

## 3: Overview of COVID-19

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*Last Updated: December 16, 2021*

### Epidemiology

The COVID-19 pandemic has exploded since cases were first reported in China in December 2019. As of December 14, 2021, more than 270 million cases of COVID-19—caused by SARS-CoV-2 infection—have been reported globally, including more than 5.3 million deaths.<sup>1</sup>

Individuals of all ages are at risk for SARS-CoV-2 infection and severe disease. However, the probability of serious COVID-19 disease is higher in people aged  $\geq 60$  years, those living in a nursing home or long-term care facility, and those with chronic medical conditions. In an analysis of more than 1.3 million laboratory-confirmed cases of COVID-19 that were reported in the United States between January and May 2020, 14% of patients required hospitalization, 2% were admitted to the intensive care unit, and 5% died.<sup>2</sup> The percentage of patients who died was 12 times higher among those with reported medical conditions (19.5%) than among those without medical conditions (1.6%), and the percentage of those who were hospitalized was 6 times higher among those with reported medical conditions (45.4%) than among those without medical conditions (7.6%). The mortality rate was highest in those aged  $>70$  years, regardless of the presence of chronic medical conditions. Among those with available data on health conditions, 32% had cardiovascular disease, 30% had diabetes, and 18% had chronic lung disease. Other conditions that may lead to a high risk for severe COVID-19 include cancer, kidney disease, liver disease (especially in patients with cirrhosis), obesity, sickle cell disease, and other immunocompromising conditions. Transplant recipients and pregnant people are also at a higher risk of severe COVID-19.<sup>3-10</sup>

Data from the United States suggest that racial and ethnic minorities experience higher rates of COVID-19 and subsequent hospitalization and death.<sup>11-15</sup> However, surveillance data that include race and ethnicity are not available for most reported cases of COVID-19 in the United States.<sup>4,16</sup> Factors that contribute to the increased burden of COVID-19 in these populations may include over-representation in work environments that confer higher risks of exposure to COVID-19, economic inequality (which limits people's ability to protect themselves against COVID-19 exposure), neighborhood disadvantage,<sup>17</sup> and a lack of access to health care.<sup>16</sup> Structural inequalities in society contribute to health disparities for racial and ethnic minority groups, including higher rates of comorbid conditions (e.g., cardiac disease, diabetes, hypertension, obesity, pulmonary diseases), which further increases the risk of developing severe COVID-19.<sup>15</sup>

### SARS-CoV-2 Variants

Like other RNA viruses, SARS-CoV-2 is constantly evolving through random mutations. New mutations can potentially increase or decrease infectiousness and virulence. In addition, mutations can increase the virus' ability to evade adaptive immune responses from past SARS-CoV-2 infection or vaccination. This may increase the risk of reinfection or decrease the efficacy of vaccines.<sup>18</sup> There is already evidence that some SARS-CoV-2 variants have reduced susceptibility to plasma from people who were previously infected or immunized, as well as to certain monoclonal antibodies (mAbs) that are being considered for prevention and treatment.<sup>19</sup>

Since December 2020, several variants have been identified that have now been assigned Greek letter designations by the World Health Organization (WHO). SARS-CoV-2 variants are designated as variants of concern (VOC) if they display certain characteristics, such as increased transmissibility or virulence. In addition, vaccines and/or therapeutics may have decreased effectiveness against VOC, and

the mutations found in these variants may interfere with diagnostic test targets. The designation variant of interest (VOI) is used for important variants that have not yet been fully characterized; however, the designations and definitions for these variants differ between organizations.<sup>20,21</sup> In September 2021, the Centers for Disease Control and Prevention (CDC) added a new designation for variants: [variants being monitored](#) (VBM). This refers to variants for which the data indicate a potential or clear impact on approved or authorized medical countermeasures, or variants that have been associated with more severe disease or increased transmission rates; however, these variants are either no longer detected or are circulating at very low levels in the United States. As such, these variants do not pose a significant and imminent risk to public health in the United States.

The B.1.617.2 (Delta) variant, which was first identified in India and has been designated a VOC, is the dominant variant in the United States since the summer of 2021. The Delta variant is more infectious than other variants, leading to increased transmissibility.<sup>22</sup> The B.1.1.529 (Omicron) variant was designated a VOC in November 2021. It has become the predominant variant in parts of Africa, and cases of COVID-19 caused by the Omicron variant have been reported across the globe. Early evidence suggests that the Omicron variant may spread more easily than other variants, but data are limited on the severity of disease caused by this variant.<sup>23</sup> The B.1.1.7 (Alpha) variant that was first seen in the United Kingdom is more infectious and may be more virulent than earlier variants.<sup>24-26</sup> The B.1.351 (Beta) variant that was originally identified in South Africa has spread to many other countries, including the United States. The P.1 (Gamma) variant was originally identified in Manaus, Brazil, and has also emerged in the United States. These variants, which were previously designated as VOC, are now classified as VBM. Other VBM in the United States include the B.1.427/B.1.429 (Epsilon) variants that were originally identified in California, the B.1.526 (Iota) variant that was originally identified in New York, and the B.1.617.1 (Kappa) variant that was first identified in India. For a detailed discussion on the susceptibility of certain VOC, VOI, and VBM to available anti-SARS-CoV-2 mAbs, please see [Anti-SARS-CoV-2 Monoclonal Antibodies](#).

The data on the emergence, spread, and clinical relevance of these new variants is rapidly evolving; this is especially true for research on how variants might affect transmission rates, disease progression, vaccine development, and the efficacy of current therapeutics. Because the research on variants is moving quickly and the classification of the different variants may change over time, websites such as the CDC [COVID Data Tracker](#), [CoVariants.org](#), and WHO's [Tracking SARS-CoV-2 Variants](#) provide regular updates on the data for SARS-CoV-2 variants. The COVID-19 Treatment Guidelines Panel reviews the emerging data on these variants, paying particular attention to research on the impacts of these variants on testing, prevention, and treatment.

## Clinical Presentation

The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days.<sup>6,27,28</sup> The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death. Among 72,314 people with COVID-19 in China, 81% of cases were reported to be mild (defined in this study as no pneumonia or mild pneumonia), 14% were severe (defined as dyspnea, respiratory frequency  $\geq 30$  breaths/min, oxygen saturation [SpO<sub>2</sub>]  $\leq 93\%$ , a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO<sub>2</sub>/FiO<sub>2</sub>]  $< 300$  mm Hg, and/or lung infiltrates  $> 50\%$  within 24 to 48 hours), and 5% were critical (defined as respiratory failure, septic shock, and/or multiorgan dysfunction or failure).<sup>29</sup> In a report on more than 370,000 confirmed COVID-19 cases with reported symptoms in the United States, 70% of patients experienced fever, cough, or shortness of breath, 36% had muscle aches, and 34% reported headaches.<sup>2</sup> Other reported symptoms have included, but are not limited to, diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting.

The abnormalities seen in chest X-rays of patients with COVID-19 vary, but bilateral multifocal opacities are the most common. The abnormalities seen in computed tomography of the chest also vary, but the most common are bilateral peripheral ground-glass opacities, with areas of consolidation developing later in the clinical course of COVID-19.<sup>30</sup> Imaging may be normal early in infection and can be abnormal in the absence of symptoms.<sup>30</sup>

Common laboratory findings in patients with COVID-19 include leukopenia and lymphopenia. Other laboratory abnormalities have included elevated levels of aminotransferase, C-reactive protein, D-dimer, ferritin, and lactate dehydrogenase.

Although COVID-19 is primarily a pulmonary disease, emerging data suggest that it also leads to cardiac,<sup>31,32</sup> dermatologic,<sup>33</sup> hematologic,<sup>34</sup> hepatic,<sup>35</sup> neurologic,<sup>36,37</sup> renal,<sup>38,39</sup> and other complications. Thromboembolic events also occur in patients with COVID-19, with the highest risk occurring in critically ill patients.<sup>40</sup>

The long-term sequelae of COVID-19 survivors are currently unknown. Persistent symptoms after recovery from acute COVID-19 have been described (see [Clinical Spectrum of SARS-CoV-2 Infection](#)). Lastly, SARS-CoV-2 infection has been associated with a potentially severe inflammatory syndrome in children (multisystem inflammatory syndrome in children, or MIS-C).<sup>41,42</sup> Please see [Special Considerations in Children](#) for more information.

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# Testing for SARS-CoV-2 Infection

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## Summary Recommendations

- To diagnose acute infection of SARS-CoV-2, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using a nucleic acid amplification test (NAAT) with a sample collected from the upper respiratory tract (i.e., a nasopharyngeal, nasal, or oropharyngeal specimen) **(AIII)**.
- For intubated and mechanically ventilated adults who are suspected to have COVID-19 but who do not have a confirmed diagnosis:
  - The Panel recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 if an initial upper respiratory tract sample is negative **(BII)**.
  - The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage samples when collecting lower respiratory tract samples to establish a diagnosis of COVID-19 **(BII)**.
- A NAAT should not be repeated in an asymptomatic person within 90 days of a previous SARS-CoV-2 infection, even if the person has had a significant exposure to SARS-CoV-2 **(AIII)**.
- SARS-CoV-2 reinfection has been reported in people who have received an initial diagnosis of infection; therefore, a NAAT should be considered for persons who have recovered from a previous infection and who present with symptoms that are compatible with SARS-CoV-2 infection if there is no alternative diagnosis **(BIII)**.
- The Panel **recommends against** the use of serologic (i.e., antibody) testing as the sole basis for diagnosis of acute SARS-CoV-2 infection **(AIII)**.
- The Panel **recommends against** the use of serologic (i.e., antibody) testing to determine whether a person is immune to SARS-CoV-2 infection **(AIII)**.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

## Diagnostic Testing for SARS-CoV-2 Infection

Everyone who has symptoms that are consistent with COVID-19, as well as people with known high-risk exposures to SARS-CoV-2, should be tested for SARS-CoV-2 infection. Such testing should employ either a nucleic acid amplification test (NAAT) or an antigen test to detect SARS-CoV-2. Ideally, diagnostic testing should also be performed for people who are likely to be at repeated risk of exposure to SARS-CoV-2, such as health care workers and first responders. Testing should also be considered for individuals who spend time in heavily populated environments (e.g., teachers, students, food industry workers) and for travelers. Testing requirements may vary by state, local, and employer policies. Travelers may need evidence of a recent negative test result to enter some states or countries; such documentation may be an acceptable alternative to quarantine upon arrival.

A number of diagnostic tests for SARS-CoV-2 infection (e.g., NAATs, antigen tests) have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA),<sup>1</sup> but no diagnostic test has been approved by the FDA.

Although nasopharyngeal specimens remain the recommended samples for SARS-CoV-2 diagnostic testing, nasal (anterior nares or mid-turbinate) or oropharyngeal swabs are acceptable alternatives.<sup>2</sup> Lower respiratory tract samples have a higher yield than upper tract samples, but they are often not obtained because of concerns about aerosolization of the virus during sample collection procedures. Some tests that have received EUAs can also be performed on saliva specimens. Studies are currently evaluating the use of other sample types, including stool samples.

Some tests that have received EUAs allow for self-collection of specimens at home, but these specimens

must be sent to a laboratory for processing. In addition, some tests allow trained personnel to collect and test specimens in nonclinical settings, such as in the home or in nursing or assisted living facilities. This allows real-time antigen results to be obtained on site.

## Nucleic Acid Amplification Testing for SARS-CoV-2 Infection

Reverse transcriptase polymerase chain reaction (RT-PCR)-based diagnostic tests (which detect viral nucleic acids) are considered the gold standard for detecting current SARS-CoV-2 infection. More recently, NAATs have included a variety of additional platforms (e.g., reverse transcriptase loop-mediated isothermal amplification [RT-LAMP]). Clinically, there may be a window period of up to 5 days after exposure before viral nucleic acids can be detected. Diagnostically, some NAATs may produce false negative results if a mutation occurs in the part of the virus' genome that is assessed by that test.<sup>3</sup> The FDA monitors the potential effects of SARS-CoV-2 genetic variations on NAAT results and issues updates when specific variations could affect the performance of NAATs that have received EUAs. Generally, false negative results are more likely to occur when using NAATs that rely on only one genetic target. Therefore, a single negative test result does not exclude the possibility of SARS-CoV-2 infection in people who have a high likelihood of infection based on their exposure history and/or their clinical presentation.<sup>4</sup>

Many commercial NAATs that use RT-PCR rely on multiple targets to detect the virus, such that even if a mutation impacts one of the targets, the other RT-PCR targets will still work.<sup>5</sup> NAATs that use multiple targets are less likely to be impacted by an increased prevalence of genetic variants. In fact, because each of these tests target multiple locations on the virus' genome, they can be helpful in identifying new genetic variants before they become widespread in the population. For example, the B.1.1.7 variant that has been associated with increased transmission carries many mutations, including a double deletion at positions 69 and 70 on the spike protein gene (S-gene). This mutation appears to impact the detection of the S-gene but does not impact other genetic targets in certain NAATs. If COVID-19 is still suspected after a patient receives a negative test result, clinicians should consider repeating testing; ideally, they should use a NAAT with different genetic targets.<sup>3</sup>

SARS-CoV-2 poses several diagnostic challenges, including potentially discordant shedding of virus from the upper versus the lower respiratory tract. However, due to the high specificity of NAATs, a positive result on a NAAT of an upper respiratory tract sample from a patient with recent onset of SARS-CoV-2-compatible symptoms is sufficient to diagnose COVID-19. In patients with COVID-19, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS), lower respiratory tract specimens have a higher viral load and thus a higher yield than upper respiratory tract specimens.<sup>6-12</sup> For intubated or mechanically ventilated patients with clinical signs and symptoms that are consistent with COVID-19 pneumonia, the COVID-19 Treatment Guidelines Panel (the Panel) recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 if an initial upper respiratory tract sample is negative (**BII**). The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage (BAL) samples when collecting lower respiratory tract samples to establish a diagnosis of COVID-19 (**BII**).

BAL and sputum induction are aerosol-generating procedures that should be performed only after careful consideration of the risk of exposing staff to infectious aerosols. Endotracheal aspiration appears to carry a lower risk of aerosol-generation than BAL, and some experts consider the sensitivity and specificity of endotracheal aspirates and BAL specimens comparable in detecting SARS-CoV-2.

## ***Nucleic Acid Amplification Testing for Individuals With a Previous Positive SARS-CoV-2 Test Result***

NAATs can detect SARS-CoV-2 RNA in specimens obtained weeks to months after the onset of COVID-19 symptoms.<sup>13,14</sup> However, the likelihood of recovering replication-competent virus >10 days from the onset of symptoms in those with mild disease and >20 days in those with severe disease is very low.<sup>15,16</sup> Furthermore, both virologic studies and contact tracing of high-risk contacts show a low risk for SARS-CoV-2 transmission after these intervals.<sup>17,18</sup> Based on these results, the [Centers for Disease Control and Prevention \(CDC\)](#) recommends that NAATs should not be repeated in asymptomatic persons within 90 days of a previous SARS-CoV-2 infection, even if the person has had a significant exposure to SARS-CoV-2 (**AIII**).<sup>19</sup> If there are concerns that an immunocompromised health care worker may still be infectious >20 days from the onset of SARS-CoV-2 infection, consultation with local employee health services regarding return-to-work testing policies is advised.

SARS-CoV-2 reinfection has been reported in people who have received an initial diagnosis of infection; therefore, a NAAT should be considered for persons who have recovered from a previous infection and who present with symptoms that are compatible with SARS-CoV-2 infection if there is no alternative diagnosis (**BIII**). However, it should be noted that persons infected with SARS-CoV-2 may have a negative result on an initial NAAT and then have a positive result on a subsequent test due to intermittent detection of viral RNA and not due to reinfection.<sup>13</sup> When the results for an initial and a subsequent test are positive, comparative viral sequence data from both tests are needed to distinguish between the persistent presence of viral fragments and reinfection. In the absence of viral sequence data, the cycle threshold (Ct) value from a positive NAAT result may provide information about whether a newly detected infection is related to the persistence of viral fragments or to reinfection. The Ct value is the number of PCR cycles at which the nucleic acid target in the sample becomes detectable. In general, the Ct value is inversely related to the SARS-CoV-2 viral load. Because the clinical utility of Ct values is an area of active investigation, an expert should be consulted if these values are used to guide clinical decisions.

## **Antigen Testing for SARS-CoV-2 Infection**

Antigen-based diagnostic tests (which detect viral antigens) are less sensitive than RT-PCR-based tests, but they have similarly high specificity. Antigen tests perform best early in the course of symptomatic SARS-CoV-2 infection, when the viral load is thought to be highest. Advantages of antigen-based tests are their low cost and rapid turnaround time. The availability of immediate results makes them an attractive option for point-of-care testing in high-risk congregate settings where preventing transmission is critical. Antigen-based tests also allow for repeat testing to quickly identify persons with SARS-CoV-2 infection.

Increasingly, data are available to guide the use of antigen tests as screening tests to detect or exclude SARS-CoV-2 infection in asymptomatic persons, or to determine whether a person who was previously confirmed to have SARS-CoV-2 infection is still infectious. The CDC has developed an antigen testing algorithm for persons who have symptoms of COVID-19, those who are asymptomatic and have a close contact with COVID-19, and those who are asymptomatic and have no known exposure to a person with COVID-19.<sup>20</sup>

The CDC testing algorithm recommends additional NAATs when a person who is strongly suspected of having SARS-CoV-2 infection (i.e., a person who is symptomatic) receives a negative result, and when a person who is asymptomatic receives a positive result. Antigen tests can yield false positive results for a variety of reasons, including:

- Incomplete adherence to the instructions for antigen test performance (e.g., reading the results outside the specified time interval or storing test cartridges/cards inappropriately)



- Test interference due to human antibodies (e.g., rheumatoid factor or other nonspecific antibodies)
- Use in communities that have a low prevalence of SARS-CoV-2 infection

## Serologic or Antibody Testing for Diagnosis of SARS-CoV-2 Infection

Unlike NAATs and antigen tests for SARS-CoV-2 that detect the presence of the virus, serologic or antibody tests can detect recent or prior SARS-CoV-2 infection. Because it may take 21 days or longer after symptom onset for seroconversion to occur (i.e., the development of detectable immunoglobulin [Ig] M and/or IgG antibodies to SARS-CoV-2),<sup>21-26</sup> the Panel **does not recommend** serologic testing as the sole basis for diagnosing acute SARS-CoV-2 infection (**AIII**). Because NAATs and antigen tests for SARS-CoV-2 occasionally yield false negative results, serologic tests have been used in some settings as an additional diagnostic test for patients who are strongly suspected to have SARS-CoV-2 infection. Using a serologic test in combination with a NAAT to detect IgG or total antibodies 3 to 4 weeks after symptom onset maximizes the sensitivity and specificity to detect past infection.

No serologic tests for SARS-CoV-2 are approved by the FDA; some, but not all, commercially available serologic tests for SARS-CoV-2 have received EUAs from the FDA.<sup>1</sup> Several professional societies and federal agencies, including the [Infectious Diseases Society of America](#), the [CDC](#), and the [FDA](#), provide guidance on the use of serologic testing for SARS-CoV-2.

Several factors should be considered when using serologic tests for SARS-CoV-2, including:

- Important performance characteristics of many of the commercially available serologic tests have not been fully characterized, including the sensitivity and specificity of these tests (i.e., the rates of true positive and true negative results). Serologic assays that have FDA EUAs should be used for public health and clinical use. Formal comparisons of serologic tests are in progress.
- Two types of serologic tests have received EUAs from the FDA. The first type are antibody tests that detect the presence of binding antibodies, which bind to a pathogen (e.g., a virus). The second type of tests detect neutralizing antibodies from recent or prior SARS-CoV-2 infection. It is unknown whether one type of test is more clinically meaningful than the other.
- Serologic assays may detect IgM, IgG, IgA, and/or total antibodies, or a combination of IgM and IgG antibodies. Serologic assays that detect IgG and total antibodies have higher specificity to detect past infection than assays that detect IgM and/or IgA antibodies or a combination of IgM and IgG antibodies.
- False positive test results may occur due to cross-reactivity from pre-existing antibodies to other coronaviruses.

## Serologic Testing and Immunity to SARS-CoV-2 Infection

The Panel **recommends against** the use of serologic testing to determine whether a person is immune to SARS-CoV-2 infection (**AIII**).

If SARS-CoV-2 antibodies are detected during a serologic test, the results should be interpreted with caution for the following reasons:

- It is unclear how long antibodies persist following infection; *and*
- It is unclear whether the presence of antibodies confers protective immunity against future infection.

In communities that have a low prevalence of SARS-CoV-2 infection, the proportion of positive test results that are false positives may be quite high. In these situations, confirmatory testing using a distinct antibody assay, ideally one that uses a different antigenic target (e.g., the nucleocapsid phosphoprotein

if the first assay targeted the spike protein), can substantially improve the probability that persons with positive test results are antibody positive.

Assuming that the test is reliable, serologic tests that identify recent or prior SARS-CoV-2 infection may be used to:

- Differentiate SARS-CoV-2 antibody responses to natural infection from vaccine-induced antibody responses to the SARS-CoV-2 spike protein antigen. Because nucleocapsid protein is not a constituent of vaccines that are currently available through EUAs or in late-stage clinical trials, serologic tests that detect antibodies by recognizing nucleocapsid protein can be used to distinguish antibody responses to natural infection from vaccine-induced antibody responses.
- Determine who may be eligible to donate convalescent plasma
- Estimate the proportion of the population that has been exposed to SARS-CoV-2

Based on current knowledge, serologic tests **should not be used to (AIII)**:

- Make decisions about how to group persons in congregate settings (e.g., schools, dormitories, correctional facilities)
- Determine whether persons may return to the workplace
- Assess for prior infection solely to determine whether to vaccinate an individual
- Assess for immunity to SARS-CoV-2 following vaccination, except in clinical trials

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# Prevention of SARS-CoV-2 Infection

Last Updated: December 16, 2021

Summary Recommendations
<ul style="list-style-type: none"><li>• The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for everyone who is eligible according to the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices <b>(AI)</b>.</li><li>• The Panel recommends using 1 of the following anti-SARS-CoV-2 monoclonal antibodies (listed alphabetically) as post-exposure prophylaxis (PEP) for people who are at high risk of progressing to severe COVID-19 if infected with SARS-CoV-2 <b>AND</b> who have the vaccination status <b>AND</b> exposure history outlined in the text below:<ul style="list-style-type: none"><li>• <b>Bamlanivimab 700 mg plus etesevimab 1,400 mg</b> administered as an intravenous (IV) infusion <b>(BIII)</b>; <i>or</i></li><li>• <b>Casirivimab 600 mg plus imdevimab 600 mg</b> administered as subcutaneous injections <b>(AI)</b> or an IV infusion <b>(BIII)</b>.</li></ul></li><li>• The Panel <b>recommends against</b> the use of <b>hydroxychloroquine</b> for SARS-CoV-2 PEP <b>(AI)</b>.</li><li>• The Panel <b>recommends against</b> the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial <b>(AIII)</b>.</li><li>• The Panel <b>recommends against</b> the use of any drugs for SARS-CoV-2 pre-exposure prophylaxis (PrEP), except in a clinical trial <b>(AIII)</b>.</li></ul>
<b>Rating of Recommendations:</b> A = Strong; B = Moderate; C = Optional
<b>Rating of Evidence:</b> I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

## General Prevention Measures

Transmission of SARS-CoV-2 is thought to occur primarily through exposure to respiratory droplets. Exposure can occur when someone inhales droplets or particles that contain the virus (with the greatest risk of transmission occurring within 6 feet of an infectious source) or touches their mucous membranes with hands that have been contaminated with the virus. Exhaled droplets or particles can also deposit the virus onto exposed mucous membranes.<sup>1</sup>

Less commonly, airborne transmission of small droplets and particles of SARS-CoV-2 to people further than 6 feet away can occur; in rare cases, people passing through a room that was previously occupied by an infectious person may become infected. SARS-CoV-2 infection via airborne transmission of small particles tends to occur after prolonged exposure (i.e., >15 minutes) to an infectious person who is in an enclosed space with poor ventilation.<sup>1</sup>

The risk of SARS-CoV-2 transmission can be reduced by covering coughs and sneezes and maintaining a distance of at least 6 feet from others. When consistent distancing is not possible, face coverings may reduce the spread of infectious droplets from individuals with SARS-CoV-2 infection to others. Frequent handwashing also effectively reduces the risk of infection.<sup>2</sup> Health care providers should follow the Centers for Disease Control and Prevention (CDC) recommendations for infection control and the appropriate use of personal protective equipment.<sup>3</sup>

Vaccination is highly effective in preventing SARS-CoV-2 infection. Anti-SARS-CoV-2 monoclonal antibodies (mAbs) may also be effective as post-exposure prophylaxis (PEP) for certain groups of people who are at risk of progression to serious COVID-19 and who have not been fully vaccinated or who are not expected to mount an adequate immune response to vaccines.

## Vaccines

The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for everyone who is eligible according to CDC's Advisory Committee on Immunization Practices **(AI)**.

*COVID-19 Treatment Guidelines*



CDC regularly updates the clinical considerations for using the COVID-19 vaccines that are currently approved by the Food and Drug Administration (FDA) or authorized for use in the United States.<sup>4</sup> Currently, 2 mRNA vaccines are available in the United States. The 2-dose series of the BNT162b2 (Pfizer-BioNTech) vaccine was approved by FDA for individuals aged  $\geq 16$  years, and it is authorized for use in individuals aged  $\geq 12$  years to  $< 16$  years under an Emergency Use Authorization (EUA). Emerging data suggest that this vaccine may have potential for use in younger individuals. A pediatric formulation of this vaccine has been authorized for use in children aged 5 to 11 years under an EUA. The 2-dose series of the mRNA-1273 (Moderna) vaccine has an EUA for individuals aged  $\geq 18$  years. The single-dose human adenovirus type 26 (Ad26) vectored vaccine, Ad26.COV2.S (Johnson & Johnson/Janssen), has an EUA for individuals aged  $\geq 18$  years.

These products have also been authorized for additional doses and booster doses in certain populations.<sup>5</sup> Studies that have evaluated the role of heterologous boosters (i.e., using a different vaccine product for the booster than was used for the primary series) indicate that, regardless of the vaccine used for the primary series, an additional dose of any of these products boosts antibody levels. The current vaccine authorizations support this approach. Immunocompromised individuals who have received 2 doses of the mRNA-1273 or BNT162b2 vaccines are eligible for an additional mRNA vaccine dose 28 days after the primary series and a booster at 6 months. Some people who have received 2 doses of the mRNA-1273 or BNT162b2 vaccines are eligible for a booster at 6 months. Recipients of the Ad26.COV2.S vaccine should receive a booster  $\geq 2$  months after their primary dose. CDC regularly updates the details on the timing, dose, and volume for these additional doses and boosters, as well as the recommendations for the populations that are eligible for these additional doses and boosters.

For people who received anti-SARS-CoV-2 mAbs for the treatment of COVID-19, CDC recommends deferring COVID-19 vaccination until at least 90 days after therapy. For people who received anti-SARS-CoV-2 mAbs for PEP, vaccination should be deferred until at least 30 days after PEP. This is a precautionary measure to accommodate the theoretical possibility that anti-SARS-CoV-2 mAbs may interfere with vaccine-induced immune responses.<sup>4</sup>

### ***Adverse Events***

Local and systemic adverse events are relatively common with these vaccines. Most of the adverse events that occurred during vaccine trials were mild or moderate in severity (i.e., they did not prevent vaccinated people from engaging in daily activities) and resolved after 1 or 2 days. There have been a few reports of severe allergic reactions following COVID-19 vaccination, including rare reports of patients who experienced anaphylaxis after receiving an mRNA vaccine.<sup>6,7</sup>

Reports have suggested that there is an increased risk of thrombosis with thrombocytopenia in adults who have received the Ad26.COV2.S vaccine.<sup>7</sup> Most reports of this rare and serious condition have been in women aged 18 to 49 years.<sup>8</sup> Similar reports from Europe describe thrombocytopenia and venous thrombosis in patients who received the ChAdOx1 nCoV-19 (Oxford/AstraZeneca) vaccine, which uses a chimpanzee adenoviral vector.<sup>9,10</sup> The American Society of Hematology and the American Heart Association/American Stroke Association Stroke Council Leadership have published considerations that are relevant to the diagnosis and treatment of the type of thrombosis with thrombocytopenia that occurs in people who receive the Ad26.COV2.S vaccine. These considerations include information on administering a nonheparin anticoagulant and intravenous (IV) immunoglobulin to these patients.<sup>11,12</sup> Given the rarity of this syndrome and the unique treatment required, consider consulting a hematologist when treating these patients.

Myocarditis and pericarditis are rarely reported in people who have received COVID-19 vaccines, and most of the cases that have been reported were very mild and self-limiting. These conditions have occurred most often in male adolescents and young adults and people who have received mRNA vaccines.<sup>13</sup>

Guillain-Barré syndrome (GBS), a rare neurologic disorder, has been reported in approximately 12 people per million who received the Ad26.COV2.S vaccine. Most people with GBS fully recover, but some have permanent nerve damage. Onset typically occurs about 2 weeks after vaccination. GBS has mostly been reported in men aged  $\geq 50$  years.<sup>13</sup>

CDC provides regular updates on selected adverse events of COVID-19 vaccines [on their website](#).

### ***Vaccination in Pregnant or Lactating People***

Pregnant and lactating individuals were not included in the initial COVID-19 vaccine trials. However, CDC, the American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal Fetal Medicine recommend vaccination for pregnant and lactating people based on the accumulated safety and efficacy data on the use of these vaccines in pregnant people, as well as the increased risk of severe disease in pregnant individuals with COVID-19. These organizations also recommend vaccination for people who are trying to become pregnant now or who may become pregnant in the future.<sup>14-20</sup> The ACOG publication includes a guide to assist clinicians during conversations about COVID-19 vaccination with pregnant patients.<sup>21</sup>

## **Post-Exposure Prophylaxis**

### ***Anti-SARS-CoV-2 Monoclonal Antibodies***

Vaccination remains a highly effective way to prevent SARS-CoV-2 infection. However, despite widespread availability of COVID-19 vaccines, a number of individuals are either not fully vaccinated or cannot mount adequate responses to the vaccine. Some of these individuals, if infected, are at high risk of progressing to serious COVID-19. Based on the results of 2 large randomized controlled trials, the FDA expanded the EUA indication for the anti-SARS-CoV-2 mAbs bamlanivimab plus etesevimab and casirivimab plus imdevimab to allow these combinations to be used as PEP for selected individuals.<sup>22</sup>

### **Recommendations**

The Panel recommends using 1 of the following anti-SARS-CoV-2 mAbs (listed alphabetically) as PEP for people who are at high risk for progressing to severe COVID-19 if infected with SARS-CoV-2 **AND** who have the vaccination status **AND** exposure history outlined in the text below.

- **Bamlanivimab 700 mg plus etesevimab 1,400 mg** administered as an IV infusion (**BIII**); *or*
- **Casirivimab 600 mg plus imdevimab 600 mg** administered as subcutaneous (SQ) injections (**AI**) or an IV infusion (**BIII**).

### ***Vaccination Status:***

- Not fully vaccinated (defined as people who were never vaccinated, those who received the first dose of a 2-dose series, or those who received the second dose of a 2-dose series or a single-dose vaccine  $< 2$  weeks ago); *or*
- Fully vaccinated, but not expected to mount an adequate immune response (e.g., those with immunocompromising conditions, including those who are taking immunosuppressive medications).

## **AND**

### ***Exposure History to SARS-CoV-2:***

- Had a recent exposure to an individual with SARS-CoV-2 infection that is consistent with CDC close contact criteria; *or*

- Had a high risk of exposure to an individual with SARS-CoV-2 infection because of a recent occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (e.g., nursing homes, prisons).

The doses should be administered as soon as possible and preferably within 7 days of high-risk exposure (**BIII**). The patient should be observed for at least 1 hour after the injections or infusion for anaphylaxis and infusion-related reactions.

It should be noted that even though the EUA calls for the combination of bamlanivimab 700 mg plus etesevimab 1,400 mg administered as a single IV infusion, the clinical trial that was used to support the EUA only studied bamlanivimab monotherapy at a single dose of 4,200 mg (see [Anti-SARS-CoV-2 Monoclonal Antibodies](#)).

The EUA for casirivimab plus imdevimab allows for repeat dosing of casirivimab 300 mg plus imdevimab 300 mg once every 4 weeks using SQ injections or an IV infusion for those who meet the EUA criteria for PEP and have ongoing exposures. However, there are no data from the COVID-19 Phase 3 Prevention Trial or other studies on the utility of repeat dosing for individuals who continue to have high-risk exposures. Therefore, the Panel finds that there is insufficient evidence to recommend either for or against repeat dosing every 4 weeks for those who received PEP and who continue to have high-risk exposures.

If there are shortages of anti-SARS-CoV-2 mAbs or logistical constraints (e.g., limited space, not enough staff who can administer therapy), it may be difficult to administer these agents to all eligible patients. In situations where it is necessary to triage eligible patients, the Panel suggests prioritizing the treatment of COVID-19 over PEP. For further guidance on prioritizing the use of these mAbs, see [this statement from the Panel](#).

### **Clinical Trial Data for Bamlanivimab Monotherapy**

BLAZE-2 is a double-blind, Phase 3 randomized trial that enrolled residents and staff of 74 skilled nursing and assisted living facilities in the United States. Each facility had had at least 1 confirmed index case of SARS-CoV-2 infection, and the staff and residents had no known history of COVID-19.<sup>23</sup> All participants provided both nasal and nasopharyngeal (NP) swabs for reverse transcription polymerase chain reaction (RT-PCR)-based diagnostic tests and blood for SARS-CoV-2 antibody testing. Nasal and NP swabs were obtained weekly for 57 days.

Participants who were found to be RT-PCR and antibody negative were considered the prevention population. Between August and November 2020, the study randomized 1,175 participants 1:1 to receive either bamlanivimab monotherapy at a dose of 4,200 mg or placebo by IV infusion. The prevention population included 484 participants who received bamlanivimab (323 staff and 161 residents) and 482 participants who received placebo (343 staff and 139 residents). The baseline characteristics of the staff and resident populations were very different; for example, the residents had a median age that was >30 years higher than the staff (76 years vs. 43 years) and had greater risks for disease progression.

In the overall prevention population, 114 participants (11.9%) experienced mild or worse COVID-19 by Day 57. There was a significantly lower incidence of mild or worse COVID-19 in the bamlanivimab arm than in the placebo arm (8.5% vs. 15.2%; OR 0.43; 95% CI, 0.28–0.68;  $P < 0.001$ ), with an absolute risk difference of -6.6 percentage points (95% CI, -10.7 to -2.6). The difference was most significant in the resident population, where the incidence of mild or worse COVID-19 was 8.8% in the bamlanivimab arm compared to 22.5% in the placebo arm (OR 0.20; 95% CI, 0.08–0.49;  $P < 0.001$ ), with an absolute difference of -13.7 percentage points (95% CI, -21.9 to -5.4). In contrast, the difference between the bamlanivimab and placebo arms did not achieve statistical significance in the staff prevention population. Similar findings were observed for the secondary endpoint of the incidence of moderate or

worse COVID-19.

In the prevention population, 198 participants (20.6%) had positive RT-PCR results within 4 weeks of randomization. The frequency of positive results was significantly lower in the bamlanivimab arm than in the placebo arm (17.9% vs. 23.3%; OR 0.66; 95% CI, 0.46–0.94;  $P = 0.02$ ), with an absolute risk difference of -5.4 percentage points (95% CI, -10.5 to -0.3). The difference was significant for the resident prevention population but not the staff prevention population. An additional secondary endpoint in this study was mortality due to COVID-19; a total of 4 participants died, all of whom were residents who were randomized to receive placebo.

The overall safety population included 1,175 participants. Serious adverse events were reported in 3.7% of bamlanivimab recipients and 3.2% of placebo recipients. Any adverse events were reported in 20.1% of participants in the bamlanivimab arm and 18.9% of those in the placebo arm. The types of events were balanced across the study arms. Hypersensitivity reactions that occurred within 24 hours of study product infusion were reported in 3 participants (0.5%) in the bamlanivimab arm and none in the placebo arm.

### **Clinical Trial Data for Casirivimab Plus Imdevimab**

Casirivimab plus imdevimab was evaluated as PEP in a Phase 3, double-blind randomized placebo-controlled trial that was conducted at 112 sites in the United States, Romania, and Moldova.<sup>24</sup> The trial enrolled individuals aged  $\geq 12$  years who were exposed to a household contact (the index patient) who had a positive SARS-CoV-2 RT-PCR result from a NP swab specimen that was collected within the previous 96 hours. Study participants were asymptomatic, had a negative NP RT-PCR result for SARS-CoV-2, and intended to live with the index patient for the 28-day duration of follow-up.

Participants were randomized 1:1 to receive casirivimab 600 mg plus imdevimab 600 mg or placebo administered as 4 SQ injections (2.5 mL per injection) at different sites. NP swabs were collected weekly. The primary efficacy endpoint was the proportion of participants who developed symptomatic, RT-PCR-confirmed SARS-CoV-2 infection during the 28 days of follow-up. Additional key efficacy endpoints included asymptomatic infection and the quantity and duration of viral shedding detected by NP swabs.

The primary analysis included 1,505 participants (753 in the casirivimab plus imdevimab arm and 752 in the placebo arm) who had negative SARS-CoV-2 RT-PCR results at baseline and who were subsequently found to be serum SARS-CoV-2 antibody negative. The mean age was 42.9 years, 45.9% of participants were men, and 9.3% of participants were Black or African American and 40.5% were Hispanic/Latino. The protocol-specified risk factors for progression to severe COVID-19 were present in 30.5% of participants, with approximately 75% meeting the high-risk criteria in the revised EUA.

The use of casirivimab plus imdevimab resulted in a significant reduction in the risk of symptomatic SARS-CoV-2 infection when compared with placebo (81.4% risk reduction: 11 of 753 participants [1.5%] vs. 59 of 752 patients [7.8%]; OR 0.17;  $P < 0.001$ ). This risk reduction was present throughout the follow-up period, starting from the first week and continuing through Week 4. Using both asymptomatic and symptomatic infections as an endpoint, the use of casirivimab plus imdevimab was associated with a significant reduction in risk compared to placebo (66.4% risk reduction; 36 of 753 participants [4.8%] vs. 107 of 752 participants [14.2%]; OR 0.31; 95% CI, 0.21–0.46;  $P < 0.0001$ ). Among the subset of participants who were found to be seropositive at baseline (and were therefore excluded from the primary analysis), only a small number of participants reached the study endpoints, and there was no significant difference in the number who reached the endpoints between the casirivimab plus imdevimab arm (1 of 235 patients [0.4%]) and the placebo arm (5 of 222 participants [2.3%]; OR 0.19; 95% CI, 0.02–1.68;  $P = 0.14$ ).



Hospitalizations were rare, with no hospitalized participants in the casirivimab plus imdevimab arm and 4 in the placebo arm. Some participants in the study received casirivimab plus imdevimab before they received their RT-PCR results; among these participants, those who eventually received positive RT-PCR results had a shorter duration of viral detection than the participants in the placebo arm (mean of 1.1 vs. 2.2 weeks). The frequencies of adverse events were similar between the 2 arms.

### ***Chloroquine and Hydroxychloroquine***

- The Panel **recommends against** the use of **hydroxychloroquine** for SARS-CoV-2 PEP (AI).

Both chloroquine and hydroxychloroquine have in vitro activity against SARS-CoV and SARS-CoV-2.<sup>25,26</sup> A small cohort study without a control group suggested that hydroxychloroquine might reduce the risk of SARS-CoV-2 transmission to close contacts.<sup>27</sup> There have been several large trials to determine whether hydroxychloroquine can reduce the risk of infection after exposure to infected individuals. These studies used different dosing schedules and targeted different at-risk populations. In addition, some studies were unable to confirm infection using molecular or antigen tests. None of these studies demonstrated any evidence of efficacy for hydroxychloroquine, and all showed a higher risk of generally mild adverse events in those who received the drug.<sup>28-30</sup>

### ***Other Drugs for PEP***

- The Panel **recommends against** the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial (AIII).

A number of other agents (e.g., ivermectin, hyperimmune gamma globulin, convalescent plasma, interferons, tenofovir with or without emtricitabine, vitamin D) are currently being investigated for SARS-CoV-2 PEP. The latest clinical trials for SARS-CoV-2 PEP can be found at [ClinicalTrials.gov](https://clinicaltrials.gov).

High concentrations of ivermectin have been shown to inhibit SARS-CoV-2 replication in vitro.<sup>31,32</sup> Population data indicated that country-wide, mass-use of prophylactic chemotherapy for parasitic infections, including the use of ivermectin, was associated with a lower incidence of COVID-19.<sup>33</sup> At this time, few clinical trials have evaluated the safety and efficacy of using ivermectin for SARS-CoV-2 pre-exposure prophylaxis (PrEP) or PEP. Although several studies have reported potentially promising results, the findings are limited by the design of the studies, their small sample sizes, and the lack of details regarding the safety and efficacy of ivermectin.

In a descriptive, uncontrolled, interventional study of 33 contacts of patients with laboratory-confirmed COVID-19, no cases of SARS-CoV-2 infection were identified within 21 days of initiating ivermectin for PEP.<sup>34</sup> In a small case-control study in SARS-CoV-2-exposed health care workers, 186 participants who became infected were matched with 186 uninfected controls. Of those who received ivermectin after exposure to SARS-CoV-2, 38 were in the infected group and 77 were in the uninfected group, which led the investigators to conclude that ivermectin reduced the incidence of SARS-CoV-2 infection.<sup>35</sup>

### **Pre-Exposure Prophylaxis**

- The Panel **recommends against** the use of any drugs for SARS-CoV-2 PrEP, except in a clinical trial (AIII).

### ***Rationale***

At present, there is no known agent that is effective in preventing infection when administered before exposure to SARS-CoV-2 (i.e., as PrEP). Clinical trials are investigating several agents, including emtricitabine plus tenofovir alafenamide or tenofovir disoproxil fumarate, hydroxychloroquine,

ivermectin, and supplements such as zinc, vitamin C, and vitamin D. Studies of anti-SARS-CoV-2 mAbs that target SARS-CoV-2 are also underway. Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information.

Hydroxychloroquine, given at different doses and durations, has been studied in randomized controlled trials to assess whether it could prevent SARS-CoV-2 infection in those at risk for being exposed to infected individuals, such as health care workers. One study reported no evidence of a benefit of hydroxychloroquine, and it was ultimately halted due to futility before it reached its target enrollment.<sup>36</sup> In another hydroxychloroquine study, which also did not meet its target enrollment and was stopped early, the majority of the potential transmission events were not confirmed by virologic testing.<sup>37</sup> Neither study demonstrated any evidence of a reduction in rate of acquiring infection. Both studies reported an increased frequency of mild adverse events in the treatment group.

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# Clinical Spectrum of SARS-CoV-2 Infection

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Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness. In general, adults with SARS-CoV-2 infection can be grouped into the following severity of illness categories; however, the criteria for each category may overlap or vary across clinical guidelines and clinical trials, and a patient's clinical status may change over time.

- *Asymptomatic or Presymptomatic Infection:* Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but who have no symptoms that are consistent with COVID-19.
- *Mild Illness:* Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.
- *Moderate Illness:* Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation ( $\text{SpO}_2$ )  $\geq 94\%$  on room air at sea level.
- *Severe Illness:* Individuals who have  $\text{SpO}_2 < 94\%$  on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ )  $< 300$  mm Hg, a respiratory rate  $> 30$  breaths/min, or lung infiltrates  $> 50\%$ .
- *Critical Illness:* Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Patients with certain underlying comorbidities are at a higher risk of progressing to severe COVID-19. These comorbidities include being aged  $\geq 65$  years; having cardiovascular disease, chronic lung disease, sickle cell disease, diabetes, cancer, obesity, or chronic kidney disease; being pregnant; being a cigarette smoker; being a transplant recipient; and receiving immunosuppressive therapy.<sup>1</sup> Health care providers should monitor such patients closely until clinical recovery is achieved.

The optimal pulmonary imaging technique has not yet been defined for people with symptomatic SARS-CoV-2 infection. Initial evaluation for these patients may include a chest X-ray, ultrasound screening, or, if indicated, a computed tomography scan. An electrocardiogram should be performed if indicated. Laboratory testing includes a complete blood count with differential and a metabolic profile, including liver and renal function tests. Although inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin are not routinely measured as part of standard care, results from such measurements may have prognostic value.<sup>2-4</sup>

The definitions for the severity of illness categories listed above also apply to pregnant patients. However, the threshold for certain interventions may be different for pregnant patients and nonpregnant patients. For example, oxygen supplementation is recommended for pregnant patients when  $\text{SpO}_2$  falls below 95% on room air at sea level to accommodate physiologic changes in oxygen demand during pregnancy and to ensure adequate oxygen delivery to the fetus.<sup>5</sup> If laboratory parameters are used for monitoring pregnant patients and making decisions about interventions, clinicians should be aware that normal physiologic changes during pregnancy can alter several laboratory values. In general, leukocyte cell count increases throughout gestation and delivery and peaks during the immediate postpartum period. This increase is mainly due to neutrophilia.<sup>6</sup> D-dimer and CRP levels also increase during pregnancy and are often higher in pregnant patients than nonpregnant patients.<sup>7</sup> Detailed information on treating COVID-19 in pregnant patients can be found in [Special Considerations in Pregnancy](#) and in the pregnancy considerations subsection of each section of the Guidelines.

In pediatric patients, radiographic abnormalities are common and, for the most part, should not be the only criteria used to determine the severity of illness. The normal values for respiratory rate also vary with age in children; therefore, hypoxemia should be the primary criterion used to define severe COVID-19, especially in younger children. In a small number of children and in some young adults, SARS-CoV-2 infection may be followed by a severe inflammatory condition called multisystem inflammatory syndrome in children (MIS-C).<sup>8,9</sup> This syndrome is discussed in detail in [Special Considerations in Children](#).

## Asymptomatic or Presymptomatic Infection

Asymptomatic SARS-CoV-2 infection can occur, although the percentage of patients who remain truly asymptomatic throughout the course of infection is variable and incompletely defined. It is unclear what percentage of individuals who present with asymptomatic infection progress to clinical disease. Some asymptomatic individuals have been reported to have objective radiographic findings that are consistent with COVID-19 pneumonia.<sup>10,11</sup> Increasing the availability of virologic testing for SARS-CoV-2 and reliable serologic assays for SARS-CoV-2 antibodies will help determine the true prevalence of asymptomatic and presymptomatic infection. See [Therapeutic Management of Nonhospitalized Adults With COVID-19](#) for recommendations regarding SARS-CoV-2-specific therapy.

## Mild Illness

Patients with mild illness may exhibit a variety of signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell). They do not have shortness of breath, dyspnea on exertion, or abnormal imaging. Most mildly ill patients can be managed in an ambulatory setting or at home through telemedicine or telephone visits. No imaging or specific laboratory evaluations are routinely indicated in otherwise healthy patients with mild COVID-19. Older patients and those with underlying comorbidities are at higher risk of disease progression; therefore, health care providers should monitor these patients closely until clinical recovery is achieved. See [Therapeutic Management of Nonhospitalized Adults With COVID-19](#) for recommendations regarding SARS-CoV-2-specific therapy.

## Moderate Illness

Moderate illness is defined as evidence of lower respiratory disease during clinical assessment or imaging, with  $\text{SpO}_2 \geq 94\%$  on room air at sea level. Given that pulmonary disease can progress rapidly in patients with COVID-19, patients with moderate disease should be closely monitored. If bacterial pneumonia or sepsis is suspected, administer empiric antibiotic treatment, re-evaluate the patient daily, and de-escalate or stop antibiotics if there is no evidence of bacterial infection. See [Therapeutic Management of Nonhospitalized Adults With COVID-19](#) for recommendations regarding SARS-CoV-2-specific therapy.

## Severe Illness

Patients with COVID-19 are considered to have severe illness if they have  $\text{SpO}_2 < 94\%$  on room air at sea level,  $\text{PaO}_2/\text{FiO}_2 < 300$  mm Hg, a respiratory rate  $> 30$  breaths/min, or lung infiltrates  $> 50\%$ . These patients may experience rapid clinical deterioration. Oxygen therapy should be administered immediately using a nasal cannula or a high-flow oxygen device. See [Therapeutic Management of Hospitalized Adults With COVID-19](#) for recommendations regarding SARS-CoV-2-specific therapy. If secondary bacterial pneumonia or sepsis is suspected, administer empiric antibiotics, re-evaluate the patient daily, and de-escalate or stop antibiotics if there is no evidence of bacterial infection.

## Critical Illness

Critically ill patients may have acute respiratory distress syndrome, septic shock that may represent virus-induced distributive shock, cardiac dysfunction, an exaggerated inflammatory response, and/or exacerbation of underlying comorbidities. In addition to pulmonary disease, patients with critical illness may also experience cardiac, hepatic, renal, central nervous system, or thrombotic disease.

As with any patient in the intensive care unit (ICU), successful clinical management of a patient with COVID-19 includes treating both the medical condition that initially resulted in ICU admission and other comorbidities and nosocomial complications. For more information, see [Care of Critically Ill Adult Patients With COVID-19](#).

## Infectious Complications in Patients With COVID-19

Some patients with COVID-19 may have additional infections that are noted when they present for care or that develop during the course of treatment. These coinfections may complicate treatment and recovery. Older patients or those with certain comorbidities or immunocompromising conditions may be at higher risk for these infections. The use of immunomodulators such as dexamethasone, interleukin-6 inhibitors (e.g., tocilizumab, sarilumab), or Janus kinase inhibitors (e.g., baricitinib, tofacitinib) to treat COVID-19 may also be a risk factor for infectious complications; however, when these therapies are used appropriately, the benefits outweigh the risks.

Infectious complications in patients with COVID-19 can be categorized as follows:

- *Coinfections at Presentation With COVID-19:* Although most individuals present with only SARS-CoV-2 infection, concomitant viral infections, including influenza and other respiratory viruses, have been reported.<sup>12</sup> Community-acquired bacterial pneumonia has also been reported, but it is uncommon, with a prevalence that ranges from 0% to 6% of people with SARS-CoV-2 infection.<sup>12,13</sup> Antibacterial therapy is generally not recommended unless additional evidence for bacterial pneumonia is present (e.g., leukocytosis, the presence of a focal infiltrate on imaging).
- *Reactivation of Latent Infections:* There are case reports of underlying chronic hepatitis B virus and latent tuberculosis infections reactivating in patients with COVID-19 who receive immunomodulators as treatment,<sup>14-16</sup> although the data are currently limited. Reactivation of herpes simplex virus and varicella zoster virus infections have also been reported.<sup>17</sup> Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.<sup>18,19</sup> Many clinicians would initiate empiric treatment (e.g., treatment with ivermectin) with or without serologic testing in patients who are from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).<sup>20</sup>
- *Nosocomial Infections in Patients With COVID-19:* Hospitalized patients with COVID-19 may acquire common nosocomial infections, such as hospital-acquired pneumonia (including ventilator-associated pneumonia), line-related bacteremia or fungemia, catheter-associated urinary tract infection, and *Clostridioides difficile*-associated diarrhea. Early diagnosis and treatment of these infections are important for improving outcomes in these patients.
- *Opportunistic Fungal Infections:* Invasive fungal infections, including aspergillosis and mucormycosis, have been reported in hospitalized patients with COVID-19.<sup>21-24</sup> Although these infections are relatively rare, they can be fatal, and they may be more commonly seen in immunocompromised patients and in patients who are on mechanical ventilation. The majority of mucormycosis cases have been reported in India and are associated with diabetes mellitus and/or the use of corticosteroids.<sup>25,26</sup> The approach for managing these fungal infections should be the same as the approach for managing invasive fungal infections in other settings.

## SARS-CoV-2 Reinfection

As seen with other viral infections, reinfection with SARS-CoV-2 after recovery from prior infection has been reported.<sup>27</sup> The true prevalence of reinfection is not known, although there are concerns that the frequency of reinfection may increase with the circulation of new variants.<sup>28</sup> SARS-CoV-2 can often be detected from a nasal swab for weeks to months after the initial infection; therefore, repeat testing to evaluate for reinfection should be considered only for those who have recovered from the initial infection and present with COVID-19-compatible symptoms with no obvious alternate etiology (AIII).<sup>29</sup> Diagnostic testing in this setting is summarized in [Testing for SARS-CoV-2 Infection](#). In addition, if reinfection is suspected, guidelines for the diagnosis and evaluation of suspected SARS-CoV-2 reinfection are provided by the Centers for Disease Control and Prevention (CDC).<sup>30</sup>

It has been speculated that reinfection may occur more frequently in those who have a less robust immune response during the initial infection, as is often reported in those with mild illness. Reinfection may also occur as initial immune responses wane over time. Nevertheless, one review noted that SARS-CoV-2 reinfection occurred after previous severe disease in three cases and as early as 3 weeks after the initial infection was diagnosed.<sup>31</sup> A public site that posts a variety of published and unpublished reports of reinfection notes that reinfection has occurred anywhere from a few weeks to many months after the initial infection, and it occasionally follows episodes of severe COVID-19.<sup>32</sup> Although data are limited, there is no evidence to suggest that the treatment of suspected or documented SARS-CoV-2 reinfection should be different from the treatment used during the initial infection, as outlined in [Therapeutic Management of Nonhospitalized Adults With COVID-19](#) and [Therapeutic Management of Hospitalized Adults With COVID-19](#).

## Persistent Symptoms or Organ Dysfunction After Acute COVID-19

There have been an increasing number of reports of patients who experience persistent symptoms and/or organ dysfunction after acute COVID-19. Data about the incidence, natural history, and etiology of these symptoms are emerging. However, these reports have several limitations. For example, there is currently no agreed-upon case definition for persistent symptoms or organ dysfunction after acute COVID-19. In addition, most of these reports only included patients who attended post-COVID-19 clinics, and they often lack comparator groups. No specific treatments for the persistent effects of COVID-19 have yet been identified, although this [COVID-19 rapid guideline](#) proposes general management strategies.

The nomenclature for this phenomenon is evolving, and there is no established clinical terminology to date. It has been referred to as post-COVID-19 condition, or, colloquially, “long COVID,” and affected patients have been referred to as “long haulers.” The term “post-acute sequelae of COVID-19” (PASC) has also been used to describe late sequelae of SARS-CoV-2 infection that include these persistent symptoms, as well as other delayed syndromes such as MIS-C and multisystem inflammatory syndrome in adults (MIS-A). To date, no case definition and no specific time frame have been established to define the syndrome of persistent symptoms and/or organ dysfunction after acute COVID-19. However, CDC recently proposed defining late sequelae as sequelae that extend >4 weeks after initial infection.<sup>33,34</sup> The [Patient-Led Research Collaborative for COVID-19](#) defines long COVID as a collection of symptoms that develop during or following a confirmed or suspected case of COVID-19 and that continue for >28 days.<sup>35</sup> Incidence rates vary widely, from about 10% in some reports to one cohort study in which 87% of patients reported at least one persistent symptom.<sup>36</sup>

Some of the symptoms overlap with the post-intensive care syndrome (PICS) that has been described in patients without COVID-19, but prolonged symptoms and disabilities after COVID-19 have also been reported in patients with milder illness, including outpatients (see [General Considerations](#) for information on PICS).<sup>37,38</sup>



Despite the limitations of the available descriptive data on these persistent symptoms, some representative studies have suggested that common findings include fatigue, joint pain, chest pain, palpitations, shortness of breath, cognitive impairment, and worsened quality of life.<sup>39,40</sup>

CDC conducted a telephone survey of a random sample of 292 adult outpatients who had positive polymerase chain reaction results for SARS-CoV-2. Among the 274 respondents who were symptomatic at the time of testing, 35% reported not having returned to their usual state of health 2 weeks or more after testing; this included 26% of patients aged 18 to 34 years, 32% of those aged 35 to 49 years, and 47% of those aged  $\geq 50$  years.<sup>38</sup> An age of  $\geq 50$  years and the presence of three or more chronic medical conditions were associated with not returning to usual health within 14 to 21 days. Moreover, one in five individuals aged 18 to 34 years who did not have chronic medical conditions had not returned to baseline health when interviewed at a median of 16 days from the testing date.

In a cohort study from Wuhan, China, 1,733 discharged patients with COVID-19 were evaluated for persistent symptoms at a median of 186 days after symptom onset.<sup>41</sup> The most common symptoms were fatigue or muscle weakness and sleep difficulties (reported among 63% and 26% of participants, respectively). Anxiety or depression was reported among 23% of patients.

In a longitudinal prospective cohort of mostly outpatients with laboratory-confirmed SARS-CoV-2 infection at the University of Washington, 177 participants completed a follow-up questionnaire between 3 and 9 months after illness onset.<sup>42</sup> Overall, 91% of the respondents were outpatients (150 with mild illness and 11 with no symptoms), and only 9% had moderate or severe disease that required hospitalization. Among those who reported symptoms, 33% of outpatients and 31% of hospitalized patients reported at least one persistent symptom. Persistent symptoms were reported by 27% of the patients aged 18 to 39 years, 30% of those aged 40 to 64 years, and 43% of those aged  $\geq 65$  years. The most common persistent symptoms were loss of sense of smell or taste and fatigue (both reported by 14% of patients).

Persistent symptoms after acute COVID-19 have also been reported in pregnant people.<sup>43</sup> Systematic data on persistent symptoms in children following recovery from the acute phase of COVID-19 are not currently available, although case reports suggest that children may experience long-term effects similar to those experienced by adults after clinical COVID-19.<sup>44,45</sup> MIS-C is discussed in [Special Considerations in Children](#).

### ***Fatigue***

The prevalence of fatigue among 128 individuals from Ireland who had recovered from the acute phase of COVID-19 was examined using the Chalder Fatigue Scale (CFQ11). More than half of patients (67 of 128 patients [52.3%]) reported persistent fatigue at a median of 10 weeks after initial symptoms first appeared. There was no association between illness severity and fatigue.<sup>46</sup> An outpatient service that was developed in Italy for patients recovering from acute COVID-19 reported that 87% of 143 patients surveyed had persistent symptoms for a mean of 60 days after symptom onset. The most common symptom was fatigue, which occurred in 53.1% of these patients.<sup>36</sup>

### ***Cardiopulmonary***

A study from the United Kingdom reported that among 100 hospitalized patients with COVID-19 (32 received care in the ICU and 68 received care in hospital wards only), 72% of the ICU patients and 60% of the ward patients experienced fatigue and breathlessness at 4 to 8 weeks after hospital discharge. The authors suggested that posthospital rehabilitation may be necessary for some of these patients.<sup>39</sup> A retrospective study from China found that pulmonary function (as measured by spirometry) was still impaired 1 month after hospital discharge in 31 of 57 patients (54.4%) with COVID-19.<sup>47</sup> In a study

from Germany that included 100 patients who had recently recovered from COVID-19, cardiac magnetic resonance imaging (MRI) performed a median of 71 days after diagnosis revealed cardiac involvement in 78% of patients and ongoing myocardial inflammation in 60% of patients.<sup>48</sup> A retrospective study from China of 26 patients who had recovered from COVID-19 and who had initially presented with cardiac symptoms found abnormalities on cardiac MRI in 15 patients (58%).<sup>49</sup> This assessment of the prevalence of cardiac abnormalities in people with PASC should be viewed with caution, however, as the analysis included only patients with cardiac symptoms.

### ***Neuropsychiatric***

Neurologic and psychiatric symptoms have also been reported among patients who have recovered from acute COVID-19. High rates of anxiety and depression have been reported in some patients using self-report scales for psychiatric distress.<sup>40,50</sup> Younger patients have been reported to experience more psychiatric symptoms than patients aged >60 years.<sup>39,40</sup> Patients may continue to experience headaches, vision changes, hearing loss, loss of taste or smell, impaired mobility, numbness in extremities, tremors, myalgia, memory loss, cognitive impairment, and mood changes for up to 3 months after diagnosis of COVID-19.<sup>51-53</sup> One study in the United Kingdom administered cognitive tests to 84,285 participants who had recovered from suspected or confirmed SARS-CoV-2 infection. These participants had worse performances across multiple domains than would be expected for people with the same ages and demographic profiles; this effect was observed even among those who had not been hospitalized.<sup>54</sup> However, the study authors did not report when the tests were administered in relation to the diagnosis of COVID-19.

More research and more rigorous observational cohort studies are needed to better understand the pathophysiology and clinical course of post-acute COVID-19 sequelae and to identify management strategies for patients. More information about ongoing studies can be found at [ClinicalTrials.gov](https://www.clinicaltrials.gov).

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