective [850].

In the absence of quality evidence specific to COVID-19, analogy to existing quality evidence and evidence-based guidance is recommended for screening, diagnosis, and treatments. These are addressed in detail in guidelines on Anxiety Disorders, Depressive Disorders, and Posttraumatic Stress Disorder.

Utilizing evidence for generalized anxiety disorder, anxiety related to COVID-19 is recommended to be best initially treated with education (I), CBT (B,C), aerobic exercise (C), and strengthening exercise (I). Due to strong addictive potential, benzodiazepines are not recommended for routine use (C). Other potential early treatments include insight-oriented therapies (I), distractive methods (C), exposure therapy/prolonged exposure therapy (I), virtual reality exposure therapy (I) and mindfulness therapy (I). Other medications with evidence of efficacy include buspirone (C), quetiapine (B), beta-blockers (B), pregabalin (B), and hydroxyzine (C). Details are in the Anxiety Disorders Guideline.

Utilizing evidence for major depressive disorder, depression related to COVID is best treated initially by reducing or eliminating sedating medication (I), education (I), antidepressant medication (SSRI, SNRI, TCA, MAOI) (B), cognitive behavioral therapy (B), aerobic exercise (C), and strengthening exercise (I). Benzodiazepine medication is not recommended. Other recommended medications include antipsychotics, olanzapine/fluoxetine, agomelatine, eszopiclone, nefazodone, zolpidem for sleep disorders (C). Weight loss may be selectively indicated in patients with obesity (B). Transcranial magnetic stimulation (C), repetitive transcranial magnetic stimulation (C), low-field magnetic stimulation (B), and light therapy (C) are also potential treatments. Severe cases may be treated with electroconvulsive therapy (B). See Depressive Disorders Guideline.

Utilizing evidence for posttraumatic stress disorder, PTSD related to COVID is best treated initially with aerobic exercise (B), strengthening exercise (B), cognitive behavioral therapy (B), exposure therapy (B), prolonged exposure therapy (B), virtual reality (B), imagery rehearsal training (B), and narrative exposure therapy (C). Medications with evidence of efficacy include sertraline (B), paroxetine (B), fluoxetine (I), escitalopram (I), citalopram (C), venlafaxine (B), mirtazpine (B), phenelzine (C), nefazodone (C), quetiapine (I), olanzapine (C), and prazosin (I). Other treatments potentially indicated include guided imagery (I), deep breathing exercises (I), meditation (I), and mindfulness (I). See the Postraumatic Stress Disorder Guideline.

Appendix A. Additional Considerations for School Re-opening

Efforts at reintegration in the school environment present multiple challenges. Different stakeholders will have responsibilities that must be communicated to be effective. Below are the identified groups and potential guides. Many US districts have reopened. The guidance below is particularly designed for districts that have not yet reopened and/or for those continuing to experience community-based COVID-19 spread. Physical distancing and other measures may not be needed in districts without ongoing community spread.

Administration

- Oversee all communications to stakeholders
- Hold explanatory sessions for all groups beginning at least 1 month before the resumption of school year
- Provide written documentation to all groups identifying each one's responsibilities and expectations, such as the following:
    - Wash hands after blowing nose, coughing, sneezing, eating food, using a restroom, or working in close proximity to a colleague/student.
    - Use masks where there is community prevalence ≥5%.
    - Provide security staff with gloves and perform visual inspections of any packages, but avoid touching those packages.

    - Limit the doors for ingress and egress. Only security staff, administration, and teachers should open or close doors. Students avoid opening or closing doors.
    - If possible, have doors left open.
- Place disposable alcohol wipes throughout the facility with open garbage cans nearby, particularly near student lockers.
- Provide disposable gloves and alcohol wipes in each classroom.
- Function as an employer by following the ACOEM guidelines on return to work.
- Oversee cleaning and disinfection of the school:
    - Cleaning and disinfection should ideally be done at night after all parties have left the facility. This also allows any virus located on a fomite to degrade during that waiting period.
    - Staff should have their symptoms assessed and take their temperature every evening. If they have an elevated temperature and/or feel ill, they may not report to school.
    - Cleaning staff should use disposable gloves and gowns. After removal, they should wash hands in soap and water.
    - Cleaning staff should follow physical distancing guidelines.
    - Most dirty surfaces should be cleaned with standard cleaning products before disinfectant is used.
    - Electronic surfaces and peripheral pieces should be cleaned per manufacturer's recommendations for disinfection. These recommendations may include, e.g., cleaning with 70% alcohol with EPA-approved disinfectants for COVID-19[**] then applied. Caution is warranted as a 70% alcohol solution is flammable.
    - Trash should be removed nightly.
- Regularly monitor state and local health authority guidelines.
- Establish a stakeholder committee to monitor school issues and progress.
- Establish regular staff and student avenues to report distress from the new school experience.
- Assemblies should be avoided.
- If there is widespread transmission, consider avoiding most sport teams with some exceptions (e.g., tennis, golf, baseball, and certain track events).
- Physical education can proceed, especially outdoors, with distancing standards.
- Stagger school start times and end times to minimize crowds.
- Stagger mealtimes and break times.
- Consider bringing in portable classrooms to allow for decreased class size.
- If there is a proven or suspected case of COVID-19, the following steps are recommended:
    - All students and faculty who were in contact with the student should be informed. They do not have to get tested but should isolate for 14 days.
    - All rooms and areas used by the student should be wiped down with disposable alcohol wipes.

[**] https://www.epa.gov/pesticide-registration/list-n-disinfectants-use-against-sars-cov-2

Security Personnel

- Continue to practice physical distancing when possible.
- Monitor symptoms with an electronic questionnaire and take temperature every morning. If they have an elevated temperature and/or feel ill, they should not report to work.
- If outdoors, a face covering is recommended.
- If indoors, a face covering is required, although it does not have to be N95. N95 respirator use is a consideration for those at highest risk (e.g., oldest age groups and those with multiple comorbidities).
- Gloves should be worn.
- Request a visual inspection of any items, rather than physical, hands-on inspection.
- Doors should ideally be opened and closed by security or staff members only. Limit the doors that are used for regular ingress and egress.
- Consider using a volunteer at each entrance to provide a pumped dose of hand sanitizer for each person entering the building.
- Have a volunteer temperature-screen all entering students and staff.

Teachers and the Classroom

- Continue to practice physical distancing when possible (see current CDC guidance at https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/operation-strategy.html).
- Monitor symptoms with an electronic questionnaire and take their temperature every morning. If they have an elevated temperature and/or feel ill, they should not report to work.
- Wipe down each desk with alcohol disposable wipes between classes.
- Wear simple face coverings of loose cloth. Masks are not needed unless the teacher is in an increased risk group or community prevalence is rising above 5%.
- Teachers with multiple risk factors who are not vaccinated (e.g., comorbidities and increased age) should wear an N95 respirator if available in the classroom and must maintain strict physical distancing. If the teacher is unable to maintain strict physical distancing, then the teacher should wear an N95 respirator at all times, unless vaccinated.
- Classroom desks should ideally be set up for physical distancing (see current CDC guidance at https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/operation-strategy.html).
- Teach the science and math of COVD-19 as a practical benefit and to inform students so they can have a reasoned understanding of the pandemic.

- In space that does not allow ideal physical distancing (see current CDC guidance at https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/operation-strategy.html), considerations can include the following:
    - Half the class should participate in the class online. Online students may be at home for that day with all classes or in another room of the school.
    - Divide the lesson plan so that each group of students receives instruction but at different times of the day.
    - Increase the total amount of instruction days for the year to compensate for missed days or class size.
    - Increase the amount of distance learning material (online courses) that is covered in a topic to supplement reduced class time.
    - Install clear plastic shields on the desks and/or as room dividers. A physical barrier has a greater chance of success as an engineering solution that would minimize disruption of regularly scheduled activities.

Parents

- Continue to practice physical distancing when possible.
- Monitor symptoms with an electronic questionnaire and take their temperature every morning. If they have an elevated temperature and/or feel ill, they should not drive a carpool or enter the school.
- Discourage gatherings of large groups of children, especially if the group includes regular friends seen commonly.
- Continue an open dialogue with children about current science and best practices.
- Direct questions to their family doctor.

Students

- Continue to practice physical distancing when possible.
- Monitor symptoms with an electronic questionnaire and take their temperature every morning. If they have an elevated temperature and/or feel ill, they should not report to school.
- Assist the teachers and staff in wiping down each desk with disposable alcohol wipes between classes.
- Do not share food, drinks, or snacks with classmates.
- Wear simple face cloths. Masks are not needed unless community prevalence is ≥5%.
- Avoid large group gatherings, especially if other children are unknown.
- Do not provide transportation for classmates to and from school unless families involved are in agreement.
- Outdoor exercise is strongly encouraged.
- Meet with faculty or staff if they are experiencing difficulties in adjusting to the current social requirements.
- Special circumstances include the following:

- Special needs children may find resources strained and their ability to comply highly limited. Unless a dedicated caregiver can be provided, they may be safer to remain in distance learning for the current time, although the balance between successful learning and safety must be addressed.
- Nursery/preschool and kindergarten-age children cannot be expected to have reasonable boundary control. The recommendation for this group would be that each school have staggered drop-off and pick-up times. All children should stay in the same group (cohorting) and not switch rooms or be in the play areas outside with other children from another cohort. All toys, games, books, and outdoor play equipment will need to be wiped with alcohol at the end of the day. Outdoor games, if to be used by a different class, would need to be wiped down after each class. During times of close contact (children sitting on a lap, reading time), the teacher should use an appropriate mask. Depending on the children being taught, glove use and/or disposable gown use may be needed.
- Elementary school should ideally use staggered drop-off and pick-up times.

References

1. CDC. *Situation Summary*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/summary.html.
2. Lu, R., et al., *Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding.* The Lancet, 2020. **395**(10224): p. 565-574.
3. Lam, T.T.-Y., et al., *Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins.* Nature, 2020. **583**(7815): p. 282-285.
4. CDC. *World Map*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/world-map.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Flocations-confirmed-cases.html.
5. CDC. *Symptoms*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/about/symptoms.html.
6. Ma, V.L. and M.S. Nair. *Coronavirus May Have Spread in China Last August, Preliminary Harvard Study Suggests*. 2020; Available from: https://www.thecrimson.com/article/2020/6/12/coronavirus-satellite-research/.
7. Kuo, L. and S. Boseley. *Coronavirus may have been in Wuhan in August, study suggests*. 2020; Available from: https://www.theguardian.com/world/2020/jun/09/coronavirus-may-have-been-in-wuhan-in-august-study-suggests.
8. Faulconbridge, G., et al. *China, scientists dismiss Harvard study suggesting COVID-19 was spreading in Wuhan in August*. 2020; Available from: https://www.reuters.com/article/us-health-coronavirus-china-research/china-scientists-dismiss-harvard-study-suggesting-covid-19-was-spreading-in-wuhan-in-august-idUSKBN23G0OM.
9. Everington, K., *US investigating 'hazardous event' in Wuhan lab in October.* 2020.
10. Dilanian, K., et al. *Report says cellphone data suggests October shutdown at Wuhan lab, but experts are skeptical*. 2020; Available from: https://www.nbcnews.com/politics/national-security/report-says-cellphone-data-suggests-october-shutdown-wuhan-lab-experts-n1202716.
11. Ghosal, A. and L. Neergaard. *Health officials worry as untraceable virus clusters emerge*. 2020; Available from: https://apnews.com/783c7a396adf5f99b8cff399f9478e36.
12. He, X., et al., *Temporal dynamics in viral shedding and transmissibility of COVID-19.* Nat Med, 2020.
13. CDC. *COVID-19 Pandemic Planning Scenarios*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html.
14. Bai, Y., et al., *Presumed asymptomatic carrier transmission of COVID-19.* Jama, 2020.
15. Honein, M.A., et al., *Summary of Guidance for Public Health Strategies to Address High Levels of Community Transmission of SARS-CoV-2 and Related Deaths, December 2020.* Morbidity and Mortality Weekly Report, 2020. **69**(49): p. 1860.
16. Pahuja, S., et al., *Weather Parameters and COVID-19: A Correlational Analysis.* Journal of Occupational and Environmental Medicine, 2020. **Publish Ahead of Print**.
17. Adnan, S., et al., *Impact of Heat Index and Ultraviolet Index on COVID-19 in Major Cities of Pakistan.* Journal of Occupational and Environmental Medicine, 2020. **Publish Ahead of Print**.
18. Ahlawat, A., A. Wiedensohler, and S.K. Mishra, *An Overview on the role of relative humidity in airborne transmission of SARS-CoV-2 in indoor environments.* Aerosol Air Qual. Res, 2020. **20**(9): p. 1856-1861.
19. Vally, H. *6 countries, 6 curves: how nations that moved fast against COVID-19 avoided disaster*. 2020; Available from: https://theconversation.com/6-countries-6-curves-how-nations-that-moved-fast-against-covid-19-avoided-disaster-137333.
20. Wikipedia. *COVID-19 pandemic lockdowns*. 2020; Available from: https://en.wikipedia.org/wiki/COVID-19_pandemic_lockdowns#Countries_and_territories_without_lockdowns.
21. Kaplan, J., L. Frias, and M. McFall-Johnsen. *Countries around the world are reopening — here's our constantly updated list of how they're doing it and who remains under lockdown*. 2020; Available from: https://www.businessinsider.com/countries-on-lockdown-coronavirus-italy-2020-3.
22. Worldometer. *Sweden*. 2020; Available from: https://www.worldometers.info/coronavirus/country/sweden/.

23. Worldometer. *Japan*. 2020; Available from: https://www.worldometers.info/coronavirus/country/japan/.
24. Worldometer. *Denmark*. 2020; Available from: https://www.worldometers.info/coronavirus/country/denmark/.
25. Statista. *Number of tested and confirmed coronavirus (COVID-19) cases in Denmark since January 2020*. 2020; Available from: https://www.statista.com/statistics/1106073/tested-and-confirmed-coronavirus-cases-in-denmark/.
26. Paton, C. *Coronavirus: Sweden's neighbours wary of reopening borders after surge in deaths*. 2020; Available from: https://www.thenational.ae/world/europe/coronavirus-sweden-s-neighbours-wary-of-reopening-borders-after-surge-in-deaths-1.1025898.
27. Milne, R. *First to close - first to reopen: Denmark's gain from virus response*. 2020; Available from: https://www.ft.com/content/ca2f127e-698a-4274-917f-cbe2231a08d7.
28. Centeno, C. *Did Our Coronavirus Shutdown Work? You Decide*. 2020; Available from: https://regenexx.com/blog/did-our-coronavirus-shutdown-work-yes-and-no/.
29. Mortensen, A. and N. Skydsgaard. *Reopening schools in Denmark did not worsen outbreak, data shows*. 2020; Available from: https://www.reuters.com/article/us-health-coronavirus-denmark-reopening/reopening-schools-in-denmark-did-not-worsen-outbreak-data-shows-idUSKBN2341N7.
30. Fehr, A.R. and S. Perlman, *Coronaviruses: an overview of their replication and pathogenesis*, in *Coronaviruses*. 2015, Springer. p. 1-23.
31. Poutanen, S.M., *222 - Human Coronaviruses*, in *Principles and Practice of Pediatric Infectious Diseases (Fourth Edition)*, S.S. Long, Editor. 2012, Content Repository Only!: London. p. 1117-1120.e4.
32. Wiersinga, W.J., et al., *Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review.* Jama, 2020.
33. Council, N.R., *Rapid expert consultation on the possibility of bioaerosol spread of SARS-CoV-2 for the COVID-19 pandemic (April 1, 2020)*. 2020, Washington, DC: National Academies Press.
34. Wei, W.E., et al., *Presymptomatic Transmission of SARS-CoV-2—Singapore, January 23–March 16, 2020.* Morbidity and Mortality Weekly Report, 2020. **69**(14): p. 411.
35. Yu, I.T., et al., *Evidence of airborne transmission of the severe acute respiratory syndrome virus.* N Engl J Med, 2004. **350**(17): p. 1731-9.
36. Ames, M. *Why an Idaho ski destination has one of the highest COVID-19 infection rates in the nation*. 2020; Available from: https://www.newyorker.com/news/news-desk/why-an-idaho-ski-destination-has-one-of-the-highest-covid-19-rates-in-the-nation.
37. Read, R. *A choir decided to go ahead with rehearsal. Now dozens of members have COVID-19 and two are dead*. 2020; Available from: https://www.latimes.com/world-nation/story/2020-03-29/coronavirus-choir-outbreak.
38. Guo, Z.-D., et al., *Aerosol and surface distribution of severe acute respiratory syndrome coronavirus 2 in hospital wards, Wuhan, China, 2020.* Emerg Infect Dis, 2020. **26**(7): p. 10.3201.
39. Liu, Y., et al., *Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals.* Nature, 2020: p. 1-4.
40. Santarpia, J.L., et al., *Transmission potential of SARS-CoV-2 in viral shedding observed at the University of Nebraska Medical Center.* MedRxIV, 2020.
41. Anderson, E.L., et al., *Consideration of the Aerosol Transmission for COVID-19 and Public Health.* Risk analysis : an official publication of the Society for Risk Analysis, 2020. **40**(5): p. 902-907.
42. Tang, S., et al., *Aerosol transmission of SARS-CoV-2? Evidence, prevention and control.* Environment international, 2020. **144**: p. 106039-106039.
43. Jimenez, J.-L. *COVID-19 Data Dives: Why Arguments Against SARS-CoV-2 Aerosol Transmission Don't Hold Water*. 2020; Available from: https://www.medscape.com/viewarticle/934837.
44. Hamner, L., et al. *High SARS-CoV-2 Attack Rate Following Exposure at a Choir Practice — Skagit County, Washington, March 2020*. 2020; Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6919e6.htm.
45. Miller, S.L., et al., *Transmission of SARS-CoV-2 by inhalation of respiratory aerosol in the Skagit Valley Chorale superspreading event.* medRxiv, 2020: p. 2020.06.15.20132027.
46. Bourouiba, L., *Turbulent gas clouds and respiratory pathogen emissions: potential implications for reducing transmission of COVID-19.* Jama, 2020. **323**(18): p. 1837-1838.
47. Lewis, D., *Is the coronavirus airborne? Experts can't agree.* Nature, 2020. **580**(7802): p. 175.

48. Zhang, R., et al., *Identifying airborne transmission as the dominant route for the spread of COVID-19.* Proc Natl Acad Sci U S A, 2020. **117**(26): p. 14857-14863.
49. Morawska, L. and D.K. Milton, *It is Time to Address Airborne Transmission of COVID-19.* Clin Infect Dis, 2020.
50. Li, Y., et al., *Evidence for probable aerosol transmission of SARS-CoV-2 in a poorly ventilated restaurant.* medRxiv, 2020.
51. van Doremalen, N., et al., *Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1.* New England Journal of Medicine, 2020.
52. Verma, S. *Airborne Transmission & Face Masks: How Do Different Types of Masks Protect Against Various Ranges of Transmitted Droplets? How Far Can Aerosolized Droplets Travel in the Air From an Uncovered Cough & For How Long?* 2020; Available from: https://webcache.googleusercontent.com/search?q=cache:0bFdbUBat_YJ:https://www.vumedi.com/video/airborne-transmission-face-masks-how-do-different-types-of-masks-protect-against-various-ranges-of-t/+&cd=1&hl=en&ct=clnk&gl=us.
53. Lewis, D. *Mounting evidence suggests coronavirus is airborne — but health advice has not caught up*. 2020; Available from: https://www.nature.com/articles/d41586-020-02058-1.
54. IES. *IES Committee Report: Germicidal Ultraviolet (GUV) – Frequently Asked Questions*. 2020; Available from: https://media.ies.org/docs/standards/IES%20CR-2-20-V1a-20200507.pdf.
55. Schuit, M., et al., *Airborne SARS-CoV-2 Is Rapidly Inactivated by Simulated Sunlight.* The Journal of Infectious Diseases, 2020. **222**(4): p. 564-571.
56. Fears, A.C., et al., *Persistence of severe acute respiratory syndrome coronavirus 2 in aerosol suspensions.* Emerging infectious diseases, 2020. **26**(9): p. 2168.
57. Stadnytskyi, V., et al., *The airborne lifetime of small speech droplets and their potential importance in SARS-CoV-2 transmission.* Proceedings of the National Academy of Sciences, 2020. **117**(22): p. 11875-11877.
58. Zhang, R., et al., *Identifying airborne transmission as the dominant route for the spread of COVID-19.* Proceedings of the National Academy of Sciences, 2020. **117**(26): p. 14857-14863.
59. Flaxman, S., S. Mishra, and A. Gandy, *Estimating the number of infections and the impact of non-pharmaceutical interventions on COVID-19 in 11 European countries.* Imperial College preprint, 2020.
60. WHO. *Statement on the meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)*. 2020; Available from: https://www.who.int/news-room/detail/23-01-2020-statement-on-the-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov).
61. Statista. *Average number of people who become infected by an infectious person with COVID-19 in the U.S. as of December 2, 2020, by state*. 2020; Available from: https://www.statista.com/statistics/1119412/covid-19-transmission-rate-us-by-state/.
62. Adam, D.C., et al., *Clustering and superspreading potential of SARS-CoV-2 infections in Hong Kong.* Nature Medicine, 2020. **26**(11): p. 1714-1719.
63. Havers, F.P., et al., *Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020.* JAMA Internal Medicine, 2020.
64. Bajema, K.L., et al., *Estimated SARS-CoV-2 Seroprevalence in the US as of September 2020.* JAMA Internal Medicine, 2020.
65. CDC. *Estimated Disease Burden of COVID-19*. 2021; Available from: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html.
66. Holland, L.A., et al., *An 81 nucleotide deletion in SARS-CoV-2 ORF7a identified from sentinel surveillance in Arizona (Jan-Mar 2020).* Journal of virology, 2020.
67. Korber, B., et al., *Spike mutation pipeline reveals the emergence of a more transmissible form of SARS-CoV-2.* bioRxiv, 2020.
68. Oran, D.P. and E.J. Topol, *Prevalence of Asymptomatic SARS-CoV-2 Infection: A Narrative Review.* Annals of Internal Medicine, 2020.
69. Nishiura, H., et al., *Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19).* International Journal of Infectious Diseases, 2020. **94**: p. 154-155.

70. Gudbjartsson, D.F., et al., *Spread of SARS-CoV-2 in the Icelandic Population.* New England Journal of Medicine, 2020. **382**(24): p. 2302-2315.
71. Lavezzo, E., et al., *Suppression of COVID-19 outbreak in the municipality of Vo, Italy.* medRxiv, 2020.
72. Moriarty, L.F., *Public health responses to COVID-19 outbreaks on cruise ships—worldwide, February–March 2020.* MMWR. Morbidity and mortality weekly report, 2020. **69**.
73. Baggett, T.P., et al., *COVID-19 outbreak at a large homeless shelter in Boston: Implications for universal testing.* medRxiv, 2020: p. 2020.04.12.20059618.
74. Chou, E. *Dozens positive for coronavirus at LA's Skid Row homeless shelter, after all residents tested*. 2020; Available from: https://www.dailynews.com/2020/04/21/dozens-positive-for-coronavirus-at-las-skid-row-homeless-shelter-after-all-residents-tested/.
75. Sutton, D., et al., *Universal Screening for SARS-CoV-2 in Women Admitted for Delivery.* New England Journal of Medicine, 2020. **382**(22): p. 2163-2164.
76. Navy, U.S. *U.S. Navy COVID-19 updates. Daily Update: April 24, 2020*. 2020; Available from: https://navylive.dodlive.mil/2020/03/15/u-s-navy-covid-19-updates.
77. Figaro, L. *Coronavirus : bilan définitif de 1046 cas sur le Charles de Gaulle*. 2020; Available from: www.lefigaro.fr/international/coronavirus-bilan-definitif-de-1046-cas-sur-le-charles-de-gaulle-20200418.
78. Lytras, T., et al., *High prevalence of SARS-CoV-2 infection in repatriation flights to Greece from three European countries.* Journal of Travel Medicine, 2020. **27**(3).
79. Arons, M.M., et al., *Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility.* New England journal of medicine, 2020.
80. So, L. and G. Smith, *In four US state prisons, nearly 3,300 inmates test positive for coronavirus—96% without symptoms. Reuters. 25 April 2020*. 2020.
81. Barrett, E.S., et al., *Prevalence of SARS-CoV-2 infection in previously undiagnosed health care workers at the onset of the U.S. COVID-19 epidemic.* medRxiv, 2020.
82. Ratliff, V. *About 45 % of COVID-19-positive Hoosiers don't know it*. 2020; Available from: https://www.newsandtribune.com/about-45-of-covid-19-positive-hoosiers-don-t-know-it/article_1f424a76-9570-11ea-ae01-037620a46735.html.
83. Ing, A.J., C. Cocks, and J.P. Green, *COVID-19: in the footsteps of Ernest Shackleton.* Thorax, 2020. **75**(8): p. 693-694.
84. Diego, N.S., *USS Roosevelt's Asymptomatic Cases Helping Scientists Understand Virus.* 2020.
85. Peniston, B. *The Battle of USS Theodore Roosevelt: a Timeline*. 2020; Available from: https://www.defenseone.com/threats/2020/04/timeline-battle-uss-theodore-roosevelt/164408/.
86. Seligman, L. *Sailors keep testing positive on aircraft carrier, despite 2-week isolation*. 2020; Available from: https://www.politico.com/news/2020/04/21/navy-extends-isolation-for-uss-theodore-roosevelt-sailors-may-delay-ship-departure-198081.
87. University, I. *IU, ISDH release preliminary findings about impact of COVID-19 in Indiana*. 2020; Available from: https://news.iu.edu/stories/2020/05/iupui/releases/13-preliminary-findings-impact-covid-19-indiana-coronavirus.html.
88. Mcfarling, U.L. *When hard data are 'heartbreaking': Testing blitz in San Francisco shows Covid-19 struck mostly low-wage workers*. 2020; Available from: https://www.statnews.com/2020/05/28/sobering-finding-covid19-struck-mostly-low-wage-essential-workers-san-francisco/.
89. Park, Y.J., et al., *Contact tracing during coronavirus disease outbreak, South Korea, 2020.* Emerging infectious diseases, 2020. **26**(10): p. 2465-2468.
90. Kampf, G., et al., *Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidal agents.* Journal of Hospital Infection, 2020.
91. Bhardwaj, R. and A. Agrawal, *How coronavirus survives for days on surfaces.* Physics of Fluids, 2020. **32**(11): p. 111706.
92. Hirose, R., et al., *Survival of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Influenza Virus on Human Skin: Importance of Hand Hygiene in Coronavirus Disease 2019 (COVID-19).* Clinical Infectious Diseases, 2020.
93. Eslami, H. and M. Jalili, *The role of environmental factors to transmission of SARS-CoV-2 (COVID-19).* AMB Express, 2020. **10**(1): p. 92.

94. Huang, Z., et al., *Optimal temperature zone for the dispersal of COVID-19.* Sci Total Environ, 2020. **736**: p. 139487.
95. Beaubien, J. *Will Heat And Humidity Kill The Coronavirus?* 2020; Available from: https://www.npr.org/2020/04/24/843529615/will-heat-and-humidity-kill-the-coronavirus.
96. Adnan, S., et al., *Impact of Heat Index and Ultraviolet Index on COVID-19 in Major Cities of Pakistan.* Journal of Occupational and Environmental Medicine, 2021. **63**(2): p. 98-103.
97. Chan, K.H., et al., *The Effects of Temperature and Relative Humidity on the Viability of the SARS Coronavirus.* Advances in Virology, 2011. **2011**: p. 734690.
98. Ratnesar-Shumate, S., et al., *Simulated Sunlight Rapidly Inactivates SARS-CoV-2 on Surfaces.* J Infect Dis, 2020.
99. Amherst, U.o.M. *Median incubation period for COVID-19*. 2020; Available from: https://www.sciencedaily.com/releases/2020/03/200317175438.htm.
100. Lauer, S.A., et al., *The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application.* Annals of internal medicine, 2020. **172**(9): p. 577-582.
101. Guan, W.-j., et al., *Clinical characteristics of 2019 novel coronavirus infection in China.* MedRxiv, 2020.
102. Wölfel, R., et al., *Virological assessment of hospitalized patients with COVID-2019.* Nature, 2020. **581**(7809): p. 465-469.
103. Widders, A., A. Broom, and J. Broom, *SARS-CoV-2: The viral shedding vs infectivity dilemma.* Infection, disease & health, 2020. **25**(3): p. 210-215.
104. Cevik, M., et al., *SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis.* The Lancet Microbe, 2020.
105. Benefield, A.E., et al., *SARS-CoV-2 viral load peaks prior to symptom onset: a systematic review and individual-pooled analysis of coronavirus viral load from 66 studies.* medRxiv, 2020: p. 2020.09.28.20202028.
106. Agency, K.D.C.a.P. *Findings from investigation and analysis of re-positive cases*. 2020; Available from: https://www.cdc.go.kr/board/board.es?mid=a30402000000&bid=0030&act=view&list_no=367267&nPage=1external%20icon.
107. Li, L., et al., *Molecular and serological characterization of SARS-CoV-2 infection among COVID-19 patients.* Virology, 2020. **551**: p. 26-35.
108. Xiao, A.T., et al., *Dynamic profile of RT-PCR findings from 301 COVID-19 patients in Wuhan, China: A descriptive study.* Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology, 2020. **127**: p. 104346-104346.
109. Gousseff, M., et al., *Clinical recurrences of COVID-19 symptoms after recovery: Viral relapse, reinfection or inflammatory rebound?* J Infect, 2020. **81**(5): p. 816-846.
110. To, K.K.-W., et al., *Serum antibody profile of a patient with COVID-19 reinfection.* Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 2020: p. ciaa1368.
111. Bonifácio, L.P., et al., *Are SARS-CoV-2 reinfection and Covid-19 recurrence possible? a case report from Brazil.* Revista da Sociedade Brasileira de Medicina Tropical, 2020. **53**: p. e20200619-e20200619.
112. Parry, J., *Covid-19: Hong Kong scientists report first confirmed case of reinfection.* BMJ, 2020. **370**: p. m3340.
113. To, K.K., et al., *COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing.* Clin Infect Dis, 2020.
114. Hong, J. and J. Gale. *Hong Kong Reports First Confirmed Coronavirus Re-Infection*. 2020; Available from: https://www.bloomberg.com/news/articles/2020-08-24/hong-kong-reports-first-coronavirus-re-infection-in-it-worker.
115. Kang, H., et al., *Retest positive for SARS-CoV-2 RNA of "recovered" patients with COVID-19: Persistence, sampling issues, or re-infection?* Journal of Medical Virology, 2020. **92**(11): p. 2263-2265.
116. Gidari, A., et al., *Is recurrence possible in coronavirus disease 2019 (COVID-19)? Case series and systematic review of literature.* Eur J Clin Microbiol Infect Dis, 2020: p. 1-12.
117. Torres, D.d.A., et al., *Reinfection of COVID-19 after 3 months with a distinct and more aggressive clinical presentation: Case report.* Journal of Medical Virology, 2020. **n/a**(n/a).
118. Gupta, V., et al., *Asymptomatic reinfection in two healthcare workers from India with genetically distinct SARS-CoV-2.* Clin Infect Dis, 2020.

119. Van Loon, N., et al., *Diagnosis of COVID-19 Based on Symptomatic Analysis of Hospital Healthcare Workers in Belgium: Observational Study in a Large Belgian Tertiary Care Center during Early COVID-19 Outbreak.* Journal of Occupational and Environmental Medicine, 2020. **Publish Ahead of Print**.
120. WHO. *Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)*. 2020; Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf.
121. Zhu, J., et al., *Clinical characteristics of 3,062 COVID-19 patients: a meta-analysis.* J Med Virol, 2020.
122. Lovato, A. and C. de Filippis, *Clinical Presentation of COVID-19: A Systematic Review Focusing on Upper Airway Symptoms.* Ear Nose Throat J, 2020: p. 145561320920762.
123. Michelen, M., N. Jones, and C. Stavropoulou. *In patients of COVID-19, what are the symptoms and clinical features of mild and moderate cases?* 2020; Available from: https://www.cebm.net/covid-19/in-patients-of-covid-19-what-are-the-symptoms-and-clinical-features-of-mild-and-moderate-case/.
124. Pan, L., et al., *Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study.* Am J Gastroenterol, 2020. **20**.
125. Wu, P., et al., *Characteristics of Ocular Findings of Patients With Coronavirus Disease 2019 (COVID-19) in Hubei Province, China.* JAMA ophthalmology, 2020.
126. Moein, S.T., et al., *Smell dysfunction: a biomarker for COVID-19.* Int Forum Allergy Rhinol, 2020.
127. Gandhi, M., C. Beyrer, and E. Goosby, *Masks Do More Than Protect Others During COVID-19: Reducing the Inoculum of SARS-CoV-2 to Protect the Wearer.* Journal of General Internal Medicine, 2020. **35**(10): p. 3063-3066.
128. Gandhi, M. and G.W. Rutherford, *Facial Masking for Covid-19 — Potential for "Variolation" as We Await a Vaccine.* New England Journal of Medicine, 2020. **383**(18): p. e101.
129. Guzik, T.J., et al., *COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options.* Cardiovasc Res, 2020.
130. Siddamreddy, S., et al., *Corona Virus Disease 2019 (COVID-19) Presenting as Acute ST Elevation Myocardial Infarction.* Cureus, 2020. **12**(4): p. e7782.
131. Hu, Y., et al., *Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis.* J Clin Virol, 2020. **127**: p. 104371.
132. Zheng, Y., et al., *Epidemiological characteristics and clinical features of 32 critical and 67 noncritical cases of COVID-19 in Chengdu.* J Clin Virol, 2020. **127**: p. 104366.
133. Liu, P.P., et al., *The Science Underlying COVID-19: Implications for the Cardiovascular System.* Circulation, 2020.
134. Fried, J.A., et al., *The variety of cardiovascular presentations of COVID-19.* Circulation, 2020.
135. Nicolai, L., et al., *Immunothrombotic dysregulation in COVID-19 pneumonia is associated with respiratory failure and coagulopathy.* Circulation, 2020. **142**(12): p. 1176-1189.
136. Wichmann, D., et al., *Autopsy Findings and Venous Thromboembolism in Patients With COVID-19.* Ann Intern Med, 2020. **173**: p. 268-277.
137. Zhang, Y., et al., *Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19.* N Engl J Med, 2020. **382**(17): p. e38.
138. Oxley, T.J., et al., *Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young.* N Engl J Med, 2020.
139. Avula, A., et al., *COVID-19 presenting as stroke.* Brain, Behavior, and Immunity, 2020. **87**: p. 115-119.
140. Klok, F.A., et al., *Incidence of thrombotic complications in critically ill ICU patients with COVID-19.* Thromb Res, 2020. **191**: p. 145-147.
141. Middeldorp, S., et al., *Incidence of venous thromboembolism in hospitalized patients with COVID-19.* J Thromb Haemost, 2020.
142. Levi, M., et al., *Coagulation abnormalities and thrombosis in patients with COVID-19.* Lancet Haematol, 2020. **7**(6): p. e438-e440.
143. Rajpal, S., et al., *Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection.* JAMA cardiology, 2020.
144. Ehsani, A.H., M. Nasimi, and Z. Bigdelo, *Pityriasis rosea as a cutaneous manifestation of COVID-19 infection.* J Eur Acad Dermatol Venereol, 2020.

145. Bouaziz, J.D., et al., *Vascular skin symptoms in COVID-19: a french observational study.* J Eur Acad Dermatol Venereol, 2020.
146. van Damme, C., et al., *Acute urticaria with pyrexia as the first manifestations of a COVID-19 infection.* J Eur Acad Dermatol Venereol, 2020.
147. Henry, D., et al., *Urticarial eruption in COVID-19 infection.* J Eur Acad Dermatol Venereol, 2020.
148. Zhao, Q., et al., *COVID-19 and cutaneous manifestations: a systematic review.* Journal of the European Academy of Dermatology and Venereology, 2020. **n/a**(n/a).
149. Al Saiegh, F., et al., *Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke.* J Neurol Neurosurg Psychiatry, 2020.
150. Baig, A.M., *Updates on What ACS Reported: Emerging Evidences of COVID-19 with Nervous System Involvement.* ACS Chem Neurosci, 2020. **11**(9): p. 1204-5.
151. Chacón-Aguilar, R., et al., *COVID-19: Fever syndrome and neurological symptoms in a neonate.* An Pediatr (Engl Ed), 2020.
152. Gutiérrez-Ortiz, C., et al., *Miller Fisher Syndrome and polyneuritis cranialis in COVID-19.* Neurology, 2020.
153. Mao, L., et al., *Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China.* JAMA Neurol, 2020.
154. Poyiadji, N., et al., *COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features.* Radiology, 2020: p. 201187.
155. Yan, Y., et al., *Clinical characteristics and outcomes of patients with severe covid-19 with diabetes.* BMJ Open Diabetes Res Care, 2020. **8**(1).
156. Varatharaj, A., et al., *Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study.* Lancet Psychiatry, 2020.
157. Ronco, C. and T. Reis, *Kidney involvement in COVID-19 and rationale for extracorporeal therapies.* Nat Rev Nephrol, 2020.
158. Velez, J.C.Q., T. Caza, and C.P. Larsen, *COVAN is the new HIVAN: the re-emergence of collapsing glomerulopathy with COVID-19.* Nature Reviews Nephrology, 2020. **16**(10): p. 565-567.
159. Durvasula, R., et al., *COVID-19 and Kidney Failure in the Acute Care Setting: Our Experience From Seattle.* Am J Kidney Dis, 2020.
160. Tang, N., et al., *Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia.* J Thromb Haemost, 2020. **18**(4): p. 844-847.
161. Rodriguez-Morales, A.J., et al., *Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis.* Travel medicine and infectious disease, 2020: p. 101623.
162. Xu, X., et al., *Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2.* European Journal of Nuclear Medicine and Molecular Imaging, 2020: p. 1-6.
163. Wong, J.E., Y.S. Leo, and C.C. Tan, *COVID-19 in Singapore—current experience: critical global issues that require attention and action.* Jama, 2020.
164. Bernheim, A., et al., *Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection.* Radiology, 2020: p. 200463.
165. Matthews, A. and N. McDermott. *IT'S SPREADING First coronavirus case confirmed in London as woman diagnosed with deadly bug brings total in UK to nine*. 2020; Available from: https://www.thesun.co.uk/news/uknews/10950656/first-coronavirus-case-confirmed-in-london-as-officials-worst-fears-come-true/.
166. Chua, G.T., et al., *Saliva viral load better correlates with clinical and immunological profiles in children with coronavirus disease 2019.* Emerg Microbes Infect, 2021. **10**(1): p. 235-241.
167. Baggio, S., et al., *SARS-CoV-2 viral load in the upper respiratory tract of children and adults with early acute COVID-19.* Clin Infect Dis, 2020.
168. Czeisler, M.É., et al., *Mental health, substance use, and suicidal ideation during the COVID-19 pandemic—United States, June 24–30, 2020.* Morbidity and Mortality Weekly Report, 2020. **69**(32): p. 1049.
169. Goldstein, J. and P. Belluck. *Children Are Falling Ill With a Baffling Ailment Related to Covid-19*. 2020; Available from: https://www.nytimes.com/2020/05/05/nyregion/kawasaki-disease-coronavirus.html?searchResultPosition=1.
170. CDC. *COVID-19 Science Update released: November 24, 2020*. 2020; Available from: https://www.cdc.gov/library/covid19/112420_covidupdate.html.

171. Kobayashi, T., et al., *Communicating the Risk of Death from Novel Coronavirus Disease (COVID-19).* J Clin Med, 2020. **9**(2).
172. Ledberg, A., *Mortality of the COVID-19 outbreak in Sweden in relation to previous severe disease outbreaks.* medRxiv, 2020.
173. Payne, D. *Antibody tests continue to suggest COVID-19 far more widespread, less deadly than initially thought*. 2020; Available from: https://justthenews.com/politics-policy/coronavirus/antibody-tests-continue-suggest-covid-19-far-more-widespread-less.
174. Hamilton, J. *Antibody Tests Point To Lower Death Rate For The Coronavirus Than First Thought*. 2020; Available from: https://www.npr.org/sections/health-shots/2020/05/28/863944333/antibody-tests-point-to-lower-death-rate-for-the-coronavirus-than-first-thought.
175. Ioannidis, J., *The infection fatality rate of COVID-19 inferred from seroprevalence data.* medRxiv, 2020.
176. CDC. *Safer Communities Mean Safer Schools*. 2021; Available from: www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html.
177. Garibaldi, B.T., et al., *Patient Trajectories Among Persons Hospitalized for COVID-19: A Cohort Study.* Annals of internal medicine, 2020.
178. Society, A.G., *American Geriatrics Society (AGS) Policy Brief: COVID-19 and Nursing Homes.* J Am Geriatr Soc, 2020.
179. McMichael, T.M., et al., *COVID-19 in a Long-Term Care Facility - King County, Washington, February 27-March 9, 2020.* MMWR Morb Mortal Wkly Rep, 2020. **69**(12): p. 339-342.
180. Kimball, A., et al., *Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility - King County, Washington, March 2020.* MMWR Morb Mortal Wkly Rep, 2020. **69**(13): p. 377-381.
181. Davidson, P.M. and S.L. Szanton, *Nursing homes and COVID-19: we can and should do better.* J Clin Nurs, 2020.
182. Mills, J.P., K.S. Kaye, and L. Mody, *COVID-19 in older adults: clinical, psychosocial, and public health considerations.* JCI Insight, 2020.
183. Tartof, S.Y., et al., *Obesity and mortality among patients diagnosed with COVID-19: results from an integrated health care organization.* Annals of internal medicine, 2020.
184. Sabourin, K.R., et al., *Risk Factors of SARS-CoV-2 Antibodies in Arapahoe County First Responders - the COVID-19 Arapahoe SErosurveillance Study (CASES) Project.* Journal of Occupational and Environmental Medicine, 2020. **Publish Ahead of Print**.
185. CDC. *People Who Are at Higher Risk for Severe Illness*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fspecific-groups%2Fhigh-risk-complications.html.
186. Zhang, J., et al., *Risk factors for disease severity, unimprovement, and mortality of COVID-19 patients in Wuhan, China.* Clin Microbiol Infect, 2020.
187. Li, X., et al., *Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan.* J Allergy Clin Immunol, 2020.
188. Zuin, M., et al., *Arterial hypertension and risk of death in patients with COVID-19 infection: systematic review and meta-analysis.* J Infect, 2020.
189. Zhang, Y. *The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020*. 2020; Available from: http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51.
190. Ellinghaus, D., et al., *Genomewide Association Study of Severe Covid-19 with Respiratory Failure.* N Engl J Med, 2020.
191. Ritchie, H., et al. *Coronavirus (COVID-19) Vaccinations*. 2021; Available from: https://ourworldindata.org/covid-vaccinations.
192. Craven, M., et al. *COVID-19: Implications for business*. 2020; Available from: https://www.mckinsey.com/business-functions/risk/our-insights/covid-19-implications-for-business?cid=other-eml-alt-mip-mck&hlkid=29f0e15f26f24962b86688c0f90319c7&hctky=2523830&hdpid=0a24bf6c-15ec-4e50-9709-381e0f5b160a#.

193. CDC. *COVID-19 Vaccination Communication Toolkit*. 2021; Available from: https://www.cdc.gov/vaccines/covid-19/health-systems-communication-toolkit.html.
194. CDC. *Customizable COVID-19 Vaccine Content for Essential Workers*. 2021; Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/toolkits/essential-workers/newsletters.html.
195. CDC. *COVID-19 ACIP Vaccine Recommendations*. 2021; Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html.
196. CDC. *COVID-19 Vaccine Distribution Allocations by Jurisdiction - Pfizer*. 2021; Available from: https://data.cdc.gov/vaccinations/covid-19-vaccine-distribution-allocations-by-juris/saz5-9hgg.
197. CDC. *Frequently Asked Questions about COVID-19 Vaccination*. 2021; Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html.
198. CDC, *Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States.* 2021.
199. Richardson, S., et al., *Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area.* Jama, 2020.
200. CDC. *How to Protect Yourself & Others*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fprepare%2Fprevention.html.
201. CDC. *Return-to-Work Criteria*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/return-to-work.html.
202. CDC. *Discontinuation of Isolation for Persons with COVID-19 Not in Healthcare Settings*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html.
203. CDC. *Duration of Isolation and Precautions for Adults with COVID-19*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html.
204. CDC. *Appendices*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/php/contact-tracing/contact-tracing-plan/appendix.html.
205. CDC. *Contact Tracing*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/php/open-america/contact-tracing-resources.html.
206. CDC. *Interim U.S. Guidance for Risk Assessment and Public Health Management of Healthcare Personnel with Potential Exposure in a Healthcare Setting to Patients with Coronavirus Disease 2019 (COVID-19)*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html.
207. Mass.gov. *Information and Guidance for Persons in Quarantine due to COVID-19*. 2020; Available from: https://www.mass.gov/guidance/information-and-guidance-for-persons-in-quarantine-due-to-covid-19.
208. CDC. *When to Quarantine*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html.
209. CDC. *Interim Guidance for Implementing Safety Practices for Critical Infrastructure Workers Who May Have Had Exposure to a Person with Suspected or Con rmed COVID-19*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/downloads/critical-workers-implementing-safety-practices.pdf.
210. Williamson, E., et al., *OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients.* medRxiv, 2020.
211. Liang, W., et al., *Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19.* JAMA Internal Medicine, 2020.
212. Chu, D.K., et al., *Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis.* The Lancet, 2020.
213. Richterman, A., E.A. Meyerowitz, and M. Cevik, *Hospital-Acquired SARS-CoV-2 Infection: Lessons for Public Health.* JAMA, 2020. **324**(21): p. 2155-2156.
214. Seidelman, J.L., et al., *Universal masking is an effective strategy to flatten the severe acute respiratory coronavirus virus 2 (SARS-CoV-2) healthcare worker epidemiologic curve.* Infection Control & Hospital Epidemiology, 2020. **41**(12): p. 1466-1467.
215. Wang, X., et al., *Association Between Universal Masking in a Health Care System and SARS-CoV-2 Positivity Among Health Care Workers.* JAMA, 2020.

216. Baker, M.A., et al., *Low risk of COVID-19 among patients exposed to infected healthcare workers.* Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 2020: p. ciaa1269.
217. Rhee, C., et al., *Incidence of Nosocomial COVID-19 in Patients Hospitalized at a Large US Academic Medical Center.* JAMA Network Open, 2020. **3**(9): p. e2020498-e2020498.
218. van der Sande, M., P. Teunis, and R. Sabel, *Professional and Home-Made Face Masks Reduce Exposure to Respiratory Infections among the General Population.* PLOS ONE, 2008. **3**(7): p. e2618.
219. Bartoszko, J.J., et al., *Medical masks vs N95 respirators for preventing COVID-19 in healthcare workers: A systematic review and meta-analysis of randomized trials.* Influenza and other respiratory viruses, 2020.
220. Bahl, P., et al., *Airborne or droplet precautions for health workers treating COVID-19?* The Journal of infectious diseases, 2020.
221. Steensels, D., et al., *Hospital-wide SARS-CoV-2 antibody screening in 3056 staff in a tertiary center in Belgium.* Jama, 2020. **324**(2): p. 195-197.
222. Radonovich, L.J., et al., *N95 respirators vs medical masks for preventing influenza among health care personnel: a randomized clinical trial.* Jama, 2019. **322**(9): p. 824-833.
223. MacIntyre, C.R., et al., *A cluster randomized clinical trial comparing fit-tested and non-fit-tested N95 respirators to medical masks to prevent respiratory virus infection in health care workers.* Influenza and other respiratory viruses, 2011. **5**(3): p. 170-179.
224. MacIntyre, C.R., et al., *A randomized clinical trial of three options for N95 respirators and medical masks in health workers.* Am J Respir Crit Care Med, 2013. **187**(9): p. 960-6.
225. Loeb, M., et al., *Surgical mask vs N95 respirator for preventing influenza among health care workers: a randomized trial.* Jama, 2009. **302**(17): p. 1865-71.
226. Adawee, M.O., R.E. Brum, and L.J. Ellsworth, *Examining Common Characteristics among Healthcare Personnel Positive for COVID-19 and the Effectiveness of Healthcare Personnel Mask Use in Preventing COVID-19 in a Large Health System in Central Michigan.* Journal of Occupational and Environmental Medicine, 2020. **Publish Ahead of Print**.
227. Yeap, R. *NEJM: Visualizing Speech Generated Oral Fluid Droplets with Laser Light Scattering*. 2020; Available from: https://www.youtube.com/watch?v=UNHgQq0BGLI&feature=youtu.be.
228. CenturalHealth. *The Do's and Don'ts of Wearing Masks and Gloves*. 2020; Available from: https://www.youtube.com/watch?v=eVJbenwzR1s.
229. Fischer, E.P., et al., *Low-cost measurement of facemask efficacy for filtering expelled droplets during speech.* Science Advances, 2020: p. eabd3083.
230. Chinazzi, M., et al., *The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak.* Science, 2020. **368**(6489): p. 395-400.
231. University, J.H. *Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)*. 2020; Available from: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6.
232. Braine, T. *Planes almost entirely safe from coronavirus transmission if everyone wears masks: study*. 2020; Available from: https://www.aol.com/2020-10-16-planes-almost-entirely-safe-from-coronavirus-transmission-if-everyone-wears-masks-study-24652910.html.
233. Khan, R.F. and J.D. Meyer, *How Does the Hierarchy of Controls Integrate With the Epidemiologic Triangle to Help Address and Understand Transmission of SARS-CoV-2?* Journal of Occupational and Environmental Medicine, 2020. **62**(11).
234. WHO. *COVID-19 table of PPE with description and related standard (simplified version)*. 2020; Available from: https://www.who.int/publications/m/item/from-DCP-v5-list-PPE-v8082020.
235. WHO. *COVID-19 Technical Specifications for personal protective equipment, list of standards and checklists*. 2020; Available from: https://www.who.int/publications/m/item/technical-specs-PPE-Covid19-07082020.
236. WHO. *Coronavirus disease (COVID-19): Masks*. 2020; Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-covid-19-masks

237. WHO. *Mask use in the context of COVID-19: interim guidance, 1 December 2020*. 2020; Available from: https://apps.who.int/iris/handle/10665/337199
238. Perencevich, E.N., D.J. Diekema, and M.B. Edmond, *Moving Personal Protective Equipment Into the Community: Face Shields and Containment of COVID-19.* JAMA, 2020. **323**(22): p. 2252-2253.
239. Hubbard, K. *These States Have COVID-19 Mask Mandates*. 2021; Available from: https://www.usnews.com/news/best-states/articles/these-are-the-states-with-mask-mandates.
240. Lyu, W. and G.L. Wehby, *Community Use Of Face Masks And COVID-19: Evidence From A Natural Experiment Of State Mandates In The US.* Health Affairs, 2020. **39**(8): p. 1419-1425.
241. Wycliffe, W.E., et al. *Presymptomatic Transmission of SARS-CoV-2 — Singapore, January 23–March 16, 2020*. 2020; Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e1.htm?s_cid=mm6914e1_w.
242. Zhanwei, D., et al. *Serial Interval of COVID-19 among Publicly Reported Confirmed Cases*. 2020; Available from: https://wwwnc.cdc.gov/eid/article/26/6/20-0357_article.
243. Bundgaard, H., et al., *Effectiveness of adding a mask recommendation to other public health measures to prevent SARS-CoV-2 infection in Danish mask wearers: a randomized controlled trial.* Annals of Internal Medicine, 2020.
244. OSHA. *Expanded Temporary Enforcement Guidance on Respiratory Protection Fit-Testing for N95 Filtering Facepieces in All Industries During the Coronavirus Disease 2019 (COVID-19) Pandemic*. 2020; Available from: https://www.osha.gov/memos/2020-04-08/expanded-temporary-enforcement-guidance-respiratory-protection-fit-testing-n95.
245. OSHA. *U.S. Department of Labor Issues Temporary Enforcement Guidance for Respirator Fit-Testing in Healthcare during COVID-19 Outbreak*. 2020; Available from: https://www.osha.gov/news/newsreleases/national/03142020.
246. PAHO. *Technical and Regulatory Aspects of the Extended Use, Reuse, and Reprocessing of Respirators during Shortages, 10 June 2020*. 2020; Available from: https://iris.paho.org/bitstream/handle/10665.2/52431/PAHOIMSHSSCOVID-19200025_eng.pdf?sequence=1&isAllowed=y.
247. NIOSH. *Recommended Guidance for Extended Use and Limited Reuse of N95 Filtering Facepiece Respirators in Healthcare Settings*. 2020; Available from: https://www.cdc.gov/niosh/topics/hcwcontrols/recommendedguidanceextuse.html.
248. ASHRAE, *Core Recommendations for Reducing Airborne Infectious Aerosol Exposure.* 2021.
249. ASHRAE, *General Information.* 2021.
250. CDC. *Ventilation in Buildings*. 2021; Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/ventilation.html.
251. ASHRAE. *ASHRAE Position Document on Infectious Aerosols*. 2020; Available from: https://www.ashrae.org/file%20library/about/position%20documents/pd_infectiousaerosols_2020.pdf.
252. ACGIH. *White Paper on Ventilation for Industrial Settings during the COVID-19 Pandemic*. 2020; Available from: https://www.acgih.org/docs/default-source/vent-committee/iv_position-test.pdf?sfvrsn=4b10ba0d_2.
253. CDC. *Interim Guidance for Businesses and Employers to Plan and Respond to Coronavirus Disease 2019 (COVID-19)*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/guidance-business-response.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fspecific-groups%2Fguidance-business-response.html.
254. ASHRAE. *ASHRAE Epidemic Task Force*. 2020; Available from: https://www.ashrae.org/file%20library/technical%20resources/covid-19/ashrae-filtration_disinfection-c19-guidance.pdf.
255. CDC. *Frequently Asked Questions*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/faq.html.
256. EPA. *List N: Disinfectants for Use Against SARS-CoV-2*. 2020; Available from: https://www.epa.gov/pesticide-registration/list-n-disinfectants-use-against-sars-cov-2#filter_col1.
257. Ferner, R. *Hand Disinfectant and COVID-19*. 2020; Available from: https://www.cebm.net/covid-19/hand-disinfectant-and-covid-19/.

258. Health, S. *COVID Symptoms Tracker and Automated Decision Support Tool*. 2020; Available from: https://c19.safelanehealth.com/.
259. Medicine, J.H. *Coronavirus (COVID-19) Self-Checker*. 2020; Available from: https://www.hopkinsmedicine.org/coronavirus/covid-19-self-checker.html.
260. CDC. *Symptoms of Coronavirus*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.
261. Hospital, M.G. *COVID-19 Symptom Tracker App*. 2020; Available from: https://www.massgeneral.org/cancer-center/news/covid-symptom-tracker-app.
262. Dyal, J.W., et al. *COVID-19 Among Workers in Meat and Poultry Processing Facilities — 19 States, April 2020*. 2020; Available from: https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6918e3-H.pdf.
263. Zhu, Y., et al., *Children are unlikely to have been the primary source of household SARS-CoV-2 infections.* medRxiv, 2020: p. 2020.03.26.20044826.
264. Liu, Z., B. Xing, and Z. Xue Za, *The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China.* 2020. **41**(2): p. 145-151.
265. Cristiani, L., et al., *Will children reveal their secret? The coronavirus dilemma.* The European respiratory journal, 2020. **55**(4): p. 2000749.
266. Rubin, R., *School Superintendents Confront COVID-19—"There Are No Good Options for Next Year".* JAMA, 2020.
267. Davies, N.G., et al., *Age-dependent effects in the transmission and control of COVID-19 epidemics.* Nature Medicine, 2020.
268. Dorn, E., et al., *COVID-19 and student learning in the United States: The hurt could last a lifetime.* McKinsey & Company, 2020.
269. Horowitz, J., *Lower-income parents most concerned about their children falling behind amid COVID-19 school closures.* Pew Research Center, 2020.
270. Bacher-Hicks, A., J. Goodman, and C. Mulhern, *Inequality in Household Adaptation to Schooling Shocks: Covid-Induced Online Learning Engagement in Real Time*. 2020, National Bureau of Economic Research.
271. Van Lancker, W. and Z. Parolin, *COVID-19, school closures, and child poverty: a social crisis in the making.* The Lancet Public Health, 2020. **5**(5): p. e243-e244.
272. Burgess, S. and H.H. Sievertsen. *Schools, skills, and learning: The impact of COVID-19 on education*. 2020; Available from: https://voxeu.org/article/impact-covid-19-education.
273. Azevedo, J.P., et al., *Simulating the potential impacts of covid-19 school closures on schooling and learning outcomes: A set of global estimates*. 2020, The World Bank.
274. Fitzpatrick, B.R., et al., *Virtual illusion: Comparing student achievement and teacher and classroom characteristics in online and brick-and-mortar charter schools.* Educational Researcher, 2020. **49**(3): p. 161-175.
275. Durlak, J.A., et al., *Collaborative for Academic, Social, and Emotional Learning (CASEL).* 2007.
276. Loades, M.E., et al., *Rapid Systematic Review: The Impact of Social Isolation and Loneliness on the Mental Health of Children and Adolescents in the Context of COVID-19.* Journal of the American Academy of Child & Adolescent Psychiatry, 2020.
277. Birnbaum, M. *Reopened schools in Europe and Asia have largely avoided coronavirus outbreaks. They have lessons for the U.S.* 2020; Available from: https://www.washingtonpost.com/world/europe/schools-reopening-coronavirus/2020/07/10/865fb3e6-c122-11ea-8908-68a2b9eae9e0_story.html.
278. Stein-Zamir, C., et al., *A large COVID-19 outbreak in a high school 10 days after schools' reopening, Israel, May 2020.* Eurosurveillance, 2020. **25**(29): p. 2001352.
279. Schwartz, F. and D. Lieber. *Israelis Fear Schools Reopened Too Soon as Covid-19 Cases Climb*. 2020; Available from: https://www.wsj.com/articles/israelis-fear-schools-reopened-too-soon-as-covid-19-cases-climb-11594760001.
280. CDC. *Schools and Childcare Programs*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/index.html.
281. CDC. *Considerations for Schools*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/schools.html.
282. CDC. *Interim Considerations for K-12 School Administrators for SARS-CoV-2 Testing*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/k-12-testing.html.

283. CDC. *Back to School Planning: Checklists to Guide Parents, Guardians, and Caregivers*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/parent-checklist.html.
284. CDC. *The Importance of Reopening America's Schools this Fall*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/reopening-schools.html.
285. CDC. *Preparing K-12 School Administrators for a Safe Return to School in Fall 2020*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/prepare-safe-return.html.
286. Rothamer, D.A., et al., *Strategies to minimize SARS-CoV-2 transmission in classroom settings: Combined impacts of ventilation and mask effective filtration efficiency.* medRxiv, 2021: p. 2020.12.31.20249101.
287. CDC. *Schools and Child Care Programs*. 2021; Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/index.html.
288. CDC. *Screening K-12 Students for Symptoms of COVID-19: Limitations and Considerations*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/symptom-screening.html.
289. Carfì, A., R. Bernabei, and F. Landi, *Persistent symptoms in patients after acute covid-19.* JAMA, 2020.
290. Mahase, E. and Z. Kmietowicz, *Covid-19: Doctors are told not to perform CPR on patients in cardiac arrest.* Bmj, 2020. **368**: p. m1282.
291. Bowles, K.H., et al., *Surviving COVID-19 After Hospital Discharge: Symptom, Functional, and Adverse Outcomes of Home Health Recipients.* Annals of internal medicine, 2020.
292. NICE. *COVID-19 rapid guideline: managing the long-term effects of COVID-19*. 2020; Available from: https://www.nice.org.uk/guidance/ng188.
293. Tenforde, M.W., et al. *Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020*. 2020; Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6930e1.htm.
294. DiSilvio, B., et al., *Complications and outcomes of acute respiratory distress syndrome.* Critical care nursing quarterly, 2019. **42**(4): p. 349-361.
295. Dinglas, V.D., et al., *Perspectives of survivors, families and researchers on key outcomes for research in acute respiratory failure.* Thorax, 2018. **73**(1): p. 7-12.
296. Chen, J., et al., *Long term outcomes in survivors of epidemic Influenza A (H7N9) virus infection.* Scientific reports, 2017. **7**(1): p. 1-8.
297. Chiumello, D., et al., *What's next after ARDS: long-term outcomes.* Respiratory care, 2016. **61**(5): p. 689-699.
298. Herridge, M.S., et al., *Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers.* Intensive care medicine, 2016. **42**(5): p. 725-738.
299. Mason, C., N. Dooley, and M. Griffiths, *Acute respiratory distress syndrome.* Clinical Medicine, 2016. **16**(Suppl 6): p. s66.
300. Rogers, J.P., et al., *Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic.* The Lancet Psychiatry, 2020.
301. Society, I.C. *Psychology of COVID-19 critical care patients*. 2020; Available from: https://www.ics.ac.uk/ICS/Psychology_in_COVID-19.aspx.
302. Wilcox, M.E., et al., *Radiologic outcomes at 5 years after severe ARDS.* Chest, 2013. **143**(4): p. 920-926.
303. Files, D.C., M.A. Sanchez, and P.E. Morris, *A conceptual framework: the early and late phases of skeletal muscle dysfunction in the acute respiratory distress syndrome.* Crit Care, 2015. **19**: p. 266.
304. Guo, T., et al., *Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19).* JAMA cardiology, 2020.
305. Lindner, D., et al., *Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases.* JAMA cardiology, 2020.
306. Driggin, E., et al., *Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic.* Journal of the American College of Cardiology, 2020. **75**(18): p. 2352.
307. Puntmann, V.O., et al., *Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19).* JAMA Cardiology, 2020.
308. Disser, N.P., et al., *Musculoskeletal Consequences of COVID-19.* JBJS, 2020. **102**(14).

309. Hyman, M.H., J.B. Talmage, and K.T. Hegmann, *Evaluating Covid-19 Injury Claims With a Focus on Workers' Compensation.* Journal of Occupational and Environmental Medicine, 2020. **62**(9).
310. Andersson, G.B.J. and L. Cocchiarella, *AMA Guides to the Evaluation of Permanent Impairment, 5th edition*. 2000, Chicago, IL: American Medical Association.
311. Rondinelli, R.D., *AMA Guides to the Evaluation of Permanent Impairment, Sixth Edition*. 2008, Chicago, IL: American Medical Association.
312. Parker, E.P.K., M. Shrotri, and B. Kampmann, *Keeping track of the SARS-CoV-2 vaccine pipeline.* Nature Reviews Immunology, 2020. **20**(11): p. 650-650.
313. Callaway, E. *The race for coronavirus vaccines: a graphical guide*. 2020; Available from: https://www.nature.com/articles/d41586-020-01221-y?utm_source=Nature+Briefing&utm_campaign=0abf903597-briefing-dy-20200428_COPY_01&utm_medium=email&utm_term=0_c9dfd39373-0abf903597-45137854.
314. Zhu, F.-C., et al., *Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial.* The Lancet, 2020.
315. Lanese, N. *When will a COVID-19 vaccine be ready?* 2020; Available from: https://www.livescience.com/coronavirus-covid-19-vaccine-timeline.html.
316. Medicine, L.S.o.H.T. *COVID-19 Vaccine Tracker*. 2020; Available from: https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/.
317. Amit, S., et al., *Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients.* The Lancet, 2021.
318. CDC, *Science Brief: Background Rationale and Evidence for Public Health Recommendations for Fully Vaccinated People.* 2021.
319. CDC. *Late Sequelae of COVID-19*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/late-sequelae.html.
320. Banerji, A., et al., *mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach.* The Journal of Allergy and Clinical Immunology: In Practice, 2020.
321. Zhou, Z.-H., et al., *Anti-PEG IgE in anaphylaxis associated with polyethylene glycol.* The Journal of Allergy and Clinical Immunology: In Practice, 2020.
322. Blumenthal, K.G., et al., *Delayed Large Local Reactions to mRNA-1273 Vaccine against SARS-CoV-2.* New England Journal of Medicine, 2021.
323. Cecinati, V., et al., *Vaccine administration and the development of immune thrombocytopenic purpura in children.* Human Vaccines & Immunotherapeutics, 2013. **9**(5): p. 1158-1162.
324. Zhang, L., et al., *SARS-CoV-2 spike-protein D614G mutation increases virion spike density and infectivity.* Nature communications, 2020. **11**(1): p. 1-9.
325. Hou, Y.J., et al., *SARS-CoV-2 D614G variant exhibits efficient replication ex vivo and transmission in vivo.* Science, 2020. **370**(6523): p. 1464-1468.
326. Kemp, S., et al., *Neutralising antibodies drive Spike mediated SARS-CoV-2 evasion.* medRxiv, 2020: p. 2020.12.05.20241927.
327. Galloway, S.E., et al., *Emergence of SARS-CoV-2 b. 1.1. 7 lineage—united states, december 29, 2020–january 12, 2021.* Morbidity and Mortality Weekly Report, 2021. **70**(3): p. 95.
328. Challen, R., et al., *Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study.* BMJ, 2021. **372**: p. n579.
329. Wu, K., et al., *mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants.* bioRxiv, 2021: p. 2021.01.25.427948.
330. Xie, X., et al., *Neutralization of N501Y mutant SARS-CoV-2 by BNT162b2 vaccine-elicited sera.* bioRxiv, 2021: p. 2021.01.07.425740.
331. Liu, Y., et al., *Neutralizing Activity of BNT162b2-Elicited Serum.* New England Journal of Medicine, 2021.
332. Wang, Z., et al., *mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants.* bioRxiv, 2021: p. 2021.01.15.426911.
333. Tarke, A., et al., *Negligible impact of SARS-CoV-2 variants on CD4⁺ and CD8⁺ T cell reactivity in COVID-19 exposed donors and vaccinees.* bioRxiv, 2021: p. 2021.02.27.433180.

334. FDA. *Janssen COVID-19 Vaccine Frequently Asked Questions*. 2021; Available from: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/janssen-covid-19-vaccine-frequently-asked-questions.
335. Gee, J., et al. *First Month of COVID-19 Vaccine Safety Monitoring — United States, December 14, 2020–January 13, 2021*. 2021; Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7008e3.htm?s_cid=mm7008e3_w.
336. Soiza, R.L., C. Scicluna, and E.C. Thomson, *Efficacy and safety of COVID-19 vaccines in older people.* Age and Ageing, 2021. **50**(2): p. 279-283.
337. Polack, F.P., et al., *Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine.* New England Journal of Medicine, 2020. **383**(27): p. 2603-2615.
338. FDA. *Coronavirus (COVID-19) Update: FDA Allows More Flexible Storage, Transportation Conditions for Pfizer-BioNTech COVID-19 Vaccine*. 2021; Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-allows-more-flexible-storage-transportation-conditions-pfizer.
339. ASTM. *ASTM Standards & COVID-19*. 2021; Available from: https://www.astm.org/COVID-19/.
340. Wilson, A.M., et al., *COVID-19 and use of non-traditional masks: how do various materials compare in reducing the risk of infection for mask wearers?* The Journal of hospital infection, 2020. **105**(4): p. 640-642.
341. Darby, S., et al., *COVID-19: mask efficacy is dependent on both fabric and fit.* Future Microbiology, 2021. **16**(1): p. 5-11.
342. Asadi, S., et al., *Efficacy of masks and face coverings in controlling outward aerosol particle emission from expiratory activities.* Scientific Reports, 2020. **10**(1): p. 15665.
343. Lindsley, W.G., et al., *Efficacy of face masks, neck gaiters and face shields for reducing the expulsion of simulated cough-generated aerosols.* Aerosol Science and Technology, 2021. **55**(4): p. 449-457.
344. Zhang, M., et al., *Masks or N95 Respirators During COVID-19 Pandemic–Which One Should I Wear?* Journal of Oral and Maxillofacial Surgery, 2020. **78**(12): p. 2114-2127.
345. Brooks, J.T., et al., *Maximizing Fit for Cloth and Medical Procedure Masks to Improve Performance and Reduce SARS-CoV-2 Transmission and Exposure, 2021.* Morbidity and Mortality Weekly Report, 2021. **70**(7): p. 254.
346. MacIntyre, C.R., et al., *A cluster randomised trial of cloth masks compared with medical masks in healthcare workers.* BMJ open, 2015. **5**(4): p. e006577.
347. MacIntyre, C.R. and A.A. Chughtai, *A rapid systematic review of the efficacy of face masks and respirators against coronaviruses and other respiratory transmissible viruses for the community, healthcare workers and sick patients.* International journal of nursing studies, 2020. **108**: p. 103629-103629.
348. Jones, P., et al., *What proportion of healthcare worker masks carry virus? A systematic review.* Emergency Medicine Australasia, 2020. **32**(5): p. 823-829.
349. Gupta, M., K. Gupta, and S. Gupta, *The use of facemasks by the general population to prevent transmission of Covid 19 infection: A systematic review.* medRxiv, 2020: p. 2020.05.01.20087064.
350. Bundgaard, H., et al., *Effectiveness of Adding a Mask Recommendation to Other Public Health Measures to Prevent SARS-CoV-2 Infection in Danish Mask Wearers : A Randomized Controlled Trial.* Ann Intern Med, 2020.
351. Li, Y., et al., *Face masks to prevent transmission of COVID-19: a systematic review and meta-analysis.* American Journal of Infection Control, 2020.
352. Ippolito, M., et al., *Medical masks and Respirators for the Protection of Healthcare Workers from SARS-CoV-2 and other viruses.* Pulmonology, 2020.
353. Coclite, D., et al., *Face mask use in the Community for Reducing the Spread of COVID-19: a systematic review.* medRxiv, 2020: p. 2020.08.25.20181651.
354. Jefferson, T., et al., *Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review.* Bmj, 2009. **339**: p. b3675.
355. Liang, M., et al., *Efficacy of face mask in preventing respiratory virus transmission: a systematic review and meta-analysis.* Travel Medicine and Infectious Disease, 2020: p. 101751.
356. Long, Y., et al., *Effectiveness of N95 respirators versus surgical masks against influenza: a systematic review and meta-analysis.* Journal of Evidence-Based Medicine, 2020. **13**(2): p. 93-101.

357. Canini, L., et al., *Surgical mask to prevent influenza transmission in households: a cluster randomized trial.* PloS one, 2010. **5**(11): p. e13998.
358. Simmerman, J.M., et al., *Findings from a household randomized controlled trial of hand washing and face masks to reduce influenza transmission in Bangkok, Thailand.* Influenza and other respiratory viruses, 2011. **5**(4): p. 256-267.
359. Suess, T., et al., *The role of facemasks and hand hygiene in the prevention of influenza transmission in households: results from a cluster randomised trial; Berlin, Germany, 2009-2011.* BMC infectious diseases, 2012. **12**(1): p. 26.
360. MacIntyre, C.R., et al., *Face mask use and control of respiratory virus transmission in households.* Emerging infectious diseases, 2009. **15**(2): p. 233.
361. Jacobs, J.L., et al., *Use of surgical face masks to reduce the incidence of the common cold among health care workers in Japan: a randomized controlled trial.* American journal of infection control, 2009. **37**(5): p. 417-419.
362. Aiello, A.E., et al., *Mask use, hand hygiene, and seasonal influenza-like illness among young adults: a randomized intervention trial.* The Journal of infectious diseases, 2010. **201**(4): p. 491-498.
363. Cowling, B.J., et al., *Preliminary findings of a randomized trial of non-pharmaceutical interventions to prevent influenza transmission in households.* PloS one, 2008. **3**(5): p. e2101.
364. Cowling, B.J., et al., *Facemasks and hand hygiene to prevent influenza transmission in households: a cluster randomized trial.* Annals of internal medicine, 2009. **151**(7): p. 437-446.
365. MacIntyre, C.R., et al., *The efficacy of medical masks and respirators against respiratory infection in healthcare workers.* Influenza and other respiratory viruses, 2017. **11**(6): p. 511-517.
366. MacIntyre, C.R., et al., *Efficacy of face masks and respirators in preventing upper respiratory tract bacterial colonization and co-infection in hospital healthcare workers.* Preventive medicine, 2014. **62**: p. 1-7.
367. Chou, R., et al., *Masks for prevention of respiratory virus infections, including SARS-CoV-2, in health care and community settings: a living rapid review.* Annals of internal medicine, 2020. **173**(7): p. 542-555.
368. Kolewe, E.L., et al., *Check the gap: Facemask performance and exhaled aerosol distributions around the wearer.* PLOS ONE, 2020. **15**(12): p. e0243885.
369. Noti, J.D., et al., *Detection of Infectious Influenza Virus in Cough Aerosols Generated in a Simulated Patient Examination Room.* Clinical Infectious Diseases, 2012. **54**(11): p. 1569-1577.
370. Ueki, H., et al., *Effectiveness of Face Masks in Preventing Airborne Transmission of SARS-CoV-2.* mSphere, 2020. **5**(5): p. e00637-20.
371. Godoy, L.R.G., et al., *Facial protection for healthcare workers during pandemics: a scoping review.* BMJ global health, 2020. **5**(5): p. e002553.
372. Mueller, A. and L. Fernandez, *Assessment of Fabric Masks as Alternatives to Standard Surgical Masks in Terms of Particle Filtration Efficiency*. 2020.
373. Schaller, G., et al., *Efficacy of surgical helmet systems for protection against COVID-19: a double-blinded randomised control study.* International orthopaedics, 2020: p. 1-4.
374. MacIntyre, C.R., et al., *Cluster randomised controlled trial to examine medical mask use as source control for people with respiratory illness.* BMJ open, 2016. **6**(12).
375. Leung, N.H., et al., *Respiratory virus shedding in exhaled breath and efficacy of face masks.* Nature medicine, 2020. **26**(5): p. 676-680.
376. Larson, E.L., et al., *Impact of non-pharmaceutical interventions on URIs and influenza in crowded, urban households.* Public Health Reports, 2010. **125**(2): p. 178-191.
377. Alfelali, M., et al., *Facemask against viral respiratory infections among Hajj pilgrims: A challenging cluster-randomized trial.* PLoS One, 2020. **15**(10): p. e0240287.
378. Alfelali, M., et al., *Facemask versus no facemask in preventing viral respiratory infections during hajj: a cluster randomised open label trial.* 2019.
379. MacIntyre, C.R., et al., *Contamination and washing of cloth masks and risk of infection among hospital health workers in Vietnam: a post hoc analysis of a randomised controlled trial.* BMJ open, 2020. **10**(9): p. e042045.
380. MacIntyre, C.R., et al., *A randomized clinical trial of three options for N95 respirators and medical masks in health workers.* American journal of respiratory and critical care medicine, 2013. **187**(9): p. 960-966.

381. MacIntyre, C.R., et al., *A cluster randomized clinical trial comparing fit-tested and non-fit-tested N95 respirators to medical masks to prevent respiratory virus infection in health care workers.* Influenza and other respiratory viruses, 2011. **5**(3): p. 170-179.
382. Alfano, V. and S. Ercolano, *The efficacy of lockdown against COVID-19: a cross-country panel analysis.* Applied health economics and health policy, 2020. **18**: p. 509-517.
383. Makinde, O.S., et al., *Comparison of Predictive Models and Impact Assessment of Lockdown for COVID-19 over the United States.* Journal of Epidemiology and Global Health, 2021.
384. Guy, G.P., *Association of State-Issued Mask Mandates and Allowing On-Premises Restaurant Dining with County-Level COVID-19 Case and Death Growth Rates—United States, March 1–December 31, 2020.* MMWR. Morbidity and Mortality Weekly Report, 2021. **70**.
385. Shlomai, A., *National lockdown not cost effective in Israel during COVID-2 pandemic.* PharmacoEcon Outcomes News, 2021.
386. Miles, D.K., M. Stedman, and A.H. Heald, *"Stay at Home, Protect the National Health Service, Save Lives": A cost benefit analysis of the lockdown in the United Kingdom.* Int J Clin Pract, 2020: p. e13674.
387. Holland, K.M., et al., *Trends in US Emergency Department Visits for Mental Health, Overdose, and Violence Outcomes Before and During the COVID-19 Pandemic.* JAMA Psychiatry, 2021.
388. Henderson, E. *FAIR Health study highlights the impact of COVID-19 on pediatric mental health*. 2021; Available from: https://www.news-medical.net/news/20210302/FAIR-Health-study-highlights-the-impact-of-COVID-19-on-pediatric-mental-health.aspx.
389. Amsalem, D., L.B. Dixon, and Y. Neria, *The Coronavirus Disease 2019 (COVID-19) Outbreak and Mental Health: Current Risks and Recommended Actions.* JAMA Psychiatry, 2021. **78**(1): p. 9-10.
390. Magson, N.R., et al., *Risk and Protective Factors for Prospective Changes in Adolescent Mental Health during the COVID-19 Pandemic.* Journal of Youth and Adolescence, 2021. **50**(1): p. 44-57.
391. Ravens-Sieberer, U., et al., *Impact of the COVID-19 pandemic on quality of life and mental health in children and adolescents in Germany.* European Child & Adolescent Psychiatry, 2021.
392. Health, G.I.o.R. *Calculation Tool For Predicting Critical-ill COVID-19 At Admission*. 2020; Available from: http://118.126.104.170.
393. Yuan, J., et al., *The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients.* Inflammation Research, 2020: p. 1-8.
394. CDC. *Evaluating and Testing Persons for Coronavirus Disease 2019 (COVID-19)*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-criteria.html.
395. Hahn, S.M. and J.E. Shuren. *Coronavirus (COVID-19) Update: FDA Authorizes First Antigen Test to Help in the Rapid Detection of the Virus that Causes COVID-19 in Patients*. 2020; Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-antigen-test-help-rapid-detection-virus-causes.
396. Kucirka, L.M., et al., *Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction-Based SARS-CoV-2 Tests by Time Since Exposure.* Ann Intern Med, 2020. **173**(4): p. 262-267.
397. Pérez, D.A.G., et al., *Saliva Pooling Strategy for the Large-Scale Detection of SARS-CoV-2, Through Working-Groups Testing of Asymptomatic Subjects for Potential Applications in Different Workplaces.* Journal of Occupational and Environmental Medicine, 2021. **Publish Ahead of Print**.
398. Wyllie, A.L., et al., *Saliva is more sensitive for SARS-CoV-2 detection in COVID-19 patients than nasopharyngeal swabs.* medRxiv, 2020.
399. Azzi, L., et al., *Saliva is a reliable tool to detect SARS-CoV-2.* Journal of Infection, 2020.
400. Mina, M.J., R. Parker, and D.B. Larremore, *Rethinking Covid-19 test sensitivity—A strategy for containment.* New England Journal of Medicine, 2020. **383**(22): p. e120.
401. Burbelo, P.D., et al., *Sensitivity in Detection of Antibodies to Nucleocapsid and Spike Proteins of Severe Acute Respiratory Syndrome Coronavirus 2 in Patients With Coronavirus Disease 2019.* The Journal of Infectious Diseases, 2020.
402. Woelfel, R., et al., *Clinical presentation and virological assessment of hospitalized cases of coronavirus disease 2019 in a travel-associated transmission cluster.* medRxiv, 2020.
403. Yang, Y., et al., *Laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections.* medRxiv, 2020.

404. Carver, C. and N. Jones. *Comparative accuracy of oropharyngeal and nasopharyngeal swabs for diagnosis of COVID-19*. 2020; Available from: https://www.cebm.net/covid-19/comparative-accuracy-of-oropharyngeal-and-nasopharyngeal-swabs-for-diagnosis-of-covid-19/.
405. Domeracki, S., et al., *Cycle Threshold to Test Positivity in COVID-19 for Return to Work Clearance in Health Care Workers.* Journal of Occupational and Environmental Medicine, 2020. **62**(11).
406. Iyer, A.S., et al., *Dynamics and significance of the antibody response to SARS-CoV-2 infection.* medRxiv, 2020: p. 2020.07.18.20155374.
407. Cheng, M.P., et al., *Serodiagnostics for Severe Acute Respiratory Syndrome–Related Coronavirus-2: A Narrative Review.* Annals of Internal Medicine, 2020.
408. Guo, L., et al., *Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19).* Clin Infect Dis, 2020.
409. Zhao, J., et al., *Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019.* Clin Infect Dis, 2020.
410. Li, Z., et al., *Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis.* J Med Virol, 2020.
411. Bonelli, F., et al., *Clinical and Analytical Performance of an Automated Serological Test That Identifies S1/S2-Neutralizing IgG in COVID-19 Patients Semiquantitatively.* J Clin Microbiol, 2020. **58**(9).
412. Jacofsky, D., E.M. Jacofsky, and M. Jacofsky, *Understanding antibody testing for covid-19.* The Journal of Arthroplasty, 2020.
413. FDA. *EUA Authorized Serology Test Performance*. 2020; Available from: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/eua-authorized-serology-test-performance.
414. Pollán, M., et al., *Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study.* The Lancet, 2020.
415. Caturegli, G., et al., *Clinical Validity of Serum Antibodies to SARS-CoV-2: A Case-Control Study.* Annals of internal medicine, 2020: p. M20-2889.
416. Ripperger, T.J., et al., *Detection, prevalence, and duration of humoral responses to SARS-CoV-2 under conditions of limited population exposure.* medRxiv, 2020: p. 2020.08.14.20174490.
417. Seow, J., et al., *Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection.* medRxiv, 2020: p. 2020.07.09.20148429.
418. Sekine, T., et al., *Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19.* BioRXiv, 2020.
419. Nelde, A., et al., *SARS-CoV-2 T-cell epitopes define heterologous and COVID-19-induced T-cell recognition.* 2020.
420. Blanchard, S. *Blow to getting Britain back to work after Oxford scientist tasked with evaluating crucial coronavirus antibody tests says it may take a MONTH before one is ready for Britain to use as another expert warns the kits may only be 50% accurate*. 2020; Available from: https://www.dailymail.co.uk/news/article-8190949/None-UKs-coronavirus-antibody-tests-good-use.html.
421. Canada, G.o. *Diagnostic devices for use against coronavirus (COVID-19): List of applications received*. 2020; Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/covid-19/diagnostic-devices-applications.html.
422. Wong, H.Y.F., et al., *Frequency and Distribution of Chest Radiographic Findings in COVID-19 Positive Patients.* Radiology, 2020: p. 201160.
423. Udugama, B., et al., *Diagnosing COVID-19: The Disease and Tools for Detection.* ACS Nano, 2020.
424. Sun, Z., *Diagnostic Value of Chest CT in Coronavirus Disease 2019 (COVID-19).* Current medical imaging, 2020.
425. Chan, J.F.-W., et al., *A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster.* The Lancet, 2020. **395**(10223): p. 514-523.
426. Li, B., et al., *Diagnostic Value and Key Features of Computed Tomography in Coronavirus Disease 2019.* Emerging Microbes & Infections, 2020(just-accepted): p. 1-14.
427. Iwasawa, T., et al., *Ultra-high-resolution computed tomography can demonstrate alveolar collapse in novel coronavirus (COVID-19) pneumonia.* Jpn J Radiol, 2020.
428. Li, M., et al., *Coronavirus Disease (COVID-19): Spectrum of CT Findings and Temporal Progression of the Disease.* Academic Radiology, 2020.

429. Liu, K.C., et al., *CT manifestations of coronavirus disease-2019: A retrospective analysis of 73 cases by disease severity.* Eur J Radiol, 2020. **126**: p. 108941.
430. NIH. *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines*. 2020; Available from: https://www.covid19treatmentguidelines.nih.gov.
431. NIH. *COVID-19 Treatment Guidelines Introduction*. 2020; Available from: https://www.covid19treatmentguidelines.nih.gov/introduction/.
432. IDSA. *Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19*. 2020; Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/.
433. Bai, C., et al., *Updated guidance on the management of COVID-19: From an american thoracic society/european respiratory society coordinated international task force (29 July 2020).* European Respiratory Review, 2020. **29**(157).
434. CDC. *Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19)*. 2020; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html.
435. SHEA. *Novel Coronavirus 2019 (2019-nCOV) Resources*. 2020; Available from: https://shea-online.org/index.php/practice-resources/priority-topics/emerging-pathogens/novel-coronavirus-2019-2019-ncov-resources.
436. ASHP. *Assessment of Evidence for COVID-19-Related Treatments: Updated 12/01/2020*. 2020; Available from: https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx?
437. WHO. *Clinical management of COVID-19*. 2020; Available from: https://www.who.int/publications/i/item/clinical-management-of-covid-19.
438. FDA. *Coronavirus Disease 2019 (COVID-19) Frequently Asked Questions*. 2020; Available from: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/coronavirus-disease-2019-covid-19-frequently-asked-questions
439. Derwand, R., M. Scholz, and V. Zelenko, *COVID-19 outpatients–early risk-stratified treatment with zinc plus low dose hydroxychloroquine and azithromycin: a retrospective case series study.* 2020.
440. Skalny, A.V., et al., *Zinc and respiratory tract infections: Perspectives for COVID-19 (Review).* Int J Mol Med, 2020. **46**(1): p. 17-26.
441. Finzi, E., *Treatment of SARS-CoV-2 with high dose oral zinc salts: A report on four patients.* International Journal of Infectious Diseases, 2020.
442. Carlucci, P., et al., *Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients.* medRxiv, 2020.
443. Thomas, S., et al., *Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection: The COVID A to Z Randomized Clinical Trial.* JAMA Network Open, 2021. **4**(2): p. e210369-e210369.
444. Alipio, M., *Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-19).* Available at SSRN 3571484, 2020.
445. Ruiz-Irastorza, G., et al., *Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences.* Rheumatology, 2008. **47**(6): p. 920-923.
446. Lau, F.H., et al., *Vitamin D insufficiency is prevalent in severe COVID-19.* medRxiv, 2020.
447. D'Avolio, A., et al., *25-hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2.* Nutrients, 2020. **12**(5): p. 1359.
448. Zhang, X.-J., et al., *In-hospital Use of Statins is Associated with a Reduced Risk of Mortality among Individuals with COVID-19.* Cell metabolism, 2020.
449. Oxford, U.o. *Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19*. 2020; Available from: http://www.ox.ac.uk/news/2020-06-16-low-cost-dexamethasone-reduces-death-one-third-hospitalised-patients-severe#.
450. Ledford, H. *Coronavirus breakthrough: dexamethasone is first drug shown to save lives*. 2020; Available from: https://www.nature.com/articles/d41586-020-01824-5.
451. Russell, B., et al., *COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting?* ecancermedicalscience, 2020. **14**.

452. Beigel, J.H., et al., *Remdesivir for the Treatment of Covid-19 — Preliminary Report.* New England Journal of Medicine, 2020.
453. Winck, J.C. and N. Ambrosino, *COVID-19 pandemic and non invasive respiratory management: every Goliath needs a David. An evidence based evaluation of problems.* Pulmonology, 2020. **26**(4): p. 213-220.
454. Lazzeri, M., et al., *Respiratory physiotherapy in patients with COVID-19 infection in acute setting: a Position Paper of the Italian Association of Respiratory Physiotherapists (ARIR).* Monaldi Archives for Chest Disease, 2020. **90**(1).
455. Poston, J.T., B.K. Patel, and A.M. Davis, *Management of Critically Ill Adults With COVID-19.* Jama, 2020.
456. Khan, F., et al., *A systematic review of Anakinra, Tocilizumab, Sarilumab and Siltuximab for coronavirus-related infections.* medRxiv, 2020.
457. Sinha, P., M.A. Matthay, and C.S. Calfee, *Is a "cytokine storm" relevant to COVID-19?* JAMA Internal Medicine, 2020.
458. CHEN, J., et al., *A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19).* Journal of Zhejiang University (Medical Science), 2020. **49**(1): p. 0-0.
459. Ladapo, J.A., et al., *Randomized Controlled Trials of Early Ambulatory Hydroxychloroquine in the Prevention of COVID-19 Infection, Hospitalization, and Death: Meta-Analysis.* medRxiv, 2020.
460. NIH. *ClinicalTrials.gov*. 2020; Available from: https://clinicaltrials.gov.
461. Arnold, K.D. and J. Skillings. *Adapted Treatment Protocol for COVID19-Related Healthcare Professionals: A Holistic Model and Clinical Health Application of Cognitive-Behavioral Therapy to Pandemics*. 2020; Available from: https://ccbtcolumbus.com/wp-content/uploads/2020/04/Adapted-Treatment-CBT-Protocol-for-COVID19-Healthcare-Workers.pdf.
462. Trust, W.B. *The COVID Pandemic Could Lead to 75,000 Additional Deaths from Alcohol and Drug Misuse and Suicide*. 2020; Available from: https://wellbeingtrust.org/areas-of-focus/policy-and-advocacy/reports/projected-deaths-of-despair-during-covid-19/.
463. Arnold, K.D. and J.L. Skillings. *Treating front-line workers: A step-by-step guide*. 2020; Available from: https://www.apaservices.org/practice/news/front-line-workers-covid-19.
464. Arnold, K.D. and J.L. Skillings. *Treating anxiety and stress in front-line workers: A step-by-step CBT guide*. 2020; Available from: https://www.apaservices.org/practice/news/anxiety-stress-front-line-workers.
465. Association, A.P. *Serious mental illness and COVID-19: How to help your patients right now*. 2020; Available from: https://www.apaservices.org/practice/legal/technology/serious-mental-illness-covid-19.
466. Trivedi, N., *COVID-19 (Coronavirus) Mental Health Guide: Strategies to manage mood effectively in times of Global Distress*. 2020.
467. Affairs, U.D.o.V. *COVID Coach*. 2020; Available from: https://apps.apple.com/app/apple-store/id1504705038?mt=8.
468. Mail, D. *28 August 2020 News Archive*. 2020; Available from: https://www.dailymail.co.uk/home/sitemaparchive/day_20200828.html.
469. Wilson, J.M., et al., *Job Insecurity and Financial Concern During the COVID-19 Pandemic Are Associated With Worse Mental Health.* Journal of Occupational and Environmental Medicine, 2020. **62**(9).
470. Tang, W., et al., *Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial.* bmj, 2020. **369**.
471. Tang, W., et al., *Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial.* medRxiv, 2020.
472. te Velthuis, A.J.W., et al., *Zn2+ Inhibits Coronavirus and Arterivirus RNA Polymerase Activity In Vitro and Zinc Ionophores Block the Replication of These Viruses in Cell Culture.* PLOS Pathogens, 2010. **6**(11): p. e1001176.
473. Xue, J., et al., *Chloroquine Is a Zinc Ionophore.* PLOS ONE, 2014. **9**(10): p. e109180.
474. Borba, M.G.S., 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 Network Open, 2020. **3**(4): p. e208857-e208857.
475. Capra, R., et al., *Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia.* Eur J Intern Med, 2020. **76**: p. 31-35.

476. Lagier, J.-C., et al., *Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis.* Travel medicine and infectious disease, 2020: p. 101791.
477. Gautret, P., et al., *Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial.* International Journal of Antimicrobial Agents, 2020: p. 105949.
478. Lover, A.A., *Quantifying treatment effects of hydroxychloroquine and azithromycin for COVID-19: a secondary analysis of an open label non-randomized clinical trial (Gautret et al, 2020).* medRxiv, 2020.
479. Raoult, D. *Abstract*. 2020; Available from: https://www.mediterranee-infection.com/wp-content/uploads/2020/04/Abstract_Raoult_EarlyTrtCovid19_09042020_vD1v.pdf.
480. Raoult, D. *Table 1*. 2020; Available from: https://www.mediterranee-infection.com/wp-content/uploads/2020/04/Table_final_website_IHU_09_04_2020.pdf.
481. Davido, B., et al., *Hydroxychloroquine plus azithromycin: a potential interest in reducing in-hospital morbidity due to COVID-19 pneumonia (HI-ZY-COVID)?* medRxiv, 2020.
482. Arshad, S., et al., *Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19.* International Journal of Infectious Diseases, 2020.
483. Guérin, V., et al., *Azithromycin and hydroxychloroquine accelerate recovery of outpatients with mild/moderate COVID-19.* 2020.
484. Rosenberg, E.S., et al., *Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State.* Jama, 2020.
485. Sbidian, E., et al., *Hydroxychloroquine with or without azithromycin and in-hospital mortality or discharge in patients hospitalized for COVID-19 infection: a cohort study of 4,642 in-patients in France.* medRxiv, 2020.
486. Mahévas, M., et al., *Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data.* Bmj, 2020. **369**: p. m1844.
487. Boulware, D.R., et al., *A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19.* New England Journal of Medicine, 2020.
488. Lane, J.C., et al., *Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study.* medRxiv, 2020.
489. Geleris, J., et al., *Observational study of hydroxychloroquine in hospitalized patients with Covid-19.* New England Journal of Medicine, 2020.
490. Magagnoli, J., et al., *Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19.* medRxiv, 2020: p. 2020.04.16.20065920.
491. Risch, H.A., *Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis.* American Journal of Epidemiology, 2020.
492. Oxford, U.o. *No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19*. 2020; Available from: http://www.ox.ac.uk/news/2020-06-05-no-clinical-benefit-use-hydroxychloroquine-hospitalised-patients-covid-19.
493. Cavalcanti, A.B., et al., *Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19.* New England Journal of Medicine, 2020.
494. Voisin, O., et al., *Acute QT Interval Modifications During Hydroxychloroquine-Azithromycin Treatment in the Context of COVID-19 Infection.* Mayo Clin Proc, 2020. **95**(8): p. 1696-1700.
495. Mercuro, N.J., et al., *Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19).* JAMA cardiology, 2020.
496. Ramireddy, A., et al., *Experience With Hydroxychloroquine and Azithromycin in the Coronavirus Disease 2019 Pandemic: Implications for QT Interval Monitoring.* J Am Heart Assoc, 2020. **9**(12): p. e017144.
497. Pothen, L., et al., *Safety use of hydroxychloroquine and its combination with azithromycin in the context of Sars-CoV-2 outbreak: Clinical experience in a Belgian tertiary center.* Travel Medicine and Infectious Disease, 2020. **36**.
498. Kuate, L.M., et al., *Electrocardiographic safety of daily Hydroxychloroquine 400mg plus Azithromycin 250mg as an ambulatory treatment for COVID-19 patients in Cameroon.* medRxiv, 2020.

499. Maraj, I., et al., *Incidence and Determinants of QT Interval Prolongation in COVID-19 Patients Treated with Hydroxychloroquine and Azithromycin.* Journal of cardiovascular electrophysiology, 2020.
500. Chorin, E., et al., *The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin.* medRxiv, 2020.
501. Chorin, E., et al., *QT interval prolongation and torsade de pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin.* Heart Rhythm, 2020.
502. Saleh, M., et al., *Effect of Chloroquine, Hydroxychloroquine, and Azithromycin on the Corrected QT Interval in Patients With SARS-CoV-2 Infection.* Circ Arrhythm Electrophysiol, 2020. **13**(6): p. e008662.
503. Omrani, A.S., et al., *Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19.* EClinicalMedicine, 2020. **29**: p. 100645.
504. Catteau, L., et al., *Low-dose hydroxychloroquine therapy and mortality in hospitalised patients with COVID-19: a nationwide observational study of 8075 participants.* International journal of antimicrobial agents, 2020. **56**(4): p. 106144.
505. Cipriani, A., et al., *Arrhythmic profile and 24-hour QT interval variability in COVID-19 patients treated with hydroxychloroquine and azithromycin.* International journal of cardiology, 2020. **316**: p. 280-284.
506. Ip, A., et al., *Hydroxychloroquine and Tocilizumab Therapy in COVID-19 Patients-An Observational Study.* medRxiv, 2020.
507. Marzolini, C., et al., *Effect of systemic inflammatory response to SARS-CoV-2 on lopinavir and hydroxychloroquine plasma concentrations.* Antimicrobial agents and chemotherapy, 2020. **64**(9).
508. Nagaraja, B.S., et al., *HyPE study: hydroxychloroquine prophylaxis-related adverse events' analysis among healthcare workers during COVID-19 pandemic: a rising public health concern.* Journal of Public Health, 2020.
509. Yu, B., et al., *Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19.* Science China Life Sciences, 2020: p. 1-7.
510. Sekhavati, E., et al., *Safety and effectiveness of azithromycin in patients with COVID-19: An open-label randomised trial.* International journal of antimicrobial agents, 2020. **56**(4): p. 106143-106143.
511. WHO. *"Solidarity" clinical trial for COVID-19 treatments*. 2020; Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments.
512. Liu, J., et al., *Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro.* Cell Discovery, 2020. **6**(1): p. 1-4.
513. Yao, X., et al., *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, 2020.
514. Colson, P., *Chloroquine for the 2019 novel coronavirus SARS-CoV-2.* International Journal of Antimicrobial Agents, 2020. **55**(3).
515. Colson, P., et al., *Chloroquine and hydroxychloroquine as available weapons to fight COVID-19.* Int J Antimicrob Agents, 2020. **105932**.
516. Wang, M., et al., *Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro.* Cell research, 2020. **30**(3): p. 269-271.
517. Vincent, M.J., et al., *Chloroquine is a potent inhibitor of SARS coronavirus infection and spread.* Virology journal, 2005. **2**(1): p. 69.
518. Woodyatt, A., et al. *March 30 coronavirus news*. 2020; Available from: https://www.cnn.com/world/live-news/coronavirus-outbreak-03-30-20-intl-hnk/h_3c0b470af744b6dd92b77b7.
519. Savarino, A., et al., *Effects of chloroquine on viral infections: an old drug against today's diseases?* Lancet Infect Dis, 2003. **3**(11): p. 722-7.
520. Rolain, J.-M., P. Colson, and D. Raoult, *Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century.* International journal of antimicrobial agents, 2007. **30**(4): p. 297-308.
521. Marmor, M.F., et al., *Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision).* Ophthalmology, 2016. **123**(6): p. 1386-1394.

522. Ulrich, R.J., et al. *Treating COVID-19 With Hydroxychloroquine (TEACH): A Multicenter, Double-Blind Randomized Controlled Trial in Hospitalized Patients*. in *Open Forum Infectious Diseases*. 2020. Oxford University Press US.
523. Lyngbakken, M.N., et al., *A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics.* Nature communications, 2020. **11**(1): p. 1-6.
524. Abd-Elsalam, S., et al., *Hydroxychloroquine in the treatment of COVID-19: a multicenter randomized controlled study.* The American Journal of Tropical Medicine and Hygiene, 2020. **103**(4): p. 1635-1639.
525. Horby, P., et al., *Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial.* MedRxiv, 2020.
526. Lammers, A.J.J., et al., *Early hydroxychloroquine but not chloroquine use reduces ICU admission in COVID-19 patients.* International Journal of Infectious Diseases, 2020. **101**: p. 283-289.
527. Ip, A., et al., *Hydroxychloroquine in the treatment of outpatients with mildly symptomatic COVID-19: a multi-center observational study.* BMC Infectious Diseases, 2021. **21**(1): p. 1-12.
528. Skipper, C.P., et al., *Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial.* Annals of internal medicine, 2020. **173**(8): p. 623-631.
529. Rajasingham, R., et al., *Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial.* MedRxiv, 2020.
530. Watanabe, M., *Efficacy of Hydroxychloroquine as Prophylaxis for Covid-19.* arXiv preprint arXiv:2007.09477, 2020.
531. Mitja, O., et al., *A Cluster-Randomized Trial of Hydroxychloroquine as Prevention of Covid-19 Transmission and Disease.* medRxiv, 2020: p. 2020.07.20.20157651.
532. Abella, B.S., et al., *Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: A randomized clinical trial.* JAMA internal medicine, 2020.
533. Hernandez, A.V., et al., *Update alert 2: hydroxychloroquine or chloroquine for the treatment or prophylaxis of COVID-19.* Annals of internal medicine, 2020. **173**(7): p. W128-W129.
534. Chen, Z., et al., *Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial.* medRxiv, 2020.
535. Huang, M., et al., *Treating COVID-19 with chloroquine.* Journal of molecular cell biology, 2020. **12**(4): p. 322-325.
536. Mitjà, O., et al., *Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial.* Clinical Infectious Diseases, 2020.
537. Million, M., et al., *Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France.* Travel Med Infect Dis, 2020. **35**: p. 101738.
538. Gautret, P., et al. *Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study* 2020; Available from: https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf.
539. Molina, J.M., 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.* Médecine et Maladies Infectieuses, 2020: p. 30085-8.
540. Mehra, M.R., et al., *Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis.* The Lancet, 2020.
541. Gendelman, O., et al., *Continuous hydroxychloroquine or colchicine therapy does not prevent infection with SARS-CoV-2: Insights from a large healthcare database analysis.* Autoimmunity Reviews, 2020: p. 102566.
542. Retallack, H., et al., *Zika virus cell tropism in the developing human brain and inhibition by azithromycin.* Proc Natl Acad Sci U S A, 2016. **113**(50): p. 14408-14413.
543. Madrid, P.B., et al., *Evaluation of Ebola Virus Inhibitors for Drug Repurposing.* ACS Infect Dis, 2015. **1**(7): p. 317-26.
544. Bosseboeuf, E., et al., *Azithromycin Inhibits the Replication of Zika Virus.* J. Antivir. Antiretrovir, 2018. **10**: p. 6-11.

545. Bacharier, L.B., et al., *Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial.* Jama, 2015. **314**(19): p. 2034-2044.
546. Albani, F., et al., *Impact of Azithromycin and/or Hydroxychloroquine on Hospital Mortality in COVID-19.* Journal of clinical medicine, 2020. **9**(9): p. 2800.
547. Hsia, B.C., et al., *QT prolongation in a diverse, urban population of COVID-19 patients treated with hydroxychloroquine, chloroquine, or azithromycin.* Journal of Interventional Cardiac Electrophysiology, 2020. **59**(2): p. 337-345.
548. Rodríguez-Molinero, A., et al., *Observational study of azithromycin in hospitalized patients with COVID-19.* PloS one, 2020. **15**(9): p. e0238681.
549. Furtado, R.H.M., et al., *Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial.* The Lancet, 2020. **396**(10256): p. 959-967.
550. Irie, K., et al., *Pharmacokinetics of Favipiravir in Critically Ill Patients with COVID-19.* Clinical and Translational Science, 2020.
551. Pongpirul, W.A., et al., *Clinical course and potential predictive factors for pneumonia of adult patients with Coronavirus Disease 2019 (COVID-19): A retrospective observational analysis of 193 confirmed cases in Thailand.* PLoS neglected tropical diseases, 2020. **14**(10): p. e0008806.
552. Sano, T., et al., *COVID-19 in older adults: Retrospective cohort study in a tertiary hospital in Japan.* Geriatrics & gerontology international, 2020.
553. Yaylaci, S., et al., *The effects of favipiravir on hematological parameters of covıd-19 patients.* Revista da Associação Médica Brasileira, 2020. **66**: p. 65-70.
554. Yamamura, H., et al., *Effect of favipiravir and an anti-inflammatory strategy for COVID-19.* Critical Care, 2020. **24**(1): p. 1-3.
555. Ivashchenko, A.A., et al., *AVIFAVIR for treatment of patients with moderate COVID-19: interim results of a phase II/III multicenter randomized clinical trial.* medRxiv, 2020.
556. Khamis, F., et al., *Randomized Controlled Open Label Trial on the Use of Favipiravir Combined with Inhaled Interferon beta-1b in Hospitalized Patients with Moderate to Severe COVID-19 Pneumonia.* International Journal of Infectious Diseases, 2020.
557. Dabbous, H.M., et al., *A Randomized Controlled Study Of Favipiravir Vs Hydroxychloroquine In COVID-19 Management: What Have We Learned So Far?* 2020.
558. Khamis, F., et al., *Randomized controlled open label trial on the use of favipiravir combined with inhaled interferon beta-1b in hospitalized patients with moderate to severe COVID-19 pneumonia.* Int J Infect Dis, 2021. **102**: p. 538-543.
559. Doi, Y., et al., *A prospective, randomized, open-label trial of early versus late favipiravir in hospitalized patients with COVID-19.* Antimicrobial agents and chemotherapy, 2020.
560. Chen, C., et al., *Favipiravir versus Arbidol for COVID-19: a randomized clinical trial.* MedRxiv, 2020.
561. Lou, Y., L. Liu, and Y. Qiu, *Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: an Exploratory Randomized, Controlled Trial.* medRxiv, 2020.
562. Cai, Q., et al., *Experimental treatment with favipiravir for COVID-19: an open-label control study.* Engineering, 2020.
563. Yao, T.T., et al., *A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus—A possible reference for coronavirus disease-19 treatment option.* Journal of medical virology, 2020. **92**(6): p. 556-563.
564. Verdugo-Paiva, F., et al., *Lopinavir/ritonavir for COVID-19: a living systematic review.* Medwave, 2020. **20**(6).
565. Lê, M.P., et al., *Pharmacokinetics of lopinavir/ritonavir oral solution to treat COVID-19 in mechanically ventilated ICU patients.* Journal of Antimicrobial Chemotherapy, 2020. **75**(9): p. 2657-2660.
566. Gao, G., et al., *Brief Report: Retrospective Evaluation on the Efficacy of Lopinavir/Ritonavir and Chloroquine to Treat Nonsevere COVID-19 Patients.* Journal of acquired immune deficiency syndromes (1999), 2020. **85**(2): p. 239.
567. Karolyi, M., et al., *Hydroxychloroquine versus lopinavir/ritonavir in severe COVID-19 patients.* Wiener Klinische Wochenschrift, 2020: p. 1-8.

568. Kim, J.-W., et al., *Lopinavir-ritonavir versus hydroxychloroquine for viral clearance and clinical improvement in patients with mild to moderate coronavirus disease 2019.* The Korean journal of internal medicine, 2020.
569. Lecronier, M., et al., *Comparison of hydroxychloroquine, lopinavir/ritonavir, and standard of care in critically ill patients with SARS-CoV-2 pneumonia: an opportunistic retrospective analysis.* Critical Care, 2020. **24**(1): p. 1-9.
570. Zhu, Z., et al., *Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19.* Journal of Infection, 2020. **81**(1): p. e21-e23.
571. Cao, B., et al., *A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19.* New England Journal of Medicine, 2020.
572. Hung, I.F.-N., et al., *Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial.* The Lancet, 2020.
573. Rahmani, H., et al., *Interferon β-1b in treatment of severe COVID-19: A randomized clinical trial.* International immunopharmacology, 2020. **88**: p. 106903.
574. Li, Y., et al., *An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI).* MedRxiv, 2020.
575. Horby, P.W., et al., *Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial.* The Lancet, 2020. **396**(10259): p. 1345-1352.
576. Li, L., et al., *Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial.* Jama, 2020.
577. Deng, L., et al., *Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study.* Journal of Infection, 2020.
578. Yan, D., et al., *Factors associated with prolonged viral shedding and impact of Lopinavir/Ritonavir treatment in patients with SARS-CoV-2 infection.* medRxiv, 2020.
579. Ye, X., et al., *Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019.* European Review for Medical and Pharmacological Sciences, 2020. **24**(6): p. 3390-3396.
580. Shih, W.J., et al., *Remdesivir is Effective for Moderately Severe Patients: A Re-Analysis of the First Double-Blind, Placebo-Controlled, Randomized Trial on Remdesivir for Treatment of Severe COVID-19 Patients Conducted in Wuhan City.* Open Access Journal of Clinical Trials, 2020. **Volume 12**: p. 15-21.
581. Susan A. Olender, K.K.P., Alan S. Go, Bindu Balani, Eboni G. Price-Haywood, Nirav S. Shah, Su Wang, Theresa L. Walunas, Shobha Swaminathan, Jihad Slim, BumSik Chin, Stéphane De Wit, *Remdesivir for Severe COVID-19 versus a Cohort Receiving Standard of Care.* Oxford University Press for the Infectious Diseases Society of America, 2020.
582. Pasquini, Z., et al., *Effectiveness of remdesivir in patients with COVID-19 under mechanical ventilation in an Italian ICU.* J Antimicrob Chemother, 2020. **75**(11): p. 3359-3365.
583. Kalligeros, M., et al., *Remdesivir Use Compared With Supportive Care in Hospitalized Patients With Severe COVID-19: A Single-Center Experience.* Open Forum Infect Dis, 2020. **7**(10): p. ofaa319.
584. Lee, C., et al., *Clinical Experience with Use of Remdesivir in the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2: a Case Series.* Infect Chemother, 2020. **52**(3): p. 369-380.
585. Hsu, C.-Y., et al., *Efficacy of remdesivir in COVID-19 patients with a simulated two-arm controlled study* medRxiv, 2020.
586. Kaka, A.S., et al., *Major Update: Remdesivir for Adults With COVID-19: A Living Systematic Review and Meta-analysis for the American College of Physicians Practice Points.* Annals of Internal Medicine, 2021.
587. Qaseem, A., et al., *Should Remdesivir Be Used for the Treatment of Patients With COVID-19? Rapid, Living Practice Points From the American College of Physicians (Version 1).* Annals of internal medicine, 2020.
588. Hinton, D.M. *Letter*. 2020; Available from: https://www.fda.gov/media/137564/download.
589. Grein, J., et al., *Compassionate Use of Remdesivir for Patients with Severe Covid-19.* New England Journal of Medicine, 2020.
590. Wang, Y., et al., *Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial.* The Lancet, 2020.
591. Spinner, C.D., et al., *Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial.* JAMA, 2020. **324**(11): p. 1048-1057.

592. Antinori, S., et al., *Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: Clinical outcome and differences in post-treatment hospitalisation status.* Pharmacol Res, 2020. **158**: p. 104899.
593. Goldman, J.D., et al., *Remdesivir for 5 or 10 days in patients with severe Covid-19.* New England Journal of Medicine, 2020.
594. Kalil, A.C., et al., *Baricitinib plus Remdesivir for hospitalized adults with Covid-19.* New England Journal of Medicine, 2020.
595. Hasan, S.S., et al., *Venous thromboembolism in critically ill COVID-19 patients receiving prophylactic or therapeutic anticoagulation: a systematic review and meta-analysis.* Journal of thrombosis and thrombolysis, 2020. **50**(4): p. 814-821.
596. Falcone, M., et al., *Role of low-molecular weight heparin in hospitalized patients with SARS-CoV-2 pneumonia: a prospective observational study.* Open Forum Infectious Diseases, 2020.
597. Viecca, M., et al., *Enhanced platelet inhibition treatment improves hypoxemia in patients with severe Covid-19 and hypercoagulability. A case control, proof of concept study.* Pharmacological Research, 2020. **158**: p. 104950.
598. Di Perri, G., *The rationale for Low-Molecular Weight Heparin (LMWH) use in SARS-CoV-2 infection.* Infez Med, 2020. **28**(suppl 1): p. 52-56.
599. Fontana, P., et al., *Venous thromboembolism in COVID-19: systematic review of reported risks and current guidelines.* Swiss Med Wkly, 2020. **150**: p. w20301.
600. Nittari, G., et al., *Current pharmacological treatments for SARS-COV-2: A narrative review.* European journal of pharmacology, 2020. **882**: p. 173328-173328.
601. van Haren, F.M.P., et al., *Nebulised heparin as a treatment for COVID-19: scientific rationale and a call for randomised evidence.* Critical Care, 2020. **24**(1): p. 454.
602. Ayerbe, L., C. Risco, and S. Ayis, *The association between treatment with heparin and survival in patients with Covid-19.* Journal of thrombosis and thrombolysis, 2020. **50**(2): p. 298-301.
603. Hippensteel, J.A., et al., *Heparin as a therapy for COVID-19: current evidence and future possibilities.* American Journal of Physiology-Lung Cellular and Molecular Physiology, 2020. **319**(2): p. L211-L217.
604. Birocchi, S., et al., *High rates of pulmonary artery occlusions in COVID-19. A meta-analysis.* European Journal of Clinical Investigation. **n/a**(n/a): p. e13433.
605. Shah, A., et al., *Thrombotic and haemorrhagic complications in critically ill patients with COVID-19: a multicentre observational study.* Critical Care, 2020. **24**(1): p. 561.
606. Rosovsky, R.P., et al., *Anticoagulation Practice Patterns in COVID-19: A Global Survey.* Res Pract Thromb Haemost, 2020. **4**(6): p. 969-83.
607. Lu, Y.-f., et al., *A meta-analysis of the incidence of venous thromboembolic events and impact of anticoagulation on mortality in patients with COVID-19.* International Journal of Infectious Diseases, 2020. **100**: p. 34-41.
608. Moores, L.K., et al., *Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019: CHEST guideline and expert panel report.* Chest, 2020. **158**(3): p. 1143-1163.
609. De Havenon, A., et al., *Endovascular thrombectomy in acute ischemic stroke patients with COVID-19: prevalence, demographics, and outcomes.* Journal of neurointerventional surgery, 2020. **12**(11): p. 1045-1048.
610. Canoglu, K. and B. Saylan, *Therapeutic dosing of low-molecular-weight heparin may decrease mortality in patients with severe COVID-19 infection.* Ann Saudi Med, 2020. **40**(6): p. 462-468.
611. D'Ardes, D., et al., *Low molecular weight heparin in COVID-19 patients prevents delirium and shortens hospitalization.* Neurol Sci, 2020.
612. Falcone, M., et al., *Role of Low-Molecular-Weight Heparin in Hospitalized Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Pneumonia: A Prospective Observational Study.* Open Forum Infect Dis, 2020. **7**(12): p. ofaa563.
613. Jose Ramon Gonzalez-Porras, M.B.-G., Amparo Lopez-Bernus, Luis Mario Vaquero-Roncero, Beatriz Rodriguez, Cristina Carbonell, Raul Azibeiro, Alberto Hernandez-Sanchez, Jose Ignacio Martin-Gonzalez, Juan Miguel Manrique, Gloria Alonso-Claudio, Felipe Alvarez-Navia, Jose Ignacio Madruga-Martin, Ronald Paul Macias-Casanova, Jorge García-Criado, Francisco Lozano, Jose Carlos Moyano, Miguel Vicente Sanchez-Hernandez, Víctor Sagredo-Meneses, Rafael Borras, Jose María Bastida, Guillermo Hernández-

Pérez, Antonio Javier Chamorro, Miguel Marcos, Jose Angel Martin-Oterino, *Low molecular weight heparin in adults inpatient COVID-19.* The Lancet, 2020.
614. Ma, L., et al., *Low Molecular Weight Heparin Protects Lung, Renal and Microcirculation Function in Patients with Covid-19 Pneumonia.* Research Square, 2020.
615. Marc Blockman, K.C., Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish (Chair), Helen Rees, Gary Reubenson (Vice-chair). *A REVIEW OF THE OPTIMAL DOSE OF EITHER UNFRACTIONATED HEPARIN OR LOW MOLECULAR WEIGHT HEPARIN IN THE PREVENTION OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH SEVERE COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM.* South African National Department of Health, 2020.
616. Mattioli, M., et al., *Safety of intermediate dose of low molecular weight heparin in COVID-19 patients.* J Thromb Thrombolysis, 2020.
617. Paolisso, P., et al., *Preliminary Experience With Low Molecular Weight Heparin Strategy in COVID-19 Patients.* Front Pharmacol, 2020. **11**: p. 1124.
618. Pavoni, V., et al., *Venous thromboembolism and bleeding in critically ill COVID-19 patients treated with higher than standard low molecular weight heparin doses and aspirin: A call to action.* Thromb Res, 2020. **196**: p. 313-317.
619. Shi, C., et al., *The Potential of Low Molecular Weight Heparin to Mitigate Cytokine Storm in Severe COVID-19 Patients: A Retrospective Cohort Study.* Clin Transl Sci, 2020. **13**(6): p. 1087-1095.
620. Stattin, K., et al., *Inadequate prophylactic effect of low-molecular weight heparin in critically ill COVID-19 patients.* J Crit Care, 2020. **60**: p. 249-252.
621. Vergori, A., et al., *Prophylactic heparin and risk of orotracheal intubation or death in patients with mild or moderate COVID-19 pneumonia.* Research Square, 2020.
622. White, D., et al., *Heparin resistance in COVID-19 patients in the intensive care unit.* J Thromb Thrombolysis, 2020. **50**(2): p. 287-291.
623. Zhang, P., et al., *Applicability of bedside ultrasonography for the diagnosis of deep venous thrombosis in patients with COVID-19 and treatment with low molecular weight heparin.* J Clin Ultrasound, 2020. **48**(9): p. 522-526.
624. Gonzalez-Ochoa, A.J., et al., *Sulodexide in the treatment of patients with early stages of COVID-19: a randomised controlled trial.* medRxiv preprint, 2020.
625. Nadeem, R., et al., *Pattern of anticoagulation prescription for patients with Covid-19 acute respiratory distress syndrome admitted to ICU. Does it impact outcome?* Heart Lung, 2021. **50**(1): p. 1-5.
626. Nadkarni, G.N., et al., *Anticoagulation, Bleeding, Mortality, and Pathology in Hospitalized Patients With COVID-19.* Journal of the American College of Cardiology, 2020. **76**(16): p. 1815-1826.
627. Lemos, A.C.B., et al., *Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID).* Thromb Res, 2020. **196**: p. 359-366.
628. Atallah, B., et al., *The impact of protocol-based high-intensity pharmacological thromboprophylaxis on thrombotic events in critically ill COVID-19 patients.* Anaesthesia, 2020.
629. Albani, F., et al., *Thromboprophylaxis with enoxaparin is associated with a lower death rate in patients hospitalized with SARS-CoV-2 infection. A cohort study.* EClinicalMedicine, 2020. **27**: p. 100562.
630. Hsu, A., et al., *Intensity of anticoagulation and survival in patients hospitalized with COVID-19 pneumonia.* Thrombosis research, 2020. **196**: p. 375-378.
631. Paranjpe, I., et al., *Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19.* Journal of the American College of Cardiology, 2020. **76**(1): p. 122-124.
632. Ionescu, F., et al., *Association of anticoagulation dose and survival in hospitalized COVID-19 patients: A retrospective propensity score-weighted analysis.* Eur J Haematol, 2020.
633. Hanif, A., et al., *Thrombotic complications and anticoagulation in COVID-19 pneumonia: a New York City hospital experience.* Annals of hematology, 2020. **99**(10): p. 2323-2328.
634. Dobesh, P.P. and T.C. Trujillo, *Coagulopathy, Venous Thromboembolism, and Anticoagulation in Patients with COVID-19.* Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2020. **40**(11): p. 1130-1151.
635. Daughety, M.M., et al., *COVID-19 associated coagulopathy: Thrombosis, hemorrhage and mortality rates with an escalated-dose thromboprophylaxis strategy.* Thrombosis research, 2020. **196**: p. 483-485.

636. Xu, X., et al., *Effective treatment of severe COVID-19 patients with tocilizumab.* ChinaXiv, 2020. **202003**(00026): p. v1.
637. Gritti, G., et al., *Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support.* medRxiv, 2020.
638. Gritti, G., et al., *IL-6 signalling pathway inactivation with siltuximab in patients with COVID-19 respiratory failure: an observational cohort study.* 2020.
639. Campochiaro, C., et al., *Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study.* Eur J Intern Med, 2020. **76**: p. 43-49.
640. Somers, E.C., et al., *Tocilizumab for treatment of mechanically ventilated patients with COVID-19.* medRxiv, 2020.
641. Alattar, R., et al., *Tocilizumab for the Treatment of Severe COVID-19.* Journal of Medical Virology, 2020.
642. Biran, N., et al., *Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study.* The Lancet Rheumatology, 2020. **2**(10): p. e603-e612.
643. Campochiaro, C., et al., *Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study.* European Journal of Internal Medicine, 2020.
644. Canziani, L.M., et al., *Interleukin-6 receptor blocking with intravenous tocilizumab in COVID-19 severe acute respiratory distress syndrome: a retrospective case-control survival analysis of 128 patients.* Journal of autoimmunity, 2020. **114**: p. 102511.
645. Chilimuri, S., et al., *Tocilizumab use in patients with moderate to severe COVID-19: A retrospective cohort study.* J Clin Pharm Ther, 2020.
646. Dastan, F., et al., *Promising effects of tocilizumab in COVID-19: A non-controlled, prospective clinical trial.* International immunopharmacology, 2020. **88**: p. 106869-106869.
647. de Cáceres, C., et al., *The effect of tocilizumab on cytokine release syndrome in COVID-19 patients.* Pharmacological Reports, 2020: p. 1-9.
648. Della-Torre, E., et al., *Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study.* Annals of the rheumatic diseases, 2020. **79**(10): p. 1277-1285.
649. Guaraldi, G., et al., *Tocilizumab in patients with severe COVID-19: a retrospective cohort study.* The Lancet Rheumatology, 2020. **2**(8): p. e474-e484.
650. Sanz Herrero, F., et al., *Methylprednisolone added to tocilizumab reduces mortality in SARS-CoV-2 pneumonia: An observational study.* Journal of internal medicine, 2020.
651. Jurado, A., et al., *COVID-19: Age, Interleukin-6, C-reactive protein, and lymphocytes as key clues from a multicentre retrospective study.* Immunity and Ageing, 2020. **17**(1).
652. Kaminski, M.A., et al., *Tocilizumab therapy for COVID-19: A comparison of subcutaneous and intravenous therapies.* International Journal of Infectious Diseases, 2020. **101**: p. 59-64.
653. Kewan, T., et al., *Tocilizumab for treatment of patients with severe COVID–19: A retrospective cohort study.* EClinicalMedicine, 2020. **24**: p. 100418.
654. Luo, P., et al., *Tocilizumab treatment in COVID-19: A single center experience.* Journal of medical virology, 2020. **92**(7): p. 814-818.
655. Malekzadeh, R., et al., *Subcutaneous tocilizumab in adults with severe and critical COVID-19: A prospective open-label uncontrolled multicenter trial.* International immunopharmacology, 2020. **89**: p. 107102.
656. Masiá, M., et al., *Impact of interleukin-6 blockade with tocilizumab on SARS-CoV-2 viral kinetics and antibody responses in patients with COVID-19: A prospective cohort study.* EBioMedicine, 2020. **60**: p. 102999.
657. Mastroianni, A., et al., *Subcutaneous tocilizumab treatment in patients with severe COVID-19–related cytokine release syndrome: an observational cohort study.* EClinicalMedicine, 2020. **24**: p. 100410.
658. Meng, J., et al., *Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension.* Emerging Microbes and Infections, 2020. **9**(1): p. 757-760.
659. Menzella, F., et al., *Efficacy of tocilizumab in patients with COVID-19 ARDS undergoing noninvasive ventilation.* Critical Care, 2020. **24**(1): p. 1-9.
660. Mikulska, M., et al., *Tocilizumab and steroid treatment in patients with COVID-19 pneumonia.* Plos one, 2020. **15**(8): p. e0237831.

661. Perrone, F., et al., *Tocilizumab for patients with COVID-19 pneumonia. The single-arm TOCIVID-19 prospective trial.* Journal of translational medicine, 2020. **18**(1): p. 1-11.
662. Toniati, P., et al., *Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy.* Autoimmunity reviews, 2020: p. 102568.
663. Price, C.C., et al., *Tocilizumab treatment for cytokine release syndrome in hospitalized patients with coronavirus disease 2019: Survival and clinical outcomes.* Chest, 2020. **158**(4): p. 1397-1408.
664. Ramiro, S., et al., *Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study.* Annals of the rheumatic diseases, 2020. **79**(9): p. 1143-1151.
665. Rossotti, R., et al., *Safety and efficacy of anti-il6-receptor tocilizumab use in severe and critical patients affected by coronavirus disease 2019: A comparative analysis.* Journal of Infection, 2020. **81**(4): p. e11-e17.
666. Sciascia, S., et al., *Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in severe patients with COVID-19.* Clin Exp Rheumatol, 2020. **38**(3): p. 529-532.
667. Tomasiewicz, K., et al., *Tocilizumab for patients with severe COVID-19: a retrospective, multi-center study.* Expert Review of Anti-infective Therapy, 2020: p. 1-8.
668. Tsai, A., et al., *Impact of tocilizumab administration on mortality in severe COVID-19.* Scientific reports, 2020. **10**(1): p. 1-7.
669. Borku, U.B., H. Ikitimur, and S. Yavuzer, *''Tociluzumab challenge: A series of cytokine storm therapy experience in hospitalized Covid-19 pneumonia patients''.* Journal of Medical Virology, 2020.
670. Zhang, J., et al., *Serum interleukin-6 is an indicator for severity in 901 patients with SARS-CoV-2 infection: a cohort study.* J Transl Med, 2020. **18**(1): p. 406.
671. Zheng, K.L., et al., *Efficacy and safety of tocilizumab in COVID-19 patients.* Aging (Albany NY), 2020. **12**(19): p. 18878-18888.
672. Salama, C., et al., *Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia.* New England Journal of Medicine, 2020. **384**(1): p. 20-30.
673. Stone, J.H., et al., *Efficacy of tocilizumab in patients hospitalized with COVID-19.* New England Journal of Medicine, 2020.
674. Salvarani, C., et al., *Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial.* JAMA internal medicine, 2020.
675. Rosas, I.O., et al., *Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia.* New England Journal of Medicine, 2021.
676. Hermine, O., et al., *Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial.* JAMA Internal Medicine, 2020.
677. Milligan, P.S., et al., *Clinical Outcomes in a Cohort of Non-Ventilated COVID-19 Patients with Progressive Hypoxemia and Hyper-Inflammatory Response Treated with Baricitinib.* Available at SSRN 3594565, 2020.
678. Rodriguez-Garcia, J.L., et al., *Baricitinib improves respiratory function in patients treated with corticosteroids for SARS-CoV-2 pneumonia: an observational cohort study.* Rheumatology (Oxford, England), 2020.
679. Titanji, B.K., et al., *Use of baricitinib in patients with moderate and severe COVID-19.* Clinical Infectious Diseases, 2020.
680. Bronte, V., et al., *Baricitinib restrains the immune dysregulation in patients with severe COVID-19.* The Journal of clinical investigation, 2020. **130**(12).
681. Cantini, F., et al., *Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact.* The Journal of Infection, 2020.
682. Administration, U.F.a.D. *Letter of authorization: Emergency use authorization (EUA) for emergency use of baricitinib, in combination with remdesivir, for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients 2 years of age or older, requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).* 2020; Available from: https://www.fda.gov/media/143822/download.

683. Administration, U.F.a.D. *Fact sheet for health care providers: emergency use authorization (EUA) of baricitinib*. 2020; Available from: https://www.fda.gov/media/143823/download.
684. Administration, U.F.a.D. *Fact sheet for healthcare providers: emergency use authorization (EUA) of casirivimab and imdevimab*. 2020; Available from: https://www.fda.gov/media/143892/download.
685. NIH. *The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of the Casirivimab Plus Imdevimab Combination for the Treatment of COVID-19*. 2020; Available from: https://www.covid19treatmentguidelines.nih.gov/statement-on-casirivimab-plus-imdevimab-eua/.
686. NIH. *The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Bamlanivimab for the Treatment of COVID-19*. 2020; Available from: https://www.covid19treatmentguidelines.nih.gov/statement-on-bamlanivimab-eua/.
687. Administration, U.F.a.D. *Fact sheet for healthcare providers: emergency use authorization (EUA) of bamlanivimab*. 2020; Available from: https://www.fda.gov/media/143603/download.
688. IDSA. *IDSA Guidelines on the Treatment and Management of Patients with COVID-19*. 2021; Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-12.
689. Gottlieb, R.L., et al., *Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial.* JAMA, 2021. **325**(7): p. 632-644.
690. López-Medina, E., et al., *Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial.* JAMA, 2021.
691. Podder, C.S., et al., *Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study.* IMC J. Med. Sci, 2020. **14**(002).
692. Chaccour, C., et al., *The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with mild COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial.* 2020.
693. Krolewiecki, A., et al., *Antiviral Effect of High-Dose Ivermectin in Adults with COVID-19: A Pilot Randomised, Controlled, Open Label, Multicentre Trial.* 2020.
694. Niaee, M.S., et al., *Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial.* 2020.
695. Chowdhury, A.T.M.M., et al., *A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients.* 2020.
696. Hashim, H.A., et al., *Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq.* medRxiv, 2020.
697. Elgazzar, A., et al., *Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic.* 2020.
698. Ahmed, S., et al., *A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness.* International Journal of Infectious Diseases, 2020.
699. Alam, M.T., et al., *A case series of 100 COVID-19 positive patients treated with combination of ivermectin and doxycycline.* Journal of Bangladesh College of Physicians and Surgeons, 2020: p. 10-15.
700. Behera, P., et al., *Role of ivermectin in the prevention of COVID-19 infection among healthcare workers in India: A matched case-control study.* medRxiv, 2020.
701. Cadegiani, F.A., et al., *Hydroxychloroquine, nitazoxanide and ivermectin have similar effects in early COVID-19: a head-to-head comparison of the Pre-AndroCoV Trial.* 2020.
702. Camprubí, D., et al., *Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients.* Plos one, 2020. **15**(11): p. e0242184.
703. Gorial, F.I., et al., *Effectiveness of ivermectin as add-on therapy in COVID-19 management (pilot trial).* medRxiv, 2020.
704. Heidary, F. and R. Gharebaghi, *Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen.* The Journal of Antibiotics, 2020: p. 1-10.
705. Ortiz-Muñoz, L.E., et al., *Ivermectin for COVID-19: A living systematic review.[version 1.0; 20 July, 2020].* 2020.
706. Padhy, B.M., et al., *Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta-analysis.* Journal of pharmacy & pharmaceutical sciences: a publication of the Canadian

Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques, 2020. **23**: p. 462-469.
707. Rajter, J.C., et al., *ICON (Ivermectin in COvid Nineteen) study: Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID19.* medRxiv, 2020.
708. Soto-Becerra, P., et al., *Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru.* Azithromycin, and Ivermectin Among Hospitalized COVID-19 Patients: Results of a Target Trial Emulation Using Observational Data from a Nationwide Healthcare System in Peru, 2020.
709. Joyner, M.J., et al., *Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients.* Mayo Clinic Proceedings, 2020. **95**(9): p. 1888-1897.
710. Joyner, M.J., et al., *Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience.* medRxiv, 2020: p. 2020.08.12.20169359.
711. Joyner, M.J., et al., *Early safety indicators of COVID-19 convalescent plasma in 5,000 patients.* The Journal of Clinical Investigation, 2020.
712. Salazar, E., et al., *Treatment of Coronavirus Disease 2019 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality.* The American Journal of Pathology, 2020. **190**(11): p. 2290-2303.
713. Wang, Y., et al., *Kinetics of viral load and antibody response in relation to COVID-19 severity.* The Journal of clinical investigation, 2020. **130**(10).
714. Salazar, E., et al., *Relationship between Anti-Spike Protein Antibody Titers and SARS-CoV-2 In Vitro Virus Neutralization in Convalescent Plasma.* bioRxiv, 2020: p. 2020.06.08.138990.
715. Olivares-Gazca, J.C., et al., *Infusion of convalescent plasma is associated with clinical improvement in critically ill patients with COVID-19: a pilot study.* Rev Invest Clin, 2020. **72**(3): p. 159-164.
716. Nora, H., et al., *Assessment of SARS-CoV-2 in human semen-a cohort study.* Fertility and Sterility, 2020.
717. Klein, S.L., et al., *Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population.* The Journal of clinical investigation, 2020. **130**(11): p. 6141-6150.
718. Isho, B., et al., *Persistence of serum and saliva antibody responses to SARS-CoV-2 spike antigens in COVID-19 patients.* Science Immunology, 2020. **5**(52): p. eabe5511.
719. Hansen, J., et al., *Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail.* Science, 2020. **369**(6506): p. 1010-1014.
720. Faqihi, F., et al., *Therapeutic plasma exchange in adult critically ill patients with life-threatening SARS-CoV-2 disease: a pilot study.* Journal of critical care, 2020.
721. Bradfute, S.B., et al., *Severe Acute Respiratory Syndrome Coronavirus 2 Neutralizing Antibody Titers in Convalescent Plasma and Recipients in New Mexico: An Open Treatment Study in Patients With Coronavirus Disease 2019.* The Journal of Infectious Diseases, 2020. **222**(10): p. 1620-1628.
722. Liu, S.T.H., et al., *Convalescent plasma treatment of severe COVID-19: a propensity score–matched control study.* Nature Medicine, 2020. **26**(11): p. 1708-1713.
723. Wang, X., et al., *Neutralizing antibody responses to severe acute respiratory syndrome coronavirus 2 in coronavirus disease 2019 inpatients and convalescent patients.* Clin Infect Dis, 2020.
724. Gharbharan, A., et al., *Convalescent Plasma for COVID-19. A randomized clinical trial.* MEDRxiv, 2020.
725. Zhao, Q. and Y. He, *Challenges of Convalescent Plasma Therapy on COVID-19.* J Clin Virol, 2020. **127**: p. 104358.
726. FDA. *Investigational COVID-19 Convalescent Plasma - Emergency INDs*. 2020; Available from: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds.
727. Simonovich, V.A., et al., *A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia.* New England Journal of Medicine, 2020. **384**(7): p. 619-629.
728. Li, L., et al., *Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial.* JAMA, 2020. **324**(5): p. 460-470.
729. AlQahtani, M., et al., *Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease.* medRxiv, 2020.

730. Agarwal, A., et al., *Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial).* bmj, 2020. **371**.
731. Avendaño-Solà, C., et al., *Convalescent Plasma for COVID-19: A multicenter, randomized clinical trial.* medRxiv, 2020: p. 2020.08.26.20182444.
732. Tian, X., et al., *Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody.* Emerg Microbes Infect, 2020. **9**(1): p. 382-385.
733. Wrapp, D., et al., *Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation.* Science, 2020. **367**(6483): p. 1260-1263.
734. Hung, I.F., et al., *Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection.* Clinical Infectious Diseases, 2011. **52**(4): p. 447-456.
735. Mulangu, S., et al., *A randomized, controlled trial of Ebola virus disease therapeutics.* New England Journal of Medicine, 2019. **381**(24): p. 2293-2303.
736. Zhai, P., et al., *The epidemiology, diagnosis and treatment of COVID-19.* Int J Antimicrob Agents, 2020: p. 105955.
737. Duan, K., et al., *The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study.* medRxiv, 2020.
738. Chen, C., et al., *Thalidomide combined with low-dose glucocorticoid in the treatment of COVID-19 pneumonia.* 2020.
739. Lamontagne, F., et al., *Corticosteroid therapy for sepsis: a clinical practice guideline.* bmj, 2018. **362**: p. k3284.
740. Alhazzani, W., et al., *Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19).* Intensive Care Med, 2020: p. 1-34.
741. Wu, C., et al., *Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China.* JAMA Internal Medicine, 2020. **180**(7): p. 934-943.
742. Sterne, J.A.C., et al., *Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis.* Jama, 2020. **324**(13): p. 1330-1341.
743. Angus, D.C., et al., *Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial.* Jama, 2020. **324**(13): p. 1317-1329.
744. Tomazini, B.M., et al., *Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial.* Jama, 2020. **324**(13): p. 1307-1316.
745. Horby, P., et al., *Dexamethasone in hospitalized patients with Covid-19-preliminary report.* The New England journal of medicine, 2020.
746. Edalatifard, M., et al., *Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial.* European Respiratory Journal, 2020.
747. Jeronimo, C.M.P., et al., *Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With Coronavirus Disease 2019 (COVID-19; Metcovid): A Randomized, Double-blind, Phase IIb, Placebo-controlled Trial.* Clinical Infectious Diseases, 2020.
748. Dequin, P.F., et al., *Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial.* Jama, 2020. **324**(13): p. 1298-1306.
749. Lu, X., et al., *Adjuvant corticosteroid therapy for critically ill patients with COVID-19.* medRxiv, 2020.
750. Wang, Y., et al., *Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China.* medRxiv, 2020.
751. Estebanez, M., et al., *Clinical evaluation of IFN beta1b in COVID-19 pneumonia: a retrospective study.* medRxiv, 2020: p. 2020.05.15.20084293.
752. Monk, P.D., et al., *Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial.* The Lancet Respiratory Medicine, 2021. **9**(2): p. 196-206.
753. Davoudi-Monfared, E., et al., *A Randomized Clinical Trial of the Efficacy and Safety of Interferon β-1a in Treatment of Severe COVID-19.* Antimicrobial Agents and Chemotherapy, 2020. **64**(9): p. e01061-20.

754. Fu, W., et al., *An open-label, randomized trial of the combination of IFN-κ plus TFF2 with standard care in the treatment of patients with moderate COVID-19.* EClinicalMedicine, 2020. **27**.
755. Eslami, G., et al., *The impact of sofosbuvir/daclatasvir or ribavirin in patients with severe COVID-19.* J Antimicrob Chemother, 2020. **75**(11): p. 3366-3372.
756. Gong, W.-J., et al., *Clinical Efficacy of Ribavirin in Adults Hospitalized With Severe Covid-19: A Retrospective Analysis of 208 Patients.* 2020.
757. Tong, S., et al., *Ribavirin therapy for severe COVID-19: a retrospective cohort study.* Int J Antimicrob Agents, 2020. **56**(3): p. 106114.
758. Cheng, C.-Y., et al., *Lopinavir/ritonavir did not shorten the duration of SARS CoV-2 shedding in patients with mild pneumonia in Taiwan.* Journal of Microbiology, Immunology and Infection, 2020.
759. Huang, Y.-Q., et al., *No statistically apparent difference in antiviral effectiveness observed among ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha, and ribavirin plus lopinavir/ritonavir plus interferon-alpha in patients with mild to moderate coronavirus disease 2019: Results of a randomized, open-labeled prospective study.* Frontiers in Pharmacology, 2020. **11**: p. 1071.
760. Abbaspour Kasgari, H., et al., *Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: a single-centre, randomized controlled trial.* J Antimicrob Chemother, 2020. **75**(11): p. 3373-3378.
761. Jothimani, D., et al., *COVID-19: Poor outcomes in patients with zinc deficiency.* International Journal of Infectious Diseases, 2020. **100**: p. 343-349.
762. Yasui, Y., et al., *Analysis of the predictive factors for a critical illness of COVID-19 during treatment-relationship between serum zinc level and critical illness of COVID-19–.* International Journal of Infectious Diseases, 2020. **100**: p. 230-236.
763. Vogel-González, M., et al., *Low zinc levels at clinical admission associates with poor outcomes in COVID-19.* 2020.
764. Frontera, J.A., et al., *Treatment with Zinc is Associated with Reduced In-Hospital Mortality Among COVID-19 Patients: A Multi-Center Cohort Study.* Research square, 2020.
765. Abd-Elsalam, S., et al., *Do Zinc Supplements Enhance the Clinical Efficacy of Hydroxychloroquine?: a Randomized, Multicenter Trial.* Biol Trace Elem Res, 2020: p. 1-5.
766. Butler-Laporte, G., et al., *Vitamin D and Covid-19 Susceptibility and Severity: a Mendelian Randomization Study.* medRxiv, 2020.
767. Hastie, C.E., et al., *Vitamin D concentrations and COVID-19 infection in UK Biobank.* Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 2020.
768. Raisi-Estabragh, Z., et al., *Greater risk of severe COVID-19 in Black, Asian and Minority Ethnic populations is not explained by cardiometabolic, socioeconomic or behavioural factors, or by 25 (OH)-vitamin D status: study of 1326 cases from the UK Biobank.* Journal of Public Health, 2020. **42**(3): p. 451-460.
769. De Smet, D., et al., *Vitamin D deficiency as risk factor for severe COVID-19: a convergence of two pandemics.* MedRxiv, 2020.
770. Darling, A.L., et al., *Vitamin D status, body mass index, ethnicity and COVID-19: Initial analysis of the first-reported UK Biobank COVID-19 positive cases (n 580) compared with negative controls (n 723).* MedRxiv, 2020.
771. Brenner, H., B. Holleczek, and B. Schöttker, *Vitamin D insufficiency and deficiency and mortality from respiratory diseases in a cohort of older adults: potential for limiting the death toll during and beyond the COVID-19 pandemic?* Nutrients, 2020. **12**(8): p. 2488.
772. Tan, C.W., et al., *A cohort study to evaluate the effect of combination Vitamin D, Magnesium and Vitamin B12 (DMB) on progression to severe outcome in older COVID-19 patients.* medRxiv, 2020.
773. Raharusun, P., *Patterns of COVID-19 Mortality and Vitamin D: An Indonesian Study.* Available at SSRN 3585561, 2020.
774. Radujkovic, A., et al., *Vitamin D deficiency and outcome of COVID-19 patients.* Nutrients, 2020. **12**(9): p. 2757.
775. Pizzini, A., et al., *Impact of vitamin d deficiency on covid-19—a prospective analysis from the covild registry.* Nutrients, 2020. **12**(9): p. 2775.
776. Meltzer, D.O., et al., *Association of vitamin D status and other clinical characteristics with COVID-19 test results.* JAMA network open, 2020. **3**(9): p. e2019722-e2019722.

777. Merzon, E., et al., *Low plasma 25 (OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study.* The FEBS journal, 2020. **287**(17): p. 3693-3702.
778. Maghbooli, Z., et al., *Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection.* PloS one, 2020. **15**(9): p. e0239799.
779. Macaya, F., et al., *Interaction between age and vitamin D deficiency in severe COVID-19 infection.* Nutrición hospitalaria: Organo oficial de la Sociedad española de nutrición parenteral y enteral, 2020. **37**(5): p. 1039-1042.
780. Kaufman, H.W., et al., *SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels.* PloS one, 2020. **15**(9): p. e0239252.
781. Jain, A., et al., *Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers.* Scientific Reports, 2020. **10**(1): p. 1-8.
782. Ilie, P.C., S. Stefanescu, and L. Smith, *The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality.* Aging Clinical and Experimental Research, 2020: p. 1-4.
783. Hernández, J.L., et al., *Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection.* The Journal of Clinical Endocrinology & Metabolism, 2020.
784. Entrenas Castillo, M., et al., *"Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study".* The Journal of steroid biochemistry and molecular biology, 2020. **203**: p. 105751-105751.
785. Rastogi, A., et al., *Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study).* Postgraduate medical journal, 2020.
786. Murai, I.H., et al., *Effect of Vitamin D3 Supplementation vs Placebo on Hospital Length of Stay in Patients with Severe COVID-19: A Multicenter, Double-blind, Randomized Controlled Trial.* medRxiv, 2020.
787. Sire, A.D., et al., *Rehabilitation and COVID-19: the Cochrane Rehabilitation 2020 rapid living systematic review. Update as of August 31st, 2020.* Eur J Phys Rehabil Med, 2020. **56**(6): p. 839-845.
788. Halpin, S.J., et al., *Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation.* Journal of medical virology, 2021. **93**(2): p. 1013-1022.
789. Blair, P.W., et al., *The Clinical Course of COVID-19 in the Outpatient Setting: A Prospective Cohort Study.* Open Forum Infectious Diseases, 2021. **8**(2).
790. Moreno-Pérez, O., et al., *Post-acute COVID-19 Syndrome. Incidence and risk factors: a Mediterranean cohort study.* Journal of Infection, 2021.
791. Cirulli, E.T., et al., *Long-term COVID-19 symptoms in a large unselected population.* medRxiv, 2020: p. 2020.10.07.20208702.
792. Cellai, M. and J.B. O'Keefe. *Characterization of prolonged COVID-19 symptoms in an outpatient telemedicine clinic*. in *Open forum infectious diseases*. 2020. Oxford University Press US.
793. Sudre, C.H., et al., *Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the Covid Symptoms Study App.* medRxiv, 2020: p. 2020.10.19.20214494.
794. OfNS. *The prevalence of long COVID symptoms and COVID-19 complications*. 2020; Available from: https://www.ons.gov.uk/news/statementsandletters/theprevalenceoflongcovidsymptomsandcovid19complications.
795. Zapatero, D.C., G. Hanquet, and K. Van Den Heede, *Epidemiology of Long COVID: A Pragmatic Review of the Literature.* 2021.
796. Goërtz, Y.M.J., et al., *Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome?* ERJ Open Research, 2020: p. 00542-2020.
797. Davis, H.E., et al., *Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact.* medRxiv, 2020: p. 2020.12.24.20248802.
798. Vaes, A.W., et al., *Care dependency in non-hospitalized patients with COVID-19.* Journal of Clinical Medicine, 2020. **9**(9): p. 2946.
799. del Rio, C., L.F. Collins, and P. Malani, *Long-term Health Consequences of COVID-19.* JAMA, 2020. **324**(17): p. 1723-1724.
800. Mazza, M.G., et al., *Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors.* Brain, behavior, and immunity, 2020. **89**: p. 594-600.

801. Taquet, M., et al., *Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA.* The Lancet Psychiatry, 2021. **8**(2): p. 130-140.
802. Bellan, M., et al., *Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge.* JAMA Network Open, 2021. **4**(1): p. e2036142-e2036142.
803. Iannaccone, S., et al., *Role of Rehabilitation Department for Adult Individuals With COVID-19: The Experience of the San Raffaele Hospital of Milan.* Archives of physical medicine and rehabilitation, 2020. **101**(9): p. 1656-1661.
804. Salawu, A., et al., *A proposal for multidisciplinary tele-rehabilitation in the assessment and rehabilitation of COVID-19 survivors.* International journal of environmental research and public health, 2020. **17**(13): p. 4890.
805. Negrini, S., et al., *Feasibility and acceptability of telemedicine to substitute outpatient rehabilitation services in the COVID-19 emergency in Italy: an observational everyday clinical-life study.* Archives of physical medicine and rehabilitation, 2020. **101**(11): p. 2027-2032.
806. Fumagalli, A., et al., *Pulmonary function in patients surviving to COVID-19 pneumonia.* Infection, 2021. **49**(1): p. 153-157.
807. Mo, X., et al., *Abnormal pulmonary function in COVID-19 patients at time of hospital discharge.* The European respiratory journal, 2020. **55**(6): p. 2001217.
808. Akhilesh, K., et al., *A case series on post-COVID pulmonary rehabilitation: Early experiences from Kerala, South India.* Indian Journal of Case Reports, 2021. **6**(12): p. 672-675.
809. McCarthy, B., et al., *Pulmonary rehabilitation for chronic obstructive pulmonary disease.* Cochrane Database of Systematic Reviews, 2015(2).
810. Hill, N.S., *Pulmonary rehabilitation.* Proc Am Thorac Soc, 2006. **3**(1): p. 66-74.
811. Cheng, H.H. and W. Chou, *Rehabilitation can reduce mortality rate in patients who were intubated due to pneumonia.* Annals of Physical and Rehabilitation Medicine, 2018. **61**: p. e280-e281.
812. Dowman, L., et al., *Pulmonary rehabilitation for interstitial lung disease.* Cochrane Database of Systematic Reviews, 2021(2).
813. Lau, H.M., et al., *A randomised controlled trial of the effectiveness of an exercise training program in patients recovering from severe acute respiratory syndrome.* Aust J Physiother, 2005. **51**(4): p. 213-9.
814. Spruit, M.A., et al., *An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation.* American journal of respiratory and critical care medicine, 2013. **188**(8): p. e13-e64.
815. Barker-Davies, R.M., et al., *The Stanford Hall consensus statement for post-COVID-19 rehabilitation.* British journal of sports medicine, 2020. **54**(16): p. 949-959.
816. Spruit, M.A., et al., *COVID-19: interim guidance on rehabilitation in the hospital and post-hospital phase from a European Respiratory Society-and American Thoracic Society-coordinated international task force.* European respiratory journal, 2020. **56**(6).
817. Alawna, M., M. Amro, and A. Mohamed, *Aerobic exercises recommendations and specifications for patients with COVID-19: a systematic review.* European review for medical and pharmacological sciences, 2020. **24**(24): p. 13049-13055.
818. Liu, K., et al., *Effects of progressive muscle relaxation on anxiety and sleep quality in patients with COVID-19.* Complementary Therapies in Clinical Practice, 2020. **39**: p. 101132.
819. Madjid, M., et al., *Potential Effects of Coronaviruses on the Cardiovascular System: A Review.* JAMA Cardiol, 2020. **5**(7): p. 831-840.
820. Kochi, A.N., et al., *Cardiac and arrhythmic complications in patients with COVID-19.* J Cardiovasc Electrophysiol, 2020. **31**(5): p. 1003-1008.
821. Ng, M.Y., et al., *Patients Recovered From COVID-19 Show Ongoing Subclinical Myocarditis as Revealed by Cardiac Magnetic Resonance Imaging.* JACC Cardiovasc Imaging, 2020. **13**(11): p. 2476-2478.
822. Hermann, M., et al., *Feasibility and Efficacy of Cardiopulmonary Rehabilitation After COVID-19.* Am J Phys Med Rehabil, 2020. **99**(10): p. 865-869.
823. Cowie, A., et al., *Standards and core components for cardiovascular disease prevention and rehabilitation.* Heart, 2019. **105**(7): p. 510-515.
824. Dalal, H.M., P. Doherty, and R.S. Taylor, *Cardiac rehabilitation.* Bmj, 2015. **351**.

825. Piepoli, M.F., et al., *Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology.* Eur J Prev Cardiol, 2014. **21**(6): p. 664-81.
826. Balady, G.J., et al., *Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation.* Circulation, 2007. **115**(20): p. 2675-82.
827. Leon, A.S., et al., *Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American association of Cardiovascular and Pulmonary Rehabilitation.* Circulation, 2005. **111**(3): p. 369-76.
828. Piquet, V., et al., *Do Patients With COVID-19 Benefit from Rehabilitation? Functional Outcomes of the First 100 Patients in a COVID-19 Rehabilitation Unit.* Archives of Physical Medicine and Rehabilitation, 2021.
829. Hevey, D., et al., *Four-week multidisciplinary cardiac rehabilitation produces similar improvements in exercise capacity and quality of life to a 10-week program.* J Cardiopulm Rehabil, 2003. **23**(1): p. 17-21.
830. Price, K.J., et al., *A review of guidelines for cardiac rehabilitation exercise programmes: Is there an international consensus?* Eur J Prev Cardiol, 2016. **23**(16): p. 1715-1733.
831. Linden, W., *Psychological treatments in cardiac rehabilitation: review of rationales and outcomes.* Journal of Psychosomatic Research, 2000. **48**(4): p. 443-454.
832. Liu, K., et al., *Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study.* Complementary therapies in clinical practice, 2020. **39**: p. 101166.
833. Kortebein, P., *Rehabilitation for hospital-associated deconditioning.* Am J Phys Med Rehabil, 2009. **88**(1): p. 66-77.
834. Galloway, R.V., et al., *Hospital Readmission Following Discharge From Inpatient Rehabilitation for Older Adults With Debility.* Phys Ther, 2016. **96**(2): p. 241-51.
835. Timmer, A.J., C.A. Unsworth, and N.F. Taylor, *Rehabilitation interventions with deconditioned older adults following an acute hospital admission: a systematic review.* Clin Rehabil, 2014. **28**(11): p. 1078-86.
836. Thomas, P., et al., *Physiotherapy management for COVID-19 in the acute hospital setting: clinical practice recommendations.* Journal of Physiotherapy, 2020. **66**(2): p. 73-82.
837. Alexander, T., et al., *Guidance for Health Care Providers on Management of Cardiovascular Complications in Patients Suspected or Confirmed with COVID 19 Virus Infection.* J Assoc Physicians India, 2020. **68**(5): p. 46-49.
838. Johnson, J.K., et al., *Frequency of Physical Therapist Intervention Is Associated With Mobility Status and Disposition at Hospital Discharge for Patients With COVID-19.* Physical Therapy, 2021. **101**(1): p. pzaa181.
839. Sun, T., et al., *Rehabilitation of patients with COVID-19.* Expert Review of Respiratory Medicine, 2020. **14**(12): p. 1249-1256.
840. Rooney, S., A. Webster, and L. Paul, *Systematic Review of Changes and Recovery in Physical Function and Fitness After Severe Acute Respiratory Syndrome–Related Coronavirus Infection: Implications for COVID-19 Rehabilitation.* Physical Therapy, 2020. **100**(10): p. 1717-1729.
841. CDC. *What is ME/CFS?* 2021; Available from: https://www.cdc.gov/me-cfs/about/index.html.
842. Boivin, M.J., et al., *A Randomized Controlled Trial to Evaluate if Computerized Cognitive Rehabilitation Improves Neurocognition in Ugandan Children with HIV.* AIDS Res Hum Retroviruses, 2016. **32**(8): p. 743-55.
843. Boivin, M.J., et al., *Neuropsychological benefits of computerized cognitive rehabilitation training in Ugandan children surviving severe malaria: A randomized controlled trial.* Brain Res Bull, 2019. **145**: p. 117-128.
844. Faria, A.L., et al., *Benefits of virtual reality based cognitive rehabilitation through simulated activities of daily living: a randomized controlled trial with stroke patients.* J Neuroeng Rehabil, 2016. **13**(1): p. 96.

845. Bunketorp-Käll, L., et al., *Long-Term Improvements After Multimodal Rehabilitation in Late Phase After Stroke: A Randomized Controlled Trial.* Stroke, 2017. **48**(7): p. 1916-1924.
846. Cho, D.R. and S.H. Lee, *Effects of virtual reality immersive training with computerized cognitive training on cognitive function and activities of daily living performance in patients with acute stage stroke: A preliminary randomized controlled trial.* Medicine (Baltimore), 2019. **98**(11): p. e14752.
847. Yeh, T.-t., K.-c. Chang, and C.-y. Wu, *The active ingredient of cognitive restoration: A multicenter randomized controlled trial of sequential combination of aerobic exercise and computer-based cognitive training in stroke survivors with cognitive decline.* Archives of physical medicine and rehabilitation, 2019. **100**(5): p. 821-827.
848. Kemp, H.I., E. Corner, and L.A. Colvin, *Chronic pain after COVID-19: implications for rehabilitation.* British Journal of Anaesthesia, 2020. **125**(4): p. 436-440.
849. Li, J., et al., *The Effect of Cognitive Behavioral Therapy on Depression, Anxiety, and Stress in Patients With COVID-19: A Randomized Controlled Trial.* Frontiers in Psychiatry, 2020. **11**.
850. Wei, N., et al., *Efficacy of internet-based integrated intervention on depression and anxiety symptoms in patients with COVID-19.* Journal of Zhejiang University. Science. B, 2020: p. 1.

