The Coronavirus Disease (COVID-19) Pandemic

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Answer Sheet/Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty
John M. Leonard, MD, Professor of Medicine Emeritus, Vanderbilt University School of Medicine, completed his post-graduate clinical training at the Yale and Vanderbilt University Medical Centers before joining the Vanderbilt faculty in 1974. He is a clinician-educator and for many years served as director of residency training and student educational programs for the Vanderbilt University Department of Medicine. Over a career span of 40 years, Dr. Leonard conducted an active practice of general internal medicine and an inpatient consulting practice of infectious diseases.

Faculty Disclosure
Contributing faculty, John M. Leonard, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
Mark J. Szarejko, DDS, FAGD

Director of Development and Academic Affairs
Sarah Campbell

Division Planner/Director Disclosure
The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience
This course is designed for dental professionals who may identify or educate patients regarding coronavirus infection.

Accreditations & Approvals
NetCE is an ADA CERP Recognized Provider.

ADA CERP is a service of the American Dental Association to assist dental professionals in identifying quality providers of continuing dental education. ADA CERP does not approve or endorse individual courses or instructors, nor does it imply acceptance of credit hours by boards of dentistry.

Concerns or complaints about a CE provider may be directed to the provider or to ADA CERP at www.ada.org/cerp.

NetCE
Nationally Approved PACE Program Provider for FAGD/MAGD credit.
Approval does not imply acceptance by any regulatory authority or AGD endorsement.
10/1/2021 to 9/30/2027
Provider ID #217994.

NetCE is a Registered Provider with the Dental Board of California. Provider number RP3841. Completion of this course does not constitute authorization for the attendee to perform any services that he or she is not legally authorized to perform based on his or her permit type.

NetCE is approved as a provider of continuing education by the Florida Board of Dentistry, Provider #50-2405.

A complete Works Cited list begins on page 48.

Mention of commercial products does not indicate endorsement.

Designations of Credit

NetCE designates this activity for 2 continuing education credits.

AGD Subject Code: 148.

This course meets the Dental Board of California's requirements for 2 units of continuing education.

Dental Board of California course #02-3841-00384.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

The purpose of this course is to provide physicians, nurses, and other healthcare professionals an overview of the 2019–2020 global outbreak of novel human coronavirus (SARS-CoV-2) infection, including background epidemiology, clinical features, mode of transmission, epidemic potential, and the clinical and public health measures recommended to limit spread of infection and control the outbreak.

Learning Objectives

Upon completion of this course, you should be able to:

1. Differentiate between the common, ubiquitous strains of human coronavirus and novel (outbreak) strains with respect to epidemiology, modes of transmission, spectrum of illness, and public health implications.
2. Recognize clinical manifestations of acute COVID-19 and the "long COVID" syndrome, and anticipate systemic complications of severe disease in those with known risk factors.
3. Implement guideline recommendations for diagnostic testing and management of patients with recent exposure, newly diagnosed, or suspected COVID-19.
4. Discuss the dynamics of SARS-CoV-2 transmission and advise patients as to preventive measures (e.g., social distancing, masking) and the role of COVID-19 vaccines, giving special attention to those at risk for severe disease.
5. Explain public health implications of emerging SARS-CoV-2 variants, including benefits and limitations of natural, vaccine, and hybrid immunity.

BACKGROUND

CORONAVIRUS

Coronaviruses (a subfamily of Coronaviridae) are enveloped, single-stranded RNA viruses that are broadly distributed among humans, other mammals, and birds. Under electron microscopy, the outer envelope of the virion shows club-like surface projections that confer a crown-like appearance to the virus, which accounts for the name given to this family of viruses. The nucleocapsid is a long, folded strand that tends to spontaneous mutations and recombination of genomic material. When virus circulation (and replication) is high, the opportunity for random mutations within the genome grows, increasing the likelihood that such changes may impact transmissibility and pathogenicity.

In addition to four specific subtypes of coronavirus commonly found in humans, other strains are specific to many different species of animals, including bats, cats, camels, and cattle. On rare occasions, an animal coronavirus causes zoonotic infection in humans, meaning that a new (novel) coronavirus is transmitted from an animal host to one or more humans, resulting in clinical illness and the risk of secondary spread to close personal contacts. The wide distribution, genetic diversity, and frequent shifts in the genome, combined with unique human-animal interface activities, are considered important factors for novel coronavirus outbreaks in human populations [1; 2].

HUMAN CORONAVIRUS INFECTION

Common Strains

Human coronavirus (HCoV) was first identified in 1965, isolated from a patient with what was described as the common cold [3]. Subsequently, four types of HCoV have been detected frequently in respiratory secretions from children and adults in scattered regions of the globe, labeled HCoV-229E, -NL63, -OC43, and -HKU1. These agents are a common cause of mild-to-moderate upper respiratory illness, including common cold, bronchitis, bronchiolitis in infants and children, and asthma exacerbation. Rarely, HCoVs have been implicated in lower respiratory tract infection (viral pneumonia), a complication more common to persons with underlying cardiopulmonary disease or weakened immune systems.

Novel Coronavirus Outbreaks

In addition to the seasonal infections caused by the ambient, adaptive HCoVs described, widespread outbreaks of novel coronavirus infection have occurred in each of the past two decades, and the 2019–2020 Wuhan, China, outbreak poses the third threat of a severe novel coronavirus epidemic on a global scale [1; 4]. The epidemiologic feature common to these outbreaks is an initial point source cluster of zoonotic infection followed by secondary spread of the virus via human-to-human transmission. Among the factors thought to be conducive to the emergence of such outbreaks are the following: genomic recombination in an animal CoV capsid that renders the virus better adapted to human infection (and perhaps more virulent); and dietary practices and cultural determinants that bring humans into close contact with livestock or raw meat and carcasses of wild animals and birds, thereby facilitating transmission from an infected animal host to humans. After infection is established, secondary viral transmission occurs through close person-to-person contact by way of droplet nuclei propelled into the air during coughing and sneezing. The first two known novel coronavirus outbreaks, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, are considered to be zoonotic in origin and were associated with serious, sometimes fatal illness.

Severe Acute Respiratory Syndrome (SARS-CoV)

Infection with SARS-CoV was first recognized in China in November 2002, and signs of an outbreak in Asia were evident by February 2003 [3]. Epidemiologic investigation found that early cases of SARS-CoV were zoonotic infection involving transmission from civet cats to humans. Over the next several months, SARS-CoV spread to countries in North America, South America, Europe, and other parts of Asia before the global outbreak was contained later in the same year.

SARS-CoV infection began with fever, headache, malaise, and arthralgia/myalgia followed in two to seven days by cough, shortness of breath, and signs of pneumonia [3].

According to the World Health Organization (WHO), the 2002–2003 outbreak caused 8,098 probable cases of SARS worldwide and 774 deaths. Just eight cases were identified in the United States. Since 2004, no additional known cases of SARS-CoV infection have been reported anywhere in the world [3].

In response to the 2003 global SARS outbreak, the Centers for Disease Control and Prevention (CDC), working in concert with the WHO, developed a strategy for controlling the epidemic that included the following elements [3]:

- Activated the Emergency Operations Center to provide around-the-clock coordination and response.
- Committed more than 800 medical experts and support staff to work on the SARS response and to assist with ongoing investigations around the world.
- Provided assistance to state and local health departments in investigating possible cases of SARS in the United States.
- Conducted extensive laboratory testing of clinical specimens from patients with SARS to identify the cause of the disease.
- Initiated a system for distributing health alert notices to travelers who may have been exposed to cases of SARS.

This experience informed the rapid public health response to the 2019–2020 coronavirus outbreak in China.

Middle East Respiratory Syndrome (MERS-CoV)

MERS-CoV was first reported in Saudi Arabia in 2012, and all cases to date have been linked to countries in or near the Arabian Peninsula. Travel-associated cases of MERS-CoV infection have been reported in many countries, including two imported cases diagnosed in the United States in 2014 involving unlinked healthcare providers recently returned from Saudi Arabia. Two modes of transmission have been identified: zoonotic infection from an animal reservoir to humans (with camels acting as the intermediate host), and person-to-person transmission via close contact with an index case, as described in association with a family case cluster and a nosocomial outbreak [5; 6; 7].

Most persons with confirmed MERS-CoV infection have had moderately severe respiratory illness manifest by fever, cough, and shortness of breath, often complicated by pneumonia and respiratory failure. The case-fatality rate approaches 40%. Most deaths have been in patients with pre-existing chronic conditions such as diabetes, cancer, or heart, lung, or renal disease. Sporadic cases of MERS-CoV continue to appear in various parts of the Middle East [3].

THE 2019–2020 NOVEL CORONAVIRUS OUTBREAK: A GLOBAL THREAT

In December 2019, Chinese physicians in Hubei Province, China, began an investigation of a cluster of cases of severe viral pneumonia in area hospitals. In the weeks following, it became evident that a large outbreak of respiratory illness was rapidly emerging within Wuhan City and nearby communities, reaching the thousands by mid-January.

On January 24, scientists in Wuhan City, China, reported clinical and diagnostic findings of viral studies conducted on bronchoalveolar lavage specimens from three patients with severe bilateral interstitial, alveolar pneumonia [2]. The investigation identified a viral genome matched to lineage B of the genus betacoronavirus, showing more than 85% match with a SARS-like CoV genome previously described in bats. Ultrathin sections of infected human airway epithelial cells showed inclusion bodies filled with virus particles in membrane-bound vesicles in the cytoplasm. The morphology of the virion on electron microscopy is consistent with the Coronaviridae family. This newly identified coronavirus was responsible for a widespread outbreak of severe respiratory illness in Wuhan City, beginning December 2019.

The novel Wuhan coronavirus was named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The disease caused by SARS-CoV-2 is referred to as coronavirus infectious disease-2019 (COVID-19). Like SARS-CoV and MERS-CoV, SARS-CoV-2 is a betacoronavirus that likely had its origin in bats, with one or more animals serving as the intermediate host. The actual source and timing of initial human infection is unclear. Evidence appears to support origin from a large wet market that deals in exotic animals; however, this does not definitively exclude other hypotheses, including a local, state-sponsored virology laboratory that conducts basic research on animal coronaviruses [120]. CDC investigation of initial SARS-CoV-2 cases imported into the United States found that virus sequences were similar to the one posted by China, indicating emergence of this virus from a point-source in Wuhan, China [12].

The rapid spread of COVID-19 in Wuhan City, followed by cases in nearby provinces of central China and acute infection in healthcare workers, indicated that facile human-to-human transmission of SARS-CoV-2 was the key factor responsible for propagation of the outbreak. Within weeks, cases of confirmed COVID-19 were identified in multiple countries outside China, associated with travel to or from Wuhan City and other parts of central China. The role of person-to-person transmission unrelated to travel became increasingly evident from the pace of community spread and from results of contact investigations. By mid-March 2020, SARS-CoV-2 had spread to Europe, the United States, and other areas of the world, prompting the WHO Director General to declare the COVID-19 outbreak a global pandemic. After three years, the global COVID-19 disease burden totaled more than 659 million confirmed cases and more than 6.6 million deaths, of which 100 million cases and 1 million deaths were in the United States [8; 137].

Despite the availability of effective COVID-19 vaccines beginning in December 2020, the pandemic remained undiminished in Europe and the United States throughout the summer and fall of 2021, in part because of a slow rollout and limited acceptance of COVID-19 vaccines and the emergence of new SARS-CoV-2 strains (variants) more infectious than the original. By July 2021, SARS-CoV-2 Delta variant accounted for 99% of all COVID-19 cases reported in the United States; in December 2021, Delta was rapidly supplanted by the less severe but highly infectious Omicron variant [132].

The scope of the ongoing pandemic creates an enormous pool of replicating virus, greatly magnifying the number of spontaneous genomic mutations and increasing the likelihood new variants of SARS-CoV-2 will emerge. Many variants emerge and disappear; variants having a transmission advantage gradually replace the SARS-CoV-2 strains in circulation. Because of concerns that emerging SARS-CoV-2 variants could circumvent COVID-19 countermeasures, the SARS-CoV-2 Interagency Group (SIG) was established to monitor the transmission, disease severity, and potential of variants to evade vaccine-induced immunity [123]. Using genetic sequencing of SARS-CoV-2 isolates, the CDC's national genomic surveillance program identifies SARS-CoV-2 variants and tracks the geographic distribution and proportion of COVID-19 cases caused by variants. Closely genetically related variants derived from a common ancestor are designated a lineage.

Throughout most of 2022, an estimated 100% of new COVID-19 cases in the United States were caused by subvariants of SARS-CoV-2 Omicron lineage [123; 124]. As of January 2023, a new, more highly transmissible Omicron derivative (XBB.1.5) has emerged, threatening yet another surge of COVID-19 in the first quarter of 2023. CDC projection estimates show that XBB.1.5 accounted for approximately 66% of COVID-19 for the week ending February 3, 2023 [124]. Omicron XBB.1.5 is less sensitive to neutralizing antibody acquired from previous infection and vaccination, raising concern for higher risk of SARS-CoV-2 reinfection than in the past. Although Omicron XBB.1.5 is outpacing other subvariants in circulation, there is no apparent change in clinical profile or risk of adverse outcomes; weekly reported cases, hospitalization, and deaths from COVID-19 declined in mid-January 2023 [124].

CLINICAL MANIFESTATIONS OF COVID-19

The incubation period of SARS-CoV-2 infection is 5 to 7 days, with a range of 2 to 14 days. It is estimated that 97.5% of persons with COVID-19 who develop symptoms will do so within 11.5 days of infection [15; 18]. The onset and progression of illness is variable; most patients experience some combination of fever, cough, fatigue, anorexia, myalgias, and shortness of breath. Less common presenting symptoms include rhinorrhea, sudden loss of smell (anosmia) and/or taste (ageusia), and sore throat. Numerous atypical presentations of COVID-19 have been reported. Elderly adults and persons with comorbidities may have delayed presentation of fever and respiratory symptoms [15]. Headache, confusion, rhinorrhea, sore throat, hemoptysis, vomiting, and diarrhea have been reported but are less common (<10%). Some with COVID-19 have experienced gastrointestinal symptoms, such as diarrhea and nausea, prior to developing fever or lower respiratory tract symptoms. Anosmia or ageusia preceding the onset of respiratory symptoms was frequently reported during the original and Delta COVID-19 periods, a clinical feature that differentiates SARS-CoV-2 from other viral upper respiratory infections.

In order to better characterize the symptom profiles of patients with COVID-19 in the United States, especially among nonhospitalized patients, the CDC used an optional questionnaire to collect detailed information from a sample of confirmed COVID-19 cases reported from 16 participating states [60]. Among 164 symptomatic patients with onset of illness between January 14 and April 4, 2020, a total 158 (96%) reported fever, cough, or shortness of breath. Of 57 hospitalized adult patients, 39 (68%) reported all three of these symptoms, compared with 25 (31%) of the 81 nonhospitalized adult patients. Each of the following symptoms was reported by more than half of patients: cough (84%), fever

(80%), myalgia (63%), chills (63%), fatigue (62%), headache (59%), and shortness of breath (57%). Gastrointestinal symptoms were relatively common, most frequently diarrhea (38%) and least frequently vomiting (13%). Shortness of breath was more common in hospitalized patients (82%) than nonhospitalized patients (38%). Anosmia and ageusia were reported by a higher percentage of nonhospitalized patients (22%) than hospitalized patients (7%) [60].

An array of cutaneous symptoms and signs has been described in patients with COVID-19. Although the exact frequency remains unknown, reports have ranged from 0.2%, early in the pandemic, to as high as 20.4% [15]. In addition to the exanthems common to many viral infections, pernio-like lesions have been described [105]. Pernio (chilblains) is a superficial inflammatory vascular response that occurs on acral skin, usually after cold exposure. In patients with COVID-19, these lesions appear as discolored edematous plaques on the toes and fingers. An international registry was organized early in the pandemic to characterize the diversity of dermatologic manifestations. In a study of 171 registry patients with confirmed COVID-19, the most common morphologies were morbilliform (22%), pernio-like (18%), urticarial (16%), macular erythema (13%), vesicular (11%), papulosquamous (9.9%), and retiform purpura (6.4%) [106]. Morbilliform rashes were often pruritic and involved the trunk. Pernio morphologies were often painful/burning and involved the hands/feet. Pernio-like lesions were generally observed in patients with mild disease, whereas retiform purpura was seen exclusively in critically ill patients. Cutaneous manifestations usually appeared at the onset of or after other COVID-19 symptoms. However, in 12% of cases skin lesions occurred before other COVID-19 symptoms or signs [106]. Images of cutaneous findings are available from the American Academy of Dermatology at https://www.aad.org/public/diseases/coronavirus/covid-toes.

Although most symptomatic patients with COVID-19 experience a mild-to-moderate illness with slow convalescence, there is substantial risk of progression to bilateral pneumonia complicated by respiratory failure and death. In February 2020, the overall case fatality rate for confirmed cases of COVID-19 reported from China was approximately 3%. As the pandemic progressed, reported case fatality rates varied considerably among countries and regions, ranging from 3% to as high as 14%. Multiple factors account for this variance, including available health resources and access to care, differences in public health mitigation strategies, lack of uniformity in the way deaths are attributed to COVID, and the extent to which testing and contact tracing identifies asymptomatic infections. Based on reported cases and attributable deaths through mid-July 2020, the COVID-19 case fatality rate during the first six months of the pandemic was 3.6% in the United States [8]. It is more useful to consider age-adjusted case fatality rates, which range from less than 1% in persons younger than 20 years of age to more than 15% for those older than 75 years of age.

SEVERITY AND PROGRESSION OF ILLNESS

The first description of clinical features in hospitalized patients with COVID-19-related pneumonia in Wuhan City was published online January 24, 2020 [9]. Of 41 patients with laboratory-confirmed SARS-CoV-2 infection; 30 (73%) were men and 27 (66%) had been exposed to the open-air Huanan Seafood Market. The median age was 49 years, and fewer than half of the patients had a history of underlying chronic disease. Common symptoms at onset of illness were fever (98%), cough (76%), and myalgia or fatigue (44%). Dyspnea developed in 22 patients (55%), at a median time of eight days after onset of illness. Common laboratory abnormalities included leukopenia, lymphopenia, and mild hepatic enzyme elevations. All 41 patients were reported to have pneumonia, and in all save one case there was radiographic evidence of bilateral involvement. The

typical findings on chest computed tomography (CT) images of intensive care unit (ICU) patients were bilateral multilobar and segmental areas of consolidation. Acute respiratory distress syndrome developed in 12 (32%) patients, 13 (32%) were admitted to an ICU, and 6 died (15%).

A larger retrospective study examined the clinical characteristics of COVID-19 in a cohort of 1,099 hospitalized patients in China during the first two months of the outbreak [17]. The most common symptoms were fever (43.8% on admission, 88.7% during hospitalization), cough (67.8%), and fatigue (38.1%) [17]. The most common patterns on chest CT were ground-glass opacification (36.4%) and bilateral patchy shadowing (51.8%). Some degree of radiographic or CT abnormality was evident in 82% of patients with non-severe disease and 97% of patients with severe disease. Lymphocytopenia was present in 83.2% of the patients on admission. Sixty-seven patients (6.1%) were admitted or transferred to the ICU, 2.3% required mechanical ventilation, and 1.4% died [17].

In a summary of 72,314 cases reported to the Chinese Center for Disease Control and Prevention, the severity of illness ranged from mild to critical with approximately the following distribution [15; 23]:

- Mild to moderate (mild symptoms up to mild pneumonia): 81%
- Severe (dyspnea, hypoxia or >50% lung involvement on imaging): 14%
- Critical (respiratory failure, shock, or multiorgan dysfunction): 5%

The majority of cases (81%) were characterized as mild, with no or mild pneumonia [23]. The overall case-fatality rate was 2.3%, with higher rates among patient subgroups. Specifically, the case-fatality rate was 49% among critical patients, and all reported deaths occurred in critical patients [23].

Classification of COVID-19 Severity

For purposes of risk stratification and prioritization of care, adults with COVID-19 can be grouped into the following severity of illness categories:

- Asymptomatic or presymptomatic infection: Individuals who test positive for SARS-CoV-2 using a virologic test but who have no symptoms consistent with COVID-19.
- Mild illness: Individuals who have any of the signs or symptoms of COVID-19 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 measured by pulse oximetry (SpO_2) ≤94% on room air at sea level.
- Severe illness: Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, a respiratory rate >30 breaths/minute, or lung infiltrates.
- Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Risk Factors for Severe Disease

Persons of all ages are at risk for SARS-CoV-2 infection and severe COVID-19. The likelihood of severe disease is greater for children younger than 4 years and adults older than 65 years of age, those living in nursing home or long-term care facilities, those with multiple comorbidities, and those unvaccinated against COVID-19. Individual risk factors for severe disease include advanced age, obesity (body mass index ≥30), cardiovascular disease, diabetes, cancer, and chronic obstructive pulmonary disease (COPD).

Of more than 70,000 cases reported in China the first two months of the pandemic, 87% occurred in persons 30 to 79 years of age [23]. The proportion of case fatalities among patients 70 to 79 years of age was 8%, among those 80 years of age or older, the rate was 14.8%. The case fatality rate for patients with comorbidities was elevated as well, specifically those with cardiovascular disease (10.5%), diabetes (7.3%), chronic respiratory disease (6.3%), hypertension (6%), and cancer (5.6%). Only 2% of cases in persons younger than 20 years of age were fatal, and no deaths were reported in those younger than 10 years of age.

In June 2020, the CDC issued an epidemiologic report on 1,320,488 laboratory-confirmed COVID-19 cases in the United States and territories, reported to CDC between January 22 and May 30, 2020 [55]. Cumulative incidence (403.6 cases per 100,000 persons) was similar among males (401.1) and females (406.0), highest among persons 80 years of age or older (902.0), and lowest among children younger than 9 years of age (51.1). Among 599,636 cases with known information on both race and ethnicity, 36% were non-Hispanic White, 33% were Hispanic, 22% were Black, 4% were Asian, and 1.3% were American Indian or Alaska Native. Among 287,320 cases with sufficient data on underlying health conditions, the most frequently reported comorbidities were cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%). Overall, 14% were hospitalized, 2% admitted to an ICU, and 5% died. The rate of hospitalization was six times higher among patients with underlying health conditions (45.4%) than among those without reported underlying comorbidities (7.6%). The mortality rate was 12 times higher among patients with reported underlying conditions (19.5%) compared with those reporting none (1.6%). Approximately 4% of reported cases were asymptomatic. Among 373,833 cases with data on individual symptoms, 70% noted fever, cough, or shortness of breath; 35% experienced muscle aches and/or headache; 8% reported loss of taste or smell [55].

During the course of the pandemic in the United States, obesity has been identified as an important independent risk factor for severe COVID-19, especially among adult patients younger than 60 years of age. Multiple reports, ranging from single-center studies to analyses of records from large patient care networks, have found that severe obesity (body mass index >35) is associated with higher rates of hospitalization, respiratory failure, and mortality from COVID-19 [77; 78]. The risk varies directly with degree of obesity and is independent of obesity-associated comorbidities. The impact is more striking among men than women. There are multiple mechanisms by which obesity may contribute to adverse outcomes in patients with COVID-19. In addition to obstructive pulmonary physiology, severe obesity is associated with immune dysfunction (depression of anti-inflammatory signaling and increased pro-inflammatory signaling), alterations in vascular endothelium, and renin-angiotensin stimulation, which together may worsen lung inflammation and alveolar damage [78].

SYSTEMIC COMPLICATIONS OF COVID-19

At the cellular level, susceptibility to virus infection requires some affinity of the virion for the host cell combined with mechanisms that facilitate attachment and entry into the cell. Cell entry of SARS-CoV-2 depends on binding of the surface spike protein to angiotensin-converting enzyme (ACE2) receptors, followed by activation of the spike protein by host cell transmembrane protease serine 2 [30]. ACE2 is highly expressed by epithelial cells in the nasopharynx and type II alveolar cells in the lung. ACE2 is also expressed in the heart, kidney, vascular endothelium, and intestinal epithelium, which may explain, in part, the propensity for multiorgan dysfunction and vascular complications in patients with severe COVID-19. An autopsy series of 27 patients with COVID-19 reported detectable SARS-CoV-2 in multiple organs, including the lungs, pharynx, kidney, heart, liver, and brain [31]. Measurable SARS-CoV-2 viral load, with preferential targeting of glomerular cells, was present in all kidney compartments examined.

Renal and cardiac complications are common in severe COVID-19. In a retrospective study from China, 251 of 333 (75%) hospitalized patients with COVID-19 pneumonia exhibited some degree of renal involvement, as evidenced by proteinuria or hematuria, and 35 (10%) met criteria for acute kidney injury [32]. In another case series of 138 hospitalized COVID-19 patients, 7% overall and 22% of those admitted to the ICU developed elevated troponin levels or electrocardiogram abnormalities indicative of myocarditis or cardiac injury at some point during hospitalization [33]. A review of cardiac complications found that myocardial injury affects more than one-quarter of COVID-19 cases classified as critical, with two patterns: acute myocardial injury and dysfunction on presentation, and myocardial injury developing as illness severity intensifies [34]. While headache and confusion are seen in some patients presenting with severe COVID-19, there is no indication that SARS-CoV-2 causes primary infection of the central nervous system (e.g., encephalitis). In an autopsy series of 18 consecutive patients who died 0 to 32 days after onset of COVID-19, histopathologic examination of brain specimens did not show encephalitis or other specific brain changes referable to the virus [56].

Coagulopathy

Hospitalized patients with advanced COVID-19 may have laboratory signs of a coagulopathy and increased risk for arterial and venous thromboembolic complications [15; 39; 40]. The pathogenesis is unknown but likely involves some combination of systemic inflammation, endothelial dysfunction, platelet activation, immobility, and stasis of blood flow [40]. The earliest abnormalities are elevated D-dimer levels and mild thrombocytopenia; with disease progression, fibrin degradation products are elevated and prothrombin time becomes prolonged. Laboratory measure of coagulation factors in a patient hospitalized with COVID-19 provides a way to track disease severity. The presence of an elevated D-dimer on admission carries a poor prognosis and has been associated with increased risk of requiring mechanical ventilation, ICU admission, and mortality [40; 41]. The most frequently reported complications of COVID-19 coagulopathy are deep venous thrombosis (DVT) and pulmonary emboli (PE). In a prospective study of 150 critically ill patients from two centers in France, 25 patients developed PE and 3 developed DVT despite prophylactic anticoagulation [42]. In a report of 184 patients with severe COVID-19 from three centers in the Netherlands, the cumulative incidence of venous thromboembolism was 27%, including PE in 80% of the cases affected [43]. Other centers have reported lower rates. Among 393 patients from New York, venous thromboembolism was diagnosed in only 13 patients (3.3%), 10 of whom were on mechanical ventilation [44]. These differences point to the need for studies that control for clinical severity, underlying comorbidities, prophylactic regimen, and COVID-19-related therapies. At present, there are limited data available to inform clinical management around prophylaxis or treatment of venous thromboembolic complications in patients with COVID-19 [15]. One source of interim guidance recommends regularly monitoring hemostatic markers—namely D-dimer, prothrombin time, and platelet count—in all patients presenting with COVID-19 and prophylactic use of low-molecular-weight heparin in all hospitalized patients, unless there are contraindications [40]. Clinical guidance on use of antithrombotic therapy for patients with COVID-19 is provided by the National Institutes of Health (NIH) at https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy.

In summary, the clinical features of COVID-19 range from self-limited upper respiratory syndrome to pneumonia and rapid-onset respiratory insufficiency to vascular complications and critical organ dysfunction. Older patients and those with comorbidities are at significant risk for severe disease. Among patients with COVID-19 who progress to pneumonia, the median time from initial symptoms to onset of dyspnea is 5 to 8 days, to ARDS is 8 to 12 days, and to ICU admission is 10 to 12 days. Therefore, in monitoring at-risk patients, clinicians should bear in mind the anticipated period of rapid clinical deterioration is 7 to 8 days after onset of

symptoms. Data from clinical series show that in patients hospitalized for COVID-19, 26% to 42% require ICU admission; in those admitted to ICU, 65% to 85% develop ARDS [15]. Reported mortality rates among patients requiring ICU admission range from 39% to 72%. The median length of hospitalization for survivors is 10 to 13 days.

PREGNANCY AND COVID-19

Although the absolute risk of severe COVID-19 is low among people of child-bearing age, the risk of severe illness and complications is substantial when infection is acquired during pregnancy. Evidence for this comes from an analysis of 409,462 women (15 to 44 years of age) with symptomatic COVID-19 reported to the CDC between January 22 and October 3, 2020 [107]. Of the total, 23,434 women (5.7%) were pregnant at the time of infection. Pregnant patients were admitted to an ICU more frequently than nonpregnant patients (10.5 versus 3.9 per 1,000 cases) and were more likely to receive invasive ventilation (2.9 versus 1.1 per 1,000 cases) or extracorporeal membrane oxygenation (ECMO) (0.7 versus 0.3 per 1,000 cases). The mortality rate was 1.5 per 1,000 cases for pregnant women compared with 1.2 per 1,000 cases for nonpregnant women. Older pregnant patients (35 to 44 years of age) with symptomatic COVID-19 were nearly four times more likely to require invasive ventilation and twice as likely to die than were nonpregnant patients of the same age [107].

Following the emergence of the Delta variant and 2021 summer surge of COVID-19, the risk for unvaccinated pregnant individuals infected with SARS-CoV-2 became more serious. A retrospective cohort study comparing COVID-19 outcomes among unvaccinated pregnant patients infected in the pre-Delta period with those infected during the Delta surge found that proportions of severe-critical illness and ICU admissions were three-fold higher among patients in the Delta cohort than those in the pre-Delta cohort [149]. Rates of intubation and mechanical ventilation were higher among those with Delta variant infection. Maternal COVID-19 from SARS-CoV-2 Delta infection also had an adverse effect on perinatal outcomes; rates of cesarean delivery, stillbirth, preterm birth, and neonatal intensive care unit admission were all higher during the period of Delta predominance [149].

Vertical Transmission and Neonatal COVID-19

Multiple cohort studies and meta-analyses have found that vertical transmission of SARS-CoV-2 is rare, though severe maternal COVID-19 has been associated with SARS-CoV-2 infection in newborn infants. The majority of SARS-CoV-2 infections reported in newborns result from exposure to maternal COVID-19 at the time of birth or shortly after. One systemic review and meta-analysis found that 1.8% of newborn infants from mothers with SARS-CoV-2 infection tested positive for the virus [177]. In a subset of 592 SARS-CoV-2-positive infants with data on time of exposure and testing, 7 had evidence of confirmed mother-to-child transmission in utero. Risk factors associated with neonatal SARS-CoV0-2 infection in offspring included severe maternal COVID-19, maternal admission to ICU, maternal death, and postnatal maternal COVID-19 [177].

Several small clinical series have reported fetal demise or stillbirth following maternal COVID-19, resulting from placental SARS-CoV-2 infection without evidence of intrauterine transmission to fetus. Data from a prospective clinicopathologic study of placentas from unvaccinated pregnant individuals affected by COVID-19 were used to examine the placental pathology associated with autopsy findings in six stillbirth cases [178]. In all six stillbirths, the maternal placentas showed extensive inflammation and massive perivillous fibrinoid deposition with trophoblast damage, associated with the presence of virions on electron microscopy and positive immunostaining for SARS-CoV-2 spike protein. Thus, severe "placentitis," with near 75% obliteration of the maternal intervillous space, accounted for intrauterine fetal death. Complete fetal autopsy examination found signs of tissue asphyxia as mode of death and no evidence of viral transmission to the fetus [178]. The interval between maternal COVID-19 diagnosis and fetal death ranged from 3 to 15 days.

RECOVERY FROM COVID-19

Convalescence following SARS-CoV-2 infection follows a variable course, and symptomatic recovery from severe COVID-19 may take weeks to months. In a cohort study of 146 patients with moderate-to-severe COVID-19 hospitalized a median of two weeks with interstitial viral pneumonia, 87% had persistent symptoms two months or more after discharge from hospital [68]. On follow-up clinical assessment 60 days after onset of the first COVID-19 symptom, 18 (13%) were symptom free; of the remaining participants, 32% had one or two symptoms and 55% had three or more symptoms. The most common persistent symptoms were fatigue (53%), dyspnea (43%), joint pain (27%), and chest pain (22%). None had fever or signs of acute illness. Of the total, 44% reported persisting decline in quality of life imposed by COVID-19.

"Long COVID" is the term applied to the syndrome of persistent symptoms four weeks or later after recovery from acute COVID-19. The majority of reported cases are adults in the 35-to-69-year age group, and women are 30% more likely to get long COVID than men [133]. The range of complaints includes residual cough, fatigue, loss of smell or taste, shortness of breath, headache, and "brain fog." The prevalence of post-COVID-19 cognitive impairment and association with disease severity was investigated in 740 adult patients with no prior history of dementia. Study participants were 38 to 59 years of age, prior COVID severity ranged mild to severe, and evaluations were performed an average of 7.6 months after diagnosis. Deficits were found in processing speed (18%), executive functioning (16%), phonetic fluency (15%) and category fluency (20%), memory encoding (24%), and memory recall (23%) [134]. Executive functioning, processing speed, and memory encoding and recall impairments were predominant among hospitalized patients.

A multistate survey conducted by the CDC found that persistent symptoms three weeks after diagnosis of SARS-CoV-2 infection was common among outpatients with milder illness [69]. Of 270 respondents who were symptomatic at diagnosis, 95 (35%) had not returned to their usual state of health 14 to 21 days from the test date, including 26% of those 18 to 34 years of age and 47% of those older than 50 years of age. Among respondents reporting cough, fatigue, or shortness of breath at the time of COVID-19 diagnosis, 43%, 35%, and 29%, respectively, continued to experience these symptoms at the time of the interview [69].

A cohort study of long-term symptoms in healthcare professionals found that after mild COVID-19, 26% of participants reported at least one moderate-to-severe symptom lasting two months and 15% reported at least one moderate-to-severe symptom lasting eight months [108]. The most common symptoms were anosmia, fatigue, ageusia, and dyspnea. These studies show that low-risk adults with mild COVID-19 commonly experience a slow convalescence with diverse long-term symptoms that may disrupt work and social activity.

LATE SEQUELAE OF COVID-19

In addition to the lingering functional impairments represented by long COVID syndrome, there is growing evidence that beyond acute infection, SARS-CoV-2 may have late adverse effects on critical organ function that impacts the subsequent incidence of cardiovascular disease and diabetes. The lung/vascular/heart involvement of acute-phase moderate-to-severe COVID-19 reflects the trophism of SARS-CoV-2 augmented by a dysregulated (hyperimmune) inflammatory response to infection, resulting in multiple potential complications. Microvascular dysfunction and endothelial injury may precipitate thromboembolic events. Myocarditis is usually transient but may lead to cardiomyopathy. Acute coronary syndromes from vasculitis and plaque instability may cause myocardial ischemic injury, resulting in heart failure. Parenchymal lung injury and microvascular thrombosis may lead to interstitial fibrosis and hypoxemia, adding to the cardiac workload and subsequent risk of clinical or subclinical heart failure [159].

The cardiovascular sequelae of post-acute COVID-19 were analyzed using the databases of the U.S. Department of Veterans Affairs to build a cohort of 153,769 individuals with COVID-19, as well as cohorts of contemporary and historical controls. The study was designed to estimate risks and one-year burdens of a set of prespecified incident cardiovascular outcomes. The analysis showed that beyond 30 days after diagnosis, individuals with COVID-19 were at increased risk of subsequent cardiovascular diseases in several categories, including dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure, and thromboembolic disease [160]. Increased risk and additional disease burden were evident among hospitalized and nonhospitalized patients. Overall, the impact increased in graded fashion according to the clinical care setting. In a separate report, using the same database and study protocol, investigators also found that the risks and 12-month burdens of incident diabetes and antihyperglycemic use were increased among people who survived COVID-19, compared to a contemporary control group that had not contracted SARS-CoV-2 infection [161]. The post-acute diabetes risks and disease burdens increased in graded fashion according to severity of the acute phase of COVID-19.

Chronic, persistent SARS-CoV-2 infection following COVID-19 has been reported in patients with hematologic malignancies and immunodeficiency disorders. The common features are protracted virus shedding, fluctuating symptoms, and failure of humeral immunity many months after acute infection. In addition to the burden of ongoing symptoms and added cost of care, these patients often have to endure prolonged self-isolation and inability to resume productive lives. COVID-19 vaccines may be beneficial in such cases; in a reported case study, mRNA COVID-19 vaccination elicited humoral and cellular immune responses to SARS-CoV-2, which had failed in response to ongoing infection itself, followed by viral clearance [162].

COVID-19 IN CHILDREN

The CDC and NIH websites provide updated clinical guidance for pediatric healthcare providers on the evaluation and management of childhood COVID-19 and neonates at risk for COVID-19 [45; 57]. Acute SARS-CoV-2 infection in childhood tends to be asymptomatic or mild, consisting of transient fever, cough, and other signs common to an upper respiratory viral syndrome. Severe manifestations of COVID-19 have been reported in children of all ages, though the incidence is far less common than in adults and fatalities following acute childhood infection are rare. Among more than 2,000 pediatric cases in China, 4% were asymptomatic, 51% had mild symptoms, 39% were moderately ill with some evidence of pneumonia, and 5% were severely ill with dyspnea, hypoxia, and central cyanosis [45]. Only 0.6% developed respiratory failure, shock, or multi-organ dysfunction.

Children younger than 18 years of age account for 22% of the U.S. population and represent 18% of cumulative COVID-19 cases reported since the onset of the pandemic [136]. As of January 2023, more than 15.2 million children have tested positive for COVID-19, including 172,000 child cases added in the month of December 2022. Reported cases are likely a substantial undercount of COVID-19 cases among children [136]. Severe illness from SARS-CoV-2 infection is uncommon. Among states reporting, pediatric cases account for 1.2% to 4.6% of COVID-19-related hospitalizations. Less than 1.5% of all child COVID-19 cases result in hospitalization. The childhood COVID-19 case fatality rate is 0.03% [46; 136]. Although the childhood COVID-19 mortality rate is low (about 1 death per 100,000 population), the mortality burden in children is best understood in the context of all causes of death. An epidemiological analysis for the years 2019 to 2022 found that among children and young people 0 to 19 years of age, COVID-19 ranked eighth among all causes of death, fifth among disease-related causes of death, and first in deaths caused by infectious

or respiratory diseases [155]. COVID-19 was the underlying cause in at least 821 childhood and adolescent deaths occurring in theone-year period from August 1, 2021, to July 31, 2022. As among adults with COVID-19, children with underlying medical conditions and special healthcare needs, including genetic, neurologic, and metabolic disorders or congenital heart disease, are at increased risk of severe illness and adverse outcomes.

Following emergence of the highly infectious SARS-CoV-2 Omicron variant in December 2021, COVID-19-associated hospitalization rates increased rapidly among children 0 to 4 years of age, a group at that time not yet eligible for vaccination. During the period December 2021 to February 2022, weekly hospitalizations among children 0 to 4 years of age peaked at 14.5 per 100,000, a level fivefold higher than during the previous six months (Delta predominance) [163]. During the period of Omicron predominance, 63% of hospitalized children had no underlying medical conditions. Monthly pediatric COVID-19 ICU admission rates were approximately 3.5 times higher during peak Omicron predominance in January 2022, than during peak Delta predominance in September 2021 [163].

Although most SARS-CoV-2 infections in childhood are asymptomatic or mild, the percentage of ICU admissions among hospitalized children with COVID-19 is comparable to that for hospitalized adults. Clinical studies have identified multiple risk factors for severe disease and adverse outcomes in childhood COVID-19. These risk factors include prematurity in young infants, obesity, diabetes, chronic lung disease, cardiac disease, neurologic disorders, and immunocompromising conditions [57]. Certain age groups (infants younger than 1 year of age, children 10 to 14 years of age) and non-White race/ethnicity also are associated with increased risk of severe disease and adverse outcomes among hospitalized children with COVID-19.

Long COVID has also been described in children, though to a lesser degree than in adults. Adolescents and teenagers account for the majority (70%) of reported cases [133]. In a study of 151 children with documented SARS-CoV-2 infection, 8% had post-acute COVID-19 symptoms lasting three to eight weeks [135]. The most common symptoms were residual cough and/or fatigue. On follow-up survey at six months, all 151 children had fully recovered.

PEDIATRIC MULTISYSTEM INFLAMMATORY SYNDROME

During the first year of the pandemic, reports from United Kingdom, Italy, and New York described a serious inflammatory disorder in children linked to COVID-19, with many features common to Kawasaki disease and toxic shock syndrome [46; 47; 48]. The term applied to this condition is multisystem inflammatory syndrome in children (MIS-C). Kawasaki disease is an acute vasculitis of unknown cause that affects infants and young children, first described in Japan and thought to involve an aberrant immune response to an unidentified pathogen in certain persons with genetic predisposition [47]. COVID-related MIS-C is an acute, rapidly progressive inflammatory disorder with signs of intravascular volume depletion and critical organ failure. Symptoms and signs include persistent fever, abdominal complaints, rash, leukocytosis, elevated C-reactive protein, and evidence of single- or multiple-organ dysfunction [49]. Hypotension on presentation is common; myocarditis and other cardiovascular changes (e.g., mitral regurgitation, coronary artery dilatation) may be seen. The majority of patients have tested positive for recent SARS-CoV-2 infection by molecular diagnostic and/or antibody testing. The onset of MIS-C may come days or weeks after what appears to have been an asymptomatic or mild case of COVID-19.

During a 10-day period in mid-April 2020, pediatricians at an intensive care hospital in England noted an unprecedented cluster of eight children with hyperinflammatory shock and other clinical features similar to atypical Kawasaki disease [47]. All had previously been healthy; five of the children were boys. Four of the children had known family exposure to SARS-CoV-2. Clinical presentations were similar, with unrelenting fever, variable rash, conjunctivitis, peripheral edema, and warm shock refractory to intravenous fluids, eventually requiring vasopressors. No clinical or virologic evidence of lower respiratory involvement was observed. All patients were treated with IV immunoglobulin (IVIG); seven recovered and one died following arrhythmia, shock, and cerebral infarction. During the course of the COVID-19 epidemic in northern Italy, physicians in Bergamo observed 10 children (median age: 7.5 years) in the span of two months with a severe form of Kawasaki-like disease, a 30-fold increase in incidence when compared to the previous five years [48]. All were positive for recent SARS-CoV-2 infection. In June 2020, the New York State Department of Health investigated 195 reported cases of MIS-C and 3 deaths in children. Of these patients, 28% were younger than 5 years of age and 69% were between 5 and 19 years of age, and 93% have tested positive for COVID-19 [46]. A targeted surveillance for MIS-C in pediatric health centers across the United States identified 186 cases in 26 states during a five-week period between March and May 2020 [61]. The median age was 8.3 years, 165 (62%) were male, and 131 (70%) tested positive for SARS-CoV-2 infection by rT-PCR or serologic antibody test.

The clinical features in the MIS-C cases investigated by the New York Department of Health have been reported [62]. Of 191 patients in the study, all presented with fever and tachycardia, 80% were admitted to the ICU, and 62% required vasopressor support. Abdominal complaints and gastrointestinal symptoms were common (62%), as was rash (60%), conjunctival injection (56%), and mucosal changes (27%). Laboratory markers of inflammation included elevated levels of C-reactive protein in all patients, positive D-dimer (91%), and elevated troponin (71%). Evidence of myocarditis was present in 53% of patients. At least one echocardiogram was obtained for 93 patients (94%); 51 (52%) had some degree of ventricular dysfunction, 32 (32%) had pericardial effusion, and 9 (9%) had a documented coronary artery aneurysm. The majority of patients were treated with IVIG and/or glucocorticoids in addition to vasopressors. The median duration of hospitalization was six days. Two patients died. As observed in cases reported from Italy, MIS-C cases in New York followed the peak of the COVID-19 epidemic in that state and nearly all patients tested seropositive for recent SARS-CoV-2 infection [62].

The onset of MIS-C after SARS-CoV-2 infection is two to four weeks and presents with fever, multisystem organ involvement, and elevated markers of inflammation. Early recognition of MIS-C and prompt referral (hospitalization) is essential. Approximately 50% to 60% of children and adolescents with MIS-C present with cardiovascular signs, hypotension, and warm shock requiring vasopressor support, compared with about 5% of children with Kawasaki disease [61; 62]. Cardiac abnormalities include a 9% incidence of coronary artery aneurysm. Echocardiography is recommended in all patients presenting with MIS-C, and until more is known about long-term cardiac sequelae of MIS-C, providers should consider follow-up imaging one to two weeks and four to six weeks after treatment [61].

Clinical evaluation should include inquiry as to recent COVID-19 illness and known exposure to COVID-19. Clinical management of children with MIS-C includes close observation, correction of hemodynamic instability, diagnostic evaluation for bacterial infection (e.g., streptococcal or staphylococcal sepsis, toxic shock syndrome), and consideration of treating with IVIG. The CDC recommends that patients younger than 21 years of age meeting MIS-C criteria be reported to local, state, and territorial health departments. The CDC case definition for MIS-C is [49]:

- An individual younger than 21 years of age presenting with fever (>38.0°C for at least 24 hours), laboratory evidence of inflammation (including, but not limited to, one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or interleukin-6, elevated neutrophils, reduced lymphocytes, and low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (at least two) organ involvement; AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection or exposure to a suspected or confirmed COVID-19 case within the four weeks prior to the onset of symptoms

All individuals should be reported if they meet the case definition for MIS-C, regardless of whether they fulfill criteria for Kawasaki disease. In addition, MIS-C should be considered in any pediatric death with evidence of SARS-CoV-2 infection.

The CDC tracks case reports of MIS-C associated with COVID-19. As of January 2023, the number of patients meeting the case definition of MIS-C in the United States totaled 9,333, with 76 deaths [137]. The median age of reported cases was 9 years, and half of children with MIS-C are 5 to 13 years of age. Of the total MIS-C cases reported, 56% are Hispanic/Latino or non-Hispanic Black, 60% are male, and 98% had a positive test for recent SARS-CoV-2 infection [137].

Vaccination of children 12 to 18 years of age with mRNA vaccine is highly effective in preventing COVID-19-associated MIS-C. A multi-state, case-control study comparing 124 patients with MIS-C with 181 hospitalized controls across 24 pediatric hospitals found that the estimated effectiveness against MIS-C following two doses of Pfizer-BioNTech vaccine was 91% [164]. Ninety-five percent of patients hospitalized with MIS-C were unvaccinated, and of 38 MIS-C patients requiring life support, all were unvaccinated.

Information for healthcare providers about MIS-C, including clinical evaluation, diagnostic testing, treatment, and a compendium of additional resources for clinicians (e.g., links American Academy of Pediatrics and American College of Rheumatology clinical guidance) and parents is available on the CDC website at https://www.cdc.gov/mis/mis-c/hcp.

DIAGNOSTIC TESTING FOR SARS-COV-2

There are two types of diagnostic tests for determining active SARS-CoV-2 infection: molecular tests that use the real-time reverse transcription-polymerase chain reaction (RT-PCR) to detect viral RNA, and antigen immunoassays that detect the presence of specific proteins on the surface of the virion. For clinical assessment of a symptomatic patient, the most widely used and reliable of these is RT-PCR, which can be applied to mucus specimens from the upper or lower respiratory tracts and to serum samples. SARS-CoV-2 viral RNA can be detected more readily in secretions taken by swab from the nasopharynx than in samples obtained by throat swab [15]. RT-PCR testing of deep nasopharyngeal swab specimens has become the standard procedure for the laboratory diagnosis of active SARS-CoV-2 infection [79; 80]. This test is highly accurate and results can be obtained within one or two days.

Antigen tests for the diagnosis of active SARS-CoV-2 infection are performed on nasopharyngeal, nasal swab, or saliva specimens placed directly into the assay's extraction buffer or reagent. Currently authorized antigen tests include point-of-care, laboratory-based, and self-tests. Although antigen tests for SARS-C0V-2 are generally less sensitive than RT-PCR, antigen test results are produced quickly (within approximately 15 to 20 minutes) [80]. Clinicians should bear in mind that unlike molecular detection of viral DNA, which may persist for weeks, the sample concentration of antigen required for detection by assay decreases rapidly as the duration of illness increases. Specimens collected more than seven days after onset of illness are considered more likely to be negative compared to a RT-PCR assay [80]. Thus, a positive antigen test result is highly reliable, but a negative test may need to be confirmed with RT-PCR. Updated CDC guidance for healthcare providers for SARS-C0V-2 antigen testing, including case management (isolation) strategies according to clinical status and test results, is available at https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html.

The availability of safe, reliable, and timely SARS-CoV-2 diagnostic testing is essential for effective public health measures to control the COVID-19 pandemic. The nasopharyngeal swab specimen collection method involves close interaction between healthcare workers and patients, requires personal protective equipment, and entails a measure of discomfort for the test subject—all disadvantages to community drive-through diagnostic testing and contact tracing. Self-collected saliva could prove to be a simple, less expensive alternative that alleviates the need for personal protective equipment. Studies show that the molecular test detection rate for saliva specimens from individuals with symptomatic and asymptomatic SARS-CoV-2 is comparable to deep nasopharyngeal swab specimens. Yale investigators found that among 70 inpatients with confirmed COVID-19 and 495 asymptomatic healthcare workers, the use of self-collected saliva specimens for SARS-CoV-2 molecular diagnostic testing compared favorably with nasopharyngeal swab specimens collected by personnel [81]. In another study of 354 patients presenting to a drive-through testing center with at least one symptom consistent with COVID-19, the SARS-CoV-2 positivity rate was 22.6% for nasopharyngeal swab specimens compared with 22.9% for salivary specimens [82]. Between nasopharyngeal swab specimens and salivary specimens, the positive percent agreement was 93.8% and the negative percent agreement 97.8%.

COVID-19 diagnostic testing in the United States is available at all state and local public health laboratories and at commercial laboratories authorized by the U. S. Food and Drug Administration (FDA) [16; 80]. Although in some cases viral nucleic acid can be detected in nasopharyngeal specimens for weeks after infection, studies show that SARS-CoV-2 viral cultures are usually negative within 8 to 10 days after onset of infection. Shedding of live virus may persist longer in severely ill, hospitalized patients (median range of viral shedding: 12 to 20 days) [15]. Information on specimen collection, handling, and storage is available online at https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html.

ANTIBODY TESTING

SARS-CoV-2 antibody assays are useful for epidemiologic investigation of prevalence in the general population and to identify groups at risk for infection. Unlike RT-PCR and antigen detection tests that identify acute infection, antibody tests determine whether there is evidence of prior infection, even if the person being tested never developed symptoms. The FDA has not authorized the use of serology to detect active SARS-CoV-2 infection, and the CDC does not recommend antibody testing for routine diagnosis of acute infection [79]. However, antibody testing in conjunction with viral RT-PCR may be used to support clinical assessment of persons who present late in the course of COVID-19, or a patient suspected of having a post-infectious syndrome caused by recent SARS-CoV-2 infection (e.g., MIS-C).

Following SARS-CoV-2 infection, IgM and IgG antibodies appear almost simultaneously in the serum within two to three weeks after symptom onset, at which time infectiousness likely is greatly decreased and some degree of immunity from future infection has developed [83]. Thus, early IgM assay without IgG testing is of little value. The duration of detectable antibody is unknown, and the absence of detectable IgM or IgG antibodies does not necessarily rule out previous infection. Several commercially marketed serologic assays for SARS-CoV-2 have emergency use authorization (EUA) by the FDA, which has independently reviewed their performance. A list of all tests authorized for emergency use under EUA is maintained on the FDA website [84]. All currently authorized tests are qualitative (providing a result that is positive, negative, or indeterminate) rather than quantitative (providing a quantitative assessment of antibody levels). It is important to minimize false-positive test results by choosing an assay with high specificity and by testing individuals with an elevated likelihood of previous exposure to SARS-CoV-2 [83].

COVID-19 TREATMENT OPTIONS

After the SARS-CoV-2 viral genome was mapped in mid-January 2020, NIH-sponsored efforts were initiated to improve diagnostics, identify effective treatments, and develop vaccines against SARS-CoV-2 [10]. In addition to repurposed antiviral agents with activity against coronavirus, other modes of therapy for COVID-19 included passive enhancement of immunity (e.g., convalescent plasma, monoclonal antibody) early after onset and anti-inflammatory corticosteroids (dexamethasone) at a later stage and severity of illness. Effective COVID-19 vaccines for prevention of SARS-CoV-2 and protection against severe disease have been in distribution since December 2020.

The majority of patients with mild-to-moderate COVID-19 do not progress to more severe illness. Management of nonhospitalized, low-risk patients with acute COVID-19 should include supportive care under Isolation Precautions, steps to reduce the risk of SARS-CoV-2 transmission, and advising patients on when to seek further evaluation. Those at high risk of progression to severe illness should be triaged for pharmacologic therapy. Patients with persistent or progressive dyspnea, especially those with an oxygen saturation measured by pulse oximetry (SpO_2) <94% on room air or have symptoms suggestive of high acuity illness (e.g., chest discomfort, weakness, confusion), should be referred to a healthcare provider for in-person evaluation [57].

RACIAL/ETHNIC MINORITIES AND MARGINALIZED GROUPS

Communities that have been historically marginalized or made socially vulnerable through lack of access to health care or inability to socially isolate are at increased risk of SARS-CoV-2 acquisition, COVID-19-related hospitalization, and death. This includes racial and ethnic minorities, essential non-healthcare workers, and some people with disabilities. Clinicians, healthcare systems, and public health agencies should work to ensure equitable access to high-quality care and treatment for all patients, regardless of race, ethnic, or social status [57].

COVID-19 THERAPEUTICS

Two main processes are thought to drive the pathogenesis of COVID-19 [57]. Early in the clinical course, disease activity is driven by the replication of SARS-CoV-2; later in the clinical course, the disease is primarily driven by a dysregulated immune/inflammatory response to the virus that leads to tissue damage. Antiviral therapies that directly target SARS-CoV-2 are anticipated to have the greatest effect early in the course of disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19. As noted, the NIH Treatment Guidelines Panel provides updated clinical information and guidance on the treatment COVID-19, including recommendations for risk assessment, patient prioritization, and selection of therapeutic regimens in hospitalized and nonhospitalized patients [57].

Antiviral Therapy

As of January 2023, there is no highly effective, safe, and easily administered antiviral therapy for routine treatment of COVID-19. Remdesivir, which must be administered intravenously, is the only drug approved by FDA for treatment of COVID-19. Two oral antiviral drugs, ritonavir-boosted nirmatrelvir (Paxlovid) and molnupiravir, have received EUA from the FDA for early treatment in nonhospitalized patients with mild-to-moderate COVID-19 who are at risk of progressing to severe illness. Recommendations for use of antiviral therapies apply to adults and children (of certain age and weight limitations). The NIH Panel guidelines recommend selecting from the following antiviral agents, in order of preference [57]:

- Ritonavir-boosted nirmatrelvir (Paxlovid): Adults and children at least 12 years of age
- Remdesivir: Adults and children older than 28 days of age and weighing at least 3 kg
- Molnupiravir as alternative therapy when ritonavir-boosted nirmatrelvir and remdesivir are not available

Remdesivir

Remdesivir is a nucleotide analog RNA polymerase inhibitor having in-vitro activity against SARS-CoV-2 [15]. A multinational study at the onset of the pandemic described favorable outcomes when hospitalized patients were given a 10-day course of intravenous remdesivir as part of a compassionate use program [26]. The study enrolled patients from the United States, Canada, Europe, and Japan with confirmed SARS-CoV-2 infection and signs of lower respiratory tract disease severe enough to require oxygen supplementation and/or ventilatory support. Of 53 patients in the data analysis, 32 (68%) showed significant improvement in oxygenation with use of remdesivir. Mortality at 18 days follow-up was 13% overall, 18% among patients who required invasive ventilation, and 5% among those who had received noninvasive ventilation. The authors observed that although this was not a randomized study and patients were not directly comparable, observed mortality was considerably less than that reported contemporaneously in other COVID-19 case series and reports [26].

Remdesivir is approved by the FDA for treatment of adults and pediatric patients with COVID-19. The approval was supported by three randomized, controlled clinical trials showing that remdesivir reduces risk of disease progression and shortens the time to recovery in adult patients hospitalized with moderate-to-severe COVID-19 [90]. The analysis included data from a double-blind, placebo-controlled trial that enrolled 1,062 patients, randomized to receive either intravenous remdesivir or placebo. The primary outcome was time to recovery, defined by discharge from hospital or resolution of need for clinical care (hospitalization for infection-control purposes only). The median time to recovery was 10 days for the remdesivir group, compared with 15 days for the placebo group [35]. In an analysis of secondary outcomes, patients who received remdesivir were more likely than those who received placebo to have clinical improvement at day 15. The proportion of serious adverse events related to respiratory failure and the need for higher levels of ventilatory support were lower among patients in the remdesivir group. Kaplan-Meier estimates of mortality showed a trend in favor of the treatment group: 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% versus 15.2% by day 29 [35].

The NIH Panel recommends remdesivir for treatment of COVID-19 in hospitalized patients with SpO_2 <94% on ambient air, or require supplemental oxygen, and for those who require noninvasive or mechanical ventilation [57]. The duration of treatment recommendation, including advisability of combining remdesivir with a glucocorticoid such as dexamethasone, depends on severity of illness and level of ventilatory support. For patients who require supplemental oxygen but have no need for delivery of oxygen through a high-flow device, the recommended regimen is remdesivir 200 mg IV for one day, followed by 100 mg daily for four days or

until hospital discharge, whichever comes first. The duration of remdesivir therapy may be extended up to 10 days when there is no substantial clinical improvement by day 5 (57).

The FDA has approved the use of remdesivir (three-day regimen) in nonhospitalized patients with COVID-19 who are at risk of severe disease in settings where intravenous therapy and close patient monitoring are feasible. In a randomized, placebo-controlled clinical trial among nonhospitalized adults (mean age: 50 years) with symptomatic COVID-19 and at least one risk factor for disease progression, a three-day course of remdesivir resulted in an 87% lower risk of hospitalization or death than placebo [165]. COVID-19-related hospitalizations and deaths from any cause occurred in 2 patients (0.7%) in the remdesivir group and 15 patients (5.3%) in the placebo group.

Remdesivir is indicated for treatment of mild-to-moderate COVID-19 in adults and children (28 days of age and older and weighing at least 3 kg), whether hospitalized or not hospitalized, who are at risk for progression to severe disease, hospitalization, or death [57]. The recommended dosage for adults and pediatric patients weighing at least 40 kg is a single loading dose of 200 mg, followed by once-daily doses of 100 mg, administered by intravenous infusion. For younger/smaller pediatric patients weighing 3 kg to less than 40 kg, the initial dosage is 5 mg/kg, followed by 2.5 mg/kg daily. For nonhospitalized patients, the total duration of therapy is 3 days; for hospitalized patients, duration of therapy is 5 or 10 days, determined by severity of respiratory insufficiency (need for mechanical ventilation) and clinical response.

Oral Anti-SARS-CoV-2 Agents

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Nirmatrelvir is a protease inhibitor active against a constitutive protein (protease) essential for virus replication. It has demonstrated antiviral activity against all human coronaviruses [57]. Nirmatrelvir is used in combination with ritonavir, a pharmacokinetic booster required to increase nirmetrelvir concentration into therapeutic range. A randomized, placebo-controlled clinical trial of nirmatrelvir-riyonavir (Paxlovid) was conducted among unvaccinated, nonhospitalized high-risk adults with symptomatic COVID-19. The incidence of disease progression to hospitalization or death was 89% lower in the treatment group than in the placebo group [166]. The incidence was 0.77% (3 of 389 patients) in the nirmatrelvir group, with 0 deaths, compared with 7.01% (27 of 385 patients) in the placebo group, with 7 deaths.

The available formulation uses nirmatrelvir 300 mg plus ritonavir 100 mg administered orally twice daily for five days in patients older than 12 years of age and weighing more than 40 kg. Treatment should be initiated as soon as possible and within five days of symptom onset. The NIH Panel recommends nirmatrelvir-riyonavir for high-risk, nonhospitalized patients with mild-to-moderate COVID-19 [57]. Because ritonavir is a potent P450 3A4 inhibitor, it may increase blood concentrations of certain concomitant medications and the potential for serious drug toxicities. Many potential drug-drug interactions can be safely managed (e.g., with certain statins, calcium channel blockers, or direct oral anticoagulants) [57]. Before using nirmatrelvir-ritonavir, clinicians should review the patient's concomitant medications and consider consulting with a pharmacist. The following online resources are available to assist in identifying and managing drug-drug interactions:

- The FDA ritonavir-boosted nirmatrelvir EUA Fact Sheet: https://www.fda.gov/media/155050/download
- NIH ritonavir-boosted nirmatrelvir (Paxlovid) factsheet: https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions

There are reports of SARS-CoV-2 viral rebound and clinical relapse of COVID-19 in some patients who have completed treatment with nirmatrelvir-ritonavir [57; 176]. These patients reportedly have had mild, self-limited symptoms without illness progression or need of additional treatment. Viral rebound and recurrence of COVID-19 symptoms also occurs in patients who have not been treated with nirmatrelvir-ritonavir. Patients with suspected COVID-19 rebound following treatment should be advised to re-isolate for at least five days to prevent further transmission of the virus.

Molnupiravir

Molnupiravir is the prodrug of a ribonucleoside that exhibits antiviral activity against RNA viruses, including SARS-CoV-2. Uptake by viral RNA-dependent RNA polymerases causes mutations that are lethal to the virus. In clinical trials, 800-mg molnupiravir twice daily for five days reduced the rate of hospitalization or death among patients with COVID-19 by 30% compared with placebo [57]. Molnupiravir is not recommended for use in pregnant patients due to concerns about potential fetal toxicity. The NIH Panel recommends using molnupiravir as an alternative when nirmatrelvir-ritonavir and remdesivir are not available, not feasible to use, or clinically inappropriate [57]. Molnupiravir appears to have lower clinical efficacy than the other treatment options.

Other Potential Therapeutic Antiviral Drugs

Several other approaches to antiviral therapy have been explored for the treatment of COVID-19, with poor results. Hydroxychloroquine and ivermectin are of historical interest, have been evaluated in multiple clinical trials, and therefore are discussed in detail below. The NIH guidelines for the treatment of COVID-19 recommend against the use of nitazoxanide, lopinavir/ritonavir, and other HIV protease inhibitors to manage or prevent COVID-19 outside of clinical trials [57].

Hydroxychloroquine

In-vitro studies show that chloroquine phosphate and hydroxychloroquine sulphate (commonly used to treat malaria) interfere with the replication cycle of coronaviruses, including SARS-CoV-2, and thus may offer some therapeutic efficacy for treatment of COVID-19 [21]. Randomized controlled clinical trials of hydroxychloroquine are underway in the United States. Based on small case studies and anecdotal reports of possible efficacy, many clinicians have been inclined to administer hydroxychloroquine to patients with COVID-19 who are so ill as to require hospitalization and having risk factors for severe disease (i.e., age older than 65 years, underlying medical conditions, and/or signs of viral pneumonia). On March 28, 2020, the FDA issued an EUA that allowed chloroquine phosphate or hydroxychloroquine sulphate to be used for the treatment of patients hospitalized with COVID-19 when clinical trials are not available or participation is not feasible [36]. However, this letter was revoked in June 2020 [58]. If used, hydroxychloroquine is generally preferred as it is better tolerated. The suggested dosage regimen is hydroxychloroquine sulphate administered orally in a loading dose of 400 mg twice daily (for one day) then 200 mg twice daily for four days [22]. Potential adverse effects include cardiac conduction QT-prolongation and a number of drug-drug interactions.

An observational study examined the association between hydroxychloroquine use and clinical outcomes, analyzing data from 1,376 consecutive patients with COVID-19 admitted to a clinical center in New York City between March 7 and April 8, 2020 [37]. To assess potential benefit or detrimental effect, the primary end point selected was a composite of intubation or death in a time-to-event analysis, comparing outcomes in patients who received hydroxychloroquine with those who did not. A total of 811 patients (59%) were treated with hydroxychloroquine for a median of five days, 60% of whom also received azithromycin. After adjusting for severity of illness, the investigators

found no significant difference in the rate of the composite end point of intubation or death over a median follow-up of 22.5 days. Thus, the risk of intubation or death was not significantly different among hospitalized patients with COVID-19 who received hydroxychloroquine than among those who did not [37].

Randomized, controlled clinical trials to assess efficacy of hydroxychloroquine in patients hospitalized with COVID-19 have not shown a benefit. A multicenter study of hospitalized patients with mild-to-moderate COVID-19 found that hydroxychloroquine, alone or in combination with azithromycin, was no more effective than standard care in improving clinical status at 15 days [70]. Preliminary analysis of data from a multicenter, randomized trial in the United Kingdom found no reduction in 28-day mortality among those treated with hydroxychloroquine when compared with the control group [71]. Hydroxychloroquine use was associated with increased length of hospital stay and increased risk of progressing to invasive mechanical ventilation. An NIH-sponsored, controlled clinical trial was halted (after the fourth interim analysis) because hydroxychloroquine was found unlikely to be beneficial to hospitalized patients with COVID-19 [72]. As of November 2021, multiple randomized, controlled trials have failed to demonstrate any significant benefit for hydroxychloroquine in outpatient treatment of mild COVID-19 or as primary or secondary prophylaxis against SARS-CoV-2 infection.

On June 15, 2020, the FDA revoked the EUA that allowed for chloroquine and hydroxychloroquine donated to the Strategic National Stockpile to be used to treat certain hospitalized patients with COVID-19 when a clinical trial was not available or feasible [58]. This decision was based on an ongoing analysis of emerging data indicating that these drugs are unlikely to be effective for patients hospitalized with COVID-19. As of December 28, 2022, the NIH Panel continues to recommend against the use of hydroxychloroquine or chloroquine with or without azithromycin [57].

Ivermectin

Ivermectin is an antiparasitic drug approved by the FDA for the treatment of several tropical diseases (e.g., onchocerciasis, helminthiases, scabies) and under investigation for the prevention of malaria transmission. Ivermectin is poorly absorbed from the intestinal tract, which enhances its effectiveness against parasitic infections confined largely to the intestinal tracts of humans and large mammals (e.g., sheep, cattle, horses). Reports from in vitro studies suggest that ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host's antiviral response. In addition, ivermectin docking may interfere with the attachment of the SARS-CoV-2 spike protein to the human cell membrane. Although ivermectin inhibits SARS-CoV-2 replication in vitro (cell culture), the effect is dose-dependent, meaning that inhibition is observed when the concentration of ivermectin is raised to a certain level. Furthermore, the ivermectin concentration required for in vitro inhibition of SARS-CoV-2 is 50 to 60 times higher than can be achieved in humans by standard oral doses of the drug. Pharmacokinetic and pharmacodynamic studies suggest that achieving the plasma concentrations necessary for the antiviral efficacy detected in vitro would require administration of doses up to 100-fold higher than those approved for use in humans.

In 2021, ivermectin dispensing by retail pharmacies increased dramatically, as did the use of available over-the-counter veterinary formulations not intended for human consumption. The number of ivermectin prescriptions dispensed in the United States increased from 3,600 per week at the prepandemic baseline to more than 88,000 per week in August 2021 [167]. During the same period, state poison control centers across the country reported a fivefold increase in consultations for human exposures to ivermectin [167; 168]. Misuse of prescription ivermectin by excess dosage or duration can have adverse effects. Veterinary formulations

intended for use in horses and cattle are often highly concentrated and unsafe for ingestion by humans. Clinical signs of ivermectin toxicity include gastrointestinal upset, confusion, ataxia, hypotension, disturbances of vision, hallucinations, seizures, and coma.

Ivermectin is neither authorized nor approved by FDA for prevention or treatment of COVID-19. Clinical studies regarding the use of ivermectin to treat or prevent COVID-19 have been conflicting, and many studies had incomplete information and significant methodological limitations. Among 400 patients with mild COVID-19, a double-blind, randomized, placebo-controlled trial of ivermectin 300 mg/kg twice daily for five days found that ivermectin had no significant effect on time to resolution of symptoms compared with placebo [169]. A larger, double-blind, randomized, placebo-controlled trial of early ivermectin treatment for COVID-19 (679 patients in each comparator group) found that ivermectin did not lower the rate of hospitalization (progression of disease) or duration of time required for emergency department observation [170]. In a randomized, placebo-controlled trial among patients hospitalized with mild-to-moderate COVID-19, treatment with ivermectin on admission had no beneficial effect on the rate of disease progression (21.6%) compared with standard care (17.3%) [171]. The rates of COVID-19-associated ICU admission, mechanical ventilation, and mortality were not significantly different for the ivermectin group than the control group. Due to the lack of reliable and accurate data, the NIH Panel does not recommend either for or against the use of ivermectin for the treatment of COVID-19 [57].

Approaches to Disease Modification

Severe SARS-Cov-2 infection results in progressive interstitial-alveolar pneumonia and respiratory failure. Disease pathogenesis is linked to activation of the innate immune system and dysregulation of adaptive immune responses, with release of proinflammatory cytokines and chemokines. Death from COVID-19 is often preceded by signs of a hyperimmune inflammatory response ("cytokine storm") that leads to ARDS, multi-organ dysfunction, and circulatory collapse. Laboratory markers of heightened inflammation include elevated C-reactive protein, ferritin, and interleukin-6. Novel approaches to clinical treatment attempt to modify disease progression and prevent or ameliorate pulmonary and systemic complications of cytokine storm, thereby reducing mortality from COVID-19.

COVID-19 Convalescent Plasma

In the past, passive immunization with plasma obtained from surviving patients has been used to treat life-threatening infections absent specific therapy. Early in the COVID-19 pandemic, before emergence of SARS-CoV-2 variants that evade neutralizing antibody, studies demonstrated that intravenous transfusion of convalescent plasma with high-titer antibody directed against SARS-CoV-2 was effective in reducing mortality in hospitalized patients with COVID-19 pneumonia. In a preliminary, uncontrolled case series of five critically ill Chinese patients with COVID-19 and ARDS, administration of convalescent plasma containing neutralizing antibody was followed by improvement in clinical status, including resolution of ARDS in four patients at 12 days after transfusion [27].

A study from the Mayo Clinic Expanded Access Protocol (EAP) involving 35,322 registered patients found that plasma infusion was safe and reduced COVID-19 mortality if administered early after hospitalization [76]. A subset analysis showed a gradient of mortality in relation to IgG antibody levels in transfused plasma. The risk of dying from COVID-19 was lower among patients who had received convalescent plasma units containing high titer anti-SARS-CoV-2 antibody than among those who received plasma containing low antibody levels. The pooled relative risk reduction among patients transfused with high antibody level plasma units versus low-level antibody plasma was 35% at 7 days and 23% at 30 days. The Mayo EAP report is an analysis of registry data and not a randomized controlled study.

On August 23, 2020, the FDA granted an EUA to COVID-19 convalescent plasma for treatment of patients hospitalized with COVID-19 [73]. This decision was based on historical evidence derived from the use of plasma in prior outbreaks of respiratory virus infection, small case series, and non-randomized clinical trials conducted during the current outbreak. The only double-blind, placebo-controlled clinical trial of convalescent plasma failed to demonstrate a reduction in mortality or improvement in other clinical outcomes [93]. This study enrolled 333 patients with severe COVID-19 pneumonia, randomized in a 2:1 ratio to receive convalescent plasma (228 subjects) or placebo (105 subjects). Of the total, 68% were men and 65% had a coexisting condition at entry into the trial. The median time from onset of COVID-19 symptoms to enrollment was eight days. More than 90% were receiving oxygen and glucocorticoids at the time of entry into the trial. The infused convalescent plasma had a median titer of 1:3,200 of total SARS-CoV-2 antibodies. At 30 days, the clinical status of patients in the convalescent plasma group did not differ significantly from that of patients in the placebo group. The proportion of ICU admissions and invasive ventilatory support requirements were similar in both groups. Overall mortality was 11.43% in the placebo group and 10.96% in the convalescent plasma group. In a subset analysis, no differences favoring convalescent plasma were noted in a group of 39 patients who received the intervention within 72 hours of symptom onset [93]. Of note, all patients in this study had signs of severe pneumonia; thus, no firm conclusion can be drawn as to the potential efficacy of COVID-19 convalescent plasma initiated at an earlier stage of illness.

Convalescent plasma therapy is not beneficial for hospitalized patients with COVID-19 pneumonia; however, high-titer convalescent plasma administered within three to five days of symptom onset was shown to reduce the risk of disease progression caused by strains of SARS-CoV-2 circulating early in the pandemic. Evidence for this comes from a randomized, placebo-controlled trial of convalescent plasma with high IgG titers against SARS-CoV-2 administered to older adults within 72 hours after onset of mild COVID-19 symptoms. In a subset of patients who received high-titer plasma therapy, 13 of 80 (16%) patients progressed to severe respiratory disease, compared with 25 of 80 patients (31%) who received placebo [109]. This corresponds to a relative risk reduction of 48%. The study population consisted of adults 75 years of age or older, or between 65 and 74 years of age with at least one coexisting condition.

The FDA has subsequently revised the EUA to limit authorization to the use of COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies for treatment of COVID-19 in patients with immunosuppressive disease or immunosuppressive treatment [179]. The FDA also issued new guidance for healthcare providers and investigators, with recommendations on pathways for use of investigational convalescent plasma, collection of convalescent plasma, and record keeping [179].

Monoclonal Antibody to SARS-CoV-2

Modern immunologic techniques enable the identification of pathogen-specific memory B cells and recovery of immunoglobulin genes that can be expressed to produce monoclonal antibodies [85]. FDA-approved monoclonal antibody products are available to treat or prevent respiratory-syncytial virus, anthrax, and *Clostridioides difficile*. Memory B cells harvested from patients recovering from COVID-19 have been used to produce anti-SARS-CoV-2 monoclonal antibodies directed against the surface spike glycoprotein, preventing entry of virus into host cells. Monoclonal antibody infusions have potential for preventing COVID-19 in vulnerable people and for blocking disease progression in patients at risk for severe illness. Given the long half-life of immunoglobulin (approximately three weeks), a single monoclonal antibody infusion should suffice for either prevention or treatment of COVID-19 [85]. A phase 2 randomized study among outpatients with mild or moderate COVID-19, during circulation of the original strain SARS-CoV-2, found that infusion of bamlanivimab (a monoclonal neutralizing antibody) was followed by a rapid decline in viral load and reduced need for further medical attention

[94]. Subsequent COVID-related hospitalization or emergency department care was required in 1.6% of patients in the monoclonal antibody group, compared with 6.3% in the placebo group.

Four monoclonal antibody products (bamlanivimab plus etexevemab, casirivimab plus imdevimab, sotrovimab, and bebtelovimab) have received EUAs from the FDA for treatment of outpatients with mild-to-moderate COVID-19. Placebo-controlled clinical trials performed during the first year of the pandemic found that treatment with anti-SARS-CoV-2 monoclonal antibodies reduced the risk of hospitalization or death 70% to 85% [57]. Following emergence of the Omicron variant in early 2022, soltrovimab was recommended over other products when studies demonstrated that only sotrovimab exhibited acceptable activity against the Omicron subvariants in circulation at that time.

Outpatient monoclonal antibody therapy is useful during periods when the dominant SARS-CoV-2 variant in circulation shows little evidence of immune evasion. This mode of therapy is reserved for at-risk symptomatic patients and should be administered soon after confirmation of SARS-CoV-2 infection, within 7 to 10 days of symptom onset. Patients with symptomatic COVID-19 who meet one of the following criteria are eligible for treatment:

- Body mass index >35
- Diabetes
- Chronic kidney disease
- Immunosuppressive disease or current immunosuppressive treatment
- Age 65 years or older or 55 years or older with underlying cardiovascular disease, hypertension, or chronic lung disease

The NIH guidelines provide updated guidance on current efficacy, patient selection criteria, authorized dosage, and treatment precautions. As of February 2023, the NIH Panel recommends against using anti-SARS-CoV-2 monoclonal antibody for the treatment of COVD-19 because current Omicron subvariants in circulation are not expected to be susceptible to these products [57].

Anti-Inflammatory/Immunomodulatory Drugs

Dexamethasone

A large multicenter therapeutic trial demonstrated that dexamethasone (a glucocorticoid) improves survival in patients hospitalized with COVID-19 who require supplemental oxygen and/or some degree of ventilatory support [63]. In this study platform, patients were randomly assigned to a group of different therapies and efficacy was assessed using a single endpoint: mortality within 28 days after randomization. In total, 2,104 patients were assigned to receive dexamethasone at a dose of 6 mg daily, and 4,321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1,110 patients (25.7%) in the usual care group died within 28 days after randomization. The observed differences in mortality varied in relation to the level of respiratory support patients required upon entry to the study. Among patients receiving mechanical ventilation, the 28-day mortality was significantly lower in the dexamethasone group (29.3%) than that in the usual care group (41.4%). Among patients receiving supplemental oxygen without mechanical ventilation, the observed benefit was less pronounced but also significant, 23.3% in the dexamethasone group and 26.2% in the usual care group. There was no demonstrable benefit from dexamethasone treatment in patients who did not require oxygen.

The NIH Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) for the treatment of COVID-19 in patients who are mechanically ventilated and in patients who only require supplemental oxygen (not mechanical ventilation) [57]. If dexamethasone is not available, equivalent doses of another glucocorticoid may be used, such as prednisone 40 mg/day or methylprednisolone 32 mg/day. Dexamethasone is the preferred glucocorticoid to use in pregnant women with COVID-19 who require respiratory support, because of the potential benefit of decreased maternal mortality and the known low risk of fetal adverse effects associated with short-course maternal dexamethasone therapy [57]. Patients receiving dexamethasone at the time of hospital discharge should be given a prescription to complete the specified

10-day course. The NIH Panel recommends against the use of dexamethasone in patients with COVID-19 who do not require supplemental oxygen.

Potential adverse effects of glucocorticoid use include hyperglycemia and opportunistic infection. Clinicians should be mindful of Strongyloides hyperinfection syndrome as a complication of modest-dose and short-duration dexamethasone regimens [75]. Patients at risk are those who have previously resided in South America, the Caribbean, the Middle East, Africa, or Asia. Clinical indicators of possible subclinical or unrecognized Strongyloides infection include peripheral eosinophilia and unexplained gram-negative bacteremia [75].

Tocilizumab and Baricitinib

Patients hospitalized with COVID-19 and worsening hypoxemia despite high-flow supplemental oxygen and/or ventilatory support plus dexamethasone often have signs of ongoing systemic inflammation. Clinical trials have demonstrated that these patients benefit from combining dexamethasone with an additional immunomodulator, such as an interleukin (IL)-6 inhibitor (e.g., tocilizumab) or Janus kinase (JAK) inhibitor (e.g., baricitinib, tofacitinib) [57]. The NIH Panel recommends baricitinib or tofacitinib in addition to dexamethasone in hospitalized COVID-19 patients on high-flow oxygen or noninvasive/mechanical ventilation, who have evidence of systemic inflammation and increasing oxygen needs [57].

Tocilizumab, a monoclonal antibody directed against the interleukin-6 receptor, can be effective in mitigating the cytokine storm associated with COVID-19 hyperinflammatory states. A retrospective cohort study of hospitalized patients requiring ICU support found that treatment with tocilizumab was associated with reduced mortality [74]. Of 630 patients selected for analysis, 358 (57%) died—102 (49%) who received tocilizumab and 256 (61%) who did not receive tocilizumab. The primary multivariable Cox regression analysis showed an association between receipt of tocilizumab and reduction in hospital-related mortality. This association was also noted among subgroups requiring mechanical ventilation and with baseline C-reactive protein of 15 mg/dL or higher. In contrast to findings from this and other observational studies of COVID-19 pneumonia, randomized clinical trials have not demonstrated a mortality benefit with tocilizumab therapy [91]. Tocilizumab has been reported to reduce the requirement for mechanical ventilation in some patient populations, thereby alleviating the burden on ICU-level care for management of severe COVID-19. A published editorial assessment concluded that newly released randomized trials suggest a potential role for tocilizumab in COVID-19 but do not show clear evidence of efficacy [91].

JAK inhibitors interfere with phosphorylation of key proteins required for signal transduction that promotes immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as IL-6) [57]. The FDA has issued an EUA for baricitinib to treat COVID-19 in hospitalized adults and in pediatric patients 2 to 17 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO [175]. The recommended dosage of baricitinib under the EUA is 4 mg once daily for patients 9 years of age and older or 2 mg once daily for patients 2 to 8 years of age. Treatment should continue for 14 days or until hospital discharge, whichever occurs first [175].

Before initiating therapy, baseline glomerular filtration rate, liver enzyme level, and complete blood count should be assessed, as modifications in approach are necessary with abnormalities in any of these values. Baricitinib is not recommended for patients with active tuberculosis, who are on dialysis, have end-stage renal disease, or have acute kidney injury [175].

MANAGEMENT OF COVID-19 IN THE AMBULATORY CARE SETTING

Approximately 80% of patients presenting with COVID-19 have mild symptoms (having no signs of viral pneumonia or hypoxemia) and do not need medical intervention [57]. Most patients with mild COVID-19 can be managed as outpatients, with supportive care and counseling on when to seek in-person evaluation. As noted, clinical signs of progression to lower respiratory tract disease tend to become manifest toward the second week of illness. Patients 65 years of age and older and all others with risk factors for progression to severe illness should be monitored closely, including those who are obese, pregnant, or have comorbidities such as COPD, cardiovascular disease, diabetes, cancer, and immunosuppressive disorders. Patients with mild COVID-19 and risk factors for disease progression may be candidates for early antiviral therapy. All patients, regardless of risk profile, who present with moderate COVID-19 (i.e., having signs of viral pneumonia but without hypoxemia) require in-person evaluation and follow-up for signs of respiratory insufficiency. Patients with severe COVID-19 (i.e., having dyspnea, hypoxemia, or lung infiltrates) require immediate hospitalization.

Several therapeutic options are now available for treatment of nonhospitalized patients with mild COVID-19 who are at risk of progressing to severe illness, including anti-SARS-CoV-2 monoclonal antibody, parenteral remdesivir, and oral anti-SARS-CoV-2 agents. Factors to consider in selecting the best treatment option for a given patient are clinical efficacy and availability of the treatment option, feasibility of parenteral administration (for remdesivir or monoclonal antibody), potential drug-drug interactions (particularly those associated with use of nirmatrelvir-ritonavir), and the local prevalence of SARS-CoV-2 variants of concern [57]. As of February 2023, the predominant SARS-CoV-2 Omicron subvariants in circulation are not considered susceptible to available monoclonal antibody products. Administration of remdesivir requires three consecutive days of intravenous infusion. Nirmatrelvir-ritonavir is the preferred choice for most patients, but necessitates reviewing concurrent medications and supplements for potential drug-drug interactions. Molnupiravir, which has a lower efficacy than the other treatment options, should only be used when other options are not available [57].

Isolation and Transmission Precautions

The CDC advises that the decision to monitor a patient in the outpatient or inpatient setting should be made on a case-by-case basis. Important considerations are the patient's clinical status, reliability, need of clinical monitoring, and options for home isolation to reduce risk of secondary transmission. General guidance on patient isolation and transmission precautions for people with COVID-19 is available at https://www.cdc.gov/coronavirus/2019-ncov/your-health/isolation.html.

The CDC recommends that for most patients with confirmed SARS-CoV-2 infection, the decision to discontinue transmission-based precautions should be made using a symptom-based strategy [88]. Patients with mild-to-moderate COVID-19 may discontinue isolation five days after onset of illness if respiratory symptoms have improved and at least 24 hours have passed since resolution of fever (without the use of fever-reducing medications). For patients who were asymptomatic throughout their infection, precautions may be discontinued when at least five days have passed since the date of the first positive viral diagnostic test. A well-fitted face mask should be worn by symptomatic and asymptomatic persons during the period of isolation and for five additional days when around others and in public. Additional considerations, including extending the period of isolation precautions to 10 days or more, apply to patients who have sustained severe or critical illness and to those who are significantly immunocompromised [88].

COVID-19 VACCINES

Development of vaccines against coronavirus began in response to the 2002–2004 SARS outbreak, but was halted because propagation of SARS-CoV disappeared rapidly. These earlier preclinical studies identified the optimal coronavirus target antigen and laid the groundwork for current SARS-CoV-2 vaccine development. Coronaviruses encode for a single large surface glycoprotein, the spike protein, which is responsible for host receptor binding and membrane fusion [97]. As noted, SARS-CoV-2 spike protein binds to ACE2 receptors on host cells and facilitates release of the viral genome into the cytoplasm where replication of new virions begins. Antibodies that bind to the spike protein prevent attachment and neutralize virus spread [97]. On the basis of these observations, the spike protein became the principal antigenic target for development of vaccines against SARS-CoV-2.

By December 2020, more than 180 candidate vaccines were in preclinical studies worldwide, and several had entered clinical trials. The range of vaccine platforms included inactivated-virus and live-virus vaccines, recombinant protein vaccines, vectored vaccines, and novel RNA and DNA vaccines [97]. Three vaccines showed promising early results, confirmed by phase 3 clinical trials. Two vaccine candidates were messenger RNA (mRNA) vaccines developed by Pfizer-BioNTech and Moderna, and the third candidate vaccine was an adenovirus-vectored vaccine developed by Astra-Zeneca and University of Oxford. Pfizer and the German company BioNTech reported preliminary results of an ongoing phase 1 mRNA vaccine trial in 45 healthy adults 18 to 55 years of age [64]. All participants developed an immune response. Following the second dose, antibody titers and serum neutralizing antibody activity were comparable to levels measured in a control panel of SARS-CoV-2 convalescent serum. Adverse events such as fatigue, myalgia, feverishness, and pain at injection site were common after the second injection. In a follow-up report of 40 older adults (50% 56 to 70 years of age and 50% older than 70 years of age) administered the mRNA vaccine, the safety profile and immunogenicity were comparable to results in the younger cohort of participants [86]. Enrollment in a phase 3 trial began in late July 2020.

A report from the University of Oxford described early results of a clinical trial using a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCov-19) that expresses a full-length version of the SARS-CoV-2 spike protein [65]. In a phase 1/2 randomized controlled trial, 1,077 healthy adults received either the candidate vaccine or a meningococcal conjugate vaccine as control. After one dose, ChAdOx1 nCoV-19 elicited spike-specific T-cell responses that peaked on day 14 and measurable anti-spike IgG antibody by day 28. Strong humoral and cellular immune responses persisted at day 56 of the ongoing trial. Neutralizing antibody was detected in 32 (91%) of 35 participants after a single dose, and in 10 (100%) of 10 participants who received a booster dose. Adverse events such as discomfort at injection site, fever, malaise, and headache were common but mild or moderate and self-limiting. There were no serious adverse reactions. Progression to phase 2/3 trials began in the summer of 2020, recruiting older age groups with comorbidities, healthcare workers, and those at higher risk for SARS-CoV-2 exposure [65].

COVID-19 MRNA VACCINES

COVID-19 mRNA vaccine is the product of a new vaccine technology with important public health advantages. An mRNA vaccine can be produced completely in vitro, which facilitates purification and allows for rapid production of individual vaccine doses. The COVID-19 mRNA vaccine consists of a nucleoside-modified messenger RNA wrapped in a lipid-laden nanoparticle. The vaccine mRNA encodes for SARS-CoV-2 surface spike protein. The lipid envelope facilitates vaccine delivery into host cells, enhances stability, and may also augment the immune response. Following intramuscular inoculation, host myocytes utilize vaccine mRNA to express SARS-CoV-2 antigen on cell surfaces, which in turn elicits neutralizing antibody and cellular immune responses to SARS-CoV-2. Vaccine mRNA does not enter the host cell nucleus and cannot become part of the host's own DNA.

Phase 3 clinical trials demonstrated the Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines to be safe and 94% to 95% effective against the original strain of SARS-CoV-2 [98; 99]. In the Pfizer-BioNTech vaccine trial, 43,448 adults were randomized to receive vaccine (21,720 participants) or placebo (21,728 participants) in two doses 21 days apart [98]. The primary outcomes were safety and the incidence of symptomatic COVID-19 at least seven days after the second vaccine dose. The interim analysis included the first 170 cases of symptomatic COVID-19 diagnosed in the study population and covered a median of two months of safety data. Of the total, eight cases of COVID-19 were observed in the vaccine group and 162 cases in the placebo group. This corresponds to a vaccine efficacy of 95.0%. Vaccine efficacy was similar across subgroups defined by age, sex, race, body mass index, and coexisting medical conditions. Ten cases of severe COVID-19 occurred with onset after the first dose, of which nine were in placebo recipients. Post-vaccination reactions included mild-to-moderate localized pain at the injection site and transient systemic reactions such as fatigue, fever, and headache. Systemic reactions occurred more commonly in younger vaccine recipients (16 to 55 years of age) and after the second dose [98]. The Moderna phase 3 vaccine trial results were equally favorable [99]. In this trial, 30,420 adult participants were randomly assigned to receive either two doses of vaccine or placebo 28 days apart. Of 196 confirmed cases of symptomatic COVID-19 with onset at least 14 days after the second inoculation, 185 cases were in the placebo group and 11 in the vaccine group, a vaccine efficacy of 94.1%. Severe COVID-19, including one fatality, occurred in 30 participants, all of whom were in the placebo group. Transient local and systemic post-vaccination reactions occurred commonly; no safety concerns were identified [99].

In mid-December 2020, following independent verification of safety and efficacy data, the FDA issued an EUA to the Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines for use in adults and older adolescents. After reviewing efficacy and safety data in spring 2021, Pfizer mRNA COVID-19 vaccine received FDA EUA for use in adolescents 12 to 18 years of age. In November 2021, the FDA issued an EUA and the CDC/ACIP recommended Pfizer COVID-19 vaccine use, at reduced dosage, in children 5 to 11 years of age. Providers should advise mRNA COVID-19 vaccine recipients to expect local reactions (e.g., injection site pain, swelling, erythema, localized axillary lymphadenopathy) and systemic symptoms such as fever, fatigue, headache, or myalgias. Most post-vaccination side effects are mild and resolve within one to three days of onset.

COVID-19 ADENOVIRUS VECTOR VACCINE

In February 2021, Johnson and Johnson (Janssen Pharmaceuticals) received an EUA for Janssen COVID-19 vaccine use in adults [110]. This is a recombinant, replication-incompetent adenovirus vector vaccine encoded for the SARS-CoV-2 prefusion spike glycoprotein. Interim data from an international phase 3 clinical trial demonstrated that a single dose of Janssen COVID-19 vaccine was highly effective in preventing COVID-19-associated hospitalization and death [110]. The phase 3 study enrolled 43,783 participants across three regions: 44% from United States, 41% from Latin America, and 15% from South Africa. One-third of the participants were older than 60 years of age and 41% had underlying chronic health conditions. At 14 days following vaccination, the Janssen vaccine was 66% effective in preventing symptomatic COVID-19. After 28 days, vaccine efficacy was 85% against severe disease and 93% effective in preventing hospitalization. Among participants in South Africa, where 95% of COVID-19 cases were caused by the B.1.351 variant, vaccine efficacy against severe disease was 89%. No COVID-19 deaths were reported in the vaccine group, compared with seven deaths in the placebo group. Vaccine administration side

effects were mild-to-moderate, and adverse events were rare and manageable; no anaphylaxis was encountered [110].

As of January 2023, four COVID-19 vaccines are approved or authorized in the United States: Pfizer-BioNTech, Moderna, Johnson & Johnson/Janssen (J&J/Janssen), and Novavax [101]. The J&J/Janssen COVID-19 vaccine is authorized only for certain situations because of safety concerns. The CDC/ACIP recommend COVID-19 vaccination for everyone 6 months and older for prevention of COVID-19; updated guidance is available at the CDC website, including recommended schedules for primary and bivalent booster, contraindications, anticipated side effects, and COVID-19 vaccination in pregnancy and certain other underlying medical conditions [101]. While protection against Omicron subvariant infection is not as strong as for earlier SARS-CoV-2 strains, COVID-19 vaccines (bivalent booster) remain highly protective against severe illness, hospitalization, and death.

Data from clinical trials indicate that it is safe to offer vaccination to persons with evidence of a prior SARS-CoV-2 infection, and the CDC recommends doing so after 90 days have passed since diagnosis [101]. Studies show natural immunity following SARS-CoV-2 infection is enhanced by COVID-19 vaccination. Anti-spike antibody titers increased more than 140-fold from peak pre-vaccine levels following a single dose of mRNA vaccine [111]. A small cohort study in persons previously infected found that a single dose of vaccine substantially increased neutralizing activity against the important SARS-CoV-2 variants circulating in the United States [112]. Data from virologic investigations and epidemiologic studies have demonstrated that immunity derived from natural infection combined with vaccination (hybrid immunity) provides the most effective, durable level of protection against COVID-19.

COVID-19 VACCINES AND PREGNANCY, LACTATION, AND FERTILITY

As noted, observational data demonstrate that pregnant persons are at increased risk of severe illness and complications from COVID-19, and higher rates of ICU admission and mechanical ventilation [107]. Related concerns include the possibility that COVID-19 during pregnancy may increase the risk for adverse pregnancy outcomes (e.g., pre-eclampsia, coagulopathy, preterm birth) [101]. Any currently authorized COVID-19 vaccine can be administered to pregnant or lactating people; the ACIP does not state a product preference [101; 149].

Vaccination reduces the risk of getting COVID-19 and protects patient and fetus from severe consequences. Vaccination while pregnant has the added benefit of providing transplacental maternal antibody protection to the newborn for some months after delivery. Studies show that maternal neutralizing antibodies directed against SARS-CoV-2 are present in umbilical cord blood of newborn infants and in breast milk [138].

There is no expectation that COVID-19 vaccines would pose a risk to pregnant persons or the fetus based on current knowledge of human coronaviruses and the science of COVID-19 vaccine development. The authorized COVID-19 vaccines in use are non-replicating vaccines; they do not contain intact virus and cannot cause infection in either the mother or fetus [101]. No reproductive, fetal developmental, or safety concerns were demonstrated in preclinical vaccine studies in animals, nor were any adverse pregnancy-related outcomes, including fetal outcomes, determined to be related to previous use of an adenovirus vector platform in a large-scale Ebola virus vaccine trial [101].

The CDC has three national surveillance programs in place to monitor the safety and efficacy of COVID-19 vaccination in pregnant persons [139]. As of October 25, 2021, more than 169,000 participants had enrolled in the CDC v-safe Health Checker, indicating they were pregnant when vaccinated against COVID-19. The COVID-19 Vaccination Registry, a subset of 5,100 participants enrolled within 30 days of vaccination, provided direct contact and detailed surveillance, including access to medical records. To date, there has been no indication of increased risk of pregnancy loss or adverse effects on fetal growth and development, or other safety concerns among pregnant or lactating individuals. An analysis of outcomes among registry participants vaccinated before 20 weeks' gestation found no increased risk of miscarriage in association with COVID-19 vaccine use early in pregnancy [140]. A case-control analysis of outcomes from Norwegian registries on first-trimester pregnancies also found no evidence of an increased risk for early pregnancy loss after COVID-19 vaccination [141]. In general, there is no difference in the incidence of pregnancy loss, preterm birth, delayed gestational growth, congenital abnormalities, and neonatal death among pregnant persons who have received mRNA vaccine compared with the known background incidence of these events in unvaccinated pregnant persons.

The Academy of Breastfeeding Medicine has not advised cessation of breastfeeding for individuals who are vaccinated against COVID-19 [142]. The Academy considers it unlikely that vaccine lipid would enter the blood stream and reach breast tissue, and if it did, even less likely that either the intact nanoparticle or mRNA would transfer into milk. In the unlikely event mRNA is present in milk, it would be digested by the child and be unlikely to have any biological effects. In a study of seven breastfeeding mothers who received either Pfizer or Moderna COVID-19 vaccine, analysis of 13 samples of breast milk obtained 4 to 48 hours after vaccination found no detectable mRNA or any other vaccine-related particles in any of the samples tested [143].

On September 14, 2021, the Society for Maternal and Fetal Health and the American College of Obstetrics and Gynecology, along with 18 other professional organizations representing nurse practitioners, nurse-midwives, pediatricians, infectious disease specialists, and public health professionals, issued a joint Statement of Strong Medical Consensus for Vaccination of Pregnant Individuals Against COVID-19 [144]:

> As the leading organizations representing experts in maternal care and public health professionals that advocate and educate about vaccination, we strongly urge all pregnant individuals—along with recently pregnant, planning to become pregnant, lactating, and other eligible individuals—to be vaccinated against COVID-19.

A conversation between the patient and clinical team may assist with decisions about the selection and timing of a COVID-19 vaccine during pregnancy, though a discussion with a healthcare provider is not required before vaccination [101]. In making a decision, patient and provider should consider the level of SARS-CoV-2 community transmission, the patient's risk of contracting COVID-19, the risks of COVID-19 to the patient and potential risks to the fetus, the efficacy and side effects of the vaccine, and data about COVID-19 vaccine use in pregnancy [101]. Pregnant persons who choose to receive COVID-19 vaccine are encouraged to enroll in the CDC's v-safe registry, established to follow outcomes among people who are vaccinated [113].

Concerning infertility, there is no scientific basis for COVID-19 vaccines having any impact on fertility, and no scientific evidence that these vaccines cause sterility in either women or men. Claims that vaccine-derived antibodies directed against SARS-CoV-2 spike protein cross-react with uterine syncytin-1 protein, causing damage to the developing trophoblast and preventing implantation of the embryo, are unfounded. A study comparing implantation and sustained pregnancy success rates among individuals receiving frozen embryo transfer found

no significant difference in outcomes among vaccine seropositive, infection seropositive, and seronegative participants. Rates of sustained embryo implantation for seronegative, vaccine seropositive, and infection seropositive patients were 52.3%, 65.7%, and 47.4%, respectively [150]. These success rates were comparable to those achieved pre-COVID-19. The investigators concluded that seropositivity to the SARS-CoV-2 spike protein derived from either vaccination or infection, had no adverse effect on embryo implantation or early pregnancy development.

There are no studies showing COVID vaccination reduces sperm concentration or motility. Among 45 male volunteers for baseline and post-vaccination measure of sperm parameters, no significant differences in semen volume, sperm counts, or sperm motility were found after two doses of mRNA COVID-19 vaccine [151]. On the other hand, male sexual dysfunction and related fertility issues have been reported as potential late complications of symptomatic COVID-19 [152].

COVID-19 VACCINE SAFETY

Adverse Reactions to COVID-19 mRNA Vaccines

Early side effects, such as soreness at injection site, fatigue, and headache, occur in about 50% of vaccine recipients; feverishness is less common, and all side effects usually resolve in 12 to 36 hours. Immediate, severe allergic reactions (anaphylaxis) do occur rarely within 15 minutes after injection, as with influenza vaccine. Anaphylaxis was not observed during clinical trials, in part because potential participants who had experienced reactions to vaccines were excluded. However, according to a review of SARS-CoV-2 vaccine safety, several cases of anaphylaxis associated with the Pfizer mRNA vaccine were reported following vaccination of 2 million healthcare workers in the United States [102]. For most vaccines in common use, vaccine-associated anaphylaxis has been a rare event, at about one case per million injections. The estimated risk of anaphylaxis associated with use of the Pfizer mRNA vaccine is 1 in 100,000 inoculations—10 times higher [102]. The explanation for this is unclear. One component unique to mRNA vaccines is a polyethylene glycol (PEG) 200 lipid conjugate used to stabilize the nanoparticle carrier system. PEG is a stabilizing compound commonly used in medications and other products and has been implicated in IgE-mediated reactions and recurrent anaphylaxis [102]. This has raised concern that individuals sensitized by past exposure to PEG (or its polysorbate derivative) in commercial products may be at risk of anaphylactic reactions from mRNA vaccination. Anaphylaxis is an acute allergic reaction that can lead to upper airway obstruction, bronchospasm, and circulatory collapse. Prompt recognition and treatment with epinephrine is necessary to prevent life-threatening complications.

A detailed discussion of contraindications and precautions to be observed with mRNA vaccine administration is included in the guidance provided by the CDC [101]. The history of any one of the following reactions is considered a contraindication to vaccination with either the Pfizer-BioNTech or Moderna COVID-19 vaccines [101]:

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA vaccine or any of its components
- Immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including PEG)
- Immediate allergic reaction of any severity to polysorbate (due to potential cross-reactive hypersensitivity with the vaccine ingredient PEG)

Persons with an immediate allergic reaction to the first dose of an mRNA vaccine should not receive additional doses of either of the mRNA COVID-19 vaccines [101]. Healthcare providers who participate in mRNA vaccine administration should be familiar with signs and symptoms of hypersensitivity reactions and have access to medications and supplies needed for assessing and managing anaphylaxis. The CDC has provided interim guidance on preparation for the potential management of anaphylaxis after COVID-19 vaccination [103].

Delayed-onset local reactions have been reported after mRNA vaccination in some individuals beginning a few days through the second week after the first dose [101; 114]. The suspected cause is delayed-type or T-cell-mediated hypersensitivity, and reactions resolve within a few days. In a small series report, the recurrence rate following the second dose was less than 50% [114]. Vaccinees with only a delayed-onset local reaction (e.g., erythema, induration, pruritis) around the injection site do not have a contraindication or precaution to the second dose of vaccine. The CDC recommends these individuals receive the second dose using the same vaccine product as the first dose at the recommended interval, preferably in the opposite arm [101].

Immune Thrombotic Thrombocytopenia and Adenovirus-Vectored Vaccines

On April 13, 2021, after more than 6.8 million doses of the Janssen COVID-19 vaccine had been administered in the United States. the FDA placed a pause on use of this vaccine while the CDC investigated reports of severe intravascular clotting events in six vaccine recipients within two weeks following vaccination [127]. A rare form of blood clot (cerebral venous sinus thrombosis) combined with thrombocytopenia was observed between the 6th and 13th day after vaccination. All cases were women 18 to 48 years of age, one of whom died. The pause was for purposes of further analysis and so health professionals could become familiar with the diagnostic and management implications. Treatment of this clotting disorder is different from heparin anticoagulant typically administered for treatment of blood clots. Administration of heparin may be dangerous, and alternative therapies are needed for management of COVID-19 vaccine-associated thrombotic complications [127]. The risk of cerebral venous thrombosis following Jenssen COVID-19 vaccination was approximately 1 in 1,000,000 vaccinees.

AstraZenica COVID-19 vaccine, the other primate adenovirus-vectored vaccine used in Europe, has also been linked to thrombotic events in vaccinees. In two separate reviews (11 cases from Germany and Austria, and 5 cases from Norway), patients presented 5 to 16 days after vaccination with thrombocytopenia and signs of vascular thrombosis at unusual sites [128; 129]. In patients with one or more thrombotic events, there were 13 instances of cerebral venous thrombosis, 4 of splanchnic-vein thrombosis, 2 of pulmonary embolism, and 4 involving other sites. The patient age range was 22 to 54 years, and 13 of 16 cases were women. The timing of events and character of clinical features were similar to that observed in cases of severe autoimmune heparin-induced thrombocytopenia, suggesting an antibody-mediated thrombotic thrombocytopenia triggered by the vaccine. All patients in each series had high levels of antibodies directed against antigenic complexes of platelet factor 4 (PF4). None of the patients had previously received heparin. This disorder is thought to represent vaccine-induced immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4 [128; 129].

These reports, and the action taken by the FDA and the CDC, have important implications for health professionals. Surveillance data from millions of vaccine doses administered indicate that the risk of thrombotic events is extremely low. The risk may be highest in women younger than 50 years of age.

Vaccinees who are beyond three weeks from date of vaccination are not considered at risk of thrombotic complications. Individuals who develop any of the following new-onset symptoms within three weeks of vaccination should be evaluated for possible thrombotic complications: severe headache, abdominal pain, swelling or pain in the leg, chest pain, or shortness of breath. The evaluation should include a platelet count and imaging studies appropriate to clinical exam findings. A screening immunoassay for antibodies against PF4-heparin, or an enzyme-linked immunosorbent assay for antibodies against PF4-polyanion should be ordered. Hematology consultation is advisable. Patients with thrombocytopenia and suspicion of a thrombotic event should not be treated initially with a heparin product. Potential treatment options include high-dose immunoglobulins and non-heparin anticoagulants [128; 130].

Guillain-Barré syndrome (GBS) has also been reported after Janssen COVID-19 vaccination. As of June 2021, approximately 12.6 million doses of Janssen COVID-19 vaccine had been administered in the United States, with 100 reports of GBS with disease onset 3 to 42 days after vaccination [145]. The median age of reported cases was 57 years, and 61 were male. The GBS reporting rate for all recipients was 7.8 cases per million doses administered; among men 50 to 64 years of age, the rate is 15.6 cases per million doses [145].

Myocarditis/Pericarditis and mRNA COVID-19 Vaccines

Myocarditis and pericarditis have been reported more frequently than expected following receipt of either the Pfizer or Moderna mRNA COVID-19 vaccine, usually within seven days after the second dose of vaccine. The majority were male adolescents or young adult, and most cases were mild, responded well to treatment, and improved rapidly without evident long-term effects. Because a background level of seasonal myocarditis/pericarditis is associated with several common viral infections, at issue is whether and how many additional (excess) cases are precipitated by COVID vaccination. Following a nationwide vaccination program, a one-to-one comparison study with 800,000 subjects each in the vaccinated and control groups found that mRNA COVID-19 vaccine was associated with an excess risk of myocarditis (2.7 events per 100,000 persons) [146]. SARS-CoV-2 infection in the same time period was associated with a higher incidence of myocarditis (11 events per 100,000 persons). The estimated incidence of vaccine-associated myocarditis among males 16 to 29 years of age was 10 events per 100,000 vaccinees; among females 16 to 29 years of age, 0.3 events per 100,000 vaccinees; and among men 30 years of age or older, 2 events per 100,000 [153].

Data from a network of 40 healthcare systems (subserving 15 million people) found the risk of cardiac complications (myocarditis/pericarditis) was significantly higher after SARS-CoV-2 infection than after mRNA COVID-19 vaccination in all age groups evaluated. For example, among males 12 to 17 years of age, the incidence rate of myocarditis/pericarditis was 50 to 65 cases per 100,000 after infection, 2 to 3 cases per 100,000 after the first dose of vaccine, and 22 to 36 after the second dose; among males 18 to 29 years of age, the corresponding incidence rates (cases per 100,000) were 55 to 100 after infection, to -8 after the first and 7 to 15 after the second dose of vaccine. Among young children 5 to 11 years of age, the incidence of myocarditis/pericarditis was considerably lower. After infection, the rate was 13 to 18 cases per 100,000 among males and 5 to 11 cases per 100,000 among females; after COVID-19 vaccination, the rate was 0 to 4 cases per 100,000 among males and 0 cases among females [173]. These findings show that the risk of myocarditis/pericarditis in adolescent and young adult males is 5 to 8 times higher after SARS-CoV-2 infection than after mRNA COVID-19 vaccination.

On July 22, 2021, the ACIP reviewed updated benefit-risk analyses after Janssen and mRNA COVID-19 vaccination and concluded that the benefits of COVID-19 vaccination outweigh the risks for rare serious adverse events after COVID-19 vaccination [145]. In reaching this conclusion, the ACIP reviewed population-level considerations, including that COVID-19 cases were rising in the United States, the predominance of the highly transmissible Delta variant, and the importance of providing options for the type of COVID-19 vaccines offered in relation to epidemiologic considerations. The Department of Health and Human Services, American Academy of Pediatrics, American Heart Association, and other health professional organizations issued a joint statement concurring with the ACIP findings and recommended COVID-19 vaccination of all eligible persons [147].

DURABILITY OF IMMUNITY AND REINFECTION

Three years into the COVID-19 pandemic, there is limited information on durability of immunity following SARS-CoV-2 infection and COVID-19 vaccination. Despite the scope of the pandemic and burgeoning number of COVID-19 cases, reports of reinfection were uncommon before the emergence of SARS-CoV-2 variants. Natural and vaccine immunity to SARS-CoV-2 appeared to be quite durable for protection against reinfection by the original infecting strain, but less robust or predictable for protection against reinfection by variant strains of the virus.

As with most viral infections, pathogen-specific IgG antibody assays in the weeks following onset of COVID-19 are useful for diagnostic purposes but not for measuring the durability of immunity provided by (unmeasured) neutralizing antibody and memory B- and T-cell immune responses, which often persist for months to years. In a population-based study designed to assess durability of humoral immune responses to SARS-CoV-2, serum samples from 1,107 seropositive persons were collected up to four months after diagnosis of COVID-19. Antiviral Ig-antibody titers increased during the first two months and had not declined four months after infection [116]. In a longitudinal study of healthcare workers at the University of Oxford Hospitals undergoing periodic SARS-CoV-2 testing, the presence of antibodies in persons with previous asymptomatic or symptomatic COVID-19 substantially reduced the risk of reinfection [117]. Workers were offered nasopharyngeal SARS-CoV-2 PCR testing every two weeks and antibody testing at two-month intervals. Of 11,364 workers who were initially seronegative, 223 subsequently acquired SARS-CoV-2 infection. Among 1,265 workers who were seropositive, 2 subsequently developed asymptomatic reinfection, evidenced by a positive PCR. During eight months surveillance, no symptomatic SARS-CoV-2 reinfections were detected among workers who had serologic evidence of prior SARS-CoV-2 infection [117].

Population-based studies conducted early in the pandemic found that reinfection with SARS-CoV-2 was uncommon, occurring in less than 1% of individuals who had previously tested positive by SARS-CoV-2 PCR. Using a PCR-test data set from 4 million inhabitants of Denmark, researchers analyzed infection rates across separate surges of COVID-19 to estimate the degree of protection afforded by natural immunity against SARS-CoV-2 reinfection more than seven months later [118]. Among 11,068 persons who tested PCR-positive during the first COVID-19 surge (March to May 2020), 72 (0.65%) tested positive again during the second surge (September to December 2020). By comparison, the rate of infection among uninfected persons who became PCR-positive during the second surge was 3.27%. Thus, the estimate of protection against SARS-CoV-2 reinfection was 80.5%. However, protection against reinfection among persons older than 65 years of age was lower (47%). Limitations of the study included absence of information about severity of infection and the possibility individuals infected during the first COVID-19 surge may have altered their subsequent behavior, affecting risk of exposure. These findings highlight the importance of administering SARS-CoV-2 vaccines to previously infected individuals, especially the elderly [118].

Durable protective immunity after SARS-CoV-2 infection or COVID-19 vaccination consists of a repertoire of immune responses, often referred to as "immunological memory" [119]. Components of immunologic memory include pathogen-specific antibodies and cellular immune responses (memory B cells, CD4+ T cells, and/or memory CD8+ T cells). Cellular immune responses play a crucial role in clearance of viruses by eliminating virus-infected cells. Immunologic memory provides protection against SARS-CoV-2 reinfection and severity of disease in the event of reinfection, and thus determines the quality and durability of vaccine efficacy. Cellular immune responses induced by COVID-19 vaccines have shown greater durability than serum neutralizing antibody activity. Because CD8+ T cell responses control viral replication after infection, anti-SARS-CoV-2 vaccines will likely continue to provide substantial protection against severe disease even after measurable antibody wanes [29; 121].

An analysis of 254 blood samples from 188 COVID-19 cases, including some samples up to eight months after infection, found that substantial immune memory involving all four types of immune response was retained in 95% of subjects over the six- to eight-month period of observation [119]. Antibodies to SARS-CoV-2 spike and receptor binding domains declined over eight months, and memory B cell activity increased between one month and eight months after infection. Circulating antibody titers were not predictive of memory T-cell activity. The authors concluded that simple serologic tests for SARS-CoV-2 antibodies do not reflect the quality and durability of immune memory to the virus [119]. Another study demonstrated that memory B cells and strong CD4+ T cell immune responses persisted up to eight months after mRNA COVID-19 vaccination [156]. Furthermore, vaccine-induced cellular immune responses impacting cell binding to SARS-CoV-2 variants were found to be superior to infection-induced natural immunity. This may account in part for epidemiologic study results showing COVID-19 vaccination provided greater protection against subsequent Delta COVID-19 than did prior SARS-CoV-2 infection. An analysis of hospitalizations for COVID-19-like illness during January–September 2021 found that the adjusted odds of having laboratory-confirmed COVID-19 were five-fold higher in unvaccinated patients with documented previous SARS-CoV-2 infection than in previously vaccinated (mRNA COVID-19 vaccine) patients with no prior SARS-CoV-2 infection [157].

These findings suggest that the primary function of neutralizing antibodies is to block acquisition of SARS-CoV-2 infection; both antibody and cellular immune responses (immunological memory) are necessary for durable protection against severe disease. Current COVID-19 vaccines provide limited, short-term protection against Omicron subvariant infection. In contrast to neutralizing antibodies, vaccine-induced memory CD8+ T cell responses are highly cross-reactive against Omicron and likely contributes substantially to protection against severe disease [121].

Natural immunity to SARS-CoV-2 augmented by COVID-19 vaccination against SARS-CoV-2 may provide the most effective and durable protection against subsequent COVID-19. In a retrospective cohort study, using data from national health registries subserving the entire population of Sweden, investigators analyzed the impact of postinfectious natural immunity on risk of SARS-CoV-2 reinfection and COVID-19 hospitalization and further benefit from COVID-19 vaccination (hybrid immunity). Natural immunity from SARS-CoV-2 infection was associated with a 95% lower risk of reinfection and 87% lower risk of COVID-19 hospitalization up to 20 months follow-up. One- and two-dose hybrid immunity was associated with a lower risk of SARS-CoV-2 reinfection than natural immunity up to nine months follow-up. One-dose hybrid immunity conferred a 94% lower risk of subsequent COVID-19 hospitalization than natural immunity alone, though differences in absolute numbers were small [174].

SARS-CoV-2 Variants of Concern and Evasion of Immunity

In late 2020, variant strains of SARS-CoV-2 began to appear in countries with high COVID-19 case rates. Widespread circulation of SARS-CoV-2 combined with spontaneous mutations in the genome increases the probability that mutations affecting transmissibility will lead to emergence of a variant strain. The CDC's national genomic surveillance program identifies SARS-CoV-2 variants and tracks the proportion and distribution of COVID-19 cases attributable to variants [123; 124]. SARS-CoV-2 variants circulating in the United States are characterized as variants of concern (VOC) or variants of interest (VOI). In spring 2021, three VOCs accounted for 40% of COVID-19 cases in the United States: B.1.1.7, B.1.351, P.1, and California (B.1.351, 427/429) [123]. The defining characteristics of VOC include increased transmission (B.1.1.7), increased disease severity (B.1.1.7), and decreased neutralization by monoclonal antibody therapeutics (evasion of immunity) (P.1, B.1.351, 427/429). By June/July 2021, these variants had been superseded by a single highly transmissible VOC: B.1.617.2 (Delta) variant [132].

Delta Variant

Compared with the original SARS-CoV-2 strain, Delta variant was more infectious, spread faster, and caused more severe illness in unvaccinated people than previous variants [132]. First detected in December 2020, the Delta variant spread rapidly to 43 countries across six continents. In spring 2021, the COVID-19 surge in the United States had receded to the lowest point of the pandemic; the seven-day moving average of daily new cases was 12,000. By mid-July, the daily average of new cases had again surged to more than 60,000, of which 98% were caused by the SARS-CoV-2 Delta variant [132]. During the period of Delta predominance, breakthrough infection (usually asymptomatic or mild) occurred in vaccinated persons, but the majority of hospitalizations and deaths caused by Delta variant COVID-19 were in unvaccinated people. During the summer COVID-19 surge in Los Angeles County, unvaccinated individuals were five times more likely to acquire Delta variant infection and 29 times more likely to be hospitalized than persons who had been fully vaccinated [158]. The principal risk of secondary household and community transmission was also attributable to unvaccinated people, who were much more likely to become infected and thus shed the virus. Fully vaccinated individuals with breakthrough Delta infection did spread virus to others, but to a lesser degree and for a shorter period of time [132]. An investigation of virologic characteristics among healthcare workers with Delta variant breakthrough COVID-19 found that illness was uniformly mild; shedding of virus from the nose and throat was either unmeasurable or rapidly dissipated within one to three days [115].

Omicron Variant and Subvariants

In mid-November 2021, a new SARS-CoV-2 strain (the Omicron variant) emerged in South Africa among children, college students, and international travelers. By December, Omicron COVID-19 cases were identified in 50 countries, indicating a high level of transmission. Initial cases of SARS-CoV-2 Omicron in the United States were reported in December 2021; by end of month, Omicron replaced Delta as the predominant variant and principal cause of COVID-19 in the United States [123; 124]. Omicron SARS-CoV-2 was unique because for the number of genomic mutations and substitutions identified—50 overall, with more than 30 in the spike protein, some associated with reduced susceptibility to monoclonal antibody therapeutics and reduced neutralization by convalescent and vaccinee sera [123]. Epidemiologic studies demonstrated the Omicron variant had a 13-fold increase in infectivity and was three times more infectious than Delta variant [29]. Clinical reports indicated

Omicron-associated COVID was mild (e.g., nasal congestion, cough, and fatigue); rates of hospitalization were less than half than with Delta variant. Apparent moderation in disease severity and lower rates of hospitalization for COVID-19 could be misleading, as many early Omicron patients were children and vaccinated adults, in whom illness would is expected to be mild. However, in vitro studies have found that, in hamsters, the Omicron variant was less likely to infect the lungs, and in human alveolar cells, the replication rate was lower, compared with the Delta variant [29].

It was expected that the Omicron variant might evade immune protection gained from prior SARS-CoV-2 infection or COVID-19 vaccination. Studies showed that two-dose mRNA vaccine (Pfizer, Moderna) efficacy in prevention of Omicron COVID-19 waned after four to six months, though protection against severe illness and hospitalization was preserved. Evasion of vaccine immunity was reversed following receipt of a booster dose in persons who previously received the primary COVID-19 vaccine series; an interval-appropriate third (booster) dose increased neutralizing antibody levels 25- to 60-fold, reducing the risk of breakthrough infection by 75% and providing >90% protection against severe illness and hospitalization.

Continued, wide-spread circulation of SARS-CoV-2 has led to new lineages of the Omicron variant and subvariants more transmissible than the previous strain. The BA.5 and BA.4.6 lineages emerged in mid-2022, replaced by XBB subvariant and XBB.1.5 in January 2023. XBB.1.5 is a combination of two earlier Omicron lineages and became the predominant Omicron lineage in the United States, accounting for an estimated 66.4% of cases the week ending February 3, 2023 [124]. Apart from heightened transmissibility and risk of reinfection, the severity of COVID-19 caused by current subvariants is unchanged and the degree of protection against hospitalization and serious outcomes derived from natural and boosted vaccine immunity appears similar to that with prior SARS-CoV-2 strains.

The emergence and subsequent surges of Delta and Omicron COVID-19 demonstrate that SARS-CoV-2 variants can impact transmission, disease severity, risk of reinfection, and vaccine efficacy. At issue is whether and to what extent adaptive immunity (CD4+ and CD8+ T cell responses) acquired from prior infection and/or vaccination recognizes conserved epitopes on new SARS-CoV-2 variants of concern. Fortunately, studies to date have demonstrated that SARS-CoV-2 T cell epitopes are not appreciably affected by mutations found in newly described variants [125; 126]. Overall, CD4+ and CD8+ T cell responses in convalescing COVID-19 patients and COVID-19 mRNA vaccinees remain active against VOC circulating in the United States in 2023, including Delta and Omicron variants.

Emerging SARS-CoV-2 Variants, Vaccine Efficacy, and Booster Doses

Following initial rollout in December 2020, COVID-19 vaccines were 94% effective in preventing SARS-CoV-2 infection and nearly 100% effective against severe disease, hospitalization, and death. Six months later, after emergence of the Delta variant in May/June 2021, vaccine protection against severe outcomes remained high (92% to 95%) while efficacy against infection (70%) had declined. From January to May 2021, 100 million adults were vaccinated against SARS-CoV-2; an analysis of COVID-19 hospitalizations for the same period found that 600 previously vaccinated adults had been hospitalized for breakthrough COVID-19. Of this group, 74% were older than 65 years of age and 130 died (all patients 71 to 89 years of age) [154].

By mid-2021, vaccine effectiveness against SARS-CoV-2 infection was gradually diminishing among healthcare and other frontline workers, most likely because of decreased immune protection and greater infectiousness of the Delta variant. Clinical trials demonstrated that administration of a COVID-19 vaccine booster dose enhanced significantly the anti-SARS-CoV-2 immune response in previously immunized participants [131]. In response, CDC/ACIP recommended that all persons 5 years of age

and older receive an interval-appropriate COVID-19 vaccine booster dose; specifically, six months after having received either a Pfizer or Moderna mRNA primary series, or two months after receiving Johnson & Johnson vaccine. Choice of vaccine booster was left open, meaning that one may "mix and match" vaccine selected for the booster dose; however, selecting one of the mRNA vaccines was preferred. In April 2022, a second interval-appropriate COVID-19 vaccine booster dose was recommended for vaccinees 50 years of age and older, and for others at risk of severe illness because of underlying medical conditions.

Efficacy of COVID-19 vaccine booster against SARS-CoV-2 variants was demonstrated in an analysis of data from a multistate hospital network comprising 7,544 patients enrolled between March 11, 2021, and January 24, 2022. This study found that two or three doses of COVID-19 mRNA vaccine conferred 90% protection against COVID-19-related invasive mechanical ventilation or in-hospital death [172]. Vaccine effectiveness against adverse outcomes was consistent throughout the periods of Delta and Omicron predominance; protection against mechanical ventilation and death (94%) in the Omicron period was higher in patients with COVID-19 who had received a third (booster) dose. In a large cohort study of nursing home residents, receipt of a second mRNA COVID-19 booster dose during circulation of Omicron subvariants was 74% effective at 60 days against severe COVID-19-related outcomes (including hospitalization and death) and 90% against death alone compared with receipt of a single booster [180].

Bivalent Vaccine Booster

Following emergence in November 2021, Omicron SARS-CoV-2 has evolved into multiple sublineages, accumulating additional mutations that facilitate evasion of neutralizing antibody activity elicited by both natural infection and COVID-19 vaccination. SARS-CoV-2 circulation persisted in the general population, new cases of COVID-19 continued, and reports of reinfection increased among persons previously infected or vaccinated. In order to bring the pandemic under better control, the CDC/ACIP recommended replacing monovalent mRNA vaccine boosters with a newly developed Pfizer bivalent mRNA vaccine composed of Omicron BA.4/BA.5 spike and ancestral SARS-CoV-2 spike protein. Beginning September 2022, bivalent mRNA vaccine replaced the monovalent vaccine for COVID-19 booster dose vaccination in the United States and other countries.

During the intervening period, September 2022 to January 2023, studies of bivalent mRNA COVID-19 vaccine effectiveness demonstrated greater immunogenicity and additional benefit against Omicron subvariants when compared with monovalent COVID-19 vaccine. A comparison study found that neutralizing antibody titers elicited against all Omicron sublineages (including XBB.1) were several times higher with bivalent vaccine compared to monovalent vaccine when administered as a fourth booster dose [181]. Participants with a history of prior SARS-CoV-2 infection exhibited higher titers to bivalent vaccination than those without prior history of infection. CDC surveillance data from a healthcare network demonstrated that bivalent boosters provided significant additional protection against symptomatic SARS-CoV-2 infection in participants who had received at least two prior monovalent vaccines. Relative benefits increased with time since receipt of the most recent monovalent vaccine dose [182]. In another report, bivalent boosters provided substantial additional protection against Omicron COVID-19 disease severity and hospitalization, higher (59%) than monovalent boosters (25%) [183]. An observational cohort study in Great Britain found that people 65 years of age and older who received the bivalent vaccine had lower COVID-19 hospitalization and mortality rates than non-recipients up to 70 days after vaccination.

Of the 622,700 participants in the study, 85,300 (14%) received a bivalent booster during the 70-day study period. Hospitalization due to COVID-19 occurred in 6 bivalent vaccine recipients and 297 non-recipients, corresponding to 80% effectiveness against hospitalization for bivalent vaccine. Death from COVID-19 occurred in 1 bivalent booster dose recipient and 73 non-recipients of bivalent vaccine booster [184]. In a January 2023 early release, CDC investigators reported that receipt of bivalent mRNA booster dose provided additional protection against symptomatic XBB/XBB.1.5 subvariant infection for at least three months after vaccination in persons who had previously received two to four monovalent vaccine doses [185]. These finding indicate the importance of continued monitoring of vaccine effectiveness and the value of staying up to date with recommended COVID-19 vaccines, including receiving a bivalent booster dose when eligible.

The CDC uses public health surveillance data from participating health departments, hospitals, and long-term care facilities to monitor rates of COVID-19 cases, hospitalizations, and deaths by vaccination status. Participating jurisdictions represent a large proportion of the United States population and all regions of the country. Age-standardized weekly rates of COVID-19 cases and deaths are displayed by vaccination status, including receipt of an updated booster (bivalent) dose [124]. As of December 2022, all age-matched vaccinated groups had lower rates of dying from COVID-19 and lower rates of testing positive for SARS-CoV-2 compared with those who were unvaccinated. People who were vaccinated with an updated (bivalent) booster dose had lower rates of dying and testing positive compared with those vaccinated but who had not received an updated (bivalent) booster dose. People 5 years of age and older who were vaccinated with an updated (bivalent) booster had 3.1 times decreased risk of testing positive for SARS-CoV-2 and 12.7 times decreased risk of dying from COVID-19. In people 65 to 79 years of age, the death rate from COVID-19 was 24 times lower among those vaccinated and (bivalent) boosted (0.3 per 100,000 population) compared with those unvaccinated (8 per 100,000) [124].

As of January 2023, COVID-19 vaccines have been in use in the United States for two years; more than 665 million COVID-19 vaccine doses have been administered and 229.5 million people have completed a primary series, comprising 69% of the total population [124]. In people 65 years of age and older, 71.4% have completed a primary series and received at least one booster dose. Approximately 52% of the eligible general population have received a primary COVID-19 series and an interval-appropriate booster dose. The efficacy of COVID-19 vaccines in reducing the incidence of symptomatic SARS-CoV-2 infection and protecting against severe outcomes (hospitalization and death) has been demonstrated in clinical trials and confirmed by real-world observational studies.

COVID-19 VACCINATION STRATEGY AND VEXATIONS OF AN ONGOING PANDEMIC

The development in 10 months' time of vaccines 90% effective in preventing SARS-CoV-2 infection and 95% effective against severe COVID-19 was a remarkable achievement. Rapid deployment of vaccines on a worldwide scale was expected to hasten population "herd immunity" and quickly end the pandemic. In reality, the task proved to be too enormous, cumbersome, and slow to outpace the adaptive advantages gained by spontaneous mutations within the SARS-CoV-2 genome. New, more highly transmissible variants were emerging even as the vaccine roll-out began. Continued propagation of SARS-CoV-2 infection begets continued spontaneous virus mutations, increasing the probability that subsequent variants or subvariants will emerge better able to evade both natural and vaccine immunity. The moderating effect of population immunity will continue to increase through a combination of widespread vaccination and infection [121].

Immunologists have pointed to another potential vexation, the possibility that repeated dosing with modified COVID-19 vaccines fail to achieve the expected antigen-specific, robust immune response because of a phenomenon within the primed immune system referred to as "immune imprinting."

Experience with yearly influenza vaccination has shown that after primary exposure to an antigen, B call memory tends to "lock in" on the original antigenic epitope; re-exposure to a modified (vaccine) viral epitope quickens immune memory and antibody production in the direction of the original antigen, thereby preventing the immune system from mounting a robust antibody response specific for the newly modeled vaccine. In effect, antibody titers elicited to ancestral virus epitopes in a prior vaccine may be robust, while antibody titers specific to a new vaccine epitope modeled after a circulating variant is lower than expected. Vaccine-derived imprinting has been shown to affect subsequent antibody responses stimulated by COVID-19 vaccination as well as SARS-CoV-2 infection [28]. Immune imprinting might blunt efficacy and durability of vaccine-elicited antibody protection against SARS-CoV-2 infection, while cellular immune protection against severe illness is preserved and possibly enhanced. At the three-year point of the COVID-19 pandemic, there is something of a stalemate. SARS-CoV-2 infection remains endemic, but ambient population immunity augmented by interval-appropriate vaccine boosters does blunt transmission, shelter the vulnerable, and provide significant protection against severe illness and death from COVID-19.

TRANSMISSION DYNAMICS AND MITIGATION MEASURES

Epidemiologic investigation of the COVID-19 outbreak provided early evidence that human-to-human transmission, including close contact with persons having mild, nonspecific symptoms, is the principal means of SARS-CoV-2 spread within the community. Studies indicate that infected droplet nuclei expelled during coughing, sneezing, loud talking, or singing is the primary mode of transmission. Sustained close personal contact (being within 6 feet for at least 15 minutes) with an infected person increases the risk of transmission. Limiting exposure time and lengthening distance reduce the risk [87].

Upper respiratory virus sheading begins to decline three days after onset of COVID-19; recovery of replication-competent SARS-CoV-2 from secretions obtained more than10 days after onset is rare [88]. Recovery of replication-competent virus between 10 and 20 days after symptom onset has been documented in patients with severe COVID-19.

Unlike the 2003 SARS-CoV, whereby replication occurred mostly in the lower respiratory tract and virus shedding was temporally associated with symptom onset, SARS-CoV-2 is characterized by high-level viral replication and shedding in the upper respiratory tract, even during the pre-symptomatic phase of infection [38]. Newly infected individuals are infectious 1 or 2 days before and for 7 to 10 days after the onset of symptoms. This means that asymptomatic and pre-symptomatic SARS-CoV-2 infection may produce a high viral load in nasopharyngeal secretions, rendering the individual an efficient vector of transmission. Therefore, a strategy for prevention that relies solely on symptom-based detection and isolation of COVID-19 cases is likely to have limited effectiveness. In a study of skilled nursing facility residents who acquired SARS-CoV-2 infection from a healthcare worker, half were asymptomatic or pre-symptomatic at the time of contact tracing evaluation and testing [15].

These considerations have important public health implications. Close personal contact implies touching and the sharing of common utensils; it is also defined by a proximity of 6–8 feet—the distance respiratory droplets travel after coughing or sneezing. As noted, the risk of infection is greatest for persons who have prolonged, unprotected close contact (i.e., within 6 feet for 15 minutes or longer) with someone recently diagnosed with SARS-CoV-2 infection, regardless of whether the patient has symptoms [89]. A CDC contact investigation demonstrated that even brief periods of unprotected close contact, if repeated and cumulative (exceeding 15 minutes) over the course of a day, significantly increases the risk [92]. This highlights the importance of avoiding congregate settings (e.g., assisted living facilities, college dormitories, family gatherings, indoor dining and bars) because of the increased likelihood

of repetitive or sustained close contact. People can reduce the community spread of SARS-CoV-2 by practicing social distancing, wearing face coverings in public, and washing their hands.

For purposes of contact investigation and public health guidance, the CDC defines "close contact" as someone who was within 6 feet of an infected person for a cumulative total of 15 minutes within any 24-hour period starting from two days before symptom onset (or, for asymptomatic patients, two days prior to test specimen collection) until the person begins isolation precautions [59]. The cumulative 15-minute exposure refers to any combination of individual exposures (e.g., three 5-minute exposures) over a 24-hour period. Factors to consider when assessing close contact include proximity, duration of exposure, whether the individual has symptoms (as the period around onset of symptoms is associated with highest levels of viral shedding), whether the infected person was likely to generate aerosols (e.g., was coughing, shouting, singing), and other environmental factors (e.g., crowding, adequacy of ventilation, whether exposure was indoors or out of doors) [59].

Several emerging reports and epidemiologic studies indicate that children younger than 10 years of age may play only a small role in transmission of SARS-CoV-2. An investigation of 36 childhood COVID-19 cases in China found that 89% acquired the infection from exposure to an older household family member [50]. A population-based surveillance study in Iceland, drawing from a nationwide random sample, found that of 848 children younger than 10 years of age, none tested positive for SARS-CoV-2, whereas 100 of 12,232 (0.8%) adolescents and adults tested positive [51]. Contact tracing in relation to a cluster of COVID-19 among family and friends in France revealed that despite several days of potential exposure to a symptomatic pediatric case, there was no evidence of secondary transmission among 172 school contacts [52]. One possible explanation for these observations is the finding that gene expression of ACE2 in nasal epithelium is age-dependent; it is significantly lower in young children and increases as one develops into adulthood [53]. Lower ACE2 expression in children relative to adults could impact transmission dynamics and may help explain why COVID-19 is less prevalent in children.

Assumptions about childhood transmission of COVID-19 have been tempered somewhat since emergence of the highly transmissible SARS-CoV-2 Delta in 2021and Omicron subvariants in 2022. Compared with original strain infection, nasal and pharyngeal virus shedding is significantly higher; persons with Delta or Omicron infection are two and four times more infectious, respectively. Consequently, transmission now occurs more readily among children and from child to adult. Because most children were unvaccinated, symptomatic childhood infection has increased and with it the need for hospitalization. COVID-19-associated hospitalization rates among children and adolescents in the United States increased five-fold from June 2021 to mid-August 2021 [148]. Hospitalization rates were 10 times higher among unvaccinated than among vaccinated adolescents.

The stability of SARS-CoV-2 on environmental surfaces has been studied in order to assess whether surface contamination (fomites) could play a role in virus transmission. After application of aerosols containing a standard dose of SARS-CoV-2, viable virus was detected up to 72 hours on plastic and stainless steel, though the virus titer was greatly reduced; on cardboard, no viable SARS-CoV-2 was measured after 24 hours [19]. These data should be interpreted with caution, as it is unclear to what extent environmental detection of virus in much reduced titer at a given interval, experimentally, can be equated with actual risk of transmission from common environmental surfaces. In an April 2021 scientific brief, a CDC analysis of quantitative microbial risk assessment studies concluded the risk of SARS-CoV-2 infection via the fomite transmission route is less than 1 in 10,000, which means that each contact with a contaminated surface has less than a 1 in 10,000 chance of causing an infection [122].

When population immunity from natural infection is low and effective vaccines are unavailable, public health control of an infectious disease outbreak must rely on mitigation strategies to reduce exposure and limit transmission. These measures may include the following: suspension or cancellation of common public events such as cinema, theatre, concerts, and collegiate and professional sports competition; closure of schools and cancellation of classes at colleges and universities; observing social distancing in smaller venues such as restaurants and churches; the wearing of masks or cloth face coverings at indoor commercial venues and social gatherings. By slowing the degree and pace of virus transmission, effective mitigation helps to protect those most vulnerable and to ensure that the clinical case load does not overwhelm local hospital and critical care resources.

GLOBAL PUBLIC HEALTH CONCERNS AND WHO RESPONSE

The WHO monitors developments and tracks progress of the pandemic, providing weekly situation reports on its website [8]. In an effort to curb the spread of infection, The WHO and national agencies have developed public health measures and clinical criteria to guide the evaluation and management of persons with significant exposure and/or compatible illness.

ADVICE TO THE PUBLIC

Both the WHO and the CDC have published guidance designed to protect the general public and mitigate transmission of SARS-CoV-2 [11]. CDC recommendations on how to best protect oneself and others include the following [24]:

- Get vaccinated and stay up to date with recommended COVID-19 vaccine boosters.
- Wash hands often with soap and water for at least 20 seconds, especially after having been in a public place or after coughing, sneezing, or blowing your nose. If soap and water are not readily available, a hand sanitizer that contains at least 60% alcohol may be used.
- Avoid touching eyes, nose, and mouth with unwashed hands.
- Avoid crowds and close contact with people who are sick
- Put distance (3 to 6 feet) between yourself and other people.
- When community level of COVID-19 activity is medium or high, cover the mouth and nose with a high-quality face mask when in public places or using public modes of transportation. Note: This recommendation does not apply to children younger than 2 years of age, persons with breathing difficulties, or those who are unable to remove the mask unassisted.
- Cover coughs and sneezes.

WHO and CDC guidance on the use of a face covering, whether by prefabricated mask or fashioned from cloth, was predicated on evidence that asymptomatic and presymptomatic individuals infected with SARS-CoV-2 can transmit the virus to others in close proximity [54]. Therefore, anyone out in public should consider that he or she could, unwittingly, be an agent of transmission to others. The simple act of coughing, sneezing, talking, singing, or forceful breathing can release virus-laden droplets and respiratory particles into the air and onto nearby environmental surfaces. Multi-layered cloth masks block 50% to 70% of fine droplets and particles and limit the forward spread of those not captured [104]. Although the primary function of a face covering is prevention of inadvertent transmission of virus to others ("source control"), it may also provide a degree of barrier protection to the one wearing it. The CDC recommends wearing a face mask in settings where social distancing measures are difficult to maintain (e.g., grocery stores, pharmacies), especially in areas experiencing significant community-based transmission. Detailed guidance on the construction, proper usage, and cleaning of cloth face coverings is provided on the CDC website [12].

As public health restrictions have lifted, professional and social interactions in the community present more opportunities for spread of SARS-CoV-2. The risk of transmission varies in proportion to how closely a person interacts with an infected individual and for how long. In a scientific brief updated November 20, 2020, the CDC summarized the experimental and epidemiologic data supporting community masking to reduce the spread of SARS-CoV-2 and concluded that the prevention benefit of masking is derived from the combination of source control and personal protection for the mask wearer [104]. Studies confirm that wearing face masks or double-layer cloth face coverings reduces the risk of transmission for medical personnel, patients, and the general public when in social and community settings, especially when social distancing is not possible [66; 67]. A CDC report of a contact investigation involving a hair salon where universal face covering was practiced is illustrative. Two stylists with COVID-19 symptoms had worked closely with 139 clients over an eight-day period before learning of their COVID-19 diagnosis, yet there was no evidence of secondary transmission [67]. None of the clients developed COVID-19 symptoms and of 67 individuals tested for SARS-CoV-2, all were negative. Both stylists and 98% of clients interviewed had followed posted company policy and city ordinance requiring face coverings by employees and clients in businesses providing personal care services.

As noted, COVID-19 vaccination is not 100% effective at preventing SARS-CoV-2 breakthrough infection, especially since the advent of variant strains. Most breakthrough infections in immunized individuals are asymptomatic or mild and have little public health import when community COVID-19 activity is low. In order to mitigate risk during periods of heightened SARS-CoV-2 transmission, the CDC website provides updated public health recommendations for vaccinated people [131]. The CDC recommends that fully vaccinated persons wear a face mask in public, when indoors, if local SARS-CoV-2 transmission is sustained or high, and get tested for COVID-19 if experiencing symptoms or within five to seven days after exposure to someone with known or suspected COVID-19.

CDC MONITORING AND GUIDANCE FOR HEALTHCARE PROFESSIONALS

COVID-19 Data Tracker

The CDC's surveillance program maintains a COVID-19 Data Tracker and Weekly Review of reported COVID-19 cases, hospitalizations, and deaths in the United States [124]. This website also provides updated information on COVID-19 vaccination rates, prevalence of SARS-CoV-2 variant strains in circulation, and the current community levels of COVID-19 by county, district, and territory. As of February 1, 2023, the seven-day average of weekly new cases (40,130) decreased 6.7% compared with the previous week, and the Omicron lineage (e.g., XBB.1.5, BQ.1, XBB) accounted for 100% of new cases. The seven-day daily average of new hospital admissions was 3,319, a decrease of 8.4% from the prior week. The seven-day average of new COVID-19 deaths (493) decreased 9% compared with the previous seven-day average. Overall, about 229.7 million people (69.2% of the population) have completed a primary COVID-19 vaccine series. Approximately 71% of people >65 years of age have completed a primary COVID-19 vaccine series followed by at least one interval-appropriate booster. About 111 million people (49% of the eligible population) have completed a primary series plus one additional booster dose of COVID-19 vaccine. More than 42.1 million people, or 20% of the eligible population 5 years of age and older, have received an updated (bivalent) booster dose [124].

The CDC recommends use of their COVID-19 Community Levels site to determine the impact of COVID-19 on communities, the local risk of exposure, and advisable precautions. As of February 3, 2023, 4% of counties, districts, or territories had a high COVID-19 Community Level, 25% had a medium Community Level, and 71% had a Low Community Level [124]. Compared with the prior week, the number of counties in the high and medium levels increased by 1.5%.

The CDC website also provides updated COVID-19 clinical guidance for providers, laboratories and health facilities, and public health officials [124]. Included are recommendations for the evaluation of persons/patients under investigation, laboratory specimen transport, and protection of healthcare workers and transmission precautions in clinical settings. Recommendations for patient assessment and care in hospitals, clinics, and other healthcare facilities emphasize the importance of adherence to isolation and barrier precautions, including proper use of personal protective equipment (PPE). Selected materials from the CDC website, including recommendations for travelers, are reproduced in the following sections. Please note that language and/or cultural barriers may impede assessment of risk and patient education on the topics pertaining to transmission of infection and public safety; using interpreters and translated materials are recommended, when appropriate.

CDC Guidance on Travel During COVID-19

The CDC provides updated information and guidance on domestic and international travel precautions [13]. The CDC recommends being up to date with COVID-19 vaccines before travel and checking COVID-19 community level at destination. Vaccinated and unvaccinated individuals who travel should observe the following precautions [13]:

- Avoid contact with sick people.
- Avoid touching your eyes, nose, or mouth with unwashed hands.
- Wash hands often with soap and water for at least 20 seconds or use an alcohol-based hand sanitizer that contains at least 60% to 85% alcohol.
- Avoid traveling if you are sick.
- Wear a high-quality mask over the nose and mouth in terminals and other public venues.
- Cover coughs and sneezes.
- Pick up food at drive-throughs, curbside restaurant service, or stores.

Unvaccinated persons should consider obtaining a SARS-CoV-2 nasopharyngeal swab test one to three days before the trip, and repeat the viral test three to five days after return from destinations with medium or high COVID-19 activity. Returning travelers from any destination are encouraged to observe standard precautions, monitor health, and follow state, territorial, tribal, and local recommendations or requirements after travel [13].

As of May 2022, the CDC recommends that persons who are up to date with COVID-19 vaccination can travel with low risk to themselves and others [13]. Up-to-date COVID-19 vaccination status is defined as having received the initial primary series and an interval-appropriate booster dose. Such persons can travel safely within the United States without the need for pre-travel testing or post-travel self-quarantine if they continue to take COVID-19 precautions while traveling.

Recommended Criteria to Guide Evaluation of Patients Under Investigation for COVID-19

CDC guidance specifies who should be tested for COVID-19 and encourages clinicians to use clinical judgment in determining whether a patient with signs and symptoms compatible with COVID-19 should be tested [14]. Symptoms to be considered include fever, chills, cough, sore throat, muscle aches, shortness of breath, new loss of taste or smell, and vomiting or diarrhea. As noted, SARS-CoV-2 can cause asymptomatic, pre-symptomatic, and minimally symptomatic infection, leading to virus shedding that may result in transmission to others who are particularly vulnerable to severe disease and death. Special attention should be paid to older adults and to patients with underlying conditions or immunosuppressed states. Even mild signs and symptoms of COVID-19 should be evaluated among potentially exposed healthcare personnel because of their extensive contact with vulnerable patients in healthcare settings.

The CDC has established priorities for COVID-19 diagnostic testing [14]. High priority for testing applies to hospitalized patients with compatible clinical features, healthcare facility workers and those who work in congregate living settings with symptoms, and residents in long-term care facilities (including prisons and shelters) with symptoms. Priority designation for testing applies to any person in the community with symptoms of potential COVID-19. In addition, persons without symptoms may be prioritized by health departments or clinicians for reasons such as public health monitoring, sentinel surveillance, or screening purposes.

Clinicians should work with their local and state health departments to coordinate testing through public health laboratories or work with commercial or clinical laboratories using SARS-CoV-2 diagnostic tests granted an Emergency Use Authorization by the FDA. Patients should be evaluated and discussed with public health departments on a case-by-case basis if their clinical presentation or exposure history is equivocal.

Other considerations that may guide testing include epidemiologic factors (e.g., close contact with an individual who in the past 14 days has tested positive for SARS-CoV-2) and the occurrence of local transmission or a cluster of COVID-19 within a specific community setting (e.g., nursing home, manufacturing facility) [14]. Close contact is defined as one of the following:

- Being within approximately 6 feet (2 meters), or within the room or care area, of a novel coronavirus case for a prolonged period of time while not wearing recommended personal protective equipment or PPE (e.g., gowns, gloves, certified disposable N95 respirator, eye protection); close contact can include caring for, living with, visiting, or sharing a healthcare waiting area or room with a novel coronavirus case.
- Having direct contact with infectious secretions of a novel coronavirus case (e.g., being coughed on) while not wearing recommended personal protective equipment.

Any patient with fever and severe acute lower respiratory illness (e.g., pneumonia, ARDS) requiring hospitalization and without alternative explanatory diagnosis (e.g., influenza) should be evaluated for COVID-19, even if no source of exposure has been identified [14].

Symptomatic patients should be provided a surgical mask and placed on respiratory isolation, preferably in an airborne isolation negative pressure room. Caregivers should observe enhanced precautions (i.e., wear gloves, gown, eye protection device [other than prescription eye glasses], and N95 respirator). For information on the management of patients with COVID-19, see https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/clinical-considerations-index.html.

Diagnostic Testing

The CDC recommends that healthcare providers should immediately notify both infection control personnel at their healthcare facility and their local or state health department in the event of a newly diagnosed or suspected case of COVID-19.

Confirmation of COVID-19 is performed using the RT-PCR assay for SARS-CoV-2 on respiratory specimens (which can include nasopharyngeal or oropharyngeal aspirates or washes, nasopharyngeal or oropharyngeal swabs, bronchoalveolar lavage, tracheal aspirates, or sputum) and serum. The FDA has worked to expedite the availability of tests through emergency authorization of commercial laboratories that have developed SARS-CoV-2 testing capability. Information on specimen collection, handling, and storage is available at https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html. After initial confirmation of COVID-19, additional testing of clinical specimens can help inform clinical management, including discharge planning. Additional guidance for collection, handling, and testing of clinical specimens is available at the CDC website [12].

Infection with both SARS-CoV-2 and with other respiratory viruses has been reported, and detection of another respiratory pathogen does not rule out COVID-19 [15].

Interim Clinical Guidance for Management of Patients with Confirmed COVID-19

The CDC and NIH websites provide updated clinical guidance and additional resources for clinicians caring for patients with COVID-19 [15; 57]. Clinical management entails prompt implementation of recommended infection prevention and control measures, and resources to support patients with complications, including advanced organ support if indicated [15]. Healthcare personnel should care for patients in an airborne infection isolation room. Isolation Precautions should be used when caring for the patient. For detailed recommendations, see the CDC's Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) in Healthcare Settings at https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html. The NIH and the Infectious Diseases Society of America provide updated COVID-19 management guidelines, including specific recommendations for the use of remdesivir and dexamethasone in hospitalized patients [10; 57].

OTHER AVAILABLE RESOURCES

CDC Information for Healthcare Professionals about Coronavirus (COVID-19)
https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html

CDC Information for Healthcare Professionals about COVID-19 Vaccination
https://www.cdc.gov/vaccines/covid-19/index.html

CDC Coronavirus Disease 2019 (COVID-19) Resources for Health Departments
https://www.cdc.gov/coronavirus/2019-ncov/php/index.html

World Health Organization Coronavirus Disease 2019 (COVID-19) Pandemic
https://www.who.int/emergencies/diseases/novel-coronavirus-2019

Johns Hopkins University and Medicine Coronavirus Resource Center
https://coronavirus.jhu.edu

NIH Coronavirus Disease 2019 (COVID-19) Treatment Guidelines
https://www.covid19treatmentguidelines.nih.gov

Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19
https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management

Works Cited

1. Periman S. Another decade, another coronavirus. *N Engl J Med.* 2020;382:760-762.
2. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020;382:727-733.
3. Centers for Disease Control and Prevention. More Resources About COVID-19. Available at https://www.cdc.gov/coronavirus/2019-ncov/more/index.html. Last accessed February 14, 2023.
4. Munster VJ, Koopmans M, van Doremalen N, et al. A novel coronavirus emerging in China: key questions for impact assessment. *N Engl J Med.* 2020;382:692-694.
5. Azhar EI, El-Kafrawy SA, Farraj SA, et al. Evidence for camel-to-human transmission of MERS Coronavirus. *N Engl J Med.* 2014;370:2499-2505.
6. Drosten C, Meyer B, Muller MA, et al. Transmission of MERS-Coronavirus in household contacts. *N Engl J Med.* 2014;371:828-835.
7. Assiri A, McGeer A, Peri TM, et al. Hospital outbreak of Middle East Respiratory Syndrome Coronavirus. *N Engl J Med.* 2013;369:407-416.
8. World Health Organization. Coronavirus Disease (COVID-19) Pandemic. Available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Last accessed February 14, 2023.
9. Huang C, Wang Y, Li X. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506.
10. Infectious Disease Society of America. COVID-19 Resource Center. Available at https://www.idsociety.org/covid-19-real-time-learning-network. Last accessed February 14, 2023.
11. World Health Organization. Coronavirus Disease (COVID-19) Advice for the Public. Available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public. Last accessed February 14, 2023.
12. Centers for Disease Control and Prevention. COVID-19. Available at https://www.cdc.gov/coronavirus/2019-ncov/index.html. Last accessed February 14, 2023.
13. Centers for Disease Control and Prevention. Domestic Travel During COVID-19. Available at https://www.cdc.gov/coronavirus/2019-ncov/travelers/travel-during-covid19.html. Last accessed February 14, 2023.
14. Centers for Disease Control and Prevention. Overview of Testing for SARS-CoV-2, the Virus the Causes COVID-19. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html. Last accessed February 14, 2023.
15. Centers for Disease Control and Prevention. Clinical Care Considerations. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/clinical-considerations-index.html. Last accessed February 14, 2023.
16. U.S. Food and Drug Administration. FDA Takes Significant Step in Coronavirus Response Efforts, Issues Emergency Use Authorization for the First 2019 Novel Coronavirus Diagnostic. Available at https://www.fda.gov/news-events/press-announcements/fda-takes-significant-step-coronavirus-response-efforts-issues-emergency-use-authorization-first. Last accessed February 14, 2023.
17. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020;382:1708-1720.
18. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus disease (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi.* 2020;41(2):145-151.
19. van Doremalen N, Bushmaker T, Morris DH, et al. To the editor: aerosolized and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med.* 2020;382:1564-1567.
20. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. *N Engl J Med.* 2020;382:1787-1799.
21. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis.* 2020;71(15):732-739.
22. Devaux CA, Rolain JM, Colson P, et al. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents.* 2020;55(5):105938.
23. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases From the Chinese Center for Disease Control and Prevention. *JAMA.* 2020;323(13):1239-1242.
24. Centers for Disease Control and Prevention. How to Protect Yourself and Others. Available at https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html. Last accessed February 14, 2023.
25. Centers for Disease Control and Prevention. Interim Infection Prevention and Control Recommendations for Healthcare Personnel During the Coronavirus Disease 2019 (COVID-19) Pandemic. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html. Last accessed February 14, 2023.
26. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe COVID-19. *N Engl J Med.* 2020;382:2327-2336.
27. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA.* 2020;323(16):1582-1589.

28. Roltgen K, Nielsen ScA, Silva O, et al. Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination. *Cell.* 2022;185:1025-1040.
29. Ao D, Lan T, He X, et al. Sars-CoV-2 Omicron variant: immune escape and vaccine development. *MedComm. 2022;3(1):e126.*
30. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* 2020;181(2):271-280.
31. Puelles VG, Lütgehetmann M, Lindenmeyer MT, et al. Multiorgan and renal tropism of SARS-CoV-2. *N Engl J Med.* 2020;383:590-592.
32. Pei G, Zhang Z, Peng J, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. *J Am Soc Neph.* 2020;31(6):1157-1165.
33. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* 2020;323:1061-1069.
34. Clerkin KJ, Fried JA, Raikhelkar J, et al. Coronavirus disease 2019 (COVID-19) and cardiovascular disease. *Circulation.* 2020;141:1648-1655.
35. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19: final report. *N Engl J Med.* 2020;383:1813-1826.
36. U.S. Food and Drug Administration. Revoked: Emergency Use Authorization for Use of Chloroquine Phosphate or Hydroxychloroquine Sulphate for Treatment of 2019 Coronavirus Disease. Available at https://www.fda.gov/media/136534/download. Last accessed February 14, 2023.
37. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med.* 2020;382:2411-2418.
38. Gandhi M, Yokie DS, Havlir DV. Asymptomatic transmission, the Achilles' heel of current strategies to control COVID-19. *N Engl J Med.* 2020;382:2158-2160.
39. Cannegieter S, Klok FA. COVID-19-associated coagulopathy and thromboembolic disease: commentary on an interim expert guidance. *Res Pract Thromb Haemost.* 2020;4(4):439-445.
40. COVID-19 coagulopathy: an evolving story. *Lancet.* 2020;7(6):E425.
41. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18(4):844-847.
42. Helms J, Tacquard C, Severac F, et al. for the CRICS TRIGGERSEP Group. High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med.* 2020;46(6):1089-1098.
43. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Research.* 2020;191:145-147.
44. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of COVID-19 in New York City. *N Engl J Med.* 2020;382:2372-2374.
45. Centers for Disease Control and Prevention. Information for Pediatric Healthcare Providers. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html. Last accessed February 14, 2023.
46. New York State Department of Health. Novel Coronavirus (COVID-19): Multisystem Inflammatory Syndrome in Children (MIS-C). Available at https://coronavirus.health.ny.gov/multisystem-inflammatory-syndrome-children-mis-c. Last accessed February 14, 2023.
47. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet.* 2020;395(10237):P1607-P1608.
48. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational study. *Lancet.* 2020;395(10239):P1771-P1778.
49. Centers for Disease Control and Prevention. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). Available at https://www.cdc.gov/mis/mis-c/hcp/index.html. Last accessed February 14, 2023.
50. Qui H, Wu J, Hang L, et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational study. *Lancet.* 2020;20(6):P689-P696.
51. Gudbjartsson D, Helgason A, Jonsson H, et al. Spread of SARS-CoV-2 in the Icelandic population. *N Engl J Med.* 2020;382:2302-2315.
52. Danis K, Epaulard O, Bénet T, et al. Cluster of coronavirus disease 2019 (Covid-19) in the French Alps, 2020. *Clin Infect Dis.* 2020;71(15):825-832.
53. Bunvavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. *JAMA.* 2020;323(23):2427-2429.
54. Centers for Disease Control and Prevention. Use and Care of Masks. Available at https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/about-face-coverings.html. Last accessed February 14, 2023.
55. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance—United States, January 22–May 30, 2020. *MMWR.* 2020;69(24):759-765.
56. Solomon IH, Normandin E, Bhattacharyya S, et al. Neuropathological features of Covid-19. *N Engl J Med.* 2020;383:989-992.
57. National Institutes of Health. COVID-19 Treatment Guidelines. Available at https://www.covid19treatmentguidelines.nih.gov. Last accessed February 14, 2023.

58. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine. Available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and. Last accessed February 14, 2023.
59. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): Health Departments, Appendices. Available at https://www.cdc.gov/coronavirus/2019-ncov/php/contact-tracing/contact-tracing-plan/appendix.html. Last accessed February 14, 2023.
60. Burke RM, Killerby ME, Newton S, et al. Symptom profiles of a convenience sample of patients with COVID-19—United States, January–April 2020. *MMWR*. 2020;69:904-908.
61. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383:334-346.
62. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York state. *N Engl J Med*. 2020;383:347-358.
63. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *N Engl J Med*. 2021;384:693-704.
64. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2—preliminary report. *N Engl J Med*. 2020;383:1920-1931.
65. Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomized controlled trial. *Lancet*. 2020;396(10249):P467-P478.
66. Brooks JT, Butler JC, Redfield RR. Universal masking to prevent SARS-CoV-2 transmission—the time is now. *JAMA*. 2020;324(7):635-637.
67. Hendrix MJ, Wade C, Findley K, Trotman R. Absence of transmission of SARS-CoV-2 after exposure at a hair salon with universal face mask policy—Springfield, Missouri. *MMWR*. 2020;69(28):930-932.
68. Carfi A, Bernabei R, Landi F, et al. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324:603-605.
69. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network—United States, March–June 2020. *MMWR*. 2020;69:993-998.
70. Cavalcanti AB, Zampieri FG, Rosa RC, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N Engl J Med*. 2020;383:2041-2052.
71. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, et al. Effect of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med*. 2020;383(21):2030-2040.
72. National Institutes of Health. NIH Halts Clinical Trial of Hydroxychloroquine. Available at https://www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine. Last accessed February 14, 2023.
73. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) of COVID-19 Convalescent Plasma for Treatment of COVID-19 in Hospitalized Patients. Available at https://www.fda.gov/media/141478/download. Last accessed February 14, 2023.
74. Biran N, Andrew I, Ahn J, et al. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicenter observational study. *Lancet Rheumatology*. 2020;2(10):e603-e612.
75. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related *Strongyloides* hyperinfection. *JAMA*. 2020;324(7):623-624.
76. Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. *medRxiv*. 2020;Preprint.
77. Tartof SY, Qian L, Hong V, et al. Obesity and mortality among patients diagnosed with COVID-19: results from an integrated health care system. *Ann Int Med*. 2020;M20-3742.
78. Kass DA. COVID-19 and obesity: a big problem? *Ann Int Med*. 2020;M20-5677.
79. Centers for Disease Control and Prevention. Overview of Testing for SARS-CoV-2, the Virus that Causes COVID-19. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html. Last accessed February 14, 2023.
80. U. S. Food and Drug Administration. Coronavirus Disease 2019 (COVID-19) Emergency Use Authorization for Medical Devices: In Vitro Diagnostics EUAs. Available at https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas. Last accessed February 14, 2023.
81. Fournier J, Casanovas-Massana A, Campbell M, et al. To the editor: Saliva or nasopharyngeal swab specimens for detection of SARS-CoV-2. *N Engl J Med*. 2020;383:1283-1286.
82. Hanson KE, Barker AP, Hillyard DR, et al. Self-collected anterior nasal and salivary specimens versus healthcare worker-collected nasopharyngeal swabs for the molecular detection of SARS-CoV-2. *J Clin Microbiol*. 2020;58(11):e01824-e01830.
83. Centers for Disease Control and Prevention. Interim Guidelines for COVID-19 Antibody Testing. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing/antibody-tests-guidelines.html. Last accessed February 14, 2023.

84. U.S. Food and Drug Administration. EUA Authorized Serology Test Performance. Available at https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance. Last accessed February 14, 2023.
85. Marovich M, Mascola JR, Cohen MS. Monoclonal antibodies for prevention and treatment of COVID-19. *JAMA*. 2020;324:131-132.
86. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med*. 2020;383:2427-2438.
87. Chu DK, Aki EA, Duda S, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systemic review and meta-analysis. *Lancet*. 2020;395:1973-1987.
88. Centers for Disease Control and Prevention. Ending Isolation and Precautions for People with COVID-19: Interim Guidance. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html. Last accessed February 14, 2023.
89. Centers for Disease Control and Prevention. Clinical Questions about COVID-19: Questions and Answers: COVID-19 Risk. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html#COVID-19-Risk. Last accessed February 14, 2023.
90. U.S. Food and Drug Administration. FDA Approves First Treatment for COVID-19. Available at https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19. Last accessed February 14, 2023.
91. Parr JB. Time to reassess tocilizumab's role in COVID-19 pneumonia. *JAMA Intern Med*. 2021;181(1):12-15.
92. Pringle JC, Leikauskas J, Ransom-Kelly S, et al. COVID-19 in a correctional facility employee following multiple brief exposures to persons with COVID-19—Vermont, July–August 2020. *MMWR*. 2020;69(43):1569-1570.
93. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med*. 2021;384:619-629.
94. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med*. 2021;384:229-237.
95. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Monoclonal Antibody Bamlanivimab. Available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab. Last accessed February 14, 2023.
96. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Casirivimab and Imdevimab. Available at https://www.fda.gov/media/145611/download. Last accessed February 14, 2023.
97. Krammer F. SARS-CoV-2 vaccines in development. *Nature*. 2020;586:516-527.
98. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383:2603-2615.
99. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384:403-416.
100. Dooling K, Marin M, Wallace M, et. al. The Advisory Committee on Immunization Practices' updated interim recommendation for allocation of COVID-19 vaccine—United States, December 2020. *MMWR*. 2021;69:1657-660.
101. Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html. Last accessed February 14, 2023.
102. Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines. *N Engl J Med*. 2021;384:643-649.
103. Centers for Disease Control and Prevention. COVID-19 Vaccination, Interim Considerations: Preparing for the Potential Management of Anaphylaxis after COVID-19 Vaccination. Available at https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html. Last accessed February 14, 2023.
104. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19) Scientific Brief: Community Use of Cloth Masks to Control the Spread of SARS-CoV-2. Available at https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/masking-science-sars-cov2.html. Last accessed February 14, 2023.
105. Freeman EE, McMahon DE, Lipoff JB, et al. Pernio-like skin lesions associated with COVID-19: a case series of 318 patients from 8 countries. *J Am Acad Dermatol*. 2020;83:486-492.
106. Freeman EE, McMahon DE, Lipoff JB, et al. The spectrum of COVID-19-associated dermatologic manifestations: an international registry of 716 patients from 31 countries. *J Am Acad Dermatol*. 2020;83:1118-1129.
107. Zambrano LD, Ellington S, Strid P, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status—United States, January 22–October 3, 2020. *MMWR*. 2020;69:1641-1647.
108. Havervall S, Rosell A, Phillipson M. Symptoms and functional impairment assessed 8 months after mild COVID-19 among health care workers. *JAMA*. 2021;325(19):2015-2016.
109. Libster R, Marc GP, Wappner D, et al. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med*. 2021;384:610-618.
110. Oliver SE, Gargano JW, Scobie H, et al. The Advisory Committee on Immunization Practices' interim recommendation for use of Janssen COVID-19 vaccine—United States, February 2021. *MMWR*. 2021;70:329-332.

111. Manisty C, Otter AD, Treibel TA, et al. Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals. *Lancet*. 2021;397:1057-1058.

112. Lustig Y, Nemer I, Kliker L, et al. Neutralizing response against variants after SARS-CoV-2 infection and one dose of BNT162b2. *N Engl J Med*. 2021;384(25):2453-2454.

113. Centers for Disease Control and Prevention. V-Safe After Vaccination Health Checker. Available at https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html. Last accessed February 14, 2023.

114. Blumenthal KG, Freeman EE, Saff RR, et al. Delayed large local reactions to mRNA-1273 vaccine against SARS-CoV-2. *N Engl J Med*. 2021;384:1273-1277.

115. Shamier MC, Tostmann A, Bogers S, et al. Virologic Characteristics of SARS-CoV-2 Vaccine Breakthrough Infections in Health Care Workers. Available at https://ncrc.jhsph.edu/research/virological-characteristics-of-sars-cov-2-vaccine-breakthrough-infections-in-health-care-workers/. Last accessed February 14, 2023.

116. Gudbjartsson DF, Norddahl GL, Melsted P, et al. Humoral immune response to SARS-CoV-2 in Iceland. *N Engl J Med*. 2020;383:1724-1734.

117.Lumley SF, O'Donnell D, Stoesser NE, et al. Antibody status and incidence of SARS-CoV-2 infection in health care workers. *N Engl J Med*. 2021;384:533-540.

118. Hansen CH, Michlmayr D, Gubbels SM, et al. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-positive individuals in Denmark in 2020: a population-level observational study. *Lancet*. 2021;397(10280):1204-1212.

119. Dan JM, Mateus J, Kato Y, et al. Immunological memory to SARS-CoV-2 assessed up to 8 months after infection. *Science*. 2021;371(6529):eabf4063.

120. Worobey M, Levy JI, Serrano LM, et al. The Huanan Seafood Wholesale Market in Wuhan was the early epicenter of the COVID-19 pandemic. *Science*. 2022;377(6609):951-959.

121. Barouch DH. Covid-19 vaccines: Immunity, variants, boosters. *N Engl J Med*. 2022;387:1011-1020.

122. Centers for Disease Control and Prevention. COVID-19 Science Brief: SARS-CoV-2 and Surface (Fomite) Transmission for Indoor Community Environments. Available at https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/surface-transmission.html. Last accessed February 14, 2023.

123. Centers for Disease Control and Prevention. SARS-CoV-2 Variant Classifications and Definitions. Available at https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html. Last accessed February 14, 2023.

124. Centers for Disease Control and Prevention. COVID Data Tracker Weekly Review. Available at https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html. Last accessed February 14. 2023.

125. Tarke A, Sidney J, Methot N, et al. Negligible impact of SARS-CoV-2 variants on CD4+ and CD8+ T cell reactivity in COVID-19 exposed donors and vaccinees. *bioRxiv*. 2021; [Epub ahead of print].

126. Redd AD, Nardin A, Kared H, et al. CD8+ T cell responses in COVID-19 convalescent individuals target conserved epitopes from multiple prominent SARS-CoV-2 circulating variants. *Open Forum Infectious Diseases*. 2021; [Epub ahead of print].

127. U. S. Food and Drug Administration. Joint CDC and FDA Statement on Johnson & Johnson COVID-19 Vaccine. Available at https://www.fda.gov/news-events/press-announcements/joint-cdc-and-fda-statement-johnson-johnson-covid-19-vaccine. Last accessed February 14, 2023.

128. Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med*. 2021;384(22):2092-2101.

129. Schultz NH, Sorvoll IH, Michelsen AE, et al. Brief report: thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med*. 2021;384(22):2124-2130.

130. Hunter PR. Editorial: thrombosis after covid-19 vaccination. *BMJ*. 2021;373:n958.

131. Centers for Disease Control and Prevention. Stay Up to Date with COVID-19 Vaccines Including Boosters. Available at https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html. Last accessed February 14, 2023.

132. Centers for Disease Control and Prevention. Delta Variant: What We Know About the Science. Available at https://stacks.cdc.gov/view/cdc/108671. Last accessed February 14, 2023.

133. Le Page M, Thomson H, Vaughan A, Wilson C. Getting to grips with long COVID. *New Sci*. 2021;250:10-13.

134. Becker JH, Lin JJ, Doernberg M, et al. Assessment of cognitive function in patients after COVID-19 infection. *JAMA Netw Open*. 2021;4(10):e2130645.

135. Say D, Crawford N, McNab S, et al. Post-acute COVID-19 outcomes in children with mild and asymptomatic disease. *Lancet: Child & Adolescent Health*. 2021;5(6):e22-e23.

136. American Academy of Pediatrics. Children and COVID-19: State-Level Data Report. Available at https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report. Last accessed February 14, 2023.

137. Centers for Disease Control and Prevention. COVID Data Tracker: Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States. Available at https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance. Last accessed February 14, 2023.

138. Gray KJ, Bordt EA, Atyeo C, et al. Coronavirus disease 2019 vaccine response in pregnant and lactating women: a cohort study. *Am J Obstet Gynecol.* 2021;225(3):303.e1-303.e17.

139. Centers for Disease Control and Prevention. V-safe COVID-19 Vaccine Pregnancy Registry. Available at https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafepregnancyregistry.html. Last accessed February 14, 2023.

140. Zauche LH, Wallace B, Smoots AN, et al. To the editor: receipt of mRNA vaccines and risk of spontaneous abortion. *NEJM.* 2021;385:1533-1535.

141. Magnus MC, Gjessing HK, Eide HN, et al. To the editor: COVID-19 vaccination during pregnancy and first-trimester miscarriage. *NEJM.* 2021;385:2008-2010.

142. Academy of Breastfeeding Medicine. ABM Statement: Considerations for COVID-19 Vaccination in Lactation. Available at https://abm.memberclicks.net/abm-statement-considerations-for-covid-19-vaccination-in-lactation. Last accessed February 14, 2023.

143. Golan Y, Prahi M, Cassidy A, et al. Evaluation of messenger RNA from COVID-19 BTN162b2 and mRNA-1273 vaccines in human milk. *JAMA Pediatr.* 2021;10:1069-1071.

144. The American College of Obstetricians and Gynecologists. Statement of Strong Medical Consensus for Vaccination of Pregnant Individuals Against COVID-19. Available at https://www.acog.org/news/news-releases/2021/08/statement-of-strong-medical-consensus-for-vaccination-of-pregnant-individuals-against-covid-19. Last accessed February 14, 2023.

145. Rosenblum HG, Hadler SC, Moulia D, et al. Use of COVID-19 vaccines after reports of adverse events among adult recipients of Janssen (Johnson & Johnson) and mRNA COVID-19 vaccines (Pfizer-BioNtech and Moderna): update from the Advisory Committee on Immunization Practices—United States, July 2021. *MMWR.* 2021;70:1094-1099.

146. Barda N, Dagan N, Shiomo YB, et al. Safety of the BNT162b2 mRNA COVID-19 vaccine in a nation-wide setting. *N Eng J Med.* 2021;385:1078-1090.

147. U.S. Department of Health and Human Services. Statement Following CDC ACIP Meeting from Nations Leading Doctors, Nurses, Pharmacists and Public Health Leaders on Benefits of Vaccination. Available at https://www.aap.org/en/news-room/news-releases/aap/2021/statement-following-cdc-acip-meeting-from-nations-leading-doctors-nurses-and-public-health-leaders/. Last accessed February 14, 2023.

148. Delahoy MJ, Ujamaa D, Whitaker M, et al. Hospitalizations associated with COVID-19 among children and adolescents—COVID-NET, 14 states, March 1, 2020–August 14, 2021. *MMWR.* 2021;70:1255-1260.

149. Seasely AR, Blanchard CT, Arora N, et al. Maternal and perinatal outcomes associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta (B.1.617.2) variant. *Obstetrics & Gynecology.* 2021;138(6):842-844.

150. Morris RS. SARS-CoV-2 spike protein seropositivity from vaccination or infection does not cause sterility. *Amer Soc Reproduct Med, F & S Rep.* 2021;2(3):253-255.

151. Gonzalez DC, Nassau DE, Khodamoradi K, et al. Sperm parameters before and after COVID-19 mRNA vaccination. *JAMA.* 2021;326:273-274.

152. Hezavehei M, Shokoohian B, Nasr-Esfahani MH, et al. Possible male reproduction complications after Coronavirus pandemic. *Cell J.* 2021;23:382-388.

153. Witberg G, Barda N, Hoss S, et al. Myocarditis after Covid-19 vaccination in a large health care organization. *N Engl J Med.* 2021;385:2132-2139.

154. Centers for Disease Control and Prevention. COVID-19 vaccine breakthrough infections reported to CDC—United States, January 1–April 30, 2021. *MMWR.* 2021;70:792-793.

155. Flaxman S, Whittaker C, Semenova E, et al. Assessment of COVID-19 as the underlying cause of death among children and young people aged 0 to 19 years in the US. *JAMA Netw Open.* 2023;6(1):e2253590.

156. Goel RR, Painter MM, Apostolidis SA, et al. mRNA vaccines induce durable immune memory to SARS-CoV-2 and variants of concern. *Science.* 2021;374(6572):abm0829.

157. Bozio CH, Grannis SJ, Naleway AL, et al. Laboratory-confirmed COVID-19 among adults hospitalized with COVID-19-like illness with infection-induced or mRNA vaccine-induced SARS-CoV-2 immunity—nine states, January–September 2021. *MMWR.* 2021;70(44):1539-1544.

158. Griffin JB, Haddix M, Danza P, et al. SARS-CoV-2 infections and hospitalizations among persons aged >16 years, by vaccination status—Los Angeles County, May 1–July 25, 2021. *MMWR.* 2021;70(34):1170-1176.

159. Richter DR, Guasti L, Koehler F, et al. Late phase of COVID-18 pandemic in general cardiology: a position paper of the ESC Council for Cardiology Practice. *ESC Heart Failure.* 2021;8:3483-3494.

160. Xie Y, Xu E, Bowe B, et al. Long-term cardiovascular outcomes of COVID-19. *Nat Med.* 2022;28:583-590.

161. Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet Diabetes & Endocrinology.* 2022;10(5):311-321.

162. Bradley RE, Ponsford MJ, Scurr MJ, et al. Therapeutic vaccination: a case report. *J Clin Immun.* 2022;42:32-35.

163. Marks KJ, Whitaker M, Agathis NT, et al. Hospitalization of infants and children aged 0-4 years with laboratory-confirmed COVID-19—COVID-NET, 14 states, March 2020–February 2022. *MMWR.* 2022;71(11):429-436.

164. Zambrano LD, Newhams MM, Olson SM, et al. Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA vaccination against multisystem inflammatory syndrome in children among persons aged 12-18 years—United States, July–December 2021. *MMWR.* 2022;71(2): 52-58.

165. Gottlieb RL, Vaca CE, Peredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med.* 2022;386:305-315.

166. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N Engl J Med.* 2022;386:1397-1408.

167. Centers for Disease Control and Prevention, Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with Use of Products Containing Ivermectin to Prevent or Treat COVID-19. Available at https://emergency.cdc.gov/han/2021/han00449.asp. Last accessed February 14, 2023.

168. Yemple C, Hoang R, Hendrickson RG. Toxic effects of ivermectin use associated with prevention and treatment of Covid-19. *N Engl J Med.* 2021;385:2197-2198.

169. Lopez-Medina E, Lopez P, Hurtado IC, et al. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19. *JAMA.* 2021;325:1426-1435.

170. Reis G, Silva E, Silva D, et al. Effect of early treatment with ivermectin among patients with Covid-19. *N Engl J Med.* 2022;386:1721-1731.

171. Lim SCL, Hor CP, Tay KH, et al. Efficacy of ivermectin treatment on disease progression among adults with mild to moderate COVID-19 and comorbidities: the I-TECH randomized clinical trial. *JAMA Intern Med.* 2022;182(4):426-435.

172. Tenforde MW, Self WH, Gaglani M, et al. Effectiveness of mRNA vaccination in preventing COVID-19-associated invasive mechanical ventilation and death—United States, March 2021–January 2022. *MMWR.* 2022;71(12):459-465.

173. Block JP, Borhmer TK, Forrest CB, et al. Cardiac complications after SARS-CoV-2 infection and mRNA COVID-19 vaccination—PCORnet, United States, January 2021–January 2022. *MMWR.* 2022;71(14);517-523.

174. Nordstrom P, Ballin M, Nordstrom A. Risk of SARS-CoV-2 reinfection and COVID-19 hospitalization in individuals with natural and hybrid immunity: a retrospective study, total population cohort study in Sweden. *Lancet Infect Dis.* 2022;22(6):781-790.

175. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of Baricitinib. Available at https://www.fda.gov/media/143823/download. Last accessed February 14, 2023.

176. Centers for Disease Control and Prevention. COVID-19 Rebound After Paxlovid Treatment. Available at https://emergency.cdc.gov/han/2022/pdf/CDC_HAN_467.pdf. Last accessed February 14, 2023.

177.Allotey J, Chatterjee S, Kew T, et al. SARS-CoV-2 positivity in offspring and timing of mother-to-child transmission: living systematic review and meta-analysis. *BMJ.* 2022;376:e067696.

178. Konstantinidou AE, Angelidou S, Havaki S, et al. Stillbirth due to SARS-CoV-2 placentitis without evidence of intrauterine transmission to fetus: association and maternal risk factors. *Ultrasound Obstet Gynecol.* 2022;59:813-822.

179. U.S. Food and Drug Administration. Recommendations for Investigational COVID-19 Convalescent Plasma. Available at https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-applications-inds-cber-regulated-products/recommendations-investigational-covid-19-convalescent-plasma. Last accessed February 14, 2023.

180. McConeghy KW, White EM, Blackman C, et al. Effectiveness of a second COVID-19 vaccine booster dose against infection, hospitalization, or death among nursing home residents—19 states, March 29–July 25, 2022. *MMWR.* 2022;71:1235-1238.

181. Zou J, Kurhade C, Patel S, et al. Neutralization of BA.4–BA.5, BA.4.6, BA.2.75.2, BQ.1.1, and XBB.1 with bivalent vaccine. *N Engl J Med.* 2023; [Epub ahead of print].

182. Link-Gelles R, Ciesla AA, Fleming-Dutra KE, et al. Effectiveness of bivalent mRNA vaccines in preventing symptomatic SARS-CoV-2 infection: Increasing Community Access to Testing Program, United States, September–November 2022. *MMWR.* 2022;71:1526-*1530.*

183. Lin D-Y, Xu Y, Gu Y, et al. Letter: Effectiveness of bivalent boosters against severe Omicron infection. *N Engl J Med.* 2023; (Epub ahead of print).

184. Arbel, Ronen, Peretz, et al. Effectiveness of bivalent mRNA vaccine in preventing severe COVID-19 outcomes: an observational cohort study. *Lancet.* 2023; [Epub ahead of print].

185. Link-Gelles R, Ciesla AA, Roper LE, et al. Early estimates of bivalent mRNA booster dose vaccine effectiveness in preventing symptomatic SARS-CoV-2 infection attributable to Omicron BA.5- and XBB/XBB.1.5-related sublineages among immunocompetent adults – Increasing Community Access to Testing Program, United States, December 2022–January 2023. *MMWR.* 2023;72(5);119-124.

COURSE TEST - #54151 THE CORONAVIRUS DISEASE (COVID-19) PANDEMIC

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 70% must be achieved in order to receive credit for this course.

This 2 CE Credit Hour activity must be completed by February 28, 2026.

Accreditations & Approvals: NetCE is an ADA CERP Recognized Provider.

ADA CERP is a service of the American Dental Association to assist dental professionals in identifying quality providers of continuing dental education. ADA CERP does not approve or endorse individual courses or instructors, nor does it imply acceptance of credit hours by boards of dentistry.

Concerns or complaints about a CE provider may be directed to the provider or to ADA CERP at www.ada.org/cerp.

NetCE
Nationally Approved PACE Program
Provider for FAGD/MAGD credit.
Approval does not imply acceptance by
any regulatory authority or AGD endorsement.
10/1/2021 to 9/30/2027
Provider ID #217994.

NetCE is a Registered Provider with the Dental Board of California. Provider number RP3841.
Completion of this course does not constitute authorization for the attendee to perform any services that he or she is not legally authorized to perform based on his or her permit type.

NetCE is approved as a provider of continuing education by the Florida Board of Dentistry, Provider #50-2405.

Designations of Credit: NetCE designates this activity for 2 continuing education credits.
AGD Subject Code: 148.
This course meets the Dental Board of California's requirements for 2 units of continuing education.
Dental Board of California course #02-3841-00384.

1. **Human coronavirus (CoV) was first identified in**
   - A) *1906.*
   - B) *1965.*
   - C) *1999.*
   - D) *2019.*

2. **Which of the following statements regarding common human coronaviruses is TRUE?**
   - A) *There are about four antigenic strains in frequent circulation.*
   - B) *They are a common cause of mild-to-moderate upper respiratory illness.*
   - C) *Lower respiratory tract complications, such as pleurisy and pneumonia, are rare.*
   - D) *All of the above.*

3. **The common epidemiologic feature in novel coronavirus outbreaks is**
   - A) *chronic substance abuse among patients.*
   - B) *vegetarianism or veganism among patients.*
   - C) *viruses can exchange RNA segments during replication and create viruses with new gene combinations.*
   - D) *an initial point source cluster of zoonotic infection followed by secondary spread via human-to-human transmission.*

4. **Early cases of severe acute respiratory syndrome coronavirus (SARS-CoV)-2002–2003 represented a zoonotic infection originating in**
   - A) *pigs.*
   - B) *camels.*
   - C) *civet cats.*
   - D) *migratory birds.*

5. **By summer 2021, which variant accounted for 99% of COVID-19 cases reported in the United States?**
   - A) *Alpha*
   - B) *Delta*
   - C) *Lambda*
   - D) *Omega*

6. **In a report of clinical features of patients hospitalized with COVID-19, the most common symptom at the onset of illness was**
   - A) *fever.*
   - B) *cough.*
   - C) *dyspnea.*
   - D) *myalgia or fatigue.*

Test questions continue on next page →

7. Of the following PCR-positive cases, which one most likely has severe COVID-19?

A) Sick three days with "cold" plus anosmia, fatigue, temperature of 99.2, new-onset cough, and SpO_2 97% by pulse oximetry

B) Sick three days with headache, myalgias, fatigue, temperature 100.4, new-onset cough, and SpO_2 97% by pulse oximetry

C) Sick seven days with fatigue, feverishness, new-onset cough, shortness of breath, and SpO_2 92% by pulse oximetry

D) All of the above.

8. The preferred first-line antiviral therapy for the treatment of COVID-19 in adults is

A) remdesivir.

B) molnupiravir.

C) hydroxychloroquine.

D) ritonavir-boosted nirmatrelvir (Paxlovid).

9. Which of the following statements regarding COVID vaccination is TRUE?

A) The CDC recommends booster doses for eligible persons.

B) Natural immunity that follows SARS-CoV-2 infection is enhanced by vaccination.

C) COVID-19 mRNA vaccine represents a new vaccine technology that has important public health advantages.

D) All of the above

10. The real-time reverse transcription polymerase chain reaction (rRT-PCR) assay for SARS-CoV-2 can be conducted using

A) serum.

B) sputum.

C) broncheoalveolar lavage.

D) Any of the above

Be sure to transfer your answers to the Answer Sheet.
DO NOT send these test pages to NetCE. Retain them for your records.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.