

# Overview of COVID-19

Last Updated: December 17, 2020

## Epidemiology

The COVID-19 pandemic has exploded since cases were first reported in China in December 2019. As of December 5, 2020, more than 66 million cases of COVID-19—caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection—have been reported globally, including more than 1.5 million deaths.<sup>1,2</sup>

Individuals of all ages are at risk for 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 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>3</sup> The percentage of patients who died was 12 times higher (19.5% vs. 1.6%) and the percentage of patients who were hospitalized was six times higher (45.4% vs. 7.6%) in those with reported medical conditions than in those without medical conditions. 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, obesity, sickle cell disease, and other immunocompromising conditions. Transplant recipients and pregnant people are also at a higher risk of severe COVID-19.<sup>2,4-10</sup>

Emerging 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>2,16</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>

## 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>6,18,19</sup> The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) and death. Among 72,314 persons 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, saturation of oxygen [ $\text{SpO}_2$ ]  $\leq 93\%$ , a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [ $\text{PaO}_2/\text{FiO}_2$ ]  $< 300$  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>20</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>3</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 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.<sup>21</sup> Imaging may be normal early in infection and can be abnormal in the absence of symptoms.<sup>21</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.

While COVID-19 is primarily a pulmonary disease, emerging data suggest that it also leads to cardiac,<sup>22,23</sup> dermatologic,<sup>24</sup> hematological,<sup>25</sup> hepatic,<sup>26</sup> neurological,<sup>27,28</sup> renal,<sup>29,30</sup> and other complications. Thromboembolic events also occur in patients with COVID-19, with the highest risk occurring in critically ill patients.<sup>31</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>32,33</sup> Please see [Special Considerations in Children](#) for more information.

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# Testing for SARS-CoV-2 Infection

Last Updated: February 11, 2021

## Summary Recommendations

- To diagnose acute infection of severe acute respiratory syndrome coronavirus 2 (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., 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)**.
- In asymptomatic persons, a NAAT should not be repeated within 90 days of previous SARS-CoV-2 infection, even following a significant exposure to SARS-CoV-2 **(AIII)**.
- Because of reports of SARS-CoV-2 reinfection after an initial diagnosis of infection, a NAAT should be considered for persons who have recovered from previous infection and present with symptoms compatible with SARS-CoV-2 infection, in the absence of an 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 (see below for details) **(AIII)**.

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

**Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, 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 severe acute respiratory syndrome coronavirus 2 (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) issued by 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. Testing of other sample types, including stool samples, is currently being studied.

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 for collection and testing of specimens by trained personnel 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., real-time 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. However, false negative NAAT results can also occur outside of this 5-day window. Therefore, a single negative test result does not completely exclude SARS-CoV-2 infection in people with a high likelihood of infection based on their exposure history and/or their clinical presentation, and repeat testing using a NAAT should be considered.<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 NAAT, 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>4-10</sup> For intubated or mechanically ventilated patients with clinical signs and symptoms 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***

NAAT can detect SARS-CoV-2 RNA in specimens obtained weeks to months after the onset of COVID-19 symptoms.<sup>11,12</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>13,14</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>15,16</sup> On the basis of these results, the [Centers for Disease Control and Prevention \(CDC\)](https://www.cdc.gov) recommends that NAAT should not be repeated in asymptomatic persons within 90 days of previous infection, even following a significant exposure to SARS-CoV-2 (**AIII**).<sup>17</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. Because of reports of SARS-CoV-2 reinfection after an initial diagnosis of SARS-CoV-2 infection, NAAT should be considered in those who have recovered from previous infection and present with compatible symptoms of SARS-CoV-2 infection in the absence of an 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>11</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 persistent presence of viral fragments and reinfection. In the absence of viral sequence data, the cycle threshold (Ct) value from a positive NAAT 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 obtained 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. CDC has developed an antigen testing algorithm for persons who have symptoms of COVID-19, persons who are asymptomatic and have a close contact with COVID-19, and persons who are asymptomatic and have no known exposure to a person with COVID-19.<sup>18</sup>

The CDC testing algorithm recommends additional NAAT testing when a person who is strongly suspected of having SARS-CoV-2 infection (i.e., 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, such as 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 (i.e., development of detectable immunoglobulin [Ig] M and/or IgG antibodies to SARS-CoV-2) to occur,<sup>19-24</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 issued by 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, including the sensitivity and specificity (i.e., the rates of true positive and true negative results) of many of the commercially available serologic tests, have not been fully characterized. 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 serologic tests are performed and SARS-CoV-2 antibodies are detected, 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 tests 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 glycoprotein), 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 response 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 currently available under EUA or in late-stage clinical trials, serologic tests that detect antibodies recognizing nucleocapsid protein can be used to distinguish natural infection from vaccine-induced antibody responses.
- Determine who may be eligible to donate convalescent plasma.
- Estimate the proportion of the population 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 and Prophylaxis of SARS-CoV-2 Infection

Last Updated: February 11, 2021

Summary Recommendations
<ul style="list-style-type: none"><li>• The COVID-19 Treatment Guidelines Panel (the Panel) <b>recommends against</b> the use of any drugs for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pre-exposure prophylaxis (PrEP), except in a clinical trial (<b>AIII</b>).</li><li>• The Panel <b>recommends against</b> the use of <b>hydroxychloroquine</b> for SARS-CoV-2 post-exposure prophylaxis (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 recommends that health care providers follow recommendations from the Advisory Committee on Immunization Practices when using SARS-CoV-2 vaccines (<b>AI</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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is thought to mainly occur through respiratory droplets transmitted from an infectious person to others within six feet of the person. Less commonly, airborne transmission of small droplets and particles of SARS-CoV-2 can occur at distances greater than six feet, and 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 (more than 30 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 six feet from others. When consistent distancing is not possible, face coverings may further 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 appropriate use of personal protective equipment (PPE).<sup>3</sup>

## Vaccines

Currently, no SARS-CoV-2 vaccine has been approved by the Food and Drug Administration (FDA). In December 2020, the FDA issued Emergency Use Authorizations for two mRNA vaccines, BNT162b2 (Pfizer-BioNTech)<sup>4</sup> and mRNA-1273 (Moderna).<sup>5</sup> BNT162b2 can be administered to individuals aged  $\geq 16$  years, whereas mRNA-1273 can be given to individuals aged  $\geq 18$  years.

In large, placebo-controlled trials, these vaccines were 94% to 95% efficacious in preventing COVID-19 after participants completed a two-dose series. Cases of COVID-19 were confirmed by the presence of symptoms and a positive result on a nucleic acid amplification test (NAAT).<sup>6,7</sup> Both vaccines also showed efficacy against severe COVID-19. Local and systemic adverse events are relatively common with these vaccines, especially after the second dose; most adverse events were mild or moderate in severity (i.e., they did not prevent recipients from engaging in daily activities). There have been a few reports of severe allergic reactions, including some reports of patients who experienced anaphylaxis after receiving a SARS-CoV-2 mRNA vaccine.<sup>8</sup> Safety data continue to be collected. Certain populations, such as pregnant and lactating individuals, were not included in the initial vaccine trials. The American College of Obstetricians and Gynecologists has published interim guidance on the use of the SARS-CoV-2 mRNA vaccines in pregnant and lactating people.<sup>9</sup>

It is not known how long SARS-CoV-2 vaccines' protective effect will last or whether SARS-CoV-2 vaccines can prevent asymptomatic infection or transmission, whether they will prevent infection by all current or emergent strains of SARS-CoV-2, whether they will be effective in immunocompromised patients, or whether they will work as well in patients that are at high risk for severe COVID-19 as in those who are at low risk. The efficacy and safety of SARS-CoV-2 vaccines have not been established in children, pregnant people, or immunocompromised patients. Clinical trials for other SARS-CoV-2 vaccine candidates are ongoing.

CDC sets the U.S. adult and childhood immunization schedules based on recommendations from the Advisory Committee on Immunization Practices (ACIP). ACIP considers disease epidemiology, burden of disease, vaccine efficacy and effectiveness, vaccine safety, the quality of the available evidence, and potential implementation issues. ACIP also sets priorities regarding who receives vaccines in the event of a shortage. ACIP COVID-19 vaccine recommendations are reviewed by CDC's Director and, if adopted, are published as official CDC recommendations in the *Morbidity and Mortality Weekly Report*.<sup>10</sup>

## Pre-Exposure Prophylaxis

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of any drugs for SARS-CoV-2 pre-exposure prophylaxis (PrEP), except in a clinical trial (AIII).

### *Rationale*

At present, there is no known agent that can be administered before exposure to SARS-CoV-2 (i.e., as PrEP) to prevent infection. 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 monoclonal antibodies that target SARS-CoV-2 are in development. Please check [ClinicalTrials.gov](https://clinicaltrials.gov) for the latest information.

### *Clinical Trial Data*

#### **Randomized Controlled Trial of Hydroxychloroquine for SARS-CoV-2 Pre-Exposure Prophylaxis Among Health Care Workers**

This randomized, double-blind, placebo-controlled trial was designed to determine whether hydroxychloroquine 600 mg per day reduced the frequency of SARS-CoV-2 infection over an 8-week period in hospital-based health care workers. The primary outcome was incidence of SARS-CoV-2 infection as determined by reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasopharyngeal swabs collected at 4 and 8 weeks or the occurrence of COVID-19 symptoms.<sup>11</sup>

#### *Study Population*

- Participants included health care workers at two Philadelphia hospitals who worked  $\geq 20$  hours per week in a hospital-based unit, had no known history of SARS-CoV-2 infection, and had no COVID-19-like symptoms in the 2 weeks before enrollment. The study enrolled workers in the emergency department and in dedicated COVID-19 treatment units.
- The study excluded individuals who were allergic to hydroxychloroquine and those with glucose-6-phosphate dehydrogenase deficiency, retinal disease, or substantial cardiac disease.

#### *Results*

- The study was based on the assumption of a 10% infection rate for the planned inclusion of 100 participants per arm.
- Between April 9 and July 14, 2020, community infection rates declined. At the time of the second

interim analysis (when 125 of 132 participants who provided consent were evaluable for the primary endpoint), the Data Safety Monitoring Board recommended early termination of the study for futility.

- Four participants in each group developed SARS-CoV-2 infection (positivity rate of 6.3% vs. 6.6% in the hydroxychloroquine and placebo groups, respectively;  $P > 0.99$ ). Across the groups, six individuals developed symptoms of COVID-19, but none required hospitalization.
- Serologic testing for anti-spike protein immunoglobulin (Ig) M, IgG, and nucleocapsid protein IgG demonstrated more positive results among participants in the hydroxychloroquine group (four participants [7.4%]) than in the placebo group (two participants [3.7%]), although the difference was not statistically significant ( $P = 0.40$ ).
- Mild adverse events were more common among participants in the hydroxychloroquine group than in the placebo group (45% vs. 26%;  $P = 0.04$ ). The greatest difference was the increased frequency of mild diarrhea in the hydroxychloroquine group.
- The rates of treatment discontinuation were similar in the hydroxychloroquine group (19%) and the placebo group (16%).
- There were no cardiac events in either arm and no significant difference in the median frequency of changes in QTc between the study arms ( $P = 0.98$ ).

### *Limitations*

- The study was stopped early.
- Due to the low SARS-CoV-2 infection rate among the participants, the study was underpowered to detect a prophylactic benefit of hydroxychloroquine.
- The study population was mostly young, healthy health care workers; therefore, the applicability of the study findings to other populations is uncertain.

### *Interpretation*

There was no clinical benefit of administering hydroxychloroquine 600 mg per day for 8 weeks as PrEP among health care workers who were exposed to patients with COVID-19. Compared to placebo, hydroxychloroquine was associated with an increased risk of mostly mild adverse events.

### **Hydroxychloroquine as Pre-Exposure Prophylaxis for COVID-19 in Health Care Workers: a Randomized Trial (COVID PREP Study)**

This was a randomized, double-blind, placebo-controlled clinical trial to evaluate whether hydroxychloroquine 400 mg given once- or twice-weekly for 12 weeks (compared to placebo) can prevent SARS-CoV-2 infection in health care workers at high-risk of exposure. The primary outcome was COVID-19-free survival time. Diagnosis of COVID-19 was defined as having laboratory-confirmed SARS-CoV-2 infection or having cough, shortness of breath, or difficulty breathing or having two or more of the following symptoms: fever, chills, rigors, myalgia, headache, sore throat, or new olfactory and taste disorders. COVID-19-compatible illness was included as a primary outcome even if a SARS-CoV-2 PCR test was not performed or if it was performed and the result was negative.<sup>12</sup>

### *Study Population*

- The study participants had to be working in the emergency department, in the intensive care unit, on a dedicated COVID-19 hospital ward, or as a first responder; alternatively, they had to have a job description that included regularly performing aerosol-generating procedures.
- Participants were recruited via social media platforms. Informed consent was obtained remotely,

and the study drug was delivered to the participants by couriers.

### *Results*

- The study was powered based on an anticipated 10% event rate of new symptomatic infections. The investigators determined that the study needed to enroll 1,050 participants per arm to have 80% power. However, it became apparent before the first interim analysis that the study would not meet the enrollment target. As a result, enrollment was stopped without unblinding. The investigators attributed the marked decline in enrollment to the negative reports related to the safety of hydroxychloroquine, including a warning from the FDA.
- Among the 1,483 participants who were randomized, baseline characteristics were similar across the study arms.
- The number of individuals who met the primary endpoint of confirmed or suspected SARS-CoV-2 infection was 39 (7.9%) in the placebo group and 29 (5.9%) in both the once- and twice-weekly hydroxychloroquine groups. Among the 97 participants, only 17 were confirmed to be SARS-CoV-2 PCR positive.
- Compared to placebo, the hazard ratio for the primary endpoint was 0.72 (95% CI, 0.4–1.16;  $P = 0.18$ ) for the once-weekly hydroxychloroquine arm and 0.74 (95% CI, 0.46–1.19;  $P = 0.22$ ) for the twice-weekly hydroxychloroquine arm.
- There were no significant differences for any of the secondary efficacy endpoints among the three groups.
- There were significantly more adverse events reported in the once- and twice-weekly hydroxychloroquine arms (31% vs. 36% of participants experienced adverse events;  $P < 0.001$  for both groups) than in the placebo group (21% of participants). The most common side effects were upset stomach and nausea.
- Drug concentrations were measured in dried whole blood samples from a subset of 180 participants who received hydroxychloroquine. The median hydroxychloroquine concentrations for the twice- and once-weekly hydroxychloroquine groups were 200 ng/mL and 98 ng/mL, respectively; both of these concentrations are substantially below the in vitro half-maximal effective concentration ( $EC_{50}$ ) of hydroxychloroquine. The investigators noted that the simulations that were used to determine the hydroxychloroquine dose for the study predicted much higher drug concentrations than the observed levels.

### *Limitations*

- The study was prematurely halted due to poor enrollment; therefore, the study population was insufficient to detect differences in outcomes among the study arms.
- The study only assessed the SARS-CoV-2 inhibitory activity of two doses of hydroxychloroquine, neither of which achieved concentrations that exceeded the in vitro  $EC_{50}$  of the drug.
- Only 17.5% of the participants who met study endpoints had positive SARS-CoV-2 test results; the remainder had compatible symptoms without a confirmatory diagnosis.

### *Interpretation*

Administering hydroxychloroquine 400 mg once- or twice-weekly did not reduce the number of people with documented SARS-CoV-2 infection or symptoms that were compatible with COVID-19 among health care workers who were at a high risk of infection. These findings suggest that hydroxychloroquine was not effective for SARS-CoV-2 PrEP or that the dose used for this indication was suboptimal.

## Post-Exposure Prophylaxis

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

### *Rationale*

At present, there are no known agents that have been shown to be efficacious in preventing infection after exposure to SARS-CoV-2 infection (i.e., as PEP). Several randomized controlled trials have evaluated the use of hydroxychloroquine for SARS-CoV-2 PEP.<sup>13-15</sup> None of these studies have reported any evidence of efficacy, and all showed an increased risk of adverse events among participants who received hydroxychloroquine compared to controls. A number of agents (e.g., anti-SARS-CoV-2 monoclonal antibodies, hyperimmune gammaglobulin, convalescent plasma, ivermectin, interferons, tenofovir with or without emtricitabine, vitamin D) are currently being investigated for SARS-CoV-2 PEP. Please check [ClinicalTrials.gov](https://clinicaltrials.gov) for the latest information.

### *Clinical Trial Data*

Both chloroquine and hydroxychloroquine have in vitro activity against severe acute respiratory syndrome-associated coronavirus (SARS-CoV) and SARS-CoV-2.<sup>16,17</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>18</sup>

### **Household-Randomized, Double-Blind, Controlled Trial of SARS-CoV-2 Post-Exposure Prophylaxis With Hydroxychloroquine**

A household-randomized, double-blind, controlled trial evaluated the use of hydroxychloroquine as PEP to prevent SARS-CoV-2 infection. The study was conducted at seven institutions in the United States between March and August 2020. Participants were recruited using online advertising, social media, and referrals from hospitals, health departments, and those with laboratory-confirmed SARS-CoV-2 infection.<sup>13</sup>

Households were randomized to receive oral hydroxychloroquine 400 mg once daily for 3 days, followed by hydroxychloroquine 200 mg once daily for an additional 11 days, or oral ascorbic acid 500 mg once daily for 3 days, followed by ascorbic acid 250 mg once daily for 11 days. Mid-turbinate nasal swabs were collected daily during the first 14 days, with the primary endpoint being PCR-confirmed SARS-CoV-2 infection during the first 14 days after enrollment in those who were not infected at baseline.

### *Study Population*

- Eligible participants had close contact with an infected person, which included household contacts or other close contacts (82%) or health care workers (18%) who cared for an infected person without wearing appropriate PPE. Participants must have come into contact with an index person who had received a diagnosis of SARS-CoV-2 infection within the past 14 days, and high-risk exposure to the index people must have occurred within the previous 96 hours.
- Enrollment included 829 participants from 671 households; 407 participants (in 337 households) received hydroxychloroquine, and 422 participants (in 334 households) received ascorbic acid.

### *Results*

- A total of 98 SARS-CoV-2 infections were detected during the first 14 days of follow-up, with an

overall cumulative incidence of 14.3% (95% CI, 11.5% to 17%). Fifty-three events occurred in the hydroxychloroquine group, and 45 events occurred in the control group (aHR 1.10; 95% CI, 0.73–1.66;  $P > 0.20$ )

- In preplanned analyses, hazard ratios were not significantly different within subgroups based on type of contact, time between the most recent contact and the first dose of the study drug, duration of contact, number of contacts enrolled within the household, quarantine status, index case symptoms, or number of adults or children in the household.
- Adverse events that are associated with the use of hydroxychloroquine, including gastrointestinal symptoms and rash, occurred in 112 participants: 66 participants (16.2%) in the hydroxychloroquine group and 46 participants (10.9%) in the control group ( $P = 0.026$ ).

### *Limitations*

- There was an average window of 2 days between the time of the most recent exposure and the time the study drugs were administered, which may have affected the efficacy of hydroxychloroquine if early initiation is important for efficacy.
- The primary analysis excluded approximately 10% of enrolled people who were shown to be infected at baseline.

### *Interpretation*

In this study, hydroxychloroquine was ineffective when used as PEP for SARS-CoV-2 infection. Participants who received hydroxychloroquine had an expected increased risk of adverse events when compared to those who received ascorbic acid.

### **Randomized, Double-Blind, Controlled Trial of High-Risk or Moderate-Risk Occupational or Household Exposures**

This randomized, double-blind, controlled trial included 821 participants who self-enrolled in the study using an internet-based survey. Participants were randomized to receive either hydroxychloroquine 800 mg given once, followed by hydroxychloroquine 600 mg given 6 to 8 hours later, and then hydroxychloroquine 600 mg given once daily for 4 additional days or placebo. Because enrollment was done online, study drugs were sent by overnight mail, resulting in more than 50% of participants initiating the first dose of their assigned treatment 3 to 4 days after exposure to SARS-CoV-2.<sup>15</sup>

### *Study Population*

- Participants had a high or moderate risk of occupational exposure (66% of participants) or household exposure (34% of participants) to SARS-CoV-2.
- High-risk exposure was defined as being within six feet of an individual with confirmed SARS-CoV-2 infection for more than 10 minutes while not wearing a face mask or eye shield (87.6% of participants). Moderate-risk exposure was defined as the same distance and duration of exposure while wearing a face mask but no eye shield (12.4% of participants).

### *Results*

- A total of 107 participants developed the primary outcome of symptomatic illness. Illness was confirmed by a positive result on a SARS-CoV-2 molecular test; if testing was not available, participants were considered to have symptomatic illness if they developed a compatible COVID-19-related syndrome based on CDC criteria.
- Due to limited access to molecular diagnostic testing, SARS-CoV-2 infection was confirmed in only 16 of the 107 participants (15%). There was no statistically significant difference in the incidence of the primary outcome (symptomatic illness) between the hydroxychloroquine group

and the placebo group (11.8% vs. 14.3%;  $P = 0.35$ ).

- There were more adverse events in the hydroxychloroquine group (mostly nausea, loose stools, and abdominal discomfort), with no serious adverse reactions or cardiac arrhythmias.

### *Limitations*

- Initiation of therapy was delayed for at least 3 days after exposure to SARS-CoV-2 in most participants.
- Only 15% of participants who reached the primary outcome had SARS-CoV-2 infection confirmed by molecular diagnostics.
- The study population was young (with a median age of 40 years) and consisted of participants who had a relatively low risk of severe COVID-19.

### *Interpretation*

There was no difference in the incidence of observed symptomatic COVID-19 between participants who received hydroxychloroquine 600 mg once daily and those who received placebo. Although hydroxychloroquine 600 mg per day was associated with an increase in the frequency of adverse events, these adverse events were mostly mild.

### **Cluster-Randomized Trial of High-Risk Exposures in Spain**

This open-label, cluster-randomized trial included 2,314 asymptomatic contacts of 672 COVID-19 cases in Spain.<sup>14</sup> Participants who were epidemiologically linked to a PCR-positive COVID-19 case were defined as study clusters (called rings). All contacts in a ring were simultaneously cluster-randomized 1:1 to receive usual care (the control arm) or hydroxychloroquine 800 mg once daily for 1 day followed by hydroxychloroquine 400 mg once daily for 6 days (the intervention arm). Participants were informed of their allocated study arm after being randomized to the intervention or control arm and signing a consent form.

The primary outcome was onset of laboratory-confirmed COVID-19, defined as a positive result on a SARS-CoV-2 PCR test and at least one of the following symptoms: fever, cough, difficulty breathing, myalgia, headache, sore throat, new olfactory and taste disorders, or diarrhea. A secondary outcome was onset of SARS-CoV-2 infection, defined as either a positive SARS-CoV-2 PCR test result or the presence of any of the symptoms compatible with COVID-19. An additional secondary outcome was development of serological positivity at Day 14.

### *Study Population*

- Study participants were health care or nursing home workers (60.3%), household contacts (27.1%), or nursing home residents (12.7%) who were documented to have spent >15 minutes within two meters of a PCR-positive COVID-19 case during the 7 days prior to enrollment.
- The baseline characteristics of the participants were similar between the two study arms, including comorbidities, number of days of exposure to SARS-CoV-2 before enrollment and randomization, and type of contact.

### *Results*

- A total of 138 study participants (6.0%) developed PCR-confirmed, symptomatic SARS-CoV-2 infection, with no statistical difference for this outcome between the control and intervention arms (6.2% vs. 5.7%; risk ratio 0.86; 95% CI, 0.52–1.42).
- There was no statistical difference between the study arms in the incidence of either PCR-confirmed or symptomatically compatible COVID-19, which occurred in 18.2% of participants:

17.8% in the control arm and 18.7% in the intervention arm (risk ratio 1.03; 95% CI, 0.77–1.38).

- There was no statistical difference between the arms in the rate of positivity for SARS-CoV-2 IgM and/or IgG (8.7% in the control arm vs. 14.3% in the intervention arm; risk ratio 1.57; 95% CI, 0.94–2.62).
- There were more adverse events among the hydroxychloroquine-treated participants (56.1%) than among the controls (5.9%), although most of the adverse events were mild. Common adverse events included gastrointestinal events, nervous system disorders, myalgia, fatigue, and malaise. No serious adverse events were attributed to the study drug.

### Limitations

- The study lacked a placebo comparator, which could have had an impact on safety reporting.
- Data regarding the extent of the exposure to the index cases was limited.
- For >50% of the study participants, the time from exposure to the index case to randomization was  $\geq 4$  days.

### Interpretation

The hydroxychloroquine regimen used for PEP in this study did not prevent SARS-CoV-2 infection in healthy individuals who were exposed to a PCR-positive case.

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# Clinical Spectrum of SARS-CoV-2 Infection

Last Updated: December 17, 2020

Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can experience a range of clinical manifestations, from no symptoms to critical illness. This section of the Guidelines discusses the clinical presentation of patients according to illness severity.

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 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 saturation of oxygen ( $\text{SpO}_2$ )  $\geq 94\%$  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, respiratory frequency  $> 30$  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 65 years or older; having cardiovascular disease, chronic lung disease, sickle cell disease, diabetes, cancer, obesity, or chronic kidney disease; being pregnant; being a smoker; and being a recipient of transplant or 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 chest X-ray, ultrasound, or, if indicated, computerized tomography. 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. While not part of standard care, measuring the levels of inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin 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 and for 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 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

individual 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 category. The normal values for respiratory rate also vary with age in children; thus, hypoxia should be the primary criterion used to define severe illness, 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> The availability of widespread virologic testing for SARS-CoV-2 and the development of reliable serologic assays for antibodies to the virus will help determine the true prevalence of asymptomatic and presymptomatic infection. See [Therapeutic Management of Patients 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 Patients 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 Patients 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, a respiratory rate of  $> 30$  breaths/min,  $\text{PaO}_2/\text{FiO}_2 < 300$  mm Hg, 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 Patients 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, elevation in levels of multiple inflammatory cytokines that provoke a cytokine storm, 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 Patients 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. At this time, there is limited information on the prevalence, duration, underlying causes, and effective management strategies for these lingering signs and symptoms.<sup>12</sup> The nomenclature for this phenomenon is evolving, but it has been referred to as “postacute COVID-19 syndrome” or “long COVID,” and affected patients have been referred to as “long haulers.” The incidence, natural history, and etiology of these symptoms are currently unknown. Currently, there is no case definition for postacute COVID-19 syndrome, and no specific time frame has been established to define late sequelae of COVID-19. However, the Centers for Disease Control and Prevention (CDC) recently proposed defining late sequelae as sequelae that extend beyond 4 weeks after initial infection.<sup>13,14</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>15,16</sup>

Common persistent symptoms include fatigue, joint pain, chest pain, palpitations, shortness of breath, cognitive impairment, and worsened quality of life.<sup>17,18</sup> The 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; 26% of these patients were aged 18 to 34 years (n = 85), 32% were aged 35 to 49 years (n = 96), and 47% were aged  $\geq 50$  years (n = 89).<sup>16</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 achieved baseline health when interviewed at a median of 16 days from the testing date.

Persistent symptoms have also been reported in pregnant people.<sup>19</sup> Systematic data on persistent symptoms in children following recovery from the acute phase of COVID-19 are not currently available.<sup>20</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 (CFQ-11). More than half of patients reported persistent fatigue at a median of 10 weeks after initial symptoms first appeared (67 of 128 patients; 52.3%). There was no association between illness severity and fatigue.<sup>21</sup> A postacute outpatient

service developed in Italy reported that 87% of 143 patients surveyed reported persistent symptoms at a mean of 60 days after symptom onset, with the most common symptom being fatigue (which occurred in 53.1% of these patients).<sup>22</sup>

### ***Cardiopulmonary***

A study from the United Kingdom reported that among 100 hospitalized patients (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>17</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%).<sup>23</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>24</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>25</sup> One should review these data and assess the prevalence of cardiac abnormalities in people with postacute COVID-19 syndrome with caution, however, as the results were likely biased by only including 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>18,26</sup> Younger patients have been reported to experience more psychiatric symptoms than patients aged >60 years.<sup>17,18</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>27,28</sup> One study in the United Kingdom administered cognitive tests to 84,285 participants who had recovered from suspected or confirmed cases of SARS-CoV-2 infection. These participants had worse performances across multiple domains than would be expected for people with the given age and demographic profiles; this effect was observed even among those who had not been hospitalized.<sup>29</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 these postinfection sequelae and to identify management strategies for patients. More information about ongoing studies can be found at [ClinicalTrials.gov](https://clinicaltrials.gov).

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