# Table of Contents

## Overview
- Summary 3
- Definition 3

## Theory
- Epidemiology 4
- Etiology 6
- Pathophysiology 13
- Classification 15
- Case history 17

## Diagnosis
- Approach 19
- History and exam 35
- Risk factors 38
- Investigations 50
- Differentials 62
- Criteria 65
- Screening 66

## Management
- Approach 68
- Treatment algorithm overview 87
- Treatment algorithm 90
- Emerging 119
- Primary prevention 129
- Patient discussions 149

## Follow up
- Monitoring 153
- Complications 155
- Prognosis 165

## Guidelines
- Diagnostic guidelines 174
- Treatment guidelines 177

## Online resources 183

## References 188

## Images 311

## Disclaimer 318
Coronavirus disease 2019 (COVID-19) is an infectious acute respiratory disease caused by a novel coronavirus. The World Health Organization (WHO) was informed of cases of pneumonia of unknown microbial etiology associated with Wuhan City, Hubei Province, China on 31 December 2019. The WHO later announced that a novel coronavirus had been detected in samples taken from these patients. Since then, the epidemic has escalated and rapidly spread around the world, with the WHO first declaring a public health emergency of international concern on 30 January 2020, and then formally declaring it a pandemic on 11 March 2020. Clinical trials and investigations to learn more about the virus, its origin, how it affects humans, and its management are ongoing. This topic is based on the best evidence currently available, but as this is a rapidly evolving situation, evidence is limited in some areas and some recommendations may be based on observational studies and retrospective analyses, as well as randomized controlled trials and guidelines.

**Definition**

A potentially severe acute respiratory infection caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The clinical presentation is generally that of a respiratory infection with a symptom severity ranging from a mild common cold-like illness, to a severe viral pneumonia leading to acute respiratory distress syndrome that is potentially fatal. Characteristic symptoms include fever, cough, dyspnea, and loss of taste/smell, although some patients may be asymptomatic. Complications of severe disease include, but are not limited to, multi-organ failure, septic shock, and venous thromboembolism. Symptoms may be persistent and continue for more than 12 weeks in some patients.
Epidemiology

Over 170.8 million cases have been reported globally, with approximately 3.5 million deaths according to the World Health Organization. The US has the highest number of reported infections and deaths in the world, currently followed by India, Brazil, France, and Turkey.


Detailed data for the US situation is available.


Adults

- In China, 87% of confirmed cases were ages 30 to 79 years and 3% were ages 80 years or older. Approximately 51% of patients were male.[4]
- In Italy, the median age and prevalence of comorbidities was higher compared with China.[5]
- In the UK, the median age of patients was 73 years and males accounted for 60% of admissions in a prospective observational cohort study of more than 20,000 hospitalized patients.[6]
- In the US, older patients (ages ≥65 years) accounted for 31% of all cases, 45% of hospitalizations, 53% of intensive care unit admissions, and 80% of deaths, with the highest incidence of severe outcomes in patients ages ≥85 years.[7]

Children

- Evidence suggests that children have a lower susceptibility to infection compared with adults, with an odds ratio of 0.56 for being an infected contact compared with adults. Adolescents appear to have similar susceptibility to adults.[8]
• The mean age of children with infection is 6.5 years.[9] Infection rates in children and adolescents vary according to geographic location.[4] [10] [11] [12] [13] [14] [15]

• In the UK, a prospective observational cohort study found that children and young adults represented 0.9% of all hospitalized patients at the time. The median age of children admitted to hospital was 4.6 years, 56% were male, 35% were under 12 months of age, and 42% had at least one comorbidity. In terms of ethnicity, 57% were White, 12% were South Asian, and 10% were Black. Age under 1 month, age 10 to 14 years, and Black race were risk factors for admission to critical care.[16]

• In the US, a retrospective cohort study of over 135,000 children found that the mean age of infected children was 8.8 years, and 53% were male. In terms of ethnicity, 59% were White, 15% were Black, 11% were Hispanic, and 3% were Asian. Only 4% of children tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in this population, and clinical manifestations were typically mild.[17] Cases in children, adolescents, and young adults increased between October to December 2020; however, hospitalizations, intensive care unit admissions, and deaths remain low for these groups (2.5%, 0.8%, and <0.1% respectively, based on available data).[18]

• Globally, the case fatality rate in children appears to be higher in low- and middle-income countries compared with high-income countries.[19]

• Most cases in children are from familial clusters, or children who have a history of close contact with an infected patient. It is rare for children to be the index case in household transmission clusters.[20] Unlike adults, children do not seem to be at higher risk for severe illness based on age or sex.[21]


Pregnant women

• The overall prevalence in pregnant and recently pregnant women attending or admitted to hospital for any reason has been estimated to be 10%; however, the rate varies across studies and countries. Most studies with a prevalence greater than 15% were from the US, except for two studies from the UK, and one each from Mexico, Turkey, France, and Iran.[22] [23]

• A meta-analysis of over 2500 pregnant women with confirmed COVID-19 found that 73.9% of women were in the third trimester; 50.8% were from Black, Asian, or minority ethnic groups; 38.2% were obese; and 32.5% had chronic comorbidities.[24]

• In the UK, the estimated incidence of admission to hospital with confirmed SARS-CoV-2 infection in pregnancy is 4.9 per 1000 maternities. Most women were in the second or third trimester. Of these patients, 41% were ages 35 years or older, 56% were from Black or other ethnic minority groups, 69% were overweight or obese, and 34% had preexisting comorbidities.[25]

• In the US, 94,519 cases have been reported in pregnant women (as of 31 May 2021), with 16,108 hospitalizations and 103 deaths.[26] According to an analysis of approximately 400,000 women ages 15 to 44 years with symptomatic disease, Hispanic and non-Hispanic Black pregnant women appear to be disproportionately affected during pregnancy.[27]

Healthcare workers

• The incidence of infection in healthcare workers ranged from 0% to 49.6% (by polymerase chain reaction), and the prevalence of SARS-CoV-2 seropositivity ranged from 1.6% to 31.6%. The wide ranges are likely related to differences in settings, exposures, rates of community transmission, symptom status, use of infection control measures, and other factors. There was no consistent association between sex, age, or healthcare worker role (i.e., nurse versus physician) and risk for infection or seropositivity. However, Black or Hispanic ethnicity was significantly associated with an
increased risk of infection compared with White people. Working in a hospital unit with COVID-19 patients, being a frontline worker, and direct or prolonged patient contact were also associated with an increased risk for infection. The presence of immunoglobulin G antibodies was associated with a decreased risk for reinfection.[28] [29]

- A systematic review and meta-analysis of nearly 130,000 healthcare workers estimated the overall seroprevalence of SARS-CoV-2 antibodies to be 8.7%, with higher seroprevalence reported in North America (12.7%) compared with Europe (8.5%), Africa (8.2%), and Asia (4%). Risk factors for seropositivity included male sex; Black, Asian, or Hispanic ethnicity; working in a COVID-19 unit; patient-facing work; and frontline healthcare work.[30]

- Approximately 14% of the cases reported to the World Health Organization are in healthcare workers (range 2% to 35%).[31]

- The majority of healthcare workers with COVID-19 reported contact in the healthcare setting. In a study of over 9000 cases reported in healthcare workers in the US, 55% had contact only in a healthcare setting, 27% only in a household, 13% only in the community, and 5% in more than one setting.[32]

- The most frequently affected healthcare workers were nurses. Only 5% of healthcare workers developed severe disease and 0.5% died.[33] The incidence of severe or critical disease and mortality in healthcare workers was lower than the incidence of severe or critical disease and mortality in all patients.[34]

- Analysis of hospitalization data from 13 sites in the US found that 6% of hospitalized adults were healthcare workers, and 36% of these people were in nursing-related roles. Around 90% of hospitalized healthcare workers had at least one underlying condition, the most common conditions being obesity, hypertension, and diabetes.[35]

**Etiology**

**Virology**

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a previously unknown betacoronavirus that was discovered in bronchoalveolar lavage samples taken from clusters of patients who presented with pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019.[36]

- Coronaviruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]), and others that circulate among mammals and birds. Rarely, animal coronaviruses can spread to humans and subsequently spread between people, as was the case with SARS and MERS.

- SARS-CoV-2 belongs to the *Sarbecovirus* subgenus of the *Coronaviridae* family, and is the seventh coronavirus known to infect humans. The virus has been found to be similar to SARS-like coronaviruses from bats, but it is distinct from SARS-CoV and MERS-CoV.[37] [38] The full genome has been determined and published in GenBank. [GenBank](https://www.ncbi.nlm.nih.gov/genbank)
Emerging SARS-CoV-2 variants

- All viruses, including SARS-CoV-2, change over time. Over 490,000 variants of the virus have been sequenced by the COVID-19 Genomics UK Consortium (COG-UK) as of 3 June 2021. [COG-UK: data] (https://www.cogconsortium.uk)
- Noteworthy SARS-CoV-2 variants of concern (VOC) include the following.
  - Alpha (VOC-20DEC-01; B.1.1.7 lineage): first identified in Kent, South East of England in September 2020, and reported to the World Health Organization in December 2020. The origin is unclear. It is currently the dominant variant in the UK. The variant has been reported in at least 137 countries, and community transmission has been reported in 35 of these countries (as of 19 April 2021). There is evidence that suggests this variant may be more transmissible. Secondary attack rates have been reported to be higher if the index case has this variant. The reported secondary attack rate is 10% in contacts of people with the variant (who have not traveled). However, secondary attack rates for nonvariant forms are known to vary quite widely (see Secondary attack rate below). The variant does not appear to be associated with more severe disease compared with the wild-type virus, although data are conflicting.[39] [40] There is consistent evidence of cross-neutralizing activity in convalescent sera (i.e., sera from individuals who have been infected with B.1.1.7 shows neutralizing activity against viruses from other lineages, and the converse is also true). There is evidence that there is no increase in reinfection rate, and that vaccine performance is preserved against this variant.[41] [42] [43] The variant has mutations that have been associated with attenuation in other variants.[44]
• Beta (VOC-20DEC-02; B.1.351 lineage): first detected in Nelson Mandela Bay, South Africa in October 2020. The variant has been reported in at least 97 countries, including the UK (as of 19 April 2021). The variant has similar spike protein mutations to the B.1.1.7 lineage. Sequence analysis reveals that the N501Y mutation reported in the UK and South Africa originated independently. These mutations may affect its transmissibility and antigenic profile.[41]

• Gamma (VOC-21JAN-02; P.1 lineage): a descendant of the B.1.1.28 lineage first detected in Japan in travelers from Brazil. The variant has been reported in at least 55 countries (as of 19 April 2021), including the UK. Based on modeling and laboratory data, it is plausible that there is some degree of immune escape, or increased transmissibility, or both with this variant. However, the magnitude and clinical significance of these effects are yet to be determined.[41]

• Delta (VOC-21APR-02; B.1.617.2): first identified in India in April 2021. Both travel-associated and locally-acquired cases are rising in the UK, mainly in London, the North West, and the East of England. Preliminary evidence suggests that this variant is likely to be more transmissible than the B.1.1.7 variant based on available data. The secondary attack rate among contacts of cases that have not traveled is 13.5% (as of 25 May 2021). This is slightly higher compared with the B.1.1.7 variant, which is currently 10% among contacts of cases that have not traveled (see above). Hospitalizations are rising in some affected areas; however, there is currently insufficient evidence to indicate whether this variant can cause more severe disease. This variant has been reported in many countries around the world. Emerging evidence suggests that current vaccines may be effective against the variant after two doses, but with reduced efficacy after one dose.[41] [45] [46]

• Epsilon (B.1.427 and B.1.429 lineages): first detected in California in the US, these variants have been classified as variants of concern by the Centers for Disease Control and Prevention, but not the World Health Organization or Public Health England. They may have an increased risk of transmission, may cause more severe disease, and may not be as responsive to certain treatments; however, data are limited.[47] [48]

• Further investigations are required to more fully understand the impact of these variants. There are many other variants under investigation.

Origin of virus

• A majority of patients in the initial stages of this outbreak reported a link to the Huanan South China Seafood Market, a live animal or “wet” market, suggesting a zoonotic origin of the virus.[49] [50] [51] An initial assessment of the transmission dynamics in the first 425 confirmed cases found that 55% of cases before 1 January 2020 were linked to the market, whereas only 8.6% of cases after this date were linked to the market. This suggests that person-to-person spread was occurring among close contacts since the middle of December 2019.[51]

• Some studies suggest that SARS-CoV-2 may be a recombinant virus between a bat coronavirus and an origin-unknown coronavirus.[37] [38] [52] [53] Pangolins and minks have been suggested as possible intermediate hosts.[54] [55] [56] [57] However, there is currently no evidence to demonstrate the possible route of transmission from a bat reservoir to human through one or several intermediary animal species.[58] Further research is required to determine the origin of SARS-CoV-2.

Transmission dynamics

• Respiratory transmission is the dominant mode of transmission, with proximity and ventilation being the key determinants of transmission risk.[59] Available evidence suggests that transmission between people occurs primarily through direct, indirect, or close contact with infected people through infected
Coronavirus disease 2019 (COVID-19)

Theory

secretions such as saliva and respiratory secretions, or through their respiratory droplets, which are expelled when an infected person coughs, sneezes, talks, or sings.[60]

• Airborne transmission can occur in healthcare settings during aerosol-generating procedures. There are also some outbreak reports that suggest aerosol transmission is possible in the community under certain conditions; however, these reports relate to enclosed indoor crowded spaces with poor ventilation where the infected person may have been breathing heavily (e.g., restaurants, choir practice, fitness classes). A detailed investigation of these clusters suggests that droplet and fomite transmission could also explain the transmission in these reports.[60][61] While the air close to, and distant from, patients has been found to frequently be contaminated with SARS-CoV-2 RNA, few of these samples contained viable virus.[62] Evidence that nebulizer treatments increase the risk of transmission of coronaviruses similar to SARS-CoV-2 is inconclusive, and there is minimal direct evidence about the risk for transmission of SARS-CoV-2.[63]

• Fomite transmission (from direct contact with fomites) may be possible, but there is currently no conclusive evidence for this mode of transmission. In the few cases where fomite transmission has been presumed, respiratory transmission has not been completely excluded.[59] The virus has been found to be more stable on plastic and stainless steel (up to 72 hours) compared with copper (up to 4 hours) and cardboard (up to 24 hours) under experimental conditions, but this does not reflect real-life conditions.[64] In healthcare settings, the virus is widely distributed in the air and on object surfaces in both general wards and intensive care units.[65] However, no virus has been cultured from these samples indicating that the deposition may reflect nonviable viral RNA.[66][67][68]

• Fecal-oral transmission (or respiratory transmission through aerosolized feces) may be possible, but there is only limited circumstantial evidence to support this mode of transmission.[59] The pooled detection rate of fecal SARS-CoV-2 RNA in patients with COVID-19 is approximately 51%, with 64% of samples remaining positive for a mean of 12.5 days (up to 33 days maximum) after respiratory samples became negative.[69]

• Transmission via other body fluids (including sexual transmission or bloodborne transmission) has not been reported.[59] While the virus has been detected in blood, cerebrospinal fluid, pericardial fluid, pleural fluid, urine, semen, saliva, ocular tissue including the cornea, tears, and conjunctival secretions, as well as in the middle ear and mastoid, the presence of virus or viral components does not equate with infectivity.[70][71][72][73][74][75][76][77][78][79][80][81][82] SARS-CoV-2 is not sexually transmitted, but may have an effect on male fertility, although this is yet to be confirmed.[83]

• Vertical transmission occurs rarely and transplacental transmission has been documented. There is limited evidence on the extent of vertical transmission and its timing.[84] Overall, 6.3% of infants born to mothers with COVID-19 tested positive for SARS-CoV-2 at birth. Transmission was reported in both preterm and full-term infants. There is also evidence for antibodies against SARS-CoV-2 among infants born to mothers with COVID-19 who tested negative for SARS-CoV-2.[85] The rate of infection appears to be no greater when the baby is born vaginally, breastfed, or allowed contact with the mother.[86] Viral fragments have been detected in breast milk; however, this finding is uncommon and, when it occurs, has been associated with mild symptoms in infants. Anti-SARS-CoV-2 antibodies are more prevalent in breast milk compared with viral fragments.[87] Vertical transmission is unlikely to occur if correct hygiene precautions are taken.[88]

• Nosocomial transmission was reported in 44% of patients in one systematic review; however, this review was limited to case series conducted early in the outbreak in Wuhan before the institution of appropriate infection prevention and control measures.[89] Hospital-acquired infections (defined as patients diagnosed more than 7 days after hospital admission) accounted for approximately 17% of infections in the NHS England as of 26 October 2020, and rates have been as high as 25% in some areas.[90] Studies of healthcare workers exposed to index cases (not in the presence of
Transmission dynamics in relation to symptoms

- **Symptomatic transmission**
  
  - Transmission appears to mainly be spread via droplets and close contact with infected symptomatic cases. Transmissibility depends on the amount of viable virus being shed and expelled by a person (viral load is highest just before or around the time of symptom onset and during the first 5-7 days of illness), the type of contact, the setting, and what infection prevention and control measures are in place.

- **Presymptomatic transmission**
  
  - Transmission may occur during the incubation period, usually 1 to 3 days before symptom onset.
  - Presymptomatic transmission was reported in 12.6% of cases in China, and 6.4% of cases in Singapore.
  - People without symptoms may be presymptomatic, or they may remain persistently asymptomatic.

- **Asymptomatic transmission**
  
  - Transmission from asymptomatic cases (laboratory-confirmed cases who never develop symptoms) has been reported; however, most of the evidence is based on early data from China and has limitations (e.g., small number of cases, cases may have been presymptomatic).
  - The World Health Organization states that asymptomatic cases are not the major driver of the overall epidemic dynamics. Numerous studies have reported no evidence of asymptomatic transmission from carriers of SARS-CoV-2.
  - In a post-lockdown screening study in nearly 10 million residents in Wuhan, there were no positive tests among 1174 close contacts of asymptomatic cases. In addition to this, virus culture was carried out on samples from asymptomatic positive cases and all cultures were negative, indicating that asymptomatic positive cases in the study were not infectious.
  - Estimating the prevalence of asymptomatic cases in the population is difficult. A meta-analysis of over 50,000 people found that 15.6% of confirmed cases were asymptomatic at the time of testing (range 2% to 75%), and nearly half developed symptoms later. The overall estimate of the proportion of people who become infected and remain asymptomatic throughout infection has been estimated to be 17% to 33%.
  - Healthcare workers may play a role in asymptomatic transmission. About 7.6% of healthcare workers who worked in hospital units with infected patients tested positive for SARS-CoV-2 antibodies; however, only 58% of these workers reported prior symptoms.
  - A cross-sectional study of nearly 2800 healthcare workers found that 5.4% of COVID-19-facing asymptomatic healthcare workers tested positive, compared with 0.6% of non-COVID-19-facing asymptomatic healthcare workers.
  - Children are more likely to be asymptomatic. The pooled proportion of asymptomatic cases in children was thought to be significant (around 40%). However, recent studies have found that the rate of asymptomatic infection in children was very low (1% compared with 9%...
in adults in one study, and 0.6% compared with 1.8% in adults in another study), indicating that children appear not to be particular drivers of the pandemic.\[116\] \[117\]

Superspreading events

- Superspreading events have been reported. These events are associated with explosive growth early in an outbreak and sustained transmission in later stages.\[118\]
- Reported events include church/religious gatherings, family or social gatherings, weddings, choir practices, overnight youth camps or high school retreats, fitness classes, indoor recreational sporting activities, business conferences, and working in call centers.\[59\] \[119\] \[120\] \[121\] \[122\]

Widespread transmission has also been reported in long-term care facilities, homeless shelters, prisons, immigration detention centers, and meat and poultry processing facilities, as well as on board cruise ships.\[123\] \[124\] \[125\] \[126\] \[127\] \[128\] \[129\] \[130\] \[131\]
- Limited transmission has been reported in childcare, school, and university settings, and infected cases may transmit the infection to their household members.\[132\] \[133\] \[134\] There is limited high-quality evidence to quantify the extent of transmission in schools, or to compare it with community transmission. However, emerging evidence suggests a lower overall infection attack rate in students (0.15%) compared with school staff (0.7%).\[135\]
- Some individuals are supershedders of virus, but the reasons underlying superspreader events are often more complex than just excess virus shedding and can include a variety of behavioral, host, and environmental factors.\[136\]

Viral transmission factors

- Incubation period
  - The incubation period is estimated to be between 1 and 14 days, with a median of 5 to 7 days.\[2\] \[137\] Viable virus is relatively short lived; infectiousness peaks around 1 day before symptom onset and declines within 7 days.\[59\]
  - The pooled mean incubation period is 9.6 days in children.\[9\]
- Reproduction number (R₀)
  - Reports suggest that the reproduction number, the number of people who acquire the infection from an infected person, is estimated to be 2.2 to 3.3. However, there is very high heterogeneity across studies and the number varies between countries.\[51\] \[138\] \[139\] \[140\] \[141\] The Centers for Disease Control and Prevention gives a current best estimate of 2.5 (as of 19 March 2021).\[142\]
  - The R₀ decreases when public health measures (e.g., social distancing) are put in place.\[143\]
- Serial interval
  - The time between the start of symptoms in the primary patient and the onset of symptoms in the patient being infected in a chain of transmission has been estimated to be approximately 5.45 days (range 4.2 to 6.7 days).\[144\]
- Secondary attack rate
  - The secondary attack rate is the proportion of people exposed to an index (or primary) case that go on to develop the disease as a result of the exposure.
• The pooled secondary attack rate among all close contacts of an index case has been estimated to be 7%.[145]

• The secondary attack rate differs between contact settings. More familiar prolonged contact increases the potential for transmission. Pooled estimates of the secondary attack rate range from 1.2% to 5.9% in social settings (depending on level of contact and whether contact is with strangers or family and friends), 1.9% in workplaces (based on limited data), 3.6% in healthcare facilities, and 21.1% for household settings (increases with exposure >5 days).[146]

• Another systematic review and meta-analysis of household transmission estimates the pooled household secondary attack rate to be slightly lower at 16.6%. The rate is higher for symptomatic index cases (18%) compared with asymptomatic cases (0.7%), and adults have a higher susceptibility to infection compared with children. Spouses of the index case are more likely to be infected compared with other household members.[147]

• The secondary attack rate increases with the severity of the index case (i.e., 0.3% for asymptomatic cases to 6.2% for severe/critical cases) according to a study of 3410 close contacts of 391 index cases.[102]

• The secondary attack rate for close contacts of presymptomatic people has been estimated to be approximately 7%, compared with 1% in asymptomatic people and 6% in symptomatic people.[148]

• Children ages <5 years had lower secondary attack rates compared with older children, and the risk of infection was higher if the household index case was the mother.[149] The secondary attack rate was 1.2% in children in a childcare setting or school.[150]

• Secondary attack rates for SARS-CoV-2 variants may differ (see Emerging SARS-CoV-2 variants above).

• Viral load

• Viral load is highest in the upper respiratory tract (nasopharynx and oropharynx) early in the course of infection (usually peaks in the first week of illness), and then increases in the lower respiratory tract (sputum). Viral load decreases after symptom onset. Patients with severe disease have higher viral loads compared with those with mild disease. Viral load in the upper respiratory tract is comparable in asymptomatic and symptomatic patients; however, most studies demonstrate faster viral clearance among asymptomatic people compared with symptomatic people.[151]

• Viral load appears to be a leading driver of virus transmission. In one cohort study, the secondary attack rate was 17% among 753 contacts of index cases, with a variation from 12% when the index case had a viral load lower than 1x10⁶ copies/mL to 24% when the index case had a viral load of 1x10¹⁰ copies/mL or higher (in nasopharyngeal swabs). Higher viral loads in swabs of asymptomatic contacts were associated with a higher risk of developing symptomatic disease, and these contacts had shorter incubation periods than those with a lower viral load.[152]

• Viral shedding

• The mean duration of shedding was 17 days in the upper respiratory tract, 14.6 days in the lower respiratory tract, 17.2 days in stool, and 16.6 days in serum samples. The maximum duration of shedding was 83 days in the upper respiratory tract, 59 days in the lower respiratory tract, 126 days in stool, and 60 days in serum samples. However, no live virus was detected beyond day 9 of symptoms, despite persistently high viral loads. Duration of viral shedding
was longer in symptomatic patients compared with asymptomatic patients, and in patients with severe illness compared with those with nonsevere illness.\[151\] • The period of infectiousness is far shorter than the duration of detectable viral shedding. No viable virus has been isolated in patients with mild or moderate disease after 10 days of symptoms, or after 20 days in those with severe or critical disease, despite ongoing viral shedding. Data about the dynamics of viral shedding in people with persistent asymptomatic infection are inconsistent.\[59\] There is no convincing evidence that duration of viral shedding correlates with duration of infectivity.\[153\] • Factors associated with prolonged viral shedding include male sex, older age, comorbid hypertension, delayed admission to hospital after symptom onset or severe illness on admission, and use of invasive mechanical ventilation or corticosteroids.\[154\] Immunocompromised patients may shed for at least 2 months.\[155\]

Pathophysiology

The pathophysiology is not yet fully understood; however, details are emerging.\[156\]
Coronavirus disease 2019 (COVID-19)

Theory

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the ACE2 receptor in humans, which suggests a similar pathogenesis to SARS.[38] [157]
- A unique structural feature of the spike glycoprotein receptor-binding domain of SARS-CoV-2 (which is responsible for the entry of the virus into host cells) confers potentially higher binding affinity for ACE2 on host cells compared with SARS-CoV-1.[158] This furin-like cleavage site does not exist in other SARS-like coronaviruses.[159] The binding energy between the SARS-CoV-2 spike protein and ACE2 was highest for humans out of all species tested, suggesting that the SARS-CoV-2 spike protein is uniquely evolved to bind to and infect human cells expressing ACE2.[160]
- Mechanistic evidence from other coronaviruses suggests that SARS-CoV-2 may downregulate ACE2, leading to a toxic overaccumulation of plasma angiotensin-II, which may induce acute respiratory distress syndrome and fulminant myocarditis.[161] [162]
- Based on an analysis of single-cell RNA sequencing datasets derived from major human physiologic systems, the organs considered more vulnerable to SARS-CoV-2 infection due to their ACE2 expression levels include the lungs, heart, esophagus, kidneys, bladder, and ileum.[163] This may explain the extrapulmonary manifestations associated with infection. ACE2 expression has also been identified in the diaphragm, which may lead to diaphragm fibrosis and myopathy.[164]
- Lower expression of ACE2 in the nasal epithelium of children ages <10 years compared with adults may explain why COVID-19 is less prevalent in children; however, further research on this is required.[165]
- SARS-CoV-2 variants may be more transmissible, at least in part, due to enhanced spike protein binding affinity for the ACE2 receptor.[166]

Transmembrane protease serine 2 (TMPRSS2)

- SARS-CoV-2 uses host TMPRSS2 for S protein priming and fusion of viral and host cell membranes.[167]
- Higher expression of TMPRSS2 has been noted in the nasal epithelium of Black people compared with Asian people, Latin people, White people, and people of mixed race/ethnicity, which may be a contributing factor to the higher burden of infection among Black people.[168]

Spike protein

- The SARS-CoV-2 spike protein plays a key role in the recognition of the ACE2 receptor and cell membrane fusion process. However, emerging evidence suggests that the spike protein alone may damage endothelial cells by downregulating ACE2 and consequently inhibiting mitochondrial function.[169] Further research is required on whether the spike protein can by itself trigger cell signaling that could lead to various biologic processes.[170]

Autopsy studies

- Pulmonary: autopsy studies have revealed that patients who died of respiratory failure had evidence of exudative diffuse alveolar damage with massive capillary congestion, often accompanied by microthrombi. Hyaline membrane formation and pneumocyte atypical hyperplasia are common. Pulmonary artery obstruction by thrombotic material at both the macroscopic and microscopic levels has been identified. Patients also had signs of generalized thrombotic microangiopathy. Severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes has been noted. Other findings include bronchopneumonia, pulmonary embolism, alveolar hemorrhage, and vasculitis. Significant new blood vessel growth through intussusceptive angiogenesis distinguishes the pulmonary pathology of COVID-19 from severe influenza infection.[171] [172] [173] [174]
Some patients with severe disease may develop fibrotic lung disease for which lung transplantation may be the only treatment option.[177]

- Neurologic: histopathologic examination of brain specimens showed hypoxic changes but no encephalitis or other specific brain changes due to the virus in one autopsy study. The virus was detected at low levels in brain tissue.[178] Another study found mild neuropathologic changes, with pronounced neuroinflammatory changes in the brainstem being the most common finding.[179]
- Cardiac: SARS-CoV-2 has been frequently detected in the myocardium in autopsy studies. While cardiac pathologic findings are prevalent, acute myocarditis is uncommon. The most frequent findings were cardiac dilatation, myocardial ischemia, and thrombosis.[180] The virus, along with inflammatory changes, has been reported in the cardiac tissue of a child with pediatric inflammatory multisystem syndrome.[181]
- Immunology: the mechanisms contributing to increased thrombosis involve extensive cross-talk between the immune system and hemostasis.[182] Evaluation of immune infiltrate has revealed a notable presence of aggregated neutrophils in the lungs and several other organs. Neutrophilic plugs, composed of neutrophils with neutrophil extracellular traps (NETs) or as aggregates of NETs and platelets, were present in the heart, kidney, liver, and brain. NETs may therefore play a role in coagulopathy associated with SARS-CoV-2 infection. The disproportionate presence of aggregate neutrophils and NETs in comparison with the sporadic presence of virus suggests an autonomous maladaptive immune response.[183] NETs appear to play a role in the pathogenesis of ST-elevation myocardial infarction in COVID-19 patients based on a small case series of patients with COVID-19 and myocardial infarction.[184]
- Hepatic: a high prevalence of hepatic steatosis, congestion of hepatic sinuses, vascular thrombosis, and fibrosis have been noted, along with portal and lobular inflammation and Kupffer cell hyperplasia or proliferation.[185]
- Other: other novel findings at autopsy include pancreatitis, pericarditis, adrenal microinfarction, secondary disseminated mucormycosis, and brain microglial activation.[186]

Endothelial dysfunction

- There is a hypothesis that COVID-19 is a disease of the endothelium.[187] [188] [189] Endotheliopathy and platelet activation appear to be important features of COVID-19 in hospitalized patients and are likely to be associated with coagulopathy, critical illness, and death.[190]
- Hyperviscosity has been reported in patients. It is known to damage the endothelium, and is a known risk factor for thrombosis. The potential link between hyperviscosity and thrombotic complications warrants further investigation.[191]

Genetic factors

- Genetic factors are thought to play a role. ACE2 and TMPRSS2 polymorphisms have been shown to be strongly associated with susceptibility, severity, and clinical outcomes. Several other genetic patterns of susceptibility for COVID-19 have also been identified and may affect treatment and prevention. Genetic factors may also explain why males are at higher risk of infection and poor outcomes.[192]
- A novel susceptibility locus has been detected at a chromosome 3p21.31 gene cluster in patients with respiratory failure, which may confirm the involvement of the ABO blood-group system.[193]

Mild illness

- Symptomatic patients meeting the case definition for COVID-19 without evidence of hypoxia or pneumonia.
- Common symptoms include fever, cough, fatigue, anorexia, dyspnea, and myalgia. Other nonspecific symptoms include sore throat, nasal congestion, headache, diarrhea, nausea/vomiting, and loss of smell/taste. Additional neurologic manifestations reported include dizziness, agitation, weakness, seizures, or findings suggestive of stroke. Children may not report fever or cough as frequently as adults.
- Older people and immunosuppressed people may present with atypical symptoms (e.g., fatigue, reduced alertness, reduced mobility, diarrhea, loss of appetite, delirium, absence of fever).
- Symptoms due to physiologic adaptations of pregnancy or adverse pregnancy events (e.g., dyspnea, fever, gastrointestinal symptoms, fatigue) or other diseases (e.g., malaria) may overlap with COVID-19 symptoms.

Moderate disease

- Adolescent or adult: clinical signs of pneumonia (i.e., fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including blood oxygen saturation levels (SpO₂) ≥90% on room air.
- Children: clinical signs of nonsevere pneumonia (i.e., cough or difficulty breathing plus fast breathing and/or chest indrawing) and no signs of severe pneumonia. Fast breathing is defined as:
  - <2 months of age: ≥60 breaths/minute
  - 2-11 months of age: ≥50 breaths/minute
  - 1-5 years of age: ≥40 breaths/minute.
- While the diagnosis can be made on clinical grounds, chest imaging may assist in diagnosis and identify or exclude pulmonary complications.

Severe disease

- Adolescent or adult: clinical signs of pneumonia (i.e., fever, cough, dyspnea, fast breathing) plus one of the following:
  - Respiratory rate >30 breaths/minute
  - Severe respiratory distress
  - SpO₂ <90% on room air.
- Children: clinical signs of pneumonia (i.e., cough or difficulty in breathing) plus at least one of the following:
  - Central cyanosis or SpO₂ <90%
  - Severe respiratory distress (e.g., fast breathing, grunting, very severe chest indrawing)
  - General danger signs: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions
  - Fast breathing (<2 months: ≥60 breaths per minute; 2-11 months: ≥50 breaths per minute; 1-5 years: ≥40 breaths per minute).
• While the diagnosis can be made on clinical grounds, chest imaging may assist in diagnosis and identify or exclude pulmonary complications.

Critical disease

• Presence of acute respiratory distress syndrome (ARDS), sepsis, septic shock, acute thrombosis, or multisystem inflammatory syndrome in children.

National Institutes of Health: clinical classification of COVID-19[3]

Asymptomatic or presymptomatic infection

• People who test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using a virologic test but have no symptoms consistent with COVID-19.

Mild illness

• People who have any of various signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) without shortness of breath, dyspnea, or abnormal chest imaging.

Moderate illness

• People who have evidence of lower respiratory disease by clinical assessment or imaging and an oxygen saturation (SpO₂) ≥94% on room air at sea level.

Severe illness

• People who have respiratory frequency >30 breaths per minute, SpO₂ <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) <300 mmHg, or lung infiltrates >50%.

Critical illness

• People who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Persistent symptoms or organ dysfunction after acute COVID-19

• People who experience persistent symptoms and/or organ dysfunction after acute disease. Also known as post-acute COVID-19 syndrome or long COVID. See the Complications section for more information.

Case history

Case history #1

A 61-year-old man presents to the hospital with fever, dry cough, and difficulty breathing. He also reports feeling very tired and unwell. He has a history of hypertension, which is controlled with enalapril. On exam, his pulse is 120 bpm, his temperature is 101.6°F (38.7°C), and his oxygen saturation is 88%. He appears acutely ill. He is admitted to hospital in an isolation room and is started on oxygen, intravenous fluids, and venous thromboembolism prophylaxis. Blood and sputum cultures are ordered. Chest x-ray shows bilateral lung infiltrates, and computed tomography of the chest reveals multiple bilateral
lobular and subsegmental areas of ground-glass opacity. A nasopharyngeal swab is sent for real-time reverse transcriptase polymerase chain reaction testing, and the result comes back positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) the next day. The patient is started on dexamethasone.

Case history #2

A 26-year-old woman presents at her local COVID-19 testing clinic with symptoms of a sore throat and loss of taste. She denies having a fever, and has not knowingly been in contact with a confirmed case of COVID-19. After being tested, she is advised to go home, self-isolate until her test results are sent to her via text message, and call her doctor if her symptoms get worse. She receives a text message later that day confirming that her test is positive for SARS-CoV-2, and that she must self-isolate according to her local public health recommendations.

Other presentations

See the Diagnosis section for more information on other presentations.
Approach

COVID-19 is a notifiable disease. Report all suspected or confirmed cases to your local health authorities.

Early recognition and rapid diagnosis are essential to prevent transmission and provide supportive care in a timely manner. Have a high index of clinical suspicion for COVID-19 in all patients who present with fever and/or acute respiratory illness; however, be aware that some patients may not present with signs or symptoms of a febrile respiratory illness.

COVID-19 care pathways should be established at local, regional, and national levels for people with suspected or confirmed COVID-19. Screen patients at the first point of contact within the health system based on case definitions and an assessment of symptoms, and enter suspected or confirmed cases into the pathway. Suspected cases should remain in the pathway until proven negative. Immediately isolate all suspected and confirmed cases and implement local infection prevention and control procedures. Triage patients with a standardized triage tool and evaluate the patient to assess the severity of disease. Use clinical judgment, including consideration of the patient’s values and preferences and local and national policy if available, to guide management decisions including admission to hospital and to the intensive care unit, rather than currently available prediction models for prognosis.[2]

Best Practice has published a separate topic on the management of coexisting conditions in the context of COVID-19. [BMJ Best Practice: Management of coexisting conditions in the context of COVID-19] (https://bestpractice.bmj.com/topics/en-us/3000190#important-update)

Key recommendations

- Isolate all suspected or confirmed cases immediately. Triage patients with a standardized triage tool and evaluate the severity of disease. Follow local infection prevention and control guidelines.[2]
- Have a high index of clinical suspicion in all patients who present with fever and/or acute respiratory illness. People with a history of residence/work/travel in a location with a high risk of transmission or community transmission and contacts of probable and confirmed cases are at higher risk of infection.[194]
- Suspect the diagnosis in patients with a new continuous cough, fever, or altered sense of taste or smell.[532] Patients may also present with symptoms including dyspnea, fatigue, myalgia/arthralgia, sore throat, headache, nasal congestion or rhinorrhea, sputum production, chest tightness, or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).[533]
- Order a real-time reverse transcription polymerase chain reaction (RT-PCR) to confirm the diagnosis. Upper and lower respiratory specimens are preferred. Serologic testing may be useful in some settings.[534] Results should be interpreted in the context of the pretest probability of disease.
- Be on high alert for children and adolescents with acute gastrointestinal symptoms and signs of cardiac inflammation. Evidence so far suggests a milder or asymptomatic course of disease in children.[535] However, a rare multisystem inflammatory condition with some features similar to those of Kawasaki disease and toxic shock syndrome has been temporally associated with COVID-19 in children and adolescents.[536]
- Order the following laboratory investigations in hospitalized patients: complete blood count, comprehensive metabolic panel, arterial blood gas, blood glucose level, coagulation screen, inflammatory markers, cardiac biomarkers, serum creatine kinase, and blood and sputum cultures for other pathogens. Pulse oximetry may reveal low oxygen saturation.
Coronavirus disease 2019 (COVID-19)

Diagnosis

- Prioritize a chest x-ray in patients who are seriously ill with suspected pneumonia. Consider a computed tomography (CT) scan of the chest if chest x-ray is uncertain or normal.[537] Consult local guidelines.
- For full details and guidance see information below.

History

Take a detailed history to ascertain the level of risk for COVID-19 and assess the possibility of other causes, including a travel history and an assessment of risk factors.

Suspect the diagnosis in:[194]

- People residing or working in an area with a high risk of transmission (e.g., closed residential settings, humanitarian setting), people residing in or traveling to an area with community transmission, and people working in a health setting (including within health facilities and households) at any time within the 14 days prior to symptom onset
- People who have had contact with a probable or confirmed case. A contact is a person who has experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:
  - Face-to-face contact with a probable or confirmed case within 3 feet (1 meter) and for at least 15 minutes
  - Direct physical contact with a probable or confirmed case
  - Direct care for a patient with probable or confirmed COVID-19 without using recommended personal protective equipment
  - Other situations as indicated by local risk assessments.

The Centers for Disease Control and Prevention defines a close contact as someone who has been within 6 feet (2 meters) of an infected person for at least 15 minutes over a 24-hour period, beginning 2 days before symptom onset (or 2 days before testing in asymptomatic patients).[195]

Ask anyone seeking routine or emergency care, regardless of whether they have symptoms, about recent travel to countries where there is transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern (consult local guidance for current list of countries), or whether they are a contact of a returning traveler from these countries.[196]

Clinical presentation in adults

Approximately 15% of patients present with the symptom triad of fever, cough, and dyspnea, and 90% present with more than one symptom.[50] Some patients may be minimally symptomatic or asymptomatic, while others may present with severe pneumonia or complications such as acute respiratory syndrome, septic shock, acute myocardial infarction, venous thromboembolism, or multi-organ failure. According to a UK study, approximately 25% of people who had evidence of past infection were asymptomatic, and 40% did not have one of the three classic symptoms (i.e., fever, persistent dry cough, altered sense of taste/smell).[538]

The most common symptoms are:

- Fever
- Cough
Coronavirus disease 2019 (COVID-19)

Diagnosis

- Dyspnea
- Altered sense of taste/smell.

Less common symptoms include:

- Myalgia or arthralgia
- Fatigue
- Sputum production
- Chest tightness
- Gastrointestinal symptoms
- Sore throat
- Headache
- Dizziness
- Neurologic symptoms
- Ocular symptoms
- Audio-vestibular symptoms
- Cutaneous symptoms
- Rhinorrhea/nasal congestion
- Chest pain
- Hemoptysis.

Signs and symptoms of febrile respiratory illness may not possess the necessary sensitivity for early diagnostic suspicion. A Cochrane review found that at least half of patients had a cough, sore throat, fever, myalgia/arthralgia, fatigue, or headache. Anosmia and/or ageusia was also common. The presence of fever, myalgia/arthralgia, fatigue, and headache substantially increased the likelihood of COVID-19 when present. Cough and sore throat were common in people without COVID-19, so these symptoms alone were less helpful for diagnosis. No single symptom or sign included in the review could accurately diagnose COVID-19 and the authors concluded that neither the absence or presence of signs or symptoms are accurate enough to rule in or rule out disease. However, the presence of anosmia and/or ageusia may be useful as a red flag for diagnosis. The presence of fever or cough may also be useful to identify people for further testing. Nonrespiratory symptoms may appear before the onset of fever and lower respiratory tract symptoms. Lower urinary tract symptoms have also been reported rarely.

The clinical presentation has varied slightly across geographic locations. Initial impressions from the US note that the clinical presentation may be broader than that observed in China and Italy, with chest pain, headaches, altered mental status, and gastrointestinal symptoms all observed on initial presentation. Severe hepatic and renal dysfunction that spares the lungs has also been observed. Data from the first hospitalized patients in New York found that while the most common presenting symptoms were fever, cough, dyspnea, and myalgia, gastrointestinal symptoms appeared to be more common than in China.

Severity

- 80% of adults present with mild to moderate illness
- 14% of adults present with severe illness
- 5% of adults present with critical illness
- 1% of adults present with asymptomatic illness.

The most prevalent symptoms in patients with mild to moderate illness, according to one European study, are headache, loss of smell, nasal congestion, cough, asthenia, myalgia, rhinorrhea, gustatory
dysfunction, and sore throat. Fever was reported less commonly. The mean duration of symptoms was 11.5 days. The presentation varied according to age, with younger patients generally having ear, nose, and throat complaints, and older patients generally having fever, fatigue, and loss of appetite.[543] More common symptoms in patients with severe disease include fever, dyspnea, and anorexia.[139]

Pregnant women

- The clinical characteristics in pregnant women are similar to those reported for nonpregnant adults.[544] The most common symptoms in pregnant women are fever and cough. However, pregnant women are less likely to report fever, dyspnea, and myalgia compared with nonpregnant women of reproductive age. Pregnant and recently pregnant women were more likely to be asymptomatic than nonpregnant women of reproductive age.[22] [23]
- It is important to note that symptoms such as fever, dyspnea, gastrointestinal symptoms, and fatigue may overlap with symptoms due to physiologic adaptations of pregnancy or adverse pregnancy events.[2]

Atypical presentations

- Atypical presentations may occur, especially in older patients and patients who are immunocompromised (e.g., falls, delirium/confusion, functional decline, reduced mobility, syncope, persistent hiccups, absence of fever). Older patients and those with comorbidities may present with mild symptoms, but have a high risk of deterioration.[2]
- There have been case reports of parotitis (possibly related to intraparotid lymphadenitis), oral vesiculobullous lesions, retinal lesions, and androgenetic alopecia in patients with COVID-19; however, it is unknown whether these findings are associated with SARS-CoV-2 infection as yet.[545] [546] [547] [548]

Coinfections

- The pooled prevalence of coinfection in SARS-CoV-2-positive patients was 19%, and the pooled prevalence of superinfection was 24%. The highest prevalence of superinfection was in intensive care unit patients. Pooled prevalence stratified by pathogen type was: viral coinfections 10%; viral superinfections 4%; bacterial coinfections 8%; bacterial superinfections 20%; fungal coinfections 4%; and fungal superinfections 8%. The most frequently identified bacteria were Klebsiella pneumonia, Streptococcus pneumoniae, and Staphylococcus aureus. The most frequent bacteria identified in superinfected patients was Acinetobacter species, which is common in ventilated patients. The most frequently identified viruses were influenza type A, influenza type B, and respiratory syncytial virus. The most frequently identified fungi was Aspergillus. Patients with a coinfection or superinfection had higher risk of mortality compared with those who only had SARS-CoV-2 infection. Patients with superinfections had a higher prevalence of mechanical ventilation compared with those with coinfections.[549]
- Be alert for the development of mucormycosis.[550] Diagnose and manage urgently - see the Complications section for more information.

Clinical presentation in children

Signs and symptoms may be similar to other common viral respiratory infections and other childhood illnesses, so a high index of suspicion for COVID-19 is required in children.
Evidence suggests a milder, or asymptomatic, disease course in the majority of children, with low rates of severe disease and mortality. Infants under 1 year of age and adolescents 10 to 14 years of age have a higher risk for developing severe disease. Risk factors for severe disease include the presence of comorbidities and higher viral load. The clinical presentation in children is heterogeneous and includes a wide spectrum of clinical features. The most common presenting symptoms in children are fever and cough. Gastrointestinal symptoms (nausea, vomiting, diarrhea) are also common in children. Other less common symptoms include dyspnea, nasal congestion, rhinorrhea, rash, conjunctivitis, fatigue, abdominal pain, and neurologic symptoms. A higher prevalence of gastrointestinal symptoms has been reported in children >5 years of age compared with children ≤5 years of age.\textsuperscript{[535]} Fever, cough, appetite loss, and dyspnea are less common in children compared with adults.\textsuperscript{[551]} The presence of diarrhea has been associated with a severe clinical course in children.\textsuperscript{[552]}

The most common symptoms in neonates include fever, inability to feed, lethargy, irritability, feeding difficulties, dyspnea, silent hypoxia, and neurologic symptoms. Cases of late-onset neonatal sepsis and encephalitis have been reported rarely.\textsuperscript{[535]} \textsuperscript{[553]} \textsuperscript{[554]} \textsuperscript{[555]}

Be alert for signs and symptoms of pediatric inflammatory multisystem syndrome (PIMS), also known as multisystem inflammatory syndrome in children (MIS-C). Consider PIMS/MIS-C in children presenting with fever and abdominal symptoms, particularly if they develop conjunctivitis or a rash. Refer to a pediatric emergency department for evaluation.\textsuperscript{[556]} See the Complications section for more information.

Coinfections may be more common in children.\textsuperscript{[557]} Coinfection was documented in 6% of children in US and Italian studies, with the most common pathogens being respiratory syncytial virus, rhinoviruses, Epstein-Barr virus, enteroviruses, influenza A, non-SARS coronaviruses, and \textit{Streptococcus pneumoniae}.\textsuperscript{[11]} \textsuperscript{[558]}

\section*{Physical exam}

Perform a physical exam. Avoid use of a stethoscope if possible due to risk of viral contamination. Patients may be febrile (with or without chills/rigors) and have obvious cough and/or difficulty breathing. Auscultation of the chest may reveal inspiratory crackles, rales, and/or bronchial breathing in patients with pneumonia or respiratory distress. Patients with respiratory distress may have tachycardia, tachypnea, or cyanosis accompanying hypoxia. Bradycardia has been noted in a small cohort of patients with mild to moderate disease.\textsuperscript{[559]}

\section*{Pulse oximetry}

Pulse oximetry may reveal low oxygen saturation (SpO$_2$ <90\%). Clinicians should be aware that patients with COVID-19 can develop "silent hypoxia": their oxygen saturations can drop to low levels and precipitate acute respiratory failure without the presence of obvious symptoms of respiratory distress.\textsuperscript{[560]}

The UK National Institute for Health and Care Excellence recommends using oxygen saturation levels below 94\% for adults (or below 88\% for adults with known type 2 respiratory failure) and below 91\% for children in room air at rest to identify people who are seriously ill.\textsuperscript{[561]}

Pulse oximeters may exhibit suboptimal accuracy in certain populations. Limited data from studies with small numbers of participants suggest that skin pigmentation can affect pulse oximeter accuracy. In one study, occult hypoxemia (defined in the study as arterial oxygen saturation <88\% by arterial blood gas despite oxygen saturation of 92\% to 96\% on pulse oximetry) was not detected by pulse oximetry nearly three times more frequently in Black patients compared with White patients.\textsuperscript{[562]} The US Food and Drug
Coronavirus disease 2019 (COVID-19) Diagnosis

Administration (FDA) has warned that multiple factors can affect the accuracy of a pulse oximeter reading (e.g., poor circulation, skin pigmentation, skin thickness, skin temperature, current tobacco use, use of fingernail polish). The FDA recommends considering accuracy limitations when using a pulse oximeter to assist in diagnosis and treatment decisions, and to use trends in readings over time rather than absolute cut-offs if possible.[563]

Only a small proportion of patients have other organ dysfunction, meaning that after the initial phase of acute deterioration, traditional methods of recognizing further deterioration (e.g., National Early Warning Score 2 [NEWS2] scores) may not help predict those patients who go on to develop respiratory failure.[560]

While NEWS2 is still recommended for use in patients with COVID-19, the UK Royal College of Physicians now advises that any increase in oxygen requirements in these patients should trigger an escalation call to a competent clinical decision maker, and prompt an initial increase in observations to at least hourly until a clinical review happens.[564]

Pulse oximeters can be used at home to detect hypoxia. Home pulse oximetry requires clinical support (e.g., regular phone contact from a health professional in a virtual ward setting).

[BMJ Practice Pointer: remote management of covid-19 using home pulse oximetry and virtual ward support] (https://www.bmj.com/content/372/bmj.n677)

Initial laboratory investigations

Order the following laboratory investigations in all patients with severe illness:

- ABG
- CBC
- Comprehensive metabolic panel
- Blood glucose level
- Coagulation screen
- Inflammatory markers (e.g., serum C-reactive protein, erythrocyte sedimentation rate, interleukin-6, lactate dehydrogenase, procalcitonin, amyloid A, and ferritin)
- Cardiac biomarkers
- Serum creatine kinase and myoglobin.

The most common laboratory abnormalities are lymphopenia, leukocytosis, leukopenia, thrombocytopenia, hypoalbuminemia, elevated cardiac biomarkers, elevated inflammatory markers, elevated D-dimer, and abnormal liver and renal function.[542] [565] [566] [567] Laboratory abnormalities – in particular, lymphopenia, leukocyte abnormalities, and other markers of systemic inflammation – are less common in children.[568] [569] Most patients (62%) with asymptomatic disease present with normal laboratory parameters. Of those with laboratory abnormalities, leukopenia, lymphopenia, elevated lactate dehydrogenase, and elevated C-reactive protein were the most common findings.[570]

Collect blood and sputum specimens for culture in patients with severe or critical disease to rule out other causes of lower respiratory tract infection and sepsis, especially patients with an atypical epidemiologic history. Specimens should be collected prior to starting empiric antimicrobials if possible.[2]

Ongoing investigations
• Regularly monitor the following in hospitalized patients to facilitate early recognition of deterioration and monitor for complications:[2] [571]
  • Vital signs (temperature, respiratory rate, heart rate, blood pressure, oxygen saturation)
  • Hematologic and biochemistry parameters
  • Coagulation parameters (D-dimer, fibrinogen, platelet count, prothrombin time)
  • ECG
  • Chest imaging
  • Signs and symptoms of venous or arterial thromboembolism.
• Patients may develop bacterial or fungal coinfections; therefore, it is important to ensure appropriate imaging is ordered and microbiologic specimens are taken when this is suspected.

Molecular testing
Testing strategies vary widely between countries.[572]

Molecular testing is required to confirm the diagnosis. Molecular testing is an aid to diagnosis only. The World Health Organization (WHO) recommends that healthcare providers consider a positive or negative result in combination with specimen type, clinical observations, patient history, and epidemiologic information. Where a test result does not correspond with the clinical presentation, a new specimen should be taken and retested using the same or a different molecular test (see Limitations of molecular testing below).[573]

Order a nucleic acid amplification test, such as real-time reverse-transcription polymerase chain reaction (RT-PCR), for SARS-CoV-2 in patients with suspected infection whenever possible (see the Criteria section).[534] Tests should be performed according to guidance issued by local health authorities and adhere to appropriate biosafety practices. Commonly used assays are expected to be able to detect SARS-CoV-2 variants of concern.[196]

Who to test
• Base decisions about who to test on clinical and epidemiologic factors.[534]
• In the UK, testing is recommended in:[574]
  • People with symptoms of new continuous cough, high temperature, or altered sense of smell/taste
  • People with acute respiratory infection, influenza-like illness, clinical or radiologic evidence of pneumonia, or acute worsening of underlying respiratory illness, or fever without another cause (whether presenting in primary or secondary care).
• In the US, testing is recommended in:[575]
  • People with signs or symptoms consistent with COVID-19
  • Asymptomatic people with recent known or suspected exposure to SARS-CoV-2, including those who have been in close contact (less than 6 feet [2 meters] for a total of 15 minutes or more over a 24-hour period) with a person with documented infection
  • Asymptomatic people without recent known or suspected exposure to SARS-CoV-2 for early identification, isolation, and disease prevention (when screening testing if recommended by public health officials).
The American Academy of Pediatrics recommends testing children with symptoms consistent with COVID-19, children in close contact with an individual with probable or confirmed infection, and children who require screening based on recommendations from public health authorities or other situations (e.g., prior to a medical procedure such as elective surgery or as a school or workplace requirement). The decision to test does not differ by the age of the child. Testing is not recommended for other illnesses that lack shared symptoms (e.g., urinary tract infection, cellulitis), or for children exposed to close contacts of infected individuals unless those contacts are symptomatic or other criteria are met.[576]

Consult local health authorities for guidance as testing priorities depend on local recommendations and available resources.

Specimens

- The optimal specimen for testing depends on the clinical presentation and the time since symptom onset. The WHO recommends the following.[534]

  - Upper respiratory specimens: recommended for early-stage infections, especially asymptomatic or mild cases. Nasopharyngeal swabs yield a more reliable result than oropharyngeal swabs; combined nasopharyngeal and oropharyngeal swabs further improve reliability.
  - Lower respiratory specimens: recommended for later-stage infections, or patients in whom there is a strong suspicion for infection and their upper respiratory tract specimen test was negative. Suitable specimens are sputum and/or endotracheal aspirate or bronchoalveolar lavage in patients with more severe respiratory disease. However, consider the high risk of aerosol transmission when collecting lower respiratory specimens – an induced sputum specimen is not recommended as it may increase the risk of aerosol transmission.
  - Other respiratory specimens: studies on combined oropharyngeal and nares/nasal swabs, mid-turbinate or lower nasal or nares swabs, or tongue swabs have been conducted; however, further assessment and validation is required. Oral fluid collection may be suitable in some circumstances (e.g., young children, older patients with dementia). A systematic review and meta-analysis found that pooled nasal and throat swabs offered the best diagnostic performance of alternative sampling approaches compared with nasopharyngeal swabs for diagnosis in an ambulatory care setting. The sensitivity was 97%, the specificity was 99%, the positive predictive value was 97%, and the negative predictive value was 99%. Throat swabs gave a much lower sensitivity and positive predictive value. Self-collection was not associated with any impairment of diagnostic accuracy.[577]
  - Saliva: meta-analyses of paired saliva samples and nasopharyngeal swabs found no statistically significant difference in sensitivity or specificity between these specimens for SARS-CoV-2 detection, especially in the ambulatory setting. Sensitivity was not significantly different among asymptomatic people and outpatients. Methods of saliva collection may affect sensitivity.[578] [579] [580] [581] The WHO does not currently recommend the use of saliva as the sole specimen type for routine clinical diagnostics. In contrast, the Infectious Diseases Society of America recommends saliva as a suitable option for molecular testing in symptomatic people.[582]
  - Fecal specimens: consider when upper or lower respiratory specimens are negative and the clinical suspicion for infection remains (may be used from the second week after symptom onset).
Diagnosis

- Recommended specimen types may differ between countries. For example, in the US, the Centers for Disease Control and Prevention (CDC) recommends the following upper respiratory specimens: nasopharyngeal or oropharyngeal swab; nasal mid-turbinate swab; anterior nares swab; or nasopharyngeal/nasal wash/aspirate. Recommended lower respiratory tract specimens include: sputum, bronchoalveolar lavage, tracheal aspirate, pleural fluid, and lung biopsy.[583] Nasal mid-turbinate swab is an acceptable specimen for home or onsite self-collection.[583]
- Collect specimens under appropriate infection prevention and control procedures.

Test result

- A positive RT-PCR result confirms SARS-CoV-2 infection (in the context of the limitations associated with RT-PCR testing). If the result is negative, and there is still a clinical suspicion of infection (e.g., an epidemiologic link, typical x-ray findings, absence of another etiology), resample the patient and repeat the test. A positive result confirms infection. If the second test is negative, consider serologic testing (see below).[534]
- Genomic sequencing is not routinely recommended, but may be useful to investigate the dynamics of an outbreak, including changes in the size of an epidemic over time, its spatiotemporal spread, and testing hypotheses about transmission routes.[534]

Complications of nasal swab testing

- Complications associated with nasal swab testing are not well characterized and data is scarce. Complications were extremely low in one study (1.24 complications per 100,000 tests). Adverse effects may include epistaxis, nasal discomfort, headache, ear discomfort, rhinorrhea, and broken swabs being stuck (and requiring removal via nasal endoscopy). Bleeding may be life-threatening. Correct sampling techniques are crucial.[584] [585]
- A case of iatrogenic cerebrospinal fluid leak has been reported after nasal testing for COVID-19 in a woman with an undiagnosed skull base defect at the fovea ethmoidalis.[586]

Testing for other infections

- Collect nasopharyngeal swabs for testing to rule out infection with other respiratory pathogens (e.g., influenza, atypical pathogens) when clinically indicated according to local guidance. Depending on local epidemiology and clinical symptoms, test for other potential causes including malaria, dengue fever, and typhoid fever as appropriate. It is important to note that coinfections can occur, and a positive test for a non-COVID-19 pathogen does not rule out COVID-19.[2] [587]
- When SARS-CoV-2 and influenza viruses are cocirculating, test for both viruses in all hospitalized patients with acute respiratory illness, and only test for influenza virus in outpatients with acute respiratory illness if the results will change clinical management of the patient.[3]

Limitations of molecular testing

Molecular testing is an aid to diagnosis only. The WHO recommends that healthcare providers consider a positive or negative result in combination with specimen type, clinical observations, patient history, and epidemiologic information. It also recommends that laboratories ensure that specimens with high cycle threshold values are not incorrectly assigned a positive result due to background noise, and that they provide the cycle threshold value in the report to the healthcare provider. Disease prevalence alters the predictive value of test results. As disease prevalence decreases, the risk of a false positive increases. This means that the probability that a person who has a positive result is truly infected decreases as
prevalence decreases, irrespective of the claimed specificity of the test. Careful interpretation of weak positive results is needed.

Interpret RT-PCR test results with caution.

- The evidence for the use of RT-PCR in the diagnosis of COVID-19 is still emerging, and uncertainties about its efficacy and accuracy remain. Estimates of diagnostic accuracy need to be interpreted with caution in the absence of a definitive reference standard to diagnose or rule out COVID-19. Also, more evidence is needed about the efficacy of testing outside of hospital settings and in asymptomatic or mild cases.

- Few studies have attempted to culture live SARS-CoV-2 virus from human samples. This is an issue because viral culture is regarded as a gold standard test against which any diagnostic index test for viruses must be measured and calibrated, to understand the predictive properties of that test. Prospective routine testing of reference and viral culture specimens is necessary to establish the usefulness and reliability of RT-PCR to diagnose COVID-19, and its relation to patients factors such as date of onset of symptoms and copy threshold, in order to help predict infectivity.

- As there is no clear-cut "gold standard" for COVID-19 testing, evaluating test results can be challenging. Clinical adjudication may be the best available 'gold standard' based on repeat swabs, history, clinical presentation, and chest imaging.

It is not clear whether a positive result always indicates the presence of infectious virus.

- RT-PCR detects viral RNA, but it is not fully understood how that represents infectious virus. Complete live viruses are necessary for transmission, not the fragments identified by PCR. This could ultimately lead to restrictions for people who do not present an infection risk. Because inactivated RNA degrades slowly over time, it may still be detected many weeks after the patient is no longer infectious.

- One study found that only 28.9% of positive RT-PCR SARS-CoV-2 samples demonstrated viral growth when incubated on Vero cells. There was no growth in samples with an RT-PCR cycle threshold >24, or when the symptom onset to test time was >8 days. Therefore, infectivity of patients with a cycle threshold >24 and duration of symptoms >8 days may be low. Another study found that patients with a cycle threshold of 34 or above do not excrete infectious virus. A systematic review found that cycle threshold values were significantly lower and log copies higher in specimens that produce live virus culture. Those with high cycle threshold are unlikely to have infectious potential.

- Sensitivity and specificity: the pooled sensitivity has been estimated to be 87.8%, with the specificity estimated to be in the range of 87.7% to 100%.

- Pretest probability: the pretest probability estimate should be made using knowledge of local rates of infection from national and regional data, as well as the patient’s symptoms, potential exposure to cases, a previous medical history of COVID-19 or the presence of antibodies, and the likelihood...
of an alternative diagnosis.[591] When the pretest probability is low, positive results should be interpreted with caution, and ideally a second specimen tested for confirmation.[595]

- Post-test probability: the lower the prevalence of disease in a given population, the lower the post-test probability.[596] For example, if a test with a specificity of 99% is used to test a high-risk symptomatic population where the likelihood of infection is 50%, the positive predictive value is 99%. This means that for every 100 people with a positive test result, 99 people will have SARS-CoV-2 infection but 1 person without infection will have a false-positive result. Conversely, in a low-risk asymptomatic population where the likelihood of infection is low (e.g., 0.05%), the positive predictive value is around 4.3%. This means that for every 100 people with a positive test result, 4 to 5 people will have SARS-CoV-2 infection, but 95 to 96 people without infection will have a false-positive result.[597]
- [BMJ Practice Pointer: interpreting a covid-19 test result] (https://www.bmj.com/content/369/bmj.m1808)

False-positive results

- False-positive results can be caused by a laboratory error or a cross-reaction with antibodies formed by current and past exposure to seasonal human coronavirus infections (e.g., common cold).[598] False-positive results are more likely when the prevalence of SARS-COV-2 is moderate to low.[599]
- There is a lack of data on the rate of false-positive tests. However, preliminary estimates in the UK are in the range of 0.8% to 4%.[600] This rate could translate into a significant proportion of daily false-positive results due to the current low prevalence of the virus in the UK population, adversely affecting the positive predictive value of the test.[595]
- Examples of the potential consequences of false-positive test results include:[595]
  - Unnecessarily postponing or canceling elective procedures or treatments
  - Potential exposure to infection following a wrong pathway in hospital settings during urgent hospital admissions
  - Financial losses due to self-isolation, income losses, and canceled travel
  - Psychological damage due to misdiagnosis including fear of infecting others or stigmatization
  - Increased depression or domestic violence due to lockdown and isolation
  - Overestimating the incidence and extent of asymptomatic infection in the population.

False-negative results

- False-negative rates of between 2% and 29% have been reported.[591] A systematic review found that the false-negative rate varied across studies from 1.8% to 58% (median 11%); however, there was substantial and largely unexplained heterogeneity across studies.[601]
- The probability of a false-negative result in an infected person decreases from 100% on day 1 of infection to 67% on day 4. The median false-negative rate drops to 38% on the day of symptom onset, decreases to 20% on day 8, and then starts to increase again from day 9.[602]
- Examples of the potential consequences of false-negative test results include:[591]
  - Patients may be moved into non-COVID-19 wards leading to spread of hospital-acquired infection
  - Caregivers could spread infection to vulnerable dependents
  - Healthcare workers risk spreading the infection to multiple vulnerable individuals.
Serologic testing

Serology cannot be used as a standalone diagnostic test for acute SARS-CoV-2 infections. However, it may be useful in various settings (e.g., negative molecular testing, diagnosing patients with late presentation or prolonged symptoms, serosurveillance studies).[534] [603]

[BMJ practice pointer: testing for SARS-CoV-2 antibodies] (https://www.bmj.com/content/370/bmj.m3325)

The WHO recommends collecting a paired serum sample, one specimen in the acute phase and one in the convalescent phase 2 to 4 weeks later, in patients where infection is strongly suspected and the RT-PCR result is negative.[534]

• Seroconversion or a rise in antibody titers in paired sera help to confirm whether the infection is recent and/or acute. If the initial sample tests positive, this could be due to a past infection that is not related to the current illness.
• Seroconversion may be faster and more robust in patients with severe disease compared with those with mild disease or asymptomatic infection.

The CDC recommends serologic testing as a method to support the diagnosis of illness or complications in the following situations:[604]

• A positive antibody test at least 7 days following acute illness onset in people with a previous negative antibody test (i.e., seroconversion) and who did not receive a positive viral test may indicate SARS-CoV-2 infection between the dates of the negative and positive antibody tests.
• A positive antibody test can help support a diagnosis when patients present with complications of COVID-19 illness, such as multisystem inflammatory syndrome and other post-acute sequelae of COVID-19.

Assays with FDA emergency-use authorization are recommended. Serologic tests with very high sensitivity and specificity are preferred because they are more likely to exhibit high expected predictive values when administered at least 3 weeks following onset of illness.

The Infectious Diseases Society of America recommends serologic testing in the following circumstances:[605]

• Evaluation of patients with a high clinical suspicion for infection when molecular diagnostic testing is negative and at least 2 weeks have passed since symptom onset.
• Evaluation of pediatric inflammatory multisystem syndrome in children.
• Serosurveillance studies.

Antibody responses to SARS-CoV-2 typically occur during the first 1 to 3 weeks of illness, with the seroconversion time of IgG antibodies often being earlier than that of IgM antibodies.[606] [607]

A Cochrane review found that antibody tests for IgG/IgM only detected 30% of people with COVID-19 when the test was performed 1 week after the onset of symptoms, but accuracy increased in week 2 with 70% detected and week 3 with over 90% detected. Data beyond 3 weeks were limited. Tests gave false-positive results in 2% of patients without COVID-19. The review found that the sensitivity of antibody tests is too low in the first week since symptom onset to have a primary role in the diagnosis of COVID-19, but tests are likely to have a useful role in detecting previous infection if used 15 or more days after symptom onset (although there were very little data beyond 35 days).[608]
Limitations of serologic testing

The evidence for the use of antibody tests in the diagnosis of COVID-19 is still emerging, and uncertainties about their efficacy and accuracy remain. Estimates of diagnostic accuracy need to be interpreted with caution in the absence of a definitive reference standard to diagnose or rule out COVID-19. More evidence is needed about the efficacy of testing outside of hospital settings and in asymptomatic or mild cases. The estimated sensitivity of antibody tests ranged from 18.4% to 96.1% (the lowest reported sensitivity was from a point-of-care test, although a sensitivity <50% was reported for one laboratory test), and specificity ranged from 88.9% to 100%. [588]

Understanding of the antibody response to SARS-CoV-2 is still emerging; therefore, antibody detection tests must be used with caution, and not used to determine acute infections. [534]

- Results do not indicate the presence or absence of current or previous infection with certainty as IgM and IgG antibodies may take 1 to 3 weeks to develop after infection. [604] A reliable diagnosis is often only possible in the recovery phase when opportunities for management or interruption of transmission have passed. [534]
- The duration of the persistence of antibodies produced in response to SARS-CoV-2 is still under investigation. The presence of antibodies that bind to SARS-CoV-2 does not guarantee that they are neutralizing antibodies, or that they offer protective immunity. [534]
- Although an antibody test may employ a specific antigen(s), antibodies developed in response to different proteins may cross-react (i.e., the antigen may detect antibodies it is not intended to detect). Therefore, it may not provide sufficient information on the presence of antigen-specific antibodies. [604]
- Vaccination may cause false-positive results for tests that utilize the S antigen or subunits like receptor-binding domains, but not for tests that use the N antigen. [604]

Rapid diagnostic tests

Antibody detection

- While rapid antibody detection kits have been approved for the qualitative detection of SARS-CoV-2 IgG/IgM antibodies in serum, plasma, or whole blood, the WHO does not recommend the use of these tests outside of research settings as they have not been validated as yet. [609]
- Evidence is particularly weak for point-of-care serologic tests. A meta-analysis found that the overall sensitivity of chemiluminescent immunoassays (CLIA) for IgG or IgM was approximately 98%, and the sensitivity of enzyme-linked immunosorbent assays (ELISA) was 84%; however, lateral flow immunoassays (LFA), which have been developed as point-of-care tests, had the lowest sensitivity at 66%. Test sensitivity was highest 3 or more weeks after onset of symptoms. Available evidence does not support the use of existing point-of-care serologic tests. [610]

Antigen detection

- Antigen testing relies on direct detection of SARS-CoV-2 viral proteins in nasal swabs and other respiratory specimens using a lateral flow immunoassay. Results are usually available in less than 30 minutes. While antigen tests are substantially less sensitive than RT-PCR, they offer the possibility of rapid, inexpensive, and early detection of the most infectious cases in appropriate settings. If used, testing should occur within the first 5 to 7 days following the onset of symptoms. [611]
• The WHO recommends antigen testing only in certain scenarios where RT-PCR is unavailable or where prolonged turnaround times preclude clinical utility, provided that the test meets the minimum performance requirements of ≥80% sensitivity and ≥97% specificity compared with an RT-PCR reference assay.[611]
• The FDA has warned that false-positive results can occur with antigen tests, including when users do not follow the instructions for use, and that the number of false-positive tests increases as disease prevalence decreases.[612]
• A Cochrane review found that rapid antigen tests vary in sensitivity. Sensitivity was higher in the first week after symptom onset in symptomatic people (78.3%), compared with the second week of symptoms (51%). Sensitivity was higher in those with RT-PCR cycle threshold values ≤25 (94.5%), compared with those with cycle threshold values >25 (40.7%). Sensitivity was higher in symptomatic people (72%), compared with asymptomatic people (58.1%). Sensitivity also varied between brands of tests. Positive predictive values suggest that confirmatory testing of those with positive results may be considered in low prevalence settings. Evidence for testing in asymptomatic cohorts was limited, and no studies assessed the accuracy of repeated lateral flow testing or self-testing.[613]
• Antigen testing has demonstrated a higher positive predictive value (90%) than RT-PCR (70%) compared with viral culture results. The positive percentage agreement for detection of infectious virus for the antigen test was similar to RT-PCR when compared with culture results.[614]
• Laboratory-based (nonrapid) antigen tests are also available in some countries.

Molecular testing

• Rapid molecular tests are available. Some rapid molecular tests show accuracy levels similar to laboratory-based RT-PCR tests with high sensitivity and specificity. However, there is limited evidence available to support their use in symptomatic people, and there is no evidence for their use in asymptomatic populations. Resource implications of their use at scale are potentially high. Rapid molecular tests may be suitable for some testing scenarios (e.g., where obtaining test results within 2 hours will enable appropriate decision-making).[613]

Chest imaging

All imaging procedures should be performed according to local infection prevention and control procedures to prevent transmission. Chest imaging is considered safe in pregnant women.[615]

Order a chest x-ray in all patients with suspected pneumonia.

• Unilateral lung infiltrates are found in 25% of patients, and bilateral lung infiltrates are found in 75% of patients.[49] [50] [616]
• Chest x-ray is moderately sensitive and moderately specific for the diagnosis of COVID-19. Pooled results found that chest x-ray correctly diagnosed COVID-19 in 80.6% of people who had the disease. However, it incorrectly identified COVID-19 in 28.5% of people who did not have the disease.[617]
• Although chest x-ray appears to have a lower sensitivity compared with chest CT, it has the advantages of being less resource-intensive, associated with lower radiation doses, easier to repeat sequentially, and portable.[618]

Consider ordering a CT scan of the chest.
Coronavirus disease 2019 (COVID-19)

Diagnosis

- Chest CT may play a role in diagnosis in a limited number of hospitalized patients, particularly when initial molecular testing has been inconclusive, or when an alternative diagnosis is being considered.[619] However, it is not diagnostic for COVID-19 and local guidance should be consulted on whether to perform a CT scan.

- The British Society of Thoracic Imaging (BSTI) recommends CT imaging in patients with clinically suspected COVID-19 who are seriously ill if chest x-ray is uncertain or normal. Without the suspicion of COVID-19, the radiology is nonspecific and could represent many other disease processes. The BSTI in collaboration with NHS England have produced a radiology decision support tool to help clinicians decide whether or not chest imaging should be ordered.[537] [BSTI: radiology decision tool for suspected COVID-19] (https://www.bsti.org.uk/media/resources/files/NHSE_BSTI_APPROVED_Radiology_on_CoVid19_v6_modified1__-_Read-Only.pdf)

- Some institutions in the UK recommend a more pragmatic approach for patients with high clinical suspicion of COVID-19, with chest CT recommended only after two indeterminate or normal chest x-rays in combination with a negative RT-PCR test.[620]

- The American College of Radiology recommends reserving CT for hospitalized, symptomatic patients with specific clinical indications for CT, and emphasizes that a normal chest CT does not mean that a patient does not have COVID-19 and that an abnormal chest CT is not specific for COVID-19 diagnosis.[621]

- Chest CT is sensitive and moderately specific for the diagnosis of COVID-19. Pooled results found that chest CT correctly diagnosed COVID-19 in 87.9% of people who had the disease. However, it incorrectly identified COVID-19 in 20% of people who did not have the disease. Therefore, chest CT may have more utility for excluding COVID-19 than for differentiating it from other causes of respiratory illness.[617] Accuracy appears to be lower among children; however, there are limited data in this population.[619]

- Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[622] Some patients may present with a normal chest finding despite a positive RT-PCR.[623] Results of RT-PCR testing may be false-negative, so patients with typical CT findings should have repeat RT-PCR testing to confirm the diagnosis.[624]

- CT imaging abnormalities may be present in asymptomatic patients. The pooled estimate of the rate of positive chest CT findings in asymptomatic cases was 47.6% (mainly ground-glass opacity).[625]

- Pregnant women appear to present more commonly with more advanced CT findings compared with the general adult population; however, results are similar to those in the general adult population.[626]

Typical features of chest CT

- Abnormal chest CT findings have been reported in up to 97% of COVID-19 patients in one meta-analysis of 50,466 hospitalized patients.[627]

- The most common findings are ground-glass opacity, either in isolation or coexisting with other findings such as consolidation, interlobular septal thickening, or crazy-paving pattern. The most common distribution pattern is bilateral, peripheral/subpleural, posterior distribution of the opacities, with a lower lobe predominance. Extensive/multilobar involvement with consolidations is more common in older patients and those with severe disease.[628]
• Ground-glass opacity has the highest diagnostic performance for COVID-19 pneumonia, followed by ground-glass opacity plus consolidation, and consolidation only. The simultaneous presence of ground-glass opacity and other features of viral pneumonia had optimum performance in the detection of COVID-19 (sensitivity 90% and specificity 89%).

• CT scan generally shows an increase in the size, number, and density of ground-glass opacities in the early follow-up period, with a progression to mixed areas of ground-glass opacities, consolidations, and crazy paving peaking at day 10 to 11, before gradually resolving or persisting as patchy fibrosis.

• A small comparative study found that patients with COVID-19 are more likely to have bilateral involvement with multiple mottling and ground-glass opacity compared with other types of pneumonia.

• Children frequently have normal or mild CT chest findings. The most common signs in children are patchy ground-glass opacity and, less frequently, nonspecific patchy shadows, areas of consolidation, and a halo sign. Abnormalities are more common in the lower lobes and are predominantly unilateral. Pleural effusion is rare. Children may have signs of pneumonia on chest imaging despite having minimal or no symptoms. Ground-glass opacity and peribronchial thickening were the most prevalent findings in infants younger than 1 year of age.

Atypical features of chest CT

• Pulmonary vascular enlargement, interlobular or intralobular septal thickening, adjacent pleural thickening, air bronchograms, subpleural lines, crazy-paving pattern, bronchus distortion, bronchiectasis, vascular retraction sign, and halo sign are atypical features. Pleural effusion, pericardial effusion, cavitation, pneumothorax, and mediastinal lymphadenopathy have also been reported rarely.

The WHO recommends chest imaging in the following scenarios:

- Symptomatic patients with suspected COVID-19 when RT-PCR is not available, RT-PCR test results are delayed, or initial RT-PCR testing is negative but there is a high clinical suspicion for COVID-19 (for diagnosis)
- Patients with suspected or confirmed COVID-19 who are not currently hospitalized and have mild symptoms (to decide on hospital admission versus home discharge)
- Patients with suspected or confirmed COVID-19 who are not currently hospitalized and have moderate to severe symptoms (to help decide on regular ward admission versus intensive care unit admission)
- Patients with suspected or confirmed COVID-19 who are currently hospitalized and have moderate to severe symptoms (to inform therapeutic management).

Emerging tests

Reverse transcription loop-mediated isothermal amplification

• Reverse transcription loop-mediated isothermal amplification (RT-LAMP) assays are an emerging test to detect SARS-CoV-2 viral RNA. While assays are simple and quick, there is less evidence for their use. Assays for SARS-CoV-2 have been developed and are being evaluated.

Lung ultrasound
Coronavirus disease 2019 (COVID-19)

Diagnosis

- Lung ultrasound is used as a diagnostic tool in some centers as an alternative to chest x-ray and chest CT. Although there is only very low-certainty evidence supporting its diagnostic accuracy, it might be helpful as a supplemental or alternate imaging modality.[618]
- Ultrasound is sensitive but not specific for the diagnosis of COVID-19. Pooled results found that lung ultrasound correctly diagnosed COVID-19 in 86.4% of people with the disease. However, it incorrectly diagnosed COVID-19 in 45% of people who did not have the disease. Therefore, ultrasound may have more utility for excluding COVID-19 than for differentiating it from other causes of respiratory illness.[617]
- B-lines are the prominent pattern in patients with COVID-19, occurring with a pooled frequency of 97%. Pleural line abnormalities are also common, with a pooled frequency of 70%. While these findings are not specific for COVID-19, they increase the likelihood of disease in the context of a characteristic clinical presentation. Other findings include consolidations, pleural thickening, and pleural effusion.[637]
- It has the advantages of portability, bedside evaluation, reduced healthcare worker exposure, easier sterilization process, absence of ionizing radiation exposure, and repeatability during follow-up. It may also be more readily available in resource-limited settings. However, it also has some limitations (e.g., it is unable to discern chronicity of a lesion) and other imaging modalities may be required. Ultrasound may be used in pregnant women and children.[638] [639]
- Possible roles for ultrasound include: reducing nosocomial transmission; monitoring progress of patients; and a possible role in subpopulations who are vulnerable but are not suitable for CT (e.g., pregnant women).[640]

Viral isolation

- Viral isolation is not recommended as a routine diagnostic procedure. All procedures involving viral isolation in cell culture require trained staff and biosafety level 3 (BSL-3) facilities.[534]

Calprotectin

- Calprotectin is an emerging biomarker of interest. Calprotectin levels often increase following infection or trauma, and in inflammatory disease. Serum/fecal calprotectin levels have been demonstrated to be significantly elevated in COVID-19 patients with severe disease, and it may have prognostic significance.[641]

History and exam

Key diagnostic factors

Fever (common)

- Reported in approximately 77% of patients.[139] In one case series, only 44% of patients had a fever on presentation, but it developed in 89% of patients after hospitalization.[642] The course may be prolonged and intermittent, and some patients may have chills/rigors. The prevalence of fever is higher in adults compared with children; approximately 54% of children do not exhibit fever as an initial presenting symptom.[643] In children, fever may be absent or brief and rapidly resolving.[644]
• Reported in approximately 68% of patients. The cough is usually dry; however, a productive cough has been reported in some patients. Can persist for weeks or months after infection.

**dyspnea (common)**

• Reported in approximately 38% of patients. Median time from onset of symptoms to development of dyspnea is 5 to 8 days. May last weeks after initial onset of symptoms. Wheeze has been reported in 17% of patients.

**altered sense of smell/taste (common)**

• Presence of anosmia and/or ageusia may be useful as a red flag for diagnosis. Olfactory dysfunction (anosmia/hyposmia) has been reported in approximately 41% of patients, and gustatory dysfunction (ageusia/dygesusia) has been reported in approximately 35% of patients. Prevalence appears to be higher in European studies. May be an early symptom before the onset of other symptoms, or may be the only symptom in patients with mild to moderate illness. Prevalence of anosmia/ageusia presenting before other symptoms was 13% to 73%, at the same time as other symptoms was 14% to 39%, and after other symptoms was 27% to 49%. Complete resolution or improvement in symptoms was reported in 89% of patients 4 weeks after onset. Anosmia or hyposmia is significantly associated with an enhanced risk of testing positive for COVID-19, and is a good predictor of infection. Many drugs are associated with taste and smell changes (e.g., antibiotics, ACE inhibitors) and should be considered in the differential diagnosis.

**Other diagnostic factors**

**fatigue (common)**

• Reported in approximately 30% of patients. Patients may also report malaise. Fatigue and exhaustion may be extreme and protracted, even in patients with mild disease.

**myalgia or arthralgia (common)**

• Reported in approximately 17% (myalgia) and 11% (arthralgia) of patients. Arthritis has been reported rarely.

**sputum production/expectoration (common)**

• Reported in approximately 18% of patients.

**chest tightness (common)**

• Reported in approximately 22.9% of patients.

**gastrointestinal symptoms (common)**

• Reported in 20% of patients. The weighted pooled prevalence of specific symptoms is as follows: loss of appetite 22.3%; diarrhea 2.4%; nausea/vomiting 9%; and abdominal pain 6.2%. Gastrointestinal symptoms appear to be more prevalent outside of China, although this may be due to increased awareness and reporting of these symptoms as the pandemic progressed. Gastrointestinal symptoms are not associated with an increased likelihood for testing positive for COVID-19; however, anorexia and diarrhea, when combined with loss of smell/taste and fever, were 99% specific for COVID-19 infection in one prospective case-control study. The presence of gastrointestinal symptoms may be a predictor of progression to severe disease. However, the presence of these symptoms does not appear to affect intensive care unit admission rate or mortality.
Coronavirus disease 2019 (COVID-19)  

**Diagnosis**

Presence of diarrhea has been associated with a severe clinical course in children.[552] Hematochezia has been reported.[660]

**sore throat (common)**

- Reported in approximately 16% of patients.[139] Usually presents early in the clinical course.

**headache (common)**

- Reported in approximately 25% of patients. Headache is twice as prevalent in COVID-19 patients compared with patients with non-COVID-19 viral respiratory tract infections.[661]

**dizziness (common)**

- Reported in approximately 11% of patients.[647]

**neurologic symptoms (common)**

- Confusion has been reported in approximately 11% of patients.[647]
- The overall prevalence of delirium is 24.3%, with an increased prevalence in adults >65 years of age (28%). Delirium has been associated with a 3-fold increase in mortality.[662] Benzodiazepine use and the lack of family visitation (virtual or in-person) have been identified as risk factors for delirium.[663] The pooled prevalence of anxiety, depression, and insomnia is 15.2%, 16%, and 23.9%, respectively.[664] Altered mental status was as common in younger hospitalized patients (<60 years) as it was in older patients in one study.[665] [666]

**ocular symptoms (common)**

- Reported in 11% of patients. The most common ocular symptoms include dry eye or foreign body sensation (16%), redness (13.3%), tearing (12.8%), itching (12.6%), eye pain (9.6%), and discharge (8.8%). Conjunctivitis was the most common ocular disease in patients with ocular manifestations (88.8%).[667] Most symptoms are mild and last for 4 to 14 days with no complications. Prodromal symptoms occur in 12.5% of patients.[668] Mild ocular symptoms (e.g., conjunctival discharge, eye rubbing, conjunctival congestion) were reported in 22.7% of children in one cross-sectional study. Children with systemic symptoms were more likely to develop ocular symptoms.[669]

**rhinorrhea/nasal congestion (uncommon)**

- Rhinorrhea has been reported in approximately 8% of patients, and nasal congestion has been reported in approximately 5% of patients.[647]

**audio-vestibular symptoms (uncommon)**

- Sudden sensorineural hearing loss, tinnitus, and rotatory vertigo have been reported in 7.6%, 14.8%, and 7.2% of patients, respectively. Otalgia has also been reported.[670]

**chest pain (uncommon)**

- Reported in approximately 7% of patients.[647] May indicate pneumonia.

**cutaneous symptoms (uncommon)**

- The pooled prevalence of overall cutaneous lesions is 5.7%. The most common symptoms are a viral exanthem-like presentation (4.2%), maculopapular rash (3.8%), and vesiculobullous lesions (1.7%). Other manifestations include urticaria, chilblain-like lesions, livedo reticularis, and finger/toe gangrene.[671] [672] In the UK COVID Symptom Study, 17% of respondents reported rash as the first symptom of disease, and 21% of respondents reported rash as the only clinical sign.[673]
Cutaneous symptoms have been reported in children.\cite{674} It is unclear whether skin lesions are from viral infection, systemic consequences of the infection, or drugs the patient may be on. Further data is required to better understand cutaneous involvement and whether there is a causal relationship.


**lower urinary tract symptoms (uncommon)**

- There is emerging evidence that patients may rarely have signs, symptoms, and radiologic and laboratory features indicative of involvement of the lower urinary tract and male genital system. This may include scrotal discomfort, swelling, or pain (acute orchitis, epididymitis, or epididymo-orchitis), low-flow priapism, impaired spermatogenesis, bladder hemorrhage, acute urinary retention, and worsening of existing lower urinary tract symptoms (including exacerbation of benign prostatic hyperplasia). Further research is required.\cite{675} \cite{676}

**hemoptysis (uncommon)**

- Reported in approximately 2% of patients.\cite{647} May be a symptom of pulmonary embolism.\cite{677}

**bronchial breath sounds (uncommon)**

- May indicate pneumonia.

**tachypnea (uncommon)**

- May be present in patients with acute respiratory distress.

**tachycardia (uncommon)**

- May be present in patients with acute respiratory distress.

**cyanosis (uncommon)**

- May be present in patients with acute respiratory distress.

**crackles/rales on auscultation (uncommon)**

- May be present in patients with acute respiratory distress.

### Risk factors

#### Strong

**contact with probable or confirmed case**

- People who have been in contact with a probable or confirmed case are at increased risk of infection.
- The World Health Organization defines a contact as a person who has experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case: face-to-face contact with a probable or confirmed case within 3 feet (1 meter) and for at least 15 minutes; direct physical contact with a probable or confirmed case; direct care for a patient with probable or confirmed COVID-19 without using recommended personal protective equipment; or other situations as indicated by local risk assessments.\cite{194}
- The Centers for Disease Control and Prevention defines a close contact as someone who has been within 6 feet (2 meters) of an infected person for at least 15 minutes over a 24-hour period, beginning 2 days before symptom onset (or 2 days before testing in asymptomatic patients).\cite{195}
residence/work/travel in location with high risk of transmission

- People who live or work in, or travel to, a location with a high risk of transmission are at increased risk of infection.
- People residing or working in an area with a high risk of transmission (e.g., closed residential settings, humanitarian setting), people residing in or traveling to an area with community transmission, and people working in a health setting (including within health facilities and households) at any time within the 14 days prior to symptom onset are at higher risk of infection.[194]
- People at risk of infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern include: those who have been in, or transited through, any countries with transmission of variants of concern (consult local guidance for lists of affected countries) and who develop symptoms within 10 days of departure or transit (or date of sampling for a positive SARS-CoV-2 test if asymptomatic); those known to be infected with a variant of concern based on sequencing results, regardless of travel history; contacts of these individuals.[196]

older age

- Older people are at increased risk for infection and severe disease.[197]
- In the UK, data from a cross-sectional study indicated that people ages 40 to 64 years are at greatest risk of infection, followed by patients 75 years and older, and then people ages 65 to 74 years.[198] The highest mortality rate was observed in patients 80 years and older.[199]
- In the US, patients ≥65 years accounted for 31% of all cases, 45% of hospitalizations, 53% of intensive care unit admissions, and 80% of deaths early in the pandemic, with the highest incidence of severe outcomes in patients ages ≥85 years.[7]
- Observational studies in older adults ages ≥60 years across multiple countries found that approximately 51% of older patients had severe infection, while 22% were critically ill.[200]
- While age is an independent risk factor, the risk in older people is also partly related to the likelihood that older adults are more likely to have comorbidities. The higher prevalence of malnutrition in older patients may also contribute to poor outcomes.[201]

male sex

- Males are at increased risk for infection and severe disease.[197]
- In the UK, data from a cross-sectional study found that the adjusted odds of a positive test were greater in males (18.4%) compared with females (13.3%).[198]
- It has been hypothesized that this may be due to the presence of androgens, a lower level of SARS-CoV-2 antibodies compared with females, women mounting a stronger immune response compared with men, genetic factors, or a higher prevalence of alcohol consumption and smoking; however, further research is required.[202] [203]

ethnicity

- People who belong to Black, Asian, and minority ethnic (BAME) groups are at increased risk of infection and severe disease.[204] [205]
- In the UK, data indicate that South Asian, Black, and mixed ethnicity populations have an increased risk for testing positive and of adverse outcomes (i.e., hospitalization, intensive care unit admission, death) compared with the White population, even after accounting for differences in sociodemographic, clinical, and household characteristics.[206]
- In the US, the proportion of hospitalized patients was highest for Hispanic or Latino patients, and these racial and ethnic disparities were largest during May–July 2020 and became less pronounced as the pandemic spread throughout the country.[207] Cumulative age-adjusted data from the Centers for
Disease Control and Prevention (as of 26 May 2021) indicate that Hispanic or Latino people, non-Hispanic American Indian or Alaska Native people, and non-Hispanic Black people have approximately 2.8, 3.3, and 2.9 times the rate of hospitalizations and 2.3, 2.4, and 1.9 times the rate of deaths of non-Hispanic White people, respectively.[208] However, cohort studies in the US have found no difference in outcomes between non-Hispanic Black and Hispanic patients compared with White patients after adjusting for sociodemographic factors (e.g., age, sex, insurance) and comorbidities. These patients may have an increased risk of mortality and morbidity due to their disproportionate representation among hospitalizations.[209] [210] [211]

- Racial disparities in outcomes may be partially attributed to higher rates of comorbidities in certain ethnic groups.[212]

**residence in a long-term care facility**

- People in a long-term care facility are at increased risk for infection and severe disease.[123] [213]
- In the UK, care home residents represented approximately one third of the total number of deaths in England and Wales during the first wave of the pandemic; other countries reported a similar experience. This was likely due to shortages in personal protective equipment, a vulnerable population, and a lack of testing.[214] A study across four nursing homes found that 26% of residents died over a 2-month period, with all-cause mortality increasing by 203% compared with previous years. Approximately 40% of residents tested positive for SARS-CoV-2, and of these, 43% were asymptomatic and 18% had atypical symptoms.[215]
- In the US, the 30-day all-cause mortality rate was 21% in a cohort study of more than 5000 nursing home residents. Older age, male sex, and impaired cognitive and physical function were independently associated with mortality.[216]

**presence of comorbidities**

- People with comorbidities are at increased risk for severe disease, and the more comorbidities, the greater the risk.[217] [218]
- In the UK, the most common comorbidities reported in a cohort study of more than 20,000 hospitalized patients were cardiac disease (31%), uncomplicated diabetes (21%), nonasthmatic chronic pulmonary disease (18%), and chronic kidney disease (16%).[6]
- In the US, approximately 92% of hospitalized adults had at least one reported underlying medical condition, with the most common being hypertension, obesity, metabolic disease, and cardiovascular disease. Approximately 53% of children had at least one reported underlying medical condition, with the most common being obesity, neurologic disease, and asthma.[219] It has been estimated that approximately 56% of adults, and 32% of young adults (ages 18-25 years), are at risk for severe disease because of the presence of at least one comorbidity.[220] [221]
- Globally, hypertension (21%), obesity (18%), and diabetes (18%) were the most prevalent comorbidities. Cancer, chronic kidney disease, diabetes, and hypertension were independently associated with mortality. Chronic kidney disease was statistically the most prominent comorbidity leading to death.[222]

**obesity**

- People with obesity are at increased risk for infection and severe disease.[223]
- Of the 2.5 million deaths reported globally by the end of February 2021, 2.2 million were in countries where more than half the population is classified as overweight. In countries where less than half the adult population is classified as overweight, the likelihood of death is around one tenth of the level seen in countries where more than half the population is classified as overweight.[224]
• People with obesity (≥30 kg/m²) and people who are overweight (25-30 kg/m²) are at increased risk of severe disease.[218] Evidence from a meta-analysis suggests a linear dose-response association between body mass index and disease severity and mortality.[225] However, another meta-analysis demonstrated a J-curve relationship between body mass index and mortality, indicating that both underweight and obese patients had a higher risk of mortality compared with those of normal weight.[226]

• A cohort study in the UK found that the risk of severe outcomes (i.e., hospitalization, intensive care unit admission, death) increased progressively above a body mass index ≥23 kg/m², independent of the excess risks of related diseases (e.g., diabetes). The relative risk was particularly notable in people <40 years of age and those with Black ethnicity.[227]

• A cohort study in the US found a nonlinear relationship between body mass index and disease severity, with the lowest risk at body mass indexes near the threshold between healthy weight and overweight, then increasing with higher body mass index.[228]

• Obesity is associated with an increased risk for disease progression, hospitalization, intensive care unit admission, need for invasive mechanical ventilation, complications (e.g., venous thromboembolism and renal failure), and in-hospital mortality, especially among younger patients.[223][229][230]

cardiovascular disease

• People with cardiovascular disease are at increased risk for severe disease.[218]

• Arrhythmias, coronary artery disease, and cardiovascular disease are significantly associated with intensive care unit admission. Heart failure, arrhythmias, coronary artery disease, and cardiovascular disease are also significantly associated with an increased risk of mortality.[231] Preexisting atrial fibrillation was associated with a higher risk of short-term death.[232]

• People with risk factors for cardiovascular disease (e.g., hypertension, diabetes) are also at increased risk for severe disease and mortality (see below).[233][234]

diabetes

• People with type 1 or type 2 diabetes are at increased risk for severe disease.[218]

• Diabetes is associated with an increased risk for disease progression, intensive care admission, acute respiratory distress syndrome, need for invasive mechanical ventilation, and mortality.[235][236]

• In the UK, one third of all deaths in hospitalized patients occurred in patients with diabetes.[237] An analysis of more than 19,000 patients admitted to critical care over the entire first wave of the pandemic found that type 2 diabetes was associated with a 20% increase in mortality in patients with severe disease, independent of age, sex, ethnicity, obesity, or other major comorbidity.[238]

• Risk factors for poor prognosis and higher mortality in patients with type 1 or type 2 diabetes include older age, male sex, non-White ethnicity, socioeconomic deprivation, renal impairment/acute kidney injury, history of stroke or heart failure, poor glycemic control prior to infection, higher glycosylated hemoglobin (HbA1c) levels, higher body mass index, elevated C-reactive protein, diabetic ketoacidosis, hyperglycemic hyperosmolar state, and insulin use.[239][240][241][242][243] However, HbA1c levels were not associated with mortality in a large US cohort of hospitalized patients.[244] Patients with newly diagnosed diabetes have a higher risk of all-cause mortality compared with patients with known diabetes, hyperglycemia, or normal glucose.[245] Use of metformin or dipeptidyl peptidase-4 inhibitors has been associated with lower mortality.[246][247]

• The poor prognosis in these patients is likely due to the syndromic nature of diabetes, with factors such as hyperglycemia, older age, and the presence of comorbidities (e.g., obesity, hypertension, cardiovascular disease) all contributing to the increased risk.[248]
chronic respiratory disease

- People with chronic obstructive pulmonary disease COPD, including emphysema and chronic bronchitis, are at increased risk for severe disease. People with moderate to severe asthma, or other chronic lung diseases (e.g., interstitial lung disease, cystic fibrosis, idiopathic pulmonary fibrosis, pulmonary hypertension) may be at increased risk for severe disease; however, evidence is limited.[218] There is no clear evidence that people with asthma or COPD are at higher risk of infection.[249] [250]
- COPD is associated with an increased risk of hospitalization, intensive care unit admission, and mortality.[251] A national, multicenter prospective cohort study in the UK (75,463 patients from 258 healthcare facilities) found that patients with COPD were less likely to receive critical care than patients without an underlying respiratory condition.[252]
- It is unclear whether asthma increases the risk of infection or severe outcomes (i.e., hospitalization, intensive care unit admission, mortality). Systematic reviews do not detect a clear increase in risk, and high-quality primary studies report conflicting results. People with asthma who have comorbid COPD, and people with nonallergic asthma, appear to have worse outcomes.[253] According to meta-analyses, asthma is not associated with an increased risk for infection, severe disease, worse prognosis, mortality, or a higher risk of intubation or mechanical ventilation. Clinical outcomes were similar between patients with asthma and patients without asthma. Patients with asthma may have a lower risk of death compared with nonasthmatic patients.[254] [255] [256] [257] However, a national, multicenter prospective cohort study in the UK (75,463 patients from 258 healthcare facilities) found that patients with asthma were more likely to receive critical care than patients without an underlying respiratory condition. Severe asthma was associated with increased mortality compared with patients with nonsevere asthma in patients ages 16 years and older. Inhaled corticosteroid use in patients with asthma was associated with lower mortality compared with patients without an underlying respiratory condition in patients ages 50 years and older.[252]
- People with obstructive sleep apnea may be at increased risk for severe disease, intensive care admission, mechanical ventilation, and mortality; however, evidence is limited.[258] Obstructive sleep apnea has not been associated with an increased risk of infection.[259]
- People with cystic fibrosis do not appear to be at increased risk of infection; however, there is evidence that some patients may experience a more severe clinical course (e.g., post-transplantation).[260]
- There are no data on whether pediatric respiratory diseases (including childhood asthma) are risk factors for infection or severity.[261]

chronic kidney disease

- People with chronic kidney disease are at increased risk for severe disease, and may be at higher risk for infection.[198] [218]
- Patients with chronic kidney disease had a significantly higher risk of hospitalization and all-cause mortality compared with people without chronic kidney disease. Patients with chronic kidney disease also had a higher risk of progressing to critical illness in the pooled analysis of included studies and subgroup analyses of studies with multivariable adjustment, although neither result achieved statistical significance.[262]
- In the UK, data from a cross-sectional study found that the adjusted odds of a positive test were greater in patients with chronic kidney disease (32.9%) compared with those without (14.4%).[198]
- Preexisting chronic kidney disease is an independent risk factor for developing acute kidney injury as a complication.[263]
Coronavirus disease 2019 (COVID-19)

Diagnosis

pregnancy

- Pregnant women are at increased risk for severe disease.\[218\]
- According to an analysis of approximately 400,000 women ages 15 to 44 years with symptomatic disease, pregnant women were more likely to be hospitalized, be admitted to the intensive care unit, receive invasive mechanical ventilation or extracorporeal membrane oxygenation, and die compared with nonpregnant women.\[27\]
- See the Complications section for more information on pregnancy-related complications.

smoking

- People who are current or former smokers are at increased risk for severe disease.\[218\]
- Smoking is associated with severe or critical outcomes, and an increased risk of intensive care unit admission and mortality. The association appears to be more significant in former smokers compared with current smokers. Current smokers are at higher risk of developing severe disease compared with nonsmokers.\[264\] Smokers have double the mortality risk compared with nonsmokers.\[265\] This may be due to increased airway expression of the angiotensin-converting enzyme-2 receptor in smokers.\[266\]
- The World Health Organization has reviewed the available evidence and concluded that smoking is associated with increased severity of disease and death in hospitalized patients.\[267\]

malignancy

- People with cancer are at increased risk for infection and severe disease.\[218\] \[268\]
- Patients with cancer have an increased risk of severe disease, increased ventilatory requirements, and mortality compared with the general population. Intensive care unit admission rates were not statistically significant between the two groups. Hematologic malignancies were associated with the highest risk of mortality (possibly explained by the greater degree of immunosuppression used in the treatment of these patients), followed by lung cancer. There is no clear association between treatment modality and mortality. A higher risk of infection is likely due to immunosuppressive treatments and/or recurrent hospital visits.\[269\] The pooled in-hospital mortality risk in patients with cancer is 14.1%.\[270\]
- Mortality in cancer patients is affected by preexisting noncancer comorbidities, and is significantly higher in people with hypertension, cardiovascular disease, chronic obstructive pulmonary disease, and diabetes.\[271\]
- Children with cancer may be no more vulnerable to infection compared with children without cancer. Limited data show that the overall morbidity in pediatric patients with cancer is low, with only 5% requiring hospitalization for symptoms.\[272\] Overall survival in children with cancer is very high (99.4%), and there was no significant difference in the risk of hospitalization or intensive care unit admission between hematologic malignancies and solid tumors in children.\[273\]

cerebrovascular disease

- People with cerebrovascular disease are at increased risk for severe disease.\[218\]
- Patients with a history of cerebrovascular disease were more likely to progress to adverse outcomes compared with patients without a history of cerebrovascular disease.\[274\] Patients with preexisting cerebrovascular disease had 2.67-fold higher odds of poor outcomes including intensive care admission, mechanical ventilation, and mortality.\[275\]
solid organ or blood stem cell transplant

- People with an immunocompromised state from solid organ or blood stem cell transplant may be at increased risk for severe disease; however, evidence is limited.[218]
- Solid organ transplant recipients are at increased risk for hospitalization, intensive care unit admission, and mortality. However, the increased rate of hospitalization may reflect a preferred management strategy of closer inpatient monitoring in these patients rather than being an indicator of disease severity. Overall mortality in solid organ transplant recipients was 20%. [276]
- Hospitalization and mortality rates in liver transplant recipients are disproportionately high compared with nontransplant patients regardless of age or time after transplant. Older age and diabetes are significant risk factors for death among these patients. [277]

Down syndrome

- People with Down syndrome may be at increased risk for severe disease; however, evidence is limited.[218]
- In the UK, a cohort study found a 4-fold increased risk for hospitalization and a 10-fold increased risk for mortality in people with Down syndrome.[278] This may possibly be due to the presence of immune dysfunction, congenital heart disease, and pulmonary pathology.

hemoglobin disorders

- People with sickle cell disease or thalassemia may be at increased risk for severe disease; however, evidence is limited.[218]
- In the US, among 178 patients with sickle cell disease (mean patient age <40 years), 69% were hospitalized, 11% were admitted to intensive care, and 7% died.[279] Infection can cause acute chest syndrome in patients with sickle cell disease.[280] [281]

hypertension

- People with hypertension may be at increased risk for severe disease; however, evidence is limited.[218]
- Hypertension has been associated with increased poor composite outcome, including mortality, severe disease, acute respiratory distress syndrome, need for intensive care admission, and disease progression.[282] Patients with hypertension have a 2.98-fold higher risk of severe disease, a 1.82-fold higher risk of critical disease, and a 2.17 to 2.88-fold higher risk of fatality compared with patients without hypertension.[283] [284]
- Initially, there was a concern that people on ACE inhibitors or angiotensin-II receptor antagonists may be at increased risk for infection or severe disease due to upregulation of ACE2 receptor expression.[285] However, high-certainty evidence suggests that use of these drugs is not associated with severe disease, and there is no association between the use of these medications and a positive SARS-CoV-2 test result among symptomatic patients.[286] [287]

defementia

- People with dementia may be at increased risk for infection and severe disease; however, evidence is limited.[218] [288]
- Older adults with dementia are at a higher risk of mortality in the short term. Dementia patients are more likely to be vulnerable to having diseases such as hypertension, diabetes, and pneumonia, and be immunocompromised. The pooled mortality rate of patients with dementia was 39% compared with 20% in older adults without dementia.[289]
Coronavirus disease 2019 (COVID-19)

Diagnosis

- In the UK, over one quarter of people who died with COVID-19 from March to June 2020 had dementia. Dementia and Alzheimer disease was the most common main preexisting health condition in deaths involving COVID-19 between March and June 2020.[290]
- A retrospective case-control study of electronic patient health records in the US found that patients with dementia were at increased risk of infection compared with patients without dementia. They also had significantly worse outcomes (6-month hospitalization risk and mortality risk) compared with patients with dementia but no COVID-19 and patients with COVID-19 but no dementia. The highest risk was seen in patients with vascular dementia.[291]

Immunosuppression

- People who are immunocompromised may be at increased risk for severe disease; however, evidence is limited.[218]
- This includes people with a history of primary immune deficiencies or prolonged use of corticosteroids or other immunosuppressant medications.
- Glucocorticoid exposure of ≥10 mg/day (prednisone) has been associated with a higher odds of hospitalization in patients with rheumatologic disease.[292] Patients treated with cyclosporine/tacrolimus also had an increased risk for hospitalization; however, it was not clear whether the increased risk is related to the drug itself, the underlying condition for which the patient is treated, or other factors.[293]
- Immunosuppressed patients are not at significantly increased risk of infection compared with the general population.[294]
- Also see HIV infection and Autoimmune disease below.

HIV infection

- People living with HIV may be at increased risk for severe disease; however, evidence is limited.[218]
- It is still unclear whether HIV infection influences infection and disease course. A retrospective cohort study in the UK found that people with HIV appear to be at increased risk for mortality.[295] A retrospective cohort study in New York found that while people with HIV do not appear to be at increased risk of infection, they are at increased risk for poor outcomes (mainly higher rates of severe disease requiring hospitalization) compared with people living without diagnosed HIV infection. Hospitalization risk increased with progression of HIV disease stage.[296]
- Evidence from meta-analyses is conflicting. Some meta-analyses have found that HIV infection was not associated with composite poor outcome.[297] [298] However, other meta-analyses have found that people living with HIV infection have an increased risk for infection and mortality compared with people without HIV. People on tenofovir disoproxil-based regimens may have a lower risk of infection and poor outcomes; however, evidence is inconclusive.[299] [300] [301]

Substance use disorders

- People with substance use disorders may be at increased risk for severe disease; however, evidence is limited.[218] This includes alcohol, opioid, or cocaine use disorder.
- People with substance abuse disorders, especially those using drugs that affect the respiratory and cardiovascular systems, may be vulnerable to the adverse respiratory effects of COVID-19. Cohort studies have found substance use disorders were associated with increased hospitalization, intensive care unit admission, ventilator use, and mortality.[302] [303]
**children with certain underlying conditions**

- Children with certain underlying conditions may be at increased risk for severe disease; however, evidence is limited.[218]
- These conditions include obesity, diabetes, asthma and chronic lung disease, immunosuppression, and sickle cell disease. Children may also be at risk if they are medically complex; have serious genetic, neurologic, or metabolic disorders; or have congenital heart disease.[218]

**Weak chronic liver disease**

- People with chronic liver disease, especially cirrhosis, may be at increased risk for severe disease; however, evidence is limited.[218]
- Chronic liver disease has been associated with an increased risk for severe disease and mortality.[304] The 30-day mortality rate is higher in patients with cirrhosis, with the main causes of death being respiratory complications and sudden worsening of liver function leading to end-stage liver disease.[305]
- People with metabolic dysfunction-associated fatty liver disease (nonalcoholic fatty liver disease) are at increased risk for severe disease.[306] [307] Disease severity has been associated with age <60 years and intermediate or high fibrosis-4 (FIB-4) scores.[308] [309]

**vitamin D deficiency**

- People with vitamin D deficiency may be at higher risk for infection and severe disease; however, evidence is limited.[310] [311]
- Meta-analyses have found that low serum vitamin D level is significantly associated with a higher risk of infection (people with vitamin D deficiency were 80% more likely to be infected), and increased risk for severe disease, hospitalization, and mortality.[312] [313] [314] However, it is unclear whether these associations were statistically significant and the certainty of evidence is very low.[315] [316]

**proton-pump inhibitor use**

- People taking proton-pump inhibitors (PPIs) may be at increased risk for severe disease; however, evidence is limited.[317]
- Data on whether PPI use increases the risk for infection is conflicting. The largest meta-analysis to date found that PPI use was not associated with an increased risk for infection.[318]
- Patients taking PPIs may be at increased risk for secondary infections, severe clinical outcomes, and death.[319] [320] [321] Current or regular users of PPIs were more likely to have severe outcomes compared with non-PPI users. Also, current PPI users were more likely to be hospitalized for longer compared with non-PPI users, although this was not statistically significant. Past use of PPIs is not associated with increased susceptibility to infection or severe outcomes.[322]
- A nationwide meta-analysis of over 80,000 cases in Denmark found that while current use of a proton-pump inhibitor may be associated with an increased risk of hospital admission, it was not associated with an increased risk for infection or severe outcomes. The authors concluded that conflicting results from previous studies may be more likely due to differences in study design and population.[323]

**autoimmune disease**

- People with autoimmune disease may be at higher risk for infection and severe disease; however, evidence is limited.[324]
• Autoimmune disease has been associated with an increased risk of infection. However, clinical outcomes were not considerably worse when compared with people without autoimmune disease. Use of corticosteroids increased the risk of infection and severe outcomes, and use of combination disease-modifying antirheumatic drugs (DMARDs) increased the risk of severe outcomes. DMARD monotherapy, particularly tumor necrosis factor inhibitors, reduced the risk of severe disease and mortality. Other factors associated with severe disease in this population include older age and the presence of comorbidities.[324]

• The overall seroprevalence and severity of infection in patients with immune-mediated inflammatory diseases (rheumatoid arthritis, axial spondyloarthritis, systemic lupus erythematosus, Sjogren syndrome, and giant cell arteritis) across six European countries resembled that of the general population. Increased systemic inflammation may play a role in the occurrence of symptomatic disease in these patients, whereas biologic and targeted synthetic DMARDs appeared to be protective.[325]

Most patients with systemic lupus erythematosus produced and maintained a serologic response beyond 30 weeks despite the use of a variety of immunosuppressants.[326]

• In patients with systemic autoimmune rheumatic diseases, patients may be at a higher risk of hospitalization, intensive care unit admission, kidney injury or acute renal failure, hyperinflammation, mechanical ventilation, and venous thromboembolism when compared with patients without systemic autoimmune rheumatic diseases.[327] [328] In patients with inflammatory rheumatic and musculoskeletal diseases, use of rituximab was associated with more severe disease but not an increased risk of mortality.[329]

• In patients with multiple sclerosis, neurologic disability, older age, Black race, cardiovascular comorbidities, recent treatment with corticosteroids, and obesity were risk factors for severe disease and mortality.[330] [331] Current evidence does not suggest that multiple sclerosis significantly increases the mortality rate. Highest hospitalization and mortality rates were in patients who were not on disease-modifying therapies, followed by those who were on B cell-depleting therapies (e.g., rituximab, ocrelizumab).[332]

• In patients with inflammatory bowel disease, infection risk was comparable to the general population, and patient outcomes (hospitalization, intensive care unit admission, and mortality) were worse in ulcerative colitis and patients on corticosteroids, thiopurines, aminosalicylates, or combination therapy. Outcomes were better in patients on biologic agents.[333] [334] [335] Seroprevalence, seroconversion, and the magnitude of anti-SARS-CoV-2 antibody reactivity was significantly attenuated in infliximab-treated patients compared with vedolizumab-treated patients in one study. This may increase the patient’s susceptibility to reinfection.[336]

**Parkinson disease**

• People with Parkinson disease may be at higher risk for infection or severe disease; however, evidence is limited.[337] [338]

• Risk factors for infection may include obesity, pulmonary disease, and hospitalization. Vitamin D supplementation was associated with a lower risk of infection.[338]

• Parkinson disease was associated with severe disease, poor in-hospital outcomes, and mortality in one meta-analysis. However, the evidence for an association is still unclear. The association was influenced by age, but not by sex or the presence of dementia, hypertension, or diabetes.[337]

**Physical inactivity**

• Physical inactivity may be associated with a higher risk for severe disease; however, evidence is limited.
• A retrospective observational study in nearly 50,000 patients found that patients with COVID-19 who were consistently inactive during the 2 years before the pandemic had a greater risk of hospitalization, intensive care unit admission, and death compared with patients who were consistently meeting physical activity guidelines or who were doing some level of physical activity. Other than older age and a history of organ transplant, physical inactivity was the strongest risk factor for severe disease outcomes in this study.[339]

dyslipidemia
• Dyslipidemia appears to be associated with an increased risk for severe disease and mortality; however, evidence is limited.[340] [341] [342]
• The association was stronger in males, older age, and those with hypertension.[343]
• Initially there was a concern that people on statins may be at increased risk of infection or more severe disease, as statins have been shown to increase ACE2 expression in animals and may promote the activation of the inflammatory pathway in acute respiratory distress syndrome.[285] However, so far, studies do not support this hypothesis, and some studies have shown a protective effect.[344] [345] [346] [347]

surgery
• Surgical mortality and complications may be higher in patients with COVID-19 compared with patients without COVID-19.[348]
• A retrospective study of 34 patients in China who underwent elective surgeries during the incubation period of COVID-19 found that all patients developed pneumonia after surgery. Approximately 44% of these patients required admission to the intensive care unit, and 20% died.[349]
• Postoperative pulmonary complications occur in half of patients with perioperative SARS-CoV-2 infection, and are associated with higher mortality, particularly in men and those ages 70 years and over.[350]

blood groups A and B
• People with blood group A may be at increased risk for infection and mortality, and people with blood group B may be at increased risk for infection; however, evidence is limited.[351]
• There is no evidence for an association between blood group AB and the risk of infection. Blood group O appears to be protective against infection; however, evidence is of low/very low quality. People who are Rh-positive were more vulnerable to infection compared with those who were Rh-negative.[351] [352]
• A genome-wide association study found that patients with blood group A are at 45% increased risk of respiratory failure compared with other blood groups. It also found a protective effect in blood group O. Two chromosomal loci were associated with respiratory failure, and one of these coincided with the ABO blood group locus.[193] The SARS-CoV-2 receptor-binding domain directly binds the blood group A antigen expressed on respiratory epithelial cells, directly linking blood group A and SARS-CoV-2.[353]

gut dysbiosis
• There is limited evidence that gut microbiota dysfunction may be implicated in the pathogenesis of COVID-19.
• Patients appear to have a depletion of beneficial commensals (e.g., *Eubacterium ventriosum*, *Eubacterium rectale*, *Faecalibacterium prausnitzii*, *Roseburia* and Lachnospiraceae taxa) and an overgrowth of opportunistic pathogens (e.g., *Clostridium hathewayi*, *Actinomyces viscosus*,...
Associations between gut microbiota composition, levels of cytokines, and inflammatory markers in patients with COVID-19 suggest that the gut microbiome is involved in disease severity, possibly via modulating host immune responses. Gut dysbiosis after disease resolution may contribute to persistent symptoms.[357]

**environmental factors**

- Climate and latitude: limited evidence suggests that cold and dry conditions and higher latitude may increase transmission, and warm and humid conditions may reduce the rate of infections; however, evidence is conflicting and is not sufficient to prove causation.[358] [359] [360] [361] [362] [363] [364]
- Air pollution: limited evidence suggests an association between exposure to ambient air pollution and COVID-19; however, evidence is not sufficient to prove causation.[365] [366] [367] [368]
- Residence in urban or deprived areas: limited evidence suggests that the adjusted odds of a positive test were greater in people living in urban areas (26.2%) compared with people living in rural areas (5.6%), and in people living in more deprived areas (29.5%) compared with people living in less deprived areas (7.7%).[198]
# Investigations

## 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>real-time reverse transcription polymerase chain reaction (RT-PCR)</td>
<td>positive for SARS-CoV-2 viral RNA; may be positive for influenza A and B viruses and other respiratory pathogens</td>
</tr>
</tbody>
</table>

- **Important:** the US Food and Drug Administration has warned that false-negative results may occur with any molecular test for the detection of SARS-CoV-2 if a mutation occurs in the part of the virus’ genome assessed by that test. Multiple genetic targets to determine a final result are less likely to be impacted by increased prevalence of genetic variants. Consider negative results in combination with clinical observations, patient history, and epidemiologic information.[678]
- Order an RT-PCR for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients with suspected infection whenever possible (see the Criteria section).[534] Commonly used assays are expected to be able to detect SARS-CoV-2 variants of concern.[196]
- Molecular testing is an aid to diagnosis only. The World Health Organization recommends that healthcare providers consider a positive or negative result in combination with specimen type, clinical observations, patient history, and epidemiologic information. Where a test result does not correspond with the clinical presentation, a new specimen should be taken and retested using the same or a different molecular test.[573]
- Base decisions about who to test on clinical and epidemiologic factors.[534] Consult local health authorities for guidance as testing priorities depend on local recommendations and available resources.
- In the UK, testing is recommended in: (1) people with symptoms of new continuous cough, high temperature, or altered sense of smell/taste; (2) people with acute respiratory infection, influenza-like illness, clinical or radiologic evidence of pneumonia, or acute worsening of underlying respiratory illness, or fever without another cause (whether presenting in primary or secondary care).[574]
- In the US, testing is recommended in: (1) people with signs or symptoms consistent with COVID-19; (2) asymptomatic people with recent known or suspected exposure to SARS-CoV-2, including those who have been in close contact (less than 6 feet [2 meters] for a total of 15 minutes or more over a 24-hour period) with a person with documented infection; (3) asymptomatic people without recent known or suspected exposure to SARS-CoV-2 for early identification, isolation, and disease prevention (when screening testing if recommended by public health officials).[575]
- The American Academy of Pediatrics recommends testing children with symptoms consistent with COVID-19, children in close contact with an individual with probable or confirmed infection, and children who require screening based on recommendations from public health authorities or other situations (e.g., prior to a medical procedure such as elective surgery or as a school or workplace requirement). The decision to test does not differ by the age of the child. Testing is not recommended for other illnesses that lack shared symptoms (e.g., urinary tract infection, cellulitis), or for children exposed to close contacts of infected individuals unless those contacts are symptomatic or other criteria are met.[576]
<table>
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<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>The optimal specimen for testing depends on the clinical presentation and the time since symptom onset. The World Health Organization recommends upper respiratory specimens (nasopharyngeal and/or oropharyngeal swabs) for early-stage infections, especially asymptomatic or mild cases, and lower respiratory specimens (sputum and/or endotracheal aspirate or bronchoalveolar lavage in patients with more severe respiratory disease) for later-stage infections or patients in whom there is a strong suspicion for infection and their upper respiratory tract specimen test was negative. Other specimens (e.g., nasal mid-turbinate swab, anterior nares swab, nasopharyngeal/nasal wash/aspirate, saliva, fecal) may be recommended in some circumstances; consult local guidance.</td>
<td></td>
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<tr>
<td>A positive RT-PCR result confirms SARS-CoV-2 infection (in the context of the limitations associated with RT-PCR testing). If the result is negative, and there is still a clinical suspicion of infection (e.g., an epidemiologic link, typical x-ray findings, absence of another etiology), resample the patient and repeat the test. A positive result confirms infection. If the second test is negative, consider serologic testing (see below).</td>
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<td>The pooled sensitivity has been estimated to be 87.8%, with the specificity estimated to be in the range of 87.7% to 100%.</td>
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<tr>
<td>Interpret test results with caution. Evidence for the use of RT-PCR in the diagnosis of COVID-19 is still emerging, and uncertainties about its efficacy and accuracy remain. It is not fully understood whether a positive result always represents infectious virus, especially at high cycle thresholds. Interpreting the result depends on the accuracy of the test itself, and the pre- and post-test probabilities of disease. When the pretest probability is low, positive results should be interpreted with caution, and ideally a second specimen tested for confirmation. The lower the prevalence of disease in a given population, the lower the post-test probability. False-positive results can be caused by a laboratory error or a cross-reaction with antibodies formed by current and past exposure to seasonal human coronavirus infections (e.g., common cold), and are more likely when the prevalence of disease is moderate to low. Preliminary estimates of the false-positive rate in the UK are in the range of 0.8% to 4%. False-negative rates of between 2% and 29% have been reported. A systematic review found that the false-negative rate varied across studies from 1.8% to 58% (median 11%); however, there was substantial and largely unexplained heterogeneity across studies. Rapid molecular tests are available. They may be suitable for some testing scenarios (e.g., where obtaining test results within 2 hours will enable appropriate decision-making); however, evidence is limited. Also collect nasopharyngeal swabs to rule out influenza and other respiratory infections according to local guidance. It is important to note that coinfections can occur, and a positive test for a non-COVID-19 pathogen does not rule out COVID-19. When SARS-CoV-2 and influenza viruses are cocirculating, test for both</td>
<td></td>
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<tr>
<td>Meta-analyses of paired saliva samples and nasopharyngeal swabs found no statistically significant difference in sensitivity or specificity between these specimens for SARS-CoV-2 detection, especially in the ambulatory setting. Sensitivity was not significantly different among asymptomatic people and outpatients. Methods of saliva collection may affect sensitivity.</td>
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<td>© BMJ Publishing Group Ltd 2021. All rights reserved.</td>
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<td>Test</td>
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<tr>
<td><strong>DIAGNOSIS</strong></td>
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<td>Test</td>
<td>Result</td>
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<tr>
<td>viruses in all hospitalized patients with acute respiratory illness, and only test for influenza virus in outpatients with acute respiratory illness if the results will change clinical management of the patient.</td>
<td>may show low oxygen saturation (cut-off depends on local guidelines)</td>
</tr>
<tr>
<td>Single-test multiplex assays to diagnose infection caused by influenza A, influenza B, and SARS-CoV-2 are available in some countries.</td>
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<tr>
<td><strong>pulse oximetry</strong></td>
<td></td>
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<tr>
<td>• Clinicians should be aware that patients with COVID-19 can develop “silent hypoxia”: their oxygen saturations can drop to low levels and precipitate acute respiratory failure without the presence of obvious symptoms of respiratory distress.</td>
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</tr>
<tr>
<td>• Pulse oximetry may be available as part of remote monitoring in the community. Evidence suggests that patients who may benefit most from monitoring are those who are symptomatic and are either over 65 years of age, or are under 65 years of age and are extremely clinically vulnerable to COVID-19. [NHS England: pulse oximetry to detect early deterioration of patients with COVID-19 in primary and community care settings] (<a href="https://www.england.nhs.uk/coronavirus/publication/pulse-oximetry-to-detect-early-deterioration-of-patients-with-covid-19-in-primary-and-community-care-settings">https://www.england.nhs.uk/coronavirus/publication/pulse-oximetry-to-detect-early-deterioration-of-patients-with-covid-19-in-primary-and-community-care-settings</a>)</td>
<td></td>
</tr>
<tr>
<td>• The UK National Institute for Health and Care Excellence recommends using oxygen saturation levels below 94% for adults (or below 88% for adults with known type 2 respiratory failure) and below 91% for children in room air at rest to identify people who are seriously ill.</td>
<td></td>
</tr>
<tr>
<td>• Pulse oximeters may exhibit suboptimal accuracy in certain populations. Limited data from studies with small numbers of participants suggest that skin pigmentation can affect pulse oximeter accuracy. In one study, occult hypoxemia (defined in the study as arterial oxygen saturation &lt;88% by arterial blood gas despite oxygen saturation of 92% to 98% on pulse oximetry) was not detected by pulse oximetry nearly three times more frequently in Black patients compared with White patients.</td>
<td></td>
</tr>
<tr>
<td>• The US Food and Drug Administration (FDA) has warned that multiple factors can affect the accuracy of a pulse oximeter reading (e.g., poor circulation, skin pigmentation, skin thickness, skin temperature, current tobacco use, use of fingernail polish). The FDA recommends considering accuracy limitations when using a pulse oximeter to assist in diagnosis and treatment decisions, and to use trends in readings over time rather than absolute cut-offs if possible.</td>
<td></td>
</tr>
<tr>
<td>• Only a small proportion of patients have other organ dysfunction, meaning that after the initial phase of acute deterioration, traditional methods of recognizing further deterioration (e.g., National Early Warning Score 2 [NEWS2] scores) may not help predict those patients who go on to develop respiratory failure.</td>
<td></td>
</tr>
<tr>
<td>• Pulse oximeters can be used at home to detect hypoxia. Home pulse oximetry requires clinical support (e.g., regular phone contact from a health professional in a virtual ward setting). [BMJ Practice Pointer: remote management of covid-19 using home pulse oximetry and virtual ward support] (<a href="https://www.bmj.com/content/372/bmj.n677">https://www.bmj.com/content/372/bmj.n677</a>)</td>
<td></td>
</tr>
<tr>
<td>• Order in patients with severe illness as indicated to detect hypercarbia or acidosis.</td>
<td></td>
</tr>
<tr>
<td>• Recommended in patients with respiratory distress and cyanosis who have low oxygen saturation (SpO₂ &lt;90%).</td>
<td></td>
</tr>
<tr>
<td><strong>ABG</strong></td>
<td></td>
</tr>
<tr>
<td>may show low partial oxygen pressure</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Result</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>CBC</strong></td>
<td>lymphopenia; leukocytosis; leukopenia; thrombocytopenia; decreased eosinophils; decreased hemoglobin</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Lymphopenia, leukocytosis, thrombocytopenia, decreased eosinophils, decreased hemoglobin, and high neutrophil-to-lymphocyte ratio are significantly associated with severe disease, and may be useful for predicting disease progression. Severe cases are more likely to present with lymphopenia and thrombocytopenia, but not leukopenia. [679]</td>
<td></td>
</tr>
<tr>
<td>• Elevated red blood cell distribution width (at admission and increasing during hospitalization) has been associated with a significantly increased risk of mortality in hospitalized patients. [680]</td>
<td></td>
</tr>
<tr>
<td>• Absolute counts of major lymphocyte subsets, particularly CD4+ and CD8+ T-cell counts, are significantly decreased in patients with severe disease. [681]</td>
<td></td>
</tr>
<tr>
<td>• Late-phase thrombocytopenia (i.e., occurring 3 weeks or more after symptom onset) has been reported but is uncommon. [682]</td>
<td></td>
</tr>
<tr>
<td><strong>comprehensive metabolic panel</strong></td>
<td>elevated liver enzymes; elevated total bilirubin; renal impairment; hypoalbuminemia; electrolyte derangements</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated liver enzymes, total bilirubin, creatinine, and blood urea nitrogen, and hypoalbuminemia are significantly associated with severe disease, and may be useful for predicting disease progression. [679]</td>
<td></td>
</tr>
<tr>
<td>• Hypokalemia has been reported in 54% of patients. [683] Hypocalcemia has been reported in 63% of patients, and is associated with poor outcomes. [684] [685] Other electrolyte derangements may be present.</td>
<td></td>
</tr>
<tr>
<td><strong>blood glucose level</strong></td>
<td>variable</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Fasting hyperglycemia independently predicts poor prognosis and is associated with an increased risk of mortality, regardless of whether or not the patient has diabetes. [686] [687]</td>
<td></td>
</tr>
<tr>
<td>• Hypoglycemia has also been associated with increased mortality in a retrospective cohort study. [688]</td>
<td></td>
</tr>
<tr>
<td><strong>coagulation screen</strong></td>
<td>elevated D-dimer; prolonged prothrombin time; elevated fibrinogen</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated D-dimer, elevated fibrinogen (and fibrin degradation product), and prolonged prothrombin time are significantly associated with severe disease, and may be useful for predicting disease progression. [679] [689]</td>
<td></td>
</tr>
<tr>
<td>• The risk of severe disease and mortality is 2-fold and 4-fold higher, respectively, in patients with elevated D-dimer levels. [690] Patients with very high D-dimer levels have an increased risk of thrombosis. [691] [692]</td>
<td></td>
</tr>
<tr>
<td><strong>cardiac biomarkers</strong></td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated creatine kinase-myocardial band (CK-MB), B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP), and troponin are associated with severe disease and mortality, and may be useful for predicting disease progression or survival. [693]</td>
<td></td>
</tr>
<tr>
<td>• CK-MB has been found to be elevated in mild disease in children. The significance of this is unknown. [569]</td>
<td></td>
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<tr>
<td>Test</td>
<td>Result</td>
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<td>----------------------------------</td>
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</tr>
<tr>
<td><strong>serum C-reactive protein</strong></td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated C-reactive protein is significantly associated with severe disease, and may be useful for predicting disease progression. [679]</td>
<td></td>
</tr>
<tr>
<td>• Patients with elevated C-reactive protein at the time of initial presentation were more likely to have acute kidney injury, venous thromboembolism, critical illness, and in-hospital mortality during their hospital stay compared with patients with lower levels. [694]</td>
<td></td>
</tr>
<tr>
<td><strong>serum erythrocyte sedimentation rate</strong></td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Commonly elevated in patients with COVID-19. [567]</td>
<td></td>
</tr>
<tr>
<td><strong>serum lactate dehydrogenase</strong></td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated serum lactate dehydrogenase is significantly associated with severe disease, and may be useful for predicting disease progression. [679]</td>
<td></td>
</tr>
<tr>
<td><strong>serum interleukin-6 level</strong></td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated interleukin-6 level is significantly associated with severe disease, and may be useful for predicting disease progression. [679]</td>
<td></td>
</tr>
<tr>
<td>• Less likely to be elevated in children. [695]</td>
<td></td>
</tr>
<tr>
<td><strong>serum procalcitonin</strong></td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated serum procalcitonin is significantly associated with severe disease, and may be useful for predicting disease progression. [679]</td>
<td></td>
</tr>
<tr>
<td>• Elevated serum procalcitonin may be more common in children. [557]</td>
<td></td>
</tr>
<tr>
<td>• May be elevated in patients with secondary bacterial infection. [49] [50]</td>
<td></td>
</tr>
<tr>
<td>• There is insufficient evidence to recommend routine procalcitonin testing to guide decisions about the use of antibiotics. However, it may be helpful in identifying whether there is a bacterial infection, although the most appropriate procalcitonin threshold is uncertain. [561]</td>
<td></td>
</tr>
<tr>
<td><strong>serum ferritin level</strong></td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated ferritin is significantly associated with severe disease, and may be useful for predicting disease progression. [696]</td>
<td></td>
</tr>
<tr>
<td>• May indicate development of cytokine release syndrome. [697]</td>
<td></td>
</tr>
<tr>
<td><strong>serum amyloid A level</strong></td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression. [698]</td>
<td></td>
</tr>
<tr>
<td><strong>serum creatine kinase and myoglobin</strong></td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Order in patients with severe illness.</td>
<td></td>
</tr>
<tr>
<td>• Elevated serum creatine kinase and myoglobin are significantly associated with severe disease, and may be useful for predicting disease progression. [679]</td>
<td></td>
</tr>
<tr>
<td><strong>blood and sputum cultures</strong></td>
<td>negative for bacterial infection</td>
</tr>
</tbody>
</table>
### Test

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collect blood and sputum specimens for culture in patients with severe or critical disease to rule out other causes of lower respiratory tract infection and sepsis, especially patients with an atypical epidemiologic history.[2]</td>
<td></td>
</tr>
<tr>
<td>Specimens should be collected prior to starting empiric antimicrobials if possible.</td>
<td></td>
</tr>
<tr>
<td><strong>chest x-ray</strong></td>
<td>unilateral or bilateral lung infiltrates</td>
</tr>
<tr>
<td>• Order in all patients with suspected pneumonia.</td>
<td></td>
</tr>
<tr>
<td>• Unilateral lung infiltrates are found in 25% of patients, and bilateral lung infiltrates are found in 75% of patients.[49] [50] [616]</td>
<td></td>
</tr>
<tr>
<td>• Chest x-ray is moderately sensitive and moderately specific for the diagnosis of COVID-19. Pooled results found that chest x-ray correctly diagnosed COVID-19 in 80.6% of people who had the disease. However, it incorrectly identified COVID-19 in 28.5% of people who did not have the disease.[617]</td>
<td></td>
</tr>
<tr>
<td>• Although chest x-ray appears to have a lower sensitivity compared with chest CT, it has the advantages of being less resource-intensive, associated with lower radiation doses, easier to repeat sequentially, and portable.[618]</td>
<td></td>
</tr>
</tbody>
</table>
Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>computed tomography (CT) chest</td>
<td>ground-glass opacity in isolation or coexisting with other findings</td>
</tr>
<tr>
<td></td>
<td>(e.g., consolidation, interlobular septal thickening, crazy-paving pattern); bilateral, peripheral/subpleural, posterior distribution with a lower lobe predominance</td>
</tr>
<tr>
<td>• Consider a CT scan of the chest. Consult local guidance on whether to perform a CT scan. The British Society of Thoracic Imaging (BSTI) recommends CT imaging in patients with clinically suspected COVID-19 who are seriously ill if chest x-ray is uncertain or normal. [BSTI: radiology decision tool for suspected COVID-19] (<a href="https://www.bsti.org.uk/media/resources/files/NHSE_BSTI_APPROVED_Radiology_on_CoVid19_v6_modified1__Read-Only.pdf">https://www.bsti.org.uk/media/resources/files/NHSE_BSTI_APPROVED_Radiology_on_CoVid19_v6_modified1__Read-Only.pdf</a>) Some institutions in the UK recommend a more pragmatic approach for patients with high clinical suspicion of COVID-19, with chest CT recommended only after two indeterminate or normal chest x-rays in combination with a negative RT-PCR test.[620] The American College of Radiology recommends reserving CT for hospitalized, symptomatic patients with specific clinical indications for CT, and emphasizes that a normal chest CT does not mean that a patient does not have COVID-19 and that an abnormal chest CT is not specific for COVID-19 diagnosis.[621]</td>
<td></td>
</tr>
<tr>
<td>• Chest CT is sensitive and moderately specific for the diagnosis of COVID-19. Pooled results found that chest CT correctly diagnosed COVID-19 in 87.9% of people who had the disease. However, it incorrectly identified COVID-19 in 20% of people who did not have the disease. Therefore, chest CT may have more utility for excluding COVID-19 than for differentiating it from other causes of respiratory illness.[617] Accuracy appears to be lower among children; however, there are limited data in this population.[619]</td>
<td></td>
</tr>
<tr>
<td>• Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[622] Some patients may present with a normal chest finding despite a positive RT-PCR.[623] Results of RT-PCR testing may be false-negative, so patients with typical CT findings should have repeat RT-PCR testing to confirm the diagnosis.[624] CT imaging abnormalities may be present in asymptomatic patients. The pooled estimate of the rate of positive chest CT findings in asymptomatic cases was 47.6% (mainly ground-glass opacity).[625]</td>
<td></td>
</tr>
<tr>
<td>• Abnormal chest CT findings have been reported in up to 97% of hospitalized patients.[627] The most common findings are ground-glass opacity, either in isolation or coexisting with other findings such as consolidation, interlobular septal thickening, or crazy-paving pattern. The most common distribution pattern is bilateral, peripheral/subpleural, posterior distribution of the opacities, with a lower lobe predominance. Extensive/multilobar involvement with consolidations is more common in older patients and those with severe disease. Pulmonary vascular enlargement, interlobular or intralobular septal thickening, adjacent pleural thickening, air bronchograms, subpleural lines, crazy-paving pattern, bronchus distortion, bronchiectasis, vascular retraction sign, and halo sign are atypical features. Pleural effusion, pericardial effusion, cavitation, pneumothorax, and mediastinal lymphadenopathy have also been reported rarely.[628] Ground-glass opacity has the highest diagnostic performance for COVID-19 pneumonia, followed by ground-glass opacity plus consolidation, and consolidation only.[629]</td>
<td></td>
</tr>
<tr>
<td>• Children frequently have normal or mild CT chest findings. The most common signs in children are patchy ground-glass opacity and, less frequently, nonspecific patchy shadows, areas of consolidation, and a</td>
<td></td>
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<tr>
<td>Test</td>
<td>Result</td>
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</tr>
<tr>
<td>halo sign. Abnormalities are more common in the lower lobes and are predominantly unilateral. Pleural effusion is rare. [632] Ground-glass opacity and peribronchial thickening were the most prevalent findings in infants younger than 1 year of age. [633]</td>
<td>• CT scan generally shows an increase in the size, number, and density of ground-glass opacities in the early follow-up period, with a progression to mixed areas of ground-glass opacities, consolidations, and crazy paving peaking at day 10 to 11, before gradually resolving or persisting as patchy fibrosis. [628]</td>
</tr>
<tr>
<td>• The positive predictive value was low (1.5% to 30.7%) in low-prevalence regions, and the negative predictive value ranged from 95.4% to 99.8% in one meta-analysis. Pooled sensitivity and specificity were 94% to 96% and 37%, respectively. [699] [700] The simultaneous presence of ground-glass opacity and other features of viral pneumonia had optimum performance in the detection of COVID-19 (sensitivity 90% and specificity 89%). [630]</td>
<td></td>
</tr>
<tr>
<td>• CT is more sensitive than RT-PCR in detecting COVID-19, but has a very low specificity. [701] In a cohort of over 1000 patients in a hyperendemic area in China, chest CT had a higher sensitivity for diagnosis of COVID-19 compared with initial RT-PCR from swab samples (88% versus 59%). Improvement of abnormal CT findings also preceded change from RT-PCR positivity to negativity in this cohort during recovery. The sensitivity of chest CT was 97% in patients who ultimately had positive RT-PCR results. However, in this setting, 75% of patients with negative RT-PCR results also had positive chest CT findings. Of these patients, 48% were considered highly likely cases, while 33% were considered probable cases. [702]</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Result</td>
</tr>
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</tr>
<tr>
<td>Transverse CT scans from a 32-year-old man, showing ground-glass opacity and consolidation of lower lobe of right lung near the pleura on day 1 after symptom onset (top panel), and bilateral ground-glass opacity and consolidation on day 7 after symptom onset. Xu XW et al. BMJ. 2020;368:m606</td>
<td>positive for SARS-CoV-2 virus antibodies; seroconversion or a rise in antibody titers in paired sera</td>
</tr>
</tbody>
</table>

**serology**

- Important: a positive test for spike protein IgM or IgG could indicate either prior infection or prior vaccination with a COVID-19 vaccine. To evaluate for evidence of prior infection in an individual who has received a vaccine, a test that specifically evaluates IgM or IgG to the nucleocapsid protein should be used. A positive nucleocapsid protein-based assay indicates prior infection. Antibody testing is not currently recommended to assess immunity following vaccination.[371][703][704][374]
- Cannot be used as a standalone diagnostic for acute infections; however, may be useful in various settings (e.g. negative molecular testing, diagnosing patients with late presentation or prolonged symptoms, serosurveillance studies).[534][603]
- [BMJ practice pointer: testing for SARS-CoV-2 antibodies](https://www.bmj.com/content/370/bmj.m3325)
- The World Health Organization (WHO) recommends collecting a paired serum sample, one specimen in the acute phase and one in the convalescent phase 2 to 4 weeks later, in patients where infection is strongly suspected and the RT-PCR result is negative. Seroconversion or a rise in antibody titers in paired sera help to confirm whether the infection is recent and/or acute. If the initial sample tests positive, this could be due to a past infection that is not related to the current illness. Seroconversion may be faster and more robust in patients with severe disease compared with those with mild disease or asymptomatic infection.[534]
### Test

<table>
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<tr>
<th>Test</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>• The Centers for Disease Control and Prevention recommends serologic testing as a method to support the diagnosis of illness or complications in the following situations: a positive antibody test at least 7 days following acute illness onset in people with a previous negative antibody test (i.e., seroconversion) and who did not receive a positive viral test may indicate SARS-CoV-2 infection between the dates of the negative and positive antibody tests; a positive antibody test can help support a diagnosis when patients present with complications of COVID-19 illness, such as multisystem inflammatory syndrome and other post-acute sequelae of COVID-19.[604]</td>
<td></td>
</tr>
<tr>
<td>• The Infectious Diseases Society of America recommends serologic testing in the following circumstances: evaluation of patients with a high clinical suspicion for infection when molecular diagnostic testing is negative and at least 2 weeks have passed since symptom onset; evaluation of pediatric inflammatory multisystem syndrome in children; and serosurveillance studies.[605]</td>
<td></td>
</tr>
<tr>
<td>• Antibody responses to SARS-CoV-2 typically occur during the first 1 to 3 weeks of illness, with the seroconversion time of IgG antibodies often being earlier than that of IgM antibodies.[606] [607]</td>
<td></td>
</tr>
<tr>
<td>• The estimated sensitivity of antibody tests ranged from 18.4% to 96.1% (the lowest reported sensitivity was from a point-of-care test, although a sensitivity &lt;50% was reported for one laboratory test), and specificity ranged from 88.9% to 100%. Estimates of diagnostic accuracy need to be interpreted with caution in the absence of a definitive reference standard to diagnose or rule out COVID-19.[588]</td>
<td></td>
</tr>
<tr>
<td>• Limitations of testing: serologic testing cannot be used to determine acute infection; results do not indicate the presence or absence of current or previous infection with certainty; reliable diagnosis is often only possible in the recovery phase when opportunities for management or interruption of transmission have passed; cross-reactivity with other coronaviruses, which can result in false-positive results.[534] [604]</td>
<td></td>
</tr>
<tr>
<td>• While rapid antibody detection kits have been approved for the qualitative detection of SARS-CoV-2 IgG/IgM antibodies in serum, plasma, or whole blood, the WHO does not recommend the use of these tests outside of research settings as they have not been validated as yet.[609]</td>
<td></td>
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</tbody>
</table>

### antigen test

<table>
<thead>
<tr>
<th>antigen test</th>
<th>positive for SARS-CoV-2 virus antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rapid diagnostic test. Relies on direct detection of SARS-CoV-2 viral proteins in nasal swabs and other respiratory specimens using a lateral flow immunoassay. Results are usually available in less than 30 minutes. While antigen tests are substantially less sensitive than RT-PCR, they offer the possibility of rapid, inexpensive, and early detection of the most infectious cases in appropriate settings. If used, testing should occur within the first 5 to 7 days following the onset of symptoms. The World Health Organization recommends antigen testing only in certain scenarios where RT-PCR is unavailable or where prolonged turnaround times preclude clinical utility, provided that the test meets the minimum performance requirements of ≥80% sensitivity and ≥97% specificity compared with an RT-PCR reference assay.[611]</td>
<td></td>
</tr>
<tr>
<td>• The US Food and Drug Administration has warned that false-positive results can occur with antigen tests, including when users do not follow the instructions for use, and that the number of false-positive tests increases as disease prevalence decreases.[612]</td>
<td></td>
</tr>
</tbody>
</table>
### Test

- A Cochrane review found that rapid antigen tests vary in sensitivity. Sensitivity was higher in the first week after symptom onset in symptomatic people (78.3%), compared with the second week of symptoms (51%). Sensitivity was higher in those with RT-PCR cycle threshold values ≤25 (94.5%), compared with those with cycle threshold values >25 (40.7%). Sensitivity was higher in symptomatic people (72%), compared with asymptomatic people (58.1%). Sensitivity also varied between brands of tests. Positive predictive values suggest that confirmatory testing of those with positive results may be considered in low prevalence settings. Evidence for testing in asymptomatic cohorts was limited, and no studies assessed the accuracy of repeated lateral flow testing or self-testing.\[613\]

- Rapid, lateral flow antigen tests for home use are available over-the-counter in some countries.[705]

- Laboratory-based (nonrapid) antigen tests are also available in some countries.
# Emerging tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>reverse transcription loop-mediated isothermal amplification</strong></td>
<td><strong>positive for SARS-CoV-2 viral RNA</strong></td>
</tr>
<tr>
<td>(RT-LAMP)</td>
<td></td>
</tr>
<tr>
<td>• A similar process to RT-PCR, but uses constant temperatures and</td>
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<tr>
<td>produces more viral DNA compared with RT-PCR. While simple and</td>
<td></td>
</tr>
<tr>
<td>quick, it is a newer technology and there is less evidence for its</td>
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<tr>
<td>use. Assays for SARS-CoV-2 have been developed and are being</td>
<td></td>
</tr>
<tr>
<td>evaluated.[634] [635] [636]</td>
<td></td>
</tr>
<tr>
<td>• An at-home test kit that provides rapid results within 30 minutes</td>
<td></td>
</tr>
<tr>
<td>has been approved in the US under an emergency-use authorization for</td>
<td></td>
</tr>
<tr>
<td>self-testing at home that provides rapid results.[706]</td>
<td></td>
</tr>
<tr>
<td><strong>lung ultrasound</strong></td>
<td><strong>B-lines; pleural line abnormalities</strong></td>
</tr>
<tr>
<td>• Lung ultrasound is used as a diagnostic tool in some centers as an</td>
<td></td>
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<tr>
<td>alternative to chest x-ray and chest CT. Although there is only very</td>
<td></td>
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<tr>
<td>low-certainty evidence supporting its diagnostic accuracy, it might</td>
<td></td>
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<tr>
<td>be helpful as a supplemental or alternate imaging modality.[618]</td>
<td></td>
</tr>
<tr>
<td>• Ultrasound is sensitive but not specific for the diagnosis of</td>
<td></td>
</tr>
<tr>
<td>COVID-19. Pooled results found that lung ultrasound correctly</td>
<td></td>
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<tr>
<td>diagnosed COVID-19 in 86.4% of people with the disease. However, it</td>
<td></td>
</tr>
<tr>
<td>incorrectly diagnosed COVID-19 in 45% of people who did not have</td>
<td></td>
</tr>
<tr>
<td>the disease. Therefore, ultrasound may have more utility for</td>
<td></td>
</tr>
<tr>
<td>excluding COVID-19 than for differentiating it from other causes of</td>
<td></td>
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<tr>
<td>respiratory illness.[617]</td>
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<tr>
<td>• B-lines are the prominent pattern in patients with COVID-19,</td>
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<tr>
<td>occurring with a pooled frequency of 97%. Pleural line abnormalities</td>
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<tr>
<td>are also common with a pooled frequency of 70%. While these</td>
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<td>findings are not specific for COVID-19, they increase the</td>
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<tr>
<td>likelihood of disease in the context of a characteristic clinical</td>
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<tr>
<td>presentation. Other findings include consolidations, pleural</td>
<td></td>
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<tr>
<td>thickening, and pleural effusion.[637]</td>
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<tr>
<td>• Has the advantages of portability, bedside evaluation, reduced</td>
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<tr>
<td>healthcare worker exposure, easier sterilization process, absence</td>
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<tr>
<td>of ionizing radiation exposure, and repeatability during follow-up.</td>
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<tr>
<td>It may also be more readily available in resource-limited settings.</td>
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<tr>
<td>However, it also has some limitations (e.g., it is unable to</td>
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<tr>
<td>discern chronicity of a lesion) and other imaging modalities may be</td>
<td></td>
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<tr>
<td>required.[637]</td>
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<tr>
<td>• May be used in pregnant women and children.[638] [639]</td>
<td></td>
</tr>
<tr>
<td>• Possible roles include: reducing nosocomial transmission;</td>
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<tr>
<td>monitoring progress of patients; and a possible role in</td>
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<tr>
<td>subpopulations who are vulnerable but are not suitable for CT</td>
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<td>(e.g., pregnant women).[640]</td>
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<tr>
<td>• [BSTI: lung ultrasound (LUS) for COVID-19 patients in critical</td>
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<tr>
<td>care areas] (<a href="https://www.bsti.org.uk/media/resources/files/Lung_US_print_out_and_scoring_proforma.pdf">https://www.bsti.org.uk/media/resources/files/Lung_US_print_out_and_scoring_proforma.pdf</a>)</td>
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<td><strong>calprotectin</strong></td>
<td><strong>elevated</strong></td>
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<tr>
<td>• Calprotectin is an emerging biomarker of interest. Calprotectin</td>
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<td>levels often increase following infection or trauma, and in</td>
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<tr>
<td>inflammatory disease. Serum/fecal calprotectin levels have been</td>
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<tr>
<td>demonstrated to be significantly elevated in COVID-19 patients with</td>
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<tr>
<td>severe disease, and it may have prognostic significance.[707]</td>
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## Differentials

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
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</table>
| **Community-acquired pneumonia** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
• Differentiating COVID-19 from community-acquired bacterial pneumonia is not usually possible from signs and symptoms. However, patients with bacterial pneumonia are more likely to have rapid development of symptoms and purulent sputum. They are less likely to have myalgia, anosmia, or pleuritic pain.[708] | • Blood or sputum culture or molecular testing: positive for causative organism.  
• RT-PCR: negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA (coinfections are possible).  
• CT chest: centrilobular nodules, mucoid impactions.[709] |
| **Influenza infection**        | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
• Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.  
• Incubation period is shorter.[710] Symptoms typically peak during the first 3 to 7 days of illness with influenza, compared with week 2 or 3 of illness with COVID-19.[711]  
• More common in children.[711] Children with COVID-19 tend to be older, and are more likely to have comorbidities, fever, gastrointestinal symptoms, headache, and chest pain compared with those with influenza.[712]  
• Fever is less common. Rhinorrhea, sore throat, myalgia, headache, and dyspnea are more | • Only testing can distinguish between influenza infection and COVID-19 and identify coinfection. When SARS-CoV-2 and influenza viruses are cocirculating, test for both viruses in all hospitalized patients with acute respiratory illness, and only test for influenza virus in outpatients with acute respiratory illness if the results will change clinical management of the patient.[715]  
• RT-PCR: positive for influenza A or B viral RNA; negative for SARS-CoV-2 viral RNA (coinfections are possible).  
• Chest x-ray: less likely to be abnormal.[710]  
• CT chest: there is emerging evidence that CT can be used for differentiating between influenza and COVID-19. COVID-19 patients are more likely to have rounded or linear opacities, crazy-paving sign, vascular enlargement, and interlobular septal |
<table>
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<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
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<tbody>
<tr>
<td>Common cold</td>
<td>• Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset. • Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms. However, fever is less common, and headache, rhinorrhea, myalgia, and sore throat are more common. Patients may have a greater number of general symptoms.[713]</td>
<td>• RT-PCR: positive for causative organism; negative for SARS-CoV-2 viral RNA (coinfections are possible).</td>
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<tr>
<td>Other viral or bacterial respiratory infections</td>
<td>• Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset. • Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms. • Adenovirus and <em>Mycoplasma</em> should be considered in clusters of pneumonia patients, especially in closed settings such as military camps and schools.</td>
<td>• Blood or sputum culture of molecular testing: positive for causative organism. • RT-PCR: negative for SARS-CoV-2 viral RNA (coinfections are possible).</td>
</tr>
</tbody>
</table>

New-onset smell and/or taste disorders were less common in a case-control study.[714] Thickening, but less likely to have nodules, tree-in-bud sign, bronchiectasis, and pleural effusion.[716] [717] Inflammatory markers and coagulation screen: there is emerging evidence that inflammatory markers (lactate dehydrogenase, erythrocyte sedimentation rate, C-reactive protein) and coagulation parameters are not as high in patients with influenza compared with COVID-19.[718]
## Coronavirus disease 2019 (COVID-19)

### Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
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</table>
| **Aspiration pneumonia**         | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
   • Differentiating COVID-19 from aspiration pneumonia is not usually possible from signs and symptoms. | • RT-PCR: negative for SARS-CoV-2 viral RNA (coinfections are possible).  
   • CT chest: difficult to distinguish on CT; however, anterior lung involvement may be more suggestive of COVID-19 pneumonia.[719] |
| **Pneumocystis jirovecii pneumonia** | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
   • Differentiating COVID-19 from pneumocystis jirovecii pneumonia is not usually possible from signs and symptoms.  
   • Patients are usually immunocompromised (e.g., HIV positive) and duration of symptoms may be longer. | • Sputum culture: positive for *Pneumocystis*.  
   • RT-PCR: negative for SARS-CoV-2 viral RNA (coinfections are possible).  
   • CT chest: ground-glass opacity is usually more diffusely distributed with a tendency to spare the subpleural regions.[709] |
| **Middle East respiratory syndrome (MERS)** | • Travel history to the Middle East or contact with a confirmed case of MERS.  
   • Differentiating COVID-19 from MERS is not possible from signs and symptoms.  
   • Initial data suggest that the clinical course of COVID-19 is less severe and the case fatality rate is lower compared with MERS. | • Reverse-transcriptase polymerase chain reaction (RT-PCR): positive for MERS-CoV viral RNA. |
| **Severe acute respiratory syndrome (SARS)** | • There have been no cases of SARS reported since 2004. | • RT-PCR: positive for severe acute respiratory syndrome coronavirus (SARS-CoV) viral RNA. |
| **Avian influenza A (H7N9) virus infection** | • May be difficult to differentiate based on epidemiologic history as avian influenza H7N9 is endemic in China.  
   • Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas), or living in an area | • RT-PCR: positive for H7-specific viral RNA. |
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<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
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| Avian influenza A (H5N1) virus infection       | • Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.  
  • Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas), or living in an area when avian influenza is endemic. | • RT-PCR: positive for H5N1 viral RNA.                                                             |
| Pulmonary tuberculosis                         | • Consider diagnosis in endemic areas, especially in patients who are immunocompromised.  
  • History of symptoms is usually longer.  
  • Presence of night sweats and weight loss may help to differentiate. | • Chest x-ray: fibronodular opacities in upper lobes with or without cavitation; atypical pattern includes opacities in middle or lower lobes, or hilar or paratracheal lymphadenopathy, and/or pleural effusion.  
  • Sputum acid-fast bacilli smear and sputum culture: positive.  
  • Molecular testing: positive for *Mycoplasma tuberculosis*. |
| Febrile neutropenia                             | • Suspect neutropenic sepsis in patients with a history of recent systemic anticancer treatment who present with fever (with or without respiratory symptoms) as this can be rapid and life-threatening.  
  • Symptoms of COVID-19 and neutropenic sepsis may be difficult to differentiate at initial presentation. | • CBC: neutropenia.  
  • RT-PCR: negative for SARS-CoV-2 viral RNA. |

**Criteria**

**Case definitions**

Various case definitions are available:

Screening

Management of contacts

Definition

- The World Health Organization defines a contact as a person who has experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:[721]
  - Face-to-face contact with a probable or confirmed case within 3 feet (1 meter) and for more than 15 minutes
  - Direct physical contact with a probable or confirmed case
  - Direct care for a patient with probable or confirmed COVID-19 without using recommended personal protective equipment
  - Other situations as indicated by local risk assessments.

- The Centers for Disease Control and Prevention (CDC) defines a close contact as someone who has been within 6 feet (2 meters) of an infected person for at least 15 minutes over a 24-hour period, beginning 2 days before symptom onset (or 2 days before testing in asymptomatic patients).[195]
- Consult local guidance as definitions of a contact may vary depending on local public health advice.

Quarantine periods

- Contacts should remain in quarantine and monitor their health for up to 14 days from the last day of possible contact with the infected person.
- In the UK, Public Health England recommends a 10-day quarantine (or self-isolation) period after a potential exposure (it was reduced from 14 days to 10 days on 14 December 2020).[722]
- The CDC has shortened the minimum quarantine time after a potential exposure from 14 days to 7-10 days. Quarantine can end after day 7 if the patient tests negative and no symptoms have been reported during the quarantine period. Quarantine can end after day 10 without testing and if no symptoms have been reported during the quarantine period. Additional criteria (e.g., symptom monitoring, mask wearing) should continue until day 14 in both cases.[723]
- Consult local guidance for recommended quarantine locations and timeframes as recommendations vary depending on local public health advice.

Screening of travelers

Exit and entry screening may be recommended in countries where borders are still open, particularly when repatriating nationals from affected areas. Travelers returning from affected areas should self-monitor for symptoms for 14 days and follow local protocols of the receiving country. Some countries may require travelers to enter mandatory quarantine in a designated location (e.g., a hotel). Travelers who develop symptoms are advised to contact their local healthcare provider, preferably by phone.[724] One study of 566 repatriated Japanese nationals from Wuhan City found that symptom-based screening performed poorly and missed presymptomatic and asymptomatic cases. This highlights the need for testing and follow-up.[725]
**Drive-through screening centers**

Drive-through screening centers have been set up in some countries for safer and more efficient screening. The testee does not leave their car throughout the entire process, which includes registration and questionnaire, exam, specimen collection, and instructions on what to do after. This method has the advantage of increased testing capacity and prevention of cross-infection between testees in the waiting space.[726]

**Temperature screening**

There is little scientific evidence to support temperature screening with thermal cameras or temperature screening products as a reliable method for the detection of COVID-19 or any other febrile illness, especially if used as the main method of testing.[727]

Noncontact infrared thermometers generally have reasonable sensitivity and specificity for detecting fever; however, their performance varies in different settings. Environmental factors (e.g., absolute temperature, variation in temperature, relative humidity) play an important role in the accuracy of the result. False negatives may be seen in people wearing make-up on the target area or who are significantly perspiring. False positives may be seen in people who are pregnant, menstruating, or on hormone replacement therapy, or those who have recently consumed alcohol or hot beverages, or done strenuous physical activity. Also, fever is not present in asymptomatic or presymptomatic people, and may not be present in symptomatic people, which means infected individuals could be missed.[728]

While the forehead is the most feasible site for scanning, it is thought to be more prone to physiologic and environmental variations, and the wrist may be a better option as it may give more stable measurements under different circumstances.[729]

Noncontact infrared thermometers demonstrated variable accuracy levels across populations and had a low sensitivity for temperatures >99.5°F (>37.5°C) in adults compared with temporal artery thermometers. Therefore, they may not be the most accurate device for the mass screening of fever during a pandemic.[730]
Approach

Management predominantly depends on disease severity, and focuses on the following principles: isolation at a suitable location; infection prevention and control measures; symptom management; optimized supportive care; and organ support in severe or critical illness.

Best Practice has published a separate topic on the management of coexisting conditions in the context of COVID-19. [BMJ Best Practice: Management of coexisting conditions in the context of COVID-19](https://bestpractice.bmj.com/topics/en-us/3000190#important-update)

Key recommendations

- Consider whether the patient can be managed at home. Generally, patients with asymptomatic or mild disease can be managed at home or in a community facility.[2]
- Admit patients with moderate or severe disease to an appropriate healthcare facility. Assess adults for frailty on admission. Patients with critical disease require intensive care; involve the critical care team in discussions about admission to critical care when necessary. Monitor patients closely for signs of disease progression.[2] [561]
- Provide symptom relief as necessary. This may include treatments for fever, cough, breathlessness, anxiety, delirium, or agitation.[2] [561]
- Start supportive care according to the clinical presentation. This might include oxygen therapy, intravenous fluids, venous thromboembolism prophylaxis, high-flow nasal oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation. Sepsis and septic shock should be managed according to local protocols.[2]
- Consider empiric antibiotics if there is clinical suspicion of a secondary bacterial infection. Antibiotics may be required in patients with moderate, severe, or critical disease. Give within 1 hour of initial assessment for patients with suspected sepsis or if the patient meets high-risk criteria. Base the regimen on the clinical diagnosis, local epidemiology and susceptibility data, and local treatment guidelines.[2] [561]
- Consider systemic corticosteroid therapy for 7 to 10 days in adults with severe or critical disease. Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with severe and critical disease, and probably reduce the need for invasive ventilation.[3] [743]
- Assess whether the patient requires any rehabilitation or follow-up after discharge. Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.[2]
- For full details and guidance see information below.

Location of care

The decision about location of care depends on various factors including clinical presentation, disease severity, need for supportive care, presence of risk factors for severe disease, and conditions at home (including the presence of vulnerable people). Make the decision on a case-by-case basis using the following general principles.[2]

- Mild disease: manage in a healthcare facility, in a community facility, or at home. Home isolation can be considered in most patients, including asymptomatic patients.
Coronavirus disease 2019 (COVID-19) Management

• Moderate disease: manage in a healthcare facility, in a community facility, or at home. Home isolation can be considered in low-risk patients (i.e., patients who are not at high risk of deterioration).
• Severe disease: manage in an appropriate healthcare facility.
• Critical disease: manage in an intensive/critical care unit.

The location of care will also depend on guidance from local health authorities and available resources. Forced quarantine orders are being used in some countries.

Manage people who require hospitalization and who are at risk of being infected with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant of concern in a single room with en-suite bathroom facilities and appropriate infection control procedures for the duration of their isolation period. In those who test positive, discuss further risk assessment and appropriate case management with the local/regional specialist infectious diseases center.[196]

The strongest risk factors for hospital admission are older age (odds ratio of >2 for all age groups older than 44 years, and odds ratio of 37.9 for people ages 75 years and over), heart failure, male sex, chronic kidney disease, and increased body mass index (BMI).[744] The median time from onset of symptoms to hospital admission is around 7 days.[49] [646]

Children are less likely to require hospitalization, but, if admitted, generally only require supportive care.[21] [745] Risk factors for intensive care admission in children include age <1 month, male sex, preexisting medical conditions, and presence of lower respiratory tract infection signs or symptoms at presentation.[746] The majority of children who require ventilation have underlying comorbidities, most commonly cardiac disease.[747] Children with COVID-19 are reported to have similar hospitalization rates, intensive care admission rates, and mechanical ventilator use compared with those with seasonal influenza.[712]

Overall, 19% of hospitalized patients require noninvasive ventilation, 17% require intensive care, 9% require invasive ventilation, and 2% require extracorporeal membrane oxygenation.[647] The rate of intensive care admission varies between studies; however, a meta-analysis of nearly 25,000 patients found that the admission rate was 32%, and the pooled prevalence of mortality in patients in the intensive care unit was 39%.[748] Another more recent meta-analysis found the mortality rate in patients in the intensive care unit to be 35.5%.[749] The most common reasons for intensive care unit admission are hypoxemic respiratory failure leading to mechanical ventilation and hypotension.[750] Patients admitted to intensive care units were older, were predominantly male, and had a median length of stay of 23 days (range 12 to 32 days).[751] The strongest risk factors for critical illness are oxygen saturation <88%; elevated serum troponin, C-reactive protein, and D-dimer; and, to a lesser extent, older age, BMI >40, heart failure, and male sex.[744] The most common risk factors for intensive care unit mortality were invasive mechanical ventilation, acute kidney injury, and acute respiratory distress syndrome.[752]

Management of mild COVID-19

Patients with suspected or confirmed mild disease (i.e., symptomatic patients meeting the case definition for COVID-19 without evidence of hypoxia or pneumonia) and asymptomatic patients should be isolated to contain virus transmission.[2]

Location of care
• Manage patients in a healthcare facility, in a community facility, or at home. Home isolation can be considered in most patients, with telemedicine or remote visits as appropriate.[2] [3] This decision requires careful clinical judgment and should be informed by an assessment of the patient’s home environment to ensure that: infection prevention and control measures and other requirements can be met (e.g., basic hygiene, adequate ventilation); the caregiver is able to provide care and recognize when the patient may be deteriorating; the caregiver has adequate support (e.g., food, supplies, psychological support); the support of a trained health worker is available in the community.[721]

Isolation period

• Discontinue transmission-based precautions (including isolation) and release patients from the care pathway: 10 days after positive test (asymptomatic patients); 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms (symptomatic patients).[2]
• The Centers for Disease Control and Prevention (CDC) recommends discontinuing home isolation once at least 10 days (or up to 20 days in patients who are severely immunocompromised) have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. In asymptomatic people, the CDC recommends discontinuing home isolation once at least 10 days have passed since the date of a positive test. For severely immunocompromised patients who are asymptomatic, isolation may be discontinued when at least 10 days and up to 20 days have passed since the date of a positive test; consider consultation with infectious diseases specialists and infection control experts. Alternatively, the CDC recommends at least two negative reverse-transcription polymerase chain reaction (RT-PCR) tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients.[753] If the patient is hospitalized, the CDC guidance for discontinuing isolation is the same as for moderate disease (see below).
• Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the self-isolation period is 10 days in patients with milder disease who are managed in the community.[754]

Infection prevention and control

• For patients in home isolation, advise patients and household members to follow appropriate infection prevention and control measures:

Symptom management

• Fever and pain: acetaminophen or ibuprofen are recommended.[2] [561] There is no evidence at present of severe adverse events in COVID-19 patients taking nonsteroidal anti-inflammatory drugs
Coronavirus disease 2019 (COVID-19) Management

- (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilization, long-term survival, or quality of life in patients with COVID-19. Ibuprofen should only be taken at the lowest effective dose for the shortest period needed to control symptoms.

- **Cough:** advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough. A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity.

- **Olfactory dysfunction:** consider treatment (e.g., olfactory training) if olfactory dysfunction persists beyond 2 weeks. Often it improves spontaneously and does not require specific treatment. There is no evidence to support the use of treatments in patients with COVID-19.

**Supportive care**

- Advise patients about adequate nutrition and appropriate rehydration. Advise patients to drink fluids regularly to avoid dehydration. Fluid intake needs can be higher than usual because of fever. However, too much fluid can worsen oxygenation.

- Advise patients to improve air circulation by opening a window or door.

- Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.

- Most children with mild disease can be managed with supportive care alone and will not require any specific therapy.

**Monitor**

- Closely monitor patients with risk factors for severe illness, and counsel patients about signs and symptoms of deterioration or complications that require prompt urgent care (e.g., difficulty breathing, chest pain).

- Pulse oximetry monitoring at home is recommended in symptomatic patients with risk factors for progression to severe disease who are not hospitalized. Patient education and appropriate follow-up are required.

**Corticosteroids**

- The WHO does not recommend systemic corticosteroids in patients with nonsevere disease as they may increase the risk of mortality in these patients. In the UK, the National Institute for Health and Care Excellence does not recommend routinely using systemic corticosteroids in people who do not need supplemental oxygen, unless there is another medical indication to do so. In the US, the National Institutes of Health guidelines panel recommends against the use of systemic corticosteroids in nonhospitalized patients with mild to moderate disease in the absence of another indication.

- Inhaled budesonide is undergoing clinical trials and shows promise. The PRINCIPLE trial has reported a 3-day median benefit in self-reported recovery for patients in the community setting who received inhaled budesonide. The impact on hospitalization rates or mortality has not been established.

- At this point in time, inhaled budesonide is not being recommended for routine use, but the UK Medicines and Healthcare products Regulatory Agency states that it can be considered on a case-by-case basis in eligible patients who meet all of the following criteria (and who do not meet specific exclusion criteria):
Management

Patients with onset of symptoms within the past 14 days, and symptoms are ongoing
• Confirmation of diagnosis by molecular testing within the past 14 days
• Age 65 years and over, or age 50 to 64 years with a comorbidity consistent with a long-term health condition.

• The European Medicines Agency advises that there is currently insufficient evidence that inhaled corticosteroids are beneficial.[767]
• Results from the PRINCIPLE trial are yet to be published. This use is off-label.

Management of moderate COVID-19

Patients with suspected or confirmed moderate disease (i.e., clinical signs of pneumonia but no signs of severe pneumonia) should be isolated to contain virus transmission.[2]

Location of care

• Manage patients in a healthcare facility, in a community facility, or at home. Home isolation, with telemedicine or remote visits as appropriate, can be considered in low-risk patients. Manage patients at high risk of deterioration in a healthcare facility.[2] [3]

Isolation period

• Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.[2]
• The CDC recommends discontinuing isolation once at least 10 days (not severely immunocompromised) or up to 20 days (severely immunocompromised) have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. In asymptomatic people, the CDC recommends discontinuing isolation once at least 10 days (not severely immunocompromised) or up to 20 days (severely immunocompromised) have passed since the date of a positive test. Severely immunocompromised patients may produce replication-competent virus beyond 20 days and require additional testing and consultation with infectious diseases specialists and infection control experts before discontinuing isolation. Alternatively, the CDC recommends at least two negative RT-PCR tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients.[768] If the patient is isolated at home, the CDC guidance for discontinuing isolation is the same as for mild disease (see above).
• Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the isolation period is 14 days from a positive test in hospitalized patients, and 10 days in patients with milder disease who are managed in the community. Immunocompetent patients who tested positive on RT-PCR and have completed their 14-day isolation period are exempt from testing prior to hospital discharge if they are within 90 days from their initial illness onset or test, unless they develop new symptoms.[754]

Infection prevention and control
• Implement local infection prevention and control procedures when managing patients with COVID-19. For patients in home isolation, advise patients and household members to follow appropriate infection prevention and control measures (see above).

Symptom management and supportive care

• Manage symptoms and provide supportive care as appropriate (see above).
• Most children with moderate disease can be managed with supportive care alone and will not require any specific therapy. [3]

Antibiotics

• Do not offer an antibiotic for preventing secondary bacterial pneumonia in people with COVID-19. [561]
• Consider empiric antibiotics only if there is clinical suspicion of secondary bacterial infection. Start treatment as soon as possible, and refer to local guidelines for choice of regimen. [2] [3] [561]
• Antibiotics may also be considered in older people (particularly those in long-term care facilities) and children <5 years of age to provide empiric antibiotic treatment for possible pneumonia. [2]
• Advise patients to seek medical help without delay if their symptoms do not improve, or worsen rapidly or significantly. Reconsider whether the person has signs and symptoms of more severe disease on reassessment, and whether to refer them to hospital, other acute community support services, or palliative care services. [561]

Monitor

• Closely monitor patients for signs or symptoms of disease progression.
• If the patient is being managed at home, counsel them about signs and symptoms of deterioration or complications that require prompt urgent care (e.g., difficulty breathing, chest pain). Pulse oximetry monitoring at home is recommended in symptomatic patients with risk factors for progression to severe disease who are not hospitalized. Patient education and appropriate follow-up are required. [2]
• If the patient is being managed in hospital, monitor patients closely for signs of clinical deterioration using medical early warning scores (e.g., National Early Warning Score 2 [NEWS2]), and respond immediately with appropriate supportive care interventions. [2]

Corticosteroids

• The WHO does not recommend systemic corticosteroids in patients with nonsevere disease as they may increase the risk of mortality in these patients. [743] In the UK, the National Institute for Health and Care Excellence does not recommend routinely using systemic corticosteroids in people who do not need supplemental oxygen, unless there is another medical indication to do so. [561] In the US, the National Institutes of Health guidelines panel recommends against the use of corticosteroids in nonhospitalized patients with mild to moderate disease in the absence of another indication. [3]
• Inhaled budesonide is undergoing clinical trials and shows promise. [764] The PRINCIPLE trial has reported a 3-day median benefit in self-reported recovery for patients in the community setting who received inhaled budesonide. [765] The impact on hospitalization rates or mortality has not been established.
• At this point in time, inhaled budesonide is not being recommended for routine use, but the UK Medicines and Healthcare products Regulatory Agency states that it can be considered on a case-
by-case basis in eligible patients who meet all of the following criteria (and who do not meet specific exclusion criteria):[766]

- Patients with onset of symptoms within the past 14 days, and symptoms are ongoing
- Confirmation of diagnosis by molecular testing within the past 14 days
- Age 65 years and over, or age 50 to 64 years with a comorbidity consistent with a long-term health condition.
- The European Medicines Agency advises that there is currently insufficient evidence that inhaled corticosteroids are beneficial.[767]
- Results from the PRINCIPLE trial are yet to be published. This use is off-label.

Management of severe COVID-19

Patients with suspected or confirmed severe disease are at risk of rapid clinical deterioration.[2]

- Severe disease in adults is defined as having clinical signs of pneumonia plus at least one of the following:
  - Respiratory rate >30 breaths/minute
  - Severe respiratory distress
  - SpO₂ <90% on room air
- Severe disease in children is defined as having clinical signs of pneumonia plus at least one of the following:
  - Central cyanosis or SpO₂ <90%
  - Severe respiratory distress
  - General danger signs: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions
  - Fast breathing (<2 months: ≥60 breaths per minute; 2-11 months: ≥50 breaths per minute; 1-5 years: ≥40 breaths per minute).

Location of care

- Manage patients in an appropriate healthcare facility under the guidance of a specialist team.[2]
- Use the Clinical Frailty Scale (CFS) to assess baseline health and inform discussions on treatment expectations when appropriate and within an individualised assessment of frailty. [Clinical Frailty Scale](https://www.scfn.org.uk/clinical-frailty-scale) Do not use the CFS for younger people, or for people with stable long-term disabilities (e.g., cerebral palsy), learning disabilities, or autism. Make an individualized assessment of frailty in these people, using clinical assessment and alternative scoring methods.[561]
  - A meta-analysis found that an increase in CFS was associated with an increase in mortality (each 1-point increase in CFS was associated with a 12% increase in mortality).[769]
  - Patients with a score between 6-9 or 4-5 had significantly increased mortality compared with those with a score of 1-3. In the context of COVID-19, a score of 1-3 may be considered a lower risk of mortality, a score of 4-5 moderate risk, and a score of 6-9 high risk.[770]
Management

• However, some studies suggest that a more nuanced understanding of frailty and outcomes is needed, and you should exercise caution in placing too much emphasis on the influence of frailty alone when discussing prognosis in older people.[771]

Isolation period

• Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.[2]
• The CDC recommends discontinuing isolation once at least 10 days and up to 20 days have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. Consider consultation with infection control experts before discontinuing isolation. Severely immunocompromised patients may produce replication-competent virus beyond 20 days and require additional testing and consultation with infectious diseases specialists and infection control experts before discontinuing isolation. Alternatively, the CDC recommends at least two negative RT-PCR tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients.[768]
• Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the isolation period is 14 days from a positive test in hospitalized patients. Immunocompetent patients who tested positive on RT-PCR and have completed their 14-day isolation period are exempt from testing prior to hospital discharge if they are within 90 days from their initial illness onset or test, unless they develop new symptoms.[754]

Infection prevention and control

• Implement local infection prevention and control procedures when managing patients with COVID-19.

Oxygen

• Start supplemental oxygen therapy immediately in any patient with emergency signs (i.e., obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma and/or convulsions), or any patient without emergency signs and SpO₂ <90%.[2] [3] There is no evidence of benefit for oxygen therapy in patients with COVID-19 in the absence of hypoxemia.[772]
• Target SpO₂ to ≥94% during resuscitation in adults and children with emergency signs who require emergency airway management and oxygen therapy. Once the patient is stable, a target SpO₂ >90% in children and nonpregnant adults, and ≥92% to 95% in pregnant women is recommended. Nasal prongs or a nasal cannula are preferred in young children.[2] Some guidelines recommend that SpO₂ should be maintained no higher than 96%.[773]
• Some centers may recommend different SpO₂ targets in order to support prioritization of oxygen flow for the most severely ill patients in hospital. NHS England recommends a target of 92% to 96% (or 90% to 94% if clinically appropriate), for example.[774]
• Consider positioning techniques (e.g., high supported sitting), and airway clearance management to optimize oxygenation and assist with secretion clearance in adults. Consider awake prone positioning (for 8-12 hours/day, broken into shorter periods over the day) in severely ill patients who require supplemental oxygen.[2] [3] Awake prone positioning of nonintubated patients was associated with improvement in oxygen variables (PaO₂/FiO₂, PaO₂, and SpO₂) and respiratory
rate; however, evidence is limited. Further randomized controlled trials are required to study the impact on key parameters (e.g., reduction in mechanical ventilation or mortality).[775]

- Monitor patients closely for signs of progressive acute hypoxemic respiratory failure. Patients who continue to deteriorate despite standard oxygen therapy require advanced oxygen/ventilatory support.[2] [3]

Symptom management and supportive care

- Fluids and electrolytes: use cautious fluid management in adults and children without tissue hypoperfusion and fluid responsiveness as aggressive fluid resuscitation may worsen oxygenation.[2] Correct any electrolyte or metabolic abnormalities, such as hyperglycemia or metabolic acidosis, according to local protocols.[776]

- Fever and pain: acetaminophen or ibuprofen are recommended.[2] [561] There is no evidence at present of severe adverse events in COVID-19 patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilization, long-term survival, or quality of life in patients with COVID-19.[755] [756] [757] [758] [759] [760] [761] Ibuprofen should only be taken at the lowest effective dose for the shortest period needed to control symptoms.

- Cough: advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough. Short-term use of a cough suppressant may be considered in select patients (e.g., if the cough is distressing to the patient) provided there are no contraindications.[561] A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity.[762]

- Breathlessness: keep the room cool, and encourage relaxation, breathing techniques, and changing body positions. Identify and treat any reversible causes of breathlessness (e.g., pulmonary edema, pulmonary embolism, COPD, asthma).[561]

- Anxiety, delirium, and agitation: identify and treat any underlying or reversible causes (e.g., offer reassurance, treat hypoxia, correct metabolic or endocrine abnormalities, address co-infections, minimize use of drugs that may cause or worsen delirium, treat substance withdrawal, maintain normal sleep cycles, treat pain or breathlessness).[2] [561] Low doses of haloperidol (or another suitable antipsychotic) can also be considered for agitation.[2] Nonpharmacologic interventions are the mainstay for the management of delirium when possible, and prevention is key.[777]

- Mouth care: an important part of overall patient care in hospitalized patients who are ventilated or nonventilated and those undergoing step-down or end-of-life care.[778]

- Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia or depression as appropriate.[2]

Venous thromboembolism prophylaxis

- Assess the risk of bleeding as soon as possible after admission, or by the time of the first consultant review, using a suitable risk assessment tool.[561]

- Start venous thromboembolism (VTE) prophylaxis in acutely ill hospitalized adults and adolescents, provided there are no contraindications.[2] [3] [779] [780]

  - The National Institute for Health and Care Excellence in the UK recommends starting as soon as possible and within 14 hours of admission, and continuing for a minimum of 14 days or until discharge.[561]
• For hospitalized children, indications for VTE prophylaxis should be the same as those for children without COVID-19.[3]

• Low molecular weight heparin, unfractionated heparin, or fondaparinux are the recommended options for standard thromboprophylaxis.[2]

• The National Institute for Health and Care Excellence in the UK recommends low molecular weight heparin first-line, with fondaparinux or unfractionated heparin reserved for patients who cannot have low molecular weight heparin.[561]

• A retrospective observational study found that enoxaparin is associated with lower 28-day mortality, lower rates of bleeding events, lower intensive care admission rates, and shorter hospital stays compared with unfractionated heparin; however, the study had important limitations and further research is required.[781]

• Unfractionated heparin is contraindicated in patients with severe thrombocytopenia. Fondaparinux is recommended in patients with a history of heparin-induced thrombocytopenia. Mechanical thromboprophylaxis (e.g., intermittent pneumatic compression devices) is recommended if anticoagulation is contraindicated or not available.[780][782]

• The optimal dose is yet to be determined. Standard prophylaxis doses are generally recommended over intermediate- or full treatment-dose regimens in patients without an established indication for higher-dose anticoagulation. However, this recommendation varies and you should consult your local guidelines.

• The World Health Organization recommends standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing in patients without an established indication for higher-dose anticoagulation.[2]

• The National Institute for Health and Care Excellence in the UK recommends clinicians consider a treatment dose of a low molecular weight heparin in young people and adults who are likely to be in hospital for at least 3 days and need supplemental oxygen (but who are not yet receiving high-flow oxygen, continuous positive airway pressure, noninvasive ventilation, or invasive mechanical ventilation), unless contraindicated. This is because of fewer deaths and less likelihood of needing intensive care with this dose compared with a standard prophylaxis dose without a notable increase in major bleeding, although the evidence for this recommendation is weak. Treatment should be for a minimum of 14 days or until discharge, and the dose may need to be reduced if the clinical circumstances change (such as a need for advanced respiratory support). For those who do not need supplemental oxygen, follow standard VTE prophylaxis guidelines.[561]

• The National Institutes of Health guidelines panel recommends prophylactic-dose anticoagulation, and states that there are insufficient data to recommend increased anticoagulant doses for VTE prophylaxis in COVID-19 patients outside the setting of a clinical trial.[3]

• Dose adjustments may be required in patients with extremes of body weight or renal impairment.[561]

• For patients who are already on an anticoagulant for another condition, continue the patient’s current therapeutic dose unless contraindicated by a change in clinical circumstances. Consider switching to low molecular weight heparin if the patient’s clinical condition is deteriorating and the patient is not currently on low molecular weight heparin.[561]
Coronavirus disease 2019 (COVID-19) Management

• Monitor patients for signs and symptoms suggestive of thromboembolism and proceed with appropriate diagnostic and management pathways if clinically suspected.[2] If the patient’s clinical condition changes, assess the risk of VTE, reassess the bleeding risk, and review VTE prophylaxis.[561]

• Continue until hospital discharge.[2] Routine post-discharge VTE prophylaxis is not generally recommended, except in certain high-risk patients.[3] [779] [780] Ensure patients who require VTE prophylaxis after discharge are able to use it correctly or have arrangements made for someone to help them.[561]

• There is currently insufficient evidence to determine the risks and benefits of prophylactic anticoagulation in hospitalized patients with COVID-19.[783]

  • A systematic review and meta-analysis found that the pooled odds of mortality between anticoagulated and nonanticoagulated hospitalized patients were similar, but lower in the standard prophylactic-dose group. Prophylactic-dose anticoagulation significantly decreased the odds of in-hospital death by 17% compared with no anticoagulation. Mortality increased in the intermediate- to therapeutic-dose group with an increased risk of major bleeding.[784]

  • Clinicians should rely on pre-COVID-19 evidence-based principles of anticoagulation management combined with rational approaches to address clinical challenges.[779]

Antimicrobials

• Do not offer antibiotics for preventing or treating pneumonia if SARS-CoV-2, another virus, or a fungal infection is likely to be the cause.[561] There is insufficient evidence to recommend empiric broad-spectrum antibiotics in the absence of another indication.[3]

• Consider empiric antibiotics if there is clinical suspicion of secondary bacterial infection. Give within 1 hour of initial assessment for patients with suspected sepsis or if the patient meets high-risk criteria (or within 4 hours of establishing a diagnosis of secondary bacterial pneumonia); do not wait for microbiology results. Base the regimen on the clinical diagnosis (e.g., community-acquired pneumonia, hospital-acquired pneumonia, sepsis), local epidemiology and susceptibility data, and local treatment guidelines.[2] [3] [561]

• Consider seeking specialist advice for people who: are immunocompromised; have a history of infection with resistant organisms; have a history of repeated infective exacerbations of lung disease; are pregnant; or are receiving advanced respiratory or organ support. Seek specialist advice if there is a suspicion that the person has an infection with multidrug-resistant bacteria and may need a different antibiotic, or there is clinical or microbiologic evidence of infection and the person's condition does not improve as expected after 48 to 72 hours of antibiotic treatment.[561]

• Reassess antibiotic use daily. De-escalate empiric therapy on the basis of microbiology results and clinical judgment. Regularly review the possibility of switching from intravenous to oral therapy. Duration of treatment should be as short as possible (e.g., 5 to 7 days). Antibiotic stewardship programs should be in place.[2] A meta-analysis found that the prevalence of antibiotic prescribing in patients with COVID-19 was 75%, which is significantly higher than the estimated prevalence of bacterial coinfection. Therefore, unnecessary antibiotic use is likely to be high in these patients.[785]

• Treat laboratory-confirmed coinfections (e.g., malaria, tuberculosis, influenza) as appropriate according to local protocols.[2] The treatment of influenza is the same in all patients regardless of SARS-CoV-2 coinfection. Start empiric treatment with oseltamivir in hospitalized patients who are
suspected of having either or both infections as soon as possible without waiting for influenza test results. Antiviral therapy can be stopped once influenza has been ruled out.[3]

Corticosteroids

- The WHO strongly recommends systemic corticosteroid therapy (low-dose intravenous or oral dexamethasone or hydrocortisone) for 7 to 10 days in adults with severe or critical disease. This recommendation is based on two meta-analyses that pooled data from eight randomized trials (over 7000 patients), including the UK RECOVERY trial. Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with severe and critical disease. They also probably reduce the need for invasive ventilation. There is no evidence directly comparing dexamethasone and hydrocortisone. The harms of treatment in this context are considered to be minor. It is unclear whether these recommendations can be applied to children or those who are immunocompromised. The WHO does not recommend corticosteroids in patients with nonsevere disease as they may increase the risk of mortality in these patients.[743] [786] [787] [788] [789] There is also evidence that corticosteroids probably increase ventilator-free days (moderate certainty).[790] [791]

- In the UK, the National Institute for Health and Care Excellence recommends offering dexamethasone (or an alternative such as hydrocortisone or prednisone when dexamethasone cannot be used or is unavailable) to people who need supplemental oxygen to meet their prescribed oxygen saturation levels, or who have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it. Treatment is for up to 10 days unless there is a clear indication to stop early.[561]

- In Europe, the European Medicines Agency has endorsed the use of dexamethasone for patients with severe disease who require oxygen therapy or mechanical ventilation.[792]

- In the US, the National Institutes of Health guidelines panel recommends dexamethasone, either alone or in combination with remdesivir (see the Emerging section for information on remdesivir), in hospitalized adults who require supplemental oxygen. The panel recommends against using dexamethasone in adults who do not require supplemental oxygen. Alternative corticosteroids may be used in situations where dexamethasone is not available. It is not routinely recommended for pediatric patients who require only low levels of oxygen support (i.e., via a nasal cannula only). Use of dexamethasone for the treatment of severe disease in children who are profoundly immunocompromised has not been evaluated, may be harmful, and therefore should be considered only on a case-by-case basis.[3] The Infectious Diseases Society of America supports the use of dexamethasone in hospitalized patients with severe disease.[793]

- Monitor patients for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, reactivation of latent infections) and assess for drug-drug interactions.[3]

Monitor

- Monitor patients closely for signs of clinical deterioration, and respond immediately with appropriate supportive care interventions.[2]

Discharge and rehabilitation

- Routinely assess older patients for mobility, functional swallow, cognitive impairment, and mental health concerns, and based on that assessment determine whether the patient is ready for discharge, and whether the patient has any rehabilitation and follow-up requirements.[2]

Palliative care
Management of critical COVID-19

Patients with critical disease (i.e., presence of acute respiratory distress syndrome, sepsis, or septic shock) should be admitted or transferred to an intensive/critical care unit. Use existing care bundles (i.e., three or more evidence-informed practices delivered together and consistently to improve care), chosen locally by the hospital or intensive care unit and adapted as necessary for local circumstances.[2]

Location of care

- Manage patients in an intensive/critical care unit under the guidance of a specialist team.[2]
- Discuss the risks, benefits, and potential outcomes of treatment options with patients and their families, and allow them to express preferences about their management. Take their wishes and expectations into account when considering the ceiling of treatment. Use decision support tools if available. Put treatment escalation plans in place, and discuss any existing advance care plans or advance decisions to refuse treatment with patients who have preexisting advanced comorbidities.[561]

Isolation period

- Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.[2]
- The CDC recommends discontinuing isolation once at least 10 days and up to 20 days have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. Consider consultation with infection control experts before discontinuing isolation. Severely immunocompromised patients may produce replication-competent virus beyond 20 days and require additional testing and consultation with infectious diseases specialists and infection control experts before discontinuing isolation. Alternatively, the CDC recommends at least two negative RT-PCR tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients.[768]
- Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the isolation period is 14 days from a positive test in hospitalized patients. Immunocompetent patients who tested positive on RT-PCR and have completed their 14-day isolation period are exempt from testing prior to hospital discharge if they are within 90 days from their initial illness onset or test, unless they develop new symptoms.[754]
Management

Infection prevention and control

- Implement local infection prevention and control procedures when managing patients with COVID-19.

High-flow nasal oxygen or noninvasive ventilation

- Consider a trial of high-flow nasal oxygen (HFNO) or noninvasive ventilation (e.g., continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) in selected patients with mild acute respiratory distress syndrome (ARDS). Consider awake prone positioning (for 8-12 hours/day, broken into shorter periods over the day) in severely ill patients who require HFNO or noninvasive ventilation.[2] Awake prone positioning of nonintubated patients was associated with improvement in oxygen variables (PaO₂/FiO₂, PaO₂, and SpO₂) and respiratory rate; however, evidence is limited. Further randomized controlled trials are required to study the impact on key parameters (e.g., reduction in mechanical ventilation or mortality).[775]

- Airborne precautions are recommended for these interventions (including bubble CPAP) due to uncertainty about the potential for aerosolization.[2] Novel methods to protect clinicians without access to standard personal protective equipment during aerosol-generating procedures have been suggested.[795] [796] [797] [798]

- Patients with hypercapnia, hemodynamic instability, multi-organ failure, or abnormal mental status should generally not receive HFNO, although emerging data suggests that it may be safe in patients with mild to moderate and nonworsening hypercapnia. Patients with hypoxemic respiratory failure and hemodynamic instability, multi-organ failure, or abnormal mental status should not receive these treatments in place of other options such as invasive ventilation.[2]

- There is ongoing debate about the optimal mode of respiratory support before mechanical ventilation.[799] NHS England recommends CPAP as the preferred form of noninvasive ventilation in patients with hypoxemic (type 1) respiratory failure. It doesn't advocate the use of HFNO based on a lack of efficacy, oxygen use (HFNO can place a strain on oxygen supplies with the risk of site supply failure), and infection spread.[800] Other guidelines recommend HFNO over noninvasive ventilation, unless HFNO is not available.[3] [773] Despite the trend to avoid HFNO, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[801]

- Early CPAP may provide a bridge to invasive mechanical ventilation. Reserve the use of BiPAP for patients with hypercapnic acute on chronic ventilatory failure (type 2 respiratory failure).[800]

- Indirect and low-certainty evidence suggests that noninvasive ventilation probably reduces mortality in patients with COVID-19, similar to mechanical ventilation, but may increase the risk of viral transmission.[802] [803]

- Monitor patients closely for acute deterioration. If patients do not improve after a short trial of these interventions they require urgent endotracheal intubation.[2] [773]

- More detailed guidance on the management of ARDS in COVID-19 is beyond the scope of this topic; consult a specialist for further guidance.

Mechanical ventilation

- Consider endotracheal intubation and invasive mechanical ventilation in patients who are acutely deteriorating despite advanced oxygen/noninvasive ventilatory support measures.[2] [3]

- Two-thirds of patients who required critical care in the UK had mechanical ventilation within 24 hours of admission.[804] In New York, 33% of hospitalized patients developed respiratory failure leading to mechanical ventilation. These patients were more likely to be male, have obesity, and have elevated inflammatory markers and liver function tests.[542] Patients spent an average of 18
days on a ventilator (range 9-28 days). Patients who required invasive mechanical ventilation had an 36% to 88% mortality rate in studies.

- Endotracheal intubation should be performed by an experienced provider using airborne precautions. Intubation by video laryngoscopy is recommended if possible. Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require preoxygenation with 100% FiO₂ for 5 minutes.

- Mechanically ventilated patients with ARDS should receive a lung-protective, low tidal volume/low inspiratory pressure ventilation strategy (lower targets are recommended in children). A higher positive end-expiratory pressure (PEEP) strategy is preferred over a lower PEEP strategy in moderate to severe ARDS. However, individualization of PEEP, where the patient is monitored for beneficial or harmful effects and driving pressure during titration with consideration of the risks and benefits of PEEP titration, is recommended. NHS England recommends a low PEEP strategy in patients with normal compliance where recruitment may not be required.

- Although some patients with COVID-19 pneumonia meet the criteria for ARDS, there is some discussion about whether COVID-19 pneumonia is its own specific disease with atypical phenotypes. Anecdotol evidence suggests that the main characteristic of the atypical presentation is the dissociation between well-preserved lung mechanics and the severity of hypoxemia. However, this approach has been criticized. It has been argued that an evidence-based approach extrapolating data from ARDS not related to COVID-19 is the most reasonable approach for intensive care of COVID-19 patients. As a consequence of this, some clinicians have warned that protocol-driven ventilator use may be causing lung injury in some patients, and that ventilator settings should be based on physiologic findings rather than using standard protocols. High PEEP may have a detrimental effect on patients with normal compliance. PEEP should always be carefully titrated.

- Consider prone ventilation in patients with severe ARDS for 12 to 16 hours per day. Pregnant women in the third trimester may benefit from being placed in the lateral decubitus position. Caution is required in children. Lung recruitment maneuvers are suggested, but staircase recruitment maneuvers are not recommended.

- More detailed guidance on the management of ARDS in COVID-19, including sedation and the use of neuromuscular blockade during ventilation, is beyond the scope of this topic; consult a specialist for further guidance.

**Inhaled pulmonary vasodilator**

- Consider a trial of an inhaled pulmonary vasodilator in adults who have severe ARDS and hypoxemia despite optimizing ventilation. Taper off if there is no rapid improvement in oxygenation.

**Extracorporeal membrane oxygenation**

- Consider extracorporeal membrane oxygenation (ECMO) according to availability and expertise if the above methods fail. ECMO is not suitable for all patients, and only those who meet certain inclusion criteria may be considered for ECMO.

- There is insufficient evidence to recommend either for or against the routine use of ECMO.

  - The estimated 60-day survival rate of ECMO-rescued patients with COVID-19 (31%) was similar to that of previous studies of ECMO for severe ARDS in one study.
Coronavirus disease 2019 (COVID-19) Management

- An international cohort study of 1035 patients found that both the estimated mortality 90 days after ECMO initiation and mortality in those who achieved a final outcome of death or discharge were <40%, consistent with previously reported survival rates in acute hypoxemic respiratory failure.[825]
- A multicenter cohort study in France reported a 90-day survival rate of 46%. Factors associated with improved 90-day survival included earlier ECMO initiation, younger age, no pre-ECMO renal dysfunction, and treatment in centers managing at least 30 venovenous ECMO cases annually.[826]
- The estimated 60-day survival rate of ECMO-rescued patients with COVID-19 (31%) was similar to that of previous studies of ECMO for severe ARDS.[824] An international cohort study of 1035 patients found that both the estimated mortality 90 days after ECMO initiation and mortality in those who achieved a final outcome of death or discharge were <40%, consistent with previously reported survival rates in acute hypoxemic respiratory failure.[825]
- Single-access, dual-stage venovenous ECMO with early extubation appears to be safe and effective in patients with COVID-19 respiratory failure.[827]

Management of septic shock/sepsis

- The management of sepsis and septic shock in patients with COVID-19 is beyond the scope of this topic. See the Complications section.

Symptom management and supportive care

- Consider fluid and electrolyte management, antimicrobial treatment, VTE prophylaxis, and symptom management as appropriate (see above).
- For VTE prophylaxis, unfractionated heparin is preferred over fondaparinux in critically ill patients if low molecular weight heparin cannot be used.[780]

- The UK National Institute for Health and Care Excellence (NICE) does not recommend treatment-dose low molecular weight heparin for VTE prophylaxis for patients receiving advanced respiratory support unless the patient is part of a nationally approved clinical trial because it is likely to cause harm in this group. NICE recommends reducing the dose to a locally agreed intermediate or standard dose and reassessing VTE and bleeding risks daily in patients who progress to needing high-flow oxygen, continuous positive airway pressure, noninvasive or invasive mechanical ventilation, or palliative care.[561]
- NHS England recommends that therapeutic doses should not be offered unless there is a standard indication for therapeutic anticoagulation, as trials show that therapeutic doses do not improve clinical outcome of severe disease in the critical care setting.[828]
- Some guidelines recommend that escalated doses can be considered in critically ill patients.[779] [571]
- A multicenter randomized controlled trial found that intermediate-dose prophylactic anticoagulation did not result in a significant difference in the primary outcome of a composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or 30-day mortality compared with standard-dose prophylactic anticoagulation among patients admitted to the intensive care unit. These results do not support the routine empiric use of intermediate-dose prophylactic anticoagulation in unselected patients admitted to the intensive care unit.[829]

Corticosteroids
• Consider systemic corticosteroids for the management of critically ill patients (see above).

• In the US, the National Institutes of Health guidelines panel recommends dexamethasone, either alone or in combination with remdesivir (see the Emerging section for information on remdesivir), in hospitalized patients who require high-flow oxygen or noninvasive ventilation. The panel recommends dexamethasone (in combination with tocilizumab - see the Emerging section for information on tocilizumab) in patients on mechanical ventilation or ECMO. The panel recommends using dexamethasone in hospitalized children who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation.[3]

• A meta-analysis found an increased risk of VTE with corticosteroid administration in patients with critical disease. However, no definite findings were available due to the differing corticosteroid regimens and the heterogeneity of the studies.[830]

Discharge and rehabilitation

• Routinely assess intensive care patients for mobility, functional swallow, cognitive impairment, and mental health concerns, and based on that assessment determine whether the patient is ready for discharge, and whether the patient has any rehabilitation and follow-up requirements.[2]

Palliative care

• Palliative care interventions should be made accessible at each institution that provides care for patients with COVID-19. Identify whether the patient has an advance care plan and respect the patient’s priorities and preferences when formulating the patient’s care plan.[2] Follow local palliative care guidelines.

• There is a lack of data on palliative care in patients with COVID-19. However, a rapid systematic review of pharmacologic strategies used for palliative care in these patients, the first international review of its kind, found that a higher proportion of patients required continuous subcutaneous infusions for medication delivery than is typically seen in the palliative care population. Modest doses of commonly used end-of-life medications were required for symptom control. However, these findings should be interpreted with caution due to the lack of data available.[794]

Management of pregnant women

Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, as well as midwifery and mental health and psychosocial support. A woman-centered, respectful, skilled approach to care is recommended.[2] In women with severe or critical disease, the multidisciplinary team should be organized as soon as possible after maternal hypoxemia occurs in order to assess fetal maturity, disease progression, and the best options for delivery.[831]

There are limited data available on the management of pregnant women with COVID-19; however, pregnant women can generally be treated with the same supportive therapies detailed above, taking into account the physiologic changes that occur with pregnancy.[2]

The prevalence of asymptomatic SARS-CoV-2-positive pregnant women admitted for delivery appears to be low (<3% in a cohort in Connecticut, and 0.43% in a cohort in California).[832] [833] Screening women and their delivery partners before admission may not be helpful. More than 15% of asymptomatic maternity patients tested positive for SARS-CoV-2 infection despite having been screened negative using a telephone screening tool in one small observational study in New York. In addition to this, 58% of their asymptomatic support persons tested positive despite being screened negative.[834] Another study
in a New York obstetric population found that 88% of women who tested positive for SARS-CoV-2 at admission were asymptomatic at presentation.[835]

Location of care

- Manage pregnant women in a healthcare facility, in a community facility, or at home. Women with suspected or confirmed mild disease may not require acute care in a hospital unless there is concern for rapid deterioration or an inability to return to hospital promptly.[2] Follow local infection prevention and control procedures as for nonpregnant people.
- Consider home care in women with asymptomatic or mild illness, provided the patient has no signs of potentially severe illness (e.g., breathlessness, hemoptysis, new chest pain/pressure, anorexia, dehydration, confusion), no comorbidities, and no obstetric issues; the patient is able to care for herself; and monitoring and follow-up is possible. Otherwise, manage pregnant women in a hospital setting with appropriate maternal and fetal monitoring whenever possible.[615] [836] [837]
- Postpone routine prenatal or postpartum health visits for women who are in home isolation and reschedule them after the isolation period is completed. Delivery of counseling and care should be conducted via telemedicine whenever possible. Counsel women about healthy diet, mobility and exercise, intake of micronutrients, smoking, and alcohol and substance use. Advise women to seek urgent care if they develop any worsening of illness or danger signs, or danger signs of pregnancy.[2]

Prenatal corticosteroids

- Consider prenatal corticosteroids for fetal lung maturation in women who are at risk of preterm birth (24 to 37 weeks’ gestation). Caution is advised because corticosteroids could potentially worsen the maternal clinical condition, and the decision should be made in conjunction with the multidisciplinary team.[615] [837] [838] The WHO recommends prenatal corticosteroids only when there is no clinical evidence of maternal infection and adequate childbirth and newborn care is available, and in women with mild COVID-19 after assessing the risks and benefits.[2]
- There is no evidence that corticosteroids in the doses prescribed for fetal lung maturation cause any harm in the context of COVID-19, but there is also no evidence of safety. The unknown effect on maternal outcome should be weighed against the neonatal benefit, particularly at later preterm gestations.[839]

Treatments

- Most clinical trials to date have excluded pregnant women. However, potentially effective treatments should not be withheld from pregnant women due to theoretical concerns about the safety of these therapeutic agents in pregnancy. Decisions should be made with a shared decision-making process between the patient and the clinical team.[3]

VTE prophylaxis

- The National Institutes of Health recommends prophylactic dose anticoagulation in pregnant women who are hospitalized with severe disease, provided there are no contraindications to its
use. Anticoagulation during labor and delivery requires specialized care and planning, and should be managed in a similar way to pregnant women with other conditions that require anticoagulation. VTE prophylaxis after discharge is not recommended.[3]

- The Royal College of Obstetricians and Gynaecologists (RCOG) has also published guidance on the prevention of VTE in pregnant women.[839]

Labor and delivery

- Implement local infection prevention and control measures during labor and delivery. Screen birth partners for COVID-19 infection using the standard case definition.[2]
- Individualize mode of birth based on obstetric indications and the woman’s preferences. Vaginal delivery is preferred in women with confirmed infection to avoid unnecessary surgical complications. Induction of labor, interventions to accelerate labor and delivery, and cesarean delivery are generally only recommended when medically justified based on maternal and fetal condition. COVID-19 positive status alone is not an indication for cesarean section.[2] [615] [837]
- Delayed umbilical cord clamping (not earlier than 1 minute after birth) is recommended for improved maternal and infant health and nutrition outcomes. The risk of transmission via blood is thought to be minimal, and there is no evidence that delayed cord clamping increases the risk of viral transmission from the mother to the newborn.[2]
- Consider babies born to mothers with suspected or confirmed infection to be a person under investigation and isolate them from healthy newborns. Test them for infection 24 hours after birth, and again 48 hours after birth.[840]

Newborn care

- Experts are divided on separating mother and baby after delivery; make decisions on a case-by-case basis using shared-decision making.
- A retrospective cohort analysis, the largest series to date, found no clinical evidence of vertical transmission in 101 newborns born to mothers with suspected or confirmed SARS-CoV-2 infection, despite most newborns rooming-in and direct breastfeeding practices. This suggests that separation may not be warranted and breastfeeding appears to be safe.[841]
- The WHO recommends that mothers and infants should remain together unless the mother is too sick to care for her baby. Breastfeeding should be encouraged while applying appropriate infection prevention and control measures (e.g., performing hand hygiene before and after contact with the baby, wearing a mask while breastfeeding).[2] The WHO advises that the benefits of breastfeeding outweigh the potential risks for transmission.[842] Mother-to-infant transmission appears to be rare during rooming-in, provided that adequate droplet and contact precautions are taken.[843]
- The CDC recommends that temporary separation of a newborn from a mother with confirmed or suspected COVID-19 may be considered after weighing the risks and benefits as current evidence suggests the risk of a neonate acquiring infection from its mother is low; healthcare providers should respect maternal autonomy in the medical decision-making process. If separation is not undertaken, measures to minimize the risk of transmission should be implemented.[844] A mother with confirmed infection should be counseled to take all possible precautions to avoid transmission to the infant during breastfeeding (e.g., hand hygiene, wearing a cloth face covering). Expressed milk should be fed to the newborn by a healthy caregiver.[845]
- The RCOG recommends that mothers with confirmed infection and healthy babies are kept together in the immediate postpartum period. It is recommended that the risks and benefits are discussed with neonatologists and families in order to individualize care in babies who may be more susceptible to infection. The RCOG advises that the benefits of breastfeeding outweigh
any potential risks of transmission of the virus through breast milk, and recommends appropriate preventive precautions to limit transmission to the baby.[839]

- The American Academy of Pediatrics (AAP) recommends that mothers and newborns may room-in, with appropriate infection prevention and control precautions, according to usual center practice. However, it may be appropriate to temporarily separate the mother and newborn (or to have the newborn cared for by noninfected caregivers in the mother’s room) when the mother is acutely ill with COVID-19 and cannot care for the infant in a safe way. The AAP strongly supports breastfeeding as the best choice for feeding. Breast milk can be expressed after appropriate hygiene measures and fed by an uninfected caregiver. If the mother chooses to breastfeed the infant themselves, appropriate prevention measures are recommended. After discharge, advise mothers with COVID-19 to practice prevention measures (e.g., hand hygiene, respiratory hygiene/mask) for newborn care until: they are afebrile for 24 hours without the use of antipyretics; at least 10 days have passed since symptoms first appeared (or 10 days since a positive test in asymptomatic women); and symptoms have improved. A newborn with documented infection but no symptoms requires close outpatient follow-up after discharge for 14 days after birth.[840]

Management of people living with HIV

Recommendations for the triage, management, and treatment of COVID-19 in people with HIV are the same as those for the general population. Continue antiretroviral therapy and prophylaxis for opportunistic infections whenever possible, including patients who require hospitalization. Consult with a HIV specialist before adjusting or switching antiretroviral medications, and pay attention to potential drug-drug interactions and overlapping toxicities with COVID-19 treatments.[3]
### Acute Management (summary)

**mild COVID-19**

1st consider home isolation  
plus monitoring  
plus symptom management and supportive care  
adjunct antipyretic/analgesic  
adjunct experimental therapies

**moderate COVID-19**

1st consider home isolation or hospital admission  
plus monitoring  
plus symptom management and supportive care  
adjunct antibiotics  
adjunct antipyretic/analgesic  
adjunct experimental therapies

**severe COVID-19**

1st hospital admission  
plus consider oxygen therapy  
plus symptom management and supportive care  
plus venous thromboembolism prophylaxis  
plus monitoring  
adjunct antibiotics  
adjunct corticosteroid  
adjunct treatment of coinfections  
adjunct antipyretic/analgesic  
adjunct experimental therapies  
adjunct plan for discharge and rehabilitation  
adjunct palliative care

**critical COVID-19**

1st intensive/critical care unit admission  
plus symptom management and supportive care
<table>
<thead>
<tr>
<th>Acute</th>
<th>( summary )</th>
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<tbody>
<tr>
<td>plus</td>
<td>venous thromboembolism prophylaxis</td>
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<tr>
<td>plus</td>
<td>consider high-flow nasal oxygen or noninvasive ventilation</td>
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<tr>
<td>plus</td>
<td>consider invasive mechanical ventilation</td>
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<tr>
<td>adjunct</td>
<td>inhaled pulmonary vasodilator</td>
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<td>adjunct</td>
<td>extracorporeal membrane oxygenation</td>
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<td>adjunct</td>
<td>management of sepsis/septic shock</td>
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<td>adjunct</td>
<td>corticosteroid</td>
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<td>adjunct</td>
<td>treatment of coinfections</td>
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<td>adjunct</td>
<td>experimental therapies</td>
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<td>adjunct</td>
<td>plan for discharge and rehabilitation</td>
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<tr>
<td>adjunct</td>
<td>palliative care</td>
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Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
Coronavirus disease 2019 (COVID-19) Management

### Acute

#### mild COVID-19

1st consider home isolation

» Patients with suspected or confirmed mild disease (i.e., symptomatic patients meeting the case definition for COVID-19 without evidence of hypoxia or pneumonia) and asymptomatic patients should be isolated to contain virus transmission.[2]

» Manage patients in a healthcare facility, in a community facility, or at home. Home isolation can be considered in most patients, with telemedicine or remote visits as appropriate.[2] [3] This decision requires careful clinical judgment and should be informed by an assessment of the patient’s home environment to ensure that: infection prevention and control measures and other requirements can be met (e.g., basic hygiene, adequate ventilation); the caregiver is able to provide care and recognize when the patient may be deteriorating; the caregiver has adequate support (e.g., food, supplies, psychological support); the support of a trained health worker is available in the community.[721] The location of care will depend on guidance from local health authorities and available resources.

» Pregnant women with suspected or confirmed mild disease may not require acute care in a hospital unless there is concern for rapid deterioration or an inability to return to hospital promptly.[2]

» Advise patients and household members to follow appropriate infection prevention and control measures:


» Discontinue transmission-based precautions (including isolation) and release patients from the care pathway: 10 days after positive test (asymptomatic patients); 10 days after
## Acute

Symptom onset plus at least 3 days without fever and respiratory symptoms (symptomatic patients). The Centers for Disease Control and Prevention (CDC) recommends discontinuing home isolation once at least 10 days (or up to 20 days in patients who are severely immunocompromised) have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. In asymptomatic people, the CDC recommends discontinuing home isolation once at least 10 days have passed since the date of a positive test. For severely immunocompromised patients who are asymptomatic, isolation may be discontinued when at least 10 days and up to 20 days have passed since the date of a positive test; consider consultation with infectious diseases specialists and infection control experts. Alternatively, the CDC recommends at least two negative reverse-transcription polymerase chain reaction (RT-PCR tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients.[753] If the patient is hospitalized, CDC guidance for discontinuing isolation is the same as for moderate disease (see below). Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the isolation period is 10 days in patients with milder disease who are managed in the community.[754]

### plus monitoring

Treatment recommended for ALL patients in selected patient group

- Closely monitor patients with risk factors for severe illness and counsel patients about signs and symptoms of deterioration or complications that require prompt urgent care (e.g., difficulty breathing, chest pain).[2] [3]

- Pulse oximetry monitoring at home is recommended in symptomatic patients with risk factors for progression to severe disease who are not hospitalized. Patient education and appropriate follow-up are required.[2]

### plus symptom management and supportive care

Treatment recommended for ALL patients in selected patient group
### Acute

» Advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough. A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity.

» Advise patients about adequate nutrition and appropriate rehydration. Advise patients to drink fluids regularly to avoid dehydration. Fluid intake needs can be higher than usual because of fever. However, too much fluid can worsen oxygenation.

» Advise patients to improve air circulation by opening a window or door.

» Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.

» Consider treatment for olfactory dysfunction (e.g., olfactory training) if it persists beyond 2 weeks. There is no evidence to support the use of these treatments in patients with COVID-19.

» Most children with mild disease can be managed with supportive care alone.

#### Adjunct antipyretic/analgesic

Treatment recommended for SOME patients in selected patient group

<table>
<thead>
<tr>
<th>Primary options</th>
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<tbody>
<tr>
<td><strong>Acetaminophen</strong>: children: 10-15 mg/kg orally every 4-6 hours when required, maximum 75 mg/kg/day; adults: 325-1000 mg orally (immediate-release) every 4-6 hours when required, maximum 4000 mg/day</td>
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<tr>
<td><strong>Ibuprofen</strong>: children 6 months to 11 years of age: 5-10 mg/kg orally every 6-8 hours when required, maximum 40 mg/kg/day; children ≥12 years of age and adults: 200-400 mg orally every 4-6 hours when required, maximum 2400 mg/day</td>
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Acetaminophen or ibuprofen are recommended. There is no evidence at present of severe adverse events in COVID-19.
<table>
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| patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilization, long-term survival, or quality of life in patients with COVID-19.[755] [756] [757] [758] [759] [760] [761]  
» Ibuprofen should only be taken at the lowest effective dose for the shortest period needed to control symptoms. It is not recommended in pregnant women (especially in the third trimester) or children <6 months of age (age cut-offs vary by country).| adjunct experimental therapies  
Treatment recommended for SOME patients in selected patient group  
» Consider appropriate experimental or emerging therapies.  
» Antiviral therapies will have a greater effect early in the course of the disease, whereas immunosuppressive/anti-inflammatory therapies are likely to have a greater effect later in the course of the disease.[3]  
» See the Emerging section for more information.|
| moderate COVID-19 | 1st consider home isolation or hospital admission  
» Patients with suspected or confirmed moderate disease (i.e., clinical signs of pneumonia but no signs of severe pneumonia) should be isolated to contain virus transmission.[2]  
» Manage patients in a healthcare facility, in a community facility, or at home. Home isolation, with telemedicine or remote visits as appropriate, can be considered in low-risk patients. Manage patients at high risk of deterioration and pregnant women in a healthcare facility.[2][3]  
» Implement local infection prevention and control procedures when managing patients with COVID-19. For patients in home isolation, advise patients and household members to follow appropriate infection prevention and control measures:  
» [WHO: home care for patients with suspected or confirmed COVID-19 and management of their contacts] (https://www.who.int/publications-detail/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-
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<td>with-mild-symptoms-and-management-of-contacts</td>
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» Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.[2] The Centers for Disease Control and Prevention (CDC) recommends discontinuing isolation once at least 10 days (not severely immunocompromised) or up to 20 days (severely immunocompromised) have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. In asymptomatic people, the CDC recommends discontinuing isolation once at least 10 days (not severely immunocompromised) or up to 20 days (severely immunocompromised) have passed since the date of a positive test. Severely immunocompromised patients may produce replication-competent virus beyond 20 days and require additional testing and consultation with infectious diseases specialists and infection control experts before discontinuing isolation. Alternatively, the CDC recommends at least two negative reverse-transcription polymerase chain reaction (RT-PCR) tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients.[768] If the patient is isolated at home, CDC guidance for discontinuing isolation is the same as for mild disease (see above). Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the isolation period is 14 days from a positive test in hospitalized patients, and 10 days in patients with milder disease who are managed in the community. Immunocompetent patients who tested positive on RT-PCR and have completed their 14-day isolation period are exempt from testing prior to hospital discharge if they are within 90 days from their initial illness onset or test, unless they develop new symptoms.[754]

plus monitoring
Acute

Treatment recommended for ALL patients in selected patient group

» Closely monitor patients for signs or symptoms of disease progression. If the patient is being managed at home, counsel them about signs and symptoms of deterioration or complications that require prompt urgent care (e.g., difficulty breathing, chest pain). Pulse oximetry monitoring at home is recommended in symptomatic patients with risk factors for progression to severe disease who are not hospitalized. Patient education and appropriate follow-up are required. If the patient is being managed in hospital, monitor patients closely for signs of clinical deterioration using medical early warning scores (e.g., National Early Warning Score 2 [NEWS2]), and respond immediately with appropriate supportive care interventions.[2]  

plus symptom management and supportive care

Treatment recommended for ALL patients in selected patient group

» Advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough.[561] A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity.[762]

» Advise patients about adequate nutrition and appropriate rehydration. Advise patients to drink fluids regularly to avoid dehydration. Fluid intake needs can be higher than usual because of fever. However, too much fluid can worsen oxygenation.[2] [561]

» Advise patients to improve air circulation by opening a window or door.[561]

» Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.[2]

» Consider treatment for olfactory dysfunction (e.g., olfactory training) if it persists beyond 2 weeks. There is no evidence to support the use of these treatments in patients with COVID-19.[763]

» Most children with moderate disease can be managed with supportive care alone.[3]
### Acute

<table>
<thead>
<tr>
<th>Adjunct</th>
<th>Antibiotics</th>
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<tbody>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
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<tr>
<td>» Consider empiric antibiotics only if there is clinical suspicion of secondary bacterial infection. Start treatment as soon as possible, and refer to local guidelines for choice of regimen.[2] [3] [561] The regimen should be based on the clinical diagnosis, local epidemiology and susceptibility data, and local treatment guidelines.</td>
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<tr>
<td>» Antibiotics may also be considered in older people (particularly those in long-term care facilities) and children &lt;5 years of age to provide empiric antibiotic treatment for possible pneumonia.[2]</td>
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<tr>
<td>» Do not offer an antibiotic for preventing secondary bacterial pneumonia in people with COVID-19.[561]</td>
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<tr>
<td>» Advise patients to seek medical help without delay if their symptoms do not improve, or worsen rapidly or significantly. Reconsider whether the person has signs and symptoms of more severe disease on reassessment, and whether to refer them to hospital, other acute community support services, or palliative care services.[561]</td>
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<tr>
<th>Adjunct</th>
<th>Antipyretic/analgesic</th>
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</table>

#### Primary options

- **Acetaminophen**: children: 10-15 mg/kg orally every 4-6 hours when required, maximum 75 mg/kg/day; adults: 325-1000 mg orally (immediate-release) every 4-6 hours when required, maximum 4000 mg/day
- OR
- **Ibuprofen**: children 6 months to 11 years of age: 5-10 mg/kg orally every 6-8 hours when required, maximum 40 mg/kg/day; children ≥12 years of age and adults: 200-400 mg orally every 4-6 hours when required, maximum 2400 mg/day

» Acetaminophen or ibuprofen are recommended.[2] [561] There is no evidence at present of severe adverse events in COVID-19 patients taking nonsteroidal anti-inflammatory
## Acute

drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilization, long-term survival, or quality of life in patients with COVID-19.[755] [756] [757] [758] [759] [760] [761]

» Ibuprofen should only be taken at the lowest effective dose for the shortest period needed to control symptoms. It is not recommended in pregnant women (especially in the third trimester) or children <6 months of age (age cut-offs vary by country).

### adjunct experimental therapies

Treatment recommended for SOME patients in selected patient group

» Consider appropriate experimental or emerging therapies.

» Antiviral therapies will have a greater effect early in the course of the disease, whereas immunosuppressive/anti-inflammatory therapies are likely to have a greater effect later in the course of the disease.[3]

» See the Emerging section for more information.

## Severe COVID-19

### 1st hospital admission

» Patients with suspected or confirmed severe disease are at risk of rapid clinical deterioration and should be admitted to an appropriate healthcare facility under the guidance of a specialist team. Severe disease in adults is defined as having clinical signs of pneumonia plus at least one of the following: respiratory rate >30 breaths/minute, severe respiratory distress, or SpO₂ <90% on room air. Severe disease in children is defined as having clinical signs of pneumonia plus at least one of the following: central cyanosis or SpO₂ <90%, severe respiratory distress, general danger signs (inability to breastfeed or drink, lethargy or unconsciousness, or convulsions), or fast breathing (<2 months: ≥60 breaths per minute; 2-11 months: ≥50 breaths per minute; 1-5 years: ≥40 breaths per minute).[2]

» Use the Clinical Frailty Scale (CFS) to assess baseline health and inform discussions on treatment expectations when appropriate and within an individualised assessment of frailty. [Clinical Frailty Scale](https://www.scfn.org.uk/clinical-frailty-scale) Do not use the CFS for younger people, people with stable long-term
Coronavirus disease 2019 (COVID-19) Management

Acute disabilities (e.g., cerebral palsy), learning disabilities, or autism. Make an individualized assessment of frailty in these people, using clinical assessment and alternative scoring methods.[561] A meta-analysis found that an increase in CFS was associated with an increase in mortality (each 1-point increase in CFS was associated with a 12% increase in mortality).[769] However, some studies suggest that a more nuanced understanding of frailty and outcomes is needed, and you should exercise caution in placing too much emphasis on the influence of frailty alone when discussing prognosis in older people.[771]

» Implement local infection prevention and control procedures when managing patients with COVID-19.

» Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, as well as midwifery and mental health and psychosocial support. A woman-centered, respectful, skilled approach to care is recommended.[2] The multidisciplinary team should be organized as soon as possible after maternal hypoxemia occurs in order to assess fetal maturity, disease progression, and the best options for delivery.[831]

» Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.[2] The Centers for Disease Control and Prevention (CDC) recommends discontinuing isolation once at least 10 days and up to 20 days have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used. Consider consultation with infection control experts before discontinuing isolation. Severely immunocompromised patients may produce replication-competent virus beyond 20 days and require additional testing and consultation with infectious diseases specialists and infection control experts before discontinuing isolation. Alternatively, the CDC recommends at least two negative reverse-transcription polymerase chain reaction (RT-PCR) tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in
<table>
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<tr>
<td>severely immunocompromised patients.[768] Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the isolation period is 14 days from a positive test in hospitalized patients. Immunocompetent patients who tested positive on RT-PCR and have completed their 14-day isolation period are exempt from testing prior to hospital discharge if they are within 90 days from their initial illness onset or test, unless they develop new symptoms.[754] plus consider oxygen therapy Treatment recommended for ALL patients in selected patient group</td>
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<tr>
<td>» Start supplemental oxygen therapy immediately in any patient with emergency signs (i.e., obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma and/or convulsions), or any patient without emergency signs and $\text{SpO}_2 &lt; 90%$.[2] [3]</td>
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<tr>
<td>» Target $\text{SpO}_2$ to $\geq 94%$ during resuscitation in adults and children with emergency signs who require emergency airway management and oxygen therapy. Once the patient is stable, a target $\text{SpO}_2 &gt; 90%$ in children and nonpregnant adults, and $\geq 92%$ to $95%$ in pregnant women, is recommended. Nasal prongs or a nasal cannula are preferred in young children.[2] Some guidelines recommend that $\text{SpO}_2$ should be maintained no higher than 96%.[773]</td>
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<tr>
<td>» Some centers may recommend different $\text{SpO}_2$ targets in order to support prioritization of oxygen flow for the most severely ill patients in hospital. NHS England recommends a target of 92% to 96% (or 90% to 94% if clinically appropriate), for example.[774]</td>
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<tr>
<td>» Consider positioning techniques (e.g., high supported sitting), and airway clearance management to optimize oxygenation and assist with secretion clearance in adults. Consider awake prone positioning (for 8-12 hours/day, broken into shorter periods over the day) in severely ill patients who require supplemental oxygen.[2] [3] Awake prone positioning of nonintubated patients was associated with improvement in oxygen variables ($\text{PaO}_2$/$\text{FiO}_2$, $\text{PaO}_2$, and $\text{SpO}_2$) and respiratory rate; however, evidence is limited. Further randomized controlled trials are required to study the impact on key parameters (e.g., reduction in mechanical ventilation or mortality).[775]</td>
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<td>Acute</td>
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<tr>
<td>» Monitor patients closely for signs of progressive acute hypoxemic respiratory failure.[2] [3] plus symptom management and supportive care</td>
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<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
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<tr>
<td>» Fluids and electrolytes: use cautious fluid management in adults and children without tissue hypoperfusion and fluid responsiveness as aggressive fluid resuscitation may worsen oxygenation.[2] Correct any electrolyte or metabolic abnormalities, such as hyperglycemia or metabolic acidosis, according to local protocols.[776]</td>
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<tr>
<td>» Cough: advise patients to avoid lying on their back as this makes coughing ineffective. Use simple measures first (e.g., a teaspoon of honey in patients ages 1 year and older) to help cough. Short-term use of a cough suppressant may be considered in select patients (e.g., if the cough is distressing to the patient) provided there are no contraindications.[561] A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory tract infection symptoms, particularly cough frequency and severity.[762]</td>
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<tr>
<td>» Breathlessness: keep the room cool, and encourage relaxation, breathing techniques, and changing body positions. Identify and treat any reversible causes of breathlessness (e.g., pulmonary edema, pulmonary embolism, COPD, asthma). Consider a trial of oxygen, if available.[561]</td>
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<tr>
<td>» Anxiety, delirium, and agitation: identify and treat any underlying or reversible causes (e.g., offer reassurance, treat hypoxia, correct metabolic or endocrine abnormalities, address coinfections, minimize use of drugs that may cause or worsen delirium, treat substance withdrawal, maintain normal sleep cycles, treat pain or breathlessness).[2] [561] Low doses of haloperidol (or another suitable antipsychotic) can be considered for agitation.[2] Nonpharmacologic interventions are the mainstay for the management of delirium when possible, and prevention is key.[777]</td>
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<tr>
<td>» Mouth care: an important part of overall patient care in hospitalized patients who are ventilated or nonventilated and those undergoing step-down or end-of-life care.[778]</td>
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### Acute

<table>
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<tr>
<th>Plus</th>
<th>venous thromboembolism prophylaxis</th>
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<tr>
<td>Treatment recommended for <strong>ALL</strong> patients in selected patient group</td>
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</table>

#### Primary options

- **enoxaparin**: consult specialist for guidance on dose
- **dalteparin**: consult specialist for guidance on dose

#### Secondary options

- **fondaparinux**: consult specialist for guidance on dose
- **heparin**: consult specialist for guidance on dose

#### Management

- Mental health symptoms: provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia or depression as appropriate.\(^2\)
- **Assess the risk of bleeding as soon as possible after admission, or by the time of the first consultant review, using a suitable risk assessment tool.\(^{561}\)**
- **Start venous thromboembolism (VTE) prophylaxis in acutely ill hospitalized adults and adolescents, provided there are no contraindications.\(^2\) \(^3\) \(^{779}\) \(^{780}\)** The UK National Institute for Health and Care Excellence (NICE) recommends starting as soon as possible and within 14 hours of admission, and continuing for a minimum of 14 days or until discharge.\(^{561}\)** For hospitalized children, indications for VTE prophylaxis should be the same as those for children without COVID-19.\(^3\)
- Low molecular weight heparin, unfractionated heparin, or fondaparinux are the recommended options for standard thromboprophylaxis.\(^2\)** NICE recommends low molecular weight heparin first-line, with fondaparinux or unfractionated heparin reserved for patients who cannot have low molecular weight heparin.\(^{561}\)** Unfractionated heparin is contraindicated in patients with severe thrombocytopenia. Fondaparinux is recommended in patients with a history of heparin-induced thrombocytopenia.
Mechanical thromboprophylaxis (e.g., intermittent pneumatic compression devices) is recommended if anticoagulation is contraindicated or not available.[780] [782]

» The optimal dose is yet to be determined. Standard prophylaxis doses are generally recommended over intermediate- or full treatment-dose regimens in patients without an established indication for higher-dose anticoagulation. However, this recommendation varies and you should consult your local guidelines. The World Health Organization recommends standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing in patients without an established indication for higher-dose anticoagulation.[2] NICE recommends clinicians consider a treatment dose of a low molecular weight heparin in young people and adults who are likely to be in hospital for at least 3 days and need supplemental oxygen (but who are not yet receiving high-flow oxygen, continuous positive airway pressure, noninvasive ventilation, or invasive mechanical ventilation), unless contraindicated. This is because of fewer deaths and less likelihood of needing intensive care with this dose compared with a standard prophylaxis dose without a notable increase in major bleeding, although the evidence for this recommendation is weak. Treatment should be for a minimum of 14 days or until discharge, and the dose may need to be reduced if the clinical circumstances change (such as a need for advanced respiratory support). For those who do not need supplemental oxygen, follow standard VTE prophylaxis guidelines.[561] The National Institutes of Health guidelines panel recommends prophylactic-dose anticoagulation, and states that there are insufficient data to recommend increased anticoagulant doses for VTE prophylaxis in COVID-19 patients outside the setting of a clinical trial.[3]

» Dose adjustments may be required in patients with extremes of body weight or renal impairment.[561]

» For patients who are already on an anticoagulant for another condition, continue the patient’s current therapeutic dose unless contraindicated by a change in clinical circumstances. Consider switching to low molecular weight heparin as the preferred option for venous thromboembolism prophylaxis if the patient’s clinical condition is deteriorating and...
## Acute

the patient is not currently on low molecular weight heparin.[561]

» Monitor patients for signs and symptoms suggestive of thromboembolism and proceed with appropriate diagnostic and management pathways if clinically suspected.[2] If the patient’s clinical condition changes, assess the risk of VTE, reassess the bleeding risk, and review VTE prophylaxis.[561]

» Continue until hospital discharge.[2] Routine post-discharge VTE prophylaxis is not generally recommended, except in certain high-risk patients.[3] Ensure patients who require VTE prophylaxis after discharge are able to use it correctly or have arrangements made for someone to help them.[561]

» There is currently insufficient evidence to determine the risks and benefits of prophylactic anticoagulation in hospitalized patients with COVID-19.[783] A systematic review and meta-analysis found that the pooled odds of mortality between anticoagulated and nonanticoagulated hospitalized patients were similar, but lower in the standard prophylactic-dose group. Prophylactic-dose anticoagulation significantly decreased the odds of in-hospital death by 17% compared with no anticoagulation. Mortality increased in the intermediate- to therapeutic-dose group with an increased risk of major bleeding.[784] Clinicians should rely on pre-COVID-19 evidence-based principles of anticoagulation management combined with rational approaches to address clinical challenges.[779]

**plus monitoring**

Treatment recommended for ALL patients in selected patient group

» Monitor patients closely for signs of clinical deterioration, and respond immediately with appropriate supportive care interventions.[2]

**adjunct antibiotics**

Treatment recommended for SOME patients in selected patient group

» Consider empiric antibiotics if there is clinical suspicion of secondary bacterial infection. Give within 1 hour of initial assessment for patients with suspected sepsis or if the patient meets high-risk criteria (or within 4 hours of establishing a diagnosis of secondary bacterial pneumonia); do not wait for microbiology results. Base the regimen on the clinical diagnosis
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<td>(e.g., community-acquired pneumonia, hospital-acquired pneumonia, sepsis), local epidemiology and susceptibility data, and local treatment guidelines. [2] [3] [561]</td>
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» Do not offer antibiotics for preventing or treating pneumonia if SARS-CoV-2, another virus, or a fungal infection is likely to be the cause. [561] There is insufficient evidence to recommend empiric broad-spectrum antibiotics in the absence of another indication. [3]

» Consider seeking specialist advice for people who: are immunocompromised; have a history of infection with resistant organisms; have a history of repeated infective exacerbations of lung disease; are pregnant; or are receiving advanced respiratory or organ support. Seek specialist advice if there is a suspicion that the person has an infection with multidrug-resistant bacteria and may need a different antibiotic, or there is clinical or microbiologic evidence of infection and the person’s condition does not improve as expected after 48 to 72 hours of antibiotic treatment. [561]

» Reassess antibiotic use daily. De-escalate empiric therapy on the basis of microbiology results and clinical judgment. Regularly review the possibility of switching from intravenous to oral therapy. Duration of treatment should be as short as possible (e.g., 5 to 7 days). Antibiotic stewardship programs should be in place. [2]

**adjunct corticosteroid**

Treatment recommended for SOME patients in selected patient group

**Primary options**

» **dexamethasone**:
children: consult specialist for guidance on dose; adults: 6 mg orally/intravenously once daily for 7-10 days

OR

» **hydrocortisone**:
children: consult specialist for guidance on dose; adults: 50 mg orally/intravenously every 8 hours for 7-10 days

**Secondary options**

» **prednisone**:
children: consult specialist for guidance on dose; adults: 40 mg/day orally given in 1-2 divided doses for 7-10 days

OR
**Acute**

- **methylprednisolone**: children: consult specialist for guidance on dose; adults: 32 mg/day orally/intravenously given in 1-2 divided doses for 7-10 days

- The World Health Organization (WHO) strongly recommends systemic corticosteroid therapy (low-dose intravenous or oral dexamethasone or hydrocortisone) for 7 to 10 days in adults with severe COVID-19. This recommendation is based on two meta-analyses that pooled data from eight randomized trials (over 7000 patients), including the UK RECOVERY trial. Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with severe and critical COVID-19. They also probably reduce the need for invasive ventilation. There is no evidence directly comparing dexamethasone and hydrocortisone. The harms of treatment in this context are considered to be minor. It is unclear whether these recommendations can be applied to children or those who are immunocompromised.\[743\] \[786\] \[787\] \[788\] \[789\] There is also evidence that corticosteroids probably increase ventilator-free days (moderate certainty).\[790\] \[791\]

  - [BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19](https://www.bmj.com/content/370/bmj.m3379)

  - In the UK, the National Institute for Health and Care Excellence recommends offering dexamethasone (or an alternative such as hydrocortisone or prednisone when dexamethasone cannot be used or is unavailable) to people who need supplemental oxygen to meet their prescribed oxygen saturation levels, or who have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it. Treatment is for up to 10 days unless there is a clear indication to stop early.\[561\]

  - In Europe, the European Medicines Agency has endorsed the use of dexamethasone for patients with severe disease who require oxygen therapy or mechanical ventilation.\[792\]

  - In the US, the National Institutes of Health guidelines panel recommends dexamethasone, either alone or in combination with remdesivir (see the Emerging section for information on remdesivir), in hospitalized adults who require supplemental oxygen. The panel recommends against using dexamethasone in adults who do not require supplemental oxygen.
**Acute oxygen.** Alternative corticosteroids may be used in situations where dexamethasone is not available. It is not routinely recommended for pediatric patients who require only low levels of oxygen support (i.e., via a nasal cannula only). Use of dexamethasone for the treatment of severe disease in children who are profoundly immunocompromised has not been evaluated, may be harmful, and therefore should be considered only on a case-by-case basis.[3] The Infectious Diseases Society of America supports the use of dexamethasone in hospitalized patients with severe disease.[793]

» Monitor patients for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, reactivation of latent infections) and assess for drug-drug interactions.[3]

**adjunct treatment of coinfections**

Treatment recommended for SOME patients in selected patient group

» Treat laboratory-confirmed coinfections (e.g., malaria, tuberculosis, influenza) as appropriate according to local protocols.[2] The treatment of influenza is the same in all patients regardless of SARS-CoV-2 coinfection. Start empiric treatment with oseltamivir in hospitalized patients who are suspected of having either or both infections as soon as possible without waiting for influenza test results. Antiviral therapy can be stopped once influenza has been ruled out.[3]

**adjunct antipyretic/analgesic**

Treatment recommended for SOME patients in selected patient group

**Primary options**

» acetaminophen: children: 10-15 mg/kg orally every 4-6 hours when required, maximum 75 mg/kg/day; adults: 325-1000 mg orally (immediate-release) every 4-6 hours when required, maximum 4000 mg/day

OR

» ibuprofen: children 6 months to 11 years of age: 5-10 mg/kg orally every 6-8 hours when required, maximum 40 mg/kg/day; children ≥12 years of age and adults: 200-400 mg orally every 4-6 hours when required, maximum 2400 mg/day

» Acetaminophen or ibuprofen are recommended.[2] [561] There is no evidence at present of severe adverse events in COVID-19
Coronavirus disease 2019 (COVID-19)

Management

Acute

patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilization, long-term survival, or quality of life in patients with COVID-19.[755][756][757][758][759][760][761]

» Ibuprofen should only be taken at the lowest effective dose for the shortest period needed to control symptoms. It is not recommended in pregnant women (especially in the third trimester) or children <6 months of age (age cut-offs vary by country).

adjunct experimental therapies

Treatment recommended for SOME patients in selected patient group

» Consider appropriate experimental or emerging therapies.

» Antiviral therapies will have a greater effect early in the course of the disease, whereas immunosuppressive/anti-inflammatory therapies are likely to have a greater effect later in the course of the disease.[3]

» See the Emerging section for more information.

adjunct plan for discharge and rehabilitation

Treatment recommended for SOME patients in selected patient group

» Routinely assess older patients for mobility, functional swallow, cognitive impairment, and mental health concerns, and based on that assessment determine whether the patient is ready for discharge, and whether the patient has any rehabilitation and follow-up requirements.[2]

adjunct palliative care

Treatment recommended for SOME patients in selected patient group

» Palliative care interventions should be made accessible at each institution that provides care for patients with COVID-19. Identify whether the patient has an advance care plan and respect the patient’s priorities and preferences when formulating the patient’s care plan.[2] Follow local palliative care guidelines.

» There is a lack of data on palliative care in patients with COVID-19. However, a rapid systematic review of pharmacologic strategies used for palliative care in these patients, the first international review of its kind, found that a higher proportion of patients required continuous...
Acute

subcutaneous infusions for medication delivery than is typically seen in the palliative care population. Modest doses of commonly used end-of-life medications were required for symptom control. However, these findings should be interpreted with caution due to the lack of data available.[794]

critical COVID-19

1st Intensive/critical care unit admission

» Patients with critical disease (i.e., presence of acute respiratory distress syndrome, sepsis, or septic shock) should be admitted or transferred to an intensive/critical care unit under the guidance of a specialist team.[2]

» Discuss the risks, benefits, and potential outcomes of treatment options with patients and their families, and allow them to express preferences about their management. Take their wishes and expectations into account when considering the ceiling of treatment. Use decision support tools if available. Put treatment escalation plans in place, and discuss any existing advance care plans or advance decisions to refuse treatment with patients who have preexisting advanced comorbidities.[561]

» Implement local infection prevention and control procedures when managing patients with COVID-19.

» Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, as well as midwifery and mental health and psychosocial support. A woman-centered, respectful, skilled approach to care is recommended.[2] The multidisciplinary team should be organized as soon as possible after maternal hypoxemia occurs in order to assess fetal maturity, disease progression, and the best options for delivery.[831]

» Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.[2] The Centers for Disease Control and Prevention (CDC) recommends discontinuing isolation once at least 10 days and up to 20 days have passed since symptoms first appeared, and at least 24 hours have passed since last fever without the use of antipyretics, and symptoms have improved, if a symptom-based strategy is used.
Consider consultation with infection control experts before discontinuing isolation. Severely immunocompromised patients may produce replication-competent virus beyond 20 days and require additional testing and consultation with infectious diseases specialists and infection control experts before discontinuing isolation. Alternatively, the CDC recommends at least two negative reverse-transcription polymerase chain reaction (RT-PCR) tests on respiratory specimens collected 24 hours apart before ending isolation if a test-based strategy is used. A symptom-based strategy is preferred; however, a test-based strategy can be considered in severely immunocompromised patients.[768]

Guidance on when to stop isolation depends on local recommendations and may differ between countries. For example, in the UK the isolation period is 14 days from a positive test in hospitalized patients. Immunocompetent patients who tested positive on RT-PCR and have completed their 14-day isolation period are exempt from testing prior to hospital discharge if they are within 90 days from their initial illness onset or test, unless they develop new symptoms.[754]

**plus** symptom management and supportive care

Treatment recommended for ALL patients in selected patient group

» Consider fluid and electrolyte management, antimicrobial treatment, and symptom management as appropriate. See Severe COVID-19 above for more detailed information.

» Follow local guidelines for the management of pain, sedation, and delirium.[3]

» Implement standard interventions to prevent complications associated with critical illness.[2]

**plus** venous thromboembolism prophylaxis

Treatment recommended for ALL patients in selected patient group

**Primary options**

» enoxaparin: consult specialist for guidance on dose

OR

» dalteparin: consult specialist for guidance on dose

**Secondary options**
Coronavirus disease 2019 (COVID-19)  

**Management**

### Acute

» **heparin:** consult specialist for guidance on dose

OR

» **fondaparinux:** consult specialist for guidance on dose

» Unfractionated heparin is preferred over fondaparinux in critically ill patients if low molecular weight heparin, as the preferred option for venous thromboembolism prophylaxis, cannot be used.[780]

» The UK National Institute for Health and Care Excellence (NICE) does not recommend treatment-dose low molecular weight heparin for VTE prophylaxis for patients receiving advanced respiratory support unless the patient is part of a nationally approved clinical trial because it is likely to cause harm in this group. NICE recommends reducing the dose to a locally agreed intermediate or standard dose and reassessing VTE and bleeding risks daily in patients who progress to needing high-flow oxygen, continuous positive airway pressure, noninvasive or invasive mechanical ventilation, or palliative care.[561]

» NHS England recommends that therapeutic doses should not be offered unless there is a standard indication for therapeutic anticoagulation, as trials show that therapeutic doses do not improve clinical outcome of severe disease in the critical care setting.[828]

» Some guidelines recommend that escalated doses can be considered in critically ill patients.[779] [571]

» A multicenter randomized controlled trial found that intermediate-dose prophylactic anticoagulation did not result in a significant difference in the primary outcome of a composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or 30-day mortality compared with standard-dose prophylactic anticoagulation among patients admitted to the intensive care unit. These results do not support the routine empiric use of intermediate-dose prophylactic anticoagulation in unselected patients admitted to the intensive care unit.[829]

» Dose adjustments may be required in patients with extremes of body weight or renal impairment.[561]
» See Severe COVID-19 above for more detailed information on VTE prophylaxis.

**plus** consider high-flow nasal oxygen or noninvasive ventilation

Treatment recommended for ALL patients in selected patient group

» Consider a trial of high-flow nasal oxygen (HFNO) or noninvasive ventilation (e.g., continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) in selected patients with mild acute respiratory distress syndrome. Consider awake prone positioning (for 8-12 hours/day, broken into shorter periods over the day) in severely ill patients who require HFNO or noninvasive ventilation.[2] Awake prone positioning of nonintubated patients was associated with improvement in oxygen variables (PaO₂/\(\text{FiO}_2\), PaO₂, and SpO₂) and respiratory rate; however, evidence is limited. Further randomized controlled trials are required to study the impact on key parameters (e.g., reduction in mechanical ventilation or mortality).[775]

» Airborne precautions are recommended for these interventions (including bubble CPAP) due to uncertainty about the potential for aerosolization.[2]

» Patients with hypercapnia, hemodynamic instability, multi-organ failure, or abnormal mental status should generally not receive HFNO, although emerging data suggest that it may be safe in patients with mild to moderate and nonworsening hypercapnia. Patients with hypoxemic respiratory failure and hemodynamic instability, multi-organ failure, or abnormal mental status should not receive these treatments in place of other options such as invasive ventilation.[2]

» There is ongoing debate about the optimal mode of respiratory support before mechanical ventilation.[799] NHS England recommends CPAP as the preferred form of noninvasive ventilation in patients with hypoxemic (type 1) respiratory failure. It doesn’t advocate the use of HFNO based on a lack of efficacy, oxygen use (HFNO can place a strain on oxygen supplies with the risk of site supply failure), and infection spread.[800] Other guidelines recommend HFNO over noninvasive ventilation, unless HFNO is not available.[3][773] Despite the trend to avoid HFNO, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[801]
**Acute**

» Early CPAP may provide a bridge to invasive mechanical ventilation. Reserve the use of BiPAP for patients with hypercapnic acute on chronic ventilatory failure (type 2 respiratory failure).[800]

» Monitor patients closely for acute deterioration. If patients do not improve after a short trial of these interventions, they require urgent endotracheal intubation.[2] [773]

**plus** consider invasive mechanical ventilation

Treatment recommended for ALL patients in selected patient group

» Consider endotracheal intubation and mechanical ventilation in patients who are acutely deteriorating despite advanced oxygen/noninvasive ventilatory support measures.[2] [3]

» Endotracheal intubation should be performed by an experienced provider using airborne precautions.[2] Intubation by video laryngoscopy is recommended if possible.[3] Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require preoxygenation with 100% fraction of inspired oxygen (FiO₂) for 5 minutes.[2]

» Mechanically ventilated patients with acute respiratory distress syndrome (ARDS) should receive a lung-protective, low tidal volume/low inspiratory pressure ventilation strategy (lower targets are recommended in children). A higher positive end-expiratory pressure (PEEP) strategy is preferred over a lower PEEP strategy in moderate to severe ARDS. However, individualization of PEEP, where the patient is monitored for beneficial or harmful effects and driving pressure during titration with consideration of the risks and benefits of PEEP titration, is recommended.[2] [3] [773] NHS England recommends a low PEEP strategy in patients with normal compliance where recruitment may not be required.[809]

» Although some patients with COVID-19 pneumonia meet the criteria for ARDS, there is some discussion about whether COVID-19 pneumonia is its own specific disease with atypical phenotypes. Anecdotal evidence suggests that the main characteristic of the atypical presentation is the dissociation between well-preserved lung mechanics and the severity of hypoxemia.[810] [811] [812] [813] [814] [815] However, this approach has been criticized.[816] [817] It has been argued that an evidence-based
Acute

approach extrapolating data from ARDS not related to COVID-19 is the most reasonable approach for intensive care of COVID-19 patients.[818] As a consequence of this, some clinicians have warned that protocol-driven ventilator use may be causing lung injury in some patients, and that ventilator settings should be based on physiologic findings rather than using standard protocols. High PEEP may have a detrimental effect on patients with normal compliance.[810] PEEP should always be carefully titrated.[819]

» Consider prone ventilation in patients with severe ARDS for 12 to 16 hours per day. Pregnant women in the third trimester may benefit from being placed in the lateral decubitus position. Caution is required in children.[2] [3] [773] Longer durations may be feasible in some patients.[820]

» Lung recruitment maneuvers are suggested, but staircase recruitment maneuvers are not recommended.[3] [773]

**adjunct** inhaled pulmonary vasodilator

Treatment recommended for SOME patients in selected patient group

» Consider a trial of an inhaled pulmonary vasodilator in adults who have severe acute respiratory distress syndrome and hypoxemia despite optimizing ventilation. Taper off if there is no rapid improvement in oxygenation.[3] [773]

**adjunct** extracorporeal membrane oxygenation

Treatment recommended for SOME patients in selected patient group

» Consider extracorporeal membrane oxygenation (ECMO) according to availability and expertise if the above methods fail.[2] [773] [821] [822] ECMO is not suitable for all patients, and only those who meet certain inclusion criteria may be considered for ECMO.[823]

» There is insufficient evidence to recommend either for or against the routine use of ECMO.[3]

» The estimated 60-day survival rate of ECMO-rescued patients with COVID-19 (31%) was similar to that of previous studies of ECMO for severe ARDS in one study.[824]

» An international cohort study of 1035 patients found that both the estimated mortality 90 days after ECMO initiation and mortality in those who achieved a final outcome of death or discharge were <40%, consistent with previously reported
**Acute**

| **survival rates in acute hypoxemic respiratory failure.**[825] |
| » A multicenter cohort study in France reported a 90-day survival rate of 46%. Factors associated with improved 90-day survival included earlier ECMO initiation, younger age, no pre-ECMO renal dysfunction, and treatment in centers managing at least 30 venovenous ECMO cases annually.[826] |
| » Single-access, dual-stage venovenous ECMO with early extubation appears to be safe and effective in patients with COVID-19 respiratory failure.[827] |

**adjunct management of sepsis/septic shock**

Treatment recommended for SOME patients in selected patient group

» The management of sepsis and septic shock in patients with COVID-19 is beyond the scope of this topic. See the Complications section.

**adjunct corticosteroid**

Treatment recommended for SOME patients in selected patient group

**Primary options**

» **dexamethasone**: children: consult specialist for guidance on dose; adults: 6 mg orally/intravenously once daily for 7-10 days

OR

» **hydrocortisone**: children: consult specialist for guidance on dose; adults: 50 mg orally/intravenously every 8 hours for 7-10 days

**Secondary options**

» **prednisone**: children: consult specialist for guidance on dose; adults: 40 mg/day orally given in 1-2 divided doses for 7-10 days

OR

» **methylprednisolone**: children: consult specialist for guidance on dose; adults: 32 mg/day orally/intravenously given in 1-2 divided doses for 7-10 days

» The World Health Organization (WHO) strongly recommends systemic corticosteroid therapy (low-dose intravenous or oral dexamethasone or hydrocortisone) for 7 to 10 days in adults with critical COVID-19. This recommendation
Coronavirus disease 2019 (COVID-19)

Management

**Acute**

Acute is based on two meta-analyses that pooled data from eight randomized trials (over 7000 patients), including the UK RECOVERY trial. Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with severe and critical COVID-19. They also probably reduce the need for invasive ventilation. There is no evidence directly comparing dexamethasone and hydrocortisone. The harms of treatment in this context are considered to be minor. It is unclear whether these recommendations can be applied to children or those who are immunocompromised.[743] [786] [787] [788] [789] There is also evidence that corticosteroids probably increase ventilator-free days (moderate certainty).[790] [791]

» [BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19] (https://www.bmj.com/content/370/bmj.m3379)

» In the UK, the National Institute for Health and Care Excellence recommends offering dexamethasone (or an alternative such as hydrocortisone or prednisone when dexamethasone cannot be used or is unavailable) to people who need supplemental oxygen to meet their prescribed oxygen saturation levels, or who have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it. Treatment is for up to 10 days unless there is a clear indication to stop early.[561]

» In Europe, the European Medicines Agency has endorsed the use of dexamethasone for patients with severe disease who require oxygen therapy or mechanical ventilation.[792]

» In the US, the National Institutes of Health guidelines panel recommends using dexamethasone, either alone or in combination with remdesivir (see the Emerging section for information on remdesivir), in hospitalized patients who require high-flow oxygen or noninvasive ventilation. The panel recommends dexamethasone (in combination with tocilizumab - see the Emerging section for information on tocilizumab) in patients on mechanical ventilation or extracorporeal membrane oxygenation. Alternative corticosteroids may be used in situations where dexamethasone is not available. The panel recommends using dexamethasone in hospitalized children who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation.[3] The Infectious
### Acute

Diseases Society of America supports the use of dexamethasone in hospitalized patients with severe disease.[793]

- Monitor patients for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, reactivation of latent infections) and assess for drug-drug interactions.[3]

- A meta-analysis found an increased risk of venous thromboembolism with corticosteroid administration in patients with critical disease. However, no definite findings were available due to the differing corticosteroid regimens and the heterogeneity of the studies.[830]

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Coronavirus disease 2019 (COVID-19)

Management

Acute

**adjunct** palliative care

Treatment recommended for SOME patients in selected patient group

» Palliative care interventions should be made accessible at each institution that provides care for patients with COVID-19. Identify whether the patient has an advance care plan and respect the patient’s priorities and preferences when formulating the patient’s care plan.[2] Follow local palliative care guidelines.

» There is a lack of data on palliative care in patients with COVID-19. However, a rapid systematic review of pharmacologic strategies used for palliative care in these patients, the first international review of its kind, found that a higher proportion of patients required continuous subcutaneous infusions for medication delivery than is typically seen in the palliative care population. Modest doses of commonly used end-of-life medications were required for symptom control. However, these findings should be interpreted with caution due to the lack of data available.[794]
Emerging

Interleukin-6 (IL-6) inhibitors

IL-6 inhibitors inhibit IL-6-mediated signaling by competitively binding to IL-6 receptors. IL-6 is a proinflammatory cytokine. These drugs (e.g., tocilizumab, sarilumab, siltuximab) are being trialed in patients for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced cytokine release syndrome. They are already approved in some countries for certain conditions, but are off-label for this indication. The UK National Institute for Health and Care Excellence recommends a single dose of tocilizumab in hospitalized adults if all of the following conditions apply: they are having or have completed a course of corticosteroids such as dexamethasone (unless they cannot have corticosteroids); they have not had another IL-6 inhibitor during this admission; there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab; AND they either need supplemental oxygen and have a C-reactive protein level of ≥75 mg/L, OR they are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, noninvasive ventilation, or invasive mechanical ventilation.[561] Consider tocilizumab for children and young people who have severe disease or pediatric inflammatory multisystem syndrome only if they are ages 1 year and over, and only in the context of a clinical trial. Sarilumab may be considered an alternative option in adults only if tocilizumab cannot be used or is unavailable (use the same eligibility criteria as those for tocilizumab). These recommendations are based on data from the UK RECOVERY and REMAP-CAP trials (see below). The US National Institutes of Health guidelines panel recommends a single dose of tocilizumab, in combination with dexamethasone (or a suitable alternative corticosteroid), in certain hospitalized adults who are exhibiting rapid respiratory decompensation due to progressive COVID-19.[3] This includes: recently hospitalized patients (e.g., within 3 days) who have been admitted to the intensive care unit within the prior 24 hours and who require invasive mechanical ventilation, noninvasive mechanical ventilation, or high-flow nasal oxygen; OR recently hospitalized patients, not in the intensive care unit, with rapidly increasing oxygen needs who require noninvasive mechanical ventilation or high-flow nasal oxygen and have significantly increased markers of inflammation (e.g., C-reactive protein level is ≥75 mg/L). Tocilizumab may be used with dexamethasone alone, or dexamethasone plus remdesivir, in these patients. Some panel members also recommend tocilizumab in patients who are exhibiting rapidly increasing oxygen needs while on a corticosteroid and have a C-reactive protein level ≥75 mg/L but who do not yet require noninvasive mechanical ventilation or high-flow nasal oxygen. However, there is insufficient evidence to specify which of these patients would benefit from the addition of tocilizumab. Tocilizumab should be given only in combination with a corticosteroid. There are insufficient data for the panel to recommend either for or against the use of sarilumab for hospitalized patients who are within 24 hours of admission to the intensive care unit and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow oxygen. The panel recommends against the use of siltuximab, except in the context of a clinical trial. In children, there are insufficient data to recommend either for or against the use of tocilizumab, including those with multisystem inflammatory syndrome. The panel recommends against the use of sarilumab in hospitalized children, except in the context of a clinical trial. The Infectious Diseases Society of America recommends tocilizumab in hospitalized adults with progressive severe or critical disease who have elevated markers of systemic inflammation, in addition to standard of care (i.e., corticosteroids), rather than standard of care alone.[793] This recommendation is conditional, based on low-certainty evidence. Patients, particularly those who respond to corticosteroids alone, who put a high value on avoiding possible adverse events of tocilizumab and a low value on the uncertain mortality reduction, would reasonably decline tocilizumab. Evidence is emerging. A Cochrane living systematic review found that tocilizumab reduced all-cause mortality at day 28, and probably resulted in little or no increase in clinical improvement at day 28 (i.e., hospital discharge or improvement measured by trialist-defined scales). The impact of tocilizumab on other outcomes is uncertain. More data are needed to be able to identify which patients are more likely to benefit from this treatment. Evidence for an effect of sarilumab is uncertain.[846] Data from meta-analyses are conflicting. Some meta-analyses show that treatment with tocilizumab is associated with a clinically meaningful improvement in 28- or 30-day mortality.[847] [848] [849] However, other meta-analyses show that tocilizumab does not provide a survival benefit.[850] [851] This may be due to the weighting attributed to the two largest studies, the RECOVERY and REMAP-CAP trials, which were the only trials to find improved 28-day survival (see below), and whether the patients were on concomitant corticosteroids. Despite this uncertainty about mortality, these meta-analyses also found that tocilizumab may reduce the risk of mechanical ventilation or intensive care unit admission. A
living systematic review and network meta-analysis found that IL-6 inhibitors are likely to reduce the need for mechanical ventilation (moderate-certainty evidence) and may reduce the duration of hospitalization (low-certainty evidence) compared with standard care.[790] [791] Data from the UK RECOVERY trial found that tocilizumab reduced 28-day mortality compared with usual care in patients who required oxygen and had evidence of inflammation. The results showed that 31% of patients in the tocilizumab group died within 28 days compared with 35% in the usual care group, a 15% reduction in relative mortality. Tocilizumab also increased the probability of discharge alive within 28 days from 50% to 57%. These benefits were seen regardless of the level of respiratory support, and were additional to the benefits of corticosteroids.[852] Data from the REMAP-CAP trial showed more organ support-free days and a reduction in mortality when IL-6 inhibitors were given to critically ill patients receiving organ support in the intensive care unit within 24 hours of admission, compared with standard of care (including corticosteroids in the majority of patients).[853] A randomized controlled phase 3 trial found that there was no observed benefit of sarilumab in patients with severe or critical disease who were receiving supplemental oxygen and the local standard of care, compared with placebo.[854] Evidence is conflicting, and it has been suggested that the value of IL-6 inhibitor treatment may be dependent on the timing of treatment and the concomitant use of corticosteroids.[855] A score to assist clinicians in identifying patients who are likely to progress to mechanical ventilation or death early after tocilizumab administration, so that they can be selected for rescue therapies, is in development.[856] Tocilizumab should be avoided in patients who are significantly immunocompromised.[3] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing these drugs.

Remdesivir

Remdesivir is an investigational broad-spectrum antiviral agent that inhibits RNA-dependent RNA polymerase. It is approved in many countries for the treatment of COVID-19. In the UK and Europe, remdesivir has been conditionally approved in adolescents (≥12 years of age who weigh at least 40 kg) and adults with pneumonia who require supplemental oxygen (low- or high-flow oxygen or other noninvasive ventilation at start of treatment).[857] In the US, remdesivir has been approved for the treatment of adolescents (≥12 years of age who weigh at least 40 kg) and adults who require hospitalization, and has emergency-use authorization for use in children.[858] The World Health Organization recommends against the use of remdesivir in hospitalized patients in addition to standard care, regardless of disease severity.[743] [787] [788] This weak or conditional recommendation is based on a systematic review and network meta-analysis of four randomized trials with 7333 hospitalized patients, and included the NIAID-ACTT-1 trial (on which the original US approval of remdesivir was based) and the WHO Solidarity trial. There is currently no evidence that remdesivir improves patient outcomes such as time to clinical improvement, the need for mechanical ventilation, or mortality. However, the meta-analysis did not prove that remdesivir has no benefit.[787] [788] The WHO Solidarity trial found that remdesivir appears to have little or no effect on hospitalized patients, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[859] Another living systematic review and network meta-analysis found that remdesivir may reduce the need for mechanical ventilation (low-certainty evidence) compared with standard care.[790] [791] The UK National Institute for Health and Care Excellence recommends considering remdesivir for up to 5 days in adults and children ≥12 years of age and ≥40 kg who are in hospital and needing low-flow supplemental oxygen.[561] Do not use remdesivir in adults, young people, and children in hospital and on high-flow nasal oxygen, continuous positive airway pressure, noninvasive mechanical ventilation, or invasive mechanical ventilation, except as part of a clinical trial. There is limited evidence suggesting that remdesivir probably reduces the risk of death in hospitalized patients who need low-flow supplemental oxygen. However, evidence shows that remdesivir may increase the risk of death in people who are on high-flow nasal oxygen, continuous positive airway pressure, noninvasive ventilation, or invasive mechanical ventilation. Evidence does not suggest any greater benefit with a 10-day course of remdesivir compared with a 5-day course, but suggests an increased risk of harm. There may also be no benefit in completing the full course of remdesivir if the patient progresses to needing high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation during treatment. Evidence for remdesivir in children and young people is limited. The US National Institutes of Health guidelines panel recommends remdesivir in hospitalized adults who require supplemental oxygen.[3] It may be given alone (e.g., for patients who require minimal supplemental oxygen) or in combination with dexamethasone (e.g., for patients who require increasing amounts of supplemental oxygen). The panel also recommends remdesivir, in combination with dexamethasone, in hospitalized patients who require high-flow oxygen or noninvasive ventilation. It does not recommend remdesivir in patients who require invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). The panel acknowledges that remdesivir may also be appropriate in hospitalized patients who do not require
oxygen, but who are at high risk of disease progression. The recommended treatment course is 5 days or until hospital discharge, whichever comes first. Some experts recommend a 10-day course in patients who have not shown substantial clinical improvement by day 5. In children, the panel recommends remdesivir in those who are hospitalized, are ages ≥12 years, have risk factors for severe disease, and have an emergent or increasing need for supplemental oxygen. The panel recommends remdesivir in hospitalized children ages ≥16 years who have an emergent or increasing need for supplemental oxygen, regardless of whether they have risk factors for severe disease. The panel recommends considering remdesivir in hospitalized children of all ages who have an emergent or increasing need for supplemental oxygen, in consultation with a pediatric infectious disease specialist. The Infectious Diseases Society of America recommends remdesivir in hospitalized patients with severe disease over no antiviral treatment, based on moderate-certainty evidence.[793] The recommended treatment course is 5 days in patients on oxygen, and 10 days in patients on mechanical ventilation or ECMO. The panel suggests against the routine use of remdesivir in hospitalized patients who do not require oxygen and have an oxygen saturation >94% on room air, based on very low-certainty evidence. There are conflicting recommendations across international guidelines about the use of remdesivir, so it is important that you check local guidance and protocols. Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

Casirivimab/imdevimab

Casirivimab and imdevimab are intravenous investigational neutralizing human immunoglobulin G-1 monoclonal antibodies with activity against SARS-CoV-2. The two antibodies bind to nonoverlapping epitopes of the receptor-binding domain of the spike protein to block virus entry into host cells. Casirivimab/imdevimab (formerly known as REGN-COV2) has been granted an emergency-use authorization in the US for the treatment of mild to moderate disease in children and adults.[860] The US emergency-use authorization covers patients with positive results of direct viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe disease and/or hospitalization. This includes patients who are 65 years of age or older, or who have certain chronic medical conditions. The European Medicines Agency has issued advice that casirivimab/imdevimab may be used in patients ages 12 years and older who do not require supplemental oxygen and who are at high risk of progressing to severe disease; however, the agency is yet to issue a marketing authorization.[861] The US National Institutes of Health guidelines panel recommends casirivimab/imdevimab for the treatment of outpatients with mild to moderate disease who are at high risk of clinical progression, as defined by the emergency-use authorization criteria.[3] Treatment should be started as soon as possible after the patient receives a positive test result and within 10 days of symptom onset. The panel recommends against the use of monoclonal antibodies in hospitalized patients, except in the context of a clinical trial. However, their use may be considered in patients with mild to moderate disease who are hospitalized for a reason other than COVID-19 but who otherwise meet the emergency-use authorization criteria. In children, there are insufficient data to recommend either for or against the use of monoclonal antibody products in those who are not hospitalized but have risk factors for severe disease. However, they may be considered on a case-by-case basis for nonhospitalized children who meet emergency-use authorization criteria for high risk of severe disease (especially those who meet more than one criterion or are ages ≥16 years) in consultation with a pediatric infectious disease specialist. The Infectious Diseases Society of America suggests casirivimab/imdevimab in ambulatory patients with mild to moderate disease who are at high risk for progression to severe disease rather than no neutralising antibodies, based on low-certainty evidence.[793] Patients with mild to moderate disease who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive casirivimab/imdevimab. There are limited data on efficacy in high-risk patients between 12 and 18 years of age. Evidence is emerging. Emergency-use authorization was based on a randomized, double-blind, placebo-controlled trial in nonhospitalized adults with mild to moderate symptoms that found that casirivimab/imdevimab reduced hospitalization or emergency department visits in patients at high risk for disease progression within 28 days after treatment, when compared with placebo. This study is yet to be published.[860] An interim analysis of an ongoing, randomized, double-blind, phase 1-3 trial in nonhospitalized patients found that casirivimab/imdevimab reduced viral load from baseline through to day 7, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline.[862] Casirivimab/imdevimab is not authorized for use in hospitalized patients or those who require oxygen as it has not shown benefit in these patients. Further enrollment of patients requiring high-flow oxygen or mechanical ventilation has been placed on hold due to a potential safety signal and an unfavorable risk/benefit profile at this time. However, enrollment of hospitalized patients requiring either no or low-flow oxygen is being continued.[863] Consult local drug formulary for information about
Management

Institutes of Health guidelines panel recommends against the use of low-titer convalescent plasma. There is no evidence to show improvement of survival or other prespecified clinical outcomes among hospitalized patients. The US National Institutes of Health found that high-titer convalescent plasma did not benefit hospitalized patients with suspected or confirmed infection. UK guidance recommends that convalescent plasma should not be used in the management of hospitalized patients with suspected or confirmed infection. Low-titer convalescent plasma is no longer authorized. It has not been granted an emergency-use authorization in the UK or Europe. UK guidance recommends that convalescent plasma should not be used in the management of hospitalized patients with suspected or confirmed infection. Low-titer convalescent plasma is no longer authorized.

Bamlanivimab/etesevimab

Bamlanivimab (formerly known as LY-CoV555) and etesevimab (formerly known as LY-CoV016) are intravenous investigational neutralizing human immunoglobulin G-1 monoclonal antibodies with activity against SARS-CoV-2. The two antibodies bind to different, but overlapping, epitopes of the receptor-binding domain of the spike protein to block virus entry into host cells. Bamlanivimab/etesevimab has been granted an emergency-use authorization in the US for the treatment of mild to moderate disease in children and adults. The US emergency-use authorization for bamlanivimab monotherapy has been revoked. The US emergency-use authorization covers patients with positive results of direct viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe disease and/or hospitalization. This includes patients who are 65 years of age or older, or who have certain chronic medical conditions. The European Medicines Agency has issued advice that bamlanivimab/etesevimab may be used in patients ages 12 years and older who do not require supplemental oxygen and who are at high risk of progressing to severe disease. The agency is yet to issue a marketing authorization, but has started a rolling review of the data. The agency also concluded that despite uncertainties around the benefits of bamlanivimab monotherapy, it can be considered a treatment option for this indication. The US National Institutes of Health guidelines panel recommends bamlanivimab/etesevimab for the treatment of outpatients with mild to moderate disease who are at high risk of clinical progression, as defined by the emergency-use authorization criteria. Treatment should be started as soon as possible after the patient receives a positive test result and within 10 days of symptom onset. The panel recommends against the use of monoclonal antibodies in hospitalized patients, except in the context of a clinical trial. However, their use may be considered in patients with mild to moderate disease who are hospitalized for a reason other than COVID-19 but who otherwise meet the emergency-use authorization criteria. In children, there are insufficient data to recommend either for or against the use of monoclonal antibody products in those who are not hospitalized but have risk factors for severe disease. However, they may be considered on a case-by-case basis for nonhospitalized children who meet emergency-use authorization criteria for high risk of severe disease (especially those who meet more than one criterion or are ages ≥16 years) in consultation with a pediatric infectious disease specialist. The Infectious Diseases Society of America suggests bamlanivimab/etesevimab in ambulatory patients with mild to moderate disease who are at high risk for progression to severe disease rather than no neutralizing antibodies, based on low-certainty evidence. Patients with mild to moderate disease who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive bamlanivimab/etesevimab. There are limited data on efficacy in high-risk patients between 12 and 18 years of age. The panel recommends against the use of bamlanivimab monotherapy in hospitalized patients with severe disease, based on moderate-certainty evidence. Evidence is emerging. Among patients with mild to moderate disease, treatment with bamlanivimab/etesevimab was associated with a significant reduction in viral load at day 11 compared with placebo; however, no significant difference in viral load reduction was observed with bamlanivimab monotherapy. Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug. Circulating SARS-CoV-2 variants may be associated with resistance to monoclonal antibodies. Consult local guidance for details regarding specific variants and resistance.

Convalescent plasma

Convalescent plasma is a blood product that contains antibodies to SARS-CoV-2 from patients who have recovered. High-titer convalescent plasma (i.e., plasma with high SARS-CoV-2 antibody titers) has been granted an emergency-use authorization in the US for the treatment of hospitalized patients early in the disease course, and to those hospitalized patients who have impaired humoral immunity and cannot produce an adequate antibody response. Low-titer convalescent plasma is no longer authorized. It has not been authorized for this indication in the UK or Europe. UK guidance recommends that convalescent plasma should not be used in the management of hospitalized patients with suspected or confirmed infection. This recommendation is based on data from the UK RECOVERY and REMAP-CAP trials. Preliminary data (yet to be peer reviewed) from the UK RECOVERY trial found that high-titer convalescent plasma did not improve survival or other prespecified clinical outcomes among hospitalized patients. The US National Institutes of Health guidelines panel recommends against the use of low-titer convalescent plasma.
are insufficient data for the panel to recommend either for or against the use of high-titer convalescent plasma in hospitalized patients with impaired immunity. The panel recommends against the use of high-titer convalescent plasma in hospitalized patients who do not have impaired immunity and who do not require mechanical ventilation, except in the context of a clinical trial. The panel recommends against the use of convalescent plasma in hospitalized patients who do not have impaired immunity and who require mechanical ventilation. There are insufficient data for the panel to recommend either for or against the use of high-titer convalescent plasma in nonhospitalized patients, except in the context of a clinical trial. In children, the panel recommends against the use of convalescent plasma in hospitalized children who do not require mechanical ventilation, except in the context of a clinical trial. High-titer convalescent plasma may be considered on a case-by-case basis for hospitalized children who meet the emergency-use authorization criteria for its use, in consultation with a pediatric infectious disease specialist. The Infectious Diseases Society of America suggests against the use of convalescent plasma in hospitalized patients, based on low-certainty evidence.[793] The guideline panel recommends convalescent plasma in ambulatory patients with mild to moderate disease only in the context of a clinical trial. Evidence is emerging. Emergency-use authorization was based on the preprint (not peer reviewed) publication of an open-label, multicenter, expanded access program study of over 35,000 patients that found convalescent plasma lowered 7-day mortality by 9% in hospitalized patients when given within 3 days of diagnosis, and by 12% when given 4 or more days later.[871] Evidence from meta-analyses appears to be conflicting. A meta-analysis and systematic review of four peer-reviewed randomized controlled trials and six unpublished randomized controlled trials found that treatment with convalescent plasma was not significantly associated with a decrease in all-cause mortality (or any benefit for other outcomes) compared with placebo or standard of care, based on low- to moderate-certainty evidence.[872] However, while another meta-analyses of ten randomized controlled trials also found no association between convalescent plasma therapy and a reduction in mortality, when one of the trials was excluded due to a large proportion of patients in the convalescent plasma arm receiving plasma with low levels of SARS-CoV-2 antibodies, additional analyses found that patients treated with convalescent plasma exhibited a lower mortality rate compared with patients who did not receive convalescent plasma (11% versus 16%). Therefore, early transfusion of high-titer plasma appears to reduce mortality.[873] A Cochrane review found high-certainty evidence that convalescent plasma does not reduce mortality and has little to no impact on measures of clinical improvement for the treatment of moderate to severe disease.[874] The UK RECOVERY trial found that high-titer convalescent plasma did not improve 28-day mortality or other prespecified outcomes (hospital discharge within 28 days, progression to invasive mechanical ventilation) in hospitalized patients compared with usual care.[875] A randomized, double-blind, placebo-controlled trial in older patients with mild disease who received convalescent plasma within 72 hours after the onset of symptoms found that early administration reduced the progression to severe disease.[876] However, a National Institutes of Health clinical trial evaluating the safety and efficacy of convalescent plasma in treating emergency department patients who developed mild to moderate symptoms has been halted. An interim analysis of the trial data determined that while convalescent plasma caused no harm, it was unlikely to benefit this group of patients.[877]

**Baricitinib**

Baricitinib is an oral Janus kinase inhibitor. It is thought to prevent the dysregulated production of proinflammatory cytokines in patients with severe or critical disease. Baricitinib is already approved in some countries for certain conditions. It has been granted an emergency-use authorization for the treatment of COVID-19 in the US, in combination with remdesivir, for the treatment of suspected or confirmed disease in hospitalized children ages 2 years and older and adults who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation.[878] It has not been authorized for this indication in the UK or Europe; however, the European Medicines Agency is currently evaluating its use in hospitalized patients from 10 years of age who require supplemental oxygen.[879] The US National Institutes of Health guidelines panel recommends baricitinib, in combination with dexamethasone alone or dexamethasone plus remdesivir, in hospitalized patients on high-flow oxygen or noninvasive ventilation who have evidence of clinical progression or increased markers of inflammation.[3] The panel recommends using baricitinib in combination with remdesivir alone in hospitalized, nonintubated patients who require supplemental oxygen when corticosteroids cannot be used. There is insufficient evidence to identify which patients would benefit from the addition of baricitinib to dexamethasone (with or without remdesivir) among hospitalized patients with hypoxemia who require supplemental oxygen therapy. However, some panel members would add baricitinib in patients who are exhibiting signs of systemic inflammation and rapidly increasing oxygen needs while on dexamethasone, but who do not yet require high-flow oxygen
or noninvasive ventilation. There is insufficient evidence to recommend either for or against the use of baricitinib in combination with dexamethasone in hospitalized patients who require invasive mechanical ventilation. The panel recommends against the use of baricitinib in combination with tocilizumab except in the context of a clinical trial. There is insufficient evidence to recommend either for or against the use of baricitinib in children. The Infectious Diseases Society of America recommends baricitinib with remdesivir in hospitalized patients with severe disease who cannot receive corticosteroids because of a contraindication, rather than remdesivir alone.[793] The combination should only be given with a corticosteroid in the context of a clinical trial. Evidence is emerging. Emergency-use authorization was based on a randomized, double-blind, placebo-controlled trial that found baricitinib plus remdesivir reduced time to recovery (defined as either being discharged from the hospital, or being hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care) within 29 days after initiating treatment compared with patients who received placebo plus remdesivir. The median time to recovery was 7 days for baricitinib plus remdesivir and 8 days for placebo plus remdesivir.[880] A living systematic review and network meta-analysis found that Janus kinase inhibitors may reduce the need for mechanical ventilation (low-certainty evidence) and probably reduce the duration of mechanical ventilation (moderate-certainty evidence) compared with standard care.[790][791] Another systematic review and network meta-analysis found that Janus kinase inhibitors are also associated with a reduced risk of mortality, and clinical improvement in hospitalized patients.[881] A meta-analysis that included six cohort studies and five clinical trials involving over 2000 participants treated with either baricitinib or ruxolitinib found that use of Janus kinase inhibitors reduced the need for invasive mechanical ventilation and increased survival, but did not reduce the length of hospitalization. The evidence was most convincing for baricitinib. Timing of treatment may be important in determining the impact on outcomes.[882] There is a lack of evidence for other drugs within this drug class (e.g., tofacitinib, fedratinib, ruxolitinib); however, clinical trials are ongoing. Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

Ivermectin

Ivermectin is a broad-spectrum antiparasitic agent. It has been shown to be effective against SARS-CoV-2 in vitro.[883] Ivermectin is already approved in some countries for parasitic infections, but is off-label for this indication. The European Medicines Agency does not recommend ivermectin for the treatment or prevention of COVID-19 outside of clinical trials.[884] The World Health Organization does not recommend ivermectin except in the context of a clinical trial.[743] This recommendation applies to patients with any disease severity and any duration of symptoms. There is insufficient evidence to be clear to what extent, if any, ivermectin is helpful or harmful in treating COVID-19.[787][788] For most key outcomes, including mortality, mechanical ventilation, hospital admission, duration of hospitalization, and viral clearance, the evidence is of very low certainty. The US National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either for or against the use of ivermectin.[3] The Infectious Diseases Society of America recommends against the use of ivermectin in outpatients and hospitalized patients outside of the context of a clinical trial, adding that more trials of sufficient design are needed.[793] Other international guidelines may recommend ivermectin in select patient groups. Indian guidelines recommend that ivermectin may be considered as an option in patients with mild disease, although acknowledge that this recommendation is based on low-certainty evidence.[885] Evidence is emerging. A meta-analysis of 18 randomized controlled trials found statistically significant reductions in mortality, time to clinical recovery, and time to viral clearance.[886] A systematic review and meta-analysis found that adding ivermectin to usual care led to significant clinical improvement and a significant reduction in all-cause mortality compared with usual care; however, the quality of evidence was very low.[887] A meta-analysis of six randomized controlled trials found a preliminary positive effect on mortality associated with use in hospitalized patients. The authors concluded that this effect warrants further appropriately designed, large-scale randomized controlled trials. The meta-analysis was limited by a small number of patients included with a significant risk of biases in the majority of included trials.[888] A living systematic review and network meta-analysis found that studies on ivermectin for prophylaxis have been small and it remains very uncertain whether ivermectin reduces the risk of infection. Evidence for the effects of ivermectin on mortality is of very low certainty.[889] A randomized controlled trial in patients with mild to moderate disease found that those treated with ivermectin plus doxycycline recovered 2 days earlier and were less likely to progress to severe disease compared with placebo.[890] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

Anakinra
Anakinra is an intravenous/subcutaneous interleukin-1 inhibitor. It is being trialed in patients for the treatment of SARS-CoV-2-induced cytokine release syndrome. Anakinra is already approved in some countries for certain conditions, but is off-label for this indication. The US National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either for or against the use of anakinra.[3] The UK National Institute for Health and Care Excellence states that there is no evidence available to determine whether anakinra is effective, safe, or cost-effective for treating adults and children with secondary hemophagocytic lymphohistiocytosis triggered by SARS-CoV-2 or a similar coronavirus.[891] Evidence is limited. A systematic review and meta-analysis of nine observational studies found that anakinra reduced the need for invasive mechanical ventilation and mortality risk in hospitalized nonintubated patients compared with standard of care. However, confirmation of safety and efficacy requires randomized controlled trials.[892] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

**Regdanvimab**

Regdanvimab (formerly known as CT-P59) is an investigational neutralizing monoclonal antibody with activity against SARS-CoV-2. Regdanvimab has been granted a conditional marketing authorization in South Korea for the treatment of adults with mild symptoms who are ages ≥60 years or have at least one underlying medical condition, and all adults with moderate symptoms. The European Medicines Agency recommends that regdanvimab can be used for the treatment of confirmed COVID-19 in adult patients who do not require supplemental oxygen therapy and who are at high risk of progressing to severe disease.[893] Evidence is limited. According to a press release from the manufacturer, regdanvimab reduced progression from mild-to-moderate to severe disease by 50%, and from moderate to severe disease by 68%. However, results from the phase 2/3 trial are yet to be published.[894] Regdanvimab has also demonstrated neutralizing capability against key emerging mutations, including the B.1.1.7 variant.[895]

**Sotrovimab**

Sotrovimab (formerly known as VIR-7831) is an investigational monoclonal antibody with activity against SARS-CoV-2. It is designed to attach to the spike protein of the virus. The US Food and Drug Administration has issued an emergency-use authorization for the treatment of mild to moderate disease in adults and adolescents ages 12 years of age and above (weighing at least 40 kg) with a positive result of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe disease, including hospitalization or death.[896] This includes, for example, people who are 65 years of age and older or individuals who have certain medical conditions. Sotrovimab is not authorized for patients who are hospitalized or require oxygen therapy. Authorization was based on an interim analysis from a phase 1/2/3 randomized controlled trial in 583 nonhospitalized adults with mild to moderate disease that reported an 85% reduction in hospitalization or death compared with placebo. The European Medicines Agency recommends that sotrovimab can be used for the treatment of confirmed COVID-19 in adults and adolescents ages 12 years and above (weighing at least 40 kg) who do not require supplemental oxygen therapy and who are at risk of progressing to severe disease.[897] An emergency-use authorization application has been submitted in the US. Evidence is limited. While the manufacturer has published press releases about interim results from clinical trials, these trials have not been published as yet.

**Intravenous immune globulin**

Intravenous immune globulin (IVIG) is a blood product prepared from serum pooled from healthy donors. It has an immunomodulatory effect that suppresses a hyperactive immune response. IVIG is already approved in some countries for certain conditions, but is off-label for this indication. The US National Institutes of Health guidelines panel states that there are insufficient data to recommend either for or against the use of anti-SARS-CoV-2 specific immune globulin.[3] Evidence is limited. A retrospective study of 58 patients with severe disease found that IVIG, when used as an adjuvant treatment within 48 hours of admission, may reduce the use of mechanical ventilation, reduce hospital/intensive care unit stay, and reduce 28-day mortality; however, this study had several limitations.[898] There is currently insufficient evidence to recommend IVIG.[899] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

**Stem cell therapy**

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Mesenchymal stem cells are investigational products and have been studied for their immunomodulatory properties. It is thought that they can reduce the pathologic changes that occur in the lungs, and inhibit the cell-mediated immune inflammatory response.\[900\] Mesenchymal stem cells are not approved for this indication. The US National Institutes of Health guidelines panel recommends against the use of mesenchymal stem cells except in the context of a clinical trial.\[3\] Evidence is limited. Remestemcel-L (ex vivo cultured adult human mesenchymal stem cells from the bone marrow of healthy adult donors) is currently in phase 3 trials for the treatment of moderate to severe acute respiratory distress syndrome in ventilator-dependent patients. An interim analysis of data found that the trial is not likely to meet its 30-day mortality reduction end point and has stopped enrollment, although the trial will be completed with the patients currently enrolled, with follow-up as planned.\[901\]

**Interferons**

Interferons are a family of cytokines with antiviral properties. Interferons are already approved in some countries for certain conditions, but are off-label for this indication. The US National Institutes of Health guidelines panel recommends against the use of interferons for the treatment of severe or critically ill patients except in the context of a clinical trial.\[3\] Evidence is limited. The WHO Solidarity trial found that interferon beta-1a appears to have little or no effect on hospitalized patients, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.\[859\] A randomized, placebo-controlled, phase 2 trial found that nebulized interferon beta-1a was associated with a higher odds of clinical improvement and more rapid recovery.\[902\] A phase 2 trial found that peginterferon lambda reduced viral load and increased the number of participants with a negative nasopharyngeal swab at day 7 in outpatients with mild to moderate disease compared with placebo.\[903\] \[904\] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing these drugs.

**Vitamin D**

Vitamin D supplementation has been associated with a reduced risk of acute respiratory infections such as influenza.\[905\] \[906\] \[907\] \[908\] The US National Institutes of Health guidelines panel states that there are insufficient data to recommend either for or against vitamin D for the treatment or prevention of COVID-19.\[3\] The UK National Institute for Health and Care Excellence recommends vitamin D supplementation in adults (including pregnant and breastfeeding women), young people, and children over 4 years of age between October and early March (and at other times of the year if at risk of vitamin D deficiency) to maintain bone and muscle health. However, it does not recommend supplementation to solely prevent or treat COVID-19, except as part of a clinical trial.\[909\] Evidence is limited. A Cochrane review found there is currently insufficient evidence to determine the benefits and harms of vitamin D supplementation. The evidence is very uncertain. There was substantial clinical and methodological heterogeneity of included studies, mainly due to different supplementation strategies, formulations, vitamin D status of participants, and reported outcomes.\[910\] A meta-analysis found that there may be a potential role for vitamin D supplementation in reducing disease severity, but noted that additional evidence is required.\[911\] A pilot randomized controlled trial found that high-dose calcifediol significantly reduced the need for intensive care unit treatment in hospitalized patients, and may improve clinical outcomes.\[912\]

**Vitamin C**

Vitamin C supplementation has shown promise in the treatment of viral infections.\[913\] High-dose intravenous vitamin C is being trialed in some centers for the treatment of severe disease.\[914\] The US National Institutes of Health guidelines panel states that there are insufficient data to recommend either for or against vitamin C for the treatment of noncritically ill or critically ill patients.\[3\] Evidence is limited. There is no evidence to support or refute the use of vitamin C in the treatment of patients with COVID-19; however, several trials are ongoing.\[915\] A pilot randomized controlled trial found high-dose intravenous vitamin C may show potential benefit in improving oxygenation and reducing mortality in critically ill patients; however, the trial was underpowered.\[916\]

**Colchicine**

Colchicine is an anti-inflammatory agent that downregulates multiple pro-inflammatory pathways. It is thought that its inhibitory effects on neutrophil activity, cytokine generation, and the inflammation/
thrombosis interface, along with an overall lack of evidence for systemic immunosuppression, make it a useful treatment.[917] Colchicine is already approved in some countries for indications such as gout and familial Mediterranean fever, but is off-label for this indication. The UK National Institute for Health and Care Excellence does not recommend colchicine in hospitalized patients.[561] The guideline also recommends against its use in community settings, except in the context of a clinical trial. The US National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either for or against the use of colchicine in nonhospitalized patients.[3] The panel recommends against its use in hospitalized patients, except in the context of a clinical trial. The UK Medicines and Healthcare products Regulatory Agency states that colchicine should not be used except in the context of a clinical trial, or unless there is an additional licensed indication for its use.[918] Evidence is limited. Studies are inconclusive in patients with mild to moderate disease, and adverse effects are significant.[919] Colchicine was being studied in the RECOVERY trial; however, recruitment has now closed as an interim analysis of the trial data found no convincing evidence that further recruitment would provide conclusive proof of mortality benefit.[920] A double-blind, placebo-controlled, randomized trial of over 4400 nonhospitalized patients found that colchicine led to a lower rate of the composite of death or hospital admission compared with placebo among patients with polymerase chain reaction (PCR)-confirmed disease; however, the effect was not statistically significant when participants without a PCR-confirmed diagnosis were included.[921] More randomized controlled trials are required. A systematic review and meta-analysis found that colchicine was associated with a reduction in disease severity and mortality, especially when given early in the course of disease (within 3-6 days from the onset of symptoms or hospital admission). However, the analysis was largely based on observational studies and only included three randomized clinical trials.[922] A living systematic review and network meta-analysis found that colchicine may reduce mortality (low-certainty evidence) and probably reduces the duration of hospitalization (low-certainty evidence) compared with standard care.[790] [791] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

Fluvoxamine

Fluvoxamine is a selective serotonin-reuptake inhibitor that has anti-inflammatory effects.[923] Fluvoxamine is already approved in some countries for indications such as depression and obsessive compulsive disorder, but is off-label for this indication. The US National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either for or against the use of fluvoxamine.[3] Evidence is limited. A preliminary double-blind, randomized controlled trial found that adult outpatients had a lower likelihood of clinical deterioration over 15 days compared with placebo; however, the study was limited by a small sample size and short follow-up duration.[924] A prospective cohort study in the setting of a mass outbreak found that fluvoxamine may prevent clinical deterioration requiring hospitalization and symptoms persisting beyond 2 weeks.[925] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

Antibiotics

Azithromycin is a macrolide antibiotic, and doxycycline is a tetracycline antibiotic. Both are approved for use in various bacterial infections. The UK Medicines and Healthcare products Regulatory Agency recommends that azithromycin and doxycycline should not be used within primary care (or hospitalized patients for azithromycin) unless there are additional indications for which their use remains appropriate.[926] The US National Institutes of Health guidelines panel recommends against the use of antibacterial therapy (e.g., azithromycin, doxycycline) in the absence of another indication.[3] Evidence does not support the use of these drugs. A systematic review and meta-analysis found that azithromycin was not associated with an improvement in hospitalization rate, intensive care unit admission, need for respiratory support, or mortality rate compared with control.[927] The overall quality of evidence was low to very low. The UK RECOVERY trial found that azithromycin showed no significant clinical benefit (i.e., length of hospital stay, need for invasive mechanical ventilation, 28-day mortality) in hospitalized patients compared with usual standard care alone.[928] The UK PRINCIPLE trial is currently evaluating three treatment strategies in older people (people ages over 65 years, or people ages over 50 years with an underlying health condition): usual care alone; usual care plus azithromycin; and usual care plus doxycycline.[929] An interim analysis of the trial concluded that azithromycin and doxycycline offered no meaningful beneficial effect, in terms of time to recovery, hospitalization, or death compared with standard of care in patients ages 50 years and over who were treated at home in the early stages of infection.[926] [930] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing these drugs.
Lopinavir/ritonavir

Lopinavir/ritonavir is an oral protease inhibitor. It is approved for the treatment of HIV infection, but is off-label for this indication. The World Health Organization strongly recommends against the use of lopinavir/ritonavir, regardless of disease severity. This recommendation is based on low- to moderate-certainty evidence.[743] [787] [788] The US National Institutes of Health guidelines panel recommends against the use of lopinavir/ritonavir except in the context of a clinical trial.[3] The Infectious Diseases Society of America also recommends against the use of lopinavir/ritonavir based on moderate-certainty evidence.[793] Evidence does not support the use of this drug. The WHO Solidarity trial found that lopinavir/ritonavir appears to have little or no effect on hospitalized patients, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[859] The UK RECOVERY trial found that there is no beneficial effect of lopinavir/ritonavir in hospitalized patients, with no significant difference in 28-day mortality, risk of progression to mechanical ventilation or death, or duration of hospital stay between the two treatment arms (lopinavir/ritonavir versus usual care alone).[931] A systematic review and network meta-analysis found that lopinavir/ritonavir had no significant advantage in efficacy over standard care, no antivirals, or other antiviral treatments.[932] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

Hydroxychloroquine/chloroquine

Hydroxychloroquine and chloroquine are oral disease-modifying antirheumatic drugs with anti-inflammatory and immunomodulatory effects. These drugs have been shown to be effective against SARS-CoV-2 in vitro.[933] [934] Hydroxychloroquine and chloroquine are already approved in some countries for certain conditions, but are off-label for this indication. The World Health Organization (WHO) strongly recommends against the use of hydroxychloroquine or chloroquine, regardless of disease severity, based on low- to moderate-certainty evidence.[743] [787] [788] The WHO also strongly recommends against the use of hydroxychloroquine for prevention of COVID-19. A systematic review and network meta-analysis found that hydroxychloroquine had a small or no effect on mortality and admission to hospital. There was a small or no effect on laboratory-confirmed infection, but probably increased adverse events leading to discontinuation.[935] [936] The US National Institutes of Health guidelines panel recommends against the use of hydroxychloroquine or chloroquine in hospitalized patients.[3] The panel recommends against the use of both drugs in nonhospitalized patients, except in the context of a clinical trial. The panel recommends against the use of hydroxychloroquine for postexposure prophylaxis. The Infectious Diseases Society of America strongly recommends against the use of hydroxychloroquine or chloroquine in hospitalized patients based on moderate-certainty evidence.[793] Evidence does not support the use of these drugs for treatment. A Cochrane review found that hydroxychloroquine has no clinical benefit in hospitalized patients, with moderate- to high-certainty evidence from several randomized trials, and a probable increase in adverse events associated with its use. Evidence for prevention of hospital admission in outpatients is very uncertain. Evidence for pre- or postexposure prophylaxis is limited.[937] A living systematic review concluded that there is low-strength evidence from trials and cohort studies that hydroxychloroquine has no positive effect on all-cause mortality or the need for mechanical ventilation. Trials show low strength of evidence for no positive effect on intubation or death and discharge from the hospital, whereas evidence from cohort studies about these outcomes remains insufficient. Data are insufficiently strong to support a treatment benefit of hydroxychloroquine for other outcomes (e.g., intensive care unit admission, symptom resolution). In trials where hydroxychloroquine is initiated in the outpatient setting, there is low strength of evidence that it reduces hospitalization; however, there is insufficient evidence from cohort studies.[938] [939] The WHO Solidarity trial found that hydroxychloroquine appears to have little or no effect on hospitalized patients, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[859] The UK RECOVERY trial found that hydroxychloroquine does not reduce the risk of death at 28 days compared with usual care.[940] A living systematic review and network meta-analysis found that hydroxychloroquine did not reduce the rate of infection, admission to hospital, or mortality compared with standard care or placebo when used for prophylaxis. More patients discontinued hydroxychloroquine because of adverse events.[889] Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing these drugs.

Clinical trials

Various other treatments are in clinical trials around the world. [Global coronavirus COVID-19 clinical trial tracker](https://www.covid-trials.org) International trials to identify treatments that may be beneficial, such

Primary prevention

Vaccines

• Vaccines are available under temporary emergency-use or conditional marketing authorizations in various countries. This is not a full marketing authorization or approval.

  • Immunization programs are generally prioritizing people who are at highest risk from serious disease or death (e.g., residents and staff in care homes, older people, healthcare workers, and those with underlying health conditions). However, priorities differ between countries and you should consult local guidance.

  • Protection starts around 14 days after vaccination, and vaccination may not protect all vaccine recipients. It is unknown whether vaccines prevent asymptomatic infection or transmission from individuals who are infected despite vaccination. Vaccinated people should continue to follow public health recommendations. Safety and efficacy, including duration of immunity, beyond 2 months is unknown. Advice will be updated as information on the impact of vaccination on virus transmission and indirect protection in the community is assessed.[369] [370] [371] [372] [373] [374] See Vaccine efficacy real world data below for more information.

  • Surveillance of adverse events is extremely important, and may reveal additional, less frequent serious adverse events not detected in clinical trials.

  • Safety signals regarding thrombotic events with thrombocytopenia and anaphylaxis have been reported outside of clinical trials so far. See specific sections below for more detailed information.

  • The mRNA vaccines have not been authorized for use in humans previously, so there is no long-term safety and efficacy data available for these types of vaccines.

• Report all suspected adverse reactions via your local reporting system.

  • US: [Vaccine Adverse Event Reporting System (VAERS)] (https://vaers.hhs.gov)


  • International: [WHO: Adverse Event Following Immunization (AEFI) form] (http://investigation.gvsi-aefi-tools.org/#step-1)

• Laboratory-confirmed cases of COVID-19 have been reported after vaccination.

  • Cases of vaccine breakthrough infections in fully vaccinated people (more than 2 weeks after their second dose) have been reported.[375] [376]

  • As of 30 April 2021, 10,262 cases of vaccine breakthrough infections were reported in the US; 27% of cases were asymptomatic, 10% were hospitalized; and 2% died.[377] From 1 May 2021, the US Centers for Disease Control and Prevention only monitors breakthrough infections among patients who are hospitalized or who die. As of 24 May 2021, an additional 2454 hospitalized or fatal breakthrough cases were reported.[378]

  • Emerging (preprint) evidence suggests that older people with frailty and those living in deprived areas are at increased risk of infection post-vaccination.[379]
Symptoms can be mistaken for vaccine-related adverse effects in the initial days after vaccination. Have a high level of suspicion of reported symptoms and avoid dismissing complaints as vaccine-related until vaccine recipients are tested and true infection is ruled out.[380]

Vaccine dose schedules may differ across locations.

The World Health Organization (WHO) recommends that countries experiencing exceptional epidemiologic circumstances may consider delaying the administration of the second dose of mRNA vaccines for a short period (up to 42 days based on currently available clinical trial data) as a pragmatic approach to maximizing the number of individuals benefiting from a first dose while vaccine supply continues to increase. However, evidence for this extension is not strong. Countries should ensure that any such program adjustments to dose intervals do not affect the likelihood of receiving the second dose. The WHO does not support altering doses.[371] [372] The WHO recommends an interval of 8 to 12 weeks (rather than 4-12 weeks as the manufacturer recommends) between the two doses of the AstraZeneca vaccine, in light of the observation that two-dose efficacy and immunogenicity increase with a longer interdose interval.[373]

In the UK, the Joint Committee on Vaccination and Immunisation recommends that the second dose of a vaccine should be routinely scheduled between 4 and 12 weeks after the first dose. Ideally, an 8-week minimum interval should be observed for the AstraZeneca vaccine. An interval of 28 days may be observed when rapid protection is required (e.g., patients about to receive immunosuppressive treatment). Evidence shows that delaying the second dose to 12 weeks after the first improves the boosting effect. [Public Health England: COVID-19 vaccination information for healthcare practitioners] (https://www.gov.uk/government/publications/covid-19-vaccination-programme-guidance-for-healthcare-practitioners)

In the US, the Centers for Disease Control and Prevention recommends that the second dose of an mRNA vaccine can be scheduled for up to 6 weeks after the first dose if the recommended dosing interval cannot be met. The agency continues to emphasize that the second dose should be given as close to the recommended interval as possible, and states that the two mRNA vaccines that are available in the US may be considered interchangeable in exceptional circumstances. [CDC: interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States] (https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html)

There have been suggestions about extending the length of time between doses, reducing the number of doses, changing the dose (half-dose), or mixing and matching different COVID-19 vaccines in order to vaccinate more people. Delaying the second dose of the Pfizer/BioNTech and AstraZeneca vaccines to 12 weeks or more may increase vaccine efficacy.[381] [382] [383] However, there is no good evidence to support these strategies as yet.[384] An interim analysis of a UK multicenter, participant-masked, randomized heterologous prime-boost vaccination study found an increase in systemic reactogenicity after the boost dose in heterologous vaccine schedules in comparison to homologous vaccine schedules in participants ages 50 years and older.[385]

The tables below compare vaccines that have been recommended by the World Health Organization.

In addition to these, the AstraZeneca COVID-19 vaccine (a chimpanzee adenovirus vector vaccine that carries the genetic code for the severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] spike protein) has been authorized in many countries, CoronaVac® and Covilo® (inactivated version of the SARS-CoV-2 virus) have been authorized in China, Covaxin® (inactivated version of the SARS-CoV-2 virus) has been authorized in India, and Sputnik V® (an adenovirus vector vaccine) has been authorized in Russia and is 91.6% effective.[386] [387] Sinopharm’s Covilo® vaccine has also been authorized by the World Health Organization for global use in adults ≥18 years of age (two-dose regimen with an interval of 3 to 4 weeks between doses). A large multi-country phase 3 trial has shown that two doses, administered at an interval of 21 days, have an efficacy of 79% against symptomatic infection 14 or more days after the second dose.[388] Sinovac’s CoronaVac® vaccine has also been authorized by the World Health Organization for global use in adults ≥18 years of age (two-dose regimen with an interval of 2 to 4 weeks between doses). A large phase 3 trial in Brazil has shown that two doses, administered at an
interval of 14 days, have an efficacy of 51% against symptomatic infection, 100% against severe
disease, and 100% against hospitalization starting 14 days after the second vaccination.[389]

- Several other vaccine candidates are still in development including mRNA vaccines, DNA
  vaccines, viral vector vaccines, protein subunit vaccines, live-attenuated vaccines, inactivated
  virus vaccines, and intranasal delivery systems.[390]

- [WHO: draft landscape and tracker of COVID-19 candidate vaccines] (https://www.who.int/
  publications/m/item/draft-landscape-of-covid-19-candidate-vaccines)
### mRNA vaccines

<table>
<thead>
<tr>
<th></th>
<th>Pfizer/BioNTech</th>
<th>Moderna</th>
</tr>
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<tbody>
<tr>
<td><strong>Vaccine type</strong></td>
<td>Lipid nanoparticle-formulated mRNA vaccine that encodes the SARS-CoV-2 spike protein</td>
<td></td>
</tr>
<tr>
<td><strong>Overall efficacy in adolescents ≥16 years and adults</strong>*</td>
<td>95%</td>
<td>94%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>≥12 years of age</td>
<td>≥18 years of age</td>
</tr>
<tr>
<td><strong>Authorized dose</strong></td>
<td><strong>TWO-DOSE REGIMEN</strong> 0.3 mL (30 mcg) IM; second dose at least 21 days after</td>
<td><strong>TWO-DOSE REGIMEN</strong> 0.5 mL (100 mcg) IM; second dose at least 28 days after</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Hypersensitivity to active substance or any excipients; immediate allergic reaction to first dose (should not get second dose)</td>
<td></td>
</tr>
<tr>
<td><strong>Cautions</strong></td>
<td>History of anaphylaxis/allergic reactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute severe febrile illness</td>
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<td></td>
<td>Bleeding disorders or anticoagulation</td>
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<td></td>
<td>Immunocompromised</td>
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<td></td>
<td>Pregnancy and breastfeeding</td>
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<td></td>
<td>Previous treatment with COVID-19 monoclonal antibodies/plasma</td>
<td></td>
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<tr>
<td></td>
<td>Multisystem inflammatory syndrome in children or adults</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td><em>Common:</em> headache; arthralgia; myalgia; injection-site reactions; fatigue; fever; chills; nausea; vomiting; diarrhea; rash; axillary lymphadenopathy (on same side as injection site)</td>
<td><em>Uncommon:</em> malaise; acute peripheral facial paralysis; anaphylaxis; hypersensitivity; face swelling (if dermatologic fillers present)</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>Interactions with other vaccines/drugs have not been studied (WHO recommends at least 14 days between COVID-19 vaccines and others; however, the FDA recommends that COVID-19 vaccines and other vaccines may now be administered without regard to timing)</td>
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*Data based on phase 3 clinical trials - see Vaccine efficacy clinical trial data and Vaccine safety clinical trial data sections below for detailed information. **Dose schedules may differ in some locations. Last reviewed/updated: 3 June 2021*

Comparison of selected authorized mRNA COVID-19 vaccines. Data is evolving; consult local drug formulary or guidelines for detailed information for your location.
### Coronavirus disease 2019 (COVID-19) Management

**Comparison of selected authorized viral vector COVID-19 vaccines.** Data is evolving; consult local drug formulary or guidelines for detailed information for your location. *Data based on phase 3 clinical trials - see Vaccine efficacy clinical trial data and Vaccine safety clinical trial data sections below for detailed information. **Dose schedules may differ in some locations. Last reviewed/updated: 3 June 2021

**BMJ Best Practice editorial team; compiled using data from the US product information**

<table>
<thead>
<tr>
<th><strong>Viral vector vaccines</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Janssen (Ad26.COV2.S)</strong></td>
</tr>
<tr>
<td><strong>Vaccine type</strong></td>
</tr>
<tr>
<td><strong>Overall efficacy in adolescents ≥16 years and adults</strong>*</td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Authorized dose</strong></td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
</tr>
</tbody>
</table>
| **Cautions** | History of anaphylaxis/allergic reactions  
Acute severe febrile illness  
Bleeding disorders or anticoagulation  
Immunocompromised  
Pregnancy and breastfeeding  
Heparin-induced thrombocytopenia  
Multisystem inflammatory syndrome in children or adults |
| **Adverse events** | **Common:** injection-site reactions; headache; cough; fatigue; myalgia; arthralgia; nausea; fever; chills  
**Uncommon:** anaphylaxis; urticaria; hypersensitivity; tremor; hyperhidrosis; rash; sneezing; oropharyngeal pain; pain in extremity; back pain; muscular weakness; asthenia; malaise; thrombosis with concurrent thrombocytopenia (sometimes accompanied with bleeding) |
| **Interactions** | Interactions with other vaccines/drugs have not been studied (WHO recommends at least 14 days between COVID-19 vaccines and others; however, the FDA recommends that COVID-19 vaccines and other vaccines may now be administered without regard to timing) |

**Thrombosis with thrombocytopenia syndrome (TTS)**
Thromboembolic events with thrombocytopenia have been reported in a small number of people after receiving the AstraZeneca and Janssen vaccines during post-authorization use.

- Regulatory agencies have confirmed that a causal relationship between the vaccines and the occurrence of TTS is plausible based on current information. However, this is yet to be confirmed, and further research is required. Both vaccines use an adenovirus vector system. Evidence to date does not suggest that these vaccines cause venous thromboembolism without thrombocytopenia.[391] [392] [393] [394] [395] [396]
- Several countries temporarily paused the use of these vaccines while the safety signal was investigated. While use of the AstraZeneca vaccine has now resumed in most countries, some countries have permanently stopped its use in their immunization programs (e.g., Norway).[397] Use of the Janssen vaccine has now resumed in Europe and the US, with a warning added to the vaccine’s labels about the risk of TTS, particularly in women ages 18 to 49 years.[396] [398] However, some countries have permanently stopped the use of the Janssen vaccine in their immunization programs (e.g., Norway).[399]
- There has been no safety signal for TTS following receipt of mRNA COVID-19 vaccines, although a small number of cases have been reported and the European Medicines Agency continues to closely monitor the situation.
- Also known as vaccine-induced prothrombotic immune thrombocytopenia (VIPIT), vaccine-induced immune thrombotic thrombocytopenia (VITT), and vaccine-induced thrombosis and thrombocytopenia (VITT).

- Blood clots occur in unusual sites.

- The very rare types of thrombosis reported include cerebral venous sinus thrombosis, splanchnic vein thrombosis, and arterial thrombosis, together with thrombocytopenia and sometimes bleeding. Multifocal venous and arterial thromboses have also been reported in serious cases. Although rare, these events can rapidly progress and may be life-threatening or fatal.[391] [392] [396]
- Most cases occur in younger people after the first dose.

- Data suggest that there is a slightly higher incidence reported in younger adult age groups.[392]
- Most of the cases reported occurred in women under 60 years of age within 2 to 3 weeks of receiving their first dose.[391] [396] Cases have also been reported after this period.[400]
- Risk factors have not been identified, and there is limited experience with the second dose.

- These events are very rare.

- Monitoring of the Yellow Card reporting system in the UK has detected 332 reports of TSS after administration of the AstraZeneca vaccine, including 120 cases of cerebral venous sinus thrombosis and 212 cases of thrombosis in other major veins, with 58 deaths, an overall case fatality rate of 17% (as of 19 May 2021). Most cases occurred after the first dose; however, 17 cases have been reported after the second dose. The overall risk in the UK has currently been estimated to be 13 per million people who receive the vaccine.[392]
- A total of 17 cases of TTS have been reported with the Janssen vaccine to VAERS (as of 21 April 2021). All of these cases occurred in women between the ages of 18 and 59, with a symptom onset between 6 and 15 days after vaccination. The overall risk has currently been estimated to be 0.9 per million people who receive the vaccine, with the risk increasing to 7 per million in women ages 18 to 49 years.[398] [401] [402]
- A study in Denmark and Norway reported 11 excess venous thromboembolic events per 100,000 vaccinations, including 2.5 excess cerebral venous thrombosis events per 100,000 vaccinations with the AstraZeneca vaccine.[403]

- It is thought to be triggered by an immune response.
• The vaccine may trigger the development of an immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4, which clinically mimics autoimmune heparin-induced thrombocytopenia.[404] [405] [406]

• There are now age-related prescribing restrictions for the vaccines in some countries.

• The Joint Committee on Vaccination and Immunisation (JCVI) in the UK advises that it is preferable for adults ages 30 to 39 years without underlying health conditions to receive an alternative to the AstraZeneca vaccine, where available, and only if this does not cause substantial delays in being vaccinated.[407] The JCVI also advises that it is preferable for adults ages <30 years without underlying health conditions that put them at higher risk of severe disease to be offered an alternative vaccine. All recipients should be fully informed about the benefits and risks of vaccination.[408]

• Consult local guidelines for more information on prescribing restrictions in your country.

• There are now additional contraindications, warnings, and cautions to using the vaccines in some countries.

• In the UK, the AstraZeneca vaccine is contraindicated in patients with a history of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2). Only consider administration of the AstraZeneca vaccine in patients with a history of cerebral venous sinus thrombosis or antiphospholipid syndrome when the potential benefits outweigh the potential risks. Patients who have experienced major venous and arterial thrombosis occurring with thrombocytopenia following vaccination with any COVID-19 vaccine should not receive a second dose of the AstraZeneca vaccine.[400] The Janssen vaccine is only recommended in patients with a history of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2) if the potential benefits outweigh the risks.[409]

• The European Medicines Agency recommends that the AstraZeneca vaccine is contraindicated in people who experienced TTS after the first dose. People diagnosed with thrombocytopenia within 3 weeks after vaccination should be actively investigated for signs of thrombosis, and people who present with thrombosis within 3 weeks of vaccination should be evaluated for thrombocytopenia.[410]

• The European Medicines Agency and the US Centers for Disease Control and Prevention have recommended that a warning about the risk of TTS be added to the product information for the Janssen vaccine, particularly in women ages 18 to 49 years. However, there are no new contraindications or cautions at this point in time.[396] [398]

• The US Centers for Disease Control and Prevention recommends that people with a history of an episode of an immune-mediated syndrome characterized by thrombosis and thrombocytopenia, such as heparin-induced thrombocytopenia, should be offered an mRNA vaccine instead of the Janssen vaccine if it has been ≤90 days since their illness resolved. After 90 days, patients may be vaccinated with any authorized vaccine.[411] The AstraZeneca vaccine is not available in the US as yet; therefore, the agency does not make any recommendations for this vaccine.

• Pregnancy predisposes to thrombosis; therefore, women should discuss whether the benefits of having the vaccine outweigh the risks for them with their healthcare professional.[392]

• Be alert to the signs and symptoms of TTS.

• Advise vaccine recipients who experience any severe symptoms (e.g., dyspnea, chest pain, leg swelling, persistent abdominal pain, neurologic symptoms such as severe and persistent headaches or blurred vision, tiny blood spots under the skin beyond the site of the injection) from around 4 to 20 days after vaccination to seek urgent medical attention.[393]

• Promptly treat patients who develop TTS according to local guidelines.

• There is limited information about the optimal treatment of this condition; however, management is similar to heparin-induced thrombocytopenia. Consult a hematologist.
• Guidelines generally recommend ordering a complete blood count (with platelets), coagulation screen (including fibrinogen and D-dimer), blood film/peripheral smear, and platelet factor 4 enzyme-linked immunosorbent assay for any patient presenting with acute thrombosis or new-onset thrombocytopenia within 28 to 30 days of receiving a COVID-19 vaccination. Typical laboratory features include thrombocytopenia, raised D-dimer levels above the level expected for venous thromboembolism, and low fibrinogen. Antibodies to platelet factor 4 have also been identified. Imaging studies may also be required (e.g., suspected cerebral venous sinus thrombosis).[412] [413] [414] [415]

• First-line treatment is urgent administration of intravenous immune globulin. Some experts also recommend the use of corticosteroids. Anticoagulate with a nonheparin-based therapy such as a direct oral anticoagulant, fondaparinux, danaparoid, or argatroban, depending on the clinical picture. Heparin and platelet transfusions are best avoided. Plasma exchange may be considered under certain circumstances. Replace fibrinogen if needed.[412] [413] [414] [415]

• Consult local guidelines for more detailed information on the diagnosis and management of this condition. All cases must be reported to local authorities.

• The benefits of the vaccines continue to outweigh the risks.

  • The World Health Organization, the European Medicines Agency, and the Medicines and Healthcare products Regulatory Agency in the UK state that the benefits of the AstraZeneca vaccine continue to outweigh the risks.[391] [392] [393]

  • The European Medicines Agency and US Centers for Disease Control and Prevention state that the benefits of the Janssen vaccine continue to outweigh the risks.[396] [398]


Vaccines and allergic or vasovagal reactions

• Severe allergic reactions, including anaphylaxis, have been reported outside of clinical trials in the general population after vaccination.

  • In the UK, monitoring of the Yellow Card reporting system has detected 317 cases of anaphylaxis with the Pfizer/BioNTech vaccine, 674 cases with the AstraZeneca vaccine, and 10 cases with the Moderna vaccine (as of 19 May 2021).[416]

  • In the US, monitoring by the VAERS detected 4.7 cases of anaphylaxis per million doses of the Pfizer/BioNTech vaccine, and 2.5 cases per million doses of the Moderna vaccine as of 18 January 2021.[417]

• It has been suggested that reactions after vaccines may be due to the presence of lipid pegylated ethylene glycol (PEG), or PEG derivatives such as polysorbates.[418]

• The WHO recommends that a history of anaphylaxis to any component of the vaccine is a contraindication to vaccination for all vaccines. People with an immediate anaphylactic allergic reaction to the first dose of two-dose regimens should not receive additional doses. Administer vaccines only in settings where anaphylaxis can be treated, and observe for at least 15 minutes after vaccination.[371] [372] [373] [374]

• The WHO recommends people with an immediate nonanaphylactic allergic reaction to the first dose of an mRNA vaccine (i.e. urticaria, angioedema, or respiratory symptoms such as cough, stridor, or wheezing without any other symptoms within 4 hours of administration) should not receive additional doses unless recommended after review by a health professional with specialist expertise. A history of any immediate allergic reaction to any other vaccine or injectable therapy is considered a precaution, but not a contraindication, to vaccination. Perform a risk assessment to determine the type and severity of reaction and the reliability of the information. These people may still be vaccinated, but the risks should be weighed against the benefits of vaccination, and the recipient should be observed for 30 minutes after vaccination in healthcare settings where anaphylaxis can be treated immediately. Anaphylactic reactions have also been reported in people without a history of severe allergic reactions. Food, insect venom, contact, or seasonal allergies, and allergic rhinitis, eczema, and asthma are not considered a
precaution. There is no contraindication or precaution to vaccination for people with latex, egg, or gelatin allergies.[371] [372]

- The UK-based Medicines and Healthcare products Regulatory Agency recommends that anyone with a previous history of allergic reactions to the ingredients of the vaccine should not receive it, but those with any other allergies such as a food allergy can have the vaccine.[419]
- In the US, the Centers for Disease Control and Prevention recommends that people with a contraindication to one type of the currently authorized vaccines (e.g., an mRNA vaccine) have a precaution to the other (e.g., viral vector vaccine). However, because of potential cross-reactive hypersensitivity between ingredients in mRNA and viral vector vaccines, an allergist/immunologist should be consulted to help determine whether the patient can safely receive vaccination.[411]
- Guidelines on vaccinating people with a history of allergy or anaphylaxis may differ across locations; consult local guidance.

People with a history of receiving dermal fillers may develop swelling at or near the site of filler injection (e.g., lips, face) following administration of an mRNA vaccine. This appears to be temporary and may be treated with corticosteroids. The European Medicines Agency found that there is at least a reasonable possibility of a causal association between the vaccine and the reported cases of facial swelling.[420]

- Delayed-onset local reactions around the injection site have been reported with the Moderna vaccine (median 7-8 days after first vaccination), and are sometimes quite large (e.g., at least 10 cm in diameter). Most people who had a reaction to the first dose also developed a similar reaction to the second dose, and developed it much sooner compared with the first dose.[421] [422]
- Anxiety-related reactions, including vasovagal reactions and hyperventilation, may occur.[423] Ensure precautions are in place to avoid injury from fainting.

Vaccines and lymphadenopathy

- Axillary/supraclavicular lymphadenopathy has been reported within 2 to 4 days post-vaccination. Although UK guidelines currently recommend a 2-week suspected-cancer referral for unexplained axillary lymphadenopathy in those ages >30 years, a watchful wait approach may be appropriate in patients who have been vaccinated in the past week, provided that they have a normal breast exam and no history of breast cancer. Further examination up to 2 weeks later is recommended, with referral to secondary care for those with nonresolving lymphadenopathy. An urgent referral to the breast clinic is advisable in patients with current or previous history of breast cancer.[424]

Vaccines and Bell palsy

- There have been case reports of isolated facial paralysis after vaccination for decades with almost all viral vaccines, and it is thought to be immune-mediated or induced by viral reactivations. However, pharmacoepidemiologic studies have so far failed to identify a higher risk of facial paralysis after vaccination. When compared with other viral vaccines, mRNA COVID-19 vaccines do not appear to display a safety signal of facial paralysis, although cases have been rarely reported.[425]

Vaccines and Guillain-Barre syndrome

- The European Medicines Agency is currently assessing safety signals of Guillain-Barre syndrome with the AstraZeneca vaccine.[420]

Vaccines and myocarditis/pericarditis

- The European Medicines Agency is currently assessing safety signals of myocarditis and pericarditis with the mRNA vaccines (mainly the Pfizer/BioNTech vaccine).[420]
- The US Advisory Committee on Immunization Practices is also investigating several cases of myocarditis and pericarditis following vaccination with an mRNA vaccine. The cases occurred predominantly in adolescents and young adults, more often in males than females, more often following dose 2 than dose 1, and typically within 4 days after vaccination.[426]
- Consider myocarditis and pericarditis in adolescents or young adults with acute chest pain, shortness of breath, or palpitations.[427]

Vaccines and capillary leak syndrome
• The European Medicines Agency is currently reviewing a safety signal to assess reports of capillary leak syndrome in people who received the AstraZeneca vaccine.[428]
• In the UK, monitoring of the Yellow Card reporting system has detected 7 cases of capillary leak syndrome with the AstraZeneca vaccine (as of 19 May 2021).[429]

Vaccines and specific patient populations

• There are limited or no data available from clinical trials about the use of vaccines in specific patient populations. Despite this, the WHO recommends that the following populations may be vaccinated, depending on the vaccine used:[371] [372] [373] [374]
  - Older people (without an upper age limit)
  - People with comorbidities that have been identified as increasing the risk for severe disease
  - Immunocompromised people who are part of a group recommended for vaccination
  - People living with HIV who are part of a group recommended for vaccination
  - People with autoimmune conditions who have no contraindications to vaccination and who are part of a group recommended for vaccination
  - People with a history of Bell palsy who have no contraindications to vaccination
  - People with a history of symptomatic or asymptomatic SARS-CoV-2 infection.
• Delayed vaccination is recommended in people with an acute febrile illness or current acute COVID-19 (until they are afebrile and have recovered from acute illness), and in people who previously received passive antibody therapy for COVID-19 (for at least 90 days).
• Delayed vaccination may be considered in people who have had confirmed SARS-CoV-2 infection in the preceding 6 months (until near the end of this period) if, for example, there is limited vaccine supply. Emerging data indicate that symptomatic reinfection after natural infection may occur in settings where variants of concerns with evidence of immune escape are circulating. In these settings, earlier immunization after infection may be advisable.
  - A single dose of an mRNA vaccine has been found to elicit a rapid immune response in seropositive participants, with post-vaccination antibody titers that were similar to (or exceeded) titers found in seronegative participants who received two vaccinations.[430]
  - People with previous infection have been shown to generate strong humoral and cellular responses to one dose of the Pfizer/BioNTech COVID-19 vaccine with evidence of high titers of in vitro live virus neutralization.[431] [432]
  - A preprint study found that one dose of the vaccine may be sufficient for people who have already been infected with SARS-CoV-2; however, further research is required.[433]
• The WHO recommends an individual risk–benefit assessment for very frail older people with a life expectancy anticipated to be less than 3 months.[372] The Norwegian Medicines Agency recommends conducting more thorough evaluations of very frail older patients before vaccination, after 23 patients died shortly after receiving the Pfizer/BioNTech vaccine. However, it is currently unknown whether there is a connection between these deaths and the vaccine. The agency has investigated 13 of the deaths so far and has concluded that common adverse reactions of mRNA vaccines, such as fever, nausea, and diarrhea, may have contributed to fatal outcomes in some of the frail patients.[434] [435]
• Emerging data suggest that vaccine efficacy may be lower in cancer patients and solid organ transplant recipients; however, further research is required.[436] [437] [438] [439] [440] [441] [442] [443] [444]
• Guidance for vaccination in specific patient populations has been published for:
  - Patients with rheumatic and musculoskeletal diseases[445]
  - Patients with cancer receiving systemic chemotherapy.[446]

Vaccines and pregnant/breastfeeding women
**Coronavirus disease 2019 (COVID-19) Management**

- Use caution in pregnant and breastfeeding women as there are limited safety and efficacy data available.

- Preliminary data from the v-safe pregnancy registry and VAERS in the US did not show any obvious safety signals among pregnant women who received mRNA vaccines. These data have many limitations, and continued monitoring is needed to further assess the risk. Among 221 pregnancy-related adverse events reported to the VAERS, the most frequently reported event was spontaneous abortion (46 cases), followed by stillbirth, premature rupture of membranes, and vaginal bleeding (3 reports for each). No congenital anomalies were reported to the VAERS.[447]

- A small exploratory study found that mRNA vaccines were immunogenic in pregnant women, and vaccine-elicited antibodies were transported to infant cord blood and breast milk.[448]

- A small prospective study found robust secretion of SARS-CoV-2 specific immunoglobulin A (IgA) and IgG antibodies in breast milk for 6 weeks after vaccination.[449]

- Recommendations for use in pregnant and breastfeeding women vary. Consult your local guidance.

  - The WHO recommends not using vaccines in pregnant women, unless the benefits outweigh the potential risks (e.g., healthcare workers at high risk of exposure, women with comorbidities that place them in a high-risk group for severe disease). It recommends that women who are breastfeeding, and who are part of a group recommended for vaccination, should be offered vaccination on an equivalent basis. It does not recommend delaying pregnancy or discontinuing breastfeeding after vaccination.[371] [372] [373] [374]

  - The Joint Committee on Vaccination and Immunisation (JCVI) advises that pregnant women in the UK should be offered the COVID-19 vaccine, preferably an mRNA vaccine, at the same time as the rest of the population, based on their age and clinical risk group. However, the JCVI acknowledges that more research is needed, and advises pregnant women to discuss the risk and benefits with their clinician.[450] [451]

  - The US Centers for Disease Control and Prevention recommends that pregnant women are eligible for and can receive a COVID-19 vaccine. Pregnant women who choose to receive a vaccine are encouraged to enroll in the v-safe program. The agency also recommends that women who are trying to become pregnant and lactating women can also receive a vaccine, although it acknowledges that there are no safety data available in these patient groups.[411]


  - The American College of Obstetricians and Gynecologists recommends that COVID-19 vaccines should not be withheld from pregnant or breastfeeding women who meet criteria for vaccination based on recommended priority groups. Discuss the risks and benefits with the person before vaccination. Pregnant and breastfeeding women who decline vaccination should be supported in their decision.[452]

**Vaccines and children**

- Vaccines are not currently authorized for use in children <12 years of age.

- The US Food and Drug Administration has authorized the Pfizer/BioNTech vaccine for emergency use in adolescents ages 12 to 15 years.[453] The US Advisory Committee on Immunization Practices has made an interim recommendation for use of the Pfizer/BioNTech COVID-19 vaccine in adolescents ages 12 to 15 years for the prevention of COVID-19.[454]

- The European Medicines Agency has also authorized use of the Pfizer/BioNTech vaccine in young people ages 12 to 15 years.[455]

- Authorization was based on an ongoing randomized, placebo-controlled clinical trial in the US of over 2000 participants that reports 100% efficacy from 7 days after the second dose.[456] Due to the limited number of children included in the study, the trial could not have detected rare adverse effects.

- The European Medicines Agency and the US Advisory Committee on Immunization Practices are currently investigating reports of myocarditis and pericarditis in younger people. See Vaccines and myocarditis/pericarditis above.

**Vaccine efficacy: real world data**
• Emerging observational evidence suggests real-world efficacy in reducing the rate of symptomatic or asymptomatic infection, disease severity, hospitalization, and death; however, further research is required.

• A case control study of over 150,000 adults ages ≥70 years who were vaccinated with either the Pfizer/BioNTech or AstraZeneca vaccines and who reported symptoms between 8 December 2020 and 19 February 2021 found that vaccination with one dose of either vaccine was associated with a 60% to 70% protection against symptomatic disease, an 80% protection against hospital admission, and an 85% protection against death. Protection was maintained for at least 6 weeks, and vaccines were effective against the B.1.1.7 variant.[457]

• A prospective cohort study (preprint) in the UK found that people ages ≥70 years who received a single dose of either the Pfizer/BioNTech or AstraZeneca vaccine had a 44% and 55% reduced risk of death, respectively, compared with unvaccinated people. There was a 69% reduced risk of death after the second dose of the Pfizer/BioNTech vaccine.[458]

• A prospective cohort study (preprint) in the UK found that effectiveness in preventing hospitalization was high in people ages ≥70 years who received a single dose of either the AstraZeneca or Pfizer/BioNTech vaccines (73% and 81%, respectively, in patients ≥80 years; 84% and 81%, respectively, in patients 70-79 years), and especially after two doses of the Pfizer/BioNTech vaccine (93% in patients ≥80 years) compared with unvaccinated people.[459] A study in Scotland found that the first dose of the Pfizer/BioNTech vaccine was associated with...
a 91% reduction in hospital admissions at 28 to 34 days post-vaccination (an 88% reduction for the AstraZeneca vaccine).[460]

• A prospective cohort study (preprint) in the UK found that odds of new infection were reduced by 65% after the first dose of either the Pfizer/BioNTech or AstraZeneca vaccine compared with unvaccinated people without prior evidence of infection. A larger reduction in odds of infection was seen after the second dose (70%). There was no evidence that the benefits varied between the two vaccines.[461]

• A prospective cohort study in UK healthcare workers found that a single dose of the Pfizer/BioNTech vaccine showed effectiveness at preventing both symptomatic and asymptomatic infection of 70% at 21 days after the first dose and 85% at 7 days after two doses compared with an unvaccinated cohort. The study population was exposed to the B.1.1.7 variant.[462]

• A prospective cohort study (preprint) in the UK found that the Pfizer/BioNTech and AstraZeneca vaccines are associated with reduced likelihood of household transmission from individuals diagnosed with COVID-19 after vaccination. The secondary attack rate was reduced from 10.1% when the index case was an unvaccinated person, to 5.7% to 6.25% (depending on the vaccine) when the contact was vaccinated.[463]

• Observational studies from Israel have found that the Pfizer/BioNTech vaccine was highly effective in preventing symptomatic and asymptomatic infection, as well as hospitalizations, severe disease, need for mechanical ventilation, and death, including those caused by the B.1.1.7 variant.[464] [465] [466] [467] [468]

• Observational studies from the US have found that the Pfizer/BioNTech and Moderna vaccines were highly effective in preventing symptomatic and asymptomatic infection, as well as hospitalizations.[469] [470] [471] [472]

Vaccine efficacy: SARS-CoV-2 variants

• Pfizer/BioNTech COVID-19 vaccine

• Preliminary studies suggest that the vaccine may be effective against B.1.1.7 and B.1.351 variants; however, neutralization of the B.1.351 variant may be weaker.[473] [474] [475] [476] [477] [478] Data also show that the vaccine is effective against the B.1.526, B.1.429, and B.1.1.7 + E484K variants.[479]

• Emerging evidence suggests that the vaccine may be effective against the Indian B.1.617.1 variant.[45]

• The manufacturer is currently testing booster doses against emerging SARS-CoV-2 variants.[480]

• Moderna COVID-19 vaccine

• Preliminary studies suggest that the vaccine may be effective against B.1.1.7 and B.1.351 variants. Although neutralizing antibody titers were lower for the B.1.351 variant compared with earlier SARS-CoV-2 variants, levels were expected to be protective.[476] [481] [482]

• Emerging evidence suggests that the vaccine may be effective against the Indian B.1.617.1 variant.[45]

• The manufacturer is currently testing booster doses against emerging SARS-CoV-2 variants.[483]

• AstraZeneca COVID-19 vaccine

• A study suggests that the vaccine may be effective against symptomatic infection caused by the B.1.1.7 variant.[484] However, a randomized controlled trial found that a two-dose regimen did not show protection against mild to moderate disease due to the B.1.351 variant, reporting an efficacy rate of 21.9%.[485]

• Janssen COVID-19 vaccine

• There is a lack of data on vaccine efficacy against SARS-CoV-2 variants.

Vaccine efficacy: clinical trial data
**Pfizer/BioNTech COVID-19 vaccine**

- Efficacy is based on an interim analysis of results from a phase 3 trial of 43,448 participants (with randomization to vaccine and placebo arms in a 1:1 ratio). The vaccine is reported to be 95% effective in preventing symptomatic COVID-19 after 2 doses compared with placebo (saline), in people ages 16 years and older (data on adolescents ages 12 to 15 years is yet to be published). This is based on an analysis of 170 confirmed cases of COVID-19 with an onset at least 7 days after the second dose among recipients with no evidence of existing or prior SARS-CoV-2 infection (8 cases in the vaccine arm versus 162 cases in the placebo arm). Efficacy was 52% after the first dose. Among 10 cases of severe disease with onset after the first dose, 9 cases occurred in the placebo arm and 1 case occurred in the vaccine arm. This only provides preliminary evidence of vaccine-mediated protection against severe disease.[369]

The manufacturer reports an efficacy of 91.3% against symptomatic illness diagnosed from 1 week to 6 months after the second dose.[486]

**Moderna COVID-19 vaccine**

- Efficacy is based on an interim analysis of results from a phase 3 trial of 30,420 participants (with randomization to vaccine and placebo arms in a 1:1 ratio). The vaccine is reported to be 94.1% effective in preventing symptomatic COVID-19 after 2 doses compared with placebo (saline) in people ages 18 years and older. This is based on an analysis of 196 confirmed cases of COVID-19 with an onset at least 14 days after the second dose among recipients with no evidence of existing or prior SARS-CoV-2 infection (11 cases in the vaccine arm versus 185 cases in the placebo arm). Among 30 cases of severe disease (including one fatality) with onset after the first dose, all cases occurred in the placebo arm and none in the vaccine arm.[370]

Antibody levels remained high in 33 adults at approximately 200 days after receiving the second dose of the vaccine in an ongoing phase 1 trial.[487]

**AstraZeneca COVID-19 vaccine**

- Efficacy is based on an interim analysis of pooled data from four ongoing randomized controlled clinical trials with 11,636 participants conducted in the UK, Brazil, and South Africa. The vaccine is reported to be 70.4% effective in preventing symptomatic COVID-19 after 2 doses compared with control (meningococcal vaccine or saline) in people ages 18 years and older. This is based on an analysis of 131 confirmed cases of COVID-19 with an onset at least 15 days after the second dose among recipients with no evidence of existing or prior SARS-CoV-2 infection (30 cases in the vaccine arm versus 101 cases in the placebo arm). Trial results are yet to be published. Among 2 cases of severe disease, all cases occurred in the control arm and none in the vaccine arm.[400]

- Data from the US phase 3 trial has been reported by the manufacturer. Based on an interim analysis of 32,449 participants and 141 symptomatic cases, vaccine efficacy at preventing symptomatic disease has been reported as 79%.[488] However, the National Institutes of Health queried the accuracy of the data.[489] The manufacturer has now presented further updated data that found an overall efficacy rate of 76%.[490]

**Janssen COVID-19 vaccine**

- Efficacy is based on an interim analysis of pooled data from an ongoing randomized controlled clinical trial with 43,783 participants conducted in South Africa, South America, Mexico, and the US. The vaccine is reported to be 66.9% and 66.1% effective in preventing moderate to severe/critical disease at least 14 days and 28 days after vaccination, respectively, compared with placebo (saline) in people ages 18 years and older. Efficacy for prevention of severe/critical disease was 76.7% and 85.4% at least 14 days and 28 days after vaccination, respectively. These figures are based on an analysis of 464 confirmed cases of COVID-19 with an onset at least 14 days after vaccination among recipients with no evidence of existing or prior SARS-CoV-2 infection (116 cases in the vaccine arm versus 348 cases in the placebo arm), and 259 confirmed cases of COVID-19 with an onset at least 28 days after vaccination (66 cases in the
Coronavirus disease 2019 (COVID-19) Management

Vaccine arm versus 193 cases in the placebo arm). Vaccine efficacy was higher in the US (74%) compared with South Africa (52%). Trial results are yet to be published.[491]

Vaccine safety: clinical trial data

• Pfizer/BioNTech COVID-19 vaccine

  • Safety is based on an interim analysis of results from a phase 3 trial of 43,448 participants. The reactogenicity subset included 8183 participants.[369]
  • Local adverse reactions were more common in the vaccine group compared with placebo, with the most common reaction being injection-site pain within 7 days after injection (83% after the first dose and 78% after the second dose in younger participants; 71% after the first dose and 66% after the second dose in older participants). Less than 1% of participants reported severe pain. Local adverse reactions were similar after the first and second doses.
  • Systemic adverse reactions were more common in the vaccine group compared with placebo, and were reported more often by younger patients and after the second dose. The most commonly reported systemic adverse reactions after the second dose were fatigue (59% in younger participants; 51% in older participants), headache (52% in younger participants; 39% in older participants), and fever (16% in younger participants; 11% in older participants). Severe systemic events were reported in <2% of participants after either dose, except for fatigue and headache after the second dose.
  • Other rare adverse events included lymphadenopathy, shoulder injury (related to vaccine administration), paroxysmal ventricular arrhythmia, and right leg paresthesia.

• Moderna COVID-19 vaccine

  • Safety is based on an interim analysis of results from a phase 3 trial of 30,420 participants.[370]
  • Solicited local and systemic adverse reactions were reported in 87.8% of participants within 7 days after the first dose in the vaccine group compared with 48% in the placebo group, and 92.2% of participants within 7 days after the second dose in the vaccine group compared with 42.8% in the placebo group. The most commonly reported solicited adverse reactions included injection-site reactions, fatigue, headache, myalgia, and arthralgia. These reactions were more commonly reported and were more severe after the second dose. Solicited adverse reactions were more common among participants ages 18 to 64 years compared with adults ages ≥65 years.
  • Unsolicited adverse events related to vaccination (up to 28 days after any injection) were reported in 8.2% of participants in the vaccine group compared with 4.5% in the placebo group. The incidence of severe adverse events was higher in the vaccine group compared with the placebo group (0.5% versus 0.2%). The most commonly reported unsolicited adverse events (reported in at least 1% of participants) were fatigue and headache. The relative incidence of these events was not affected by age.
  • Bell palsy occurred more commonly in the vaccine group (three cases) compared with the placebo group (one case), suggesting that it may be more than a chance event. This will require close monitoring as larger populations are vaccinated outside of clinical trials.

• AstraZeneca COVID-19 vaccine

  • Safety is based on an interim analysis of pooled data from four ongoing randomized controlled clinical trials with 23,745 participants conducted in the UK, Brazil, and South Africa (trial results are yet to be published).[400]
• The most frequently reported adverse events were: injection-site reactions (>60%); headache, fatigue (>50%); myalgia, malaise (>40%); fever, chills (>30%); arthralgia, nausea (>20%). Adverse reactions were milder and reported less frequently after the second dose and in adults ages ≥65 years.

• Janssen COVID-19 vaccine

• Safety is based on an interim analysis of pooled data from an ongoing randomized controlled clinical trial with 43,783 participants conducted in South Africa, South America, Mexico, and the US (trial results are yet to be published). The reactogenicity subset included 6736 participants. [491]

• The most frequently reported adverse events were: injection-site reactions (48.6%); headache (38.9%); fatigue (38.2%); and myalgia (33.2%). Approximately 0.7% and 1.8% of local and systemic solicited adverse reactions, respectively, were reported as grade 3. Reports of solicited reactions were less common among participants ≥60 years of age. Other adverse reactions possibly related to the vaccine included urticaria, thromboembolic events, and tinnitus. One serious event of a hypersensitivity reaction (not classified as anaphylaxis) and one case of severe systemic reactogenicity were likely related to the vaccine.

Vaccine trial limitations

• A key limitation of the data is the short duration of safety and efficacy follow-up. Trials were not sufficiently powered to detect less common adverse events reliably, and the median follow-up time was only 2 months after the second dose. Trials do not address whether the vaccine prevents transmission or affects infectiousness, and the duration of protection is yet to be determined. There are no data on children or younger adolescents, pregnant or breastfeeding women, or immunocompromised people. There are also no data to assess efficacy in populations at high risk of severe disease, in people previously infected with SARS-CoV-2, against long-term effects of disease, or against mortality. [369] [370]

• There are concerns that the trials were not designed to detect a reduction in any serious outcome such as hospital admissions, use of intensive care, or deaths, or whether the vaccines can interrupt transmission of the virus – two key primary end points in vaccine efficacy trials. [492] Also, since the trials have been published, important questions about final efficacy data exclusions, as well as concerns about the use of pain and fever medications, unblinding, and primary event adjudication committees have been raised. [493]

• Planned long-term follow-up of participants is unlikely to occur in the context of trials due to the ethics of following a placebo recipient long-term without offering the vaccine. This could inadvertently threaten ongoing vaccine research that is yet to define immunologic correlates of protection against COVID-19, which could vary according to the vaccine platform, individual characteristics, age groups, and population subset. [494] [495] [496]

• Previous trials of coronavirus vaccines identified cellular immunopathology and antibody-dependent enhancement (ADE) as potential safety issues. There are concerns over ADE of SARS-CoV-2 due to subsequent exposure to wild-type SARS-CoV-2 post vaccination and prior exposure to other coronaviruses (such as those that cause the common cold). [497] [498] Available data do not indicate a risk of vaccine-enhanced disease with the mRNA vaccines; however, data are limited and the risk over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further. [369] [370]

Infection prevention and control for healthcare professionals

• Always consult local infection prevention and control protocols; only basic principles are detailed here.

• Immediately isolate all suspected or confirmed cases in an area that is separate from other patients. Place patients in adequately ventilated single rooms if possible. When single rooms are not available, place all cases together in the same room and ensure there is at least 3 feet (1 meter) between patients. [499]

• Implement standard precautions at all times. [499]
• Practice hand and respiratory hygiene
• Give patients a medical mask to wear
• Wear appropriate personal protective equipment
• Practice safe waste management and environmental cleaning.

• Implement additional contact and droplet precautions before entering a room where cases are admitted.[499]

• Wear a medical mask, gloves, an appropriate gown, and eye/facial protection (e.g., goggles or a face shield)
• Use single-use or disposable equipment.

• Implement airborne precautions when performing aerosol-generating procedures, including placing patients in a negative pressure room.[499]

• Some countries and organizations recommend airborne precautions for any situation involving the care of a COVID-19 patient.

• All specimens collected for laboratory investigations should be regarded as potentially infectious.[499]
• Appropriate personal protective equipment gives healthcare workers a high level of protection against COVID-19. A cross-sectional study of 420 healthcare workers deployed to Wuhan with appropriate personal protective equipment tested negative for SARS-CoV-2 on molecular and serologic testing when they returned home, despite all participants having direct contact with COVID-19 patients and performing at least one aerosol-generating procedure.[500] Standard surgical masks are as effective as respirator masks for preventing infection of healthcare workers in outbreaks of viral respiratory illnesses such as influenza, but it is unknown whether this applies to COVID-19.[501]
• Detailed infection prevention and control guidance is available:


Telehealth for primary care physicians

• It is important that primary care physicians avoid in-person assessment of patients with suspected COVID-19 in primary care when possible to avoid infection.[502] Most patients can be managed remotely by telephone or video consultations. Algorithms for dealing with these patients are available:

  • [BMJ: covid-19 – a remote assessment in primary care] (https://www.bmj.com/content/368/bmj.m1182)

General prevention measures for the general public

• People should be advised to:[503] [504]

  • Wash hands often with soap and water for at least 20 seconds or an alcohol-based hand sanitizer (that contains at least 60% alcohol), especially after being in a public place, blowing
their nose, or coughing/sneezing. Avoid touching the eyes, nose, and mouth with unwashed hands

- Avoid close contact with people (i.e., maintain a distance of at least 3 feet [1 meter]) including shaking hands, particularly those who are sick, have a fever, or are coughing or sneezing. Avoid going to crowded and poorly ventilated places. It is important to note that recommended distances differ between countries (for example, 6 feet [2 meters] is recommended in the US and UK) and you should consult local guidance. However, there is no evidence to support a distance of 6 feet (2 meters)[505]
- Practice respiratory hygiene (i.e., cover mouth and nose when coughing or sneezing, discard tissue immediately in a closed bin, and wash hands)
- Seek medical care early if they have a fever, cough, and difficulty breathing, and share their previous travel and contact history (travelers or suspected/confirmed cases) with their healthcare provider
- Stay at home and self-isolate if they are sick, even with mild symptoms, until they recover (except to get medical care)
- Clean and disinfect frequently touched surfaces daily (e.g., light switches, door knobs, countertops, handles, phones).

- [Centre for Evidence-Based Medicine: what is the evidence to support the 2-metre social distancing rule to reduce COVID-19 transmission?] (https://www.cebm.net/covid-19/what-is-the-evidence-to-support-the-2-metre-social-distancing-rule-to-reduce-covid-19-transmission)

Face masks in community settings

- Recommendations on the use of face masks in community settings vary between countries.[506] It is mandatory to wear a mask in public in certain countries or in certain situations, and masks may be worn in some countries according to local cultural habits. Consult local public health guidance for more information.
- There is no high-quality or direct scientific evidence to support the widespread use of masks by healthy people in the community setting, and there are risks and benefits that must be considered. Data on effectiveness is based on limited and inconsistent observational and epidemiologic studies.[92] The first randomized controlled trial to investigate the efficacy of masks in the community (in addition to other public health measures such as social distancing) found that the recommendation to wear surgical masks when outside the home among others did not reduce incident SARS-CoV-2 infection compared with no mask recommendation. However, the study did not assess whether masks could decrease disease transmission from mask wearers to others.[507] A Cochrane review found that wearing a mask may make little to no difference in how many people caught influenza-like illnesses; however, this is based on low-certainty evidence, and does not include results of studies from the current COVID-19 pandemic.[508] Evidence for mask effectiveness for respiratory tract infection prevention is stronger in healthcare settings compared with community settings; direct evidence on comparative effectiveness in SARS-CoV-2 infection is insufficient. The strength of evidence for any mask use versus nonuse in community settings is low.[509] [510] Randomized trials have not addressed the question of source control.
- Despite the lack of good-quality evidence, the WHO advises that in areas of known or suspected community or cluster transmission, people should wear a nonmedical mask in the following circumstances: indoor or outdoor settings where physical distancing cannot be maintained; indoor settings with inadequate ventilation, regardless of whether physical distancing can be maintained; and in situations when physical distancing cannot be maintained and the person has a higher risk of severe complications (e.g., older age, underlying condition). Caregivers and those living with suspected or confirmed cases should wear a medical mask when in the same room, regardless of whether the
Coronavirus disease 2019 (COVID-19) Management case has symptoms. Children ages up to 5 years should not wear masks for source control. A risk-based approach is recommended for children ages 6 to 11 years. Special considerations are required for immunocompromised children, or children with certain diseases, developmental disorders, or disabilities. The WHO advises that people should not wear masks during vigorous-intensity physical activity. Use of a mask alone is insufficient to provide adequate protection, and they should be used in conjunction with other infection prevention and control measures such as frequent hand hygiene and social distancing.[92]

- Potential harms and disadvantages of wearing masks include: potential increased risk of self-contamination due to manipulation of face mask and touching face/eyes, or when nonmedical masks are not changed when wet or soiled; headache and/or breathing difficulties; facial skin lesions, irritant dermatitis, or worsening acne; discomfort; difficulty communicating; social and psychological acceptance; false sense of security; poor compliance; waste management issues; and difficulties for patients with chronic respiratory conditions or breathing problems.[92] Masks may also create a humid habitat where the virus can remain active and this may increase viral load in the respiratory tract; deeper breathing caused by wearing a mask may push the virus deeper into the lungs.[511] There are insufficient data to quantify all of the adverse effects that might reduce the acceptability, adherence, and effectiveness of face masks.[512]

- Cloth masks have limited efficacy in preventing viral transmission compared with medical-grade masks.[513] Efficacy depends on the type of material used, the number of layers, the degree of moisture in the mask, and the fitting of the mask on the face. In a study comparing the use of cloth masks to surgical masks in healthcare workers, the rates of all infection outcomes were highest in the cloth mask arm, with the rate of influenza-like illness statistically significantly higher in this group. Moisture retention, reuse of cloth masks, and poor filtration may result in increased risk of infection.[514]

- [BMJ: facemasks for the prevention of infection in healthcare and community settings] (https://www.bmj.com/content/350/bmj.h694)

Alcohol-based hand sanitizers

- The Centers for Disease Control and Prevention has issued a warning about alcohol-based sanitizers containing methanol (which may be labeled as containing ethanol). Methanol poisoning should be considered in patients who present with relevant signs and symptoms (e.g., headache, impaired vision, nausea/vomiting, abdominal pain, loss of coordination, decreased level of consciousness) who report ingestion of hand sanitizer or frequent repeated topical use. Cases of permanent blindness and death have been reported.[515]

- Frequent use of hand sanitizers may result in antimicrobial resistance. Accidental ingestion and unintentional ocular exposures, especially by children, have also been reported.[516] [517]

Travel-related control measures

- Many countries have implemented travel-related control measures including complete closure of borders, partial travel restrictions, entry or exit screening, and/or quarantine of travelers. Overall, low to very low evidence suggests that travel-related control measures may help to limit the spread of infection across national borders. Cross-border travel restrictions are likely to be more effective than entry and exit screening, and screening is likely to be more effective in combination with other measures (e.g., quarantine, observation).[518]

- Entry/exit screening: people traveling from areas with a high risk of infection may be screened using questionnaires about their travel, contact with ill people, symptoms of infection, and/or measurement of their temperature. Low-certainty evidence suggests that screening at travel hubs may slightly slow the importation of infected cases; however, the evidence base comes from two mathematical model studies and is limited by their assumptions. Evidence suggests that one-time screening in apparently healthy people may miss between 40% and 100% of people who are infected, although the certainty of this ranges from very low to moderate. In very low-prevalence settings, screening for symptoms or temperature may result in few false negatives and many true negatives, despite low overall accuracy. Repeated screenings may result in more cases being identified eventually and reduced harm from false reassurance.[519] Entry screening at three major US airports found a low yield of laboratory-diagnosed cases (one case per 85,000 travelers) between January and September 2020.[520]
Coronavirus disease 2019 (COVID-19) Management

MANAGEMENT

- Quarantine: enforced quarantine is being used to isolate easily identifiable cohorts of people at potential risk of recent exposure. Despite limited evidence, a Cochrane review found quarantine to be important in reducing the number of people infected and deaths, especially when started earlier and when used in combination with other prevention and control measures. However, the current evidence is limited because most studies are based on mathematical modeling studies that make assumptions on important model parameters.[521] The psychosocial effects of enforced quarantine may have long-lasting repercussions.[522] [523]
- Travelers who arrive in the UK are required to self-isolate for 10 days unless they have traveled from an exempt country. Travelers who have visited a country with a travel ban in the 10 days before arrival must self-isolate, along with their household, for 10 days from the day of departure from these countries. [Public Health England: how to quarantine when you arrive in England] (https://www.gov.uk/guidance/how-to-quarantine-when-you-arrive-in-england)

Social distancing

- Many countries have implemented mandatory social distancing measures in order to reduce and delay transmission (e.g., city lockdowns, stay-at-home orders, curfews, nonessential business closures, bans on gatherings, school and university closures, travel restrictions and bans, remote working, quarantine of exposed people).
- Although the evidence for social distancing for COVID-19 is limited, it is emerging, and the best available evidence appears to support social distancing measures to reduce the transmission and delay spread. The timing and duration of these measures appears to be critical.[524] [525] When comparing countries with more restrictive nonpharmaceutical interventions (e.g., mandatory stay-at-home and business closure orders) to countries with less restrictive nonpharmaceutical interventions, implementing any nonpharmaceutical interventions was associated with a significant reduction in case growth. However, there was no clear, significant beneficial effect of more restrictive nonpharmaceutical interventions compared with less restrictive nonpharmaceutical interventions in any of the countries studied. It should be noted that the study has important limitations.[526]
- Researchers in Singapore found that social distancing measures (isolation of infected individuals and family quarantine, school closures, and workplace distancing) significantly decreased the number of infections in simulation models.[527]
- Harms must also be considered. Public health policies mostly rely on models and these models often ignore potential harms including excess death and inequalities arising from economic damage, negative health effects, and effects on vulnerable populations.[528] Negative consequences of community-based mass quarantine include psychological distress, food insecurity, economic challenges, diminished healthcare access, heightened communication inequalities, alternative delivery of education, and gender-based violence.[529]

Shielding extremely vulnerable people

- Shielding is a measure used to protect vulnerable people (including children) who are at very high risk of severe illness from COVID-19 because they have an underlying health condition. Shielding involves minimizing all interactions between those who are extremely vulnerable and other people to protect them from coming into contact with the virus.
- Extremely vulnerable groups include:[530]
  - Solid organ transplant recipients
  - People with specific cancers
  - People with severe respiratory conditions (e.g., cystic fibrosis, severe asthma, or severe COPD)
  - People with rare diseases that significantly increase the risk of infections (e.g., homozygous sickle cell disease, severe combined immunodeficiency)
  - People on immunosuppression therapies sufficient to significantly increase the risk of infection
  - People with spleen problems (e.g., prior splenectomy)
  - Adults with Down syndrome
  - Adults on dialysis or with chronic kidney disease
• Women who are pregnant with significant heart disease (congenital or acquired)
• Other people who have also been classed as clinically extremely vulnerable based on clinical judgment and an assessment of their needs.

• The UK government recommends that clinically extremely vulnerable people follow national restrictions for the general population:
  
  
• Consult current guidance for specific recommendations (recommendations may differ between countries).

• Shielding advice for children and young adults is available. Consult current guidance for specific recommendations (recommendations may differ between countries).

  • [Royal College of Paediatrics and Child Health: COVID-19 – guidance on clinically extremely vulnerable children and young people](https://www.rcpch.ac.uk/resources/covid-19-shielding-guidance-children-young-people)

Lifestyle modifications

• Lifestyle modifications (e.g., smoking cessation, weight loss) may help to reduce the risk of COVID-19, and may be a useful adjunct to other interventions.[531]

Pre-exposure or postexposure prophylaxis

• There are no drugs recommended for pre-exposure prophylaxis or postexposure prophylaxis, except in the context of a clinical trial.[3] See the Emerging section for more information.

Patient discussions

General discussions

• Communicate with patients and their families and caregivers, and support their mental wellbeing to help alleviate any anxiety and fear they may have. Signpost to charities and support groups.[561]
• Explain that symptoms may include cough, fever, and loss of sense of smell or taste. Patients may also experience breathlessness (which may cause anxiety), delirium (which may cause agitation), fatigue, headache, myalgia, sore throat, drowsiness (particularly in older people), poor appetite, and chest discomfort/pain. Additional symptoms in children may include grunting, nasal flare, nasal congestion, poor appetite, gastrointestinal symptoms, skin rash, and conjunctivitis. The presence of fever, rash, abdominal pain, diarrhea, or vomiting in children may indicate pediatric inflammatory multisystem syndrome (PIMS). Reassure the patient that they are likely to feel much better in a week if their symptoms are mild.[561]
• Discuss who to contact if their symptoms get worse, or if PIMS is suspected. Offer telephone or video consultations as appropriate.[561]
• Discuss the benefits and risks of hospital admission or other acute care delivery services. Explain that people may deteriorate rapidly, and discuss future care preferences at the first assessment to give people who do not have existing advance care plans an opportunity to express their preferences.[561]
General prevention measures

- Wash hands often with soap and water for at least 20 seconds or an alcohol-based hand sanitizer (that contains at least 60% alcohol), especially after being in a public place, blowing your nose, or coughing/sneezing. Avoid touching the eyes, nose, and mouth with unwashed hands.

- Avoid close contact with people (i.e., maintain a distance of at least 3 feet [1 meter]) including shaking hands, particularly those who are sick, have a fever, or are coughing or sneezing. Avoid going to crowded and poorly ventilated places. It is important to note that recommended distances differ between countries (for example, 6 feet [2 meters] is recommended in the US and UK) and you should consult local guidance.

- Practice respiratory hygiene (i.e., cover mouth and nose when coughing or sneezing, discard tissue immediately in a closed bin, and wash hands).

- Stay at home if you are sick, even with mild symptoms, until you recover (except to get medical care)

- Clean and disinfect frequently touched surfaces daily (e.g., light switches, door knobs, countertops, handles, phones).


Face masks

- Despite the lack of good-quality evidence, the World Health Organization (WHO) advises that in areas of known or suspected community or cluster transmission, people should wear a nonmedical mask in the following circumstances: indoor or outdoor settings where physical distancing cannot be maintained; indoor settings with inadequate ventilation, regardless of whether physical distancing can be maintained; and situations when physical distancing cannot be maintained and the person has a higher risk of severe complications (e.g., older age, underlying condition). Caregivers and those living with suspected or confirmed cases should wear a medical mask when in the same room, regardless of whether the case has symptoms. Children ages up to 5 years should not wear masks for source control. A risk-based approach is recommended for children ages 6 to 11 years. Special considerations are required for immunocompromised children, or children with certain diseases, developmental disorders, or disabilities. The WHO advises that people should not wear masks during vigorous-intensity physical activity. Use of a mask alone is insufficient to provide adequate protection, and they should be used in conjunction with other infection prevention and control measures such as frequent hand hygiene and social distancing.


Pulse oximetry

- Patients may be required to use a pulse oximeter in the home setting. Patient education and appropriate follow-up are required.

Travel advice

- Many countries have implemented international travel bans/closed their borders, have issued advice for domestic travel. Some countries are restricting entry to foreign nationals who have been to affected areas in the preceding 14 days, or are enforcing quarantine periods (e.g., at home or in a designated facility such as a medi-hotel) where the person’s health and infection status are closely monitored. Some countries are requiring a negative test before departure and after arrival, and are implementing travel measures to protect against new international variants of the virus. Masks may be mandatory on flights.
- Consult local guidance for specific travel restriction recommendations in your country:
  - [NaTHNac: travel health pro] (https://travelhealthpro.org.uk)
  - [UK Department for Transport] (https://www.gov.uk/government/organisations/department-for-transport)

Pets and animals

- At this time, there is no evidence that companion animals (including pets and other animals) play a significant role in the spread of COVID-19, and the risk of animals spreading COVID-19 to people is considered to be very low. There is no evidence that the virus can spread to people from the skin or fur of companion animals.[1204]
- A very small number of pets have been reported to be infected with the virus after close contact with people with confirmed COVID-19; however, thousands of pets have been tested in the US with none testing positive. There is evidence that cats and ferrets are highly susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, while dogs and other livestock have no or low susceptibility. Large cats in captivity (lions, tigers, and a puma) and domestic pet cats have tested positive after contact with symptomatic humans. Transmission between cats has also been reported. The virus has been reported in mink on farms, and once the virus is introduced on a farm, can spread between mink, and between mink and other animals on the farm. There is also the possibility that mink may transmit the infection to humans in these environments.[1205] [1206] [1207] [1208] [1209] Gorillas in a US zoo have tested positive. It is suspected that the gorillas acquired the infection from an asymptomatic staff member.[1210]
- Advise patients to limit their contact with their pets and other animals, especially while they are symptomatic. Advise people to not let pets interact with people or animals outside the household, and if a member of the household becomes unwell to isolate them from everyone else, including pets.[1211]

Return to physical activity

- Recommend a phased return to exercise only when the patient has been symptom-free for at least 7 days. Advise patients to begin with at least 2 weeks of minimal exertion, and to use daily self-monitoring to track progress and decide whether to move up or drop back a phase. Patients who have a history of severe disease, cardiac involvement, ongoing symptoms, or...

adverse psychological symptoms require further clinical assessment before returning to physical activity. [1212]

• Guidance on return to sports after COVID-19 in children is available from the American Academy of Pediatrics:
  
  
  • Clinical or subclinical myocarditis has been reported in competitive athletes with recent infection that restricts them from training and competitive play. [1213]

Resources

  
  
  
  
Monitoring

Regularly monitor the following in hospitalized patients to facilitate early recognition of deterioration and monitor for complications:[2] [571]

- Vital signs (temperature, respiratory rate, heart rate, blood pressure, oxygen saturation)
- Hematologic and biochemistry parameters
- Coagulation parameters (D-dimer, fibrinogen, platelet count, prothrombin time)
- ECG
- Chest imaging
- Signs and symptoms of venous or arterial thromboembolism.

Medical early warning scores

- Utilize medical early warning scores that facilitate early recognition and escalation of treatment of deteriorating patients (e.g., National Early Warning Score 2 [NEWS2], Pediatric Early Warning Signs [PEWS]) where possible.[2]
- There are no data on the value of using these scores in patients with COVID-19 in the primary care setting.[1185]
- The sequential organ failure assessment (SOFA) score does not possess adequate discriminant accuracy for mortality prediction in patients prior to intubation for COVID-19 pneumonia.[1186]

Pregnant women

- Monitor vital signs three to four times daily and fetal heart rate in pregnant women with confirmed infection who are symptomatic and admitted to hospital. Perform fetal growth ultrasounds and Doppler assessments to monitor for potential intrauterine growth restriction in pregnant women with confirmed infection who are asymptomatic.[837] Perform fetal growth ultrasound 14 days after resolution of symptoms.[839]

Post-discharge follow-up

- Patients who have had suspected or confirmed COVID-19 (of any disease severity) who have persistent, new, or changing symptoms should have access to follow-up care.[2]
- Guidelines for the respiratory follow-up of patients with COVID-19 pneumonia have been published. Follow-up algorithms depend on the severity of pneumonia, and may include clinical consultation and review (face-to-face or telephone) by a doctor or nurse, chest imaging, pulmonary function tests, echocardiogram, sputum sampling, walk test, and assessment of oxygen saturation.[1187]
- More than half of patients discharged from hospital had lung function and chest imaging abnormalities 12 weeks after symptom onset.[1188] Pulmonary function tests may reveal altered diffusion capacity, a restrictive pattern, or an obstructive pattern.[1189]

Prognostic scores in development

- Various prognostic and clinical risk scores are being researched or developed for COVID-19; however, further external validation across various populations is needed before their use can be recommended. The World Health Organization recommends using clinical judgment, including consideration of the patient’s values and preferences and local and national policy if available, to guide management decisions including admission to hospital and to the intensive care unit, rather than currently available prediction models for prognosis.[2]
  - A-DROP: a modified version of CURB-65 that showed better accuracy of in-hospital death prediction on admission in patients with COVID-19 pneumonia compared with other widely used community-acquired pneumonia scores.[1190]
• APACHE II: an effective clinical tool to predict hospital mortality that performed better than SOFA and CURB-65 scores in patients with COVID-19. A score of 17 or more is an early indicator of death and may help provide guidance to make further clinical decisions.[1191]
• CALL: a risk factor scoring system that scores patients based on four factors: comorbidities, age, lymphocyte count, and lactate dehydrogenase level. One study found that 96% of patients with low CALL scores did not progress to severe disease.[1192]
• COVID-GRAM: a web-based calculator that estimates the probability that a patient will develop critical illness and relies on the following 10 variables at admission: chest radiographic abnormality, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and direct bilirubin. Additional validation studies, especially outside of China, are required.[1193] A retrospective cohort study was unable to fully validate the tool for predicting critical illness among hospitalized patients in Europe as it overestimated the risk in the highest-risk patients.[1194]
• COVID-19MRS: a rapid, operator-independent clinical tool that was found to objectively predict mortality in one retrospective cohort study.[1195]
• COVID-19 SEIMC: a mortality prediction score for predicting 30-day mortality of patients attending hospital emergency departments, based on age, low age-adjusted SaO₂, neutrophil-to-lymphocyte ratio, estimated glomerular filtration rate, dyspnea, and sex. It has been externally validated with two large datasets from patients hospitalized with laboratory-confirmed disease and shows a high degree of accuracy.[1196]
• QCOVID: a novel clinical risk prediction algorithm to estimate the risk of hospital admission and mortality based on age, ethnicity, deprivation, body mass index, and a range of comorbidities. Population-based cohort studies found that the algorithm performed well, showing very high levels of discrimination for deaths and hospital admissions.[1197][1198] The risk model is being used in the UK to help clinicians identify adults with multiple risk factors that make them more vulnerable to COVID-19, and inform decisions about vaccination cohorts and shielding.[1199]
• SCARP: a novel risk calculator that provides clinically meaningful predictions of whether hospitalized patients will progress to severe illness or death based on variables that are readily available (e.g., pulse oximetry, oxygen supplementation, respiratory rate, pulse). The calculator has undergone internal and temporal validation, but further studies are required.[1200]
• SOARS: a five-predictor risk prediction score based on demographic and clinical characteristics (i.e., SpO₂, obesity, age, respiratory rate, stroke history). May be useful to identify patients who have a low probability of mortality for outpatient monitoring and management, and could potentially be used to inform clinical triage in preadmission settings. Further validation is required.[1201]
• 3F: a mortality prediction model based on three clinical features: age, minimum oxygen saturation, and type of patient encounter (i.e., inpatient vs outpatient and telehealth encounters). One study found that the model showed high accuracy when applied to retrospective and prospective data sets of COVID-19 patients.[1202]
• 4C: a score developed and validated in a UK prospective cohort study of adults admitted to hospital with COVID-19. The score uses patient demographics, clinical observations, and blood parameters commonly available at the time of hospital admission, and can accurately characterize patients as being at low, intermediate, high, or very high risk of death. The score outperformed other risk stratification tools, showed clinical decision-making utility, and had similar performance to more complex models.[1203]

[The BMJ 10-minute consultation: what is my covid risk?] (https://www.bmj.com/content/372/bmj.n637)
**Complications**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>post-intensive care syndrome</td>
<td>variable</td>
<td>high</td>
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<tr>
<td>Early reports suggest that COVID-19 patients treated in the intensive care unit can present with post-intensive care syndrome, a spectrum of psychiatric, cognitive, and/or physical disability (e.g., muscle weakness, cognitive dysfunction, insomnia, depression, anxiety, post-traumatic stress disorder, delirium, encephalopathy) that affects survivors of critical illness, and persists after the patient has been discharged from the intensive care unit. Weakness affects 33% of patients who receive mechanical ventilation, 50% of patients with sepsis, and &lt;50% of patients who remain in the intensive care unit for more than 1 week. Cognitive dysfunction affects 30% to 80% of patients. The risk can be minimized with medication management, physical rehabilitation, family support, and follow-up clinics.[3]</td>
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<tr>
<td>venous thromboembolism</td>
<td>variable</td>
<td>high</td>
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<tr>
<td>The pooled incidence of venous thromboembolism, deep vein thrombosis, and pulmonary embolism among hospitalized patients was 14.7, 11.2%, and 7.8%, respectively. The prevalence was significantly higher in patients admitted to the intensive care unit, despite thromboprophylaxis.[1040] COVID-19 patients with thromboembolic events have 1.93 times the odds of dying compared with patients without venous thromboembolism.[1041]</td>
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<td>Coagulopathy in COVID-19 has a prothrombotic character, which may explain reports of thromboembolic complications.[1042] Patients may be predisposed to venous thromboembolism due to the direct effects of COVID-19, or the indirect effects of infection (e.g., severe inflammatory response, critical illness, traditional risk factors).[1043] Thrombotic events may be due to cytokine storm, hypoxic injury, endothelial dysfunction, hypercoagulability, and/or increased platelet activity.[1044]</td>
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<td>The risk factors with the most evidence for being predictive of venous thromboembolism are older age and elevated D-dimer levels.[1045] Patients with very high D-dimer levels have the greatest risk of thrombosis and may benefit from active monitoring.[691] [692]</td>
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<td>If venous thromboembolism is suspected, perform a computed tomographic angiography or ultrasound of the venous system of the lower extremities.[1046]</td>
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<tr>
<td>Treat patients with a thromboembolic event (or who are highly suspected to have thromboembolic disease if imaging is not possible) with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19. There are currently insufficient data to recommend either for or against using therapeutic doses of antithrombotic or thrombolytic agents for COVID-19. Patients who require extracorporeal membrane oxygenation or continuous renal replacement therapy, or who have thrombosis of catheters or extracorporeal filters, should be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19.[3]</td>
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<td>Initial parenteral anticoagulation with a low molecular weight heparin or unfractionated heparin is preferred in acutely ill hospitalized patients; however, direct oral anticoagulants may be used provided there is no potential for drug-drug interactions (lead-in therapy with a parenteral anticoagulant is required for dabigatran and edoxaban). Warfarin can be used after overlap with initial parenteral anticoagulation. Parenteral anticoagulation with a low molecular weight heparin or fondaparinux is preferred over unfractionated heparin in critically ill patients. Direct oral anticoagulants are the preferred option in outpatients provided there is no potential for drug-drug interactions, with warfarin considered a suitable alternative. Anticoagulation therapy is recommended for a minimum of 3 months. Thrombolytic therapy is recommended in select patients with pulmonary embolism.[780]</td>
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<tr>
<td>The American Society of Hematology has published draft guideline recommendations on the use of anticoagulation in patients with COVID-19.[1047]</td>
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COVID-19 is associated with a high inflammatory burden that can result in cardiovascular complications with a variety of clinical presentations. Inflammation in the myocardium can result in myocarditis, heart failure, arrhythmias, acute coronary syndrome, rapid deterioration, and sudden death. These complications can occur on presentation or develop as the severity of illness worsens. It is uncertain to what extent acute systolic heart failure is mediated by myocarditis, cytokine storm, small vessel thrombotic complications, microvascular dysfunction, or a variant of stress-induced cardiomyopathy. Cardiovascular complications have been reported in 14.1% of patients during hospitalization, with an overall case fatality rate of 9.6%. Patients with preexisting cardiovascular comorbidities or risk factors are at higher risk for cardiovascular complications and mortality. Complications include arrhythmias or palpitations, myocardial injury, angina, acute myocardial infarction, and acute heart failure. Cases of fulminant myocarditis, cardiac tamponade, and pericarditis have also been reported. A Cochrane review found that the most common cardiovascular complications were cardiac arrhythmias, heart failure, and arterial and venous occlusive events. QT interval changes and ST-segment deviation have been reported. QT interval prolongation has been reported independent of whether the patient is taking drugs that prolong the QT interval. Laboratory biomarkers may help identify those at greater risk of developing cardiovascular complications and of death. Elevated cardiac biomarkers and emerging arrhythmia are associated with the development of severe disease and the need for intensive care admission. Prevalence of cardiac disease is high among patients who are severely or critically ill, and these patients usually require intensive care and have a poor prognosis and higher rate of in-hospital mortality. These patients are more likely to require noninvasive or invasive ventilation, and have a higher risk of thromboembolic events and septic shock compared with patients without a history of cardiac disease.
### Complications

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<tr>
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<tr>
<td>Performing an ECG and order high-sensitivity troponin I (hs-cTnI) or T (hs-cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in patients with symptoms or signs that suggest acute myocardial injury in order to make a diagnosis. The following test results may help inform the diagnosis: evolving ECG changes suggesting myocardial ischemia; NT-proBNP level &gt;400 nanograms/L; high levels of hs-cTnI or hs-cTnT, particularly levels increasing over time. Elevated troponin levels may reflect cardiac inflammatory response to severe disease rather than acute coronary syndrome. Seek specialist cardiology advice on further tests and imaging.</td>
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| Monitor blood pressure, heart rate, and fluid balance, and perform continuous ECG monitoring in all patients with suspected or confirmed acute myocardial injury. Monitor in a setting where cardiac or respiratory deterioration can be rapidly identified.
| Seek specialist cardiology advice on treatment and follow local treatment protocols. There are limited data to recommend any specific drug treatments for these patients. Management should involve a multidisciplinary team including intensive care specialists, cardiologists, and infectious disease specialists. It is important to consider that some drugs may prolong the QT interval and lead to arrhythmias. Guidelines for the management of COVID-19-related myocarditis are available.
| Infection may have longer-term implications for overall cardiovascular health; however, further research is required. A study of 100 patients who had recently recovered from COVID-19 found that cardiovascular magnetic resonance imaging revealed ongoing myocardial inflammation in 60% of patients, independent of preexisting conditions, severity and overall course of the acute illness, and time from the original diagnosis. | variable | high |
| The pooled incidence of acute kidney injury is 10.6%, which is higher than the incidence in hospitalized patients without COVID-19. Patients with acute kidney injury have a significantly increased risk of in-hospital mortality (odds ratio of 11.05). The mortality rate and incidence in patients in China was significantly lower than those in patients outside of China. Risk factors include older age ≥60 years, male sex, and severe infection.
| In a small UK cohort, 29% of hospitalized children met the diagnostic criteria for acute kidney injury, with most cases occurring in children admitted to the intensive care unit and in those with pediatric inflammatory multisystem syndrome.
| Can develop at any time before, during, or after hospital admission. Causes include hemodynamic changes, hypovolemia, viral infection leading directly to kidney tubular injury, thrombotic vascular processes, glomerular pathology, or rhabdomyolysis. May be associated with hematuria, proteinuria, and abnormal serum electrolyte levels (e.g., potassium, sodium). Direct kidney infection has been confirmed in an autopsy study of a single patient.
| Follow local guidelines for assessing and managing acute kidney injury. Continuous renal replacement therapy (CRRT) is recommended in critically ill patients with acute kidney injury who develop indications for renal replacement therapy; prolonged intermittent renal replacement therapy is recommended over hemodialysis if CRRT is not available or possible.
| Monitor patients with chronic kidney disease for at least 2 years after acute kidney injury.
| Cases of nephritis and collapsing glomerulopathy have been reported.
| Liver injury may be associated with preexisting liver disease, viral infection, drug toxicity, systemic inflammation, hypoxia, or hemodynamic issues; however, the underlying mechanism is unclear. The overall prevalence has been reported as 25%, although there is no uniform definition of liver injury in these patients and prevalence depends on the definition used in studies. The overall prevalence may be as low as 9% when strict criteria for diagnosis are used. The prevalence of elevated alanine aminotransferase and aspartate aminotransferase is lower. |

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Complications | Timeframe | Likelihood
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aminotransferase and aspartate aminotransferase was 19% and 22%, respectively. The prevalence of hypertransaminasemia was higher in patients with severe disease compared with patients with nonsevere disease.\[1085\] Another meta-analysis concluded that findings from the available evidence to date from observational studies and case reports indicate that transaminases and total bilirubin levels appear not to significantly change in patients with COVID-19.\[1086\]
Risk factors associated with severe liver injury include older age, preexisting liver disease, and severe COVID-19.\[1087\]
Medications used in the treatment of COVID-19 (e.g., lopinavir/ritonavir) may have a detrimental effect on liver injury.\[1087\]
Guidelines on the management of liver derangement in patients with COVID-19 have been published.\[1088\]

| neurologic complications | variable | medium |
--- | --- | ---
Patients commonly have central or peripheral neurologic complications, possibly due to viral invasion of the central nervous system, inflammatory response, or immune dysregulation.\[1089\]
Neurologic manifestations have been reported in 4% to 57% of patients in large retrospective observational studies. Central nervous system manifestations were more common than peripheral nervous system manifestations.\[1089\] However, most studies included minor symptoms such as headache and dizziness, which are classified as symptoms of COVID-19 in this topic rather than complications. Neurologic complications are rare in children.\[1090\] A retrospective electronic health records study of nearly 240,000 patients found that approximately one third of patients received a neurologic or psychiatric diagnosis in the 6 months after diagnosis, and 13% received such a diagnosis for the first time. The risk was greater in patients with severe disease.\[1091\]
Neurologic complications include acute cerebrovascular disease, impairment of consciousness, ataxia, seizures, corticospinal tract signs, meningoencephalitis, encephalopathy, encephalomyelitis, peripheral demyelinating lesions, peripheral neuropathy, intracerebral hemorrhage, cerebral venous sinus thrombosis, myopathy, myasthenia gravis, Guillain-Barre syndrome and other neuropathies, status epilepticus, dementia, catatonia, parkinsonian syndromes, mood/anxiety/psychotic/substance use disorders, and abnormal findings on brain magnetic resonance imaging.\[1089\] [1091] [1092] [1093] [1094]
Patients may present with these manifestations, or they may develop them during the course of the disease. Neurologic complications tend to develop 1 to 2 weeks after the onset of respiratory disease.\[1095\]
Acute cerebrovascular disease (including ischemic stroke, hemorrhagic stroke, cerebral venous thrombosis, and transient ischemic attack) has been reported in 0.5% to 5.9% of patients. The most common type was ischemic stroke (0.4% to 4.9%).\[1089\] Patients with severe disease are at an increased risk of ischemic stroke compared with patients with nonsevere disease.\[1096\] Stroke is relatively frequent among hospitalized COVID-19 patients relative to other viral respiratory infections, and has a high risk of in-hospital mortality. Risk factors include older age and male sex. Median time from onset of COVID-19 symptoms to stroke was 8 days.\[1097\] [1098] Stroke presents later in severe disease, and earlier in mild to moderate disease.\[1099\] Patients may present with ischemic stroke during the convalescent phase of infection, including younger people <50 years of age with asymptomatic or pauci-symptomatic COVID-19.\[1100\] Ischemic stroke appears to be more severe and result in worse outcomes (severe disability) in patients with COVID-19, with the median NIH Stroke Scale score being higher among those with COVID-19 compared with those without.\[1101\] Guidelines for the management of acute ischemic stroke in patients with COVID-19 infection have been published.\[1102\]
Guillain-Barre syndrome has been reported. Both post-infectious and pre-infectious patterns have been reported.\[1089\] The pooled prevalence among hospitalized and nonhospitalized patients was 0.15%.\[1103\] The mean age of patients was 55 years with a male predominance. Most patients had respiratory and/or severe symptoms of COVID-19, although it has also been reported in asymptomatic
Follow up

Complications | Timeframe | Likelihood
--- | --- | ---
patients. A higher prevalence of the classic sensorimotor form and acute inflammatory demyelinating polynueopathy have been reported, although rare variants have also been noted.[1104] Patients had an increased odds for demyelinating subtypes. Clinical outcomes were comparable to those for contemporary or historical controls not infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1103]

Encephalitis has been reported in <1% of patients, but increases up to 6.7% in critically ill patients. Encephalitis is associated with poorer outcomes including admission to the intensive care unit, need for mechanical ventilation, and increased mortality rate (13.4%) compared with the general population of COVID-19 patients.[1105]

Patients with preexisting neurologic disorders may develop an exacerbation of their neurologic symptoms and severe COVID-19.[1106]

Patients may show cerebral changes on magnetic resonance imaging months after recovery, suggesting that long-term consequences may be possible.[1107]

Neurologic involvement is common in children and adolescents. In a case series of 1695 patients <21 years of age, 22% of patients had documented neurologic involvement. Those with neurologic involvement were more likely to have an underlying neurologic disorder compared with those without, but a similar number were previously healthy. In the majority of cases, symptoms were transient. However, approximately 12% had life-threatening conditions including severe encephalopathy, central nervous system infection/demyelination, Guillain-Barre syndrome/variants, and acute fulminant cerebral edema.[1108]

Also known as post-acute COVID-19, post-acute COVID-19 syndrome, chronic COVID, long-haul COVID, post-acute sequelae of SARS-CoV-2 infection (PASC), and post-COVID conditions.

Post-COVID-19 syndrome (long COVID) | variable | medium
--- | --- | ---
Definition: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis. Ongoing symptomatic COVID-19 is defined as signs and symptoms from 4 weeks up to 12 weeks. The syndrome is not thought to be linked to disease severity or specific signs and symptoms during the acute phase of illness.[963] There is no standardized case definition and case definitions vary. For example, the Centers for Disease Control and Prevention defines post-COVID conditions as an umbrella term for the wide range of health consequences that are present more than 4 weeks after infection with SARS-CoV-2.[1109] Protracted symptoms are common in many viral and bacterial infections. The neurologic symptoms are similar to symptoms of other neurologic conditions such as chronic fatigue syndrome and functional neurologic disorder.[1110]

Epidemiology: frequency ranges from 4.7% to 80% across observational studies, and occurs between 3 to 24 weeks after the acute phase or hospital discharge. Potential risk factors include older age, age 40 to 49 years, female sex, severe clinical status, higher number of comorbidities, higher symptom load, hospital admission, and oxygen supplementation in the acute phase, although data is lacking.[1111] Approximately 72.5% of patients report at least one symptom at 60 days or more after diagnosis, symptom onset, or hospitalization, or at 30 days or more after recovery from acute illness or hospital discharge. The most commonly reported persistent symptoms were dyspnea and fatigue.[1113] A study in the UK found that nearly 75% of patients who are discharged from hospital remain symptomatic at 3 months.[1114] Persistent symptoms have been reported up to 12 months after discharge.[1115] Prolonged illness can occur among young adults with no underlying comorbidities, and in patients who had mild disease. Approximately 12% to 15% of patients who had mild symptoms still had symptoms up to 8 months later.[1116] The number of symptoms at follow-up was associated with the symptom load during the acute phase of infection and the number of comorbidities in nonhospitalized patients.[1118] Persistent symptoms have been reported in pregnant women and children, but appear to be less common in children compared with adults.[3] [1119]
## Complications

| Diagnosis: use a holistic, person-centered approach that includes a comprehensive clinical history (including history of suspected or confirmed acute COVID-19, nature and severity of previous and current symptoms, timing and duration of symptoms since the start of acute illness, and a history of other health conditions), and appropriate examination that involves assessing physical, cognitive, psychological, and psychiatric symptoms, as well as functional abilities. Refer patients with signs or symptoms that could be caused by an acute or life-threatening complication (e.g., severe hypoxemia, signs of severe lung disease, cardiac chest pain, multisystem inflammatory syndrome in children) urgently to the relevant acute services.[963] |
|---|---|---|
| Signs and symptoms: symptoms vary widely, may relapse and remit or fluctuate, can change unpredictably, and can occur in those with mild disease only. Common long-term symptoms include persistent cough, low-grade fever, breathlessness, fatigue, pain, chest pain/tightness, palpitations, myalgia, arthralgia, headaches, vision changes, hearing loss, earache, tinnitus, sore throat, loss of taste/smell, impaired mobility, numbness in extremities, dizziness, tremors, memory loss, mood changes, skin rashes, gastrointestinal symptoms, neurocognitive difficulties, sleep disturbances, delirium (older people), and mental health conditions (e.g., anxiety, depression).[3][963][1120] Gastrointestinal sequelae including loss of appetite, nausea, acid reflux, and diarrhea are common in patients 3 months after discharge.[1121] Some of the symptoms may overlap with post-intensive care syndrome (see above).[3] The inability to return to normal activities, emotional and mental health outcomes, and financial loss are common.[1122] |
| Investigations: tailor investigations to the clinical presentation, and to rule out any acute or life-threatening complications and alternative diagnoses. Investigations may include blood tests (e.g., complete blood count, kidney and liver function tests, C-reactive protein, ferritin, thyroid function), oxygen saturation, blood pressure and heart rate measurements, exercise tolerance test, chest imaging, electrocardiogram, and psychiatric assessment.[3][963][1120] Approximately 50% of patients had residual abnormalities on chest CT and pulmonary function tests at 3 months.[1123] Around 9% of patients had deteriorating chest x-ray appearances at follow-up, which may indicate lung fibrosis. Persistently elevated D-dimer and C-reactive protein have also been reported.[1124] |
| Management: give advice and information on self-management including ways to self-manage symptoms (e.g., set realistic goals, antipyretic for fever, breathing techniques for chronic cough, home pulse oximetry for monitoring breathlessness, pulmonary rehabilitation, staged return to exercise); who to contact if there is concern about symptoms or if there is need for support; sources of support (e.g., support groups, online forums); and how to get support from other services (e.g., social care, housing, financial support). A personalized, multidisciplinary rehabilitation plan that covers physical, psychological, and psychiatric aspects of rehabilitation is an important part of management. Many patients recover spontaneously with holistic support, rest, symptomatic treatment, and a gradual increase in activity. Referral to a specialist may be required in patients where there is clinical concern along with respiratory, cardiac, or neurologic symptoms that are new, persistent, or progressive.[963][1120] |
| Follow-up: agree with the patient how often follow-up and monitoring are needed (either in person or remotely), and which healthcare professionals should be involved. Take into account the patient’s level of need and the services involved. Tailor monitoring to the patient’s symptoms, and consider supported self-monitoring at home (e.g., heart rate, blood pressure, pulse oximetry). Be alert to symptoms that could require referral or investigation.[963] |


[BMJ webinar: long COVID – how to define it and how to manage it] (https://www.bmj.com/content/370/bmj.m3489)

[BMJ: management of post-acute covid-19 in primary care] (https://www.bmj.com/content/370/bmj.m3026)

| cardiac arrest | variable | medium |
Complications | Timeframe | Likelihood
---|---|---
In-hospital cardiac arrest is common in critically ill patients with COVID-19, and is associated with poor survival, particularly among older patients. Among 5019 critically ill patients with COVID-19, 14% had an in-hospital cardiac arrest. Risk factors included older age, male sex, presence of comorbidities, and admission to a hospital with a smaller number of intensive care unit beds. Approximately 57% of patients received cardiopulmonary resuscitation. The most common rhythms at the time of resuscitation were pulseless electrical activity (49.8%) and asystole (23.8%). Of those who received resuscitation, 12% survived to hospital discharge with most of these patients being younger than 45 years of age.\[1125\]

**septic shock** | variable | low
Reported in 4% to 8% of patients in case series.\[49\] [50] [646] [1126]

Guidelines for the management of shock in critically ill patients with COVID-19 recommend a conservative fluid strategy (crystalloids preferred over colloids) and a vasoactive agent. Norepinephrine (noradrenaline) is the preferred first-line agent, with vasopressin or epinephrine (adrenaline) considered suitable alternatives. Vasopressin can be added to norepinephrine if target mean arterial pressure cannot be achieved with norepinephrine alone.\[3\] [773] Low-dose corticosteroid therapy is recommended for refractory shock.\[3\]

**disseminated intravascular coagulation** | variable | low
Disseminated intravascular coagulation (DIC) is a manifestation of coagulation failure, and an intermediate link in the development of multi-organ failure. Patients may be at high risk of bleeding/hemorrhage or venous thromboembolism.\[1127\] The pooled incidence of DIC is 3%, and it is associated with poor prognosis. The incidence was higher in patients with severe disease and those admitted to the intensive care unit, and in nonsurvivors compared with survivors.\[1128\]

Coagulopathy manifests as elevated fibrinogen, elevated D-dimer, and minimal change in prothrombin time, partial thromboplastin time, and platelet count in the early stages of infection. Increasing interleukin-6 levels correlate with increasing fibrinogen levels. Coagulopathy appears to be related to severity of illness and the resultant thromboinflammation. Monitor D-dimer level closely.\[1129\]

Anticoagulant therapy with a low molecular weight heparin or unfractionated heparin has been associated with a better prognosis in patients with severe COVID-19 who have a sepsis-induced coagulopathy (SIC) score of ≥4 or a markedly elevated D-dimer level.\[1130\] In patients with heparin-induced thrombocytopenia (or a history of it), argatroban or bivalirudin are recommended.\[1127\]

Standard guidance for the management of bleeding manifestations associated with DIC or septic coagulopathy should be followed if bleeding occurs; however, bleeding manifestations without other associated factors is rare.\[571\] [1129]

**acute respiratory failure** | variable | low
Reported in 8% of patients in case series.\[50\]

Leading cause of mortality in patients with COVID-19.\[967\]

Children can quickly progress to respiratory failure.\[10\]

**cytokine release syndrome** | variable | low
Cytokine release syndrome may cause ARDS or multiple-organ dysfunction, which may lead to death.\[1131\] Elevated serum proinflammatory cytokines (e.g., tumor necrosis factor alpha, interleukin-2, interleukin-6, interleukin-8, interleukin-10, granulocyte-colony stimulating factor, monocyte chemoattractant protein 1) and inflammatory markers (e.g., C-reactive protein, serum ferritin) have been commonly reported in patients with severe COVID-19. This likely represents a type of virus-induced secondary
### Complications

<table>
<thead>
<tr>
<th>Hemophagocytic lymphohistiocytosis, which may be fatal.</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<tbody>
<tr>
<td>Interleukin-6, in particular, has been associated with severe COVID-19 and increased mortality.</td>
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One study found that patients who require admission to the intensive care unit have significantly higher levels of interleukin-6, interleukin-10, and tumor necrosis factor alpha, and fewer CD4+ and CD8+ T cells.

However, the pooled mean serum interleukin-6 level was markedly less in patients with severe or critical COVID-19 compared with patients with other disorders associated with elevated cytokines such as cytokine release syndrome, sepsis, and non-COVID-19-related ARDS. These findings question the role of cytokine storm in COVID-19-induced organ dysfunction, and further research is required.

Cytokine release syndrome has been reported in children, although cases appear to be rare. See the section below on pediatric inflammatory multisystem syndrome.

### Pediatric inflammatory multisystem syndrome

<table>
<thead>
<tr>
<th>Pediatric inflammatory multisystem syndrome</th>
<th>Timeframe</th>
<th>Likelihood</th>
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A rare, but severe condition, reported in children and adolescents approximately 2 to 4 weeks after the onset of COVID-19, likely due to a postinfectious inflammatory process. The syndrome has a strong temporal association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The syndrome appears to be the result of a delayed immune response to SARS-CoV-2 infection with disease peaks following pandemic peaks by 2 to 5 weeks. Also known as PIMS, multisystem inflammatory syndrome in children (MIS-C), pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), as well as other variations.

The syndrome shares common features with Kawasaki disease and toxic shock syndrome, but case definitions vary. Most patients have fever, as well as features of shock, cardiac involvement (e.g., elevated cardiac markers, congestive heart failure, cardiac dysfunction, myocarditis, coronary artery dilatation or aneurysm, hypotension, pericardial effusion, mitral regurgitation), gastrointestinal symptoms (e.g., abdominal pain, vomiting, diarrhea), and significantly elevated inflammatory markers. Additional clinical and laboratory characteristics including thrombocytopenia, fatigue, headache, myalgia, sore throat, and lymphadenopathy have been suggested to refine the case definition. Mucocutaneous findings may be present, many of which overlap with Kawasaki disease.

Three types of clinical manifestations have been recognized: persistent fever and gastrointestinal symptoms (the most common type); shock with heart dysfunction; and symptoms coincident with the diagnostic criteria for Kawasaki disease.

A systematic review of 27 studies (913 cases) globally found that the median age of patients was 9.3 years of age, and 57% of patients were male. At least one comorbidity was reported in 31% of cases, most commonly obesity, asthma, and chronic lung disease. The most common manifestations were fever (99%), gastrointestinal symptoms (87%), and cardiovascular symptoms such as myocardial dysfunction (55%), coronary artery aneurysms (22%), and shock (66%). The pooled prevalence of respiratory symptoms was 41%, and neurologic symptoms was 36%. Other symptoms included conjunctivitis (57%), rash (59%), and oral mucosal changes (42%). Inflammatory and cardiac markers were elevated in the majority of patients, and 38% had abnormal findings on chest x-ray. Approximately 79% of patients required intensive care admission, 63% required inotropic support, 57% required anticoagulation, and 33% required mechanical ventilation. The mortality rate was 1.9%.

In the UK, 78 cases were reported across 21 pediatric intensive care units in a multicenter observational study. The median age was 11 years and 67% were male. Children from minority ethnic backgrounds accounted for 78% of cases. Fever, shock, abdominal pain, vomiting, and diarrhea were the common presenting features. Around 36% had evidence of coronary artery abnormalities. In terms of treatment, 46% required invasive ventilation and 83% required vasopressor support.

In the US, 3742 cases have been reported, with 35 deaths (as of 3 May 2021). In a US case series of 1116 patients diagnosed with MIS-C, those with MIS-C were more likely to have the following...
Coronavirus disease 2019 (COVID-19)

Follow up

Complications

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<thead>
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<th>Timeframe</th>
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| characteristics compared with patients with severe COVID-19: age 6 to 12 years; non-Hispanic Black ethnicity; cardiorespiratory involvement; cardiovascular without respiratory involvement; mucocutaneous without cardiorespiratory involvement; higher neutrophil-to-lymphocyte ratio; higher C-reactive protein level; and lower platelet count. These patterns may help differentiate between MIS-C and COVID-19.[1149] Factors associated with more severe outcomes (e.g., intensive care unit admission, decreased cardiac function, shock, myocarditis) include: age >5 years; non-Hispanic Black ethnicity; symptoms of dyspnea or abdominal pain; elevated C-reactive protein, troponin, ferritin, D-dimer, brain natriuretic peptide, or interleukin-6; and reduced lymphocyte or platelet counts.[1150] The most common cardiovascular complications include shock, cardiac arrhythmias, pericardial effusion, and coronary artery dilatation.[1151] The pooled prevalence of cardiac abnormalities due to MIS-C is as follows: significant left ventricular dysfunction 38%; coronary aneurysm or dilatation 20%; ECG abnormalities or cardiac arrhythmias 28%; raised serum troponin level 33%; and raised proBNP/BNP level 44%.[1152] Management is mainly supportive and involves a multidisciplinary team (pediatric infectious disease, cardiology, rheumatology, critical care). Patients are commonly managed with intravenous immune globulin, vasopressor support, corticosteroids, immune modulators, anticoagulation, antiplatelet therapy, and respiratory support.[1138] [1139] A national consensus management pathway from the UK is available.[1153] The optimal choice and combination of immunomodulating therapies have not been definitively established, but intravenous immune globulin and/or corticosteroids are generally considered first-line treatment, with interleukin-1 antagonists reserved for refractory cases.[3] The American College of Rheumatology has published guidelines on the diagnosis and management of MIS-C.[1154] Follow-up of patients at 6 months found that while cardiac, gastrointestinal, renal, hematologic, and otolaryngology outcomes largely resolved at 6 months, muscular fatigue and emotional lability were common.[1155] While an association between this syndrome and COVID-19 seems plausible based on current evidence, the association is not definitive and further research is required. It is not clear yet whether this syndrome is Kawasaki disease with SARS-CoV-2 as the triggering agent, or whether this is a different syndrome, although increasing evidence suggests that they are two separate syndromes. The syndrome appears to occur in children who have not manifested the early stages of COVID-19, but appears similar to the later phase of COVID-19 in adults.[1156] Immunologically, PIMS appears to be a distinct clinical entity from Kawasaki disease as neutrophilia and raised monocyte counts, features of Kawasaki disease, were not observed in one cohort.[1157] Cases of MIS-C have been reported in neonates and temporally associated with prenatal exposure.[1158] [1159] Cases of multisystem inflammatory syndrome have been reported in adults.[1160] [1161] pregnancy-related complications

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| Pregnancy outcome is usually good, although there are little data on exposure during early pregnancy.[24] The odds of admission to the intensive care unit, invasive ventilation, and need for extracorporeal membrane oxygenation were higher in pregnant and recently pregnant women compared with nonpregnant reproductive-aged women. Pregnant women may also be at an increased risk of maternal death. Risk factors for serious complications include preexisting comorbidities (e.g., chronic hypertension, diabetes), high maternal age, non-White ethnicity, presence of pregnancy-specific conditions (e.g., gestational diabetes, preeclampsia), and high body mass index.[22] [23] Preterm birth was more common in pregnant women with COVID-19 compared with pregnant women without the disease. However, the overall rates of spontaneous preterm births in pregnant women with COVID-19 was broadly similar to those observed in the pre-pandemic period, so these preterm births could have been medically indicated.[22] [23]
## Complications

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<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<tbody>
<tr>
<td>Stillbirths and neonatal deaths</td>
<td>variable</td>
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<tr>
<td>Invasive pulmonary aspergillosis</td>
<td>variable</td>
<td>low</td>
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<tr>
<td>Mucormycosis</td>
<td>variable</td>
<td>low</td>
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<tr>
<td>Pancreatic injury</td>
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### Follow up

The overall rates of stillbirths and neonatal deaths do not seem to be higher than the background rates. In England, there is no evidence of an increase in stillbirths regionally or nationally during the pandemic when compared with the same months in the previous year and despite variable community infection rates in different regions.

Limited low-quality evidence suggests that the risk of infection in neonates is extremely low. Most infections are acquired in the postpartum period, although congenitally acquired infection has been reported. Unlike children who generally have asymptomatic infection, two-thirds of neonatal cases are symptomatic and a significant proportion require intensive care, although the overall prognosis appears to be excellent.

Invasive pulmonary aspergillosis has been reported in critically ill patients with moderate to severe ARDS. Aspergillosis has been reported in 10.2% of patients admitted to the intensive care unit. The mortality rate was high at 54.9%.

Intubation for more than 7 days may be a risk factor. Other potential risk factors include older age, chronic obstructive pulmonary disease, immunosuppression, critical illness, or use of high-dose corticosteroids. Consider aspergillosis in patients who deteriorate despite optimal supportive care or have other suspicious radiologic or clinical features.

Prescribe appropriate antifungal therapy according to local guidelines. Guidance on the diagnosis and management of COVID-19-associated pulmonary aspergillosis has been published.

Mucormycosis (also known as "black fungus") has been reported rarely. The number of cases in India is currently increasing in patients recently treated for COVID-19.

The main risk factors are uncontrolled diabetes and immunosuppression (e.g., due to corticosteroid therapy).

Have a low threshold of suspicion for the diagnosis. It is important not to miss warning signs and symptoms (e.g., nasal congestion; blackish/bloody nasal discharge; sinus or facial pain; toothache or loosening of teeth; vision disturbances; hemoptysis; necrotic eschar on skin, palate, or nasal turbinates). Do not hesitate to order appropriate investigations.

Management strategies in the context of COVID-19 include, but are not limited to: controlling hyperglycemia, diabetes, or diabetic ketoacidosis; reducing corticosteroid dose with the aim to rapidly discontinue; discontinuing immunomodulating drugs; extensive surgical debridement to remove all necrotic material; antifungal therapy (e.g., amphotericin-B) for 4 to 6 weeks; and appropriate supportive care and monitoring.

Patients should be under the care of a multidisciplinary team that includes an infectious disease specialist; an intensivist; a neurologist; a dentist; an ophthalmologist; an ear, nose, and throat specialist; and a surgeon.

Prevention involves controlling hyperglycemia; monitoring blood glucose level in COVID-19 patients after discharge (whether or not they are diabetic); and judicious use of corticosteroids, antibiotics, and antifungals.

Mild pancreatic injury (defined as elevated serum amylase or lipase levels) has been reported in 17% of patients in one case series. It is unknown whether this is a direct viral effect or due to the harmful immune response that occurs in some patients. Cases of acute pancreatitis have been reported; however,
<table>
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<tr>
<th>Complications</th>
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<th>Likelihood</th>
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<tbody>
<tr>
<td>pancreatic necrosis is rare.</td>
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<tr>
<td>Prior history of pancreatitis does not appear to be a risk factor for pancreatic inflammation in patients with COVID-19.</td>
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<tr>
<td>autoimmune hemolytic anemia</td>
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<tr>
<td>Warm or cold autoimmune hemolytic anemia (first episode) has been reported in 7 patients after the onset of COVID-19 symptoms and within the timeframe compatible with cytokine release syndrome. Four patients had indolent B lymphoid malignancy. It is unknown whether the hemolytic anemia is related to COVID-19 infection.</td>
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<tr>
<td>immune thrombocytopenia</td>
<td>variable</td>
<td>low</td>
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<tr>
<td>Immune thrombocytopenia has been reported rarely. The majority of cases were in patients &gt;50 years of age, with only 7% of cases reported in children. The majority of cases were in patients with moderate to severe COVID-19; however, 7% of cases were in asymptomatic COVID-19 patients. Onset occurred in 20% of cases 3 weeks after the onset of COVID-19 symptoms, with most cases reported after clinical recovery. Severe life-threatening bleeding was uncommon. Treatment involved the use of corticosteroids, intravenous immune globulin, and thrombopoietin-receptor agonists.</td>
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<tr>
<td>subacute thyroiditis</td>
<td>variable</td>
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<tr>
<td>Subacute thyroiditis is a thyroid disease of viral or post-viral origin. Emerging evidence suggests that infection with SARS-CoV-2 may trigger subacute thyroiditis. A review of 21 cases found a female predominance, with the mean number of days between the start of COVID-19 illness and the appearance of symptoms of subacute thyroiditis being 25 days. Infection had resolved in the majority of patients before the onset of subacute thyroiditis symptoms. Fever and neck pain were the most common presenting complaints. Symptoms resolved in all patients after treatment; however, 5 patients reported having hypothyroid illness on follow-up.</td>
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</tr>
<tr>
<td>gastrointestinal complications</td>
<td>variable</td>
<td>low</td>
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<tr>
<td>Critically ill patients may develop gastrointestinal complications; however, it is unclear whether this is a manifestation of critical illness in general, or whether it is specific to COVID-19. One study found that patients with COVID-19 were more likely to develop gastrointestinal complications compared with those without COVID-19, specifically transaminitis, severe ileus, and mesenteric ischemia. Macrovascular arterial/venous thrombosis has been identified in almost 50% of patients with bowel ischemia. Overall mortality in COVID-19 patients with gastrointestinal ischemia and radiologically evident mesenteric thrombotic occlusion was 38.7% and 40%, retrospectively.</td>
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**Prognosis**

**Mortality**

The leading cause of death is respiratory failure from acute respiratory distress syndrome (ARDS). The overall pooled mortality rate from ARDS in COVID-19 patients is 39%; however, this varies significantly between countries (e.g., China 69%, Iran 28%, France 19%, Germany 13%). There is no evidence to suggest worse outcomes (i.e., mechanical ventilator-free days, length of stay in intensive care unit)
Follow up

or hospital, or mortality) for patients with COVID-19-related ARDS compared with the general ARDS population.[969] Risk factors for respiratory failure include older age, male sex, cardiovascular disease, laboratory markers (such as lactate dehydrogenase, lymphocyte count, and C-reactive protein), and high viral load on admission.[970] Other common causes of death include sepsis or septic shock, sepsis-related multorgan failure, bacterial or viral coinfections, venous thromboembolism, and cardiac failure.[971]

People <65 years of age have a very small risk of death even in pandemic epicenters, and deaths in people <65 years of age without any underlying conditions is rare.[972] Data from the US indicate that only 5.5% of death certificates in 2020 had COVID-19 without any other conditions listed.[973]

Mortality rates have decreased over time despite stable patient characteristics.

• In-hospital mortality decreased from 32.3% to 16.4% between March and August 2020 in a UK cohort study of over 80,000 patients. Mortality declined in all age groups, in all ethnic groups, in men and women, and in patients with and without comorbidities, over and above contributions from declining illness severity.[974]
• Mortality rates decreased sharply in the US over the first 6 months of the pandemic.[975] [976] In-hospital mortality decreased from 10.6% to 9.3% between March and November 2020 in one US cohort study of over 500,000 patients across 209 acute care hospitals.[977] Among patients with critical illness admitted to an intensive care unit at an academic health system in the US, the mortality rate decreased from 43.5% to 19.2% over the study period.[978]
• This may reflect the impact of changes in hospital strategy and clinical processes, and better adherence to evidence-based standard of care therapies for critical illness over time, such as use of corticosteroids, high-flow nasal oxygen to avert intubation, prone positioning, and decreased use of mechanical ventilation. Further studies are needed to confirm these results and investigate causal mechanisms.

Infection fatality rate (IFR)

• Defined as the proportion of deaths among all infected individuals including confirmed cases, undiagnosed cases (e.g., asymptomatic or mildly symptomatic cases), and unreported cases. The IFR gives a more accurate picture of the lethality of a disease compared with the case fatality rate.
• It has been estimated that approximately 1.5 to 2 billion infections have occurred globally as of February 2021, with an estimated overall IFR of 0.15%. There are substantial differences in IFR and infection spread across continents, countries, and locations.[979]
• The US Centers for Disease Control and Prevention’s current best estimate of the IFR, according to age (as of 19 March 2021):[142]
  • 0 to 17 years – 0.002%
  • 18 to 49 years – 0.05%
  • 50 to 64 years – 0.6%
  • ≥65 years – 9%.
• Based on these figures, the overall IFR for people <65 years of age is approximately 0.2%.
• The IFR can vary across locations. A meta-analysis reports the point estimate of the IFR to be 0.68% across populations, with high heterogeneity (as of July 2020). The rate varied across locations from 0.17% to 1.7%.[980]
• Among people on board the Diamond Princess cruise ship, a unique situation where an accurate assessment of the IFR in a quarantined population can be made, the IFR was 0.85%. However, all deaths occurred in patients >70 years of age, and the rate in a younger, healthier population would be much lower.[981]
• These estimates have limitations and are likely to change as more data emerge over the course of the pandemic.

Seroprevalence studies

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Estimates of the IFR can be inferred from seroprevalence studies.

- Worldwide seroprevalence estimates vary. Seroprevalence in the general population has been estimated to be approximately 8%, with higher rates reported in close contacts (18%) and high-risk healthcare workers (17.1%). Pooled estimates of seroprevalence in the general population were highest in the South-East Asian (19.6%), African (16.3%), and Eastern Mediterranean (13.4%) regions. Lower estimates were reported in the Americas (6.8%), European (4.7%), and Western Pacific (1.7%) regions.[982]
- Current seroprevalence estimates for 10 sites in the US are available. [CDC: commercial laboratory seroprevalence survey data] (https://covid.cdc.gov/covid-data-tracker/#serology-surveillance)
- These studies suggest that the prevalence of infections is much higher than the official case counts suggest, and therefore the virus is much less lethal than initially thought.

Case fatality rate (CFR)

- Defined as the total number of deaths reported divided by the total number of detected cases reported. CFR is subject to selection bias as more severe/hospitalised cases are likely to be tested.
- The World Health Organization’s current estimate of the global CFR is 2.1% (as of 30 May 2021).[983] This is much lower than the reported CFR of severe acute respiratory syndrome coronavirus (SARS), which was 10%, and Middle East respiratory syndrome (MERS), which was 37%.[49]
- CFR varies considerably between countries.
  - In China, the overall CFR has been reported to be between 1.4% and 2.3% (0.9% in patients without comorbidities).[4] [984]
  - CFR increases with age.
    - In the US, the majority of deaths were in patients ages ≥65 years. The CFR was highest among patients ages ≥85 years (10% to 27%), followed by those ages 65 to 84 years (3% to 11%), then those ages 55 to 64 years (1% to 3%), and finally those ages 20 to 54 years (<1%).[7]
    - In China, the majority of deaths were in patients ages ≥60 years.[4] The CFR was highest among patients ages ≥80 years (13.4%), followed by those ages 60 to 79 years (6.4%), and then those ages <60 years (0.32%).[984]
    - In Italy, the CFR was highest among patients ages ≥80 years (52.5%), followed by those ages 70 to 79 years (35.5%), and then those ages 60 to 69 years (8.5%).[985]
    - Deaths are rare in children.[7] [21] In one study, 70% of deaths occurred in those ages 10 to 20 years, 20% in those ages 1 to 9 years, and 10% in children under 1 year of age.[986]
  - CFR increases with the presence of comorbidities.
    - In China, the majority of deaths were in patients who had preexisting underlying health conditions (10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6% for hypertension, and 5.6% for cancer).[4]
  - CFR increases with disease severity.
    - The CFR is highest in patients with critical disease, ranging from 26% to 67% in studies.[4] [987] [988]

Limitations of IFR/CFR

- Estimating the IFR and CFR in the early stages of a pandemic is subject to considerable uncertainties and estimates are likely to change as more data emerges. Rates tend to be high at the start of a pandemic and then trend downwards as more data becomes available.[989]
- There is currently no set case definition of a confirmed case, and case definitions vary. A positive polymerase chain reaction (PCR) result is sometimes the only criterion for a case to be recognized;
however, a positive PCR test does not necessarily equal a diagnosis of COVID-19, or mean that a person is infected or infectious.[990] [991]

- The number of deaths reported on a particular day may not accurately reflect the number of deaths from the previous day due to delays associated with reporting deaths. This makes it difficult to know whether deaths are falling over time in the short term.[992]
- Patients who die "with" COVID-19 and patients who die “from” COVID-19 may be counted towards the death toll in some countries. For example, in Italy only 12% of death certificates reported direct causality from COVID-19, while 88% of patients who died had at least one comorbidity.[989] [993]

Mortality rate by country

- The number of deaths (per 100,000 population) for different countries varies:[994]
  - South Korea – 0.7
  - Japan – 1.2
  - Australia – 3.3
  - Germany – 11.3
  - Canada – 24.6
  - France – 46.6
  - Sweden – 57.4
  - Italy – 59.1
  - US – 60.3
  - UK – 62.6
  - Spain – 65.0
  - Belgium – 86.8.

**Prognostic factors**

Prognostic factors that have been associated with increased risk of severe disease and mortality include:[995] [996] [997] [998]

- **Patient factors**
  - Increasing age
  - Male sex
  - Obesity
  - Smoking history
  - Blood type A
  - Frailty

- **Presence of comorbidities**
  - Hypertension
  - Cardiovascular disease
  - Heart failure
  - Cerebrovascular disease
  - Dementia
  - Diabetes
  - Chronic lung disease
  - COPD
  - Active malignancy
Coronavirus disease 2019 (COVID-19)

Follow up

- Immunosuppression
- Chronic kidney disease
- Bacterial or fungal coinfection

- Symptoms/signs
  - Myalgia
  - Sputum production
  - Chills
  - Nausea
  - Dyspnea
  - Hemoptysis
  - Tachypnea
  - Hypoxemia
  - Respiratory failure
  - Hypotension
  - Tachycardia

- Investigations
  - Lymphopenia
  - Leukocytosis
  - Neutrophilia
  - Thrombocytopenia
  - Hypoalbuminemia
  - Liver, kidney impairment, or cardiac injury
  - Elevated inflammatory markers (C-reactive protein, procalcitonin, erythrocyte sedimentation rate)
  - Elevated lactate dehydrogenase
  - Elevated creatine kinase
  - Elevated cardiac markers
  - Elevated D-dimer
  - Elevated interleukin-6
  - Bilateral pneumonia on chest imaging
  - Consolidative infiltrate or pleural effusion on chest imaging
  - High sequential organ failure assessment (SOFA) score.

The most common underlying diseases in deceased patients were hypertension, diabetes, and cardiovascular diseases.[999]

A ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) ≤200 mmHg and respiratory failure at admission are also independently associated with an increased risk of in-hospital mortality.[1000] Almost half of patients who received invasive mechanical ventilation died. The mortality rate was higher in older patients >80 years (84%) compared with younger patients ≤40 years (48%).[1001]

Hospital readmission

People discharged from hospital after acute infection had an increased risk of readmission, multi-organ dysfunction, and mortality compared with the general population. The relative increase in risk was not confined to older people and was not uniform across ethnic groups. Researchers matched approximately 50,000 patients in England who were hospitalized and discharged with COVID-19 to members of the general population; 29% of COVID-19 patients were readmitted during a mean 140 days of follow-up, while 12% died
Follow up

after discharge. Patients with COVID-19 were more frequently diagnosed with cardiovascular events, chronic kidney or liver disease, and diabetes compared with their matched controls.[1002]

Approximately 9% of over 106,000 patients were readmitted to the same hospital within 2 months of discharge from the initial hospitalization. Multiple readmissions occurred in 1.6% of patients. The median time from discharge to the first readmission was 8 days. Less than 0.1% of patients died during readmission. Risk factors for readmission include:[1003]

- Age ≥65 years
- Presence of chronic conditions (COPD, heart failure, diabetes, chronic kidney disease, obesity)
- Hospitalization within the 3 months preceding the first COVID-19 hospitalization
- Discharge to a skilled nursing facility or with home health care.

The risk of severe post-acute complications in patients who were not admitted to hospital for the primary infection appears to be low. However, they may be at slightly increased risk of venous thromboembolism, dyspnea, and initiating bronchodilator or triptan therapy compared with people who tested negative for SARS-CoV-2. These patients visited their general practitioner and outpatient hospital clinics more often after the primary infection than those who tested negative, which may indicate persistent symptoms that do not lead to specific drug treatment or hospital admission.[1004]

Reinfection

Reinfection refers to a new infection following previous confirmed infection (i.e., severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] real-time reverse transcription polymerase chain reaction [RT-PCR] positive), and is distinct from persistent infection and relapse. There is currently no standard case definition for SARS-CoV-2 reinfection.[737]

There is limited information about reinfection.

- Recurrent RT-PCR positivity in patients 1 to 60 days after recovery ranges between 7% to 23% in studies, with an estimated pooled rate of 12%. Patients with longer initial illness and younger age were more likely to experience recurrent RT-PCR positivity, while those with severe disease, diabetes, and a low lymphocyte count were less likely.[1006] It is currently unclear whether this is due to reinfection; whether it is due to factors such as the type of specimen collection and technical errors associated with swab testing, infection by mutated SARS-CoV-2, or persistent viral shedding; or whether the test result was a false-negative at the time of discharge.[1007]
- Studies have repeatedly reported positive RT-PCR tests for up to 90 days after initial infection; therefore, it is most likely that these cases are actually protracted initial infections. It is important to note that although persistent viral shedding has been reported for up to 90 days after the onset of infection, replication-competent virus has not been identified 10 to 20 days after the onset of symptoms (depending on disease severity).[1008] A cohort study of 200 patients with past infection found that despite persistent pharyngeal RT-PCR positivity for up to 90 days after recovery, transmission to close contacts was not observed, indicating that these patients are not contagious at the post-symptomatic stage of infection.[1009]
- A preprint study of residents and healthcare staff in care homes in the UK found that natural immunity substantially reduces the risk of reinfection for approximately 10 months following primary infection. The risk of reinfection was <1% per month in people who had been previously infected.[1010]

Cases of reinfection are rare.

- Cases of possible reinfection have been reported in many countries including China, India, Ecuador, the US, the Netherlands, Qatar, and Belgium. Overall, 68.8% had similar severity, 18.8% had worse symptoms, and 12.5% had milder symptoms with the second episode.[1011]
- Cases of reinfection with SARS-CoV-2 variants have been reported in Brazil, the UK, and South Africa.[1012] [1013] [1014] [1015]

Consider reinfection in the following circumstances:[737]

- A repeat positive RT-PCR test 90 days or more after a previous positive RT-PCR test
• New symptoms in a patient with previous RT-PCR-positive infection after apparent full recovery (i.e., resolution of previous symptoms) and a repeat positive RT-PCR test (including within 90 days after a previous positive RT-PCR test).

Diagnosis

• A compatible clinical presentation together with diagnostic evidence (such as a low RT-PCR cycle threshold value) may be sufficient to diagnose reinfection. However, the diagnosis should be made in conjunction with an infectious disease specialist following a risk assessment that involves reviewing available clinical, diagnostic, and epidemiologic information to inform whether reinfection is likely. Confirmation of reinfection should be obtained through whole genome sequencing of paired specimens, if available.[737]

Management

• Manage patients with suspected reinfection as if they are infectious, as for a new or first infection. Advise the patient to self-isolate pending further investigation and clinical risk assessment. It is important to note that illness due to reinfection may not necessarily follow the same clinical course as the previous episode.[737]

Immunity

The immune response to SARS-CoV-2 is not yet fully understood, but involves both cell-mediated and antibody-mediated immunity. This is an area of rapidly emerging new evidence.

Adaptive immunity is thought to occur within the first 7 to 10 days of infection. A robust memory B-cell and plasmablast response is detected early in infection, with secretion of immunoglobulin A (IgA) and IgM antibodies by day 5 to 7, and IgG by day 7 to 10 from the onset of symptoms. T cells are simultaneously activated in the first week of infection and SARS-CoV-2-specific memory CD4+ and CD8+ T cells peak within 2 weeks. Antibody and T-cell response differ among individuals, and depend on age and disease severity.[1016]

Antibody-mediated immunity

• Current evidence is uncertain to predict the presence, level, or durability of natural immunity conferred by SARS-CoV-2 antibodies against reinfection.[1017]
• Approximately 90% to 99% of infected people develop detectable neutralizing antibodies within 4 weeks following natural infection.[1018]
• Moderate-strength evidence suggests that most adults develop detectable levels of IgM and IgG antibodies after infection. IgM levels peak early in the disease course at approximately 20 days and then decline. IgG levels peak later at approximately 25 days after symptom onset and may remain detectable for at least 120 days. Most adults generate neutralizing antibodies, which may persist for several months. Some adults do not develop antibodies after infection; the reasons for this are unclear.[1019]
• Maternal IgG antibodies to SARS-CoV-2 have been found to transfer across the placenta after infection in pregnant women.[1020]
• There were some early studies that suggested asymptomatic people may have a weaker antibody response to infection; however, this has not been confirmed.[1021]
• Current evidence suggests that the immune responses remain robust and protective against reinfection in most people for at least 6 to 10 months after infection (the longest follow-up data is currently only 10 months).[1018][1022]
• Some SARS-CoV-2 variants with key changes in the spike protein have a reduced susceptibility to neutralization by antibodies. However, cellular immunity elicited by natural infection also targets other viral proteins, which tend to be more conserved across variants than the spike protein.[1018]

Cell-mediated immunity
The majority of people develop a strong and broad T-cell response with both CD4+ and CD8+ T cells, and some have a memory phenotype.[1023]

CD4+ and CD8+ T cells declined with a half-life of 3 to 5 months in adults who recovered, and are likely to be present in most adults at least 6 to 8 months after primary infection.[1024] [1025]

Emerging data suggest that T-cell responses are largely unaffected by SARS-CoV-2 variants.[1026] [1027]

Evidence suggests that infection with SARS-CoV-2 is likely to confer protective immunity against reinfection.[1028] [1029] [1030] [1031]

A Public Health England study found that naturally acquired immunity, as a result of past infection, provides 84% protection against reinfection compared with people who have not had the disease previously, and protection appeared to last for at least 7 months.[1032]

Similarly, a population-level observational study among 4 million PCR-tested people in Denmark found protection against repeat infection in the population to be 80% or higher in those younger than 65 years of age, and 47% in those older than 65 years of age. There was no evidence of waning protection over time.[1033]

An observational study from Lombardy, Italy, found that natural immunity appears to confer a protective effect for at least one year; however, the study ended before SARS-CoV-2 variants began to spread, and it is unknown how well natural immunity to the wild-type virus will protect against these variants.[1034]

A prospective study in 3000 mostly young male Marine recruits found that around 10% of seropositive participants tested positive for the virus at least once in the 6-week follow-up period compared with 48% of seronegative participants, an 82% reduced incidence rate of infection.[1035]

According to a large, retrospective study, people who were seropositive for SARS-CoV-2 appeared to be at lower risk for future infection, for at least several months.[1036]

A study in over 12,000 healthcare workers found that prior SARS-CoV-2 infection that generated antibody responses offered protection from reinfection for most people in the 6 months following infection.[1037]

Preexisting immunity to SARS-CoV-2

Testing of blood samples taken before the COVID-19 pandemic has shown that some people already have immune cells that recognize SARS-CoV-2. Studies have reported T-cell reactivity against SARS-CoV-2 in 20% to 50% of people with no known exposure to the virus.[1038] Approximately 5% of uninfected adults and 62% of uninfected children aged 6 to 16 years had antibodies that recognize SARS-CoV-2 in one study.[1039]

This may be a consequence of true immune memory derived in part from previous infection with common cold coronaviruses, or from other unknown animal coronaviruses. However, further research into whether there is preexisting immunity to SARS-CoV-2 in the human population is required.
# Diagnostic guidelines

## International

<table>
<thead>
<tr>
<th>Resource</th>
<th>Published by</th>
<th>Last published</th>
</tr>
</thead>
</table>
**International**

*Last published: 2020*

*Last published: 2021*

**Diagnostic testing for SARS-CoV-2: interim guidance** ([https://www.who.int/publications/i/item/diagnostic-testing-for-sars-cov-2](https://www.who.int/publications/i/item/diagnostic-testing-for-sars-cov-2))  
*Last published: 2020*

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*Last published: 2020*

**Prevention, identification and management of health worker infection in the context of COVID-19** ([https://www.who.int/publications/i/item/10665-336265](https://www.who.int/publications/i/item/10665-336265))  
*Last published: 2020*

*Last published: 2020*

*Last published: 2021*
<table>
<thead>
<tr>
<th>International</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Published by:</strong> Public Health England  Last published: 2021</td>
</tr>
<tr>
<td><strong>Published by:</strong> European Centre for Disease Prevention and Control  Last published: 2021</td>
</tr>
<tr>
<td>Assessment of COVID-19 in primary care (<a href="https://www.sign.ac.uk/our-guidelines">https://www.sign.ac.uk/our-guidelines</a>)  [739]</td>
</tr>
<tr>
<td><strong>Published by:</strong> Scottish Intercollegiate Guidelines Network  Last published: 2021</td>
</tr>
<tr>
<td><strong>Published by:</strong> Scottish Intercollegiate Guidelines Network  Last published: 2021</td>
</tr>
<tr>
<td><strong>Published by:</strong> Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team; Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care  Last published: 2020</td>
</tr>
<tr>
<td><strong>Published by:</strong> Peking Union Medical College Hospital  Last published: 2020</td>
</tr>
</tbody>
</table>
Treatment guidelines

International


Published by: National Institutes of Health  Last published: 2021


Published by: Infectious Diseases Society of America  Last published: 2021

Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19 (https://www.idsociety.org/practice-guideline/alphabetical-guidelines) [793]

Published by: Infectious Diseases Society of America  Last published: 2021


Published by: Centers for Disease Control and Prevention  Last published: 2021


Published by: Centers for Disease Control and Prevention  Last published: 2021

Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States (https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html) [411]

Published by: Centers for Disease Control and Prevention  Last published: 2021


Published by: Centers for Disease Control and Prevention  Last published: 2021


Published by: Centers for Disease Control and Prevention  Last published: 2021


Published by: Centers for Disease Control and Prevention  Last published: 2021
### International

<table>
<thead>
<tr>
<th>Topic</th>
<th>Published by</th>
<th>Last published</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19 interim guidance</td>
<td>American Academy of Pediatrics</td>
<td>2021</td>
</tr>
<tr>
<td>Caring for children and youth with special health care needs during</td>
<td>American Academy of Pediatrics</td>
<td>2021</td>
</tr>
<tr>
<td>the COVID-19 pandemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management of infants born to mothers with suspected or confirmed</td>
<td>American Academy of Pediatrics</td>
<td>2021</td>
</tr>
<tr>
<td>COVID-19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interim guidance for implementing home care of people not requiring</td>
<td>Centers for Disease Control and Prevention</td>
<td>2020</td>
</tr>
<tr>
<td>hospitalization for coronavirus disease 2019 (COVID-19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis and management of COVID-19 disease</td>
<td>American Thoracic Society</td>
<td>2020</td>
</tr>
<tr>
<td>Thromboembolism and anticoagulant therapy during the COVID-19</td>
<td>Anticoagulation Forum</td>
<td>2020</td>
</tr>
<tr>
<td>pandemic: interim clinical guidance from the Anticoagulation Forum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluation and management considerations for neonates at risk for</td>
<td>Centers for Disease Control and Prevention</td>
<td>2020</td>
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<tr>
<td>COVID-19</td>
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### International

<table>
<thead>
<tr>
<th>Title</th>
<th>Published by</th>
<th>Last published:</th>
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</thead>
<tbody>
<tr>
<td>COVID-19 guidance and the latest research in the Americas [946]</td>
<td>Pan American Health Organization</td>
<td>2021</td>
</tr>
<tr>
<td>Source</td>
<td>Published by</td>
<td>Last published:</td>
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<tr>
<td>International Rapid advice guidelines for management of children with COVID-19</td>
<td>International multidisciplinary working group</td>
<td>2020</td>
</tr>
<tr>
<td>ISTH interim guidance on recognition and management of coagulopathy in COVID-19</td>
<td>International Society of Thrombosis and Haemostasis</td>
<td>2020</td>
</tr>
<tr>
<td>BMJ's coronavirus (covid-19) hub</td>
<td>BMJ</td>
<td>2021</td>
</tr>
<tr>
<td>COVID-19 rapid guideline: managing COVID-19</td>
<td>National Institute for Health and Care Excellence (UK)</td>
<td>2021</td>
</tr>
<tr>
<td>Coronavirus (COVID-19)</td>
<td>National Institute for Health and Care Excellence (UK)</td>
<td>2021</td>
</tr>
<tr>
<td>Coronavirus specialty guides</td>
<td>NHS England</td>
<td>2021</td>
</tr>
</tbody>
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# International

<table>
<thead>
<tr>
<th>Topic</th>
<th>Published by</th>
<th>Last published</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Community palliative, end of life and bereavement care in the COVID-19 pandemic</strong> (<a href="https://elearning.rcgp.org.uk/mod/page/view.php?id=10537">link</a>)</td>
<td>Royal College of General Practitionans; Association for Palliative Medicine</td>
<td>2021</td>
</tr>
<tr>
<td><strong>Management of hospitalised adults with coronavirus disease-19 (COVID-19)</strong> (<a href="https://www.ersnet.org/guidelines">link</a>)</td>
<td>European Respiratory Society</td>
<td>2021</td>
</tr>
<tr>
<td><strong>Coronavirus (COVID-19) infection in pregnancy</strong> (<a href="https://www.rcog.org.uk/en/guidelines-research-services/guidelines/coronavirus-pregnancy">link</a>)</td>
<td>Royal College of Obstetricians and Gynaecologists (UK)</td>
<td>2021</td>
</tr>
<tr>
<td><strong>Clinical guidance for management of adult COVID-19 patients</strong> (<a href="https://covid.aiims.edu/clinical-guidance-for-management-of-adult-covid-19-patients">link</a>)</td>
<td>All India Institute Of Medical Sciences; Indian Council of Medical Research</td>
<td>2021</td>
</tr>
<tr>
<td><strong>Technical documents and advisory</strong> (<a href="https://www.icmr.gov.in/ctechdocad.html">link</a>)</td>
<td>Indian Council of Medical Research</td>
<td>2021</td>
</tr>
<tr>
<td><strong>Updates on COVID-19 (coronavirus disease 2019) local situation</strong> (<a href="https://www.moh.gov.sg/covid-19">link</a>)</td>
<td>Ministry of Health Singapore</td>
<td>2021</td>
</tr>
</tbody>
</table>
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**Coronavirus disease** ([http://www.chinacdc.cn/jkzt/crb/zl/szkb_11803](http://www.chinacdc.cn/jkzt/crb/zl/szkb_11803))  [959]

*Published by:* Chinese Center for Disease Control and Prevention  
*Last published:* 2021


*Published by:* National Institute of Infectious Diseases Japan  
*Last published:* 2021


*Published by:* Japanese Association for Infectious Diseases  
*Last published:* 2021


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*Last published:* 2021

**COVID-19 rapid guideline: managing the long-term effects of COVID-19** ([https://www.nice.org.uk/guidance/ng188](https://www.nice.org.uk/guidance/ng188))  [963]

*Published by:* National Institute for Health and Care Excellence (UK)  
*Last published:* 2020


*Published by:* Chinese expert working panel  
*Last published:* 2020


*Published by:* First Affiliated Hospital, Zhejiang University School of Medicine  
*Last published:* 2020


*Published by:* National Health Commission of the People’s Republic of China; National Administration of Traditional Chinese Medicine of the People’s Republic of China  
*Last published:* 2020


*Published by:* Peking Union Medical College Hospital  
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## Online resources


5. **COG-UK**: data ([https://www.cogconsortium.uk](https://www.cogconsortium.uk)) *(external link)*


7. Vaccine Adverse Event Reporting System (VAERS) ([https://vaers.hhs.gov](https://vaers.hhs.gov)) *(external link)*


10. **WHO**: Adverse Event Following Immunization (AEFI) form ([http://investigation.gvsi-aefi-tools.org/#step-1](http://investigation.gvsi-aefi-tools.org/#step-1)) *(external link)*


12. **CDC**: interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States ([https://www.cdc.gov/vaccines/](https://www.cdc.gov/vaccines/)) *(external link)*


20. **BMJ**: covid-19 – a remote assessment in primary care ([https://www.bmj.com/content/368/bmj.m1182](https://www.bmj.com/content/368/bmj.m1182)) (external link)

21. **BMJ Learning**: Covid-19 – handwashing technique and PPE videos ([https://www.youtube.com/playlist?list=PLVnZu1tiqPoTtOiGGdCiRJts6ep9vSVxE](https://www.youtube.com/playlist?list=PLVnZu1tiqPoTtOiGGdCiRJts6ep9vSVxE)) (external link)


24. **BMJ**: facemasks for the prevention of infection in healthcare and community settings ([https://www.bmj.com/content/350/bmj.h694](https://www.bmj.com/content/350/bmj.h694)) (external link)


29. **BMJ Best Practice**: Management of coexisting conditions in the context of COVID-19 ([https://bestpractice.bmj.com/topics/en-us/3000190#important-update](https://bestpractice.bmj.com/topics/en-us/3000190#important-update)) (external link)
30. BMJ Practice Pointer: remote management of covid-19 using home pulse oximetry and virtual ward support (https://www bmj com/content/372/bmj.n677) (external link)
31. Centre for Evidence-Based Medicine: are you infectious if you have a positive PCR test result for COVID-19? (https://www cebm net/covid-19/infectious-positive-pcr-test-result-covid-19) (external link)
32. BMJ Practice Pointer: interpreting a covid-19 test result (https://www bmj com/content/369/bmj.m1808) (external link)
33. BMJ practice pointer: testing for SARS-CoV-2 antibodies (https://www bmj com/content/370/bmj.m3325) (external link)
34. BSTI: radiology decision tool for suspected COVID-19 (https://www bsti org.uk/media/resources/files/NHSE_BSTI_APPROVED_Radiology_on_Covid19_v6_modified1__-_Read-Only.pdf) (external link)
35. BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas (https://www bsti org.uk/media/resources/files/Lung_US_print_out_and_scoring_proforma.pdf) (external link)
<table>
<thead>
<tr>
<th></th>
<th>Online resources</th>
</tr>
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| **44.** | Clinical Frailty Scale ([https://www.scfn.org.uk/clinical-frailty-scale](https://www.scfn.org.uk/clinical-frailty-scale))  
**46.** | BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19 ([https://www.bmj.com/content/370/bmj.m3379](https://www.bmj.com/content/370/bmj.m3379))  
**47.** | Global coronavirus COVID-19 clinical trial tracker ([https://www.covid-trials.org](https://www.covid-trials.org))  
**48.** | RECOVERY trial ([https://www.recoverytrial.net](https://www.recoverytrial.net))  
**50.** | CDC: commercial laboratory seroprevalence survey data ([https://covid.cdc.gov/covid-data-tracker/#serology-surveillance](https://covid.cdc.gov/covid-data-tracker/#serology-surveillance))  
**51.** | NICE COVID-19 rapid guideline: managing the long-term effects of COVID-19 ([https://www.nice.org.uk/guidance/ng188](https://www.nice.org.uk/guidance/ng188))  
**52.** | BMJ webinar: long COVID – how to define it and how to manage it ([https://www.bmj.com/content/370/bmj.m3489](https://www.bmj.com/content/370/bmj.m3489))  
**53.** | BMJ: management of post-acute covid-19 in primary care ([https://www.bmj.com/content/370/bmj.m3026](https://www.bmj.com/content/370/bmj.m3026))  
**54.** | The BMJ 10-minute consultation: what is my covid risk? ([https://www.bmj.com/content/372/bmj.n637](https://www.bmj.com/content/372/bmj.n637))  
**58.** | Health Education England: adult pulse oximetry monitoring video ([https://www.youtube.com/watch?v=ifnYjD4IKus&t=141s](https://www.youtube.com/watch?v=ifnYjD4IKus&t=141s))  


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Key articles


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<th>Description</th>
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References


REFERENCES


REFERENCES


Figure 1: Number of COVID-19 cases reported weekly by WHO Region, and global deaths, as of 30 May 2021

World Health Organization
Figure 2: Illustration revealing ultrastructural morphology exhibited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when viewed with electron microscopically

Centers for Disease Control and Prevention
Figure 3: Virus replication cycle

BMJ. 2020;371:m3862
### mRNA vaccines

<table>
<thead>
<tr>
<th></th>
<th>Pfizer/BioNTech</th>
<th>Moderna</th>
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</thead>
<tbody>
<tr>
<td><strong>Vaccine type</strong></td>
<td>Lipid nanoparticle-formulated mRNA vaccine that encodes the SARS-CoV-2 spike protein</td>
<td></td>
</tr>
<tr>
<td><strong>Overall efficacy</strong></td>
<td>95%</td>
<td>94%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>≥12 years of age</td>
<td>≥18 years of age</td>
</tr>
<tr>
<td><strong>Authorized dose</strong></td>
<td><strong>TWO-DOSE REGIMEN</strong> 0.3 mL (30 mcg) IM; second dose at least 21 days after</td>
<td><strong>TWO-DOSE REGIMEN</strong> 0.5 mL (100 mcg) IM; second dose at least 28 days after</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Hypersensitivity to active substance or any excipients; immediate allergic reaction to first dose (should not get second dose)</td>
<td></td>
</tr>
<tr>
<td><strong>Cautions</strong></td>
<td>History of anaphylaxis/allergic reactions; Acute severe febrile illness; Bleeding disorders or anticoagulation; Immunocompromised; Pregnancy and breastfeeding; Previous treatment with COVID-19 monoclonal antibodies/plasma; Multisystem inflammatory syndrome in children or adults</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td><strong>Common:</strong> headache; arthralgia; myalgia; injection-site reactions; fatigue; fever; chills; nausea; vomiting; diarrhea; rash; axillary lymphadenopathy (on same side as injection site)</td>
<td><strong>Uncommon:</strong> malaise; acute peripheral facial paralysis; anaphylaxis; hypersensitivity; face swelling (if dermatologic fillers present)</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>Interactions with other vaccines/drugs have not been studied (WHO recommends at least 14 days between COVID-19 vaccines and others; however, the FDA recommends that COVID-19 vaccines and other vaccines may now be administered without regard to timing)</td>
<td></td>
</tr>
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**Figure 4:** Comparison of selected authorized mRNA COVID-19 vaccines. Data is evolving; consult local drug formulary or guidelines for detailed information for your location. *Data based on phase 3 clinical trials - see Vaccine efficacy clinical trial data and Vaccine safety clinical trial data sections below for detailed information. **Dose schedules may differ in some locations. Last reviewed/updated: 3 June 2021"
### Viral vector vaccines

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<tr>
<td><strong>Janssen (Ad26.COV2.S)</strong></td>
<td>Replication-incompetent adenovirus type 26 (human) vector vaccine that carries the genetic code for the SARS-CoV-2 spike protein</td>
</tr>
<tr>
<td><strong>Vaccine type</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Overall efficacy in adolescents</strong></td>
<td>66%</td>
</tr>
<tr>
<td><strong>≥16 years and adults</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>≥18 years of age</td>
</tr>
<tr>
<td><strong>Authorized dose</strong></td>
<td>SINGLE-DOSE REGIMEN</td>
</tr>
<tr>
<td></td>
<td>0.5 mL IM (5 × 10^10 viral particles)</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine</td>
</tr>
<tr>
<td><strong>Cautions</strong></td>
<td>History of anaphylaxis/allergic reactions</td>
</tr>
<tr>
<td></td>
<td>Acute severe febrile illness</td>
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<td>Bleeding disorders or anticoagulation</td>
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<td>Immunocompromised</td>
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<td>Pregnancy and breastfeeding</td>
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<td></td>
<td>Heparin-induced thrombocytopenia</td>
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<td></td>
<td>Multisystem inflammatory syndrome in children or adults</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td><strong>Common:</strong> injection-site reactions; headache; cough; fatigue; myalgia; arthralgia; nausea; fever; chills</td>
</tr>
<tr>
<td></td>
<td><strong>Uncommon:</strong> anaphylaxis; urticaria; hypersensitivity; tremor; hyperhidrosis; rash; sneezing; oropharyngeal pain; pain in extremity; back pain; muscular weakness; asthenia; malaise; thrombosis with concurrent thrombocytopenia (sometimes accompanied with bleeding)</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>Interactions with other vaccines/drugs have not been studied (WHO recommends at least 14 days between COVID-19 vaccines and others); however, the FDA recommends that COVID-19 vaccines and other vaccines may now be administered without regard to timing</td>
</tr>
</tbody>
</table>

**Figure 5:** Comparison of selected authorized viral vector COVID-19 vaccines. Data is evolving; consult local drug formulary or guidelines for detailed information for your location. *Data based on phase 3 clinical trials - see Vaccine efficacy clinical trial data and Vaccine safety clinical trial data sections below for detailed information. **Dose schedules may differ in some locations. Last reviewed/updated: 3 June 2021

BMJ Best Practice editorial team; compiled using data from the US product information
Figure 6: Early effectiveness of covid-19 vaccination

BMJ. 2021 May 13;373:n1088
Figure 7: Transverse CT scans from a 32-year-old man, showing ground-glass opacity and consolidation of lower lobe of right lung near the pleura on day 1 after symptom onset (top panel), and bilateral ground-glass opacity and consolidation on day 7 after symptom onset

Xu XW et al. BMJ. 2020;368:m606
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BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style
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