REVIEW ARTICLE

SARS-COV-2 EPIDEMIOLOGY, PREVENTION, RISK FACTORS, EVALUATION, DIAGNOSIS, MANAGEMENT AND VACCINES

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ABSTRACT:

What we have learned about COVID-19 is ongoing as research continues to evolve. This article will serve to provide a succinct, comprehensive overview of SARS-CoV-2 with respect to epidemiology, risk factors, prevention, presentation, management and vaccinations.

EPIDEMIOLOGY, RISK FACTORS, PREVENTION

Currently, nearly 120 million cases of SARS-CoV-2 have been reported worldwide.[1] Cross-sectional and population-based studies have estimated actual infection rates may be at least 10-fold higher than reported based on seroprevalence of anti–SARS-CoV-2 antibodies in certain areas that were studied, although more research is needed to support these findings.[2,3] The initial outbreak of SARS-CoV-2 occurred on December 8, 2019, in Wuhan, China, and its surrounding province of Hubei. Twenty-two days later, SARS-CoV-2 was first isolated in the bronchoalveolar lavage fluid of three COVID-19 patients from Wuhan Jinyintan Hospital.[4,5] Epidemiologists found an association with a local seafood market that sold live animals, where most patients had worked or visited.[5] SARS-CoV-2 quickly spread to all 31 provinces of China and outside countries soon thereafter, with Antarctica as the only continent without any reported cases of SARS-CoV-2.[1]

SARS-CoV-2 is primarily transmitted through direct person-to-person transmission via respiratory droplets, which may travel up to 6 feet.[6] Additionally, if a person's hands become contaminated by droplets or if the person touches a contaminated surface and then touches their eyes, nose or mouth, they may become infected.[7] The virus has also been detected outside of respiratory droplets, including in stool, although according to a World Health Organization (WHO)-China Joint Mission report, transmission through fecal-oral route does not seem to be a significant method of transmission.[8]

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The risk of transmitting SARS-CoV-2 is highest in the first week of illness, even if asymptomatic, when viral RNA levels from upper respiratory specimens are greatest.[9,10] The risk of transmission after contact with an infected individual increases with closeness and duration of exposure, especially with household contacts, at healthcare or long-term-care facilities with insufficient personal protective equipment, or at congregate areas where individuals reside or work near each other, as well as at work or social gatherings.[11] Serious illness, hospitalization and death can result with COVID-19 infection at any age but most commonly is found in older adults and those with chronic kidney disease, diabetes mellitus (30%), hypertension, cardiovascular disease (32%), obesity, chronic lung diseases (18%), smoking or certain cancers.[12,13]

Personal protective measures are recommended for preventing the spread of COVID-19, including social distancing of 6 feet, face masks, hand hygiene, disinfecting surfaces, and avoiding crowds or those who are symptomatic.[14] The U.S. Centers for Disease Control and Prevention (CDC) recommends that people older than the age of 2 properly wear a mask over the mouth and nose when social distancing cannot be maintained and when with those who are not of the same household.[15] Masks with valves or vents for exhalation are not recommended by the CDC because they may not prevent people from spreading COVID-19 to others, as the valve allows respiratory droplets to pass through and possibly infect others.[15] Masks are shown to be a barrier preventing respiratory droplets from spreading, which can happen when someone talks, coughs or sneezes. Covering a cough or sneeze to practice proper respiratory hygiene is advised.[15] Masks, however, do not filter out all the viral particles. This had led some to study the concept of "variolation," whereby smaller viral loads that are not filtered by the mask may cause asymptomatic or mild infections (assuming viral load exposure impacts the severity of disease). This would theoretically be beneficial—pending a vaccine—by building a natural immunity to

a less severe disease, further favoring the use of widespread face masks.[16,17] Many studies demonstrate overwhelming reduction in viral particles filtered on exhalation and inhalation by cloth masks, upwards of 80% and 50%, respectively.[18–21] Furthermore, there are several epidemiologic and observational studies from around the world and in the healthcare setting that demonstrate a strong association with community mask use and overwhelming reduction of COVID-19 transmission.[22–25] Another form of protection advised by the CDC is to avoid all nonessential travel, thereby decreasing risk of exposure or asymptomatic transfer of infection.[26]

OBJECTIVE FINDINGS & DIAGNOSIS

Diagnosis of COVID-19 is based on clinical manifestations, polymerase chain reaction (PCR) tests, blood tests and imaging. Several symptoms have been associated with severe infection, including cough (50%), fever (43%), dyspnea (29%) and bilateral infiltrates on imaging.[27,28] Other symptoms are widely variable and include myalgias, headaches, diarrhea, abdominal pain, nausea/vomiting and loss of taste/smell.[29] Dermatologic findings, including urticarial rash, livedo reticularis and discolored nodules on distal digits, have been reported.[30] Acute respiratory distress syndrome (ARDS) is one of the most serious complications of COVID-19. Studies have revealed hematologic sequelae of COVID-19, including cardiovascular and thromboembolic manifestations. Reported complications include acute cardiac injury, arrhythmias, cardiogenic shock and cardiomyopathy.[31] The inflammatory response in COVID-19 patients is impressive, with fevers along with elevated inflammatory markers, transaminases, lactate dehydrogenase and cardiac markers. Patients commonly have lymphopenia and coagulation abnormalities.[31,32] Evidence supports an increased risk of pulmonary embolism and stroke in severely affected patients.[33,34] Symptoms can take 2–14 days after exposure to appear, with studies suggesting the median incubation period to be about 4 days.[35,36]

Chest x-rays and computed tomography (CT) scans have been used in the workup and diagnosis of COVID-19. In most cases of mild to moderate disease, chest radiographs were normal. In more severe disease, bilateral ground-glass opacities with or without consolidation were most prevalent on imaging, peaking between 10 and 12 days.[37] CT scans most commonly found ground-glass opacities +/- consolidation, followed by pleural thickening and air bronchograms. Findings may also be unilateral, though more often are bilateral, peripheral and in the lower lobes.[38]

All symptomatic patients should be tested. Patients may complain of cough, fever, dyspnea, anosmia, sore throat, myalgia, headache, nausea, vomiting, diarrhea or fatigue. Testing is also indicated if patients have traveled within 14 days to a location where COVID-19 has community transmission, if patients have had close contact with a confirmed or suspected case, or if dyspnea becomes prominent between the 4th and 10th day after initial symptoms.[39] Furthermore, asymptomatic patients should be tested in certain circumstances, including those at long-term–care facilities and hospitalized patients in highly prevalent areas of transmission—prior to aerosolizing procedures and arguably 5–7 days after exposure to an individual known to have COVID-19.[40,41]

If testing resources are limited, highest priority should be given to critically ill patients, health care and critical workers, individuals with close contact to a confirmed COVID-19 case in the last 2 weeks, and immunosuppressed patients.[42]

Nucleic acid amplification testing with PCR is the preferred test, with several variations targeting different genes of the virus that have been approved and are in use.[43,44] The CDC recommends nasopharyngeal swabs, oropharyngeal swabs or nasal swabs from both nares, although it is uncertain which route is optimal, and the Infectious Diseases Society of America (IDSA) further recommends to reserve lower respiratory tract specimen testing for patients who may be suspicious for false negative pharyngeal swabs.[42,45]

Positive nucleic acid amplification tests confirm the diagnosis of COVID-19, and negatives typically exclude the diagnosis, although repeat testing is recommended if suspicion remains high (repeat should be done after 24 hours of initial testing). The nucleic acid amplification tests are highly specific, although false negative rates have varied upwards of 40% (limited comparison standards and the accuracy of testing may be variable depending on type of specimen collected).[46–48] If the patient is tested immediately after exposure, the probability of false negatives is up to 100%, but false negatives drop significantly between days 5 and 8.[49] Point-of-care antigen testing is typically less sensitive than PCR, and negative testing does not exclude COVID-19 infection and should be repeated with PCR based on clinical suspicion.[50] To detect past infection, immunoglobulin G (IgG) antibody testing is highly specific and can be useful if done 3–4 weeks after the onset of symptoms in patients with high pretest probabilities. Although the IDSA recommends IgG antibody testing in this context, immunoglobulin M and immunoglobulin A are not encouraged as they perform poorly with respect to their specificity/sensitivity profiles.[51]

Patients may remain positive on COVID-19 testing weeks later, which can complicate the picture when patients who have recovered present weeks or perhaps months later with unexplained respiratory symptoms. The CDC has recommended against repeating testing within 3 months of a positive test, as it is unclear whether a repeat positive result represents an active infection. The natural immunity that may develop is a poorly understood process. The CDC recommends considering isolation and quarantining if patients present fewer than 3 months after their first COVID-19 infection with a positive test.[52,53] Still, retesting within 3 months of the first infection may be a consideration if there is concern for initial false positives, in immunocompromised patients (short-lived immunity) or suspected exposure to variant forms of COVID-19. Nevertheless, patients presenting with symptoms consistent with COVID-19 within 3 months of a prior positive test who have other etiologies ruled out should still quarantine, especially as variants become more prominent.[53]

INPATIENT AND OUTPATIENT MANAGEMENT

Outpatient management of patients with suspected COVID-19 begins with home self-assessment and—if providers and patients are capable—a virtual encounter with a medical professional to help decrease the possible spread of the virus. Patients should

be encouraged to monitor for temperature spikes above 100.3°F (37.9°C), shortness of breath, chest pain, extremity swelling, loss of taste or smell, and signs of gastrointestinal distress, including nausea, vomiting, abdominal pain and non-bloody diarrhea.[27,29,31,36,29,54] Moderate or severe dyspnea, initial oxygen saturation lower than 90%, chest pain, low blood pressure or mental status change should prompt referral to the emergency department.

If the patient's oxygen saturation is between 90% and 94% or if there is moderate dyspnea (especially in high-risk patients), this warrants an in-person evaluation. Low-risk patients with minimal dyspnea can be managed at home. Self-isolation and preventive measures as described previously are encouraged. Symptomatic treatment involves over-the-counter medications for the associated myalgias, fevers and general symptoms. Antipyretics and analgesics, cough medications (benzonatate, dextromethorphan), rest, activity as tolerated, and prone positioning can be encouraged.[55,56] Prone positioning is thought to reduce the gravitational pressure of the heart and abdominal viscera on the pulmonary system, improving ventilation perfusion (V/Q) mismatch and recruiting collapsed alveoli.[57,58]

Precautions can be discontinued in mild nonhypoxic or asymptomatic patients if at least 10 days have passed or if 2 tests 24 hours apart are negative and at least 1 day has passed since the last fever and there is improvement in symptoms.[59,60]

The recommendations for hospitalization depend on the severity of illness, a term defined by the National Institutes of Health (NIH) based on the patient's clinical picture and broken down into mild, moderate, severe and critically severe.[61] Per NIH guidelines, mild illness refers to those who have nonspecific symptoms of the disease without respiratory distress or evidence of disease on chest imaging (x-rays, CT scans, etc.). Moderate illness refers to those who develop respiratory disease but are still able to maintain their oxygen saturation above 94%. Severe illness refers to those who have tachypnea with a respiratory rate greater than 30 breaths per minute, have an oxygen saturation as measured by pulse oximetry under 94% on room air or an alveolar-arterial difference (or gradient) in partial pressure of oxygen with a fraction of inspired oxygen less than 300 mm Hg. Lastly, critical illness refers to those who have developed respiratory failure, septic shock or multisystem organ failure.[61] Patients with mild disease are usually not admitted to the hospital. Patients with moderate illness can be admitted to the general medical floor with precautions in place. It is recommended that these patients perform awake self-proning to improve V/Q mismatch and to recruit collapsed alveoli.[58,60] High-flow nasal canula (HFNC) is preferred to continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP), because these devices can aerosolize the virus and potentially increase the transmission of COVID-19.[62,63] Critically ill patients have ventilator-dependent respiratory failure and require admission to the intensive care unit (ICU). NIH recommends that these patients be intubated by video laryngoscopy when able.[61]

Pharmacotherapy is variable and evolving. Rosenburg *et al* performed a 1,438-patient study showing that the use of hydroxychloroquine—with or without azithromycin—did not reduce mortality, consistent with other studies showing potential harm.[64,65] The NIH COVID-19 panel currently recommends against the use of hydroxychloroquine with or without azithromycin.[61] The Adaptive COVID-19 Treatment Trial (ACTT-1) trial studied remdesivir, an adenosine nucleoside that binds RNA-polymerase to prevent viral replication. This study enrolled 1,063 patients and demonstrated that COVID-19 hospitalized patients who required supplemental oxygen, but not noninvasive or invasive positive pressure ventilation, recovered at 11 days, compared to 15 days with placebo. This study showed no benefit compared to placebo in patients receiving noninvasive positive pressure ventilation, intubation or extracorporeal membrane oxygenation (ECMO).[66] Goldman *et al* performed a randomized, open-label trial comparing 5- and 10-day intravenous remdesivir treatment regimens. The results showed no mortality benefit between the two groups and more adverse reactions in the patients assigned to the 10-day regimen.[67] Nevertheless, although the WHO does not recommend the use of remdesivir, the IDSA and the NIH suggest remdesivir can be used in hospitalized patients requiring oxygen.[61,68] The IDSA also suggests adding tocilizumab—an IL-6 receptor antagonist (blocking inflammatory pathways)—in patients with critical disease and elevated inflammatory markers, based on data suggesting improved outcomes in critical patients.[68,69] Convalescent plasma taken from previously recovered COVID-19 patients can give passive immunity; however, there is no clear role for the use of convalescent plasma, as available evidence is not convincing.[70,71] Monoclonal antibodies are currently being studied, with limited evidence so far on efficacy. They are recommended for patients as part of a clinical trial. [72]

Per the RECOVERY trial, any patient requiring supplemental oxygen should be given up to a 10-day course of dexamethasone at 6 mg per day, with the substitution of other corticosteroids if dexamethasone is not available. This trial showed that the mortality rate was lower among patients who received corticosteroids than placebo.[73] The International Society on Thrombosis and Haemostasis currently recommends prophylactic anticoagulation for hospitalized patients, preferably with low–molecular-weight heparins, which have shown mortality and anti-inflammatory benefit in COVID-19 infection.[74] Paranjpe *et al* suggest that therapeutic anticoagulation could be beneficial to hospitalized patients with COVID-19, but the risks should be weighed against the benefits of increasing anticoagulation.[75]

VACCINATIONS

On November 9, 2020, Pfizer and BioNTech announced that their vaccine candidate BNT162b2 against COVID-19 was successful in the first interim analysis—with over 90% efficacy in preventing symptomatic disease—which was followed shortly thereafter with similar results from Moderna's mRNA 1273 vaccine candidate.[76,77] Both products are mRNA vaccines that are delivered in lipid nanoparticles to express a full-length spike protein.[78,79] Subsequent trial results revealed roughly 95% efficacy in preventing symptomatic infection 7 days and 14 days after the second dose for BNT162b2 (given 3 weeks apart) and mRNA 1273 (given 4 weeks apart), respectively.[78,79] Both vaccines exceeded the U.S. Food and Drug Administration (FDA) threshold guidance of at least 50% efficacy.[80] After extensive review of the data, the FDA

found strong evidence of safety and effectiveness of the vaccines, and both BNT162b2 and mRNA 1273 were approved for the public under Emergency Use Authorization (EUA) for patients at least 16 and 18 years of age, respectively.[81,82] Expert organizations have given guidance on distribution of the vaccine in the setting of limited resources. The National Academies of Sciences, Engineering and Medicine, as well as the Advisory Committee on Immunization Practices (ACIP), have both recommended prioritizing vaccination initially to healthcare workers, first responders, high-risk populations (eg, long-term–care residents, elderly, those with comorbidities) and essential workers, although each state can have its own plan for distribution.[83,84] As of mid-January 2021, there have been more than 16 million vaccine doses administered in the United States, with more than 35 million doses distributed.[85]

Local and systemic effects of both mRNA vaccines were relatively common and transient after the second dose and did not usually prevent regular daily activities.[86,87] Fever (16%–17%), severe fatigue (4%–10%) and severe headache (3%–5%) were the most common adverse effects of BNT162b2 and mRNA 1273.[86,87] Per the CDC, individuals with a history of SARS-CoV-2 do not have to be retested and should still be vaccinated, although it is reasonable to delay the vaccine for 3 months in individuals who have recently recovered from symptomatic infection due to low immediate reinfection risk in the setting of limited resources.[88] As immunocompromised patients may have potentially severe COVID-19 infections, the benefits of the vaccine likely outweigh the risks.[88] Safety has not been established for children or pregnant individuals, although pregnancy is not necessarily a contraindication to the vaccine, and vaccination can be considered on a case-by-case basis.[88] Individuals with any history of immediate or severe reaction to a previous mRNA vaccine should not receive BNT162b2 or mRNA 1273 without further expert consultation.[88] All vaccine recipients should be monitored for at least 15 minutes in settings where acute adverse reactions can be managed.[88]

The Janssen COVID-19 vaccine, which has also been authorized for use in the United States, is based on an adenovirus recombinant vector that produces a spike protein, given intramuscularly as one dose.[89] Janssen's Ad26.COV2.S vaccine had a 66.9% efficacy in preventing moderate to severe COVID-19 starting 2 weeks after vaccination, while efficacy regarding critical disease approached 80% in the same time interval.[90] Injection site pain, headache, fatigue and myalgia were reported between 30% and 50% of the time, with fever 9% of the time.[90]

While pregnant patients have not been included in trials of COVID-19 vaccines, early evaluations of CDC databases of self-reported pregnancies and adverse events did not show any additional side effects in this population compared with the national baseline.[91] The CDC and the American College of Obstetricians and Gynecologists do not recommend necessarily withholding these vaccines based on pregnancy status alone. As a result, many experts suggest a personalized approach evaluating the risks of exposure, underlying health conditions and individual patient preferences in the setting of ongoing research.[92,93]

Although vaccination has been a welcome development during the COVID-19 pandemic, several questions remain unanswered. It is unknown how long a vaccinated individual will have protection from the virus or whether booster doses will be necessary. Furthermore, the impact on community transmission is not well understood. As research on this novel virus evolves, there will be further insight into these questions as well as the discussed epidemiology, risk factors, prevention, and management strategies. Furthermore, challenges regarding vaccine distribution, mutations, hesitancy to get vaccinated and access are important considerations that have not been addressed in this review. Nevertheless, the research and progress made so far during the pandemic is a testament to the commitment and cooperation of scientists, experts, medical professionals and the general population around the world. Their dedication will continue to be a vital aspect of successfully responding to the challenges of this pandemic.

REFERENCES:

1. COVID-19 situation update worldwide, as of week 1, 2021. European Centre for Disease Prevention and Control. http://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases
2. Havers FP, Reed C, Lim T, *et al*. Seroprevalence of antibodies to SARS-CoV-2 in 10 sites in the United States, March 23-May 12, 2020. *JAMA Intern Med*. 2020;180(12):1576–1586. doi:10.1001/jamainternmed.2020.4130
3. Stringhini S, Wisniak A, Piumatti G, *et al*. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. *Lancet*. 2020;396(10247):313–319. doi:10.1016/S0140-6736(20)31304-0
4. *Novel Coronavirus Situation Report - 2*. World Health Organization; 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200122-sitrep-2-2019-ncov.pdf
5. Zhou P, Yang XL, Wang XG, *et al*. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270–273. doi:10.1038/s41586-020-2012-7
6. Bahl P, Doolan C, de Silva C, Chughtai AA, Bourouiba L, MacIntyre CR. Airborne or droplet precautions for health workers treating COVID-19? *J Infect Dis*. 2020;jiaa189. Published online April 16, 2020. doi:10.1093/infdis/jiaa189
7. *Transmission of SARS-CoV-2: Implications for Infection Prevention Precautions*. World Health Organization; 2020. http://apps.who.int/iris/bitstream/handle/10665/333114/WHO-2019-nCoV-Sci_Brief-Transmission_modes-2020.3-eng.pdf?sequence=1&isAllowed=y.
8. *Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)*. World Health Organization; 2020. http://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
9. COVID-19 Investigation Team. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. *Nat Med*. 2020;26(6):861–868. doi:10.1038/s41591-020-0877-5
10. To KKW, Hung IFN, Ip JD, *et al*. Coronavirus disease 2019 (COVID-19) re-infection by a phylogenetically distinct severe acute respiratory syndrome coronavirus 2 strain confirmed by whole genome sequencing. *Clin Infect Dis*. 2020;ciaa1275. Published online August 25, 2020. doi:10.1093/cid/ciaa1275
11. Ghinai I, Woods S, Ritger KA, *et al*. Community transmission of SARS-CoV-2 at two family gatherings — Chicago, Illinois, February–March 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(15):446–450. doi:10.15585/mmwr.mm6915e1

12. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239–1242. doi:10.1001/jama.2020.2648

13. Stokes EK, Zambrano LD, Anderson KN, *et al*. Coronavirus disease 2019 case surveillance — United States, January 22–May 30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(24):759–765. doi:10.15585/mmwr.mm6924e2

14. Clase CM, Fu EL, Joseph M, *et al*. Cloth masks may prevent transmission of COVID-19: an evidence-based, risk-based approach. *Ann Intern Med*. 2020;M20-2567. Published online May 22, 2020. doi:10.7326/M20-2567

15. Guidance for wearing masks. Centers for Disease Control and Prevention. Updated April 29, 2021. https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cloth-face-cover-guidance.html

16. Gandhi M, Rutherford GW. Facial masking for COVID-19—potential for "variolation" as we await a vaccine. *N Engl J Med*. 2020;383:e101.

17. Gandhi M, Beyrer C, Goosby E. Masks do more than protect others during COVID-19: reducing the inoculum of SARS-CoV-2 to protect the wearer. *J Gen Intern Med*. 2020;35(10):3063–3066. doi:10.1007/s11606-020-06067-8

18. Lindsley WG, Blachere FM, Law BF, Beezhold DH, Noti JD. Efficacy of face masks, neck gaiters and face shields for reducing the expulsion of simulated cough-generated aerosols. *medRxiv*. 2020. doi:10.1101/2020.10.05.20207241

19. Ueki H, Furusawa Y, Iwatsuki-Horimoto K, *et al*. Effectiveness of face masks in preventing airborne transmission of SARS-CoV-2. *mSphere*. 2020;5(5):e00637-20. Published online October 21, 2020. doi:10.1128/mSphere.00637-20

20. Verma S, Dhanak M, Frankenfield J. Visualizing the effectiveness of face masks in obstructing respiratory jets. *Phys Fluids*. 2020;32(6):061708. doi:10.1063/5.0016018

21. Rengasamy S, Eimer B, Shaffer RE. Simple respiratory protection—evaluation of the filtration performance of cloth masks and common fabric materials against 20–1000 nm size particles. *Ann Occup Hyg*. 2010;54(7):789–798. doi:10.1093/annhyg/meq044

22. Wang X, Ferro EG, Zhou G, Hashimoto D, Bhatt DL. Association between universal masking in a health care system and SARS-CoV-2 positivity among health care workers. *JAMA*. 2020;324(7):703–704. doi:10.1001/jama.2020.12897

23. Wang Y, Tian H, Zhang L, *et al*. Reduction of secondary transmission of SARS-CoV-2 in households by face mask use, disinfection and social distancing: a cohort study in Beijing, China. *BMJ Glob Health*. 2020;5(5):e002794. doi:10.1136/bmjgh-2020-002794

24. Doung-ngern P, Suphanchaimat R, Panjangampatthana A, *et al*. Case-control study of use of personal protective measures and risk for SARS-CoV 2 infection, Thailand. *Emerg Infect Dis*. 2020;26(11):2607–2616. doi:10.3201/eid2611.203003

25. Payne DC, Smith-Jeffcoat SE, Nowak G, *et al*. SARS-CoV-2 infections and aerologic responses from a sample of U.S. Navy service members — USS Theodore Roosevelt, April 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(23):714–721. doi:10.15585/mmwr.mm6923e4

26. Travel. U.S. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/travelers/index.html

27. 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. doi:10.1016/S0140-6736(20)30183-5

28. Stokes EK, Zambrano LD, Anderson KN, *et al*. Coronavirus disease 2019 case surveillance — United States, January 22–May 30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(24):759–765. doi:10.15585/mmwr.mm6924e2

29. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg*. 2020;163(1):3–11. doi:10.1177/0194599820926473

30. Galván Casas C, Català A, Carretero Hernández G, *et al*. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol*. 2020;183(1):71–77. doi:10.1111/bjd.19163

31. 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(11):1061–1069. doi:10.1001/jama.2020.1585

32. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033–1034. doi:10.1016/S0140-6736(20)30628-0

33. Klok FA, Kruip MJHA, van der Meer NJM, *et al*. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145–147. doi:10.1016/j.thromres.2020.04.013

34. Merkler AE, Parikh NS, Mir S, *et al*. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. *JAMA Neurol*. 2020;77(11):1366–1372. doi:10.1001/jamaneurol.2020.2730

35. Li Q, Guan X, Wu P, *et al*. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med*. 2020;382(13):1199–1207. doi:10.1056/NEJMoa2001316

36. Guan WJ, Ni ZY, Hu Y, *et al*. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–1720. doi:10.1056/NEJMoa2002032

37. Wong HYF, Lam HYS, Fong AHT, *et al*. Frequency and distribution of chest radiographic findings in patients positive for COVID-19. *Radiology*. 2020;296(2):E72–E78. doi:10.1148/radiol.2020201160

38. Bao C, Liu X, Zhang H, Li Y, Liu J. Coronavirus disease 2019 (COVID-19) CT findings: a systematic review and meta-analysis. *J Am Coll Radiol*. 2020;17(6):701–709. doi:10.1016/j.jacr.2020.03.006

39. Cohen PA, Hall LE, John JN, Rapoport AB. The early natural history of SARS-CoV-2 infection: clinical observations from an urban, ambulatory COVID-19 clinic. *Mayo Clin Proc*. 2020;95(6):1124–1126. doi:10.1016/j.mayocp.2020.04.010

40. Overview of testing for SARS-CoV-2. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html

41. IDSA guidelines on the diagnosis of COVID-19. Infectious Diseases Society of America. https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/

42. *COVID-19 Prioritization of Diagnostic Testing*. Infectious Diseases Society of America; 2020. https://www.idsociety.org/globalassets/idsa/public-health/covid-19-prioritization-of-dx-testing.pdf

43. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases. World Health Organization. https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117

44. Emergency Use Authorizations for medical devices. Food and Drug Administration. https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations

45. Interim guidelines for collecting and handling of clinical specimens for COVID-19 testing. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html

46. Long DR, Gombar S, Hogan CA, *et al*. Occurrence and timing of subsequent severe acute respiratory syndrome coronavirus 2 reverse-transcription polymerase chain reaction positivity among initially negative patients. *Clin Infect Dis*. 2020;ciaa722. Published online June 7, 2020. doi:10.1093/cid/ciaa722

47. Weissleder R, Lee H, Ko J, Pittet MJ. COVID-19 diagnostics in context. *Sci Transl Med*. 2020;12(546):eabc1931. doi:10.1126/scitranslmed.abc1931

48. Wang W, Xu Y, Gao R, *et al*. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA*. 2020;323(18):1843–1844. doi:10.1001/jama.2020.3786

49. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in false-negative rate of reverse transcriptase polymerase chain reaction-based SARS-CoV-2 tests by time since exposure. *Ann Intern Med*. 2020;173(4):262–267. doi:10.7326/M20-1495

50. Interim guidance for rapid antigen testing for SARS-CoV-2. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html

51. Interim guidelines for COVID-19 antibody testing. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html

52. He X, Lau EHY, Wu P, *et al*. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med*. 2020;26(5):672–675. doi:10.1038/s41591-020-0869-5

53. Clinical questions about COVID-19: questions and answers. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html

54. Phone advice line tool. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/phone-guide/index.html

55. Greenhalgh T, Koh GCH, Car J. COVID-19: a remote assessment in primary care. *BMJ*. 2020;368:m1182. doi:10.1136/bmj.m1182

56. Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: a single ED's experience during the COVID-19 pandemic. *Acad Emerg Med*. 2020;27(5):375–378. doi:10.1111/acem.13994

57. Scholten EL, Beitler JR, Prisk GK, Malhotra A. Treatment of ARDS with prone positioning. *Chest*. 2017;151(1):215–224. doi:10.1016/j.chest.2016.06.032

58. Gattinoni L, Busana M, Giosa L, Macrì MM, Quintel M. Prone positioning in acute respiratory distress syndrome. *Semin Respir Crit Care Med*. 2019;40(1):94–100. doi:10.1055/s-0039-1685180

59. Ending home isolation for persons with COVID-19 not in healthcare settings. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html

60. Discontinuation of transmission-based precautions and disposition of patients with SARS-CoV-2 infection in healthcare settings (interim guidance). Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html

61. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/

62. Agarwal A, Basmaji J, Muttalib F, *et al*. High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. *Canadian Journal of Anesthesia/Journal Canadien D'anesthésie*. 2020;67:1217–1248. doi:10.1007/s12630-020-01740-2

63. Nicola M, O'Neill N, Sohrabi C, Khan M, Agha M, Agha R. Evidence based management guideline for the COVID-19 pandemic – review article. *Int J Surg*. 2020;77:206–216. doi:/10.1016/j.ijsu.2020.04.001

64. Rosenberg ES, Dufort EM, Udo T, *et al*. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA*. 2020;323(24):2493–2502. doi:10.1001/jama.2020.8630

65. Borba MGS, Val FFA, Sampaio VS, *et al*. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open*. 2020;3(4):e208857. doi:10.1001/jamanetworkopen.2020.8857

66. Beigel JH, Tomashek KM, Dodd LE, *et al*. Remdesivir for the treatment of COVID-19 — final report. *N Engl J Med*. 2020;383(19):1813–1826. doi:10.1056/NEJMoa2007764

67. Goldman JD, Lye DCB, Hui DS, *et al*. Remdesivir for 5 or 10 days in patients with severe COVID-19. *N Engl J Med*. 2020;383(19):1827–1837. doi:10.1056/NEJMoa2015301

68. IDSA guidelines on the treatment and management of patients with COVID-19. Infectious Diseases Society of America. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

69. REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021;384:1491–1502. NEJMoa2100433. doi:10.1056/NEJMoa2100433

70. Piechotta V, Chai KL, Valk SJ, *et al*. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database Syst Rev*. 2020;7(7):CD013600. doi:10.1002/14651858.CD013600.pub2.

71. Salazar E, Christensen PA, Graviss EA, *et al*. Treatment of coronavirus disease 2019 patients with convalescent plasma reveals a signal of significantly decreased mortality. *Am J Pathol*. 2020;190(11):2290–2303. doi:10.1016/j.ajpath.2020.08.001

72. ACTIV-3/TICO LY-CoV555 Study Group. A neutralizing monoclonal antibody for hospitalized patients with COVID-19. *N Engl J Med*. 2021;384(10):905–914. doi:10.1056/NEJMoa2033130

73. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19 - preliminary report. *N Engl J Med*. 2021;384:693–704. doi:10.1056/NEJMoa2021436

74. Thachil J, Tang N, Gando S, *et al*. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18(5):1023–1026. doi:10.1111/jth.14810

75. Paranjpe I, Fuster V, Lala A, *et al*. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. *J Am Coll Cardiol*. 2020;76(1):122–124. doi:10.1016/j.jacc.2020.05.001

76. Pfizer and Biontech announce vaccine candidate against COVID-19 achieved success in first interim analysis from phase 3 study. Pfizer. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against

77. Moderna's COVID-19 vaccine candidate meets its primary efficacy endpoint in the first interim analysis of the phase 3 COVE study. Moderna. https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy

78. Polack FP, Thomas SJ, Kitchin N, *et al*. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med*. 2020;383(27):2603–2615. doi:10.1056/NEJMoa2034577

79. 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. doi:10.1056/NEJMoa2035389

80. Food and Drug Administration. *Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry*. Food and Drug Administration; 2020. https://www.fda.gov/media/139638/download

81. Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 Vaccine to Prevent to Prevent Coronavirus Disease 2019 (COVID-19). *Fact Sheet for Healthcare Providers Administering Vaccine*. Food and Drug Administration; 2021. https://www.fda.gov/media/144413/download

82. Emergency Use Authorization (EUA) of the Moderna COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19). *Fact Sheet for Healthcare Providers Administering Vaccine*. Food and Drug Administration; 2021. https://www.fda.gov/media/144637/download

83. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Health Sciences Policy, *et al*, eds. *Framework for Equitable Allocation of COVID-19 Vaccine*. The National Academies Press; 2020. https://www.nap.edu/catalog/25917/framework-for-equitable-allocation-of-covid-19-vaccine

84. Dooling K, McClung N, Chamberland M, *et al*. The Advisory Committee on Immunization Practices' interim recommendation for allocating initial supplies of COVID-19 vaccine – United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1857–1859. doi:10.15585/mmwr.mm6949e1

85. COVID-19 vaccinations in the United States. Centers for Disease Control and Prevention. https://covid.cdc.gov/covid-data-tracker/#vaccinations

86. Pfizer, Biontech. Pfizer-BioNTech COVID-19 vaccine. FDA briefing document presented at: Vaccines and Related Biological Products Advisory Committee meeting; December 10, 2020. https://www.fda.gov/media/144245/download

87. Moderna. Moderna COVID-19 vaccine. FDA briefing document presented at: Vaccines and Related Biological Products Advisory Committee meeting; December 17, 2020. https://www.fda.gov/media/144434/download

88. Interim clinical considerations for use of mRNA COVID-19 vaccines currently authorized in the United States. Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

89. FDA Emergency Use Authorization (EUA) of the Janssen COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19). *Fact Sheet for Healthcare Providers Administering Vaccine*. Food and Drug Administration; 2021. https://www.fda.gov/media/146304/download

90. Janssen Biotech Inc. Janssen Ad26.COV2.S vaccine for the prevention of COVID-19. FDA briefing document presented at: Vaccines and Related Biological Products Advisory Committee meeting; February 26, 2021. https://www.fda.gov/media/146217/download

91. Shimabukuro T. *COVID-19 Vaccine Safety Update*. National Center for Immunization & Respiratory Diseases; 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/28-03-01/05-covid-Shimabukuro.pdf

92. Practice advisory: COVID-19 vaccination considerations for obstetric–gynecologic care. American College of Obstetricians and Gynecologists. https://www.acog.org/en/clinical/clinical-guidance/practice-advisory/articles/2020/12/vaccinating-Pregnant-and-Lactating-Patients-Against-COVID-19