AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

Coronavirus (COVID-19)

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

The December 14, 2020 update includes the following major changes:

- Vaccination information and recommendations
- New guidance in support of low-molecular weight heparin (I)
- Strengthened recommendation for glucocorticosteroids (B)
- New guidance recommending use of bamlanivimab (I)
- New guidance recommending use of casirivimab/imdevimab (I)
- Revised guidance on hydroxychloroquine to not recommend for delayed use beyond 3 days of symptoms (B) and to recommend for up to 3 days after symptoms onset
- New guidance recommending use of baricitinib (I)
- Revised guidance against use of interleukin-6 receptor antagonists (C)
- Revised guidance against lopinavir/ritonavir as stand-alone treatment (B)
- New guidance recommending use of convalescent antibodies (I)
- Strengthened recommendation for interferon beta-1b (C)
- Strengthened recommendation for vitamin D (C)

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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.

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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

* 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.

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.

Introduction

Note: *This guideline and its recommendations were last reviewed and updated on* ***December 14, 2020.***

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. Vaccination phase 3 trials have not been published; thus, reliance is necessarily on press releases. 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. There is indirect and strongly disputed evidence suggesting that the epidemic may have begun earlier, 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 [2-6]. Regardless, the Chinese New Year likely accelerated the spread of the virus through global travel and hastened the development of a pandemic.

[‡] 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.

Quarantines were likely ineffective at preventing the pandemic [7] for several reasons, including delayed global implementation of quarantining, travel bans, droplet/aerosol precautions, and other public health measures; the number of undiagnosed, mild, or asymptomatic patients spreading the virus [8, 9]; animals' susceptibility and potential although as-yet undocumented involvement; and the spread of cases in a region prior to the recognition of COVID-19 within that area [10]. Public health management of this pandemic has varied across countries and jurisdictions, typically using various combinations of approaches, including the quarantine of affected individuals, contact tracing, isolation, stay-at-home orders, physical distancing, mask use, and the closure of non-essential businesses.

As 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 many jurisdictions [11-13]. Additionally, despite the surge in cases, there has been considerable and growing controversy regarding the efficacy and sustainability of these various measures, especially (re)closure of businesses and schools; quality data are weak and some countries (e.g., Japan, South Korea) have instituted less stringent measures with seemingly somewhat comparable or better results [14-24]. The pandemic continues to provide numerous challenges, 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.

Control of the pandemic requires a multi-layered approach, as no one intervention can be completely effective. Physicians should be cognizant of the need for multiple controls at both systemic and individual levels to limit the spread of infection.

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 [25, 26]. When a virus mutates or changes, studies must be performed to determine the new strain's virulence (i.e., its ability to infect humans). 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 man [27, 28]. COVID-19's SARS-CoV-2 virus can now be found in humans on all continents around the world except Antarctica [29, 30].

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 [31]. Although respiratory aerosol spread was initially controversial, a committee of the National Academy of Sciences and others have subsequently concluded there is some limited evidence that it is also spread by respiratory aerosols [32-40]; other evidence of at least some spread by aerosols is rapidly accruing [41]. Currently, droplet spread continues to be viewed as the major mode of transmission [37, 40, 42-50]. 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 [50]. Whether, and to what extent, an infectious dose is able to be generated and present beyond 6-foot distances has yet to be clearly demonstrated [51-57].

The contagiousness and virulence of the SARS-CoV-2 virus appears 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 [58], which is far higher than typical influenza transmission rate of ~1.3 [59]. While the prior Centers for Disease Control and Prevention (CDC) estimate for the United States was 2.5 [9], recent estimates for the 50 US states range from 0.91 to 1.54 [60]. 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, and the majority of patients failed to infect anyone else. The majority of transmission occurred in household contacts, followed closely by external social events [61]. Beyond the transmission rates, the CDC also estimated that >10 times more cases are missed than are recorded based on seroprevalence studies [62], suggesting a far higher degree of contagiousness; this underestimate may be even greater depending on the rate of false-negatives from seroprevalence tests. Serial seroprevalence studies across all states have shown evidence of prior infection ranging from 1% to 23% [63].

More precise estimates of transmission rates will become known with time, particularly as testing rates escalate, although false-negative rates are reportedly 20-67% [31]. 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 [64]. 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) [65].

It is now estimated that 40–45% of infections develop due to exposure to asymptomatic or presymptomatic cases [66]. Yet, the proportion who remain persistently asymptomatic remains unclear [67-86]. Among 59,073 contacts of 5,706 Covid-19 index patients, 11.8% had COVID-19 compared with 1.9% of non-household contacts [87], 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 [88], 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 [89]. The total viable viral counts decline with time [50]. 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 [88]. 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) [90]. 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 not capable of transmitting an infection.

Preliminary experimental and epidemiological-ecological data suggest spread may be optimal in indoor and/or cooler climate conditions [11, 12, 91-93], and prior data on the SARS coronavirus are corroborative [94]. 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 [95]. The ecological data include that there were slower rates of infection with higher temperatures in Delhi, India and Pakistan [11, 12], although there was no correlation with humidity [11]. The data from Pakistan also suggest an inverse relationship between COVID infection rates and UV, although the UV data appear highly correlated with the heat indices [12]. Other data suggest lower infections with higher humidity [13]. 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 [92]; further, it could be predicted that even in the absence of vaccination, the pandemic will taper down by summer 2021. Similarly, disease surges in Florida and Texas in August 2020 are explicable by these conditions. Less dramatic epidemic surges are predicted to occur this winter in the deep South, assuming that the viral epidemic does not tail off and/or sufficient numbers of individuals do 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 [9, 96, 97], with 97.5% of cases occurring by 11.5 days after exposure and infrequent cases of up to 14 days [30, 31, 98]. The time between symptom onset in an individual and symptom onset in a second person infected by that individual also averages 6 days [9]. Viral shedding may antedate symptoms by 1–2 days, and viral titers are highest in the earliest phases of infection.

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 PCR [99, 100]. 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 [100].

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 [101, 102]. 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 (Korea CDC, 2020; Li et al., 2020; Xiao et al, 2020). 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 (Korea CDC, 2020). No study detected live virus beyond the ninth day [101]. These findings contrast with those of MERS and SARS, which peaked after symptom onset and lasted for shorter durations.

There are a few case reports of re-infections [103-105], which include a few cases of a different genomic Covid-19 strain [106-108]. However, whether these cases represent true reinfection or reactivation is unclear [103, 109, 110]. In a few cases, the purported second apparent infection was more severe [111]; in others, it was less severe or even asymptomatic [112].

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 [9]:

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 [31, 113-116]:

- Fever (low or high grade; 80–88%)
- Dry cough (63–69%) [30, 117]
- Loss of appetite (39–84%) [118]
- 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%) [118]
- Nasal congestion (4–5%)
- Abdominal pain (4%)
- Conjunctivitis (pink eye; 1%) [119]
- Hemoptysis (1%)
- Rhinorrhea (runny nose)
- Anosmia and dysgeusia (loss of smell and taste; 85% moderate/severe or anosmic) [120]

Severity of disease may be related to the inoculation dose [121]. The wearing of masks has been theorized to increase the proportion of asymptomatic cases by lowering that inoculation dose [121, 122].

Cardiovascular symptoms and signs may also be noted on initial presentation [123-128]. Immunothrombotic dysregulation associated with COVID-19 pneumonia has been described [129]. Coagulopathy associated with antiphospholipid antibodies and multiple infarcts have been reported [130, 131]. Seizures have been reported as a presenting disorder [132]. Young and old patients have presented with large-vessel strokes as an initial manifestation of COVID-19 infection [132, 133]. Among ICU patients, 31–59% of patients incurred venous or arterial thromboembolic event(s) [134, 135], compared with 10–25% of patients hospitalized for other reasons [135, 136]. Yet, recovering competitive athletes also have been found to have cardiac abnormalities on MRI [137].

Dermatological abnormalities such as urticaria, vasculitides, and pityriasis rosea have been described [138-141]. The most common dermatological presentations have been polymorphic and erythema, chilblain-like and urticarial lesions [142]. Various neurological and psychiatric presentations including stroke-like symptoms, altered mental status, dementia-like syndromes,

and new or recurrent affective disorders have been reported [143-150]. 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 [151]. 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 [152], along with the isolation of viral RNA from urine [153]. Most (71%) of those who die from COVID-19 have findings consistent with disseminated intravascular coagulation [154].

Because the symptoms for most patients are typical of nonspecific respiratory tract infections, they can be difficult to distinguish from other diseases [155, 156]. 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 [157]. 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 [158].

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 [8, 157, 159]. The CDC estimates that 40-45% of transmission occurs prior to symptom onset and that the infectiousness is comparable between asymptomatic and symptomatic individuals [8, 9]. Children tend to be asymptomatic or have milder symptoms, which suggests a mechanism that may accelerate disease transmission throughout the population [157], although this is not proven and is controversial. Regardless, one-third of those children hospitalized require ICU stays [160]. Also, a pediatric multisystem inflammatory syndrome 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 [161].

Mortality

The mortality rate for COVID-19 has changed considerably over the course of the epidemic, being much lower more recently [162]. The mortality of COVID-19 was estimated to be approximately 10-fold higher than that of typical seasonal influenza [163]. More recently, severity estimates have been reported as low enough to be comparable with prior influenza epidemics [85, 164-166], with a range of infection fatality rates of 0.03–0.5% and corrected rates of 0.02–0.4% [167]. More recently, CDC estimated the overall *symptomatic* case fatality ratio is 0.004, or 1 in 250 [9]. Mortality can be predicted based on risk factors and clinical findings on presentation [168].

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 [9]. The mortality rate for males is 57–64% higher than that for females. Nursing home residence is a particularly potent fatality risk [169-173]. 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 [40, 174-179]; however, approximately 1% of fatalities occur in previously healthy patients [180]. Genetic susceptibility (i.e., 3p21.31 gene cluster) has been reported in a large genomewide association study, along with a 45% increased risk among those with type A blood [181]. 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 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, and 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. McKinsey suggested risks for a given jurisdiction should be related to four metrics assessing the strength of test, trace, and quarantine efforts (adapted from [182]):

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 surveillance

Employers are recommended to implement a surveillance system that at minimum includes education of workers 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) include daily/periodic electronic questionnaires with or without temperature measurements. Electronic questionnaires are likely to be more effective than temperature measurements, as 69% of those seriously ill are afebrile [183]; temperature measurements are also likely to miss all subclinical and many symptomatic cases [9]. 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 as the false-negative rates are reportedly 20–67% [31]; thus, cases with high indices of clinical suspicion should typically be treated as presumptive cases [31]. 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 [184]. If there is believed to be COVID-19's SARS-CoV-2 virus transmission in the area (currently true of essentially all US urban and many rural areas), 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 [157], 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 [185]. Current guidance includes the following [185, 186]:

- 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 and, e.g., is currently 7 days for quarantining [187]. 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 [185, 186]. 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 must 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 those efforts.

Employees in contact with an infected coworker

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 [188, 189]. 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) [190]. 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 and 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 and, with a negative test on day 5 or later, the person may be released on day 8 with ongoing monitoring until day 14 [191, 192]. The CDC has recently 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.

Yet, 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 [193]. This option is controversial and not without considerable risks as 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 [183, 194]:

- 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 [174]
- 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 [195].

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 [196].
- Reduce public-facing work.
- Use personal protective equipment (PPE) to protect from exposure.
- Use masks; evidence that masks prevent transmission is accruing [196-205]. Randomized controlled trials have not shown differences between the effectiveness of masks and respirators for preventing influenza [206-209]; 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 [210].
- 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 [211]. Other training videos help illustrate potential transmission by contact spread and donning/doffing masks [212]. A recent study compared face mask efficacy for filtering expelled droplets during speech. A fitted N95 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 [213]. A low-cost, low-tech method to assess facemask efficacy has been reported [213].

Travel Issues

Travel risks include those associated with travel to and from a site, as well as business conducted at those sites [214]. Risks differ considerably by mode of transportation, geographic locations, and current state of the epidemic in any given locale. Businesses need to weigh the value of the travel against the risks associated with that travel. Such valuations should include costs associated with any potential illness and any post-trip quarantine period. Caution is especially advised for all non-essential travel to locales with outbreaks or community spread in progress [214], which currently includes most of the United States (see map to help with other risk considerations: https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6) [215]. International trips are currently significantly affected as many countries are limiting travel from countries with outbreaks (e.g., USA). Air travel may be safer than some other forms of travel [216], although the primary risks of air travel are more likely to be exposure risks at the destination, which may be challenging to control other than masking. As risks are reduced, travel to lower-risk locales may increasingly be acceptable, although the destination country or region may not permit visits from countries or regions with high rates of viral transmission.

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

For employees returning from personal or work-related travel, the safest course of action is to self-quarantine and work from home for 2 weeks[§] and avoid direct contact with other workers [98], especially for travel to 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. Wearing a surgical-type mask when in public as well as when ill, such as in transit to a healthcare facility, may help to reduce the spread of the virus from the wearer's sneezes or coughs.

Physical Distancing Methods

Physical distancing is believed to be one of the most effective control measures, especially as it does not rely on training and compliance (e.g., as effective masking requires) [217]. The following are some physical distancing options to consider:

- 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 [196, 218-222]) are lower on the list of controls. Detailed tables are available from the World Health Organization [218, 219]. However, PPE still appears to help to slow the spread of the COVID-19 virus and includes the following:

- 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 [199]. 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 [223].
- As well, there is increasing evidence that the COVID-19's SARS-CoV-2 virus may be spread by asymptomatic and presymptomatic individuals [224, 225]. Infection risk from these individuals is also reduced by wearing masks.
- In terms of the kinds of masks recommended, the fitted N95 was 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 [213]. 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 [226].
- 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 [227, 228].
- 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 mask would ideally be recommended (P100 is not an appropriate mask for these purposes).

Reuse, Extended Use, and Reprocessing of Respirators

The pandemic has caused demands on all types of PPE far beyond manufacturing capacities. Differences in management by sector (i.e., healthcare vs. general) have been proposed. Accordingly, protocols have been developed for reuse, extended use, and reprocessing of respirators [229, 230], 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 [229].
- 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 [229].
- 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 [230].
    - 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 [231, 232]. Consultation with an HVAC expert may be helpful. Area ventilation can provide a relatively safe zone for workers:

- Use local ventilation to supply clean air to a worker's workspace.
- Identify the number of air exchanges in the room.
- Utilize increased air exchanges in the HVAC system to dilute the general ambient air (including HEPA filters in the HVAC system). Effective filters rated with minimum efficiency reporting value (MERV) >13 are recommended and generally feasible [233, 234].
- Consider air disinfection (UV, hygiene peroxide, ozone, in-room devices) [231, 234].
- Local HEPA filtration in high-risk areas may be potentially helpful for risk mitigation.
- Where possible, use portable air purification systems for small work areas.
- Increase the proportion of fresh (rather than recirculated) air.

Disinfection Practices and Contact Spread Measures

Ventilation and other control measures addressing droplets and microaerosols are far more important than disinfection of surfaces [235]. 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 frequently (e.g., hourly or between shifts), including machine controls, door handles, bathroom doors, bathroom fixtures, faucet handles, lunch tabletops, breakrooms, etc.
- 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 [88], 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 [236].
- Encourage frequent hand hygiene (handwashing or use of alcohol-based hand disinfectants) with appropriate techniques [237].

- 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 [238-241].
- 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. Further guidance is available from the CDC [233].

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. Another option is electronically accessed and using QR codes.
- Clean and disinfect chairs and tables after each customer use (see Disinfection).
- 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. Otherwise, use gloves.
- Valet services should be provided by lower-risk employees if possible. Gloves should be used.
- 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.
- Employees should avoid using a public water fountain. Employees should be provided with bottled water.
- 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.
- When possible, consider wearing gloves while assembling parts.

Food Production Facilities

These have been hot spots of virus infection due to structural and socioeconomic challenges in meat and poultry processing facilities. 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 [242]. 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 [233].

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 [114, 243, 244]. 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 [245, 246]. Initial reports

that children do not become infected appear increasingly dubious [247]; 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 [248-252]. 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 [250]. 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 [253]. Schools also play important roles in students' social development and mental health [254-256].

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 [257]. The main contrary example is Israel, where school-based transmission to teachers has been problematic [258, 259]. 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 [260-265], which include decision logic for (re)opening schools [260]. This ACOEM guidance primarily addresses the protection of the 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 [266]. Face shields have not been recommended for children [266], 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 for seating under 6 feet apart 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, 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 [266]. It is advised to identify an isolation room for those who develop COVID-like symptoms at school [262]. While CDC guidance for teachers is limited, the CDC does not recommend universal testing of students and staff [262]. 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 masks 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 mask if available; mask if unavailable)	Respirator (N95 mask 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 [176-179].

Disability and Return-to-Work Considerations

Disability 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 [267]. However, persistent symptoms are reported in individuals with mild cases, and long-term symptoms have been reported [268]. There are many cases which require home healthcare after discharge [269].

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 [270]. 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 [271, 272]. 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 [273]. Lung diffusion abnormalities can take up to 5 years to resolve in ARDS cases [273, 274]. 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 [272-278]. 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 [272, 275, 279, 280]. Cardiac problems are common with COVID-19, with cardiomyopathy, arrhythmia, and direct cardiac muscle injury affecting approximately 30%, 20%, and 10% of patients, respectively [281], and is a contributing cause of fatality [281-283].

In general, for patients who are intubated and survive, recovery of the cardiorespiratory systems and endurance are estimated to take at least several months. Evidence of recent COVID-ARDS survivors found 78% had evidence of cardiac involvement and 60% had evidence of ongoing myocardial inflammation on MRI [284]. 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 [272-276, 285]. There is also the potential for a minority of patients to be permanently totally impaired [276].

Cardiac, respiratory, and neurological disability measures include:

- Metabolic stress echocardiogram (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
- Neuropsychological testing

For those 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 [286]. Ratings for impairment can be found in the AMA Guides 5th Edition [287] and 6th Edition [288].

Vaccines

Development work has progressed at record speed on over 270 COVID-19 vaccine candidates [184, 289-291]. These efforts use at least four types of vaccine classes or approaches against this infection (virus, viral vector, nucleic acid, and protein-based) [290]. Although vaccine development was estimated to require 12–18+ months if successful, it has been achieved in approximately 9-10 months [292]. Several of these COVID-19 vaccines are in advanced stages of development, approval, and public release (see Table 2). Few relevant efficacy data have been published in peer-reviewed publications. Safety data are largely reported from phase 2 trials; thus, they are currently based on relatively small sample sizes. Reported rates of vaccine efficacy range from 62% to 95% [293].

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 [289, 293].

The vaccines have very good to excellent rates of efficacy, which underscores support for a broad-scale vaccination program. After the vaccinations are underway, the following questions require answering going forward, although they should not delay the expeditious and widespread implementation of the vaccination program:

- Duration of vaccine-induced immunity and whether there are differences between the types of immunization
- Success of immunity, especially durability
- Whether duration of immunity differs in different subgroups, and 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

Vaccines for the Prevention of COVID-19

Recommended.

Vaccination is recommended for the prevention of COVID-19.

Strength of Evidence – **Strongly Recommended, Evidence (A) [pending]**[**]**
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). Indicated for earlier vaccination among all 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). As 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 to these populations are technically less clear. However, those with immunosuppressed states would be clinically 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.
Harms:	Reported rates of adverse effects in press releases include the following: • Moderna/NIAID: fatigue 9.7%, myalgia 8.9%, arthralgia 5.2%, headache 4.5%, injection site pain 2.7%, erythema at injection site and headache each 2.0% and fever <2.0% [293].

[**] The strength of evidence is determined based on the published evidence. Regarding vaccine trials, the currently available data are from press releases. Based on the available evidence and the Clinical Trials Registry, it appears that the evidence will be high-quality and support (A) level evidence. Should data not support level A evidence, it is possible this will be downgraded to B-level evidence.

- Anaphylactoid reactions have been reported and 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% [293].

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.

Rationale: One trial has been reported and found 95.1% efficacy [630]. 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	• 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 −20°C	• 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) [293].

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 [155, 156]:

- 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 [195]. The 10 variables included in the model are: 1) 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 [294].

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) [295].

Diagnostic Testing

Three main types of diagnostic tests are used for COVID-19: (1) polymerase chain reaction (PCR)-based testing, typically using swabs [296]; (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 [297]. 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 [298].

Saliva testing for SARS-CoV-2 detection is also available, which is appealing for ease of collection. One study detected higher SARS-CoV-2 titers in saliva compared to nasopharyngeal swabs, with less longitudinal variability [299]. If validated with larger-scale studies, saliva testing could provide near universal sampling coverage for both symptomatic and asymptomatic patients [300].

As test results when accurate may only indicate infection or no infection at the time of the test, 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 [301].

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 [302]. Because they also amplify viral fragments, they can show recent infection among those who are still clearing the viral particles including weeks after infection; thus, they may not reflect active viral shedding and/or infectiousness. Thus, 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 [303, 304]:

- 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 [305].

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 [306] is ill-advised given that the risk of false-negative tests are 20–67% [31]. 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 [297]. 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 [306], 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 [307-312]. 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 [313]. 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 [309-311]. 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 [314]. 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% [315]. 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 [316]. Others have correlated titers with disease severity [310]. 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 [317].

Evidence also suggests immunoglobulins may not be measurable over time [318]. 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 [319, 320]. 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 [321, 322]. 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 one 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 [155, 323]. 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 [323]. **Radiographs are recommended as part of the diagnostic evaluation of COVID-19.**

Computerized tomography (CT) is commonly performed [324, 325] and shows patchy infiltrates and ground-glass opacities [326-330]. 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 [156]. **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 [331-338]. The FDA has provided unprecedented flexibility to accelerate the development of new drugs and testing [339]. 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 [340-343], vitamin C, and vitamin D [344-347]. Most of these treatments have no quality evidence of efficacy. There is no clear evidence of lower risk of mortality with statin use [348]. Vitamin D levels have been strongly correlated with COVID disease severity [344, 346, 347]; 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 [344].

Only glucocorticosteroids have thus far been clearly shown in multiple quality trials to reduce mortality [349-351], 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 [352].

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 [353]. 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) [354]. 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 [355]. 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 [356], 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 [357]. There are few studies assessing the efficacy of antiviral medications within the first 1–2 days of symptom onset [358], despite the parallels with influenza medications.

Potential hierarchical approaches for 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, PTSD, substance use, divorce (30% increased), and violence [160, 359-366]. An association between adverse mental health and financial concerns has been noted [367].

Hydroxychloroquine has been used for the treatment of COVID-19 [340, 343, 356, 368-409]. There also are many in vitro studies suggesting antiviral activity [410-418].

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 [390]. HCQ is **recommended** for use in the first 3 days of symptoms onset.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
(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 [357]. Earlier clearance of pneumonia on CT scan [356].
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 [388, 398], 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 [419].
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 [343]. 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 [411].
- Hydroxychloroquine 400mg BID x 1 day, then 400mg QD for 4 day.
- Hydroxychloroquine 200mg BID x 5 days [356]
- Hydroxychloroquine 200mg TID x 10 days [375]
- Hydroxychloroquine 200mg TID x 10 days plus azithromycin 500mg x 1 day then 250mg QD x 4 days [375]
- 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 [390, 391, 420-423]. As 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, use of HCQ in that timeframe is not recommended.

There are multiple RCTs of early use of HCQ that range from pre-diagnosis to within a few days of symptoms onset [357]. These trials are naturally individually underpowered for severe outcomes such as mortality as they tend to include younger, healthier patients. A meta-analysis of five 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 [357]. 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 [424].

One early use trial found non-significant reductions of 20% being symptomatic at 14 days and a 60% reduced risk of death [425]. Another trial of HCQ used within 4 days of high-risk exposure found a 17% reduced risk of subsequent infection [385]. 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 [426]. As 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 36 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 33 from other sources. Of the 72 articles considered for inclusion, 7 randomized trials, 2 non-randomized trials, 5 case series, 10 retrospective studies and 4 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 [424].

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 [390]. 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 [424]. Thus, by analogy to hydroxychloroquine, chloroquine is not recommended for treatment of hospitalized COVID 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 [406, 427].

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 [385] and thus underpowering is possible. A cluster-randomized trial found a nonsignificant 8.1% reduction in PCR-confirmed COVID [428]. An RCT found lack of efficacy for prophylaxis among healthcare workers [429]. 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 [357]. 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 [357]. A systematic review found weak and conflicting evidence [430]. 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 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 [446]. 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 [408]. 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 [375], 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 [356].
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 [375, 435].
Rationale:	One RCT has suggested no difference between AZT, HCQ, and the combination for treatment of hospitalized patients [391]. 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 [374, 375, 379-381, 435], although some other studies have suggested a lack of efficacy [382, 383]. 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 for the Treatment of COVID-19

Not Recommended.

Favipiravir is not recommended for treatment of COVID-19.

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

Rationale: A moderate-quality RCT found no evidence of benefit of favipiravir for viral clearance, although there was faster defervescence (Doi 2020). 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 [455]. A low-quality RCT of baloxavir, marboxil, and favipiravir found no evidence that favipiravir accelerated viral clearance [456]. There is one non-randomized controlled trial suggesting acceleration of viral clearance compared with lopinavir-ritonavir [457]. 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 5 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 5 from other sources. Of the 27 articles considered for inclusion, 2 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 for the Treatment of COVID-19

Sometimes Recommended.

Lopinavir-ritonavir is recommended in combination therapy [467], 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 [467]. 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 [467] .
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 [467].

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 [467].

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 [409, 466, 468, 469]. Another double-blind RCT also suggested lack of efficacy, although it may have been underpowered [468]. 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 [457].

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 [467]. 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 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, Evidence (C)**
(Beyond 3 days of symptoms)
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 [480]. Patients included in trials had creatinine clearance >30 mL/min; ALT and AST <5 times upper limit of normal.
Benefits:	Reportedly shortened ICU stay by 31% and possible improved survival.
Harms:	Increased hepatic enzymes, diarrhea, rash, renal impairment, hypotension. However, the largest RCT did not report significantly increased adverse events in any category [352].
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect.
Frequency/Dose/Duration:	Remdesivir 200mg IV on day 1, then 100mg QD for 9 additional days [352, 481].
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 [482]. 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 [483]. However, one RCT found a lack of efficacy [409]. None of the RCTs was able to show statistically improved survival, although the NIH trial trended toward improved survival [352]. There is one case series suggesting a fairly low death rate (13%) [481] and another non-randomized study suggesting potential efficacy [484]. A low-quality RCT found no difference between 5 and 10 days of treatment [485]. There is evidence that remdesivir inhibits viral replication in vitro studies [414]. 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 5 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 5 from other sources. Of the 29 articles considered for inclusion, 5 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 for the Treatment of COVID-19

Recommended.

Low-molecular-weight heparin is recommended for the treatment of selected patients with COVID-19.

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

Indications:	Severely affected COVID-19 patients, especially those with known evidence or suspected 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 [499].
Benefits:	Possible improved survival, improved oxygenation, reduced time on ventilator [500], 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 [501]. Unfractionated heparin is another therapeutic option.

Rationale: There are no quality RCTs, but RCTs have been initiated. Reductions in mortality have been reported in non-randomized studies [493, 502-506], including an estimated 47–50% reduced risk of mortality among those on therapeutic anticoagulation among 4,389 in a hospital system [499]. Another cohort of patients on mechanical ventilation was found to have a 54% reduction in mortality [504, 507]. An early escalating thromboprophylactic approach has been suggested as preventive among hospitalized patients with less severe disease [508].

Low-molecular weight heparins are minimally invasive, have potentially significant adverse effects, are moderately costly, but have evidence suggesting associations with lower mortality rates and fewer complications among severely affected COVID-19 patients and are thus selectively recommended.

Various interleukin-6 receptor antagonists have been used for the treatment of hospitalized patients with COVID-19 [373, 509-544].

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: Two moderate-quality RCTs found a lack of efficacy of tocilizumab [545, 546]. One moderate-quality RCT found trends towards reduced mortality by 2 weeks but not 4 weeks associated with tocilizumab [547]. 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 [513]. 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 [373]. One retrospective study found no benefit of tocilizumab [512]. One case series suggested significant survival and oxygenation benefits [509].

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 4 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 4 from other sources. Of the 51 articles considered for inclusion, 3 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 for the Treatment of COVID-19

Recommended.

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

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

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 [553, 554].
Benefits:	Improved clinical outcomes, oxygenation, reduced need for ICU stay.
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 4mg loading and 2mg/day for or 4mg/day [549].
Rationale:	There are no quality trials published, although there are RCT data reported to the FDA that are reportedly supportive for use in combination with remdesivir [553, 554]. There are multiple non-randomized studies suggesting efficacy at mitigating the cytokine storm. A non-randomized trial found addition of baricitinib to glucocorticosteroids was associated with improved clinical outcomes, including an 82% reduced need for supplemental oxygen at discharge [549]. A comparative consecutive case series suggested significant benefits, such as eliminating ICU transfers and 58% vs. 8% discharge at 2 weeks [552]. 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 0 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 0 from other sources. Of the 9 articles considered for inclusion, 0 randomized trials, 0 non-randomized trials, 5 cohort studies, 2 retrospective studies, 1 case series, 0 case-control studies, and 2 systematic reviews met the inclusion criteria. There were no exclusion criteria.

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 [555].

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 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%) [556]. An NIH panel felt more data are needed prior to a recommendation. Casirivimab plus imdevimab have apparent preliminary evidence suggesting efficacy. As there are so few

	medications with proven efficacy for this stage of disease to prevent severe outcomes, these medications are recommended.

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. These have been approved for use by FDA under the emergency use authorization provision [557, 558].

Bamlanivimab for the Treatment of COVID-19

Recommended.

Bamlanivimab 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 patients with mild to moderate COVID-19 cases and 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:	Data provided to the FDA suggest a reduction of 68–84% in the risk of combined 28-day hospitalization, emergency department visit, or death [557]. Another study suggested 72% reduction in risk of hospitalization among those at high risk [557]. An NIH panel felt more data are needed prior to a recommendation. Bamlanivimab has apparent preliminary evidence suggesting efficacy. As there are so few medications with proven efficacy for this stage of disease to prevent severe outcomes, these medications are recommended.

Convalescent COVID-19 antibodies have been used to treat COVID-19 [543, 559-574].

Convalescent COVID-19 Antibodies

Recommended.

Convalescent antibodies are selectively recommended for the treatment of patients with COVID-19.

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

Indications:	Generally only for severely affected patients with COVID-19 and after other interventions with stronger evidence of efficacy are utilized. Timing of convalescent antibodies is best in the viral replication stage [575]. 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 [576].
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:	A moderate-quality RCT found significant improvement in dyspnea and fatigue, although no benefits regarding mortality or disease progression at day 28 [577]. There is one low-quality RCT suggesting a lack of efficacy, although it was prematurely terminated and may have been underpowered [470]. There are few other studies of convalescent antibodies [578, 579]. However, they were reportedly successful in one case series [580] and have been successfully used for other diagnoses, including Ebola [581, 582]. Convalescent antibodies are invasive, have adverse effects, are costly, and there is one RCT suggesting some modest efficacy; thus, they are recommended selectively for severe cases of COVID-19 generally after other treatments are instituted with stronger evidence of 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: 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 8 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 8 from other sources. Of the 23 articles considered for inclusion, 2 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 [584-587]. 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 [349, 350]).

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 [588]. 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 [589].
Rationale:	There are multiple RCTs, with all larger sized studies suggesting efficacy [589-593]. A meta-analysis estimated a 36% reduction in mortality with dexamethasone, 31% reduction with hydrocortisone, and 9% reduction with methylprednisolone [588]. A large RCT found mortality reductions with dexamethasone [349, 350, 591]. 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 [590]. Another RCT found superiority of glucocorticosteroid [589]. Two RCTs of modest size found no significant benefits, but appear underpowered [422, 594]. Another negative study used a low dose of hydrocortisone [594]. 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 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 – **Recommended, Evidence (C)**
(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 [467]. 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 [467] .
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:	A successful trial utilized sole therapy with interferon beta-1b 250ug QOD for 2 weeks [598]. 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 [467].

Rationale: A successful trial utilized sole therapy with interferon beta-1b and found accelerated clinical improvement and a non-statistically significant reduction in death by 67% at 1-month [598]. 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 [467]. However, one RCT found a lack of efficacy [409].

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 [467]. However, there is no evidence and thus no recommendation for stand-alone treatment with interferon beta-1b.

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 1 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 1 from other sources. Of the 5 articles considered for inclusion, 2 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 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 [467]. 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 [467].
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 [467].
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 [467]. Two other RCTs were underpowered for meaningful clinical differences [603, 604]. 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 [467]. 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 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 [340-343]. One trial 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 [340]. 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 [343]. This is supported by evidence that hydroxy/chloroquine are zinc ionophores, which increase intracellular zinc and reduce or prevent viral replication in laboratory studies [370, 371]. 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 1 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 1 from other sources. Of the 9 articles considered for inclusion, 0 randomized trials, 1 case study, 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 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 & 7 and weekly in addition to HCQ+AZT until hospital discharge [627]. 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 [627]. 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 [628]. 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) [629]. Vitamin D levels have been strongly correlated with COVID-19 disease severity [344, 346, 347], 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 [344]. 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.

Appendix A. Additional Considerations for School Re-opening

Efforts at re-integration 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.

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 >2%.
    - 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 7 days.
    - All rooms and areas used by the student should have 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 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.
- 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 2%.
- Teachers with multiple risk factors, (e.g., comorbidities and increased age) should wear an N95 mask 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 mask at all times.
- Classroom desks should ideally be set up for physical distancing, ideally 6 feet apart.
- 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 6-feet physical distancing, 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 >2%.
- 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.

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