American College of Occupational and Environmental Medicine

Coronavirus (COVID-19)

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

The August 19, 2020 update includes the following major changes:

- Detailed guidance for schools and approaches to protect teachers/staff
- Updated and more detailed treatment guidance, including new recommendations on vitamin D and zinc supplementation to reduce disease severity
- Updated information on microdroplets and aerosols as primary mechanisms of spread
- Data on peak contagion likely occurring at the time of symptom onset
- Evidence in support of respirator and mask use for prevention, including a discussion on the effectiveness of different mask styles
- Evidence of prolonged disability durations that correlate with disease severity
- Greater emphasis on the importance of incorporating experienced medical and public health judgment for the management of both symptomatic cases and exposed individuals instead of test-only approaches

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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 two 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.[1]
B	**Moderate evidence-base**: At least one high-quality study or multiple moderate-quality studies[2] relevant to the topic and the working population.
C	**Limited evidence-base**: At least one study of moderate quality.
I	**Insufficient Evidence**: Evidence is insufficient or irreconcilable.

For treatment, the criteria used by evidence reviewers to categorize the quality of individual randomized controlled trials as high, moderate, or low quality are: adequate randomization, concealed treatment allocation, baseline cohort comparability, patient blinded, provider blinded, assessor blinded, controlled for co-interventions, compliance acceptable, dropout rate acceptable, timing of assessments equivalent, data analyzed by intention to treat, and lack of bias.[3] 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.

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[1] 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.

[2] 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.

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

Introduction

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]. There is increasing information available about the virus.

The pandemic began in Wuhan, China in November 2019, then expanded markedly throughout the Wuhan region. Indirect and disputed evidence of increased hospital traffic and web searches for potential COVID-related symptoms in Wuhan beginning in August 2019 indicate that the epidemic may have begun earlier [2-4]. Regardless, the Chinese New Year likely accelerated the spread of the virus through global travel and hastened the development of a pandemic. Quarantines were likely ineffective at preventing the pandemic [5] 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 [6, 7]; animals' susceptibility and involvement; and the spread of cases in a region prior to the recognition of COVID-19 within that area [8]. 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. There is considerable and growing controversy regarding efficacy of these various measures, especially (re)closure of businesses and schools; quality data are weak and some countries (e.g., Japan, South Korea, Sweden) have instituted less stringent measures with seemingly somewhat comparable results [9-19]. 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.

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 [20, 21]. 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 [22, 23]. COVID-19's SARS-CoV-2 virus can now be found in humans on all continents around the world except Antarctica [24, 25].

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 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 [26]. Although respiratory aerosol spread was initially controversial, a committee of the National Academy of Sciences has subsequently concluded there is some limited evidence that it is also spread by respiratory aerosols [27-35]; other evidence of aerosol spread is rapidly accruing, with increasing opinions that this may be a primary route of spread [32, 35-43]. Aerosols cans 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 [43].

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 [44], which is far higher than typical influenza transmission rate of ~1.3 [45]. The most recent Centers for Disease Control and Prevention (CDC) estimate for the United States is 2.5 [7], although the CDC also estimates that >10 times more cases are missed than are recorded based on seroprevalence studies [46], suggesting a far higher degree of contagiousness; this underestimate may be even greater depending on the rate of false negatives from seroprevalence tests. More precise estimates of transmission rates will become known with time, particularly as testing rates escalate, although false-negative rates are reportedly 20-67% [26]. 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 [47]. A more recent publication 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) [48].

Future studies will need to further quantify infection factors, such as how many people become infected when they are close to someone with the virus, what viral load is needed to infect a contact, how many asymptomatic cases occur (especially compared with pre-symptomatic cases), how many clinical infections occur, and how many fatalities occur.

The virus's survivability on surfaces varies depending on the material; it has been estimated to survive up to 9 days [49]. The total viable viral counts decline with time [43]. 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. [49]. 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 data suggest spread may be optimal in indoor and/or cooler climate conditions [50-52], and prior data on the SARS coronavirus are corroborative [53]. 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 [54]. This suggests highly variable disease transmission risks based on seasonality and in indoor compared with outdoor environments. Taken together, these data indirectly suggest the potential for a wave of spread in northern latitudes in fall 2020 [51], assuming the viral epidemic does not tail off and/or sufficient herd immunity does not occur 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 [7, 55, 56], with 97.5% of cases occurring by 11.5 days and infrequent cases of up to 14 days [25, 26, 57]. The time between symptom onset in an individual and symptom onset in a second person infected by that individual also averages 6 days [7]. Viral shedding may antedate symptoms by 1–2 days, and viral titers are highest in the earliest phases of infection.

Pharyngeal virus shedding peaked at the time of symptom onset in a study of 94 patients [6]. Viral replication in nine cases was very high during the first week of symptoms, with a peak at 7.11×10^8 RNA copies per throat swab on day 4. Infectious virus was isolated from pharyngeal and sputum samples, but not from stool samples, despite high concentrations of viral RNA. Blood and urine samples never yielded virus. Active replication in the throat was confirmed by the presence of viral replicative RNA intermediates in pharyngeal samples. In one patient, sequence-distinct virus populations were detected in throat and lung samples, demonstrating independent replication. Infectious virus was no longer detected from 9 to 22 days after symptom onset [58].

The length of time an infected person sheds virus is affected by severity of illness. A recent study showed that no infectious virus was detected 10 days after symptom onset. A retrospective study of 113 patients with severe illness admitted to two hospitals outside of Wuhan reported that the median duration of viral shedding measured by PCR was 17 days (range: 13–22 days). Longer viral shedding was associated with male sex, age ≥54.5 years, hypertension, delayed admission after symptom onset, and mechanical ventilation [59]. A different study of 147 patients in Changsha, China, similarly found a median duration of viral shedding of 17 days (range: 12–21 days), with longer viral shedding from those more severely affected, as measured by higher temperature on admission, longer duration of symptoms before admission, and longer hospital stay [60]. However, detection of virus by PCR does not necessarily mean that the virus is infectious, as PCR may also detect non-infectious viral particles [58].

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 [7]:

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 [26, 61-63]:

- Fever (low or high grade; 80–88%)
- Dry cough (63–69%) [25, 64]
- Loss of appetite (39–84%) [65]
- 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%) [65]
- Nasal congestion (4–5%)
- Abdominal pain (4%)
- Conjunctivitis (pink eye; 1%) [66]
- Hemoptysis (1%)
- Rhinorrhea (runny nose)
- Anosmia and dysgeusia (loss of smell and taste; 85% moderate/severe or anosmic) [67]

Cardiovascular symptoms and signs may also be noted on initial presentation [68-73]. Coagulopathy associated with antiphospholipid antibodies and multiple infarcts have been reported in three elderly patients with COVID-19 infection and multiple comorbidities [74]. Five patients in New York City, ranging in age from 33 to 49, presented with large-vessel strokes as the manifestation of COVID-19 infection [75]. Among ICU patients, 31–59% of patients incurred venous or arterial thromboembolic event(s) [76, 77], compared with 10–25% of hospitalized patients [77, 78]. There also have been reports of dermatological abnormalities such as urticaria, vasculitides, and pityriasis rosea [79-82]. Various neurological and psychiatric presentations including stroke-like symptoms, altered mental status, dementia-like syndromes, and new or recurrent affective disorders have been reported [83-90]. While 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 [91]. 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, along with the isolation of viral RNA from urine [92]. Most (71%) of those who die of COVID-19 have findings consistent with disseminated intravascular coagulation [93].

Because the symptoms for most patients are typical of nonspecific respiratory tract infections, they can be difficult to distinguish from other diseases [94, 95]. 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 [96]. 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 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 [6, 96, 97]. The CDC estimates that 40% of transmission occurs prior to symptom onset and that the infectiousness is comparable between asymptomatic and symptomatic individuals [6, 7]. Children tend to be asymptomatic or have milder symptoms, which suggests a mechanism that may accelerate disease transmission throughout the population [96]. However, a pediatric

multisystem inflammatory syndrome has been reported in 50 children who presented with persistent fever and features of Kawasaki disease or toxic shock in New York City. 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 [98].

Mortality

The mortality of COVID-19 was estimated to be approximately 10-fold higher than that of typical seasonal influenza [99]. More recently, severity estimates have been reported as low enough to be comparable with prior influenza epidemics [100-103], with a range of infection fatality rates of 0.03–0.5% and corrected rates of 0.02–0.4% [104]. The current CDC estimate of the overall *symptomatic* case fatality ratio is 0.004, or 1 in 250 [7].

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 [7]. The mortality rate for males is 57–64% higher than that for females. Nursing home residence is a particularly potent fatality risk [105-109]. 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 [110-113]; however, approximately 1% of fatalities occur in previously healthy patients [114]. 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 [115]. 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. Disinfection practices and contact spread measures
5. Personal protective equipment (e.g., respirators, masks, gloves, and face shields)
6. Ventilation issues
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 [116]):

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*: Always 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 [117]; temperature measurements are also likely to miss all subclinical and many symptomatic cases [7]. 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. However, testing without experienced medical judgment is ill-advised as the false-negative rates are reportedly 20–67% [26]; thus cases with high indices of clinical suspicion should typically be treated as presumptive cases [26]. 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 [118]. 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, readily transmissible, and potentially severe COVID-19 infection [96], 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 put on a mask prior to entering any clinic or hospital.

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, 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 [119]. Current guidance includes the following [119, 120]:

- 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.

Although the above recommendations are official CDC guidance, 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 [119, 120]. 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 be recovered for up to 6 weeks after an infection onset. 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 of an infected person for at least 15 minutes starting from 2 days before illness onset (or, for asymptomatic patients, 2 days prior to positive specimen collection) until the time that the patient is isolated [121]. 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) [122]. 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 2 weeks (14 days) after the possible exposure.

Yet, in certain manpower shortage situations, medical centers, and critical services, COVID-19 exposed workers are being allowed to work while asymptomatic with twice-daily temperature checks, self-surveillance for symptoms, physical distancing, disinfection of workspaces, and consistent mask-wearing instead of being quarantined for 14 days [123]. 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 [117, 124]:

- 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
- Diabetes mellitus
- Chronic kidney disease, especially those undergoing dialysis
- Liver disease
- Hypertension
- Current cancer
- Neurological diseases, including stroke and dementia

Generally, the risks 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 [125].

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 high-risk individuals behind barriers.
- Institute physical distancing [126].
- Reduce public-facing work.
- Use personal protective equipment (PPE) to protect from exposure.
- Use masks; evidence that masks prevent transmission, although limited, is accruing [126-130]. Randomized controlled trials have not shown differences between the effectiveness of masks and respirators for preventing influenza [131-134]; however, some studies have been critiqued for power and unclear effects of outside influenza vaccination.
- 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 [135]. Other training videos help illustrate potential transmission by contact spread and donning/doffing masks [136]. 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 [137].

Travel Issues

Travel risks include those associated with travel to and from a site, as well as business conducted at those sites [138]. 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 [138], which currently includes most urban and many rural US areas (see map to help with other risk considerations: https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6) [139]. 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. 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 a maximum of 2 weeks[4] and avoid direct contact with other workers [57], 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, 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 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

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.

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[4] 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.

- 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).
- 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 a number of 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 (masks, gloves, and face shields [126]) are lower on the list of controls. However, they still appear to help to slow spread of the COVID-19 virus and include 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 [127]. 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 [140].
- As well, there is increasing evidence that the COVID-19's SARS-CoV-2 virus may be spread by asymptomatic and presymptomatic individuals, [141, 142] and 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 [137].
- Use face shields, especially where there is potential for human-related splashes or droplet exposures, and with aerosol-generating procedures.
- Follow OSHA guidance regarding requirements for fit testing of respirators and to assure proper use, donning, and doffing [143, 144].

- Appropriate PPE for cleaning a workspace contaminated by the virus is thought to normally be a face mask and gloves. If there are concerns about aerosols (e.g., an infected worker was in the room, especially with coughing, sneezing, and/or for an extended time), an option may be to leave the room overnight before cleaning it; otherwise, an N95 mask would ideally be recommended (P100 is not an appropriate mask for these purposes).

Ventilation Issues

Ventilation issues (general and local supply of fresh air) have been underutilized as potential COVID controls. Area ventilation can provide a relatively safe zone for workers:

- Use local ventilation to supply clean air to a worker's workspace.
- 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 [145, 146].
- 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

The following disinfection practices may help to slow spread by contact:
- Train staff on how to disinfect workplaces.
- Clean 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.
- Clean 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 [49], although some agents will require longer contact times. It is important to allow sufficient time for sanitizing agents to work, and directions should be carefully followed. The EPA has a list of products active against human coronavirus, with recommendations for the duration of contact time [147].
- Encourage frequent hand hygiene (hand washing or use of alcohol-based hand disinfectants) with appropriate techniques [148].
- 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 [149-152].
- 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 becoming 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 [145].

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.
- 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 while in the restaurant and kitchen.
- 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.
- 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 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 [153]. 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 [145].

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 [61, 154, 155]. 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 [156, 157]. Initial reports that children do not become infected appear increasingly dubious [158]; 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 [159-163]. 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 [161]. 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 [164]. Schools also play important roles in students' social development and mental health [165-167].

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 [168]. The main contrary example is Israel, where school-based transmission to teachers has been problematic [169, 170]. 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 [171-176], which include decision logic for (re)opening schools [171]. 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 (6) removing those students infected with COVID [177]. Face shields have not been recommended for children [177]. However, in situations where compliance is an issue, face shields may be a reasonable alternative. 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 [177]. It is advised to identify an isolation room for those who develop COVID-like symptoms at school [173]. While CDC guidance for teachers is limited, the CDC does not recommend universal testing of students and staff [173]. 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 regular symptom screening (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 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.

* Comorbidities include heart disease, hypertension, diabetes mellitus, chronic renal disease, dialysis, liver disease, chronic obstructive pulmonary disease (COPD), smoking, and obesity [110-113].

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 [178]. However, persistent symptoms are reported in individuals with mild cases, and long-term symptoms have been reported [179].

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 [180]. 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 [181, 182]. 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 [183]. Lung diffusion abnormalities can take up to 5 years to resolve in ARDS cases [183, 184]. 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 [182-188]. 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 [182, 185, 189, 190]. Cardiac problems are common with COVID-19, with cardiomyopathy, arrhythmia, and direct cardiac muscle injury affecting approximately 30%, 20%, and 10% of patients, respectively [191], and is a contributing cause of fatality [191-193].

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 [194]. 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 [182-186, 195]. There is also the potential for a minority of patients to be permanently totally impaired [186].

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 those with COVID-19 pneumonia
- Functional capacity testing
- Neuropsychological testing

Ratings for impairment can be found in the AMA Guides 5th Edition [196] and 6th Edition [197].

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 [94, 95]:

- 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 [125]. 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:lymphocyte ratio (OR: 1.06), lactate dehydrogenase (OR: 1.002), and direct bilirubin (OR: 1.15). A free online risk calculator is available [198].

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) [199].

Diagnostic Testing

There are three main types of diagnostic tests that are used for COVID-19: (1) polymerase chain reaction (PCR)-based testing, typically using swabs [200]; (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 FDA-approved and are also considered diagnostic [201]. Antibody testing detects prior infection but has limitations in specificity and sensitivity.

Work is progressing on the development of a saliva test for SARS-CoV-2 detection, which is appealing for ease of collection and is not limited by the shortages of swabs. One study detected higher SARS-CoV-2 titers in saliva compared to nasopharyngeal swabs, with less longitudinal variability [202]. If validated, saliva testing could provide near universal sampling coverage for both symptomatic and asymptomatic patients [203]. Currently, saliva testing is considered to be investigational.

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 [204]. Because they also amplify viral fragments, they can show recent infection among those who are still clearing the viral particles; thus, they may not reflect active viral shedding. 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 in fall-winter 2020-21 with the anticipation of another epidemic wave at that time.

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 [205, 206]:

- 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 [207].

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 is ill-advised given that the risk of false-negative tests are 20-67% [26]. Thus, there is a strong indication to presumptively treat cases who test negative, which requires experienced medical judgment.

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). 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.

Antigen Testing
Antigen tests detect viral proteins either on or within the virus. These have been FDA-approved and are considered diagnostic [201]. 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. Testing without experienced medical judgment is ill-advised, given the risks of false-negative tests. Thus, there is a strong indication to presumptively treat cases who test negative, which requires experienced medical judgment.

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Antibody Testing
Antibody testing detects the body's humoral response to the virus [208-210]. 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 [211]. Antibody tests are in early stages of deployment and reported reliability varies widely [208-210]. 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 [212]. 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% [213]. 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 [214]. Others have correlated titers with disease severity [209].

Evidence also suggests immunoglobulins may not be measurable over time [215]. 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. [216, 217] 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 [218, 219]. Once these problems are addressed, it is anticipated that antibody testing may become widespread if not universal 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. 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.

Imaging

Although x-rays are usually abnormal for individuals with pulmonary involvement, radiography in general should not be used as a standalone screening tool for COVID-19. X-ray abnormalities peak at 10–12 days after onset of symptoms [94, 220]. 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 [220]. **X-rays are recommended as part of the diagnostic evaluation of COVID-19.**

Computerized tomograms are commonly performed [221, 222] and show patchy infiltrates and ground glass opacities [223-227]. 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 [95]. **CT scans are recommended for the diagnostic evaluation of COVID-19.**

Treatment Recommendations

Treatment is currently guided by preliminary studies. Many additional studies are underway. The FDA has provided unprecedented flexibility to accelerate the development of new drugs and testing [228]. No treatment is indicated for asymptomatic cases or individuals with mild URI-type symptoms.

The three main classes of interventions for more serious infections are antiviral treatments, cytokine storm-reducing agents, and ventilatory support (both non-invasive and invasive). Only glucocorticosteroids have thus far been reported to reduce mortality [229, 230]. Only remdesivir has been proven to be modestly effective at shortening intensive care unit (ICU) stays in a large trial [231].

Other medications and agents being used include statins, zinc [232-235], and vitamin D [236-239]. Evidence suggests lower risk of mortality with statin use [240]. Vitamin D levels have been strongly correlated with COVID disease severity [236, 238, 239]; 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 [236].

The FDA has provided support for the use of convalescent plasma antibodies from survivors of COVID-19 through either randomized controlled trials (RCTs) or expanded use. However, antibodies are an unproven treatment for COVID-19 [241] and one RCT has now suggested a lack of efficacy [242].

No other medications are currently approved for the treatment of COVID-19, although other antiviral drugs are also under investigation (e.g., lopinavir-ritonavir). A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19 did not improve outcomes [243], although another trial of these agents combined with ribavirin and interferon beta-1b did suggest efficacy [244].

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 [245]. Evaluations should include exclusion of other causes (e.g., influenza). Glucocorticosteroids have reportedly been effective at reducing fatalities in hospitalized patients in a large UK trial using dexamethasone to treat severely ill patients requiring supplemental oxygen and/or a ventilator [229, 230, 246]. 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. In contrast, glucocorticosteroids appear to be effective in later, more severe stages of the infection, when the host inflammatory response is at its peak and may potentiate organ failure. In the United States, a trial evaluating the effectiveness of methylprednisolone (1 mg/kg/day IV for 7 days) for hospitalized patients is currently registered with ClinicalTrials.gov.

Although multiple agents addressing the purported cytokine storm are under investigation, most of the trials are centered around interleukin-6 (IL-6) [247]. Suppressing the cytokine storm to improve outcomes in an acute infection is not a new concept [248], although there is some controversy regarding a cytokine storm in relation to ARDS caused by COVID-19 [249]. While many cytokines are involved in the cytokine release syndrome (IL-2, IL-7, G-CSF, IFN-γ inducible protein 10, MIP 1-α, TNF-α), IL-6 has been shown to play a central role in orchestrating the inflammatory response in several coronavirus diseases, including SARS-CoV, MERS-CoV, and most recently SARS-CoV-2. IL-6 receptor blocker tocilizumab (Actemra) has been reported to reduce mortality in SARS-CoV-2 infection [233], and other trials are ongoing.

A recent short report described the use of pooled human high-dose polyclonal immunoglobulin G in 3 patients with severe COVID-19 pneumonia. Intravenous immunoglobulin was administered at 0.3–0.5 g per kg weight per day for 5 days, a dose based on previous use in immune modulation therapy for neuromuscular disorders and autoimmune thrombocytopenic purpura. There were no adverse events, and all patients clinically improved shortly after starting treatment. Their temperature returned to normal in 1–2 days and breathing difficulties alleviated in 3–5 days [250]. Thus, trials suggest that in selected patients with severe, COVID-19 pneumonia, tempering an excessive immune response to the virus is associated with clinical improvement.

Anti-viral medications may have minimal to no role in advanced pneumonia or ARDS [251], and one trial's subgroup analysis suggested that anti-viral treatment is needed within the first 7 days after symptom onset to be effective [244]. However, antiviral medications are typically

prescribed in later phases due to the theoretical potential that there may be some ongoing viral replication. To date, there appears to be no registered trials (of >2,000) that assess the efficacy of an anti-viral medication within the first 1–2 days of symptom onset [252].

A potential hierarchical protocol for antiviral treatment being discussed for COVID-19 without pneumonia is as follows:

1. Remdesivir
2. Combination therapy (interferon beta-1b, lopinavir-ritonavir and ribavirin)

A potential hierarchical treatment protocol for pneumonia/ARDS (in addition to possible anti-viral treatment) includes the following:

1. Oxygen supplementation
2. Glucocorticosteroid
3. Prone positioning (due to shunting) and/or non-invasive ventilation (NIV)
4. Interleukin-6 inhibition
5. Mechanical ventilation, prone
6. Extracorporeal membrane oxygenation (ECMO)

Mechanical ventilation has been associated with a survival rate of approximately 30% (and the short- to intermediate-term quality of life of those survivors is in considerable doubt). Thus, the prevention of severe outcomes should be the primary treatment emphasis [253, 254], and there is an increasing emphasis on noninvasive ventilatory measures.

There is no vaccine for COVID-19 [118], but development efforts are well underway [255, 256]. There are efforts using at least four types of vaccine classes or approaches against this infection (virus, viral vector, nucleic acid, and protein-based) [255]. Vaccine development is estimated to require 12–18+ months if successful [257].

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 [258-264].

Hydroxychloroquine for Treatment of COVID-19

Not Recommended.

Hydroxychloroquine is not recommended for the treatment of patients with COVID-19 after the first 3 days of symptoms [265]. There is no recommendation for or against the use of hydroxychloroquine 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:	There are no quality RCTs addressing early use of hydroxychloroquine (HCQ). A placebo-controlled RCT found no benefit of HCQ use when administered to patients on average 7 days in the course of symptoms [266]. Another large, but as-yet unpublished, placebo-controlled UK trial (n=1542 HCQ vs. n=3132 usual care) has reported no reductions in fatalities among patients hospitalized with COVID-19 (25.7% vs. 23.5%, p=0.10) [265].
	One moderate-quality RCT showed 31.0% fewer fever days, 35.5% fewer cough days, and 47.1% improved pneumonia on CT scan compared with placebo [251]; they also showed 0% vs. 12.9% progressed to severe disease. A second moderate-quality study found minimally faster improvements in symptoms, lymphopenia, and C-reactive protein [267]; however, the average administration began at 16–17 days in the treatment course, which was likely after viral replication had largely ceased and thus the primary outcome of viral clearance rate did not exceed that of standard care [268].
	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 [235]. This is supported by evidence that hydroxy/chloroquine are zinc ionophores that increase intracellular zinc and reduce or prevent viral replication in laboratory studies [269, 270].
	One RCT without placebo control compared very high doses of HCQ (12 g over 10 days) to lower doses and was terminated early for arrhythmias [271]. The dose used was approximately 4 times the typical dose used in other studies. One controlled but non-randomized study found tocilizumab added to a standard care regimen of HCQ, lopinavir, plus ritonavir suggested efficacy if administered earlier in the hospital course [272].
	Early treatment has been reported to result in low fatality rates in large case series and comparative trials that typically have used

adjunctive azithromycin. One of the larger of these trials included 3,119 patients and reported 62% reduced risk of hospitalization over 10 days, reduced risk of death or transfer to an ICU (HR=0.18; 95% CI 0.11-0.27), and shortened viral shedding [273]. Comparative trials also suggest earlier viral clearance with adjunctive treatment with azithromycin [273-277]. Some non-randomized but controlled studies have suggested possible efficacy alone or in combination with azithromycin [278-280], while others have suggested a lack of efficacy [281-283]. One trial of HCQ, azithromycin, and zinc suggested that earlier treatment resulted in 84% lower risk of hospitalization and lower risk of death among patients treated by ~day 4 [232]. However, while HCQ alone appears to have no significant adverse effects (only nausea and diarrhea [284]), there is a 22% increased risk of cardiovascular adverse effects suggested based on a large database study of rheumatoid arthritis and other patients [285].

There are many in vitro studies suggesting antiviral activity [286-294]. However, although in vitro studies generally show efficacy for a medication to be effective in humans, that is not necessarily a definitive measure of efficacy in humans; such studies have sometimes failed to support treatment in human trials for other diseases [295, 296].

In contrast with the bulk of the RCTs, comparative trials, and pre/post interventional studies, there are multiple large-scale, non-randomized case series that have uniformly suggested a lack of efficacy of HCQ [281, 283, 297, 298]. In all cases, the HCQ-treated patients are shown to have been more ill with many measures of multiple organ systems than those not treated with HCQ. Although these studies have typically attempted to adjust for various patient severity measure(s), whether such adjustments are adequate and can completely adjust for the severity is unknown. Thus, the RCT evidence is the highest level of evidence to address efficacy [299], and large-scale RCT results are expected later in 2020.

The largest RCT purportedly has found a lack of efficacy of HCQ among hospitalized patients [265]. Thus, based on another published RCT [266] and reports of this large trial, HCQ is not recommended for treatment of hospitalized patients. Data suggest HCQ alters the cQT interval, although trials do not show adverse effects in reports to date [285, 300-308] other than arrhythmias when 4-fold doses were used [180]. To date, there are no quality data regarding potential (in)efficacy for those within the first 1-2 days of symptoms to attempt to abort the trajectory towards hospitalization. There is some controlled evidence suggesting that earlier treatment by symptom day 3 resulted in markedly lower risks of hospitalization and death [232].

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to July 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 1,122 articles in PubMed, 2,734 in Scopus, 33 in CINAHL, 139 in Cochrane Library, 8,670 in Google Scholar, and 19 from other sources[†]. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 10 from Google Scholar, and 19 from other sources. Of the 30 articles considered for inclusion, 5 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 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 [265]. There is no recommendation for or against the use of hydroxychloroquine 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 evidence chloroquine has different efficacy. There are sparse trials of chloroquine. 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 July 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 79 articles in PubMed, 2,880 in Scopus, 8 in CINAHL, 160 in Cochrane Library, 8,330 in Google Scholar, and 2 from other sources†. We considered for inclusion 1 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 2 from other sources. Of the 5 articles considered for inclusion, 2 randomized trials, 1 retrospective analysis 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.

Hydroxychloroquine or Chloroquine for Widespread Prophylaxis Against COVID-19

Not Recommended.

Hydroxychloroquine and chloroquine are not recommended for use for widespread prophylaxis against COVID-19.

Strength of Evidence – **Not Recommended, 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 [284] and thus underpowering is possible. A cluster-randomized trial found a nonsignificant 8.1% reduction in PCR-confirmed COVID [309]. Database evidence does not suggest significant differences in HCQ or colchicine use among those infected [310].

There is rationale that prophylactic use may have short-term efficacy based on suggestive evidence of prophylactic effects in vitro studies [287]. The weaknesses of prophylaxis include that: 1) subsequent waves of this epidemic are possible if not probable; 2) the number of patients with large numbers of virions being exposed to medications markedly increases the risks of resistance, which may mean subsequent epidemic waves will be more difficult to treat (assuming efficacy is confirmed in additional studies); and 3) it is unknown if a subsequent epidemic wave may be less or more virulent. In some instances, prophylactic use may make more sense, such as in a nursing home where the virus is circulating or in selected workers with particularly high risks, especially as adverse effects are minimal and/or

not serious. However, for most situations, the potential development of immunity is likely preferable, as rescue therapy with one of the chloroquines for more severe cases currently appears possible, if needed.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to July 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 1,099 articles in PubMed, 406 in Scopus, 3 in CINAHL, 34 in Cochrane Library, 5,860 in Google Scholar, and 2 from other sources†. We considered for inclusion 0 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 3 articles considered for inclusion, 2 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 July 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 1099 articles in PubMed, 391 in Scopus, 0 in CINAHL, 37 in Cochrane Library, 3,530 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 0 randomized trials 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.

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, Insufficient Evidence (I)**
(Use beyond first 3 days of symptoms)
Level of Confidence – **Low**

Indications:	There are no quality RCTs regarding early treatment. Adjunctive use with hydroxychloroquine in severely affected patients with COVID-19. For severely affected patients, azithromycin (AZT) may be added [274], 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). 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 [251].
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 [274, 315].
Rationale:	One RCT has suggested no difference between AZT, HCQ and the combination for treatment of hospitalized patients [266]. Most non-randomized but controlled studies have suggested some evidence of efficacy, particularly for early adjunctive use when combined with HCQ [273, 274, 278-280, 315], although some other studies have suggested a lack of efficacy [281, 282]. There is low-quality evidence for adjunctive use of azithromycin but almost no other anti-viral treatment option, these medications are low cost, and adverse effects are minor for short courses of treatment; thus, these medications are recommended. Based on the available limited evidence, earlier treatment appears to be important for efficacy compared with treatment in an ICU.

Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to July 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 24 articles in PubMed, 1,927 in Scopus, 9 in CINAHL, 27 in Cochrane Library, 2,880 in Google Scholar, and 10 from other sources[†]. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 6 from Google Scholar, and 10 from other sources. Of the 16 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

No Recommendation.

There is no recommendation for or against the use of favipiravir for COVID-19.

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

Rationale:	Favipiravir, a guanine analogue to inhibit RNA-dependent RNA polymerase, has been used to treat influenza. 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 [322]. A low-quality RCT of baloxavir, marboxil and favipiravir found no evidence that favipiravir accelerated viral clearance [323]. There is one non-randomized controlled trial suggesting acceleration of viral clearance compared with lopinavir-ritonavir [324]. Although there is no quality evidence of efficacy, these studies suggest there may be potential efficacy and 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 July 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 3 articles in PubMed, 789 in Scopus, 2 in CINAHL, 15 in Cochrane Library, 2,341 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 0 from other sources. Of the 5 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

Recommended.

Lopinavir-ritonavir is recommended in combination therapy [325], but is not recommended as solitary treatment of COVID-19.

Strength of Evidence – **Recommended, Evidence (C)** (<u>Combination therapy</u>)
Level of Confidence – **Low**

Strength of Evidence – **Not Recommended, Evidence (C)** (<u>Stand-alone treatment</u>)
Level of Confidence – **Low**

Indications:	Adjunctive use with ribavirin and interferon beta-1b in moderately and severely affected patients with COVID-19 [325]. 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 [325] .
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 [325].
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 [325].

Lopinavir-ritonavir as sole antiviral treatment has been trialed in two RCTs, both of which showed a lack of efficacy compared with standard care [243, 326], while another double-blind RCT also suggested lack of efficacy, although it may have been underpowered [326]. 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 [324].

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 [325]. 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 July 2020 using the following terms: Lopinavir, rotinavir; 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 36 articles in PubMed, 2,484 in Scopus, 5 in CINAHL, 34 in Cochrane Library, 8,110 in Google Scholar, and 2 from other sources[†]. We considered for inclusion 1 from PubMed, 3 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 2 from other sources. Of the 9 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 supervised treatment of selected patients with COVID-19.

*Strength of Evidence – **Recommended, Evidence (C)***
*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 [330]. Generally, patient should have 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 [231].
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 [231, 331].
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 [332]. A larger, moderate-quality NIH trial showed modest efficacy, including 31% shorter ICU stays and earlier clinical improvements. Neither RCT was able to show statistically improved survival, although the NIH trial trended toward improved survival [231]. There is one case series suggesting a fairly low death rate (13%) [331] and another non-randomized study suggesting potential efficacy [333]. A low-quality RCT found no difference between 5 and 10 days of treatment [334]. There is evidence that remdesivir inhibits viral replication in vitro studies [290]. 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 efficacy (particularly for the treatment of hospitalized patients requiring oxygen), and thus is recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to July 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 54 articles in PubMed, 2,419 in Scopus, 7 in CINAHL, 29 in Cochrane Library, 7,340 in Google Scholar, and 2 from other sources[†]. We considered for inclusion 3 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 5 articles considered for inclusion, 3 randomized trials, 1 case series and 0 systematic reviews met the inclusion criteria. There were no exclusion criteria.

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

Recommended.

Interleukin-6 inhibitors (sarilumab, siltuximab, and tocilizumab) are recommended for the treatment of selected patients with COVID-19.

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

Indications:	Most commonly used in clinical trials for COVID. May be used off-label, as these agents are not FDA-approved for treatment of COVID-19. Severely affected patients with COVID-19 with cytokine storm manifestations, including ARDS, were assessed in a retrospective case series [335]. Patients had respiratory failure, shock, and/or other organ failure [335].
Benefits:	Improved oxygenation, reduced temperature, and reduced CRP [335]. Data also suggest potential improved survival as in one report, the hospital discharge rate of 90% was significantly above expectations.
Harms:	Estimated doubling of superinfection risks [339].
Indications for Discontinuation:	Completion of a course, intolerance, adverse effects.
Frequency/Dose/Duration:	Per trial protocols.
Rationale:	There are no published high-quality RCTs. 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 [339]. Another controlled but non-randomized study found tocilizumab added to a standard care regimen of HCQ, lopinavir, plus ritonavir suggested efficacy if administered earlier in the hospital course [272]. One retrospective study found no benefit of tocilizumab [338]. One case series suggested significant survival and oxygenation benefits [335].
	Because there are so few treatments directed at the cytokine storm, the fatality rate is >60%, and the available data are supportive, IL-6 inhibitors are recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to July 2020 using the following terms: Interleukin-6 (IL-6) Receptor Antagonists, Tocilizumab, Sarilumab; 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 74 articles in PubMed, 2,198 in Scopus, 17 in CINAHL, 60 in Cochrane Library, 8,520 in Google Scholar, and 1 from other sources†. We considered for inclusion 0 from PubMed, 3 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 1 from other sources. Of the 5 articles considered for inclusion, 0 randomized trials, 1 case series and 4 systematic reviews 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 July 2020 using the following terms: 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 7 articles in PubMed, 114 in Scopus, 1 in CINAHL, 2 in Cochrane Library, 391 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 0 randomized trials 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.

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

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

Indications:	Timing of convalescent antibodies is in the viral replication stage [340]. There are three pathways for administration: 1) clinical trials, 2) expanded use, and 3) single-patient emergency Investigational New Drug. Severely affected patients with COVID-19. 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 [241].
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:	There is one low-quality RCT suggesting a lack of efficacy, although it was prematurely terminated and may have been underpowered [242]. There are few other studies of convalescent antibodies [341, 342]. However, they were reportedly successful in one case series [244] and have been successfully used for other diagnoses, including ebola [343, 344]. The alternative is typically a fatality rate of at least 50–60%, but evidence suggests lack of efficacy; thus, there is no recommendation regarding convalescent antibodies for severe cases in the viral replication stage.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to July 2020 using the following terms: Convalescent COVID-19 antibodies, convalescent plasma, antibodies; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-Co-V 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, 767 in Scopus, 2 in CINAHL, 27 in Cochrane Library, 3,589 in Google Scholar, and 1 from other sources[†]. We considered for inclusion 1 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 1 from other sources. Of the 5 articles considered for inclusion, 1 randomized trial, 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 provisionally recommended for the treatment of COVID-19 [346-349]. 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 [229, 230]).

*Strength of Evidence – **Recommended, Insufficient Evidence (I)**[5]*
*Level of Confidence – **Low***

Indications:	Hospitalized patients with moderate or severe COVID-19. Especially effective reportedly for those critically ill on ventilators or requiring supplemental oxygen. The single trial reports no efficacy among those without either of those two parameters, although the available press release suggests there may be a trend towards efficacy among those otherwise hospitalized (p=0.14).
Benefits:	Reduced mortality by 20% if requiring supplemental oxygen, and 35% if ventilated.
Harms:	Hyperglycemia, risk of secondary infection, higher blood pressure.
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect.
Frequency/Dose/Duration:	Reportedly used dexamethasone 6 mg QD x 10 days.
Rationale:	There are no as-yet published quality trials of glucocorticosteroids for the treatment of COVID-19. However, a large placebo-controlled UK trial (n>11,500) has reported reductions in fatalities by 35% among those on a ventilator and 20% among those requiring only supplemental oxygen [229, 230]. As glucocorticosteroids have moderate adverse effects, low costs, and have been reported to have efficacy in reducing mortality, this is a provisional recommendation pending publication of the final data.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to July 2020 using the following terms: glucocorticoids, glucocorticoid steroid, prednisone, dexamethasone, hydrocortisone; 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 10 articles in PubMed, 202 in Scopus, 5 in CINAHL, 3 in Cochrane Library, 2,141 in Google Scholar, and 2 from other sources[†]. We considered for inclusion 0 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 2 from other sources. Of the 5 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.

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[5] Provisional recommendation pending publication of UK trial data [229, 230].

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)**
(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 ribavirin in moderately and severely affected patients with COVID-19 [325]. 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 [325] .
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 [325].
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 [325].
	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 [325]. 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 July 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 5 articles in PubMed, 132 in Scopus, 2 in CINAHL, 5 in Cochrane Library, 14,610 in Google Scholar, and 1 from other sources†. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria. There were no exclusion criteria.

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

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)** (<u>Combination therapy</u>)
Level of Confidence – **Low**

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

Indications:	Adjunctive use with lopinavir-ritonavir and interferon beta-1b in moderately and severely affected patients with COVID-19 [325]. 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 [325].
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 [325].
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 [325].

	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 [325]. However, there is no evidence 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 July 2020 using the following terms: Ribavirin, Tribiviran; 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 17 articles in PubMed, 1343 in Scopus, 9 in CINAHL, 4 in Cochrane Library, 4190 in Google Scholar, and 0 from other sources†. We considered for inclusion 3 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 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

[232-235]. 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 [232]. 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 [235]. This is supported by evidence hydroxy/chloroquine are zinc ionophores, which increase intracellular zinc and reduce or prevent viral replication in laboratory studies [269, 270].

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 July 2020 using the following terms: zinc, zinc compounds; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 0 articles in PubMed, 175 in Scopus, 0 in CINAHL, 2 in Cochrane Library, 6268 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 article 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, 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 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:	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:	There are no quality RCTs testing the value of vitamin D. Vitamin D levels have been strongly correlated with COVID-19 disease severity [236, 238, 239], 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 [236]. 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; thus, vitamin D supplementation 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 July 2020 using the following terms: Vitamin D, vitamin d supplement; 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, 641 in Scopus, 5 in CINAHL, 5 in Cochrane Library, 11,160 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, 2 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 0 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:
    o Wash hands after blowing nose, coughing, sneezing, eating food, using a restroom, or working in close proximity to a colleague/student.
    o Use masks where there is community prevalence >2%.
    o Provide security staff with gloves and perform visual inspections of any packages, but avoid touching those packages.
    o Limit the doors for ingress and egress. Only security staff, administration, and teachers should open or close doors. Students avoid opening or closing doors.
    o 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:
    o Cleaning 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.
    o 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.
    o Cleaning staff should use disposable gloves and gowns. After removal, they should wash hands in soap and water.
    o Cleaning staff should follow physical distancing guidelines.

- o   Most dirty surfaces should be cleaned with standard cleaning products before any disinfectant is used.
  - o   Electronic surfaces and peripheral pieces should be cleaned with 70% alcohol. EPA-approved disinfectants for COVID-19[6] are then applied.
  - o   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:
  - o   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.
  - o   All rooms and areas used by the student should have be wiped down with disposable alcohol wipes.

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.

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

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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