

# BMJ Best Practice

## Coronavirus disease 2019 (COVID-19)

Straight to the point of care



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## Summary

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 aetiology 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 an evolving situation, evidence is limited in some areas and some recommendations may be based on observational studies and retrospective analyses, as well as randomised controlled trials and guidelines.

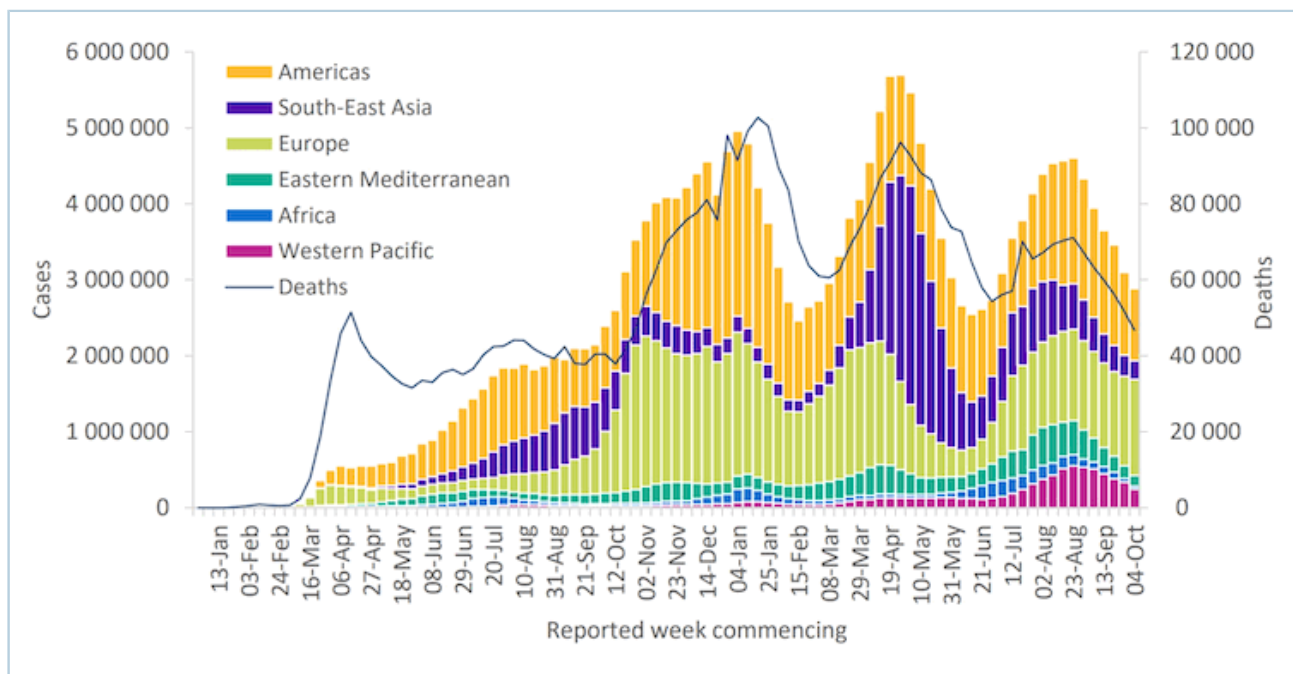
## Definition

A potentially severe acute respiratory infection caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>[1]</sup> 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, dyspnoea, and loss of taste/smell, although some patients may have mild upper respiratory tract symptoms or 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 238.5 million cases have been reported globally, with approximately 4.8 million deaths according to the World Health Organization. The US has the highest number of reported infections and deaths in the world. India, Brazil, the UK, and Russia have the highest number of infections after the US. Brazil, India, Mexico, and Russia have the highest number of deaths after the US.

[[WHO: coronavirus disease \(COVID-19\) dashboard](#)]



Number of COVID-19 cases reported weekly by WHO Region, and global deaths, as of 10 October 2021

World Health Organization

Current detailed data for the UK situation is available.

- [[UK Office for National Statistics: coronavirus \(COVID-19\) infection survey, UK statistical bulletins](#)]

### Adults

- In China, 87% of confirmed cases were aged 30 to 79 years and 3% were aged 80 years or older in the first wave of the pandemic. Approximately 51% of patients were male.[9]
- 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 hospitalised patients in the first wave.[10]
- In the US, older patients (aged  $\geq 65$  years) accounted for 31% of all cases, 45% of hospitalisations, 53% of intensive care unit admissions, and 80% of deaths in the first wave, with the highest incidence of severe outcomes in patients aged  $\geq 85$  years.[11]

### Adolescents

- Adolescents appear to have similar susceptibility to infection as adults.[12] However, evidence is conflicting and the detailed relationship between age and susceptibility to infection requires further investigation.[13]

- In the US, hospitalisations in adolescents peaked at 2.1 per 100,000 in early January 2021, declined to 0.6 per 100,000 in March, and rose to 1.3 per 100,000 in April. Among hospitalised adolescents, approximately one third required admission to the intensive care unit and 5% required mechanical ventilation. This data was based on 204 adolescents who were likely hospitalised primarily for COVID-19 during January 1 to March 31 2021.[14] The cumulative number of hospitalisations in the 5- to 17-year-old age bracket from March 2020 to June 2021 was 1909 cases.[15]

### Children

- Evidence suggests that children have a lower susceptibility to infection compared with adults.[12] However, evidence is conflicting and the detailed relationship between age and susceptibility to infection requires further investigation.[13] Emerging data suggest variants may spread more effectively and rapidly among young children, although hospitalisation rates decreased.[16]
- 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.[17] Unlike adults, children do not seem to be at higher risk for severe illness based on age or sex.[18]
- In the UK, a prospective observational cohort study found that children and young adults represented 0.9% of all hospitalised 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.[19]
- 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.[20]
- Globally, the case fatality rate in children appears to be higher in low- and middle-income countries compared with high-income countries.[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.[22] [23] A meta-analysis of over 2500 pregnant women with confirmed disease 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 infection in pregnancy is 4.9 per 1000 maternities. Most women were in the second or third trimester. Of these patients, 41% were aged 35 years or older, 56% were from Black or other ethnic minority groups, 69% were overweight or obese, and 34% had pre-existing comorbidities.[25]
- In the US, over 125,000 cases have been reported in pregnant women (as of 4 October 2021), with over 22,000 hospitalisations and 171 deaths.[26] According to an analysis of approximately 400,000 women aged 15 to 44 years with symptomatic disease, Hispanic and non-Hispanic Black pregnant women appear to be disproportionately affected during pregnancy.[27]

### Healthcare workers

- Approximately 14% of the cases reported to the World Health Organization are in healthcare workers (range 2% to 35%).[28]

- 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.[\[29\]](#) [\[30\]](#)

## 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 1 metre (3 feet) 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.[\[153\]](#)

The US Centers for Disease Control and Prevention defines a close contact as someone who has been within 2 metres (6 feet) 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).[\[154\]](#)

#### 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 travelling 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.[\[153\]](#)

People at risk of infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern include:[\[155\]](#)

- 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 individuals described above.

## older age

### Older people are at increased risk for infection and severe disease. [156]

The risk of hospitalisation and death increases with age. For example, in people aged 85 years and older, the risk of hospitalisation is 15 times higher and the risk of death is 610 times higher compared with 18- to 29-year-olds according to US data.[157]

|                 | 0-4 years | 5-17 years | 18-29 years     | 30-39 years | 40-49 years | 50-64 years | 65-74 years | 75-84 years | 85+ years |
|-----------------|-----------|------------|-----------------|-------------|-------------|-------------|-------------|-------------|-----------|
| Hospitalisation | <1 x      | <1 x       | Reference group | 2x          | 2x          | 4x          | 6x          | 9x          | 15x       |
| Death           | <1 x      | <1 x       |                 | 4x          | 10x         | 35x         | 95x         | 230x        | 610x      |

*Risk for hospitalisation and death by age group (rate ratios compared with 18- to 29-year-olds)*

*Table based on data from the CDC*

In the UK, data from a cross-sectional study indicated that people aged 40 to 64 years are at greatest risk of infection, followed by patients 75 years and older, and then people aged 65 to 74 years.[158] The highest mortality rate was observed in patients 80 years and older.[159]

In the US, patients  $\geq 65$  years accounted for 31% of all cases, 45% of hospitalisations, 53% of intensive care unit admissions, and 80% of deaths early in the pandemic, with the highest incidence of severe outcomes in patients aged  $\geq 85$  years.[11]

Observational studies in older adults aged  $\geq 60$  years across multiple countries found that approximately 51% of older patients had severe infection, while 22% were critically ill.[160]

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.[161]

## male sex

### Males are at increased risk for infection and severe disease. [156]

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%).[158]

It has been hypothesised 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.[162] [163]

## ethnicity

### People who belong to Black, Asian, and minority ethnic (BAME) groups are at increased risk of infection and severe disease. [164] [165]

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., hospitalisation, intensive care unit admission, death) compared with the White population, even after accounting for differences in sociodemographic, clinical, and household characteristics.[166] Race may play an important role in adverse outcomes in children as well as adults.[167]

In the US, the proportion of hospitalised 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.[168] Age-standardised excess deaths per 100,000 people during March–December 2020 in the US among Black, American Indian/Alaskan Native, and Latino people were more than double those among White people.[169] 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 hospitalisations.[170] [171] [172]

Racial disparities in outcomes may be partially attributed to higher rates of comorbidities in certain ethnic groups.[173]

## residence in a long-term care facility

**People in a long-term care facility are at increased risk for infection and severe disease.** [105] [174]

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.[175] 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.[176]

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.[177]

## presence of comorbidities

**People with comorbidities are at increased risk for severe disease, and the more comorbidities, the greater the risk.** [178] [179]

In the UK, the most common comorbidities reported in a cohort study of more than 20,000 hospitalised patients were cardiac disease (31%), uncomplicated diabetes (21%), non-asthmatic chronic pulmonary disease (18%), and chronic kidney disease (16%).[10]

In the US, approximately 95% of hospitalised adults had at least one reported underlying medical condition, with the most common being hypertension, disorders of lipid metabolism, and obesity. Approximately 99% of patients who died had at least one underlying health condition. The strongest risk factors for death were obesity, anxiety and fear-related disorders, and diabetes, as well as the total number of underlying conditions.[180] 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.[181] [182]

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.[183]

## obesity

**People with obesity ( $\geq 30$  kg/m<sup>2</sup>) and people who are overweight (25-30 kg/m<sup>2</sup>) are at increased risk of infection and severe disease.** [179] [184]

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.[185]

Evidence from a meta-analysis found that patients who are obese have a significantly increased risk of infection, clinically severe disease, hospitalisation, intensive care unit admission, need for mechanical ventilation, and mortality.[184]

A cohort study in the UK found that the risk of severe outcomes (i.e., hospitalisation, intensive care unit admission, death) increased progressively above a body mass index  $\geq 23$  kg/m<sup>2</sup>, 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.[186]

A cohort study in the US found a non-linear 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.[187]

## cardiovascular disease

**People with cardiovascular disease are at increased risk for severe disease.** [179]

Pre-existing cardiovascular disease is associated with adverse outcomes including disease severity, disease progression, and mortality.[188]

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.[189] Pre-existing atrial fibrillation was associated with a higher risk of short-term death.[190] Coronary heart disease has also been associated with disease progression and severe/critical disease. The association is affected by the presence of hypertension; patients with coronary heart disease and hypertension had an increased risk of poor prognosis compared with those without hypertension.[191]

People with risk factors for cardiovascular disease (e.g., hypertension, diabetes) are also at increased risk for severe disease and mortality (see below).[192] [193]

## diabetes

**People with type 1 or type 2 diabetes are at increased risk for severe disease.** [179]

Diabetes is associated with an increased risk for disease progression, intensive care admission, acute respiratory distress syndrome, need for invasive mechanical ventilation, and mortality.[194] [195] Higher mortality rates and adverse outcomes were seen in patients with new-onset diabetes compared with those with pre-existing diabetes.[196]

In the UK, one third of all deaths in hospitalised patients occurred in patients with diabetes.[197] 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 is associated with a 20% increase in mortality in patients with severe disease, independent of age, sex, ethnicity, obesity, or other major comorbidity.[198]

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 glycaemic control prior to infection, higher glycosylated haemoglobin levels, higher body mass index, elevated C-reactive protein, diabetic ketoacidosis, hyperglycaemic hyperosmolar state, and insulin use.[199] [200] [201] [202] [203] The higher risk of intensive care unit admission and mechanical ventilation in patients with type 1 diabetes may be accounted for by the presence of diabetic ketoacidosis.[204] Patients with newly diagnosed diabetes have a higher risk of all-cause mortality compared with patients with known diabetes, hyperglycaemia, or normal glucose.[205]

Use of metformin, sulfonylureas, sodium–glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, or dipeptidyl peptidase-4 inhibitors may be associated with lower mortality.[206] [207] [208] [209] [210] However, the reduction in mortality only appears to be significant with metformin.[211]

Poor outcomes in these patients may be due to the syndromic nature of diabetes, the presence of comorbidities, impaired immune function, possible upregulation of enzymes that mediate viral invasion, and chronic inflammation coupled with the acute inflammatory reaction caused by SARS-CoV-2 resulting in a propensity for inflammatory storm.[212] [213]

## 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.[179] There is no clear evidence that people with asthma or COPD are at higher risk of infection.[214] [215]

COPD is associated with an increased risk of hospitalisation, intensive care unit admission, and mortality.[216] A national, multicentre 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.[217]

It is unclear whether asthma increases the risk of infection or severe outcomes (i.e., hospitalisation, intensive care unit admission, mortality). Systematic reviews and meta-analyses 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 non-allergic asthma, appear to have worse outcomes.[218] According to meta-analyses, asthma is not associated with an increased risk for infection, severe disease, hospitalisation, intensive care unit admission, 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 infection and death compared with non-asthmatic patients.[219] [220] [221] [222] However, a national, multicentre 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 non-severe asthma in patients aged 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 aged 50 years and older.[217]

People with obstructive sleep apnoea may be at increased risk for severe disease, intensive care admission, mechanical ventilation, and mortality; however, evidence is limited.[223] Obstructive sleep apnoea has not been associated with an increased risk of infection.[224]

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).[225]

People with tuberculosis appear to be at an increased risk of severe disease and mortality.[226]

People with pre-existing interstitial lung disease are at increased risk of severe disease and mortality.[227]

There are no data on whether paediatric respiratory diseases (including childhood asthma) are risk factors for infection or severity.[228]

## chronic kidney disease

**People with chronic kidney disease are at increased risk for severe disease, and may be at higher risk for infection.** [158] [179]

Patients with chronic kidney disease had a significantly higher risk of hospitalisation 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.[229]

Incidence appears to be higher in patients receiving dialysis compared with those not requiring renal replacement therapy.[230] Patients with end-stage renal disease who were on renal replacement therapy also had an increased risk of intensive care unit admission, need for mechanical ventilation, and mortality.[231]

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%).[158]

Pre-existing chronic kidney disease is an independent risk factor for developing acute kidney injury as a complication.[232]

## pregnancy

**Pregnant women are at increased risk for severe disease.** [179]

According to an analysis of approximately 400,000 women aged 15 to 44 years with symptomatic disease, pregnant women were more likely to be hospitalised, be admitted to the intensive care unit,

receive invasive mechanical ventilation or extracorporeal membrane oxygenation, and die compared with non-pregnant women.[27]

Pregnant women and neonates are more vulnerable to adverse outcomes in low- to middle-income countries compared with high-income countries.[233]

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. [179]**

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, and in younger people. Current smokers are at higher risk of developing severe disease compared with non-smokers.[234] [235] Smokers have double the mortality risk compared with non-smokers.[236] This may be due to increased airway expression of the angiotensin-converting enzyme-2 receptor in smokers.[237]

The World Health Organization has reviewed the available evidence and concluded that smoking is associated with increased severity of disease and death in hospitalised patients.[238]

## malignancy

**People with cancer are at increased risk for infection and severe disease. [179] [239]**

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. Haematological 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.[240] The pooled in-hospital mortality risk in patients with cancer is 14.1%.[241] The pooled mortality in cancer patients admitted to the intensive care unit was 60.2%.[242]

Mortality in cancer patients is affected by pre-existing non-cancer comorbidities, and is significantly higher in people with hypertension, cardiovascular disease, chronic obstructive pulmonary disease, and diabetes.[243]

Children with cancer may be no more vulnerable to infection compared with children without cancer. Limited data show that the overall morbidity in paediatric patients with cancer is low, with only 5% requiring hospitalisation for symptoms.[244] In the largest international cohort study to date, 20% of children with cancer developed severe or critical disease, but most patients recovered without advanced support. Approximately 35% of children were asymptomatic. Lymphopenia and neutropenia were associated with more severe disease.[245] Overall survival in children with cancer is very high (99.4%), and there was no significant difference in the risk of hospitalisation or intensive care unit admission between haematological malignancies and solid tumours in children.[246]

## cerebrovascular disease

**People with cerebrovascular disease are at increased risk for severe disease. [179]**

Patients with a history of cerebrovascular disease were more likely to progress to adverse outcomes compared with patients without a history of cerebrovascular disease.[247] Patients with pre-existing cerebrovascular disease had 2.67-fold higher odds of poor outcomes including intensive care admission, mechanical ventilation, and mortality.[248]

### **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. [179]**

Solid organ transplant recipients are at increased risk for hospitalisation, intensive care unit admission, and mortality. However, the increased rate of hospitalisation 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%.[249] Solid organ transplant recipients had a 1.4-fold increased odds of mortality compared with the general population.[250]

### **Down's syndrome or disability**

**People with Down's syndrome, learning disability, or disability may be at increased risk for severe disease; however, evidence is limited. [179]**

In the UK, a cohort study found a 4-fold increased risk for hospitalisation and a 10-fold increased risk for mortality in people with Down's syndrome.[251] This may possibly be due to the presence of immune dysfunction, congenital heart disease, and pulmonary pathology.

Another study in the UK found that adults with learning disability and those with Down's syndrome or cerebral palsy have markedly increased risks of hospital admission and death over and above the risks observed for non-COVID-19 causes of death.[252]

The risk of death was higher for disabled people (including learning disability, neurological conditions, and frailty) compared with non-disabled people during the first two waves of the pandemic. Relative risks were high among younger disabled people, disabled women, and people with greater levels of activity limitation. Adverse socioeconomic, demographic, and health-related risk factors accounted for some of the elevated risk.[253]

### **haemoglobin disorders**

**People with sickle cell disease or thalassaemia may be at increased risk for severe disease; however, evidence is limited. [179]**

In the UK, patients with sickle cell disease were found to have a 4-fold increased risk for hospitalisation and a 2.6-fold increased risk for death. Sickle cell trait was also associated with increased risks for both outcomes, albeit to a lesser extent.[254]

In the US, among 178 patients with sickle cell disease (mean patient age <40 years), 69% were hospitalised, 11% were admitted to intensive care, and 7% died.[255] Infection can cause acute chest syndrome in patients with sickle cell disease.[256] [257]

### **hypertension**

**People with hypertension may be at increased risk for severe disease; however, evidence is limited. [179]**

Almost all available evidence suggests that hypertension increases the risk of severe disease or mortality, although it was sometimes unclear whether this was independent of other risk factors. There were no systematic reviews or meta-analyses studying whether people with hypertension were at greater risk of infection.[258]

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.[259] 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.[260] [261]

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.[262] 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.[263] [264]

## dementia

**People with dementia may be at increased risk for infection and severe disease; however, evidence is limited.** [179] [265]

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.[266]

In the UK, over one quarter of people who died with COVID-19 from March to June 2020 had dementia. Dementia and Alzheimer's disease was the most common main pre-existing health condition in deaths involving COVID-19 between March and June 2020.[267]

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 hospitalisation 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.[268]

## immunosuppression

**People who are immunocompromised may be at increased risk for severe disease; however, evidence is limited.** [179]

This includes people with a history of primary immune deficiencies or prolonged use of corticosteroids or other immunosuppressant medications.

Current data do not strongly suggest that medications associated with the treatment of immune-mediated inflammatory diseases increase the risk of infection or severe disease, with the exception of corticosteroids and rituximab.[269]

Glucocorticoid exposure of  $\geq 10$  mg/day (prednisolone) has been associated with a higher odds of hospitalisation in patients with rheumatological disease.[270] Patients treated with ciclosporin/

tacrolimus also had an increased risk for hospitalisation; 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.[271]

Immunosuppressed patients are not at significantly increased risk of infection compared with the general population.[272]

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.** [179]

It is still unclear whether HIV infection influences infection and disease course. Observational studies report conflicting results. A retrospective cohort study in the UK found that people with HIV appear to be at increased risk for mortality.[273] 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 hospitalisation) compared with people living without diagnosed HIV infection. Hospitalisation risk increased with progression of HIV disease stage.[274] HIV infection was not independently associated with poor outcomes among hospitalised patients in Zambia; however, patients with severe HIV disease were more likely to develop severe disease or die compared with those with controlled HIV disease.[275]

Evidence from meta-analyses is conflicting. One meta-analysis found that HIV infection was not associated with composite poor outcome.[276] 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.[277] [278] [279]

There is evidence that suggests that HIV patients at advanced stages (stage 3 or 4) manifest less severe symptoms and have reduced mortality. This may be due to the inability of HIV-positive individuals' immune systems to provoke the cytokine storm that usually causes poor clinical outcomes in COVID-19 patients.[280]

Despite the conflicting evidence, the World Health Organization states that HIV infection appears to be a significant independent risk factor for severe or critical disease at hospital admission and in-hospital mortality. HIV infection was independently associated with a higher risk of mortality compared with the HIV-negative population after adjusting for age, sex, disease severity, and underlying conditions. Age >65 years, male sex, and the presence of diabetes or hypertension were risk factors for severe or critical illness at hospital admission, as well as in-hospital mortality. Data were predominantly from South Africa, which may limit the generalisability of the results.[281]

## substance use disorders

**People with substance use disorders may be at increased risk for severe disease; however, evidence is limited.** [179] 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 hospitalisation, intensive care unit admission, ventilator use, and mortality.[282] [283]

People with opioid use disorder had higher odds of hospitalisation, maximum length of hospital stay, and invasive mechanical ventilation compared with those without an opioid use disorder. However, patients did not appear to have an increased risk of mortality. Patients treated with methadone or buprenorphine appeared to have worse outcomes in terms of hospitalisation and length of hospital stay, but better outcomes in terms of mortality risk and need for invasive mechanical ventilation compared with patients not receiving opioid agonist treatment.[284]

## children with certain underlying conditions

**Children with certain underlying conditions may be at increased risk for severe disease; however, evidence is limited.** [179]

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, neurological, or metabolic disorders; or have congenital heart disease.[179]

A cross-sectional study of over 43,000 children in the US found that the most commonly documented underlying conditions were obesity, asthma, neurodevelopmental disorders, anxiety and fear-related disorders, and depressive disorders. Children with type 1 diabetes, cardiac and circulatory congenital anomalies, obesity, hypertension, epilepsy, neuropsychiatric disorders, and asthma as well as children with chronic disease had higher risk of hospitalisation and severe disease. Limited data suggest that children with congenital heart disease might be at increased risk of severe disease.[285]

## Weak

### chronic liver disease

**People with chronic liver disease, especially cirrhosis, may be at increased risk for severe disease; however, evidence is limited.** [179]

Chronic liver disease has been associated with an increased risk for severe disease and mortality.[286] 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.[287]

People with metabolic dysfunction-associated fatty liver disease (nonalcoholic fatty liver disease) are at increased risk for severe disease.[288] Disease severity has been associated with age <60 years and intermediate or high fibrosis-4 (FIB-4) scores.[289] [290]

### vitamin D deficiency

**People with vitamin D deficiency may be at higher risk for infection and severe disease; however, evidence is limited.**

Meta-analyses have found that low serum vitamin D level is significantly associated with a higher risk of infection, and increased risk for severe disease, hospitalisation, and mortality in both adults and children.[291] [292] [293] [294] However, it is unclear whether these associations were statistically significant and the certainty of evidence is very low.[295] [296]



## proton-pump inhibitor use

**People taking proton-pump inhibitors (PPIs) may be at increased risk for severe disease; however, evidence is limited.** [297]

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.[298]

Patients taking PPIs may be at increased risk for secondary infections, severe clinical outcomes, and death.[299] [300] [301] 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 hospitalised 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.[302]

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.[303]

## autoimmune disease

**People with autoimmune disease may be at higher risk for infection and severe disease; however, evidence is limited.** [304]

Current data do not strongly suggest that the presence of an immune-mediated inflammatory disease increases the risk of infection or severe disease. The increased risk reported in some studies may be due to comorbidities associated with immune-mediated inflammatory diseases or medications the patient is taking (corticosteroids, rituximab). Increased rates of hospitalisation in these patients were not associated with increased rates of death.[269]

**Inflammatory arthritis:** evidence does not show a strong association between inflammatory arthritis (e.g., rheumatoid arthritis, spondyloarthritis) and risk of infection or adverse outcomes such as hospitalisation, intensive care unit admission, need for mechanical ventilation, or death. However, evidence is conflicting. Some studies do report an increased risk of adverse outcomes, but the studies had limitations.[269]

**Inflammatory bowel disease:** evidence suggests that the risk profile for infection and severe disease is similar to the general population if patients have good disease control and do not use corticosteroids.[269] Higher disease activity and flares may lead to increased susceptibility to infection and worse outcomes.[305] Patient outcomes (hospitalisation, 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 biological agents.[306] [307] [308]

**Connective tissues diseases:** several studies suggest an increased risk of infection in patients with connective tissue disorders (e.g., systemic lupus erythematosus, Sjogren syndrome, systemic sclerosis, polymyositis and dermatomyositis) compared with the general population and patients with other immune-mediated inflammatory diseases. This is possibly due to the widespread use of corticosteroids in these patients. There is a lack of data regarding outcomes and evidence is conflicting.[269] Patients with lupus nephritis were at increased risk of developing severe or critical disease.[309]

**Psoriasis:** data on risk and outcomes convincingly suggest a comparable risk profile as observed in the general population, with no increase in susceptibility to infection or severe disease reported in cohort studies.[269]

**Vasculitis :** corticosteroid use and comorbid respiratory disease were associated with severe outcomes, based on limited data. Disease activity and other immunosuppressive therapies were not associated with severe outcomes.[310]

**Multiple sclerosis:** neurological disability, older age, Black race, cardiovascular comorbidities, recent treatment with corticosteroids, and obesity were risk factors for severe disease and mortality.[311] [312] Current evidence does not suggest that multiple sclerosis significantly increases the mortality rate. Highest hospitalisation 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).[313]

## Parkinson's disease

**People with Parkinson's disease may be at higher risk for infection or severe disease; however, evidence is limited.** [314] [315]

Risk factors for infection may include obesity, pulmonary disease, and hospitalisation. Vitamin D supplementation was associated with a lower risk of infection.[315]

Parkinson's 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.[314]

Patients may experience substantial worsening of parkinsonian symptoms.[316]

## 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 hospitalisation, 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.[317]

## dyslipidaemia

**Dyslipidaemia appears to be associated with an increased risk for severe disease and mortality; however, evidence is limited.** [318] [319] [320]

The association was stronger in males, older age, and those with hypertension.[321]

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.[262] However, so far, studies do not support this hypothesis, and studies have shown a protective effect

(lower risk of mortality or severe disease).[322] Findings from the American Heart Association's COVID-19 Cardiovascular Disease Registry report that patients taking statins prior to hospitalisation had substantially lower odds of death, primarily among individuals with a history of cardiovascular disease and/or hypertension.[323]

## surgery

**Surgical mortality and complications may be higher in patients with COVID-19 compared with patients without COVID-19. [324]**

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.[325]

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 aged 70 years and over.[326]

## 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. [327]**

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.[327] [328]

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.[329] 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.[330]

## gut dysbiosis

**There is limited evidence that gut and lung microbiota dysfunction may be implicated in the pathogenesis of COVID-19. [331]**

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*, *Bacteroides nordii*) during hospitalisation.[332] [333] [334] 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.[335]

## environmental factors

**Climate and latitude** : higher temperatures may slow the progression of the epidemic based on low-certainty evidence and limited studies; however, climate variables alone don't explain most of the

variability in disease transmission. Temperature, humidity, wind speed, ultraviolet light, and latitude may play a role in the epidemic, but further research is required.[336]

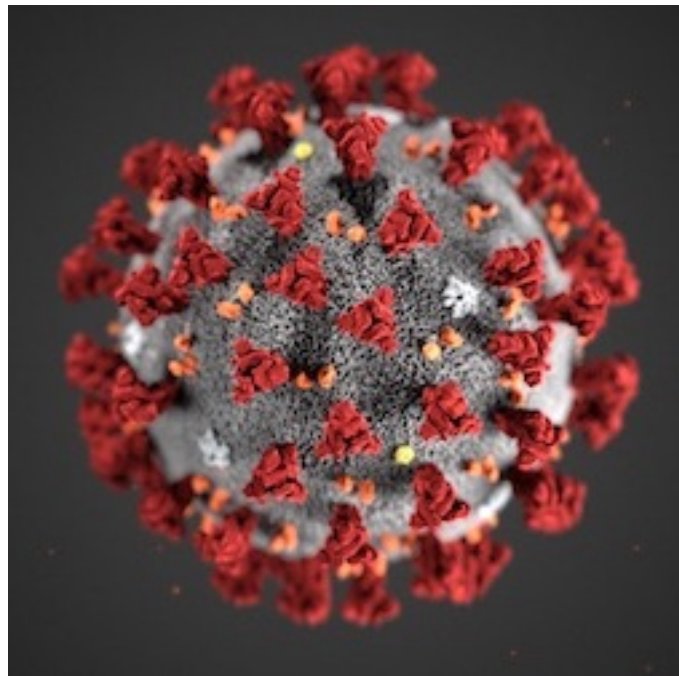
**Air pollution** : limited evidence suggests an association between exposure to ambient air pollution and COVID-19; however, evidence is not sufficient to prove causation.[337] [338] [339] [340]

**Residence in urban or deprived areas** : limited evidence suggests that the prevalence was greater in people living in urban areas compared with people living in rural areas, and in people living in more deprived areas compared with people living in less deprived areas.[158] [341]

## Aetiology

### 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.[31]
- 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.[32] [33] The full genome has been determined and published in GenBank. [GenBank]
- See the Classification section below for information on SARS-CoV-2 variants.



*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*

## 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.[34] [35] [36] 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.[36] More recent studies suggest that the virus may have emerged earlier than previously thought.[37]
- Some studies suggest that SARS-CoV-2 may be a recombinant virus between a bat coronavirus and an origin-unknown coronavirus.[32] [33] [38] [39] Pangolins and minks have been suggested as possible intermediate hosts.[40] [41] [42] [43] 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.[44] 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.[45] Available evidence suggests that transmission between people occurs primarily through direct, indirect, or close contact with infected people through infected secretions such as saliva and respiratory secretions, or through their respiratory droplets, which are expelled when an infected person coughs, sneezes, talks, or sings.[46]
- **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.[46] [47] 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.[48] The risk of transmission is much lower outdoors compared with indoors, with a limited number of studies estimating a transmission rate of <1%.[49] Evidence that nebuliser 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.[50]
- **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.[45] While the majority of studies report identification of the virus on inanimate surfaces, there is a lack of evidence to demonstrate recovery of viable virus.[51]
- **Faecal-oral transmission** (or respiratory transmission through aerosolised faeces) may be possible, but there is only limited circumstantial evidence to support this mode of transmission.[45] The pooled detection rate of faecal 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.[52]
- **Transmission via other body fluids** (including sexual transmission or bloodborne transmission) has not been reported.[45] 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.[53] [54] [55] [56] [57] [58] [59] [60] [61] [62] [63] [64] [65] While SARS-

CoV-2 is not sexually transmitted, it may have an effect on male fertility, although this is yet to be confirmed.[66]

- **Vertical transmission** occurs rarely and transplacental transmission has been documented. There is limited evidence on the extent of vertical transmission and its timing.[67] 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.[68] The rate of infection appears to be no greater when the baby is born vaginally, breastfed, or allowed contact with the mother.[69] 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.[70] Vertical transmission is unlikely to occur if correct hygiene precautions are taken.[71]
- **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.[72] Hospital-acquired infections accounted for approximately 11.3% of infections in the UK between February and August 2020. This peaked at 15.8% in the middle of May. Rates as high as 25% were reported in some areas in October 2020. Rates were notably higher in residential community care hospitals (61.9%) and mental health hospitals (67.5%) compared with acute and general care hospitals (9.7%).[73] [74] Studies of healthcare workers exposed to index cases (not in the presence of aerosol-generating procedures) found little to no nosocomial transmission when contact and droplet precautions were used.[46] [75]

### Transmission dynamics in relation to symptoms

- Transmission is more likely if contacts are exposed shortly before or after symptom onset in the index patient. In one study, the risk of transmission to close contacts was higher if exposure occurred between -2 and 3 days from symptom onset in the index patient. Among contacts who became infected, asymptomatic infection was more common if they were exposed to an asymptomatic index patient, suggesting that disease severity in the index patient may be associated with the clinical presentation of disease.[76]
- **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.[46] [77]
- **Presymptomatic transmission**
  - Transmission may occur during the incubation period, usually 1 to 3 days before symptom onset.[77]
  - Presymptomatic transmission was reported in 12.6% of cases in China, and 6.4% of cases in Singapore.[78] [79]
  - 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).[80] [81] [82] [83] [84] [85] [86] The World Health Organization states that asymptomatic cases are not the major driver of the overall epidemic dynamics.[87] Numerous studies have reported no evidence of asymptomatic transmission from carriers of SARS-CoV-2.[88] [89] [90] 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.[91]
- 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.[92] The overall estimate of the proportion of people who become infected and remain asymptomatic throughout infection has been estimated to be 17% to 33%.[93] [94] [95] [96] Another meta-analysis found that 35.1% of patients were truly asymptomatic (i.e., never developed clinical symptoms). This analysis excluded index cases, thereby correcting a bias that may lead to underestimation of asymptomaticity in other analyses.[97]
- 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.[98] 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.[99]
- Some reports from early in the pandemic suggested that children were presenting with asymptomatic disease more commonly than adults. Although there is some evidence that older children have higher rates of asymptomatic disease than infants <1 year of age, the majority of children present with symptomatic disease and do not appear to be silent spreaders of infection.[13]

### Superspreading events

- Superspreading events have been reported. These events are associated with explosive growth early in an outbreak and sustained transmission in later stages.[100]
- 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 centres.[45] [101] [102] [103] [104] Widespread transmission has also been reported in long-term care facilities, homeless shelters, prisons, immigration detention centres, and meat and poultry processing facilities, as well as on board cruise ships.[105] [106] [107] [108] [109] [110] [111] [112] [113]
- Limited transmission has been reported in childcare, school, and university settings, and infected cases may transmit the infection to their household members.[114] [115] [116] 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%).[117] In one study, infection in close contacts in secondary schools and colleges in England was uncommon (approximately 2%).[118]

- 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 behavioural, host, and environmental factors.[119]

### 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.[120] [121] Viable virus is relatively short lived; infectiousness peaks around 1 day before symptom onset and declines within 7 days.[45]
- The pooled mean incubation period is 9.6 days in children.[122]

- **Reproduction number (R#)**

- 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.[36] [123] [124] [125] [126] The US Centers for Disease Control and Prevention gives a current best estimate of 2.5.[127]
- The  $R_0$  decreases when public health measures (e.g., social distancing) are put in place.[128]

- **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).[129]
- Emerging evidence does not support a significant difference in serial interval between the Delta and wild-type variants.[130]

- **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%.[131]
- 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).[132]
- Another systematic review and meta-analysis of household transmission estimates the pooled household secondary attack rate to be slightly lower at 18.9%. The rate is higher for symptomatic index cases compared with asymptomatic cases, contacts with comorbidities compared with contacts without comorbidities, and adults compared with children. Spouses of the index case are more likely to be infected compared with other household members.[133]
- 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.[87]



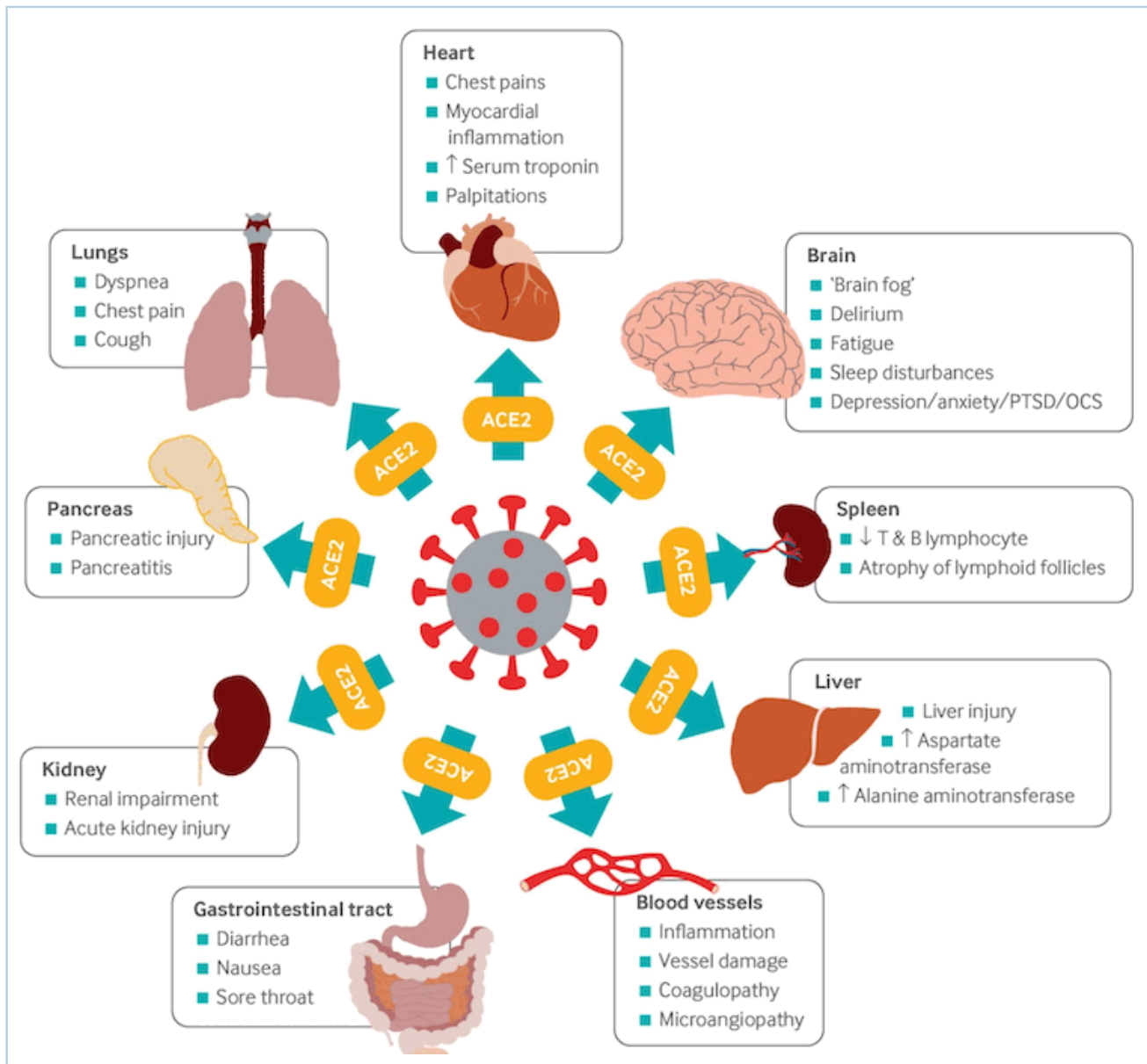
- The secondary attack rate for close contacts of presymptomatic people has been estimated to be approximately 7%, compared with 1% in asymptomatic people and 6% in symptomatic people.[134]
  - There is some evidence that children may be less infectious, as measured by secondary attack rates, than adolescents and adults.[13] Children aged <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.[135] The secondary attack rate was 1.2% in children in a childcare setting or school.[136] Among households with paediatric index cases, 27% of households experienced secondary transmission, and children aged 0 to 3 years of age were more likely to transmit the infection compared with older children.[137]
  - Secondary attack rates for SARS-CoV-2 variants may differ (see the Classification section below).
- **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.[138]
    - 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  $1 \times 10^6$  copies/mL to 24% when the index case had a viral load of  $1 \times 10^{10}$  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.[139]
  - **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 non-severe illness.[138]
    - 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.[45] There is no convincing evidence that duration of viral shedding correlates with duration of infectivity.[140]
    - 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.[141]  
Immunocompromised patients may shed for at least 2 months.[142]

## Pathophysiology

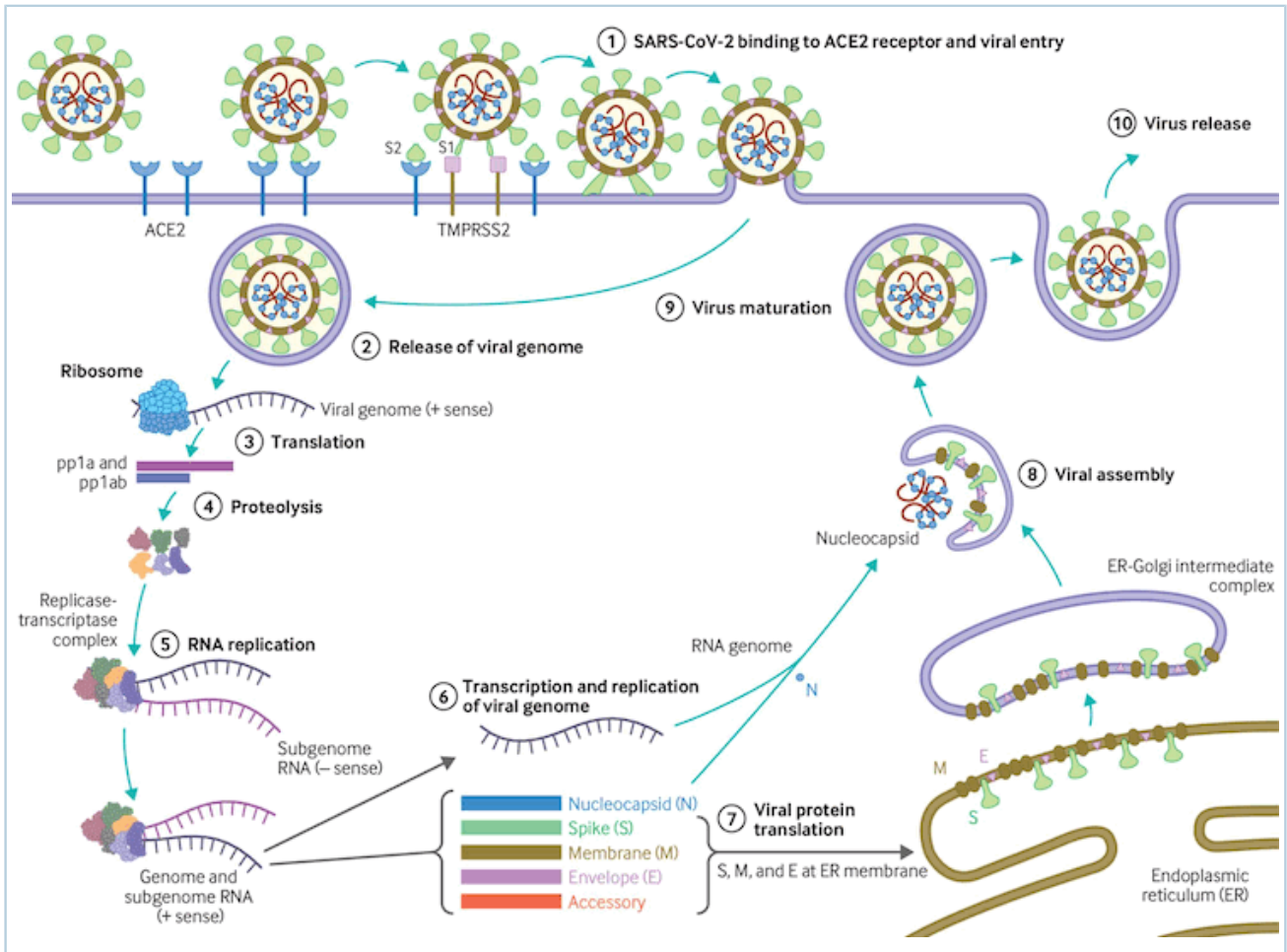
The pathophysiology resembles that of other coronavirus infections. However, emerging evidence indicates that COVID-19 has distinctive pathophysiological features that set it apart from respiratory failure of other origins.[143]

SARS-CoV-2 attaches to the angiotensin-converting enzyme-2 (ACE2) receptor on target host cells, followed by internalisation and replication of the virus. ACE2 receptors are highly expressed in the upper and lower respiratory tract cells, but are also expressed in myocardial cells, renal epithelial cells, enterocytes, and endothelial cells in multiple organs, which may explain the extrapulmonary manifestations associated with the disease.[144]



*Multi-organ complications of COVID-19 and long COVID. The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor*  
*BMJ. 2021;374:n1648*

The virus uses host transmembrane protease serine 2 (TMPRSS2) for viral spike protein priming and fusion of viral and host cell membranes.[145] The SARS-CoV-2 spike protein plays a key role in the recognition of the ACE2 receptor and cell membrane fusion process. A unique structural feature of the spike glycoprotein receptor-binding domain confers potentially higher binding affinity for ACE2 on host cells compared with SARS-CoV-1.[146] This furin-like cleavage site does not appear to exist in other coronaviruses.[147] The binding energy between the spike protein and ACE2 was highest for humans out of all species tested in one study, suggesting that the spike protein is uniquely evolved to bind to and infect human cells expressing ACE2.[148] Emerging evidence suggests that the spike protein alone may damage endothelial cells by downregulating ACE2 and consequently inhibiting mitochondrial function. Further research is required on whether the spike protein can by itself trigger cell signalling that could lead to various biological processes.[149] [150] SARS-CoV-2 variants may be more transmissible, at least in part, due to enhanced spike protein binding affinity for the ACE2 receptor.[151]



*Virus replication cycle*  
 BMJ. 2020;371:m3862

In addition to direct cytopathic viral injury, severe disease is frequently complicated by an infection-induced microangiopathy or hypercoagulable state that causes capillary, venous, and/or arterial thrombosis, which may lead to end-organ damage due to distant thrombotic or embolic disease. The predominant pathological findings in fatal cases were diffuse alveolar damage, coagulopathy, and haemodynamic compromise. Involvement of non-pulmonary organs was limited to mild parenchymal inflammation (e.g., myocarditis, hepatitis, encephalitis). Direct viral cytopathic injury of extrapulmonary organs in general was not regarded as the cause of organ failure.<sup>[144]</sup> SARS-CoV-2-induced endotheliitis may play a role in both the respiratory and non-respiratory manifestations.<sup>[152]</sup>

## Classification

### Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant classification

All viruses, including SARS-CoV-2, change over time. Most changes have little to no impact on the virus' properties; however, some changes may affect virus transmission, disease severity, and performance of diagnostic tests, therapeutics, or vaccines.

These variants have been emerging and circulating around the world since the beginning of the pandemic, and are routinely monitored and classified as either variants under monitoring, variants of interest, or variants of concern.[2] These classification systems may vary between countries. For example, in the UK, variants are classified as variants in monitoring, variants under investigation, or variants of concern.[3] In the US, variants are classified as variants being monitored, variants of interest, variants of concern, or variants of high consequence.[4]

The World Health Organization (WHO) has assigned simple labels for key variants using letters of the Greek alphabet. This does not replace existing scientific names (e.g., Pango, Nextstrain, GISAID), which continue to be used in research.[2]

### Variant of interest

- The WHO defines a variant of interest as a variant with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, or diagnostic or therapeutic escape; and that has been identified to cause significant community transmission or multiple case clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.[2]
- Current variants of interest (as designated by WHO) include the Lambda variant (C.37, first identified in Peru in December 2020) and the Mu variant (B.1.621, first identified in Colombia in January 2021).[2] There may be other variants of interest in other countries.

### Variant of concern

- The WHO defines a variant of concern as a variant that has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:[2]
  - Increase in transmissibility or detrimental change in epidemiology
  - Increased virulence or change in clinical disease presentation
  - Decrease in effectiveness of public health and social measures, or available diagnostics, therapeutics, or vaccines.
- Current variants of concern (as designated by WHO) are detailed below.[2] These variants may not be variants of concern in some countries, or may have been downgraded from a variant of concern in other countries.

## Alpha variant

The Alpha variant is classified as a variant of concern by the WHO and the UK Health Security Agency, but has been downgraded to a variant being monitored in the US.[2] [3] [4]

- **Pango lineage** : B.1.1.7.
- **Earliest documented samples** : UK (September 2020).
- **Transmissibility** : appears greater than the wild type virus.[3]
- **Disease severity** : appears to be associated with an increased risk of hospitalization and intensive care unit admission (suggesting more severe disease), but not mortality, compared with the wild-type virus, although data are conflicting. Not associated with changes in the symptoms reported or their duration.[5] [6] [7] [8]

## Beta variant

The Beta variant is classified as a variant of concern by the WHO and the UK Health Security Agency, but has been downgraded to a variant being monitored in the US.[2] [3] [4]

- **Pango lineage** : B.1.351.
- **Earliest documented samples** : South Africa (May 2020).
- **Transmissibility** : no more transmissible than Alpha.[3]
- **Disease severity** : insufficient information available.[3]

## Gamma variant

The Gamma variant is classified as a variant of concern by the WHO and the UK Health Security Agency, but has been downgraded to a variant being monitored in the US.[2] [3] [4]

- **Pango lineage** : P.1.
- **Earliest documented samples** : Brazil (November 2020).
- **Transmissibility** : appears greater than the wild type virus.[3]
- **Disease severity** : insufficient information available.[3]

## Delta variant

The Delta variant is classified as a variant of concern by the WHO, the UK Health Security Agency, and the US Centers for Disease Control and Prevention.[2] [3] [4] It is currently the dominant variant in many countries around the world including the UK and the US.

- **Pango lineage** : B.1.617.2 (including all AY sublineages).
- **Earliest documented samples** : India (October 2020).
- **Transmissibility** : appears greater than the wild type virus and Alpha. In the UK, the secondary attack rate among household contacts of cases that have not travelled is 10.6%, compared with 10.2% with Alpha (as of 28 September).[3]
- **Disease severity** : appears to be associated with an increased risk of hospitalisation (suggesting more severe disease) compared with contemporaneous Alpha cases; however, there is a high level of uncertainty in these findings. The crude case fatality rate is estimated to be 0.4%, considerably less than the Alpha variant (as of 1 October 2021).[3]

## Resources

The following resources are available:

- [WHO: tracking SARS-CoV-2 variants]
- [PHE: investigation of SARS-CoV-2 variants of concern – technical briefings]
- [CDC: SARS-CoV-2 variant classifications and definitions]

## Case history

### Case history #1

A 61-year-old man presents to 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 examination, his pulse is 120 bpm, his temperature is 38.7°C (101.6°F), 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) a few hours later. 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.

# Recommendations

## Key Recommendations

**Isolate all suspected or confirmed cases immediately.** Triage patients with a standardised triage tool and evaluate the severity of disease. Follow local infection prevention and control guidelines.[120]

**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.[153]

**Suspect the diagnosis in patients with a new continuous cough, fever, or altered sense of taste or smell.** [569] Patients may also present with symptoms including dyspnoea, fatigue, myalgia/arthralgia, sore throat, headache, nasal congestion or rhinorrhoea, sputum production, chest tightness, or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).[570]

**Order a real-time reverse transcription polymerase chain reaction (RT-PCR) to confirm the diagnosis.** Upper and lower respiratory specimens are preferred. Serological testing may be useful in some settings.[571] 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 and adolescents.[572] 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.[573]

**Order the following laboratory investigations in hospitalised patients :** full 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.

**Prioritise 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.[574] Consult local guidelines.

## Full Recommendations

### Introduction

**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 standardised triage tool and evaluate the patient to assess the severity of disease. Use clinical judgement, 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.[120]



## 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 :[153]

- People residing or working in an area with a high risk of transmission (e.g., closed residential settings, humanitarian setting), people residing in or travelling 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 1 metre (3 feet) 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 US Centers for Disease Control and Prevention defines a close contact as someone who has been within 2 metres (6 feet) 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).[154]

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 traveller from these countries.[155]

## Clinical presentation in adults

Approximately 15% of patients present with the symptom triad of fever, cough, and dyspnoea, and 90% present with more than one symptom.[35] 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).[575]

### The most common symptoms are:

- Fever
- Cough
- Dyspnoea
- Altered sense of taste/smell.

### Less common symptoms include:

- Myalgia or arthralgia
- Fatigue
- Sputum production
- Chest tightness

- Gastrointestinal symptoms
- Sore throat
- Headache
- Dizziness
- Neurological symptoms
- Ocular symptoms
- Audio-vestibular symptoms
- Mucocutaneous symptoms
- Rhinorrhoea/nasal congestion
- Chest pain
- Haemoptysis.

Signs and symptoms of febrile respiratory illness may not possess the necessary sensitivity for early diagnostic suspicion.[576] 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.[570] Non-respiratory symptoms may appear before the onset of fever and lower respiratory tract symptoms.[577] Lower urinary tract symptoms have also been reported rarely.

The clinical presentation has varied slightly across geographical 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.[578] Data from the first hospitalised patients in New York found that while the most common presenting symptoms were fever, cough, dyspnoea, and myalgia, gastrointestinal symptoms appeared to be more common than in China.[579]

### 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.[9]

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, rhinorrhoea, 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.[580] More common symptoms in patients with severe disease include fever, dyspnoea, and anorexia.[124]

Symptoms of COVID-19 may differ in patients who have been vaccinated. Data from the UK COVID Symptom Study report that the most common symptoms of COVID-19 after full vaccination are headache, runny nose, sneezing, and sore throat. The previous traditional symptoms such as anosmia, shortness of breath, fever, and cough rank further down the list and are no longer top indicators of having COVID-19 in vaccinated people, according to this data. In patients who are unvaccinated, headache, sore throat, runny nose, fever, and persistent cough are the most common symptoms, which differs from when COVID-19 appeared over a year ago.[581]

### Pregnant women

- The clinical characteristics in pregnant women are similar to those reported for non-pregnant adults.[582] The most common symptoms in pregnant women are fever and cough. However, pregnant women are less likely to report fever, dyspnoea, and myalgia compared with non-pregnant women of reproductive age. Pregnant and recently pregnant women were more likely to be asymptomatic than non-pregnant women of reproductive age.[22] [23]
- It is important to note that symptoms such as fever, dyspnoea, gastrointestinal symptoms, and fatigue may overlap with symptoms due to physiological adaptations of pregnancy or adverse pregnancy events.[120]

### 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.[120]
- 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.[583] [584] [585] [586]

### Co-infections and superinfections

- The pooled prevalence of co-infection 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 co-infections 10%; viral superinfections 4%; bacterial co-infections 8%; bacterial superinfections 20%; fungal co-infections 4%; and fungal superinfections 8%. The most frequently identified bacteria were *Klebsiella pneumoniae*, *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 co-infection 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 co-infections.[587]
- Be alert for the development of mucormycosis.[588] Diagnose and manage urgently - see the [Complications] section for more information.

## Clinical presentation in children and adolescents

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 and adolescents.

Children and adolescents usually have fewer and milder symptoms, and they are less likely to progress to severe disease compared with adults. The reasons for this are still under investigation. Early studies suggested a higher risk of severe or critical disease in infants <1 year of age compared with children of other age groups; however, the studies had limitations and there is no conclusive evidence that younger age is a risk factor for severe disease in children and adolescents. The severity of disease caused by new variants of SARS-CoV-2, in comparison with previous lineages, remains under investigation.[13]

The clinical presentation in children and adolescents is heterogeneous and includes a wide spectrum of clinical features. The most common presenting symptoms are fever and cough. Gastrointestinal symptoms (nausea, vomiting, diarrhoea) are also common. Other less common symptoms include dyspnoea, nasal congestion, rhinorrhoea, rash, conjunctivitis, fatigue, abdominal pain, and neurological symptoms. A higher prevalence of gastrointestinal symptoms has been reported in children >5 years of age compared with children ≤5 years of age.[572] Fever, cough, appetite loss, and dyspnoea are less common in children compared with adults.[589] The presence of diarrhoea has been associated with a severe clinical course.[590]

The most common symptoms in neonates include fever, inability to feed, lethargy, irritability, feeding difficulties, dyspnoea, silent hypoxia, and neurological symptoms. Cases of late-onset neonatal sepsis and encephalitis have been reported rarely.[572] [591] [592] [593]

Be alert for signs and symptoms of paediatric 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 paediatric accident and emergency department for evaluation.[594] See the [Complications] section for more information.

Co-infections may be more common in children.[595] Co-infection 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 *Streptococcus pneumoniae* .[596] [597]

## Physical examination

**Perform a physical examination.** 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, tachypnoea, or cyanosis accompanying hypoxia. Bradycardia has been noted in a small cohort of patients with mild to moderate disease.[598]

## 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.[599]

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.[600]

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 hypoxaemia (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.[601] 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.[602]

Only a small proportion of patients have other organ dysfunction, meaning that after the initial phase of acute deterioration, traditional methods of recognising further deterioration (e.g., National Early Warning Score 2 [NEWS2] scores) may not help predict those patients who go on to develop respiratory failure.[599] 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.[603]

- A systematic review and meta-analysis found that the NEWS2 score had moderate sensitivity and specificity in predicting the deterioration of patients with COVID-19. The score showed good discrimination in predicting the combined outcome of the need for intensive respiratory support, admission to the intensive care unit, or in-hospital mortality.[604]

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]

## Initial laboratory investigations

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

- ABG
- FBC
- Comprehensive metabolic panel
- Thyroid function tests
- 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, hypoalbuminaemia, elevated cardiac biomarkers, elevated inflammatory markers, elevated D-dimer, and abnormal liver and renal function.<sup>[579] [605] [606] [607]</sup> Laboratory abnormalities – in particular, lymphopenia, leukocyte abnormalities, and other markers of systemic inflammation – are less common in children.<sup>[608] [609]</sup> 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.<sup>[610]</sup>

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 epidemiological history. Specimens should be collected prior to starting empirical antimicrobials if possible.<sup>[120]</sup>

### Ongoing investigations

- **Regularly monitor the following in hospitalised patients** to facilitate early recognition of deterioration and monitor for complications:<sup>[120] [611]</sup>
  - Vital signs (temperature, respiratory rate, heart rate, blood pressure, oxygen saturation)
  - Haematological 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 co-infections** ; therefore, it is important to ensure appropriate imaging is ordered and microbiological specimens are taken when this is suspected.

## Molecular testing

Testing strategies vary widely between countries. <sup>[612]</sup>

**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 epidemiological 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).<sup>[613]</sup>

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).[\[571\]](#) 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.[\[155\]](#) However, some tests may be impacted by variants.[\[614\]](#)

### Who to test

- Base decisions about who to test on clinical and epidemiological factors.[\[571\]](#)
- The World Health Organization recommends testing all people who meet the suspected case definition of COVID-19, regardless of vaccination status or disease history. When resources are constrained, people who are at risk of developing severe disease, healthcare workers, inpatients, and the first symptomatic individuals in the setting of a suspected outbreak should be prioritised. Testing of asymptomatic individuals is currently recommended only for specific groups including contacts of confirmed or probable cases and frequently exposed groups such as healthcare workers and long-term care facility workers.[\[615\]](#)
- In the UK, testing is recommended in:[\[616\]](#)
  - 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 radiological 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:[\[617\]](#)
  - Anyone with signs or symptoms consistent with COVID-19 (regardless of vaccination status)
  - Asymptomatic people with recent known or suspected exposure to SARS-CoV-2, including those who have been in close contact (less than 2 metres [6 feet] for a total of 15 minutes or more over a 24-hour period) with a person with documented infection. Fully vaccinated people should be tested 3 to 5 days after the exposure, and people who are not fully vaccinated should be tested immediately
  - Asymptomatic people without recent known or suspected exposure to SARS-CoV-2 for early identification, isolation, and disease prevention (only when screening testing is recommended by public health officials). This may include unvaccinated people who have taken part in activities that put them at higher risk because they cannot physically distance as needed to avoid exposure (e.g., travel, attending large social or mass gatherings, being in crowded or poorly ventilated indoor settings).
- 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.[\[618\]](#)
- 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.[\[571\]](#)

- 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.[619]
- 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. Meta-analyses demonstrate that saliva is as valid as nasopharyngeal sampling for the detection of SARS-CoV-2 infections in symptomatic and asymptomatic patients. Saliva sampling is simple, fast, non-invasive, inexpensive, and painless.[620] [621] [622] [623] [624] [625] The WHO does not currently recommend the use of saliva as the sole specimen type for routine clinical diagnostics.
- Faecal 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).
- 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. Nasal mid-turbinate swab is an acceptable specimen for home or onsite self-collection. The CDC does not recommend using oral specimens (e.g., saliva) for confirmatory testing.[626] [627] In contrast, the Infectious Diseases Society of America recommends saliva as a suitable option for molecular testing in symptomatic people.[628]
  - Anterior nasal swabs appear to be less sensitive (82% to 88%) compared with nasopharyngeal swabs (98%). Mid-turbinate and anterior nares swabs perform similarly.[629]
- 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 epidemiological link, typical x-ray findings, absence of another aetiology), resample the patient and repeat the test. A positive result confirms infection. If the second test is negative, consider serological testing (see below).[571]

- 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.[571]

### Complications of nasal swab testing

- Complications associated with nasal swab testing are not well characterised 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, rhinorrhoea, and broken swabs being stuck (and requiring removal via nasal endoscopy). Bleeding may be life-threatening. Correct sampling techniques are crucial.[630] [631]
- Cases of iatrogenic cerebrospinal fluid leak have been reported after nasal testing in people with undiagnosed skull base defects and people with no pre-existing skull base conditions.[632] [633]

### 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 co-infections can occur, and a positive test for a non-COVID-19 pathogen does not rule out COVID-19.[120] [634]
- When SARS-CoV-2 and influenza viruses are co-circulating, test for both viruses in all hospitalised 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.[568]

## 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 epidemiological 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.[613]

### 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.[635]
- 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.[636] 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.[637]
- 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.[638]

### 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.[637]



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.[636]

- 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.[639] Another study found that patients with a cycle threshold of 34 or above do not excrete infectious virus.[640] 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.[637]
- [\[Centre for Evidence-Based Medicine: are you infectious if you have a positive PCR test result for COVID-19?\]](#)

**Interpreting test results depends on the accuracy of the test itself, and the pre- and post-test probabilities of disease.** The accuracy of the result depends on various factors including the site and quality of sampling, stage of disease, degree of viral multiplication or clearance, and disease prevalence.[638]

- **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%.[635]
- **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.[638] When the pretest probability is low, positive results should be interpreted with caution, and ideally a second specimen tested for confirmation.[641]
- **Post-test probability:** the lower the prevalence of disease in a given population, the lower the post-test probability.[642] 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.[643]
- [\[BMJ Practice Pointer: interpreting a covid-19 test result\]](#)

### 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).[644] False-positive results are more likely when the prevalence of SARS-COV-2 is moderate to low.[645]
- 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%.[646] 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.[641]
- Examples of the potential consequences of false-positive test results include:[641]
  - Unnecessarily postponing or cancelling 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 cancelled travel
  - Psychological damage due to misdiagnosis including fear of infecting others or stigmatisation
  - 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.[638] 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.[647]
- 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.[648]
- Examples of the potential consequences of false-negative test results include:[638]
  - Patients may be moved into non-COVID-19 wards leading to spread of hospital-acquired infection
  - Carers could spread infection to vulnerable dependents
  - Healthcare workers risk spreading the infection to multiple vulnerable individuals.

## Serological 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).[571] [649]

[BMJ practice pointer: testing for SARS-CoV-2 antibodies]

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.[571]

- Seroconversion or a rise in antibody titres 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 serological testing as a method to support the diagnosis of illness or complications in the following situations:[650]

- 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 authorisation are recommended. Serological 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 serological testing in the following circumstances:[651]

- 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 paediatric 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.[652] [653]

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).[654]

## Limitations of serological 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%.[655]

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.[571]

- 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.[650] A reliable diagnosis is often only possible in the recovery phase when opportunities for management or interruption of transmission have passed.[571]
- 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 neutralising antibodies, or that they offer protective immunity.[571]
- 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.[650]
- Vaccination may cause false-positive results for tests that utilise the S antigen or subunits like receptor-binding domains, but not for tests that use the N antigen.[650]

## Rapid diagnostic tests

### Antibody detection

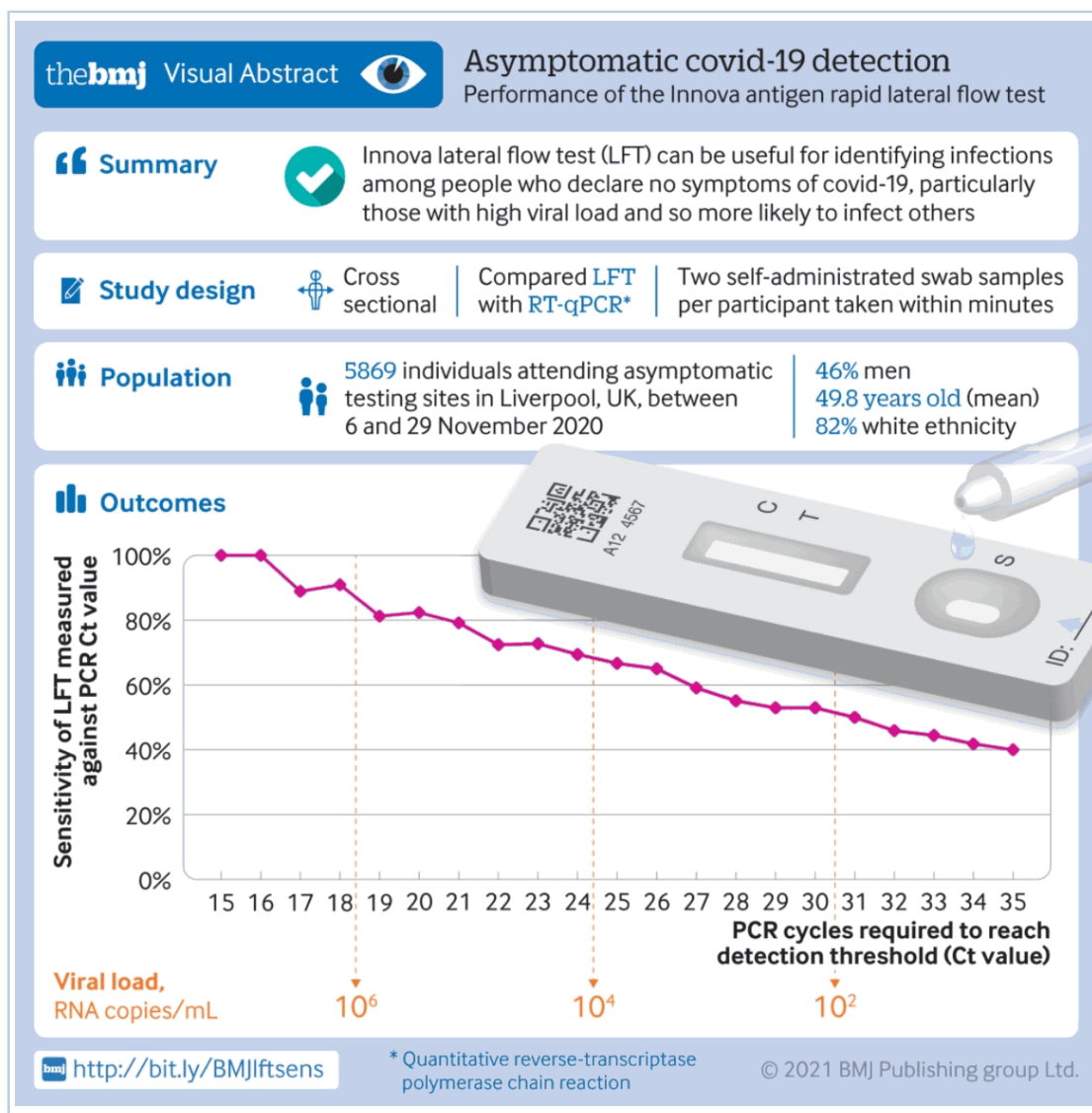
- While rapid antibody detection kits have been approved for the qualitative detection of SARS-CoV-2 IgG/IgM antibodies in serum, plasma, or whole blood, the WHO does not recommend the use of these tests outside of research settings as they have not been validated as yet.[655]
- Evidence is particularly weak for point-of-care serological tests. A meta-analysis found that the overall sensitivity of chemiluminescent immunoassays (CLIAs) for IgG or IgM was approximately 98%, and the sensitivity of enzyme-linked immunosorbent assays (ELISAs) was 84%; however, lateral flow immunoassays (LFIAs), 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 serological tests.[656]

### 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.[\[657\]](#)

- 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  $\geq 80\%$  sensitivity and  $\geq 97\%$  specificity compared with an RT-PCR reference assay.[\[657\]](#)
  - The Infectious Diseases Society of America recommends antigen testing in some individuals only when molecular testing is not readily available or is logistically infeasible, noting that the overall quality of available evidence supporting its use was graded as very low to moderate.[\[658\]](#)
  - The CDC recommends that antigen tests may be used in congregate and community settings; however, confirmatory molecular testing may be needed.[\[659\]](#)
  - 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.[\[660\]](#)
- 
- 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  $\leq 25$  (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.[\[661\]](#)
  - A systematic review found that the performance of lateral flow tests is heterogenous and depends on the manufacturer. Sensitivity ranged between 37.7% to 99.2%, with specificity ranging between 92.4% to 100% across studies.[\[662\]](#)
  - An observational cohort study that assessed the performance of rapid antigen lateral flow testing against RT-PCR in an asymptomatic general population in the UK found that the lateral flow test can be useful for detecting infections among asymptomatic adults, particularly those with a high viral load who are likely to be infectious. Lateral flow tests showed a sensitivity of 40%, specificity of 99.9%, positive predictive value of 90.3%, and negative predictive value of 99.2% in this population. Approximately 10% of people with a higher viral load detected by RT-PCR were missed by lateral flow tests.[\[663\]](#)



Performance of the Innova SARS-CoV-2 antigen rapid lateral flow test  
 BMJ. 2021;374:n1637

- Rapid antigen testing appears to be a reliable diagnostic tool to quickly detect people with a high viral load and in the first week of symptom onset, and can help to detect and isolate potential superspreaders before RT-PCR results are available. However, testing is unsuccessful in detecting people with lower viral load and asymptomatic patients.[664] [665]
- Laboratory-based (non-rapid) 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).[661]

**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.[666]

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

- Approximately 74% of patients have an abnormal chest x-ray at the time of diagnosis. The most common abnormalities are ground-glass opacity (29%) and consolidation (28%). Distribution is generally bilateral, peripheral, and basal zone predominant. Pneumothorax and pleural effusions are rare. There is no single feature on chest x-ray that is diagnostic.[667]
- 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.[668]
- 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.[669]

### Consider ordering a CT scan of the chest.

- Chest CT may play a role in diagnosis in a limited number of hospitalised patients, particularly when initial molecular testing has been inconclusive, or when an alternative diagnosis is being considered.[670] 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 non-specific 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.[574] [BSTI: radiology decision tool for suspected COVID-19]
  - 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.[671]
  - The American College of Radiology recommends reserving CT for hospitalised, symptomatic patients with specific clinical indications for CT, and emphasises 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.[672]
- 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.[668] Accuracy appears to be lower among children; however, there are limited data in this population.[670]
- Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.[673] Some patients may present with a normal chest finding despite a positive RT-PCR.[674] 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.[675]
- 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).[676]
- 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.[677]

### 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 hospitalised patients.[678]
- The most common findings are ground-glass opacity, either in isolation or co-existing 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.[679]

- Ground-glass opacity has the highest diagnostic performance for COVID-19 pneumonia, followed by ground-glass opacity plus consolidation, and consolidation only.[680] 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%).[681]
- 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.[679]
- 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.[682]
- Children frequently have normal or mild CT chest findings. The most common signs in children are patchy ground-glass opacity, non-specific patchy shadows, areas of consolidation, infected nodules, and a halo sign. Abnormalities are more common in multiple lobes and are predominantly bilateral. Pleural effusion is rare. Children may have signs of pneumonia on chest imaging despite having minimal or no symptoms.[683] Ground-glass opacity and peribronchial thickening were the most prevalent findings in infants younger than 1 year of age.[684]

### 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, vacuolar retraction sign, and halo sign are atypical features. Pleural effusion, pericardial effusion, cavitation, pneumothorax, and mediastinal lymphadenopathy have also been reported rarely.[679]

The WHO recommends chest imaging in the following scenarios:[669]

- 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 hospitalised and have mild symptoms (to decide on hospital admission versus home discharge)
- Patients with suspected or confirmed COVID-19 who are not currently hospitalised 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 hospitalised 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.[685] [686] [687]
- RT-LAMP appears to be a reliable assay, comparable to RT-PCR, particularly with medium to high viral loads (i.e., cycle threshold <35), especially in resource-limited settings.[688] A sensitivity of 95.5% and specificity of 99.5% has been reported.[689]

### Lung ultrasound

- Lung ultrasound is used as a diagnostic tool in some centres 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.[669]
- 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.[668]

- 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.[690]
- It has the advantages of portability, bedside evaluation, reduced healthcare worker exposure, easier sterilisation process, absence of ionising 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.[691] [692] [693]
- 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).[694] Lung ultrasound score may play a role in prognosis.[695]
- [BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas]

### 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.[571]

### Calprotectin

- Calprotectin is an emerging biomarker of interest. Calprotectin levels often increase following infection or trauma, and in inflammatory disease. Serum/faecal calprotectin levels have been demonstrated to be significantly elevated in COVID-19 patients with severe disease, and it may have prognostic significance.[696]

## Management of co-existing conditions

Best Practice has published a separate topic on the management of co-existing conditions in the context of COVID-19. [BMJ Best Practice: management of co-existing conditions in the context of COVID-19]

## History and exam

### Key diagnostic factors

#### fever (common)

Reported in approximately 77% of patients.[124] In one case series, only 44% of patients had a fever on presentation, but it developed in 89% of patients after hospitalisation.[697] 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.[698] In children, fever may be absent or brief and rapidly resolving.[699]

#### cough (common)

Reported in approximately 68% of patients.[124] The cough is usually dry; however, a productive cough has been reported in some patients. Can persist for weeks or months after infection.[700]

#### dyspnoea (common)

Reported in approximately 38% of patients.[124] Median time from onset of symptoms to development of dyspnoea is 5 to 8 days.[34] [35] [701] May last weeks after initial onset of symptoms. Wheeze has been reported in 17% of patients.[702]



## altered sense of smell/taste (common)

Presence of anosmia and/or ageusia may be useful as a red flag for diagnosis.[570] Olfactory dysfunction (anosmia/hyposmia) has been reported in approximately 41% of patients, and gustatory dysfunction (ageusia/dysgeusia) has been reported in approximately 35% of patients.[124] Prevalence appears to be higher in European studies.[703] May be an early symptom before the onset of other symptoms, or may be the only symptom in patients with mild to moderate illness.[704] 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%.[705] Persistent anosmia has an excellent prognosis with nearly complete recovery at 1 year.[706] Anosmia or hyposmia is significantly associated with an enhanced risk of testing positive for COVID-19, and is a good predictor of infection.[707] Many drugs are associated with taste and smell changes (e.g., antibiotics, ACE inhibitors) and should be considered in the differential diagnosis.[708] Smell and taste dysfunction are common in children.[709]

## Other diagnostic factors

### fatigue (common)

Reported in approximately 30% of patients.[124] 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.[702] Arthritis has been reported rarely.[710]

### sputum production/expectoration (common)

Reported in approximately 18% of patients.[124]

### chest tightness (common)

Reported in approximately 22.9% of patients.[606]

### gastrointestinal symptoms (common)

Reported in 20% of patients. The weighted pooled prevalence of specific symptoms is as follows: loss of appetite 22.3%; diarrhoea 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.[711] Gastrointestinal symptoms are not associated with an increased likelihood for testing positive for COVID-19; however, anorexia and diarrhoea, when combined with loss of smell/taste and fever, were 99% specific for COVID-19 infection in one prospective case-control study.[712] The presence of gastrointestinal symptoms may be a predictor of progression to severe disease.[713] [714] However, the presence of these symptoms does not appear to affect intensive care unit admission rate or mortality.[715] The presence of diarrhoea has been associated with a severe clinical course in children.[590] Haematochezia has been reported.[716]

### sore throat (common)

Reported in approximately 16% of patients.[124] 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.[717]

### **dizziness (common)**

Reported in approximately 11% of patients.[702]

### **neurological symptoms (common)**

Confusion has been reported in approximately 11% of patients.[702]

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.[718] Benzodiazepine use and the lack of family visitation (virtual or in-person) have been identified as risk factors for delirium.[719]

The pooled prevalence of anxiety, depression, and insomnia is 15.2%, 16%, and 23.9%, respectively.[720]

Altered mental status was as common in younger hospitalised patients (<60 years) as it was in older patients in one study.[721]

### **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%).[722] Most symptoms are mild and last for 4 to 14 days with no complications. Prodromal symptoms occur in 12.5% of patients.[723] 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.[724] Retinal complications that may lead to vision loss have also been reported.[725]

### **rhinorrhoea/nasal congestion (uncommon)**

Rhinorrhoea has been reported in approximately 8% of patients, and nasal congestion has been reported in approximately 5% of patients.[702]

### **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.[726]

### **chest pain (uncommon)**

Reported in approximately 7% of patients.[702] May indicate pneumonia.

### **haemoptysis (uncommon)**

Reported in approximately 2% of patients.[702] May be a symptom of pulmonary embolism.[727]

### **bronchial breath sounds (uncommon)**

May indicate pneumonia.

### **tachypnoea (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.

**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.[728] [729] 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.[730] Cutaneous signs may be the only, or the first, presenting sign.[731] Cutaneous symptoms have been reported in children.[732] 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. A prospective case series in adolescents found that chilblain-like lesions are not associated with systemic or localised severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[733]

[British Association of Dermatologists: Covid-19 skin patterns]

**oral mucosal lesions (uncommon)**

Aphthous, haemorrhagic, and necrotic ulcers have been reported in 36.3% of patients. Other lesions include pustules, macules, bullae, maculopapular enanthema, and erythema multiforme-like lesions.[734] SARS-CoV-2-associated reactive infectious mucocutaneous eruption has also been reported.[735] Severe and potential life-threatening mucocutaneous dermatological manifestations have also been reported.[736] It is unclear whether oral lesions are from viral infection, systemic consequences of the infection, secondary to existing comorbidities, or drugs the patient may be on.[737]

**lower urinary tract symptoms (uncommon)**

There is emerging evidence that patients may rarely have signs, symptoms, and radiological 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 haemorrhage, acute urinary retention, and worsening of existing lower urinary tract symptoms (including exacerbation of benign prostatic hyperplasia). Further research is required.[738] [739]

# Investigations

## 1st test to order

| Test   | Result  |
|--|---|
| <p><b>real-time reverse transcription polymerase chain reaction (RT-PCR)</b></p> <p>Order an RT-PCR for SARS-CoV-2 in patients with suspected infection whenever possible (see the <a href="#">[Criteria]</a> section).<a href="#">[571]</a></p> <p>Commonly used assays are expected to be able to detect SARS-CoV-2 variants.<a href="#">[155]</a> However, some tests may be impacted by variants.<a href="#">[614]</a> The US Food and Drug Administration has warned that false-negative results may occur with any molecular test for the detection of severe acute respiratory syndrome coronavirus 2 (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 epidemiological information.<a href="#">[740]</a></p> <p>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 epidemiological 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.<a href="#">[613]</a></p> <p>Base decisions about who to test on clinical and epidemiological factors.<a href="#">[571]</a> Consult local health authorities for guidance as testing priorities depend on local recommendations and available resources.</p> <p>The World Health Organization recommends testing all people who meet the suspected case definition of COVID-19, regardless of vaccination status or disease history. When resources are constrained, people who are at risk of developing severe disease, healthcare workers, inpatients, and the first symptomatic individuals in the setting of a suspected outbreak should be prioritised. Testing of asymptomatic individuals is currently recommended only for specific groups including contacts of confirmed or probable cases and frequently exposed groups such as healthcare workers and long-term care facility workers.<a href="#">[615]</a></p> <p>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).<a href="#">[616]</a></p> <p>In the US, testing is recommended in: (1) anyone with signs or symptoms consistent with COVID-19 (regardless of vaccination status); (2) asymptomatic people with recent known or suspected exposure to SARS-CoV-2, including those who have been in close contact (less than 2 metres [6 feet] for a total of 15 minutes or more over a 24-hour period) with a person with documented infection; (3)</p> | <p>positive for SARS-CoV-2 viral RNA; may be positive for influenza A and B viruses and other respiratory pathogens</p> |

| Test   | Result |
|--|--------|
| <p>asymptomatic people without recent known or suspected exposure to SARS-CoV-2 for early identification, isolation, and disease prevention (only when screening testing is recommended by public health officials).[617]</p> <p>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.[618]</p> <p>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, faecal) may be recommended in some circumstances; consult local guidance.[571] [628] [626] 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. Meta-analyses demonstrate that saliva is as valid as nasopharyngeal sampling for the detection of SARS-CoV-2 infections in symptomatic and asymptomatic patients. Saliva sampling is simple, fast, non-invasive, inexpensive, and painless.[620] [621] [622] [623] [624] [625]</p> <p>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 epidemiological link, typical x-ray findings, absence of another aetiology), resample the patient and repeat the test. A positive result confirms infection. If the second test is negative, consider serological testing (see below).[571]</p> <p>The pooled sensitivity has been estimated to be 87.8%, with the specificity estimated to be in the range of 87.7% to 100%.[635]</p> <p>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.[635] It is not fully understood whether a positive result always represents infectious virus, especially at high cycle thresholds.[636] [637] [639] [640] Interpreting the result depends on the accuracy of the test itself, and the pre- and post-test probabilities of disease.[638] When the pretest probability</p> |        |

| Test  | Result  |
|---|---|
| <p>is low, positive results should be interpreted with caution, and ideally a second specimen tested for confirmation.[641] The lower the prevalence of disease in a given population, the lower the post-test probability.[642] 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.[644] [645] Preliminary estimates of the false-positive rate in the UK are in the range of 0.8% to 4%.[646] False-negative rates of between 2% and 29% have been reported.[638] 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.[647]</p> <p>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.[661]</p> <p>Also collect nasopharyngeal swabs to rule out influenza and other respiratory infections according to local guidance. It is important to note that co-infections can occur, and a positive test for a non-COVID-19 pathogen does not rule out COVID-19.[120] [634] When SARS-CoV-2 and influenza viruses are co-circulating, test for both viruses in all hospitalised 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.[568]</p> <p>Single-test multiplex assays to diagnose and differentiate between infection caused by influenza A, influenza B, respiratory syncytial virus, and SARS-CoV-2 are available in some countries.</p> |   |
| <p><b>pulse oximetry</b></p> <p>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.[599]</p> <p>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 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]</p> <p>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.[600]</p> <p>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 hypoxaemia (defined in the study as</p>   | <p>may show low oxygen saturation (cut-off depends on local guidelines)</p> |

| Test   | Result   |
|--|--|
| <p>arterial oxygen saturation &lt;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.[601] 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.[602]</p> <p>Only a small proportion of patients have other organ dysfunction, meaning that after the initial phase of acute deterioration, traditional methods of recognising further deterioration (e.g., National Early Warning Score 2 [NEWS2] scores) may not help predict those patients who go on to develop respiratory failure.[599]</p> <p>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).</p> <p><a href="#">[BMJ Practice Pointer: remote management of covid-19 using home pulse oximetry and virtual ward support]</a></p> |  |
| <p><b>ABG</b></p> <p>Order in patients with severe illness as indicated to detect hypercarbia or acidosis.</p> <p>Recommended in patients with respiratory distress and cyanosis who have low oxygen saturation (SpO<sub>2</sub> &lt;90%).</p>   | <p>may show low partial oxygen pressure</p>  |
| <p><b>FBC</b></p> <p>Order in patients with severe illness.</p> <p>Lymphopenia, leukocytosis, thrombocytopenia, decreased eosinophils, decreased haemoglobin, 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.[741]</p> <p>Elevated red blood cell distribution width (at admission and increasing during hospitalisation) has been associated with a significantly increased risk of mortality in hospitalised patients.[742]</p> <p>Absolute counts of major lymphocyte subsets, particularly CD4+ and CD8+ T-cell counts, are significantly decreased in patients with severe disease.[743]</p> <p>Late-phase thrombocytopenia (i.e., occurring 3 weeks or more after symptom onset) has been reported but is uncommon.[744]</p>  | <p>lymphopenia;<br/>leukocytosis; leukopenia;<br/>thrombocytopenia; decreased eosinophils; decreased haemoglobin</p> |
| <p><b>comprehensive metabolic panel</b></p> <p>Order in patients with severe illness.</p>  | <p>elevated liver enzymes;<br/>elevated total bilirubin;<br/>renal impairment;</p>                                   |

| Test   | Result  |
|--|---|
| <p>Elevated liver enzymes, total bilirubin, creatinine, and serum urea, and hypoalbuminaemia are significantly associated with severe disease, and may be useful for predicting disease progression.[741]</p> <p>Hypokalaemia has been reported in 54% of patients.[745]<br/>Hypocalcaemia has been reported and is associated with poor outcomes.[746] Hyponatraemia has been reported in 24% of patients, and is associated with poor outcomes.[747] Other electrolyte derangements may be present.</p>  | <p>hypoalbuminaemia;<br/>electrolyte derangements</p>                                   |
| <p><b>thyroid function tests</b></p> <p>Order in patients with severe illness.</p> <p>Most patients had lower triiodothyronine (T3) levels and normal or low thyroid-stimulating hormone (TSH). However, increased TSH ranged from 5.1% to 8%, while low T3 was present in up to 28% of patients. There was significant heterogeneity among studies. Patients with hypothyroidism may be at higher risk of severe disease.[748] [749]</p>  | <p>elevated TSH; low free T3 or T4</p>  |
| <p><b>blood glucose level</b></p> <p>Order in patients with severe illness.</p> <p>Fasting hyperglycaemia independently predicts poor prognosis and is associated with an increased risk of mortality, regardless of whether or not the patient has diabetes.[750] [751]</p> <p>Hypoglycaemia has also been associated with increased mortality in a retrospective cohort study.[752]</p>  | <p>variable</p>   |
| <p><b>coagulation screen</b></p> <p>Order in patients with severe illness.</p> <p>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.[741] [753]</p> <p>The risk of severe disease and mortality is 2-fold and 4-fold higher, respectively, in patients with elevated D-dimer levels.[754] Patients with very high D-dimer levels have an increased risk of thrombosis.[755] [756]</p> <p>Prolonged international normalised ratio (INR) values have been associated with more severe disease and mortality.[757]</p> | <p>elevated D-dimer; prolonged prothrombin time; elevated fibrinogen; prolonged INR</p> |
| <p><b>cardiac biomarkers</b></p> <p>Order in patients with severe illness.</p> <p>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.[758]</p> <p>CK-MB has been found to be elevated in mild disease in children. The significance of this is unknown.[609]</p>   | <p>may be elevated</p>  |



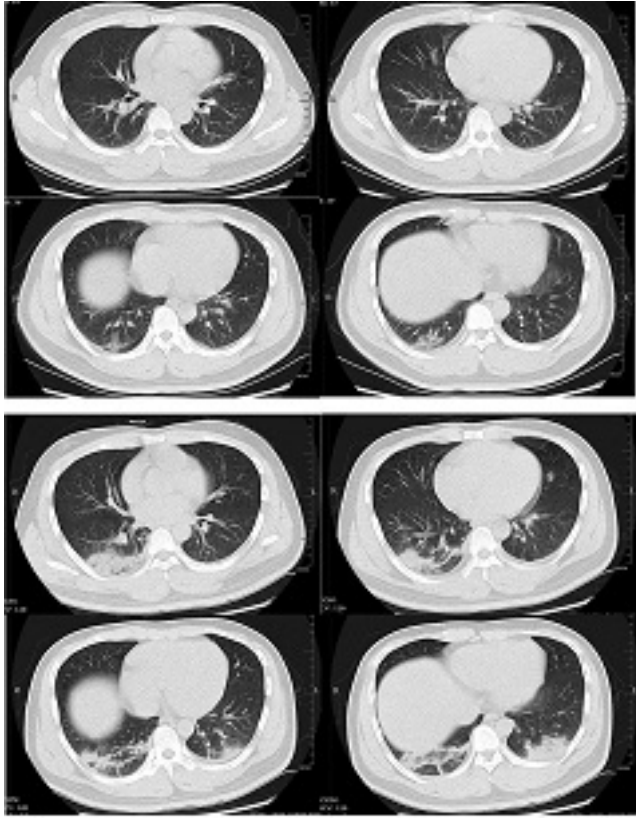
| Test   | Result          |
|--|-----------------|
| <p><b>serum C-reactive protein</b></p> <p>Order in patients with severe illness.</p> <p>Elevated C-reactive protein is significantly associated with severe disease, and may be useful for predicting disease progression.[741]</p> <p>Patients with elevated 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.[759]</p>   | may be elevated |
| <p><b>serum erythrocyte sedimentation rate</b></p> <p>Order in patients with severe illness.</p> <p>Commonly elevated in patients with COVID-19.[607]</p>  | may be elevated |
| <p><b>serum lactate dehydrogenase</b></p> <p>Order in patients with severe illness.</p> <p>Elevated serum lactate dehydrogenase is significantly associated with severe disease, and may be useful for predicting disease progression.[741]</p>  | may be elevated |
| <p><b>serum interleukin-6 level</b></p> <p>Order in patients with severe illness.</p> <p>Elevated interleukin-6 level is significantly associated with severe disease, and may be useful for predicting disease progression.[741]</p> <p>Less likely to be elevated in children.[760]</p>  | may be elevated |
| <p><b>serum procalcitonin</b></p> <p>Order in patients with severe illness.</p> <p>Elevated serum procalcitonin is significantly associated with severe disease, and may be useful for predicting disease progression.[741]</p> <p>Elevated serum procalcitonin may be more common in children.[595]</p> <p>May be elevated in patients with secondary bacterial infection.[34][35]</p> <p>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.[600]</p> | may be elevated |
| <p><b>serum ferritin level</b></p> <p>Order in patients with severe illness.</p> <p>Elevated ferritin is significantly associated with severe disease, and may be useful for predicting disease progression.[761]</p> <p>May indicate development of cytokine release syndrome.[762]</p>   | may be elevated |

| Test   | Result                                 |
|--|--|
| <p><b>serum amyloid A level</b></p> <p>Order in patients with severe illness.</p> <p>Levels increase in severe disease; therefore, it may be useful as a biomarker for predicting disease progression.[763]</p>  | may be elevated                        |
| <p><b>serum creatine kinase and myoglobin</b></p> <p>Order in patients with severe illness.</p> <p>Elevated serum creatine kinase and myoglobin are significantly associated with severe disease, and may be useful for predicting disease progression.[741]</p>   | may be elevated                        |
| <p><b>blood and sputum cultures</b></p> <p>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 epidemiological history.[120]</p> <p>Specimens should be collected prior to starting empirical antimicrobials if possible.</p>  | negative for bacterial infection       |
| <p><b>chest x-ray</b></p> <p>Order in all patients with suspected pneumonia.</p> <p>Approximately 74% of patients have an abnormal chest x-ray at the time of diagnosis. The most common abnormalities are ground-glass opacity (29%) and consolidation (28%). Distribution is generally bilateral, peripheral, and basal zone predominant. Pneumothorax and pleural effusions are rare. There is no single feature on chest x-ray that is diagnostic for COVID-19.[667]</p> <p>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.[668]</p> <p>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.[669]</p> | ground-glass opacity;<br>consolidation |

## Other tests to consider

| Test   | Result   |
|--|--|
| <p><b>computed tomography (CT) chest</b></p> <p>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. <a href="#">[BSTI: radiology decision tool for suspected COVID-19]</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.<a href="#">[671]</a> The American College of Radiology recommends reserving CT for hospitalised, symptomatic patients with specific clinical indications for CT, and emphasises 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.<a href="#">[672]</a></p> <p>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.<a href="#">[668]</a> Accuracy appears to be lower among children; however, there are limited data in this population.<a href="#">[670]</a></p> <p>Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients.<a href="#">[673]</a> Some patients may present with a normal chest finding despite a positive RT-PCR.<a href="#">[674]</a> 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.<a href="#">[675]</a> 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).<a href="#">[676]</a></p> <p>Abnormal chest CT findings have been reported in up to 97% of hospitalised patients.<a href="#">[678]</a> The most common findings are ground-glass opacity, either in isolation or co-existing 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, vacuolar retraction sign, and halo sign are atypical features. Pleural effusion, pericardial effusion, cavitation, pneumothorax, and mediastinal lymphadenopathy have also been reported rarely.<a href="#">[679]</a> Ground-glass opacity has the highest diagnostic performance for COVID-19 pneumonia, followed by ground-glass opacity plus consolidation, and consolidation only.<a href="#">[680]</a></p> <p>Children frequently have normal or mild CT chest findings. The most common signs in children are patchy ground-glass opacity, non-</p> | <p>ground-glass opacity in isolation or co-existing with other findings (e.g., consolidation, interlobular septal thickening, crazy-paving pattern); bilateral, peripheral/subpleural, posterior distribution with a lower lobe predominance</p> |

| Test  | Result |
|---|--------|
| <p>specific patchy shadows, areas of consolidation, infected nodules, and a halo sign. Abnormalities are more common in multiple lobes and are predominantly bilateral. Pleural effusion is rare.[683] [764] Ground-glass opacity and peribronchial thickening were the most prevalent findings in infants younger than 1 year of age.[684]</p> <p>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.[679]</p> <p>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.[765] [766] 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%).[681]</p> <p>CT is more sensitive than RT-PCR in detecting COVID-19, but has a very low specificity.[767] 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.[768]</p> |        |


| Test   | Result  |
|--|---|
|  <p data-bbox="269 1032 1015 1144"><i>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</i></p>   |   |
| <p data-bbox="164 1167 284 1193"><b>serology</b></p> <p data-bbox="225 1211 1034 1462"><b>Important</b> : 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.[342] [343] [344] [345]</p> <p data-bbox="225 1491 1023 1619">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).[571] [649]</p> <p data-bbox="225 1648 911 1675"><a href="#">[BMJ practice pointer: testing for SARS-CoV-2 antibodies]</a></p> <p data-bbox="225 1704 1046 1953">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 titres 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</p> | <p data-bbox="1066 1167 1430 1317">positive for SARS-CoV-2 virus antibodies; seroconversion or a rise in antibody titres in paired sera</p> |


| Test   | Result                                       |
|--|--|
| <p>robust in patients with severe disease compared with those with mild disease or asymptomatic infection.[571]</p> <p>The US Centers for Disease Control and Prevention recommends serological 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.[650]</p> <p>The Infectious Diseases Society of America recommends serological 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 paediatric inflammatory multisystem syndrome in children; and serosurveillance studies.[651]</p> <p>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.[652] [653]</p> <p>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.[635]</p> <p>Limitations of testing: serological 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.[571] [650]</p> <p>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.[655]</p> |  |
| <p><b>antigen test</b></p> <p>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%</p>   | <p>positive for SARS-CoV-2 virus antigen</p> |


| Test  | Result |
|---|--------|
| <p>sensitivity and <math>\geq 97\%</math> specificity compared with an RT-PCR reference assay.[657]</p> <p>The Infectious Diseases Society of America recommends antigen testing in some individuals only when molecular testing is not readily available or is logistically infeasible, noting that the overall quality of available evidence supporting its use was graded as very low to moderate.[658]</p> <p>The US Centers for Disease Control and Prevention recommends antigen tests may be used in congregate and community settings; however, confirmatory molecular testing may be needed.[659]</p> <p>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.[660] The agency has also recommended not using certain tests due to performance issues.[769]</p> <p>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 <math>\leq 25</math> (94.5%), compared with those with cycle threshold values <math>&gt; 25</math> (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.[661]</p> <p>An observational cohort study that assessed the performance of rapid antigen lateral flow testing against RT-PCR in an asymptomatic general population in the UK found that the lateral flow test can be useful for detecting infections among asymptomatic adults, particularly those with a high viral load who are likely to be infectious. Lateral flow tests showed a sensitivity of 40%, specificity of 99.9%, positive predictive value of 90.3%, and negative predictive value of 99.2% in this population. Approximately 10% of people with a higher viral load detected by RT-PCR were missed by lateral flow tests.[663]</p> |        |


Test

Result

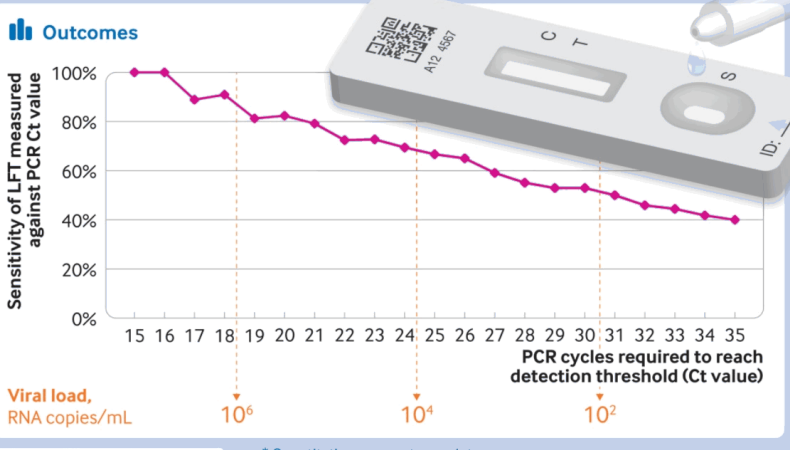
**thebmj Visual Abstract**  **Asymptomatic covid-19 detection**  
Performance of the Innova antigen rapid lateral flow test

**Summary**  Innova lateral flow test (LFT) can be useful for identifying infections among people who declare no symptoms of covid-19, particularly those with high viral load and so more likely to infect others

**Study design**  Cross sectional | Compared LFT with RT-qPCR\* | Two self-administrated swab samples per participant taken within minutes

**Population**  5869 individuals attending asymptomatic testing sites in Liverpool, UK, between 6 and 29 November 2020 | 46% men | 49.8 years old (mean) | 82% white ethnicity

**Outcomes**



**Viral load, RNA copies/mL**  
10<sup>6</sup>      10<sup>4</sup>      10<sup>2</sup>

**PCR cycles required to reach detection threshold (Ct value)**

<http://bit.ly/BMJlftsens>      \* Quantitative reverse-transcriptase polymerase chain reaction      © 2021 BMJ Publishing group Ltd.

*Performance of the Innova SARS-CoV-2 antigen rapid lateral flow test  
BMJ. 2021;374:n1637*

Rapid antigen testing appears to be a reliable diagnostic tool to quickly detect people with a high viral load and in the first week of symptom onset, and can help to detect and isolate potential superspreaders before RT-PCR results are available. However, testing is unsuccessful in detecting people with lower viral load and asymptomatic patients.[664] [665]

Rapid, lateral flow antigen tests for home use are available over-the-counter in some countries.[770]

Laboratory-based (non-rapid) antigen tests are also available in some countries.

Recommendations for the use of lateral flow tests differ between countries. For example, in the UK, lateral flow tests are only currently recommended for patients without symptoms.[771] Consult local guidance for more information.

[BMJ: interpreting a lateral flow SARS-CoV-2 antigen test]



## Emerging tests

| Test  | Result                                     |
|---|--|
| <p><b>reverse transcription loop-mediated isothermal amplification (RT-LAMP)</b></p> <p>A similar process to RT-PCR, but uses constant temperatures and produces more viral DNA compared with RT-PCR. While simple and quick, it is a newer technology and there is less evidence for its use. Assays for SARS-CoV-2 have been developed and are being evaluated.[685] [686] [687]</p> <p>RT-LAMP appears to be a reliable assay, comparable to RT-PCR, particularly with medium to high viral loads (i.e., cycle threshold &lt;35), especially in resource-limited settings.[688] A sensitivity of 95.5% and specificity of 99.5% has been reported.[689]</p> <p>An at-home test kit that provides rapid results within 30 minutes has been approved in the US under an emergency-use authorisation for self-testing at home that provides rapid results.[772]</p>   | <p>positive for SARS-CoV-2 viral RNA</p>   |
| <p><b>lung ultrasound</b></p> <p>Lung ultrasound is used as a diagnostic tool in some centres 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.[669]</p> <p>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.[668]</p> <p>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.[690]</p> <p>Has the advantages of portability, bedside evaluation, reduced healthcare worker exposure, easier sterilisation process, absence of ionising 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.[690]</p> <p>May be used in pregnant women and children.[691] [692] [693]</p> <p>Possible roles 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).[694]</p> <p>Lung ultrasound score may play a role in prognosis.[695]</p> <p>[BSTI: lung ultrasound (LUS) for COVID-19 patients in critical care areas]</p> | <p>B-lines; pleural line abnormalities</p> |

| Test   | Result   |
|--|----------|
| <b>calprotectin</b><br>Calprotectin is an emerging biomarker of interest. Calprotectin levels often increase following infection or trauma, and in inflammatory disease. Serum/faecal calprotectin levels have been demonstrated to be significantly elevated in COVID-19 patients with severe disease, and it may have prognostic significance. <a href="#">[696]</a> | elevated |

## Differentials

| Condition                           | Differentiating signs / symptoms  | Differentiating tests  |
|-------------------------------------|---|--|
| <b>Community-acquired pneumonia</b> | <ul style="list-style-type: none"> <li>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.</li> <li>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.[773]</li> </ul>   | <ul style="list-style-type: none"> <li>Blood or sputum culture or molecular testing: positive for causative organism.</li> <li>RT-PCR: negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA (co-infections are possible).</li> <li>CT chest: centrilobular nodules, mucoid impactions.[774]</li> </ul>  |
| <b>Influenza infection</b>          | <ul style="list-style-type: none"> <li>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.</li> <li>Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.</li> <li>Incubation period is shorter.[775] 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.[776]</li> <li>More common in children.[776] 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.[777]</li> <li>Fever is less common. Rhinorrhoea, sore throat, myalgia, headache, and dyspnoea are more</li> </ul> | <ul style="list-style-type: none"> <li>Only testing can distinguish between influenza infection and COVID-19 and identify co-infection. When SARS-CoV-2 and influenza viruses are co-circulating, test for both viruses in all hospitalised 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.[568]</li> <li>RT-PCR: positive for influenza A or B viral RNA; negative for SARS-CoV-2 viral RNA (co-infections are possible).</li> <li>Chest x-ray: less likely to be abnormal.[775]</li> <li>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</li> </ul> |

| Condition   | Differentiating signs / Differentiating tests symptoms  |   |
|---|---|---|
|   | <p>common.[775] [778] New-onset smell and/or taste disorders were less common in a case-control study.[779]</p>   | <p>thickening, but less likely to have nodules, tree-in-bud sign, bronchiectasis, and pleural effusion.[780] [781]</p> <ul style="list-style-type: none"> <li>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.[782]</li> </ul> |
| <p><b>Common cold</b></p>                                     | <ul style="list-style-type: none"> <li>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.</li> <li>Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms. However, fever is less common, and headache, rhinorrhoea, myalgia, and sore throat are more common. Patients may have a greater number of general symptoms.[778]</li> </ul>    | <ul style="list-style-type: none"> <li>RT-PCR: positive for causative organism; negative for SARS-CoV-2 viral RNA (co-infections are possible).</li> </ul>  |
| <p><b>Other viral or bacterial respiratory infections</b></p> | <ul style="list-style-type: none"> <li>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.</li> <li>Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.</li> <li>Adenovirus and <i>Mycoplasma</i> should be considered in clusters of pneumonia patients, especially in closed settings such as military camps and schools.</li> </ul> | <ul style="list-style-type: none"> <li>Blood or sputum culture of molecular testing: positive for causative organism.</li> <li>RT-PCR: negative for SARS-CoV-2 viral RNA (co-infections are possible).</li> </ul>   |

| Condition                                       | Differentiating signs / symptoms  | Differentiating tests  |
|---|---|--|
| <b>Aspiration pneumonia</b>                     | <ul style="list-style-type: none"> <li>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.</li> <li>Differentiating COVID-19 from aspiration pneumonia is not usually possible from signs and symptoms.</li> </ul>  | <ul style="list-style-type: none"> <li>RT-PCR: negative for SARS-CoV-2 viral RNA (co-infections are possible).</li> <li>CT chest: difficult to distinguish on CT; however, anterior lung involvement may be more suggestive of COVID-19 pneumonia.[783]</li> </ul>   |
| <b>Pneumocystis jirovecii pneumonia</b>         | <ul style="list-style-type: none"> <li>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.</li> <li>Differentiating COVID-19 from pneumocystis jirovecii pneumonia is not usually possible from signs and symptoms.</li> <li>Patients are usually immunocompromised (e.g., HIV positive) and duration of symptoms may be longer.</li> </ul> | <ul style="list-style-type: none"> <li>Sputum culture: positive for <i>Pneumocystis</i>.</li> <li>RT-PCR: negative for SARS-CoV-2 viral RNA (co-infections are possible).</li> <li>CT chest: ground-glass opacity is usually more diffusely distributed with a tendency to spare the subpleural regions.[774]</li> </ul> |
| <b>Middle East respiratory syndrome (MERS)</b>  | <ul style="list-style-type: none"> <li>Travel history to the Middle East or contact with a confirmed case of MERS.</li> <li>Differentiating COVID-19 from MERS is not possible from signs and symptoms.</li> <li>Initial data suggest that the clinical course of COVID-19 is less severe and the case fatality rate is lower compared with MERS.</li> </ul>  | <ul style="list-style-type: none"> <li>Reverse-transcriptase polymerase chain reaction (RT-PCR): positive for MERS-CoV viral RNA.</li> </ul>   |
| <b>Severe acute respiratory syndrome (SARS)</b> | <ul style="list-style-type: none"> <li>There have been no cases of SARS reported since 2004.</li> </ul>   | <ul style="list-style-type: none"> <li>RT-PCR: positive for severe acute respiratory syndrome coronavirus (SARS-CoV) viral RNA.</li> </ul>   |
| <b>Avian influenza A (H7N9) virus infection</b> | <ul style="list-style-type: none"> <li>May be difficult to differentiate based on epidemiological history as avian influenza H7N9 is endemic in China.</li> <li>Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas), or living in an area</li> </ul>  | <ul style="list-style-type: none"> <li>RT-PCR: positive for H7-specific viral RNA.</li> </ul>  |

| Condition                                       | Differentiating signs / symptoms  | Differentiating tests  |
|---|---|--|
|   | when avian influenza is endemic.  |  |
| <b>Avian influenza A (H5N1) virus infection</b> | <ul style="list-style-type: none"> <li>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.</li> <li>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.</li> </ul> | <ul style="list-style-type: none"> <li>RT-PCR: positive for H5N1 viral RNA.</li> </ul>   |
| <b>Pulmonary tuberculosis</b>                   | <ul style="list-style-type: none"> <li>Consider diagnosis in endemic areas, especially in patients who are immunocompromised.</li> <li>History of symptoms is usually longer.</li> <li>Presence of night sweats and weight loss may help to differentiate.</li> </ul>   | <ul style="list-style-type: none"> <li>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.</li> <li>Sputum acid-fast bacilli smear and sputum culture: positive.</li> <li>Molecular testing: positive for <i>Mycoplasma tuberculosis</i>.</li> </ul> |
| <b>Febrile neutropenia</b>                      | <ul style="list-style-type: none"> <li>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.<sup>[784]</sup></li> <li>Symptoms of COVID-19 and neutropenic sepsis may be difficult to differentiate at initial presentation.</li> </ul>              | <ul style="list-style-type: none"> <li>CBC: neutropenia.</li> <li>RT-PCR: negative for SARS-CoV-2 viral RNA.</li> </ul>  |

## Criteria

### World Health Organization: COVID-19 disease severity<sup>[120]</sup>

#### Mild illness

- Symptomatic patients meeting the case definition for COVID-19 without evidence of hypoxia or pneumonia.

- Common symptoms include fever, cough, fatigue, anorexia, dyspnoea, and myalgia. Other non-specific symptoms include sore throat, nasal congestion, headache, diarrhoea, nausea/vomiting, and loss of smell/taste. Additional neurological 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, diarrhoea, loss of appetite, delirium, absence of fever).
- Symptoms due to physiological adaptations of pregnancy or adverse pregnancy events (e.g., dyspnoea, 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, dyspnoea, fast breathing) but no signs of severe pneumonia, including blood oxygen saturation levels ( $\text{SpO}_2$ )  $\geq 90\%$  on room air.
- Children: clinical signs of non-severe 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:  $\geq 60$  breaths/minute
  - 2-11 months of age:  $\geq 50$  breaths/minute
  - 1-5 years of age:  $\geq 40$  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, dyspnoea, fast breathing) plus one of the following:
  - Respiratory rate  $> 30$  breaths/minute
  - Severe respiratory distress
  - $\text{SpO}_2 < 90\%$  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  $\text{SpO}_2 < 90\%$
  - 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:  $\geq 60$  breaths per minute; 2-11 months:  $\geq 50$  breaths per minute; 1-5 years:  $\geq 40$  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[568]

### A symptomatic or presymptomatic infection

- People who test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using a virological 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, diarrhoea, loss of taste and smell) without shortness of breath, dyspnoea, or abnormal chest imaging.

### Moderate illness

- People who have evidence of lower respiratory disease by clinical assessment or imaging and an oxygen saturation ( $\text{SpO}_2$ )  $\geq 94\%$  on room air at sea level.

### Severe illness

- People who have respiratory frequency  $>30$  breaths per minute,  $\text{SpO}_2 < 94\%$  on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ )  $< 300$  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 definitions

Various case definitions are available:

- [WHO: public health surveillance for COVID-19 – interim guidance]
- [CDC: coronavirus disease 2019 (COVID-19) 2020 interim case definition]
- [PHE: COVID-19 – investigation and initial clinical management of possible cases]
- [ECDC: case definition for coronavirus disease 2019 (COVID-19)]

## 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:[785]



- Face-to-face contact with a probable or confirmed case within 1 metre (3 feet) 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 US Centers for Disease Control and Prevention (CDC) defines a close contact as someone who has been within 2 metres (6 feet) 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).[154]
  - Consult local guidance as definitions of a contact may vary depending on local public health advice.

### Quarantine periods

- The World Health Organization recommends that asymptomatic contacts of confirmed or probable cases, including healthcare workers, be quarantined in a designated facility or in a separate room in the household for 14 days from the last contact with the case. Any person in quarantine who develops symptoms should be treated and managed as a suspected case and tested according to national testing strategies and guidelines. Laboratory testing is not a requirement for leaving quarantine after 14 days for contacts who do not develop symptoms.[785]
- 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).[786] From 16 August 2021, fully vaccinated people will no longer need to self-isolate if they are identified as a close contact. Instead of self-isolating, fully vaccinated people (or those who are exempt from vaccination for medical reasons) and people under 18 years of age who are identified as close contacts of positive cases are advised to get tested as soon as possible, and only self-isolate if the test is positive.[787]
- 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.[788]
- Consult local guidance for recommended quarantine locations and timeframes as recommendations vary depending on local public health advice.

## Screening of asymptomatic populations

The World Health Organization does not currently recommend widespread screening of asymptomatic individuals due to the significant costs associated with it and the lack of data on its operational effectiveness. Testing of asymptomatic individuals is currently recommended only for specific groups including contacts of confirmed or probable cases and frequently exposed groups such as healthcare workers and long-term care facility workers.[615]

## Screening of travellers

Exit and entry screening may be recommended in countries where borders are still open, particularly when repatriating nationals from affected areas. Travellers returning from affected areas should self-monitor for symptoms for 14 days and follow local protocols of the receiving country. Some countries may require travellers to enter mandatory quarantine in a designated location (e.g., a hotel). Travellers who develop symptoms are advised to contact their local healthcare provider, preferably by phone.[789] 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.[790]

## Drive-through screening centres

Drive-through screening centres 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, examination, 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.[791]

## 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.[792]

Non-contact 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.[793]

Non-contact infrared thermometers demonstrated variable accuracy levels across populations and had a low sensitivity for temperatures  $>37.5^{\circ}\text{C}$  ( $>99.5^{\circ}\text{F}$ ) 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.[794]

# Recommendations

## Key Recommendations

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

**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.[120]

**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.[120] [600]

**Provide symptom relief as necessary.** This may include treatments for fever, cough, breathlessness, anxiety, delirium, or agitation.[120] [600]

**Start supportive care according to the clinical presentation.** This might include oxygen therapy, intravenous fluids, venous thromboembolism prophylaxis, high-flow nasal oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation. Sepsis and septic shock should be managed according to local protocols.[120]

**Consider empirical 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.[120] [600]

**Consider systemic corticosteroid therapy for 7 to 10 days in patients 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.[568] [795]

**Consider an interleukin-6 inhibitor (tocilizumab or sarilumab) in patients with severe or critical disease.** High-certainty evidence suggests that interleukin-6 inhibitors reduce mortality and the need for mechanical ventilation.[795] [796] [797]

**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.[120]

## Full Recommendations

### 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.[120]

- **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.
- **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 hospitalisation 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 centre.[155]

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 aged 75 years and over), heart failure, male sex, chronic kidney disease, and increased body mass index (BMI).[798] The median time from onset of symptoms to hospital admission is around 7 days.[34] [701]

Children are less likely to require hospitalisation but, if admitted, generally only require supportive care.[18] [799] Risk factors for intensive care admission in children include age <1 month, male sex, pre-existing medical conditions, and presence of lower respiratory tract infection signs or symptoms at presentation.[800] The majority of children who require ventilation have underlying comorbidities, most commonly cardiac disease.[801] Children with COVID-19 are reported to have similar hospitalisation rates, intensive care admission rates, and mechanical ventilator use compared with those with seasonal influenza.[777]

Overall, 19% of hospitalised patients require non-invasive ventilation, 17% require intensive care, 9% require invasive ventilation, and 2% require extracorporeal membrane oxygenation.[702] 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%.[802] Another more recent meta-analysis found the mortality rate in patients in the intensive care unit to be 35.5%.[803] The most common reasons for intensive care unit admission are hypoxaemic respiratory failure leading to mechanical ventilation and hypotension.[804] 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).[805] 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.[798] The most common risk factors for intensive care unit mortality were invasive mechanical ventilation, acute kidney injury, and acute respiratory distress syndrome.[806]

## 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.[120]

### 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.[120] [568] This decision requires careful clinical judgement 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 carer is able to provide care and recognise when the patient may be deteriorating; the carer has adequate support (e.g., food, supplies, psychological support); the support of a trained health worker is available in the community.[807]
- There is some evidence to suggest that implementation of an early home treatment algorithm reduced the risk of hospitalisation and related treatment costs in a small cohort of patients.[808]

### 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).[120]
- The US Centers for Disease Control and Prevention (CDC) recommends discontinuing isolation once at least 10 days (not moderately to severely immunocompromised) or up to 20 days (moderately to 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 moderately to severely immunocompromised) or up to 20 days (moderately to severely immunocompromised) have passed since the date of a positive test. Moderately to 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 moderately to severely immunocompromised patients.[809]
- 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.[810]

### Infection prevention and control

- 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]
  - [CDC: interim guidance for implementing home care of people not requiring hospitalization for coronavirus disease 2019 (COVID-19)]

### Symptom management

- Fever and pain: paracetamol or ibuprofen are recommended.[120] [600] There is no evidence at present of severe adverse events in COVID-19 patients taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute

healthcare utilisation, long-term survival, or quality of life in patients with COVID-19.[811] [812] [813] [814] [815] [816] [817] 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 aged 1 year and older) to help cough.[600] 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.[818]
- 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.[819]

### 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.[120] [600]
- Advise patients to improve air circulation by opening a window or door.[600]
- Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate.[120]
- Most children with mild disease can be managed with supportive care alone and will not require any specific therapy.[568]

### 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).[120] [568]
- Pulse oximetry monitoring at home is recommended in symptomatic patients with risk factors for progression to severe disease who are not hospitalised. Patient education and appropriate follow-up are required.[120]

### Corticosteroids

- The WHO does not recommend systemic corticosteroids in patients with non-severe disease as they may increase the risk of mortality in these patients.[795]
- 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.[600]
- In the US, the National Institutes of Health guidelines panel recommends against the use of systemic corticosteroids in non-hospitalised patients with mild to moderate disease in the absence of another indication.[568]

## 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.[120]

### 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.[120] [568]

### 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.[120]
- The CDC recommends discontinuing isolation once at least 10 days (not moderately to severely immunocompromised) or up to 20 days (moderately to 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 moderately to severely immunocompromised) or up to 20 days (moderately to severely immunocompromised) have passed since the date of a positive test. Moderately to 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 moderately to severely immunocompromised patients.[809]
- 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 hospitalised 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.[810]

### 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.[568]

### Antibiotics

- Do not offer an antibiotic for preventing secondary bacterial pneumonia in people with COVID-19.[600]
- Consider empirical 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.[120] [568] [600]
- Antibiotics may also be considered in older people (particularly those in long-term care facilities) and children <5 years of age to provide empirical antibiotic treatment for possible pneumonia.[120]

- 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.[600]

### 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 hospitalised. Patient education and appropriate follow-up are required.[120]
- 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.[120]
  - A systematic review and meta-analysis found that the NEWS2 score had moderate sensitivity and specificity in predicting the deterioration of patients with COVID-19. The score showed good discrimination in predicting the combined outcome of the need for intensive respiratory support, admission to the intensive care unit, or in-hospital mortality.[604]

### Corticosteroids

- The WHO does not recommend systemic corticosteroids in patients with non-severe disease as they may increase the risk of mortality in these patients.[795]
- 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.[600]
- In the US, the National Institutes of Health guidelines panel recommends against the use of systemic corticosteroids in non-hospitalised patients with mild to moderate disease in the absence of another indication. However, the guideline panel recommends oral dexamethasone in patients who are discharged from the accident and emergency department despite new or increased need for supplemental oxygen (for the duration of supplemental oxygen and not to exceed 10 days), when hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured.[568]

## Management of severe COVID-19

Patients with suspected or confirmed severe disease are at risk of rapid clinical deterioration.[120]

- 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
  - SpO<sub>2</sub> <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 SpO<sub>2</sub> <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.[120]
- 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] 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 individualised assessment of frailty in these people, using clinical assessment and alternative scoring methods.[600]
  - 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).[820]
  - 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.[821]
  - 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.[822]

### 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.[120]
- 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. Moderately to 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 moderately to severely immunocompromised patients.[809]
- 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 hospitalised 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.[810]

### 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  $\text{SpO}_2 < 90\%$ .[\[120\]](#) [\[568\]](#) There is no evidence of benefit for oxygen therapy in patients with COVID-19 in the absence of hypoxaemia.[\[823\]](#)
- 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  $\text{SpO}_2 > 90\%$  in children and non-pregnant adults, and  $\geq 92\%$  to  $95\%$  in pregnant women, is recommended. Nasal prongs or a nasal cannula are preferred in young children.[\[120\]](#) Some guidelines recommend that  $\text{SpO}_2$  should be maintained no higher than  $96\%$ .[\[824\]](#)
- Some centres may recommend different  $\text{SpO}_2$  targets in order to support prioritisation 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.[\[825\]](#)
- Consider positioning techniques (e.g., high supported sitting), and airway clearance management to optimise oxygenation 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.[\[120\]](#) [\[568\]](#)
  - Awake prone positioning of non-intubated patients was associated with improvement in oxygen variables ( $\text{PaO}_2/\text{FiO}_2$ ,  $\text{PaO}_2$ , and  $\text{SpO}_2$ ), respiratory rate, and mortality, but no significant difference was noted in the rate of intubation. However, evidence is limited.[\[826\]](#) [\[827\]](#)
- Monitor patients closely for signs of progressive acute hypoxaemic respiratory failure. Patients who continue to deteriorate despite standard oxygen therapy require advanced oxygen/ventilatory support.[\[120\]](#) [\[568\]](#)

## 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.[\[120\]](#) Correct any electrolyte or metabolic abnormalities, such as hyperglycaemia or metabolic acidosis, according to local protocols.[\[828\]](#)
- Fever and pain: paracetamol or ibuprofen are recommended.[\[120\]](#) [\[600\]](#) There is no evidence at present of severe adverse events in COVID-19 patients taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilisation, long-term survival, or quality of life in patients with COVID-19.[\[811\]](#) [\[812\]](#) [\[813\]](#) [\[814\]](#) [\[815\]](#) [\[816\]](#) [\[817\]](#) 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 aged 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.[\[600\]](#) 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.[818]

- 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 oedema, pulmonary embolism, COPD, asthma).[600]
- 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, minimise use of drugs that may cause or worsen delirium, treat substance withdrawal, maintain normal sleep cycles, treat pain or breathlessness).[120] [600] Low doses of haloperidol (or another suitable antipsychotic) can also be considered for agitation.[120] Non-pharmacological interventions are the mainstay for the management of delirium when possible, and prevention is key.[829]
- Mouth care: an important part of overall patient care in hospitalised patients who are ventilated or non-ventilated and those undergoing step-down or end-of-life care.[830]
- Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia or depression as appropriate.[120]

### 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.[600]
- Start venous thromboembolism (VTE) prophylaxis in acutely ill hospitalised adults and adolescents, provided there are no contraindications.[120] [568] [831] [832]
  - The National Institute for Health and Care Excellence in the UK recommends starting as soon as possible (within 14 hours of admission) in young people and adults who need low-flow oxygen and who do not have an increased bleeding risk, and continuing for a minimum of 7 days including after discharge.[600]
  - For hospitalised children, indications for VTE prophylaxis should be the same as those for children without COVID-19.[568]
- Low molecular weight heparin, unfractionated heparin, or fondaparinux are the recommended options for standard thromboprophylaxis.[120]
  - 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.[600]
  - 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.[833]
  - 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.[832] [834]
  - Avoid direct oral anticoagulants in the absence of an evidence-based indication for oral anticoagulation. An open-label, multicentre, randomised controlled trial found that in-hospital therapeutic anticoagulation with rivaroxaban or enoxaparin followed by rivaroxaban until day

30 did not improve clinical outcomes and increased bleeding compared with prophylactic anticoagulation among hospitalised patients with an elevated D-dimer level.[835]

- The optimal dose is yet to be determined. Standard prophylaxis doses are generally recommended across most guidelines over intermediate- or full treatment-dose regimens in patients without an established indication for higher-dose anticoagulation.[836] 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.[120]
  - The National Institute for Health and Care Excellence in the UK recommends a prophylactic dose of a low molecular weight heparin for a minimum of 7 days (including after discharge) in young people and adults who need low-flow oxygen and who do not have an increased bleeding risk. A treatment dose of a low molecular weight heparin for 14 days or until discharge (whichever is sooner) may be considered in young people and adults who need low-flow oxygen and who do not have an increased bleeding risk; however, this is a conditional recommendation only. The decision should be carefully considered, and choice of the most appropriate dose regimen should be guided by bleeding risk, clinical judgement, and local protocols. For those who do not need supplemental oxygen, follow standard VTE prophylaxis guidelines.[600]
  - 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.[568]
  - Dose adjustments may be required in patients with extremes of body weight or renal impairment.[600]
- Evidence to support the best dose regimen is limited.
  - A systematic review and meta-analysis of nearly 33,000 hospitalised patients found that both prophylactic- and full-treatment doses of low molecular weight heparin were associated with reduced mortality; however, the full dose was associated with a higher risk of major bleeding.[837]
  - Another systematic review and meta-analysis found that although the use of prophylactic anticoagulation at an intermediate- or full-treatment dose was associated with a reduction in the risk of venous thromboembolism compared with standard-dose prophylactic anticoagulation (in patients without an indication for therapeutic anticoagulation), it was not associated with a reduction in all-cause mortality or other adverse ischaemic events but with a significant increase in major bleeding.[838]
  - The HEP-COVID randomised clinical trial found that therapeutic-dose low molecular weight heparin reduced the composite of thromboembolism and death (absolute risk reduction 13.2%) compared with standard prophylactic- or intermediate-dose low molecular weight heparin or unfractionated heparin for thromboprophylaxis, without an increased risk of major bleeding, among hospitalised patients with very elevated D-dimer levels. The effect was not seen in patients in intensive care.[839]
- 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.[600]
- Monitor patients for signs and symptoms suggestive of thromboembolism and proceed with appropriate diagnostic and management pathways if clinically suspected.[120] If the patient's clinical condition changes, assess the risk of VTE, reassess the bleeding risk, and review VTE prophylaxis.[600]
  - Continue until hospital discharge.[120] Routine post-discharge VTE prophylaxis is not generally recommended, except in certain high-risk patients.[568] [831] [832] Ensure patients who require VTE prophylaxis after discharge are able to use it correctly or have arrangements made for someone to help them.[600]
  - There is currently insufficient evidence to determine the risks and benefits of prophylactic anticoagulation in hospitalised patients with COVID-19.[840]
    - A systematic review and meta-analysis found that the pooled odds of mortality between anticoagulated and non-anticoagulated hospitalised 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.[841]
    - Clinicians should rely on pre-COVID-19 evidence-based principles of anticoagulation management combined with rational approaches to address clinical challenges.[831]

### 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.[600] There is insufficient evidence to recommend empiric broad-spectrum antibiotics in the absence of another indication.
- Consider empirical 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.[120] [568] [600]
- 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 microbiological evidence of infection and the person's condition does not improve as expected after 48 to 72 hours of antibiotic treatment.[600]
- Reassess antibiotic use daily. De-escalate empirical therapy on the basis of microbiology results and clinical judgement. 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 programmes should be in place.[120] 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 co-infection. Therefore, unnecessary antibiotic use is likely to be high in these patients.[842]
- Treat laboratory-confirmed co-infections (e.g., malaria, tuberculosis, influenza) as appropriate according to local protocols.[120] The treatment of influenza is the same in all patients regardless of SARS-CoV-2 co-infection. Start empirical treatment with oseltamivir in hospitalised 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.[568]

### 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 disease. This recommendation is based on two meta-analyses that pooled data from eight randomised 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 disease. 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.[795] [796] [797] [843] [844]
- In the UK, the National Institute for Health and Care Excellence recommends offering dexamethasone (or an alternative such as hydrocortisone or prednisolone 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.[600]
- 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 hospitalised adults who require supplemental oxygen. Alternative corticosteroids may be used in situations where dexamethasone is not available. It is not routinely recommended for paediatric 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.[568] The Infectious Diseases Society of America supports the use of dexamethasone in hospitalised patients with severe disease.[845]
- Monitor patients for adverse effects (e.g., hyperglycaemia, secondary infections, psychiatric effects, reactivation of latent infections) and assess for drug-drug interactions.[568]

## Corticosteroids ▼

**Corticosteroids**  
Suggested regimen

|   |   |   |  |
|---|---|---|--|
| <p><b>Dexamethasone</b></p> <p>6 mg</p> <p>Oral or intravenous</p> <p>Daily for 7-10 days</p> | <p><b>Hydrocortisone</b></p> <p>50 mg</p> <p>Intravenous</p> <p>Every 8 hours for 7-10 days</p> | <p><b>Methylprednisolone</b></p> <p>10 mg</p> <p>Intravenous</p> <p>Every 6 hours for 7-10 days</p> | <p><b>Prednisone</b></p> <p>40 mg</p> <p>Oral</p> <p>Daily for 7-10 days</p> |
|---|---|---|--|

Acceptable alternative regimens

Usual supportive care

Strong
Weak

or

Corticosteroids

Weak
Strong

Patients with severe and critical covid-19

“

We recommend corticosteroids

”

**Evidence profile** ▼

Favours usual supportive care

No important difference

Favours corticosteroids

|                                 | Events per 1000 people  | Evidence quality     |
|---------------------------------|---|----------------------|
| Mortality with critical illness | 415 <span style="font-weight: bold; color: #800040;">87 fewer</span> 328                                    | ★★★★ Moderate More ▼ |
| Mortality with severe illness   | 334 <span style="font-weight: bold; color: #800040;">67 fewer</span> 267                                    | ★★★★ Moderate More ▼ |
| Gastrointestinal bleeding       | 48 <span style="background-color: #808080; color: white; padding: 2px;">No important difference</span> 51   | ★★★★ Low More ▼      |
| Superinfections                 | 186 <span style="background-color: #808080; color: white; padding: 2px;">No important difference</span> 188 | ★★★★ Low More ▼      |
| Hyperglycaemia                  | 286 <span style="background-color: #008080; color: white; padding: 2px;">46 fewer</span> 332                | ★★★★ Moderate More ▼ |
| Neuromuscular weakness          | 69 <span style="background-color: #808080; color: white; padding: 2px;">No important difference</span> 75   | ★★★★ Low More ▼      |
| Neuropsychiatric effects        | 35 <span style="background-color: #808080; color: white; padding: 2px;">No important difference</span> 28   | ★★★★ Low More ▼      |

Critically ill

▶ See all outcomes MAGIC app

Severely ill

▶ See all outcomes MAGIC app

Recommendations and evidence for the use of corticosteroids in hospitalised patients with COVID-19  
BMJ. 2020;370:m3379

### Interleukin-6 (IL-6) inhibitors

- The WHO strongly recommends an IL-6 inhibitor (tocilizumab or sarilumab), in combination with a systemic corticosteroid and initiated at the same time, in patients with severe disease. IL-6 inhibitors are typically administered as a single intravenous dose; however, a second dose may

be administered 12 to 48 hours after the first dose if the clinical response is inadequate. This recommendation is based on high-certainty evidence that shows IL-6 inhibitors reduce mortality and the need for mechanical ventilation, and low-certainty evidence that suggests that IL-6 inhibitors may also reduce the duration of mechanical ventilation and hospitalisation. The evidence regarding the risk of severe adverse events is uncertain. The applicability of this recommendation to children is currently uncertain.<sup>[795] [796] [797]</sup> This recommendation is based on data from the UK RECOVERY and REMAP-CAP trials.<sup>[846] [847]</sup>

- In the UK, the National Institute for Health and Care Excellence recommends a single dose of tocilizumab in hospitalised 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  $\geq 75$  mg/L, OR they are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation, or invasive mechanical ventilation. Consider tocilizumab for children and young people who have severe disease or paediatric inflammatory multisystem syndrome only if they are aged 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).<sup>[600]</sup> Tocilizumab has not been granted a conditional marketing authorisation for this indication in the UK as yet.
- In the US, the Infectious Diseases Society of America recommends considering tocilizumab in hospitalised adults with progressive severe disease who have elevated markers of systemic inflammation, in addition to standard of care (i.e., corticosteroids), rather than standard of care alone. Sarilumab may be used if tocilizumab is not available.<sup>[845]</sup> Tocilizumab has been granted an emergency-use authorisation in the US for the treatment of hospitalised adults and paediatric patients 2 years of age and older who are receiving systemic corticosteroids and require supplemental oxygen.<sup>[848]</sup>
- Evidence supports the use of these drugs.
  - A Cochrane review found that tocilizumab reduced all-cause mortality at day 28, and probably resulted in slightly fewer serious adverse events compared with standard care alone or placebo. The evidence suggests uncertainty around the effect on mortality after day 60. However, tocilizumab probably results in little or no increase in clinical improvement at day 28 (i.e., hospital discharge or improvement measured by triallist-defined scales). The impact of tocilizumab on other outcomes is uncertain. Evidence for an effect of sarilumab is uncertain.<sup>[849]</sup>
  - 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 hospitalisation (low-certainty evidence) compared with standard care.<sup>[850] [851]</sup>
  - A meta-analysis of over 10,000 hospitalised patients from 27 randomised controlled trials found that IL-6 antagonists were associated with lower all-cause mortality 28 days after randomisation compared with usual care or placebo. There was no clear association between administration of IL-6 inhibitors and all-cause mortality at 90 days; however, data were limited.<sup>[852]</sup>



## IL-6 receptor blockers ▼

**Suggested regimen**

**Tocilizumab**

8mg per kg  
Max 800mg

Intravenous

Initial dose over 1 hour

or

**Sarilumab**

400mg

Intravenous

Initial dose over 1 hour

A second dose may be administered after 12 to 48 hours

### Recommendation 1

**Usual supportive care**

Strong i Weak i

or

**IL-6 receptor blockers**

Weak i Strong i

**Patients with severe and critical covid-19**

**We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab)**

### Evidence profile ▼

Favours usual supportive care i No important difference i Favours IL-6 receptor blockers

|                             | Events per 1000 people |                            | Evidence quality     |
|-----------------------------|------------------------|----------------------------|----------------------|
| Mortality                   | 130                    | 15 fewer 115               | ★★★★ High More ▼     |
| Mechanical ventilation      | 86                     | 23 fewer 63                | ★★★★ High More ▼     |
| Serious adverse events      | 9                      | No important difference 5  | ★★★★ Very low More ▼ |
| Bacterial infections        | 101                    | No important difference 96 | ★★★★ Low More ▼      |
|                             | Mean days              |                            | Evidence quality     |
| Duration of ventilation     | 14.7                   | 1.2 fewer 13.5             | ★★★★ Low More ▼      |
| Duration of hospitalisation | 12.8                   | 4.5 fewer 8.3              | ★★★★ Low More ▼      |

[▶ See all outcomes](#) **MAGIC** app

*Recommendations and evidence for the use of IL-6 inhibitors in hospitalised patients with COVID-19*  
*BMJ. 2020;370:m3379*

### Monitor

- Monitor patients closely for signs of clinical deterioration, and respond immediately with appropriate supportive care interventions.<sup>[120]</sup>

### 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.[120]

### 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.[120]
- There is a lack of data on palliative care in patients with COVID-19. However, a rapid systematic review of pharmacological 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.[853]
- Follow local palliative care guidelines.

## 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.[120]

### Location of care

- Manage patients in an intensive/critical care unit under the guidance of a specialist team.[120]
- 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 pre-existing advanced comorbidities.[600]

### 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.[120]
- 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. Moderately to 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 moderately to severely immunocompromised patients.[809]

- 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 hospitalised 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.[810]

### Infection prevention and control

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

### High-flow nasal oxygen or non-invasive ventilation

- The World Health Organization recommends considering a trial of high-flow nasal oxygen (HFNO) or non-invasive 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 non-invasive ventilation.[120]
- In the UK, the National Institute for Health and Care Excellence recommends CPAP in patients with hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of  $\geq 0.4$  (40%), and escalation to invasive mechanical ventilation would be an option but it is not immediately needed or it is agreed that respiratory support should not be escalated beyond CPAP. Ensure there is access to critical care providers for advice, regular review, and prompt escalation of treatment if needed, and regular assessment and management of symptoms alongside non-invasive respiratory support. Consider using HFNO for people having CPAP when they need a break from CPAP (e.g., mealtimes), need humidified oxygen, or need weaning from CPAP. Do not routinely offer HFNO as the main form of respiratory support for people with respiratory failure in whom escalation to invasive mechanical ventilation would be appropriate. Ensure that pharmacological and non-pharmacological management strategies, including body positioning, are optimised before escalating treatment to non-invasive respiratory support.[600]
- In the US, the National Institutes of Health guidelines panel recommends HFNO over non-invasive ventilation in patients with acute hypoxaemic respiratory failure despite conventional oxygen therapy. The panel recommends a closely monitored trial of non-invasive ventilation if HFNO is not available. A trial of awake prone positioning is recommended in patients with persistent hypoxaemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated.[568]
  - Indirect and low-certainty evidence suggests that non-invasive ventilation probably reduces mortality in patients with COVID-19, similar to mechanical ventilation, but may increase the risk of viral transmission.[854] [855]
  - The RECOVERY-RS trial (an open-label, multicenter, adaptive randomised controlled trial) found that CPAP reduced the need for invasive mechanical ventilation in adults admitted to hospital with acute respiratory failure. Neither CPAP nor HFNO reduced mortality when compared with conventional oxygen therapy. This preprint study has not been published as yet.[856]
  - Awake prone positioning of non-intubated patients was associated with improvement in oxygen variables ( $\text{PaO}_2/\text{FiO}_2$ ,  $\text{PaO}_2$ , and  $\text{SpO}_2$ ), respiratory rate, and mortality, but no significant difference was noted in the rate of intubation. However, evidence is limited.[826] [827]

- Airborne precautions are recommended for these interventions (including bubble CPAP) due to uncertainty about the potential for aerosolisation.[120] Novel methods to protect clinicians without access to standard personal protective equipment during aerosol-generating procedures have been suggested.[857] [858] [859] [860] Despite the trend to avoid HFNO, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[861]
- Patients with hypercapnia, haemodynamic 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 non-worsening hypercapnia. Patients with hypoxaemic respiratory failure and haemodynamic instability, multi-organ failure, or abnormal mental status should not receive these treatments in place of other options such as invasive ventilation.[120]
- Monitor patients closely for acute deterioration. If patients do not improve after a short trial of these interventions, they require urgent endotracheal intubation.[120] [824]
- 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/non-invasive ventilatory support measures.[120] [568]
  - Use of mechanical ventilation in COVID-19 patients carries a high risk of mortality. Mortality is highly variable across studies, ranging between 21% and 100%. An overall in-hospital mortality risk ratio of 0.70 has been reported based on random-effect pooled estimates. However, it is important to note that outcomes appear to have improved as the pandemic has progressed.[862]
- Endotracheal intubation should be performed by an experienced provider using airborne precautions.[120] Intubation by video laryngoscopy is recommended if possible.[568] Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require pre-oxygenation with 100% FiO<sub>2</sub> for 5 minutes.[120]
- 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, individualisation 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.[120] [568] [824] NHS England recommends a low PEEP strategy in patients with normal compliance where recruitment may not be required.[863]
  - 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 hypoxaemia.[864] [865] [866] [867] [868] [869] However, this approach has been criticised.[870] [871]
  - 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.[872] 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 physiological findings rather than using standard protocols. High PEEP may have a detrimental effect on patients with normal compliance.[864]

- PEEP should always be carefully titrated.[873]
- 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.[120] [568] [824] Longer durations may be feasible in some patients.[874]
- Lung recruitment manoeuvres are suggested, but staircase recruitment manoeuvres are not recommended.[568] [824]
- 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 hypoxaemia despite optimising ventilation. Taper off if there is no rapid improvement in oxygenation.[568] [824]

### Extracorporeal membrane oxygenation

- Consider extracorporeal membrane oxygenation (ECMO) according to availability and expertise if the above methods fail.[120] [824] [875] ECMO is not suitable for all patients, and only those who meet certain inclusion criteria may be considered for ECMO.[876]
- There is insufficient evidence to recommend either for or against the routine use of ECMO.[568]
  - A systematic review and meta-analysis found that in-hospital mortality in adults receiving ECMO was 37.1% during the first year of the pandemic, similar to those with non-COVID-19-related acute respiratory distress syndrome. Increasing age was a risk factor for death. The duration of treatment appears to be prolonged in COVID-19 patients; however, a prolonged treatment course was not a predictor of mortality.[877]
  - Single-access, dual-stage venovenous ECMO with early extubation appears to be safe and effective in patients with COVID-19 respiratory failure.[878]

### 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 Management of severe COVID-19 above).
- For VTE prophylaxis, unfractionated heparin is preferred over fondaparinux in critically ill patients if low molecular weight heparin cannot be used.[832]
  - The National Institute for Health and Care Excellence in the UK recommends a prophylactic dose of a low molecular weight heparin to young people and adults who need HFNO, CPAP, non-invasive ventilation, or invasive mechanical ventilation, and who do not have an increased bleeding risk. An intermediate or treatment dose of a low molecular weight heparin is only recommended in these patients as part of a clinical trial.[600]

- Some guidelines recommend that escalated doses can be considered in critically ill patients.[831] [611]
- A multicentre randomised 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 empirical use of intermediate-dose prophylactic anticoagulation in unselected patients admitted to the intensive care unit.[879]
- An open-label, multiplatform randomised controlled trial found that an initial strategy of therapeutic-dose heparin did not result in a greater probability of survival to hospital discharge or a greater number of organ support-free days in critically ill patients compared with usual-care thromboprophylaxis.[880]

### Corticosteroids

- The WHO strongly recommends systemic corticosteroid therapy (low-dose intravenous or oral dexamethasone or hydrocortisone) for 7 to 10 days in adults with critical disease. Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with critical disease. They also probably reduce the need for invasive ventilation.[795] There is also evidence that corticosteroids probably increase ventilator-free days (moderate certainty).[850] [851]
- In the US, the National Institutes of Health guidelines panel recommends dexamethasone (or a suitable alternative corticosteroid), either alone or in combination with remdesivir (see the [Emerging] section for information on remdesivir), in hospitalised patients who require high-flow oxygen or non-invasive ventilation. In patients who are on mechanical ventilation or ECMO, the panel recommends dexamethasone alone or in combination with tocilizumab for patients who are within 24 hours of admission to the intensive care unit. The panel recommends using dexamethasone in hospitalised children who require high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation.[568]
  - 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.[881]
- See the corticosteroids section under Management of severe COVID-19 above for more information.

### IL-6 inhibitors

- The WHO strongly recommends an IL-6 inhibitor, in combination with a systemic corticosteroid and initiated at the same time, in patients with critical disease.[795]
- In the US, the National Institutes of Health guidelines panel recommends adding tocilizumab to dexamethasone (or a suitable alternative corticosteroid) or dexamethasone plus remdesivir in patients who require non-invasive mechanical ventilation or high-flow nasal oxygen and have been recently hospitalised (e.g., within 3 days) with rapidly increasing oxygen needs and systemic inflammation. In patients who are on mechanical ventilation or ECMO, the panel recommends adding tocilizumab to dexamethasone for patients who are within 24 hours of admission to the intensive care unit. There is insufficient evidence for the panel to recommend either for or against the use of tocilizumab in hospitalised children. Sarilumab may be used as an alternative

if tocilizumab is not available or it is not feasible to use it.[568] The Infectious Diseases Society of America recommends considering tocilizumab in hospitalised adults with critical disease who have elevated markers of systemic inflammation, in addition to standard of care (i.e., corticosteroids), rather than standard of care alone. Sarilumab may be used if tocilizumab is not available.[845] Tocilizumab has been granted an emergency-use authorisation in the US for the treatment of hospitalised adults and paediatric patients 2 years of age and older who are receiving systemic corticosteroids and require non-invasive or invasive mechanical ventilation, or ECMO.[848]

- See the IL-6 inhibitors section under Management of severe COVID-19 above for more information.

### 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.[120]

### 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.[120]
  - There is a lack of data on palliative care in patients with COVID-19. However, a rapid systematic review of pharmacological 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.[853]
- Follow local palliative care guidelines.

## 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-centred, respectful, skilled approach to care is recommended.[120] In women with severe or critical disease, the multidisciplinary team should be organised as soon as possible after maternal hypoxaemia occurs in order to assess fetal maturity, disease progression, and the best options for delivery.[882]

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 physiological changes that occur with pregnancy.[120]

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).[883] [884] 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 people tested positive despite being screened negative.[885] 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.[886]

### 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.[120] Follow local infection prevention and control procedures as for non-pregnant people.
- Consider home care in women with asymptomatic or mild illness, provided the patient has no signs of potentially severe illness (e.g., breathlessness, haemoptysis, 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.[666] [887] [888]
- Postpone routine antenatal or postnatal health visits for women who are in home isolation and reschedule them after the isolation period is completed. Delivery of counselling 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.[120]
- The American College of Obstetricians and Gynecologists has published an algorithm to help decide whether hospital admission or home care is more appropriate. [ACOG: outpatient assessment and management for pregnant women with suspected or confirmed novel coronavirus (COVID-19)]

### Antenatal corticosteroids

- Consider antenatal 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.[666] [888] [889] The WHO recommends antenatal 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.[120]
- 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.[890]

### Treatments

- In general, the therapeutic management should be the same for pregnant women as for non-pregnant patients. 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.[568]

### VTE prophylaxis

- The National Institutes of Health recommends prophylactic dose anticoagulation in pregnant women who are hospitalised with severe disease, provided there are no contraindications to its



use. Anticoagulation during labour and delivery requires specialised 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.[568]

- The Royal College of Obstetricians and Gynaecologists (RCOG) has also published guidance on the prevention of VTE in pregnant women.[890]

### Labour and delivery

- Implement local infection prevention and control measures during labour and delivery. Screen birth partners for COVID-19 infection using the standard case definition.[120]
- Individualise 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 labour, interventions to accelerate labour and delivery, and caesarean delivery are generally only recommended when medically justified based on maternal and fetal condition. COVID-19 positive status alone is not an indication for caesarean section.[120] [666] [888]
- 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.[120]
- 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.[891]

### 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.[892] Mother-to-infant transmission appears to be rare during rooming-in, provided that adequate droplet and contact precautions are taken.[893]
- 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).[120] The WHO advises that the benefits of breastfeeding outweigh the potential risks for transmission.[894]
- 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 minimise the risk of transmission should be implemented.[895] A mother with confirmed infection should be counselled 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 carer.[896]
- The RCOG recommends that mothers with confirmed infection and healthy babies are kept together in the immediate postnatal period. It is recommended that the risks and benefits are

discussed with neonatologists and families in order to individualise 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.[890]

- The American Academy of Pediatrics (AAP) recommends that mothers and newborns may room-in, with appropriate infection prevention and control precautions, according to usual centre practice. However, it may be appropriate to temporarily separate the mother and newborn (or to have the newborn cared for by non-infected carers 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 carer. 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.[891]

## 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 hospitalisation. 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.[568]

## Management of co-existing conditions

Best Practice has published a separate topic on the management of co-existing conditions in the context of COVID-19. [\[BMJ Best Practice: management of co-existing conditions in the context of COVID-19\]](#)

## Treatment algorithm overview

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](#)

| <b>Acute</b>             |                 | <b>( summary )</b>                                   |
|--------------------------|-----------------|--|
| <b>mild COVID-19</b>     |                 |  |
|                          | <b>1st</b>      | <b>consider home isolation</b>                       |
|                          | <b>plus</b>     | <b>monitoring</b>                                    |
|                          | <b>plus</b>     | <b>symptom management and supportive care</b>        |
|                          | <b>consider</b> | <b>antipyretic/analgesic</b>                         |
|                          | <b>consider</b> | <b>experimental therapies</b>                        |
| <b>moderate COVID-19</b> |                 |  |
|                          | <b>1st</b>      | <b>consider home isolation or hospital admission</b> |
|                          | <b>plus</b>     | <b>monitoring</b>                                    |
|                          | <b>plus</b>     | <b>symptom management and supportive care</b>        |
|                          | <b>consider</b> | <b>antibiotics</b>                                   |
|                          | <b>consider</b> | <b>antipyretic/analgesic</b>                         |
|                          | <b>consider</b> | <b>experimental therapies</b>                        |
| <b>severe COVID-19</b>   |                 |  |
|                          | <b>1st</b>      | <b>hospital admission</b>                            |
|                          | <b>plus</b>     | <b>consider oxygen therapy</b>                       |
|                          | <b>plus</b>     | <b>symptom management and supportive care</b>        |
|                          | <b>plus</b>     | <b>venous thromboembolism prophylaxis</b>            |
|                          | <b>plus</b>     | <b>monitoring</b>                                    |
|                          | <b>consider</b> | <b>antibiotics</b>                                   |
|                          | <b>consider</b> | <b>corticosteroid</b>                                |
|                          | <b>consider</b> | <b>interleukin-6 (IL-6) inhibitor</b>                |
|                          | <b>consider</b> | <b>treatment of co-infections</b>                    |
|                          | <b>consider</b> | <b>antipyretic/analgesic</b>                         |
|                          | <b>consider</b> | <b>experimental therapies</b>                        |
|                          | <b>consider</b> | <b>plan for discharge and rehabilitation</b>         |
|                          | <b>consider</b> | <b>palliative care</b>                               |
| <b>critical COVID-19</b> |                 |  |
|                          | <b>1st</b>      | <b>intensive/critical care unit admission</b>        |

## Acute

( summary )

- plus** symptom management and supportive care
- plus** venous thromboembolism prophylaxis
- plus** consider high-flow nasal oxygen or non-invasive ventilation
- plus** consider invasive mechanical ventilation
- consider** inhaled pulmonary vasodilator
- consider** extracorporeal membrane oxygenation
- consider** management of sepsis/septic shock
- consider** corticosteroid
- consider** interleukin-6 (IL-6) inhibitor
- consider** treatment of co-infections
- consider** experimental therapies
- consider** plan for discharge and rehabilitation
- consider** palliative care

## Treatment algorithm

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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](#)

## Acute

## mild COVID-19

## 1st consider home isolation

» **Isolate 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 to contain virus transmission.** [120]

- 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.[120] [568]
- This decision requires careful clinical judgement 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 carer is able to provide care and recognise when the patient may be deteriorating; the carer has adequate support (e.g., food, supplies, psychological support); the support of a trained health worker is available in the community.[807]
- 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.[120]

» **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]
- [CDC: interim guidance for implementing home care of people not requiring hospitalization for coronavirus disease 2019 (COVID-19)]

» **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**

## Acute

**respiratory symptoms (symptomatic patients).** [120]

- The US Centers for Disease Control and Prevention (CDC) recommends discontinuing isolation once at least 10 days (not moderately to severely immunocompromised) or up to 20 days (moderately to 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 moderately to severely immunocompromised) or up to 20 days (moderately to severely immunocompromised) have passed since the date of a positive test. Moderately to 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 moderately to severely immunocompromised patients.[809]
- 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.[810]

**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).** [120] [568]

## Acute

- Pulse oximetry monitoring at home is recommended in symptomatic patients with risk factors for progression to severe disease who are not hospitalised. Patient education and appropriate follow-up are required.[120]

**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 aged 1 year and older) to help cough.** [600]

- 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.[818]

» **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.[120] [600]

» **Other supportive care measures include:**

- Advise patients to improve air circulation by opening a window or door[600]
- Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate[120]
- 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.[819]

» Most children with mild disease can be managed with supportive care alone.[568]

**consider antipyretic/analgesic**

Treatment recommended for SOME patients in selected patient group

**Primary options**



## Acute

» **paracetamol**: children: consult local drug formulary for guidance on dose; adults: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

## OR

» **ibuprofen**: children: consult local drug formulary for guidance on dose; adults: 300-600 mg orally (immediate-release) every 6-8 hours when required, maximum 2400 mg/day

» **Paracetamol or ibuprofen are recommended.** [120] [600]

- There is no evidence at present of severe adverse events in COVID-19 patients taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilisation, long-term survival, or quality of life in patients with COVID-19.[811] [812] [813] [814] [815] [816] [817]
- 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).

**consider experimental therapies**

Treatment recommended for SOME patients in selected patient group

» **Consider any 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.[568]
- Monoclonal antibody treatment may be recommended in certain patients; however, international guidelines vary in their recommendations.
- See the [Emerging] section for more information.

## Acute

## moderate COVID-19

- 1st**      **consider home isolation or hospital admission**
- » **Isolate patients with suspected or confirmed moderate disease (i.e., clinical signs of pneumonia but no signs of severe pneumonia) to contain virus transmission.** [120]
    - 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.[120] [568]
  - » **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]
    - [CDC: interim guidance for implementing home care of people not requiring hospitalization for coronavirus disease 2019 (COVID-19)]
  - » **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.** [120]
    - The US Centers for Disease Control and Prevention (CDC) recommends discontinuing isolation once at least 10 days (not moderately to severely immunocompromised) or up to 20 days (moderately to 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 moderately to severely immunocompromised) or up to 20 days (moderately to severely

## Acute

immunocompromised) have passed since the date of a positive test. Moderately to 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 moderately to severely immunocompromised patients.[809]

- 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 hospitalised 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.[810]

**plus monitoring**

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).** [120] [568]

- Pulse oximetry monitoring at home is recommended in symptomatic patients with risk factors for progression to severe disease who are not hospitalised. Patient education and appropriate follow-up are required.[120]
- 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

## Acute

immediately with appropriate supportive care interventions.[120]

**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 aged 1 year and older) to help cough.** [600]

- 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.[818]

» **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.[120] [600]

» **Other supportive care measures include:**

- Advise patients to improve air circulation by opening a window or door[600]
- Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression, or anxiety as appropriate[120]
- 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.[819]

» Most children with moderate disease can be managed with supportive care alone.[568]

**consider antibiotics**

Treatment recommended for SOME patients in selected patient group

» **Consider empirical 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.[120] [568] [600] The regimen

## Acute

should be based on the clinical diagnosis, local epidemiology and susceptibility data, and local treatment guidelines.

- Antibiotics may also be considered in older people (particularly those in long-term care facilities) and children <5 years of age to provide empirical antibiotic treatment for possible pneumonia.[120]
- Do not offer an antibiotic for preventing secondary bacterial pneumonia in people with COVID-19.[600]

» **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.[600]

#### consider antipyretic/analgesic

Treatment recommended for SOME patients in selected patient group

##### Primary options

» **paracetamol**: children: consult local drug formulary for guidance on dose; adults: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

##### OR

» **ibuprofen**: children: consult local drug formulary for guidance on dose; adults: 300-600 mg orally (immediate-release) every 6-8 hours when required, maximum 2400 mg/day

» **Paracetamol or ibuprofen are recommended.** [120] [600]

- There is no evidence at present of severe adverse events in COVID-19 patients taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilisation, long-term survival, or quality of life in patients with COVID-19.[811] [812] [813] [814] [815] [816] [817]
- Ibuprofen should only be taken at the lowest effective dose for the shortest period needed to control symptoms. It is

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not recommended in pregnant women (especially in the third trimester) or children <6 months of age (age cut-offs vary by country).

**consider experimental therapies**

Treatment recommended for SOME patients in selected patient group

» **Consider any 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.[\[568\]](#)
- Monoclonal antibody treatment may be recommended in certain patients; however, international guidelines vary in their recommendations.
- See the [\[Emerging\]](#) section for more information.

## severe COVID-19

**1st hospital admission**

» **Admit patients with suspected or confirmed severe disease to an appropriate healthcare facility under the guidance of a specialist team as these patients are at risk of rapid clinical deterioration.**

- 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 SpO<sub>2</sub> <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 SpO<sub>2</sub> <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).[\[120\]](#)
- Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, as well as midwifery and

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mental health and psychosocial support. A woman-centred, respectful, skilled approach to care is recommended.[120] The multidisciplinary team should be organised as soon as possible after maternal hypoxemia occurs in order to assess fetal maturity, disease progression, and the best options for delivery.[882]

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

» **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]
- Do not use the CFS for younger people, people with stable long-term disabilities (e.g., cerebral palsy), learning disabilities, or autism. Make an individualised assessment of frailty in these people, using clinical assessment and alternative scoring methods.[600]
- 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).[820] 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.[822]

» **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. [120]**

- The US 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. Moderately to severely immunocompromised patients

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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 moderately to severely immunocompromised patients.[809]

- 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 hospitalised 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.[810]

**plus consider oxygen therapy**

Treatment recommended for ALL patients in selected patient group

» **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 SpO<sub>2</sub> <90% .[120] [568]**

- Target SpO<sub>2</sub> 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 SpO<sub>2</sub> >90% in children and non-pregnant adults, and ≥92% to 95% in pregnant women, is recommended. Nasal prongs or a nasal cannula are preferred in young children.[120]
- Some guidelines recommend that SpO<sub>2</sub> should be maintained no higher than 96%.[824]
- Some centres may recommend different SpO<sub>2</sub> targets in order to support prioritisation of oxygen flow for the



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most severely ill patients in hospital. NHS England recommends a target of 92% to 96% (or 90% to 94% if clinically appropriate), for example.[825]

» **Consider positioning techniques (e.g., high supported sitting), and airway clearance management to optimise 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.[120] [568]
- Awake prone positioning of non-intubated patients was associated with improvement in oxygen variables (PaO<sub>2</sub>/FiO<sub>2</sub>, PaO<sub>2</sub>, and SpO<sub>2</sub>), respiratory rate, and mortality, but no significant difference was noted in the rate of intubation. However, evidence is limited.[826] [827]

» **Monitor patients closely for signs of progressive acute hypoxaemic respiratory failure.** [120] [568]

**plus symptom management and supportive care**

Treatment recommended for ALL patients in selected patient group

» **Fluids and electrolytes**

- Use cautious fluid management in adults and children without tissue hypoperfusion and fluid responsiveness as aggressive fluid resuscitation may worsen oxygenation.[120]
- Correct any electrolyte or metabolic abnormalities, such as hyperglycaemia or metabolic acidosis, according to local protocols.[828]

» **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 aged 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.[600]
- A meta-analysis found that honey is superior to usual care (e.g., antitussives) for the improvement of upper respiratory

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tract infection symptoms, particularly cough frequency and severity.[818]

» **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 oedema, pulmonary embolism, COPD, asthma). Consider a trial of oxygen, if available.[600]

» **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, minimise use of drugs that may cause or worsen delirium, treat substance withdrawal, maintain normal sleep cycles, treat pain or breathlessness).[120] [600]
- Low doses of haloperidol (or another suitable antipsychotic) can be considered for agitation.[120]
- Non-pharmacological interventions are the mainstay for the management of delirium when possible, and prevention is key.[829]

» **Mouth care**

- An important part of overall patient care in hospitalised patients who are ventilated or non-ventilated and those undergoing step-down or end-of-life care.[830]

» **Mental health symptoms**

- Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia or depression as appropriate.[120]

**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**

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

**OR**

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

» **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.** [600]

» **Start venous thromboembolism (VTE) prophylaxis in acutely ill hospitalised adults and adolescents, provided there are no contraindications.** [120] [568] [831] [832]

- The UK National Institute for Health and Care Excellence (NICE) recommends starting as soon as possible (within 14 hours of admission), in young people and adults who need low-flow oxygen and who do not have an increased bleeding risk, and continuing for a minimum of 7 days including after discharge.[600]
- For hospitalised children, indications for VTE prophylaxis should be the same as those for children without COVID-19.[568]

» **Low molecular weight heparin, unfractionated heparin, or fondaparinux are the recommended options for standard thromboprophylaxis.** [120]

- NICE recommends low molecular weight heparin first-line, with fondaparinux or unfractionated heparin reserved for patients who cannot have low molecular weight heparin.[600]
- 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.[832] [834]

» **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 across most guidelines.[836] However, this

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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.<sup>[120]</sup>
- NICE recommends a prophylactic dose of a low molecular weight heparin for a minimum of 7 days (including after discharge) in young people and adults who need low-flow oxygen and who do not have an increased bleeding risk. A treatment dose of a low molecular weight heparin for 14 days or until discharge (whichever is sooner) may be considered in young people and adults who need low-flow oxygen and who do not have an increased bleeding risk; however, this is a conditional recommendation only. The decision should be carefully considered, and choice of the most appropriate dose regimen should be guided by bleeding risk, clinical judgement, and local protocols. For those who do not need supplemental oxygen, follow standard VTE prophylaxis guidelines.<sup>[600]</sup>
- 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.<sup>[568]</sup>
- Dose adjustments may be required in patients with extremes of body weight or renal impairment.<sup>[600]</sup>
- 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 the patient is not currently on low molecular weight heparin.<sup>[600]</sup>

» **Monitor patients for signs and symptoms suggestive of thromboembolism and proceed with appropriate diagnostic and management pathways if clinically suspected.** <sup>[120]</sup>

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- If the patient's clinical condition changes, assess the risk of VTE, reassess the bleeding risk, and review VTE prophylaxis.[600]

» **Continue until hospital discharge.** [120]

- Routine post-discharge VTE prophylaxis is not generally recommended, except in certain high-risk patients.[568] [831] [832]
- Ensure patients who require VTE prophylaxis after discharge are able to use it correctly or have arrangements made for someone to help them.[600]

» **There is currently insufficient evidence to determine the risks and benefits of prophylactic anticoagulation in hospitalised patients with COVID-19.** [840]

- A systematic review and meta-analysis found that the pooled odds of mortality between anticoagulated and non-anticoagulated hospitalised 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.[841]
- Clinicians should rely on pre-COVID-19 evidence-based principles of anticoagulation management combined with rational approaches to address clinical challenges.[831]

**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.** [120]

**consider antibiotics**

Treatment recommended for SOME patients in selected patient group

» **Consider empirical 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

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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.[120] [568] [600]

- 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.[600]
- There is insufficient evidence to recommend empirical broad-spectrum antibiotics in the absence of another indication.[568]

» **Seek specialist advice.**

- 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.[600]
- 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 microbiological evidence of infection and the person's condition does not improve as expected after 48 to 72 hours of antibiotic treatment.[600]

» **Reassess antibiotic use daily.**

- De-escalate empirical therapy on the basis of microbiology results and clinical judgement. 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 programmes should be in place.[120]

**consider 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**

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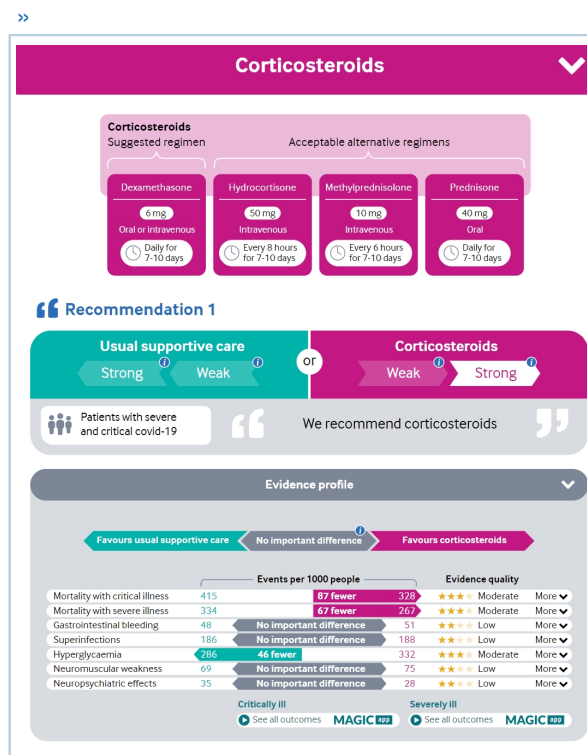
» **hydrocortisone**: children: consult specialist for guidance on dose; adults: 50 mg orally/intravenously every 8 hours for 7-10 days

Secondary options

» **prednisolone**: 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



Recommendations and evidence for the use of corticosteroids in hospitalised patients with COVID-19. *BMJ. 2020;370:m3379*

» **Consider a systemic corticosteroid. Guideline recommendations vary.**

- The **World Health Organization** strongly recommends systemic corticosteroid therapy (low-dose intravenous or oral dexamethasone or hydrocortisone) for 7 to 10 days in adults with severe disease. This

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recommendation is based on two meta-analyses that pooled data from eight randomised 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 disease. 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.[795] [796] [797] [843] [844]

- [BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19]
- In the UK, the **National Institute for Health and Care Excellence** recommends offering dexamethasone (or an alternative such as hydrocortisone or prednisolone 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.[600]
- 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. Alternative corticosteroids may be used in situations where dexamethasone is not available. It is not routinely recommended for paediatric 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.[568]
- The **Infectious Diseases Society of America** supports the use of dexamethasone in hospitalised patients with severe disease.[845]

» **Monitor patients for adverse effects (e.g., hyperglycaemia, secondary infections, psychiatric effects,**



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reactivation of latent infections) and assess for drug-drug interactions. [568]

**consider interleukin-6 (IL-6) inhibitor**

Treatment recommended for SOME patients in selected patient group

**Primary options**

» **tocilizumab**: children: consult specialist for guidance on dose; adults: 8 mg/kg intravenously as a single dose, maximum 800 mg/dose

Typically administered as a single intravenous dose; however, a second dose may be administered 12 to 48 hours after the first dose if the clinical response is inadequate. World Health Organization. Therapeutics and COVID-19: living guideline. 2021 [internet publication]. <https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.3>

**OR**

» **sarilumab**: children: consult specialist for guidance on dose; adults: 400 mg intravenously as a single dose

Typically administered as a single intravenous dose; however, a second dose may be administered 12 to 48 hours after the first dose if the clinical response is inadequate. World Health Organization. Therapeutics and COVID-19: living guideline. 2021 [internet publication]. <https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.3>

»

Acute

**IL-6 receptor blockers**

Suggested regimen

- Tocilizumab**: 8mg per kg, Max 800mg, Intravenous, Initial dose over 1 hour
- or**
- Sarilumab**: 400mg, Intravenous, Initial dose over 1 hour

A second dose may be administered after 12 to 48 hours

**Recommendation 1**

Usual supportive care: Strong to Weak  
 IL-6 receptor blockers: Weak to Strong

Patients with severe and critical covid-19: We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab)

**Evidence profile**

| Outcome                                 | Usual supportive care | IL-6 receptor blockers       | Evidence quality |
|---|-----------------------|------------------------------|------------------|
| Mortality                               | 130                   | 115 (15 fewer)               | High             |
| Mechanical ventilation                  | 86                    | 63 (23 fewer)                | High             |
| Serious adverse events                  | 9                     | 5 (No important difference)  | Very low         |
| Bacterial infections                    | 101                   | 96 (No important difference) | Low              |
| Duration of ventilation (Mean days)     | 14.7                  | 13.5 (1.2 fewer)             | Low              |
| Duration of hospitalisation (Mean days) | 12.8                  | 8.3 (4.5 fewer)              | Low              |

Recommendations and evidence for the use of IL-6 inhibitors in hospitalised patients with COVID-19  
 BMJ. 2020;370:m3379

» **Consider an IL-6 inhibitor. Guideline recommendations vary.**

- The **World Health Organization** strongly recommends an IL-6 inhibitor (tocilizumab or sarilumab), in combination with a systemic corticosteroid and initiated at the same time, in patients with severe disease. This recommendation is based on high-certainty evidence that shows IL-6 inhibitors reduce mortality and the need for mechanical ventilation, and low-certainty evidence that suggests that IL-6 inhibitors may also reduce the duration of mechanical ventilation and hospitalisation. The evidence regarding the risk of severe adverse events is uncertain. The applicability of this recommendation to children is currently uncertain.<sup>[795] [796] [797]</sup> This recommendation is based on data from the UK RECOVERY and REMAP-CAP trials.<sup>[846] [847]</sup>
- [BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19]
- In the UK, the **National Institute for Health and Care Excellence** recommends a single dose of tocilizumab in hospitalised adults if all of the following conditions apply: they are having or have completed a course of corticosteroids

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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  $\geq 75$  mg/L, OR they are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation, or invasive mechanical ventilation. Consider tocilizumab for children and young people who have severe disease or paediatric inflammatory multisystem syndrome only if they are aged 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).[600] Tocilizumab has not been granted a conditional marketing authorisation for this indication in the UK as yet.

- In the US, the **Infectious Diseases Society of America** recommends considering tocilizumab in hospitalised adults with progressive severe disease who have elevated markers of systemic inflammation, in addition to standard of care (i.e., corticosteroids), rather than standard of care alone. Sarilumab may be used if tocilizumab is not available.[845] Tocilizumab has been granted an emergency-use authorisation in the US for the treatment of hospitalised adults and paediatric patients 2 years of age and older who are receiving systemic corticosteroids and require supplemental oxygen.[848]

» **Patients on IL-6 inhibitors are at increased risk of infection including active tuberculosis, invasive fungal infections, and opportunistic pathogens.**

- Routine blood work including neutrophil count, platelets, transaminases, and total bilirubin should be checked prior to initiation of therapy. All patients should be monitored for signs and symptoms of infection given the increased risk of immunosuppression in addition to systemic corticosteroids.[795]

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- These drugs should be avoided in patients who are significantly immunocompromised.[568]

**consider treatment of co-infections**

Treatment recommended for SOME patients in selected patient group

» **Treat laboratory-confirmed co-infections (e.g., malaria, tuberculosis, influenza) as appropriate according to local protocols.** [120]

- The treatment of influenza is the same in all patients regardless of SARS-CoV-2 co-infection. Start empirical treatment with oseltamivir in hospitalised 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.[568]

**consider antipyretic/analgesic**

Treatment recommended for SOME patients in selected patient group

**Primary options**

» **paracetamol:** children: consult local drug formulary for guidance on dose; adults: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

**OR**

» **ibuprofen:** children: consult local drug formulary for guidance on dose; adults: 300-600 mg orally (immediate-release) every 6-8 hours when required, maximum 2400 mg/day

» **Paracetamol or ibuprofen are recommended.** [120] [600]

- There is no evidence at present of severe adverse events in COVID-19 patients taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, or of effects as a result of the use of NSAIDs on acute healthcare utilisation, long-term survival, or quality of life in patients with COVID-19.[811] [812] [813] [814] [815] [816] [817]
- Ibuprofen should only be taken at the lowest effective dose for the shortest

## Acute

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).

**consider experimental therapies**

Treatment recommended for SOME patients in selected patient group

» **Consider any 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.[568]
- Monoclonal antibody treatment may be recommended in certain patients; however, international guidelines vary in their recommendations.
- See the [Emerging] section for more information.

**consider 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.**

- Based on that assessment determine whether the patient is ready for discharge, and whether the patient has any rehabilitation and follow-up requirements.[120]

**consider 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.[120]
- Follow local palliative care guidelines.

## Acute

» **There is a lack of data on palliative care in patients with COVID-19.**

- A rapid systematic review of pharmacological 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.<sup>[853]</sup>

## critical COVID-19

## 1st intensive/critical care unit admission

» **Admit or transfer patients with critical disease (i.e., presence of acute respiratory distress syndrome, sepsis, or septic shock) to an intensive/critical care unit under the guidance of a specialist team.**

<sup>[120]</sup>

- 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 pre-existing advanced comorbidities.<sup>[600]</sup>
- 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-centred, respectful, skilled approach to care is recommended.<sup>[120]</sup> The multidisciplinary team should be organised as soon as possible after maternal hypoxemia occurs in order to assess fetal maturity, disease progression, and the best options for delivery.<sup>[882]</sup>

## Acute

» **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** .[120]

- The US 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. Moderately to 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 moderately to severely immunocompromised patients.[809]
- 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 hospitalised 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.[810]

**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.**

## Acute

- See Severe COVID-19 above for more detailed information.
- Follow local guidelines for the management of pain, sedation, and delirium.[568]

» **Implement standard interventions to prevent complications associated with critical illness.** [120]

**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**

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

**OR**

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

» **Start venous thromboembolism (VTE) prophylaxis in acutely ill hospitalised adults and adolescents, provided there are no contraindications.** [120] [568] [831] [832]

- 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.[832]
- The UK National Institute for Health and Care Excellence (NICE) recommends a prophylactic dose of a low molecular weight heparin to young people and adults who need high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation, or invasive mechanical ventilation, and who do not have an increased bleeding risk. An intermediate or treatment dose of a low molecular weight heparin is only recommended in these patients as part of a clinical trial.[600]



## Acute

- Some guidelines recommend that escalated doses can be considered in critically ill patients.[831] [611]
- Dose adjustments may be required in patients with extremes of body weight or renal impairment.[600]

» **Evidence is limited in patients with critical disease.**

- A multicentre randomised 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 empirical use of intermediate-dose prophylactic anticoagulation in unselected patients admitted to the intensive care unit.[879]
- An open-label, multiplatform randomised controlled trial found that an initial strategy of therapeutic-dose heparin did not result in a greater probability of survival to hospital discharge or a greater number of organ support-free days in critically ill patients compared with usual-care thromboprophylaxis.[880]

» See Severe COVID-19 above for more detailed information on VTE prophylaxis.

**plus consider high-flow nasal oxygen or non-invasive ventilation**

Treatment recommended for ALL patients in selected patient group

» **Consider a trial of high-flow nasal oxygen (HFNO) or non-invasive ventilation (e.g., continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) in selected patients with mild acute respiratory distress syndrome. [120]**

- In the UK, the National Institute for Health and Care Excellence recommends CPAP in patients with hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of  $\geq 0.4$  (40%), and escalation to invasive mechanical ventilation would be an option but it is not immediately needed or it is agreed that respiratory support should

## Acute

not be escalated beyond CPAP. Ensure there is access to critical care providers for advice, regular review, and prompt escalation of treatment if needed, and regular assessment and management of symptoms alongside non-invasive respiratory support. Consider using HFNO for people having CPAP when they need a break from CPAP (e.g., mealtimes), need humidified oxygen, or need weaning from CPAP. Do not routinely offer HFNO as the main form of respiratory support for people with respiratory failure in whom escalation to invasive mechanical ventilation would be appropriate.[\[600\]](#)

- In the US, the National Institutes of Health guidelines panel recommends HFNO over non-invasive ventilation in patients with acute hypoxaemic respiratory failure despite conventional oxygen therapy. The panel recommends a closely monitored trial of non-invasive ventilation if HFNO is not available.[\[568\]](#)
- Patients with hypercapnia, haemodynamic 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 non-worsening hypercapnia. Patients with hypoxaemic respiratory failure and haemodynamic instability, multi-organ failure, or abnormal mental status should not receive these treatments in place of other options such as invasive ventilation.[\[120\]](#)
- Airborne precautions are recommended for these interventions (including bubble CPAP) due to uncertainty about the potential for aerosolisation.[\[120\]](#) Despite the trend to avoid HFNO, it has been shown to have a similar risk of aerosol generation to standard oxygen masks.[\[861\]](#)

» **Consider awake prone positioning (for 8-12 hours/day, broken into shorter periods over the day) in severely ill patients who require HFNO or non-invasive ventilation.**  
[\[120\]](#)

- A trial of awake prone positioning is recommended in patients with persistent hypoxaemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated.[\[568\]](#)

## Acute

- Ensure that pharmacological and non-pharmacological management strategies, including body positioning, are optimised before escalating treatment to non-invasive respiratory support.[600]
- Awake prone positioning of non-intubated patients was associated with improvement in oxygen variables ( $\text{PaO}_2/\text{FiO}_2$ ,  $\text{PaO}_2$ , and  $\text{SpO}_2$ ), respiratory rate, and mortality, but no significant difference was noted in the rate of intubation. However, evidence is limited.[826] [827]

» **Monitor patients closely for acute deterioration.**

- If patients do not improve after a short trial of these interventions, they require urgent endotracheal intubation.[120] [824]

» **Evidence is limited.**

- Indirect and low-certainty evidence suggests that non-invasive ventilation probably reduces mortality in patients with COVID-19, similar to mechanical ventilation, but may increase the risk of viral transmission.[854] [855]
- The RECOVERY-RS trial (an open-label, multicentre, adaptive randomised controlled trial) found that CPAP reduced the need for invasive mechanical ventilation in adults admitted to hospital with acute respiratory failure. Neither CPAP nor HFNO reduced mortality when compared with conventional oxygen therapy. This preprint study has not been published as yet.[856]

**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/non-invasive ventilatory support measures. [120] [568]**

- Endotracheal intubation should be performed by an experienced provider using airborne precautions.[120]
- Intubation by video laryngoscopy is recommended if possible.[568]
- Young children, or adults who are obese or pregnant, may desaturate quickly during intubation and therefore require

## Acute

pre-oxygenation with 100% fraction of inspired oxygen (FiO<sub>2</sub>) for 5 minutes.[120]

» **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, individualisation 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.[120] [568] [824] NHS England recommends a low PEEP strategy in patients with normal compliance where recruitment may not be required.[863]
- 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 hypoxaemia.[864] [865] [866] [867] [868] [869] However, this approach has been criticised.[870] [871] 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.[872] 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 physiological findings rather than using standard protocols. High PEEP may have a detrimental effect on patients with normal compliance.[864] PEEP should always be carefully titrated.[873]

» **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.[120] [568] [824]

## Acute

- Longer durations may be feasible in some patients.[874]
- Lung recruitment manoeuvres are suggested, but staircase recruitment manoeuvres are not recommended.[568] [824]

**consider 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 hypoxaemia despite optimising ventilation.** [568] [824]

- Taper off if there is no rapid improvement in oxygenation.

**consider 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.** [120] [824] [875]

- ECMO is not suitable for all patients, and only those who meet certain inclusion criteria may be considered for ECMO.[876]

» **There is insufficient evidence to recommend either for or against the routine use of ECMO.** [568]

- A systematic review and meta-analysis found that in-hospital mortality in adults receiving ECMO was 37.1% during the first year of the pandemic, similar to those with non-COVID-19-related acute respiratory distress syndrome. Increasing age was a risk factor for death. The duration of treatment appears to be prolonged in COVID-19 patients; however, a prolonged treatment course was not a predictor of mortality.[877]
- Single-access, dual-stage venovenous ECMO with early extubation appears to be safe and effective in patients with COVID-19 respiratory failure.[878]

**consider management of sepsis/septic shock**

## Acute

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.

**consider 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**

» [prednisolone](#): 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

»

Acute

**Corticosteroids**

**Corticosteroids Suggested regimen**

- Dexamethasone**: 6 mg, Oral or intravenous, Daily for 7-10 days
- Hydrocortisone**: 50 mg, Intravenous, Every 8 hours for 7-10 days
- Methylprednisolone**: 10 mg, Intravenous, Every 6 hours for 7-10 days
- Prednisone**: 40 mg, Oral, Daily for 7-10 days

**Acceptable alternative regimens**

**Recommendation 1**

Usual supportive care (Strong) OR Corticosteroids (Strong)

Patients with severe and critical covid-19. We recommend corticosteroids.

**Evidence profile**

| Outcome                         | Events per 1000 people | Events per 1000 people  | Evidence quality |
|---------------------------------|------------------------|-------------------------|------------------|
| Mortality with critical illness | 415                    | 87 fewer (328)          | Moderate         |
| Mortality with severe illness   | 334                    | 67 fewer (267)          | Moderate         |
| Gastrointestinal bleeding       | 48                     | No important difference | Low              |
| Superinfections                 | 186                    | 46 fewer (140)          | Low              |
| Hyperglycaemia                  | 266                    | 46 fewer (220)          | Moderate         |
| Neuromuscular weakness          | 69                     | No important difference | Low              |
| Neuropsychiatric effects        | 35                     | No important difference | Low              |

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» Consider a systemic corticosteroid. Guideline recommendations vary.

- The **World Health Organization** strongly recommends systemic corticosteroid therapy (low-dose intravenous or oral dexamethasone or hydrocortisone) for 7 to 10 days in adults with critical disease. This recommendation is based on two meta-analyses that pooled data from eight randomised trials (over 7000 patients), including the UK RECOVERY trial. Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with 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.[795] [796] [797] [843] [844] There is also evidence that corticosteroids probably increase ventilator-free days (moderate certainty).[850] [851]

## Acute

- [\[BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19\]](#)
- In the UK, the **National Institute for Health and Care Excellence** recommends offering dexamethasone (or an alternative such as hydrocortisone or prednisolone 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.[\[600\]](#)
- 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 hospitalised patients who require high-flow oxygen or non-invasive ventilation. In patients who are on mechanical ventilation or extracorporeal membrane oxygenation, the panel recommends dexamethasone alone or in combination with tocilizumab for patients who are within 24 hours of admission to the intensive care unit. Alternative corticosteroids may be used in situations where dexamethasone is not available. The panel recommends using dexamethasone in hospitalised children who require high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation.[\[568\]](#)

» **Monitor patients for adverse effects (e.g., hyperglycaemia, secondary infections, psychiatric effects, reactivation of latent infections) and assess for drug-drug interactions.** [\[568\]](#)

- 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.[\[881\]](#)

**consider interleukin-6 (IL-6) inhibitor**

Treatment recommended for SOME patients in selected patient group

**Primary options**



Acute

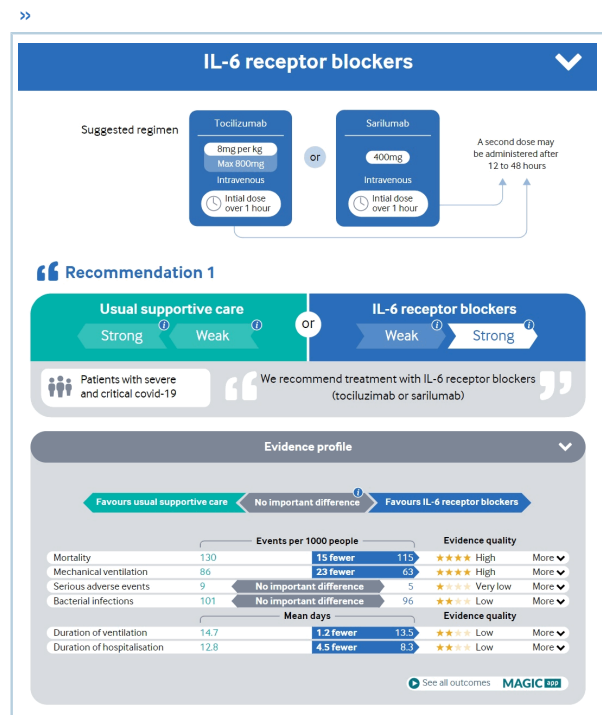
» **tocilizumab**: children: consult specialist for guidance on dose; adults: 8 mg/kg intravenously as a single dose, maximum 800 mg/dose

Typically administered as a single intravenous dose; however, a second dose may be administered 12 to 48 hours after the first dose if the clinical response is inadequate. World Health Organization. Therapeutics and COVID-19: living guideline. 2021 [internet publication]. <https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.3>

OR

» **sarilumab**: children: consult specialist for guidance on dose; adults: 400 mg intravenously as a single dose

Typically administered as a single intravenous dose; however, a second dose may be administered 12 to 48 hours after the first dose if the clinical response is inadequate. World Health Organization. Therapeutics and COVID-19: living guideline. 2021 [internet publication]. <https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.3>



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» **Consider an IL-6 inhibitor. Guideline recommendations vary.**

## Acute

- The **World Health Organization** strongly recommends an IL-6 inhibitor (tocilizumab or sarilumab), in combination with a systemic corticosteroid and initiated at the same time, in patients with critical disease. This recommendation is based on high-certainty evidence that shows IL-6 inhibitors reduce mortality and the need for mechanical ventilation, and low-certainty evidence that suggests that IL-6 inhibitors may also reduce the duration of mechanical ventilation and hospitalisation. The evidence regarding the risk of severe adverse events is uncertain. The applicability of this recommendation to children is currently uncertain.<sup>[795]</sup> <sup>[796]</sup> <sup>[797]</sup> This recommendation is based on data from the UK RECOVERY and REMAP-CAP trials.<sup>[846]</sup> <sup>[847]</sup>
- [\[BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19\]](#)
- In the US, the **National Institutes of Health** guidelines panel recommends adding tocilizumab to dexamethasone (or a suitable alternative corticosteroid) or dexamethasone plus remdesivir in patients who require non-invasive mechanical ventilation or high-flow nasal oxygen and have been recently hospitalised (e.g., within 3 days) with rapidly increasing oxygen needs and systemic inflammation. In patients who are on mechanical ventilation or extracorporeal membrane oxygenation, the panel recommends adding tocilizumab to dexamethasone for patients who are within 24 hours of admission to the intensive care unit. There is insufficient evidence for the panel to recommend either for or against the use of tocilizumab in hospitalised children. Sarilumab may be used as an alternative if tocilizumab is not available or it is not feasible to use it.<sup>[568]</sup> The Infectious Diseases Society of America recommends considering tocilizumab in hospitalised adults with critical disease who have elevated markers of systemic inflammation, in addition to standard of care (i.e., corticosteroids), rather than standard of care alone. Sarilumab may be used if tocilizumab is not available.<sup>[845]</sup> Tocilizumab has been granted an emergency-use authorisation in the US for the treatment of hospitalised adults and paediatric patients 2 years of age and older who are receiving

## Acute

systemic corticosteroids and require non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation.[848]

» **Patients on IL-6 inhibitors are at increased risk of infection including active tuberculosis, invasive fungal infections, and opportunistic pathogens.**

- Routine blood work including neutrophil count, platelets, transaminases, and total bilirubin should be checked prior to initiation of therapy. All patients should be monitored for signs and symptoms of infection given the increased risk of immunosuppression in addition to systemic corticosteroids.[795]
- These drugs should be avoided in patients who are significantly immunocompromised.[568]

**consider treatment of co-infections**

Treatment recommended for SOME patients in selected patient group

» **Treat laboratory-confirmed co-infections (e.g., malaria, tuberculosis, influenza) as appropriate according to local protocols.** [120]

- The treatment of influenza is the same in all patients regardless of SARS-CoV-2 co-infection. Start empirical treatment with oseltamivir in hospitalised 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.[568]

**consider experimental therapies**

Treatment recommended for SOME patients in selected patient group

» **Consider any 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.[568]
- See the [Emerging] section for more information.

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**consider plan for discharge and rehabilitation**

Treatment recommended for SOME patients in selected patient group

» **Routinely assess intensive care patients for mobility, functional swallow, cognitive impairment, and mental health concerns.**

- Based on that assessment determine whether the patient is ready for discharge, and whether the patient has any rehabilitation and follow-up requirements.[120]

**consider 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.[120]
- Follow local palliative care guidelines.

» **There is a lack of data on palliative care in patients with COVID-19.**

- A rapid systematic review of pharmacological 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.[853]

## Emerging

### Remdesivir

Remdesivir is a broad-spectrum antiviral agent that inhibits RNA-dependent RNA polymerase. It is approved in many countries, including the UK, US and Europe, for the treatment of COVID-19 in children  $\geq 12$  years of age (weighing  $\geq 40$  kg) and adults.[\[1010\]](#) [\[1011\]](#)

**There are conflicting recommendations across international guidelines about the use of remdesivir.**

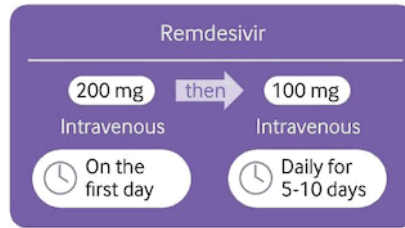
- While UK and US guidelines recommend considering remdesivir in certain patients, the World Health Organization recommends against its use. It is important that you check your local guidance and protocols.

**The World Health Organization recommends *against* the use of remdesivir in hospitalised patients in addition to standard care, regardless of disease severity .[\[795\]](#) [\[796\]](#) [\[797\]](#)**

- This weak or conditional recommendation is based on a systematic review and network meta-analysis of four randomised trials with 7333 hospitalised 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.[\[796\]](#) [\[797\]](#)

# Remdesivir

Suggested regimen



## Recommendation 1

Usual supportive care (Strong to Weak) or Remdesivir (Weak to Strong)

Patients with covid-19 at any severity

We suggest no remdesivir

### Evidence profile

Favours usual supportive care | No important difference | Favours remdesivir

|                                 | Events per 1000 people |                         | Evidence quality |                       |
|---------------------------------|------------------------|-------------------------|------------------|-----------------------|
| Mortality                       | 106                    | No important difference | 96               | ★ ★ ★ ★ Low More      |
| Mechanical ventilation          | 105                    | No important difference | 95               | ★ ★ ★ ★ Low More      |
| Serious adverse events          | 15                     | No important difference | 15               | ★ ★ ★ ★ Low More      |
| Viral clearance at 7 days       | 483                    | No important difference | 498              | ★ ★ ★ ★ Very low More |
| Acute kidney injury             | 56                     | No important difference | 48               | ★ ★ ★ ★ Low More      |
| Delirium                        | 16                     | No important difference | 19               | ★ ★ ★ ★ Very low More |
|                                 |                        | Mean days               |                  | Evidence quality      |
| Time to clinical improvement    | 11.0                   | No important difference | 9.0              | ★ ★ ★ ★ Low More      |
| Hospitalisation duration        | 12.8                   | No important difference | 12.3             | ★ ★ ★ ★ Low More      |
| Mechanical ventilation duration | 14.7                   | No important difference | 13.4             | ★ ★ ★ ★ Low More      |

See all outcomes **MAGIC app** | See patient decision aids **MAGIC app**

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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 .[600]

MANAGEMENT

- Do not use remdesivir in adults, young people, and children in hospital and on high-flow nasal oxygen, continuous positive airway pressure, non-invasive 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 hospitalised 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, non-invasive 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, non-invasive 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 hospitalised adults who require supplemental oxygen. [568]**

- 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 hospitalised patients who require high-flow oxygen or non-invasive 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 hospitalised 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 hospitalised, are aged  $\geq 12$  years, have risk factors for severe disease, and have an emergent or increasing need for supplemental oxygen. The panel recommends remdesivir in hospitalised children aged  $\geq 16$  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 hospitalised children of all ages who have an emergent or increasing need for supplemental oxygen, in consultation with a paediatric infectious disease specialist.

**The Infectious Diseases Society of America recommends remdesivir in hospitalised patients with severe disease over no antiviral treatment, based on moderate-certainty evidence . [845]**

- 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 hospitalised patients who do not require oxygen and have an oxygen saturation  $>94\%$  on room air, based on very low-certainty evidence.

**Evidence is conflicting.**

- A living systematic review and network meta-analysis found that remdesivir may reduce the need for mechanical ventilation (low-certainty evidence) compared with standard of care.[850] [851]
- The WHO Solidarity trial found that remdesivir appears to have little or no effect on hospitalised patients, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[1012]
- The DisCoVeRy trial, a phase 3 randomised controlled open-label trial, found that no clinical benefit was observed (no significant difference in clinical status at days 15 and 29, time to hospital discharge, 28-day all-cause mortality) from the use of remdesivir plus standard of care in hospitalised patients, patients who were symptomatic for more than 7 days, and those who required oxygen support, compared with standard of care alone.[1013]

Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug. Acute kidney injury and renal impairment have been reported.

## Casirivimab/imdevimab

Casirivimab and imdevimab are intravenous investigational neutralising 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 has been authorised for use in many countries, including the UK and the US, for the treatment and prophylaxis of COVID-19 in children  $\geq 12$  years of age (weighing  $\geq 40$  kg) and adults.<sup>[1014] [1015] [1016]</sup> The European Medicines Agency has issued advice that casirivimab/imdevimab may be used for treatment in patients  $\geq 12$  years of age who do not require supplemental oxygen and who are at high risk of progressing to severe disease, and is currently evaluating an application for marketing authorisation.<sup>[1017]</sup>

**The World Health Organization recommends casirivimab/imdevimab for patients with *non-severe* disease who are at highest risk of hospitalisation, and patients with severe disease with a seronegative status.** <sup>[795] [796] [797]</sup>

- Casirivimab/imdevimab probably reduces the risk of hospitalisation and duration of symptoms in patients with non-severe disease based on moderate-certainty evidence. While casirivimab/imdevimab achieves a substantial reduction in the relative risk of hospitalisation, the absolute benefit will be trivial or unimportant in absolute terms for all but those who are at highest risk of disease (e.g., unvaccinated, older people, immunodeficiencies, and/or chronic disease).
- Casirivimab/imdevimab is also recommended in seronegative patients with severe or critical disease. It probably reduces mortality and possibly reduces the need for mechanical ventilation in patients who are seronegative based on moderate- and low-certainty evidence, respectively. Treatment is in addition to the current standard of care.



## Monoclonal antibodies ▼

**Suggested regimen**

**People with non-severe disease**

Casirivimab and imdevimab

1200-2400 mg – total dose

Intravenous or subcutaneous

One off dose

**People with severe or critical disease**

Casirivimab and imdevimab

2400-8000 mg – total dose

Intravenous

One off dose

### Recommendation 1

Usual supportive care

Strong i Weak i

or

Monoclonal antibodies

Weak i Strong i

Patients with non-severe covid-19

**“ We suggest treatment with casirivimab and imdevimab, for those at highest risk of hospitalisation ”**

### Recommendation 2

Usual supportive care

Strong i Weak i

or

Monoclonal antibodies

Weak i Strong i

Patients with severe and critical covid-19

**“ We suggest treatment with casirivimab and imdevimab, if the patient has seronegative status ”**

*Recommendations for the use of casirivimab/imdevimab in patients with COVID-19  
BMJ. 2020;370:m3379*

**The UK National Institute for Health and Care Excellence recommends casirivimab/imdevimab in hospitalised patients ≥12 years of age who have no detectable SARS-CoV-2 antibodies (seronegative) , provided they meet all of the eligibility criteria and none of the exclusion criteria.[600]**

- Patients are eligible for treatment if: infection is confirmed by molecular testing, or a multidisciplinary team has a high level of confidence in the diagnosis based on clinical and radiological features; *and* patient is hospitalised specifically for the management of acute symptoms of COVID-19; *and* patient is negative for baseline serum anti-spike (anti-S) antibodies against SARS-CoV-2 (seronegative); *and* patient is either ≥50 years of age, or 12 to 49 years of age and immunocompromised.
- Do not offer casirivimab/imdevimab to people who have detectable SARS-CoV-2 antibodies (seropositive), or whose serostatus is unknown.
- Intravenous administration is recommended, and use is off-label in the UK for the dose recommended.

**The US National Institutes of Health guidelines panel recommends casirivimab/imdevimab for the *treatment* of non-hospitalised patients with mild to moderate disease who are at high risk of clinical progression , as defined by the emergency-use authorisation criteria.[568]**

- Treatment should be started as soon as possible after the patient receives a positive test result and within 10 days of symptom onset.
- Administration by intravenous infusion is recommended. However, if intravenous infusions are not feasible or would cause a delay in treatment, subcutaneous administration may be considered (note: doses differ between formulations).
- Use should be considered in patients with mild to moderate disease who are hospitalized for a reason other than COVID-19 if they otherwise meet the emergency-use authorization criteria for outpatient treatment.
- Not currently authorised for use in hospitalised patients with severe disease, but may be available through expanded access programmes for patients who are hospitalised with severe disease who have not developed an antibody response or who are not expected to mount an effective immune response (e.g., immunocompromised patients).
- In children, there are insufficient data to recommend either for or against the use of monoclonal antibody products in those who are not hospitalised but have risk factors for severe disease. However, they may be considered on a case-by-case basis for non-hospitalised children who meet emergency-use authorisation criteria for high risk of severe disease (especially those who meet more than one criterion or are aged  $\geq 16$  years) in consultation with a paediatric infectious disease specialist.

**The US National Institutes of Health guidelines panel also recommends casirivimab/imdevimab for *post-exposure prophylaxis* in people who are at high risk for progression to severe disease, provided they meet the following criteria:** [568]

- Not fully vaccinated, or fully vaccinated but not expected to mount an adequate immune response;  
**AND**
- Recent exposure to an infected individual that is consistent with the US Centers for Disease Control and Prevention close contact criteria; or at high risk of exposure to an infected individual because of recent occurrence of infection in other individuals in the same institutional setting (e.g., nursing homes, prisons).

**The Infectious Diseases Society of America suggests casirivimab/imdevimab for *treatment* 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 moderate-certainty evidence.[845]

- 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.

**The Infectious Diseases Society of America also suggests casirivimab/imdevimab for *post-exposure prophylaxis* in people who are at high risk for progression to severe disease**, based on low-certainty evidence.[845]

**Evidence supports the use of this treatment.**

- A living systematic review and network meta-analysis found that casirivimab/imdevimab probably reduces the risk of hospitalisation and reduces time to symptom resolution in patients with non-severe disease, but is not different to standard of care for other outcomes (i.e., mortality, mechanical ventilation).[1018]
- The original emergency-use authorisation was based on a randomised, double-blind, placebo-controlled trial in non-hospitalised adults with mild to moderate symptoms that found that casirivimab/imdevimab reduced hospitalisation or accident and 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.[1015]
- The UK RECOVERY trial found that among hospitalised patients who were seronegative at baseline, casirivimab/imdevimab significantly reduced the primary outcome of 28-day mortality by one fifth

compared with usual care alone. There was clear evidence that the effect of treatment in seronegative patients differed from that in seropositive patients. Results are yet to be published.[1019]

Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug. Casirivimab/imdevimab may be given as an intravenous infusion or subcutaneously.

Circulating SARS-CoV-2 variants may be associated with resistance to monoclonal antibodies. Consult local guidance for details regarding specific variants and resistance.

## Bamlanivimab/etesevimab

Bamlanivimab and etesevimab are intravenous investigational neutralising 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 authorised in many countries, including the US, for the treatment and prophylaxis of COVID-19 in children  $\geq 12$  years of age (weighing  $\geq 40$  kg) and adults who are at high risk for progressing to severe disease and/or hospitalisation.[1020] [1021] The European Medicines Agency has issued advice that bamlanivimab/etesevimab may be used in patients  $\geq 12$  years of age who do not require supplemental oxygen and who are at high risk of progressing to severe disease.[1022]

**The US National Institutes of Health guidelines panel recommends bamlanivimab/etesevimab for the treatment of non-hospitalised patients with mild to moderate disease who are at high risk of clinical progression, as defined by the emergency-use authorisation criteria.**[568]

- Bamlanivimab/etesevimab is only recommended in regions where the combined frequency of potentially resistant variants (e.g., Beta, Gamma) is low. The Delta variant has demonstrated susceptibility to bamlanivimab/etesevimab in laboratory studies; therefore, bamlanivimab/etesevimab is recommended for the Delta variant.

**The US National Institutes of Health guidelines panel also recommends bamlanivimab/etesevimab for post-exposure prophylaxis in people who are at high risk for progression to severe disease, provided they meet the following criteria :**[568]

- Not fully vaccinated, or fully vaccinated but not expected to mount an adequate immune response; **AND**
- Recent exposure to an infected individual that is consistent with the US Centers for Disease Control and Prevention close contact criteria, or at high risk of exposure to an infected individual because of recent occurrence of infection in other individuals in the same institutional setting (e.g., nursing homes, prisons).

**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 neutralising antibodies, based on moderate-certainty evidence.**[845]

- 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 hospitalised patients with severe disease, based on moderate-certainty evidence.

### Evidence is emerging.

- A living systematic review and network meta-analysis found that bamlanivimab/etesevimab may reduce the risk of hospitalisation in patients with non-severe disease, but is not different to standard of care for other outcomes (i.e., mortality, viral clearance, time to symptom resolution).[1018]

- A randomised controlled trial in patients with mild to moderate disease found that 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.[1023]
- A randomised controlled trial in high-risk ambulatory patients found that treatment with bamlanivimab/etesevimab reduced the risk of hospitalisation and death compared with placebo and accelerated the reduction in viral load.[1024]

Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug. Bamlanivimab/etesevimab is given as an intravenous infusion.

Circulating SARS-CoV-2 variants may be associated with resistance to monoclonal antibodies. Consult local guidance for details regarding specific variants and resistance.

## Sotrovimab

Sotrovimab is an investigational monoclonal antibody with activity against SARS-CoV-2. It is designed to attach to the spike protein of the virus. Sotrovimab has been authorised for use in many countries, including the US, for the treatment of COVID-19 in children  $\geq 12$  years of age (weighing  $\geq 40$  kg) and adults who are at high risk for progressing to severe disease and/or hospitalisation.[1025] The European Medicines Agency has issued advice that sotrovimab may be used for treatment in patients  $\geq 12$  years of age who do not require supplemental oxygen and who are at high risk of progressing to severe disease.[1026]

**The US National Institutes of Health guidelines panel recommends sotrovimab for the treatment of non-hospitalised patients with mild to moderate disease who are at high risk of clinical progression**, as defined by the emergency-use authorisation criteria.[568]

- Treatment should be started as soon as possible after the patient receives a positive test result and within 10 days of symptom onset.
- Use should be considered in patients with mild to moderate disease who are hospitalised for a reason other than COVID-19 if they otherwise meet the emergency-use authorisation criteria for outpatient treatment.
- Not currently authorised for use in hospitalised patients with severe disease, but may be available through expanded access programmes for patients who are hospitalised with severe disease who have not developed an antibody response or who are not expected to mount an effective immune response (e.g., immunocompromised patients).
- In children, there are insufficient data to recommend either for or against the use of monoclonal antibody products in those who are not hospitalised but have risk factors for severe disease. However, monoclonal antibody products may be considered on a case-by-case basis for non-hospitalised children who meet emergency-use authorisation criteria for high risk of severe disease (especially those who meet more than one criterion or are aged  $\geq 16$  years) in consultation with a paediatric infectious disease specialist.

**The Infectious Diseases Society of America suggests sotrovimab 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 moderate-certainty evidence.[845]

- 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 sotrovimab.
- There are limited data on efficacy in high-risk patients between 12 and 18 years of age.

**Evidence is emerging.**

- A living systematic review and network meta-analysis found that sotrovimab may reduce the risk of hospitalisation in patients with non-severe disease, but is not different to standard of care for other outcomes (i.e., mortality, mechanical ventilation).[1018]
- Authorisation was based on an interim analysis from a phase 1/2/3 randomised controlled trial in 583 non-hospitalised adults with mild to moderate disease that reported an 85% reduction in hospitalisation or death compared with placebo.[1025]

Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug. Sotrovimab is given as an intravenous infusion.

Circulating SARS-CoV-2 variants may be associated with resistance to monoclonal antibodies. Consult local guidance for details regarding specific variants and resistance.

## Regdanvimab

Regdanvimab (formerly known as CT-P59) is an investigational neutralising monoclonal antibody with activity against SARS-CoV-2. Regdanvimab has been granted a conditional marketing authorisation in South Korea for the treatment of adults with mild symptoms who are aged  $\geq 60$  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; the agency is currently evaluating an application for marketing authorisation for this indication.[1027] [1028]

### Evidence is limited.

- According to press releases from the manufacturer, regdanvimab reduced progression from mild-moderate to severe disease by 50%, and from moderate to severe disease by 68%, and reduced the risk of hospitalisation or death by 72% in patients at high risk of progressing to severe disease. However, results from the phase 2/3 trials are yet to be published.[1029] [1030] Regdanvimab has also demonstrated neutralising capability against key emerging mutations, including the Alpha variant.[1031]

## Janus kinase inhibitors

Janus kinase inhibitors are thought to prevent the dysregulated production of proinflammatory cytokines in patients with severe or critical disease. Drugs within this class include baricitinib, tofacitinib, fedratinib, and ruxolitinib. Baricitinib has been granted an emergency-use authorisation in the US for the treatment of suspected or confirmed disease in hospitalised children aged 2 years and older and adults who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (with or without remdesivir).[1032] It has not been authorised for this indication in the UK or Europe; however, the European Medicines Agency is currently evaluating its use in hospitalised patients from 10 years of age who require supplemental oxygen.[1033] Other Janus kinase inhibitors are not authorised for use in patients with COVID-19 as yet.

**The US National Institutes of Health guidelines panel currently recommends baricitinib, in combination with dexamethasone alone or dexamethasone plus remdesivir, in recently hospitalised patients on high-flow oxygen or non-invasive ventilation with rapidly increasing oxygen needs and systemic inflammation. [568]**

- The panel recommends against the use of baricitinib in combination with tocilizumab except in the context of a clinical trial. There is potential for an additive risk of infection.
- There is insufficient evidence to recommend either for or against the use of baricitinib in children.
- The panel recommends tofacitinib may be used as an alternative if baricitinib is not available or it is not feasible to use it.

**The Infectious Diseases Society of America suggests baricitinib in hospitalised adults with severe disease who have elevated inflammatory markers, but who are not on invasive**

**mechanical ventilation.** The panel suggests tofacitinib in hospitalised adults with severe disease who are not on non-invasive or invasive mechanical ventilation.[845]

- Baricitinib is recommended for up to 14 days or until discharge from hospital. It appears to demonstrate the most benefit in those on high-flow oxygen or non-invasive ventilation at baseline. The guideline panel suggests baricitinib with remdesivir, rather than remdesivir alone, in patients who cannot receive a corticosteroid because of a contraindication.
- Tofacitinib appears to demonstrate the most benefit in those on supplemental or high-flow oxygen. Patients treated with tofacitinib should be on at least prophylactic-dose anticoagulation.
- Patients who receive baricitinib or tofacitinib should not receive an interleukin-6 inhibitor.

### Evidence is emerging.

- Emergency-use authorisation of baricitinib was based on a randomised, double-blind, placebo-controlled trial that found baricitinib plus remdesivir reduced time to recovery (defined as either being discharged from the hospital, or being hospitalised 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.[1034]
- 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.[850] [851]
- 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 hospitalised patients.[1035]
- 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 hospitalisation. The evidence was most convincing for baricitinib. Timing of treatment may be important in determining the impact on outcomes.[1036]
- A meta-analysis that included four randomised controlled trials and 1300 participants found that treatment with a Janus kinase inhibitor in addition to standard of care reduced the risk of death by 43%, and mechanical ventilation or ECMO by 36% compared with control.[1037]

Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug. The US Food and Drug Administration has issued a warning about increased risk of serious heart-related events, cancer, blood clots, and death with certain JAK inhibitors.[1038]

## Convalescent plasma

Convalescent plasma is a blood product that contains antibodies to SARS-CoV-2 from patients who have recovered. High-titre convalescent plasma (i.e., plasma with high SARS-CoV-2 antibody titres) has been granted an emergency-use authorisation in the US for the treatment of hospitalised patients early in the disease course, and to those hospitalised patients who have impaired humoral immunity and cannot produce an adequate antibody response. Low-titre convalescent plasma is no longer authorised.[1039] It has not been authorised for this indication in the UK or Europe.

**UK guidance recommends that convalescent plasma *should not* be used in the management of hospitalised patients with suspected or confirmed infection.** [1040]

**The US National Institutes of Health guidelines panel recommends *against* the use of low-titre convalescent plasma.** [568]

- There are insufficient data for the panel to recommend either for or against the use of high-titre convalescent plasma in hospitalised patients with impaired immunity.
- The panel recommends against the use of high-titre convalescent plasma in hospitalised 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 hospitalised 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-titre convalescent plasma in non-hospitalised patients, except in the context of a clinical trial.
- In children, the panel recommends against the use of convalescent plasma in those who are mechanically ventilated. The panel recommends against the use of convalescent plasma in hospitalised children who do not require mechanical ventilation, except in the context of a clinical trial. High-titre convalescent plasma may be considered on a case-by-case basis for hospitalised children who meet the emergency-use authorisation criteria for its use, in consultation with a paediatric infectious disease specialist.

**The Infectious Diseases Society of America suggests *against* the use of convalescent plasma in hospitalised patients**, based on low-certainty evidence.[\[845\]](#)

- 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.

- A living systematic review and network meta-analysis found that convalescent plasma may not confer any meaningful benefit in patients with any disease severity. Whether or not high-titre convalescent plasma confers any benefit remains uncertain.[\[1018\]](#)
- 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.[\[1041\]](#)
- Evidence from meta-analyses is conflicting. While some meta-analyses 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, others have found a reduction in mortality, especially when trials with low-titre convalescent plasma were removed from the analyses.[\[1042\]](#) [\[1043\]](#) [\[1044\]](#) [\[1045\]](#) [\[1046\]](#)
- The UK RECOVERY trial found that high-titre convalescent plasma did not improve 28-day mortality or other prespecified outcomes (hospital discharge within 28 days, progression to invasive mechanical ventilation) in hospitalised patients compared with usual care.[\[1047\]](#)
- Emergency-use authorisation was based on the preprint (not peer reviewed) publication of an open-label, multicentre, expanded access programme study of over 35,000 patients that found convalescent plasma lowered 7-day mortality by 9% in hospitalised patients when given within 3 days of diagnosis, and by 12% when given 4 or more days later.[\[1048\]](#)

## Intravenous immunoglobulin

Intravenous immunoglobulin (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 immunoglobulin.** [\[568\]](#)

### Evidence is limited.

- A living systematic review and network meta-analysis found that IVIG may not confer any meaningful benefit in patients with any disease severity.[\[1018\]](#)
- A meta-analysis of four clinical trials and three cohort studies with 825 hospitalised patients found that IVIG reduced mortality in patients with critical disease; however, there was no significant difference between the severe and non-severe subgroups.[\[1049\]](#)

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.<sup>[1050]</sup> Ivermectin is already approved in some countries for parasitic infections, but is off-label for this indication.

**The World Health Organization does not recommend ivermectin except in the context of a clinical trial.** <sup>[795]</sup>

- 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.<sup>[796]</sup> <sup>[797]</sup> For most key outcomes, including mortality, mechanical ventilation, hospital admission, duration of hospitalisation, 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.** <sup>[568]</sup>

- The Infectious Diseases Society of America suggest against the use of ivermectin in outpatients and hospitalised patients outside of the context of a clinical trial.<sup>[845]</sup>

### Evidence is emerging.

- A meta-analysis of 24 randomised controlled trials with 3400 participants found moderate-certainty evidence that ivermectin provided a significant survival benefit when used for treatment. Low-certainty evidence supports a likely clinical benefit in terms of improvement and deterioration. Low-certainty evidence also suggests a significant effect in prophylaxis. Overall, the evidence suggested that early use may reduce morbidity and mortality.<sup>[1051]</sup>
- A meta-analysis of 18 randomised controlled trials found statistically significant reductions in mortality, time to clinical recovery, and time to viral clearance with use of ivermectin.<sup>[1052]</sup>
- A meta-analysis of nine randomised controlled trials found that ivermectin was associated with decreased mortality compared with standard of care or placebo, with a low certainty of evidence.<sup>[1053]</sup>
- Another meta-analysis of six randomised controlled trials found a preliminary positive effect on mortality associated with use in hospitalised patients. The authors concluded that this effect warrants further appropriately designed, large-scale randomised 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.<sup>[1054]</sup>
- 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.<sup>[1055]</sup>
- 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.<sup>[1056]</sup>
- One meta-analysis of 10 randomised controlled trials found that ivermectin did not reduce all-cause mortality, length of hospital stay, or respiratory viral clearance in patients with mild to moderate disease.<sup>[1057]</sup>
- The PRINCIPLE trial in the UK is currently investigating the use of ivermectin.<sup>[1058]</sup>

Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

## Molnupiravir

An experimental oral antiviral drug that is metabolised into a ribonucleoside analogue that resembles cytidine. The manufacturer has submitted an emergency-use authorisation application to the US Food and Drug Administration for the treatment of mild to moderate disease in at-risk adults. If authorised, it will be the first oral antiviral medication available for COVID-19.



**Evidence is limited.**

- According to a press release from the manufacturer, molnupiravir significantly reduced the risk of hospitalisation or death in at-risk, non-hospitalised adults with mild to moderate disease in a planned interim analysis of the phase 3 MOVE-OUT trial (775 patients). Molnupiravir reduced the risk of hospitalisation or death by approximately 50% (absolute risk reduced from 14% to 7%), with efficacy unaffected by the timing of symptom onset, underlying risk factors, or SARS-CoV-2 variant type. Recruitment into the study is being stopped early due to these positive results.[1059] [1060]

**Anakinra**

Anakinra is an intravenous/subcutaneous interleukin-1 inhibitor. It is being trialled 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 European Medicines Agency has started to evaluate an application to extend the use of anakinra to include the treatment of COVID-19 in adults with pneumonia who are at risk of developing severe respiratory failure.[1061]

**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.** [568]

**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 haemophagocytic lymphohistiocytosis triggered by SARS-CoV-2 or a similar coronavirus.[1062]

**Evidence is limited.**

- A systematic review and meta-analysis of nine studies (eight observational studies and one randomised controlled trial) found that anakinra significantly reduced mortality in hospitalised patients with moderate to severe disease. Subgroup analysis identified patients with C-reactive protein levels >100 mg/L may benefit most.[1063]
- A systematic review and meta-analysis of nine observational studies found that anakinra reduced the need for invasive mechanical ventilation and mortality risk in hospitalised non-intubated patients compared with standard of care.[1064]
- A systematic review and meta-analysis of 15 studies (five observational studies, five case series, four case reports, and one randomised controlled trial) also found that anakinra significantly reduced the need for invasive mechanical ventilation and mortality risk compared with standard care alone.[1065]

Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

**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.[1066] 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 hospitalised patients.** [600]

- 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 non-hospitalised patients.** [568]

- The panel recommends against its use in hospitalised patients.

**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.[\[1067\]](#)

#### Evidence is limited.

- A living systematic review and network meta-analysis found that colchicine may reduce mortality (low-certainty evidence) and probably reduces the duration of hospitalisation (low-certainty evidence) compared with standard care.[\[850\]](#) [\[851\]](#)
- 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 randomised clinical trials.[\[1068\]](#) Another systematic review and meta-analysis supports the reduction in mortality; however, meta-regression analysis found that the benefit was reduced as age increased.[\[1069\]](#)
- A double-blind, placebo-controlled, randomised trial of over 4400 non-hospitalised 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.[\[1070\]](#) More randomised controlled trials are required.
- 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.[\[1071\]](#)
- Studies are inconclusive in patients with mild to moderate disease, and adverse effects are significant.[\[1072\]](#)

Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

## Stem cell therapy

Mesenchymal stem cells are an investigational product and have been studied for their immunomodulatory properties. It is thought that they can reduce the pathological changes that occur in the lungs, and inhibit the cell-mediated immune inflammatory response.[\[1073\]](#) 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.[\[568\]](#)

#### Evidence is limited.

- A systematic review and meta-analysis found that mesenchymal stem cell therapy significantly reduced the incidence of adverse events and mortality.[\[1074\]](#)
- 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 enrolment, although the trial will be completed with the patients currently enrolled, with follow-up as planned.[\[1075\]](#)

## 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.[\[568\]](#)

**Evidence is limited.**

- The WHO Solidarity trial found that interferon beta-1a appears to have little or no effect on hospitalised patients, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[1012]
- A randomised, placebo-controlled, phase 2 trial found that nebulised interferon beta-1a was associated with a higher odds of clinical improvement and more rapid recovery.[1076]
- 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.[1077] [1078]

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.[1079] [1080] [1081] [1082]

**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. [568]**

**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.[1083]

**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.[1084]
- Meta-analyses found that vitamin D might be associated with improved clinical outcomes and that there may be a potential role for vitamin D supplementation in reducing disease severity, but noted that additional evidence is required.[1085] [1086] The evidence is currently insufficient to support the routine use of vitamin D as its effectiveness appears to depend on the dose used, baseline vitamin D levels, and the severity of disease.[1087]
- A pilot randomised controlled trial found that high-dose calcifediol significantly reduced the need for intensive care unit treatment in hospitalised patients, and may improve clinical outcomes.[1088]

**Vitamin C**

Vitamin C supplementation has shown promise in the treatment of viral infections.[1089] High-dose intravenous vitamin C is being trialled in some centres for the treatment of severe disease.[1090]

**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 non-critically ill or critically ill patients.[568]**

**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.[1091]

**Fluvoxamine**

Fluvoxamine is a selective serotonin-reuptake inhibitor that has anti-inflammatory effects.[1092] 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. [568]**

**Evidence is limited.**

- A preliminary double-blind, randomised 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.[1093]
- A prospective cohort study in the setting of a mass outbreak found that fluvoxamine may prevent clinical deterioration requiring hospitalisation and symptoms persisting beyond 2 weeks.[1094]

Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

## Nitazoxanide

Nitazoxanide is a broad-spectrum antiparasitic agent with in vitro activity against SARS-CoV-2 that is already approved in some countries for indications such as cryptosporidiosis and giardiasis, but is off-label for this indication.

**The US National Institutes of Health guidelines panel recommends *against* the use of nitazoxanide except in the context of a clinical trial. [568]**

**Evidence is limited.**

- A randomised double-blind pilot trial found an evident decrease in the time for hospital discharge, faster evolution to reverse transcription polymerase chain reaction negativity, and a higher reduction of inflammatory markers among patients treated with nitazoxanide compared with placebo. However, this was a small, proof-of-concept trial.[1095]
- A multicentre, randomised, double-blind, placebo-controlled trial in adults with mild disease found that nitazoxanide was associated with reduced viral load but not reduced time to symptom resolution.[1096]

Consult local drug formulary for information about contraindications, cautions, adverse effects, and drug interactions before prescribing this drug.

## Granulocyte-macrophage colony-stimulating factor (GM-CSF) inhibitors

GM-CSF inhibitors (e.g., lenzilumab, mavrilimumab, otilimab) may mitigate lung inflammation in severe and critical disease by minimising downstream production of numerous pro-inflammatory mediators involved in the pathogenesis of disease. These agents are currently investigational. The US Food and Drug Administration has declined an emergency-use authorisation for lenzilumab to treat hospitalised COVID-19 patients as it was unable to conclude that the known and potential benefits of lenzilumab outweigh the known and potential risks of its use.[1097] The UK Medicines and Healthcare products Regulatory Agency is currently reviewing an application for a conditional marketing authorisation for lenzilumab.

**The US National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either *for or against* the use of GM-CSF inhibitors. [568]**

**Evidence is limited.**

- A meta-analysis found that GM-CSF inhibitors were associated with a 23% reduction in the risk of mortality, but increased the risk of intensive care unit admission.[1098]

- A small multicentre, double-blind, randomised, placebo-controlled trial found that there was no significant difference in the proportion of patients with severe disease, hypoxaemia, and systemic hyperinflammation who were free of supplemental oxygen at day 14 after treatment with mavrilimumab compared with placebo.[1099]

## Inhaled corticosteroids

Inhaled budesonide is undergoing clinical trials and shows promise.[1100] It is already approved in some countries for indications such as asthma and COPD, but is off-label for this indication.

**The UK Medicines and Healthcare products Regulatory Agency states that inhaled budesonide 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):[1101]

- 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.[1102]

**The US National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either *for or against* the use of inhaled budesonide.** [568]

**Evidence is limited.**

- The PRINCIPLE trial has reported a 3-day median benefit in self-reported recovery for patients in the community setting who are at higher risk of complications and who received inhaled budesonide.[1103] The impact on hospitalisation rates or mortality has not been established.

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 National Institute for Health and Care Excellence *does not* recommend the use of azithromycin or doxycycline.** [600]

- The guideline panel considered that the results from studies of azithromycin for moderate to critical disease in the hospital setting and mild to moderate disease in the community setting showed no meaningful benefit in any of the critical outcomes.
- The UK Medicines and Healthcare products Regulatory Agency recommends that azithromycin and doxycycline should not be used within primary care (or hospitalised patients for azithromycin) unless there are additional indications for which their use remains appropriate.[1104]

**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.[568]

**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 hospitalisation rate, intensive care unit admission, need for respiratory support, or mortality rate compared with control.[1105]

- 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 hospitalised patients compared with usual standard care alone.[1106]
- The UK PRINCIPLE trial found that doxycycline use was not associated with clinically meaningful reductions in time to recovery or hospital admissions or deaths in patients with suspected disease in the community who were at high risk of adverse outcomes.[1107]
- The ATOMIC2 open-label randomized trial found that adding azithromycin to standard of care treatment in non-hospitalised patients with mild to moderate disease did not reduce the risk of subsequent hospital admission or death.[1108]
- An interim analysis of the trial concluded that azithromycin and doxycycline offered no meaningful beneficial effect, in terms of time to recovery, hospitalisation, or death compared with standard of care in patients aged 50 years and over who were treated at home in the early stages of infection.[1104] [1109]

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.[795] [796] [797]

**The US National Institutes of Health guidelines panel recommends *against* the use of lopinavir/ritonavir** except in the context of a clinical trial.[568]

- The Infectious Diseases Society of America also recommends against the use of lopinavir/ritonavir based on moderate-certainty evidence.[845]

**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 hospitalised patients, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[1012]
- The UK RECOVERY trial found that there is no beneficial effect of lopinavir/ritonavir in hospitalised 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).[1110]
- A systematic review and meta-analysis found that lopinavir/ritonavir had no significant advantage in efficacy over standard care, no antivirals, or other antiviral treatments.[1111]

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.[1112] [1113] 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.[795] [796] [797]

- 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.[1114] [1115]

**The US National Institutes of Health guidelines panel recommends *against* the use of hydroxychloroquine or chloroquine (with or without azithromycin) in hospitalised or non-hospitalised patients.** [568]

- The panel also recommends against the use of hydroxychloroquine for post-exposure prophylaxis.

**The Infectious Diseases Society of America also strongly recommends *against* the use of hydroxychloroquine or chloroquine in hospitalized patients** based on moderate-certainty evidence.[845]

- The guideline also recommends against the use of hydroxychloroquine for post-exposure prophylaxis.

**Evidence does not support the use of these drugs for treatment.**

- A Cochrane review found that hydroxychloroquine has no clinical benefit in hospitalised patients, with moderate- to high-certainty evidence from several randomised 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 post-exposure prophylaxis is limited.[1116]
- 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 hospitalisation; however, there is insufficient evidence from cohort studies.[1117] [1118]
- The WHO Solidarity trial found that hydroxychloroquine appears to have little or no effect on hospitalised patients, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[1012]
- The UK RECOVERY trial found that hydroxychloroquine does not reduce the risk of death at 28 days compared with usual care.[1119]
- 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.[1056]

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.

- [\[Global coronavirus COVID-19 clinical trial tracker\]](#)

International trials to identify treatments that may be beneficial, such as the World Health Organization's Solidarity trial, and the UK's randomised evaluation of COVID-19 therapy (RECOVERY) trial, are ongoing.

- [\[RECOVERY trial\]](#)
- [\[WHO: COVID-19 "Solidarity" therapeutics trial\]](#)

## Primary prevention

### Vaccines

- **The World Health Organization (WHO) has authorised the use of the following six vaccines for global use below.** [342] [343] [344] [345] [346] [347] Other vaccines have also been authorised in specific countries (e.g., Sputnik V® in Russia, Covaxin® in India, Convidecia® in Latin America).[348] [349]
  - Pfizer/BioNTech (mRNA) [350]
  - Moderna (mRNA)
  - AstraZeneca (adenovirus vector)
  - Janssen (adenovirus vector)
  - Sinopharm's Covilo® (inactivated SARS-CoV-2 virus)
  - Sinovac's CoronaVac® (inactivated SARS-CoV-2 virus)
  - [WHO: COVID-19 vaccines technical documents]
- **Vaccine availability and immunisation programmes differ between countries.**
  - Vaccines are generally available under emergency-use, provisional, or conditional marketing authorisations, but may be approved in some countries.
  - Consult your local guidance for information.
- **Patients must give informed consent prior to vaccination.**
  - For consent to immunisation to be valid, it must be given freely, voluntarily, and without coercion by an appropriately informed person.[351]
- **Protection starts around 14 days after full vaccination.**
  - Vaccination may not protect all vaccine recipients.
  - Have a high level of suspicion of reported symptoms post-vaccination, and avoid dismissing complaints as vaccine-related until vaccine recipients are tested and true infection is ruled out.[352]
  - Duration of protection after vaccination is unknown and is still being assessed in ongoing clinical trials.
- **Breakthrough infections are possible.**
  - Breakthrough infections that have resulted in hospitalisation or death, as well as mild or asymptomatic infections, have been reported in fully vaccinated people.[353] [354] [355] [356]
  - Risk factors for breakthrough infection after the first dose may include frailty in older adults ≥60 years, living in deprived areas, and obesity.[357] Older age, male sex, increasing number of comorbidities, hospitalisation in the previous 4 weeks, high-risk occupation, care home residence, socioeconomic deprivation, and smoking history were all associated with an increased risk of hospitalisation or death in patients with breakthrough infections after the first dose.[358]
  - In the US, 30,177 cases of hospitalised or fatal vaccine breakthrough cases have been reported (as of 4 October 2021) with 6617 deaths. However, breakthrough cases who are not hospitalised or fatal are no longer reported in the US, which means the true incidence of breakthrough infection is unknown.[359]
  - One small observational study in patients admitted to hospital with a positive test found that 46% of fully vaccinated people with breakthrough infection were asymptomatic, while 26% had severe or critical disease, 20% had moderate disease, and 7% had mild disease.[360] In another study, the rate of severe disease or death per 1000 person-days was 4.08 among those with breakthrough infections and 3.6 among unvaccinated matched controls with infection.[361]
  - Emerging data from the US and UK indicates that fully vaccinated people with breakthrough infections have similar viral loads of the Delta variant compared with unvaccinated people, and are therefore equally likely to transmit the infection.[362] [363]
- **Vaccinated people should continue to follow local public health recommendations.**



- There is insufficient evidence on the extent of vaccine impact on virus transmission.[\[342\]](#) [\[343\]](#) [\[344\]](#) [\[345\]](#) [\[346\]](#) [\[347\]](#)
- Evidence of efficacy in the real world is emerging (see Vaccines: real world efficacy data below).

|                   | <b>Pfizer/BioNTech<br/>COVID-19 vaccine</b>   | <b>Moderna<br/>COVID-19 vaccine</b>   | <b>AstraZeneca<br/>COVID-19 vaccine</b>  | <b>Janssen<br/>COVID-19 vaccine</b>   |
|-------------------|---|---|--|---|
| Brand name        | <b>Comirnaty®</b>   | <b>Spikevax®</b>  | <b>Vaxzevria®</b>  | To be confirmed   |
| Synonyms          | COVID-19 mRNA vaccine BNT162b2; tozinameran   | COVID-19 vaccine mRNA-1273; elasomeran  | COVID-19 vaccine ChAdOx1 S recombinant; AZD 1222; SII Covishield®  | Ad26.COV2.S; JNJ-78436725   |
| Vaccine type      | mRNA vaccine  |   | Adenovirus vector vaccine  |   |
| Indication        | Active immunisation of individuals $\geq 12$ years of age   |   | Active immunisation of individuals $\geq 18$ years of age  |   |
| Authorised dose*  | <p><b>TWO-DOSE REGIMEN</b></p> <p><b>0.3 mL</b> (30 micrograms) IM; second dose at least <b>21 days</b> after first dose</p> <p>A third booster dose may be administered at least 8 weeks after the second dose in certain people (e.g., immunocompromised)</p> | <p><b>TWO-DOSE REGIMEN</b></p> <p><b>0.5 mL</b> (100 micrograms) IM; second dose at least <b>28 days</b> after first dose</p> | <p><b>TWO-DOSE REGIMEN</b></p> <p><b>0.5 mL</b> IM (<math>5 \times 10^{10}</math> viral particles); second dose <b>4-12 weeks</b> after first dose</p> <p>A third booster dose may be administered at least 8 weeks after the second dose in certain people (e.g., immunocompromised)</p> <p>Different brands of the AstraZeneca vaccine are considered equivalent and interchangeable</p> | <p><b>SINGLE-DOSE REGIMEN</b></p> <p><b>0.5 mL</b> IM (<math>5 \times 10^{10}</math> viral particles)</p> |
| Contraindications | Hypersensitivity to active substance or any excipients; immediate allergic reaction to first dose of two-dose regimens (should not get second dose)   |   | Hypersensitivity to active substance or any excipients; immediate allergic reaction to first dose (should not get second dose)<br><br>Individuals who have experienced   | Hypersensitivity to active substance or any excipients  |

|                | Pfizer/BioNTech COVID-19 vaccine  | Moderna COVID-19 vaccine  | AstraZeneca COVID-19 vaccine   | Janssen COVID-19 vaccine   |
|----------------|---|---|--|--|
|                |   |   | thrombosis with with thrombocytopenia syndrome following vaccination with the AstraZeneca vaccine<br><br>History of capillary leak syndrome  |  |
| Cautions       | History of anaphylaxis/allergic reactions<br><br>Acute severe febrile illness or acute infection<br><br>Bleeding disorders or anticoagulation<br><br>Immunocompromised<br><br>Pregnancy and breastfeeding |   | History of anaphylaxis/allergic reactions<br><br>Acute severe febrile illness or acute infection<br><br>Bleeding disorders or anticoagulation<br><br>Immunocompromised<br><br>Pregnancy and breastfeeding<br><br>History of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2) or cerebral venous sinus thrombosis<br><br>Use may be restricted (or restricted in some age groups) in some countries | History of anaphylaxis/allergic reactions<br><br>Acute severe febrile illness or acute infection<br><br>Bleeding disorders or anticoagulation<br><br>Immunocompromised<br><br>Pregnancy and breastfeeding<br><br>History of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2) |
| Adverse events | <i>Common</i> : headache; arthralgia; myalgia; injection-site reactions; fatigue; fever; chills; nausea; vomiting; diarrhoea; influenza-like illness  | <i>Common</i> : headache; arthralgia; myalgia; injection-site reactions; fatigue; fever; chills; nausea; vomiting; rash; axillary lymphadenopathy | <i>Common</i> : headache; arthralgia; myalgia; injection-site reactions; pain in extremity (vaccinated arm); fatigue; malaise; fever;  | <i>Common</i> : injection-site reactions; headache; cough; fatigue; myalgia; arthralgia; nausea; fever; chills<br><br><i>Uncommon</i> : anaphylaxis;   |

|   | <b>Pfizer/BioNTech<br/>COVID-19 vaccine</b>   | <b>Moderna<br/>COVID-19 vaccine</b>   | <b>AstraZeneca<br/>COVID-19 vaccine</b>   | <b>Janssen<br/>COVID-19 vaccine</b>   |
|---|---|---|---|---|
|   | <i>Uncommon</i> :<br>lymphadenopathy;<br>malaise;<br>anaphylaxis;<br>hypersensitivity;<br>acute peripheral<br>facial paralysis;<br>insomnia; pain<br>in extremity<br>(vaccinated arm);<br>extensive swelling<br>of vaccinated limb;<br>face swelling (if<br>dermatological<br>fillers present);<br>myocarditis/<br>pericarditis | (on same side<br>as injection site);<br>delayed injection-<br>site reaction<br><br><i>Uncommon</i> :<br>acute peripheral<br>facial paralysis;<br>hypoesthesia;<br>anaphylaxis;<br>hypersensitivity;<br>face swelling (if<br>dermatological<br>fillers present);<br>myocarditis/<br>pericarditis;<br>dizziness | chills; nausea;<br>vomiting; diarrhoea;<br>influenza-like illness<br><br><i>Uncommon</i> :<br>lymphadenopathy;<br>dizziness;<br>somnolence;<br>decreased appetite;<br>abdominal pain;<br>hyperhidrosis;<br>pruritus; rash;<br>urticaria;<br>angioedema;<br>anaphylaxis;<br>hypersensitivity;<br>neuroinflammatory<br>disorders;<br>thrombosis with<br>thrombocytopenia<br>syndrome;<br>thrombocytopenia;<br>capillary leak<br>syndrome; Guillain-<br>Barre syndrome | urticaria;<br>hypersensitivity;<br>tremor;<br>hyperhidrosis;<br>rash; sneezing;<br>oropharyngeal pain;<br>pain in extremity;<br>back pain; muscular<br>weakness;<br>asthenia; malaise;<br>thrombosis with<br>thrombocytopenia<br>syndrome |
| Interactions                                | Interactions with other vaccines/drugs have not been studied (WHO recommends a minimum of 14 days between COVID-19 vaccines and other vaccines; however, the US Food and Drug Administration recommends that COVID-19 vaccines and other vaccines may now be administered without regard to timing)                             |   |   |   |
| UK Summary<br>of Product<br>Characteristics | <a href="#">[Pfizer/BioNTech<br/>COVID-19 vaccine]</a>  | <a href="#">[Moderna<br/>COVID-19 vaccine]</a>  | <a href="#">[AstraZeneca<br/>COVID-19 vaccine]</a>  | <a href="#">[Janssen COVID-19<br/>vaccine]</a>  |

Comparison of vaccines authorised for use in the UK. Information is based on the Summary of Product Characteristics (see links in tables). Consult your local drug formulary or guidelines for the prescribing information for your location. \*Dose schedules may differ in some locations. Last updated: 13 October 2021

### Vaccines: dose schedules

- **Dose schedules may differ between countries depending on vaccine coverage rates and supply constraints.**
  - The WHO recommends that countries that have not yet achieved high vaccine coverage rates in high-priority groups and who are experiencing a high incidence of cases combined with vaccine supply constraints should focus on achieving a high first-dose coverage in the high-priority groups by extending the interdose interval of mRNA vaccines by up to 12 weeks.<sup>[342] [343]</sup> The WHO recommends an interval of 8 to 12 weeks between the two doses of the AstraZeneca vaccine (rather than 4 to 12 weeks as the manufacturer recommends) as two-dose efficacy and immunogenicity increase with a longer interdose interval.<sup>[344]</sup>
  - In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) recommends that the second dose of a vaccine should be routinely scheduled between 8 and 12 weeks after the first

dose for all available vaccines. The main exception to the 8-week lower interval would be those about to commence immunosuppressive treatment. Evidence shows that delaying the second dose to 12 weeks after the first improves the boosting effect.

- [\[Public Health England: COVID-19 vaccination information for healthcare practitioners\]](#)
  - 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 emphasise 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.
  - [\[CDC: interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States\]](#)
- **Use the same vaccine product for both doses.**
    - There is a lack of data on using two different vaccines to complete a two-dose schedule. However, recommendations will be updated as further information becomes available on interchangeability between vaccines.[\[342\]](#) [\[343\]](#) [\[344\]](#) [\[345\]](#) [\[346\]](#) [\[347\]](#)
    - Heterologous vaccination schedules have been found to induce a robust humoral and cellular immune response after a second dose of an mRNA vaccine in people primed with the AstraZeneca vaccine 8 to 12 weeks earlier, and were associated with an acceptable and manageable reactogenicity profile in small cohort studies.[\[364\]](#) [\[365\]](#) [\[366\]](#) [\[367\]](#) However, an interim analysis of a UK multicentre, participant-masked, randomised 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 aged 50 years and older.[\[368\]](#) [\[369\]](#) The difference between studies may be explained, in part, by the difference in administration intervals used between the studies (i.e., 28 days versus 8 to 12 weeks).
    - Further safety and efficacy data are required before heterologous schedules can be recommended.[\[370\]](#)
  - **Booster doses may be recommended in some countries.**
    - Observational data to support the safety and efficacy of booster doses are emerging, but their follow-up periods are too short to assess long-term effectiveness, and the number of trial participants is small.[\[371\]](#) [\[372\]](#) [\[373\]](#) The studies also focus on plasma neutralising antibodies and don't take into account the protection provided by cellular immunity.
    - In the US, the Food and Drug Administration has authorised an additional (third) dose of the Pfizer/BioNTech and Moderna mRNA vaccines in moderately to severely immunocompromised people at least 28 days after the completion of the initial vaccine series.[\[374\]](#) It has also authorised a single booster dose of the Pfizer/BioNTech vaccine to be administered at least 6 months after the completion of the primary series in certain people.[\[375\]](#) The US Centers for Disease Control and Prevention recommends that the following groups should receive a booster dose: people aged  $\geq 65$  years and residents in long-term care settings; and people aged 50 to 64 years with underlying medical conditions. It recommends that the following groups may receive a booster dose: people aged 18 to 49 years with underlying medical conditions based on their individual benefits and risks; and people aged 18 to 64 years who are at increased risk for exposure and transmission because of occupational or institutional setting based on their individual benefits and risks.[\[376\]](#)
    - In the UK, the JCVI advises that a third primary dose be offered to people aged  $\geq 12$  years with severe immunosuppression. The third primary dose should ideally be given at least 8 weeks after the second dose, with special attention paid to current or planned immunosuppressive therapies. Choice of vaccine depends on age and the previous vaccine used.[\[377\]](#) The JCVI has also advised that people who were vaccinated during phase 1 of the vaccination programme in priority groups 1 to 9 (i.e., adults  $\geq 50$  years of age, frontline health and social care workers, people living in residential care homes, people aged 16 to 49 years with underlying conditions that put them at higher risk and their adult carers, adult household contacts of immunosuppressed people) should be offered a booster dose no earlier than 6

months after completion of their primary course.[378] Influenza and COVID-19 vaccines may be administered together where operationally practical, although there are a lack of data to support this.[379]

- In Europe, the European Medicines Agency recommends that a booster dose of an mRNA vaccine may be given to people with severely weakened immune systems, at least 28 days after their second dose. Although there is no direct evidence that the ability to produce antibodies in these patients offered protection, it is expected that the extra dose would increase protection at least in some patients. The risk of side effects after a booster is not known and is being carefully monitored.[380]
- Consult your local guidance for information.

## Vaccines: safety signals

### • Vaccine-induced immune thrombocytopenia and thrombosis (VITT)

- VITT has been reported after vaccination with the adenovirus vector-based COVID-19 vaccines (e.g., AstraZeneca, Janssen).[381] Regulatory agencies have confirmed that a causal relationship is plausible.[382] [383] [384] [385] [386] [387] There has been no safety signal for VITT following receipt of mRNA vaccines, although a small number of cases have been reported.[388]
- In the UK, monitoring of the Yellow Card reporting system has detected 421 reports of VITT after administration of the AstraZeneca vaccine, with 72 deaths, an overall case fatality rate of 17% (as of 29 September 2021). The overall risk has been estimated to be 15.1 cases per million doses after first or unknown doses (20.5 per million in people aged 18-49 years), and 1.9 cases per million doses after the second dose.[389]
- In the US, the overall risk of VITT with the Janssen vaccine has currently been estimated to be 3 cases per million people who receive the vaccine, with the reporting rate highest among women aged 30 to 49 years (8.8 cases per million doses).[390]
- Some countries have permanently stopped the use of these vaccines in their immunisation programme.[391] [392] Other countries have implemented age-related prescribing restrictions. For example, in the UK, the JCVI advises that it is preferable for adults aged <40 years without underlying health conditions that put them at higher risk of severe disease to receive an alternative to the AstraZeneca vaccine, where available.[393] [394] Age cut-offs vary widely between countries so it is important to consult your local guidance.
- The World Health Organization recommends that people who have had VITT following the first dose of the AstraZeneca vaccine should not receive a second dose of the same vaccine.[344]
- The US Centers for Disease Control and Prevention recommends that people with a history of an episode of an immune-mediated syndrome characterised by thrombosis and thrombocytopenia, such as heparin-induced thrombocytopenia, should be offered an mRNA vaccine instead of the Janssen vaccine (the AstraZeneca vaccine is not currently available in the US) if it has been ≤90 days since their illness resolved. After 90 days, patients may be vaccinated with any authorised vaccine.[376]
- Pregnancy predisposes to thrombosis; therefore, women should discuss with their healthcare professional whether the benefits of having these vaccines outweigh the risks.[383]
- The European Medicines Agency's safety committee has also concluded that there is a possible link to rare cases of venous thromboembolism that is distinct from VITT with the Janssen vaccine.[395]
- See the [Complications] section for more information on this condition, including diagnosis and management.

### • Myocarditis and pericarditis

- Myocarditis and pericarditis can occur in very rare cases following vaccination with mRNA vaccines.[396] [397] [398]
- Cases occurred predominantly in adolescents and young adults 12 to 29 years of age, more often in males than in females, more often following dose 2 than dose 1, and typically within 7 days after vaccination.[399]
- In the UK, monitoring of the Yellow Card reporting system estimates the overall risk of myocarditis to be 7.6 cases per million people (Pfizer/BioNTech vaccine), 29.8 cases per million

people (Moderna vaccine), and 2.4 cases per million people (AstraZeneca vaccine) who receive the vaccine. The overall risk of pericarditis has been estimated to be 5.9 cases per million people (Pfizer/BioNTech vaccine), 17.7 cases per million people (Moderna vaccine), and 3.7 cases per million people (AstraZeneca vaccine) who receive the vaccine.[389]

- In the US, monitoring by the Vaccine Adverse Event Reporting System (VAERS) detected 40.6 cases per million second doses of vaccine in males aged 12 to 29 years, and 2.4 per million in males aged  $\geq 30$  years.[399]
  - In Israel, a large study estimates the incidence to be 2.13 cases per 100,000 people, with the highest incidence between the ages of 16 to 29 years (10.7 cases per 100,000 people).[400]
  - The US Centers for Disease Control and Prevention recommends that people with a history of myocarditis or pericarditis may receive any vaccine after the episode has completely resolved. People with a history of myocarditis or pericarditis after their first dose of an mRNA vaccine should defer receiving their second dose, or may consider it under certain circumstances provided the episode has fully resolved.[376]
  - Consider myocarditis and pericarditis in adolescents or young adults with acute chest pain, shortness of breath, or palpitations.[401]
  - The short-term clinical course appears to be mild in most patients; however, the long-term risks remain unknown.[402]
  - Some countries have suspended the use of the Moderna vaccine in their immunisation programme following the detection of signals of an increased risk of side effects such as myocarditis and pericarditis.[403]
- **Anaphylaxis**
    - Severe allergic reactions, including anaphylaxis, have been reported after vaccination. Reactions may be due to the presence of lipid pegylated ethylene glycol (PEG), or PEG derivatives such as polysorbates.[404] [405]
    - In the UK, monitoring of the Yellow Card reporting system has detected 486 cases of anaphylaxis with the Pfizer/BioNTech vaccine, 820 cases with the AstraZeneca vaccine, and 40 cases with the Moderna vaccine (as of 29 September 2021).[389]
    - In the US, monitoring by 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.[406]
    - Globally, the incidence of anaphylaxis post-vaccination has been reported to be 7.91 cases per million based on available data.[407]
    - A history of anaphylaxis to any component of the vaccine is a contraindication to vaccination. People who have an anaphylactic reaction following the first dose of the vaccine should not receive a second dose of the same vaccine. Observe people for 15 to 30 minutes after vaccination in healthcare settings where anaphylaxis can be immediately treated.[342] [343] [344] [345] [346] [347] Consult local guidelines for recommendations on vaccinating people with a history of allergies or anaphylaxis as guidance may differ across locations.
    - A small retrospective study found that most patients who have immediate and potentially allergic reactions to the first dose of an mRNA vaccine tolerate the second dose; however, further research is required.[408]
  - **Capillary leak syndrome**
    - Capillary leak syndrome has been reported after vaccination with the AstraZeneca vaccine. Most cases occurred in women within 4 days of vaccination, and half of the patients had a history of capillary leak syndrome.[409]
    - The European Medicines Agency advises that the AstraZeneca and Janssen vaccines are contraindicated in people with a history of capillary leak syndrome.[409] [410]
    - Severe, life-threatening flares have also been reported with mRNA vaccines.[411] Cases of capillary leak syndrome have also been reported in patients with COVID-19.[412]
    - In the UK, monitoring of the Yellow Card reporting system has detected 12 cases of capillary leak syndrome with the AstraZeneca vaccine (as of 29 September 2021). Of these reports, 2 people had a history of capillary leak syndrome.[389]
  - **Bell's palsy**

- Clinical trials of the mRNA vaccines showed an imbalance in the incidence of Bell's palsy following vaccination compared with the placebo arm of each trial, suggesting vaccination may be associated with Bell's palsy.[413] Cases have also been reported outside of clinical trials. A case of two discrete episodes in one patient shortly after receiving both the first and second doses of the Pfizer/BioNTech vaccine has been reported.[414]
  - Analysis of data from the World Health Organization's pharmacovigilance database up until early March 2021 failed to identify a higher risk of facial paralysis after vaccination.[415]
  - A case-control study also failed to identify a higher risk after recent vaccination with the Pfizer/BioNTech vaccine.[416]
  - EudraVigilance data indicate a much higher frequency of facial paralysis after the Pfizer/BioNTech vaccine (13.6 cases per million doses) compared with the AstraZeneca vaccine (4.1 cases per million doses), indicating that the risk may be higher with mRNA vaccines.[417]
  - In the UK, the Yellow Card system has found that the number of reports of facial paralysis received so far is similar to the expected natural rate and does not currently suggest an increased risk following vaccination.[389]
  - An increased risk of Bell's palsy has been reported after vaccination with Sinovac's CoronaVac® (inactivated SARS-CoV-2 virus) vaccine compared with the Pfizer/BioNTech vaccine.[418]
- **Lymphadenopathy**
    - Ipsilateral axillary/supraclavicular lymphadenopathy has been reported within 2 to 4 days after vaccination. It occurs more commonly after the second dose, and more commonly with the Moderna vaccine compared with the Pfizer/BioNTech vaccine.[419]
    - The incidence has been reported to be 3% in one small cohort of vaccinated people.[420] A large study from Israel identified an excess risk of lymphadenopathy among vaccinated people (78.4 events per 100,000 people).[421]
    - Although UK guidelines currently recommend a 2-week suspected-cancer referral for unexplained axillary lymphadenopathy in those aged >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 examination and no history of breast cancer. Further examination up to 2 weeks later is recommended, with referral to secondary care for those with non-resolving lymphadenopathy. An urgent referral to the breast clinic is advisable in patients with current or previous history of breast cancer.[422]
  - **Guillain-Barre syndrome**
    - Guillain-Barre syndrome has been reported after vaccination and a casual relationship is possible.[423] [424] [425] [426]
    - In the UK, monitoring of the Yellow Card reporting system has detected 428 cases of Guillain-Barre syndrome and 26 cases of Miller Fisher syndrome with the AstraZeneca vaccine, 53 cases of Guillain-Barre syndrome with the Pfizer/BioNTech vaccine, and 3 reports of Guillain-Barre syndrome with the Moderna vaccine (as of 29 September 2021). The UK Medicines and Healthcare products Regulatory Agency is reviewing these cases to assess whether there is an increased risk of Guillain-Barre syndrome after vaccination. Based on the available evidence at this stage, the agency is not able to confirm or rule out a causal relationship with the vaccine.[389]
    - In the US, monitoring by VAERS detected 1 case of Guillain-Barre syndrome per 100,000 doses of the Janssen vaccine as of 24 July 2021. The median time to onset following vaccination was 13 days (range 10-42 days), and 93% of cases were serious.[427]
    - The US Centers for Disease Control and Prevention recommends that people with a history of Guillain-Barre syndrome should consider an mRNA vaccine instead of the Janssen vaccine (the AstraZeneca vaccine is not currently available in the US).[376]
  - **Menstrual disorders/unexpected vaginal bleeding**
    - Menstrual disorders including heavier than usual periods, delayed periods, and unexpected vaginal bleeding have been reported after vaccination (39,330 reports as of 29 September 2021).[389]



- Current evidence does not suggest an increased risk of either menstrual disorders or unexpected vaginal bleeding following the vaccines; however, the UK Medicines and Healthcare products Regulatory Agency is closely monitoring the situation.[389]
- **Immune thrombocytopenic purpura**
  - Immune thrombocytopenic purpura has been reported after vaccination with the AstraZeneca and Janssen vaccines.[428] [429]
  - The European Medicines Agency's safety committee has concluded that immune thrombocytopenia is a possible adverse effect of both vaccines, and that people with a history of a thrombocytopenic disorder should have their platelets monitored for the first 4 weeks following vaccination.[395]
- **Facial swelling and eruptions**
  - 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.[430]
  - Facial pustular neutrophilic eruptions have been reported after vaccination with mRNA vaccines.[431]
- **Delayed-onset local reactions**
  - 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.[432] [433]
- **Vasovagal reactions**
  - Anxiety-related reactions, including vasovagal reactions and hyperventilation, have been reported after vaccination. Ensure precautions are in place to avoid injury from fainting.[434]
- **Other**
  - The following adverse effects have also been added to the European prescribing information: paraesthesia and hypoaesthesia, asthenia, lethargy, decreased appetite, and nocturnal hyperhidrosis (Pfizer/BioNTech); erythema multiforme (Pfizer/BioNTech and Moderna); transverse myelitis, tinnitus, and dizziness (Janssen).[429] [435] [436] [437]
  - Cases of Stevens-Johnson syndrome, cutaneous vasculitis, glomerulonephritis, nephrotic syndrome, multisystem inflammatory syndrome, immune myositis, adult-onset Still's disease, appendicitis, necrotising pancreatitis, varicella zoster virus reactivation, and Graves' disease have been reported after vaccination; however, causality is yet to be established.[438] [421] [439] [440] [441] [442] [443] [444] [445] [446] [447]
- **Report all suspected adverse reactions after vaccination via your local reporting system.** This is mandatory in some countries.
  - UK: [Yellow Card: coronavirus (COVID-19)]
  - US: [Vaccine Adverse Event Reporting System (VAERS)]
  - Europe: [EudraVigilance]
  - International: [WHO: Adverse Event Following Immunization (AEFI) form]
- Surveillance of adverse events is extremely important, and may reveal additional, less frequent serious adverse events not detected in clinical trials. The mRNA vaccines have not been authorised for use in humans previously, so there is no long-term safety and efficacy data available for these types of vaccines.

### Vaccines: special patient populations

- There are limited or no data available from clinical trials about the use of vaccines in specific patient populations.
- **Pregnancy**
  - Use caution in pregnant women as there are limited safety and efficacy data available. Preliminary data from the v-safe pregnancy registry and VAERS in the US have not shown 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.[448]
  - The WHO recommends vaccines in pregnant women when the benefits outweigh the potential risks. The WHO does not recommend pregnancy testing prior to vaccination, or delaying pregnancy or terminating a pregnancy because of vaccination.[342] [343] [344] [345] [346] [347]
  - The UK Joint Committee on Vaccination and Immunisation (JCVI) advises that pregnant women should be offered the 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.[449] [450]
  - The Royal College of Obstetricians and Gynaecologists in the UK recommends that vaccination should be offered to pregnant women at the same time as the rest of the population, based on age and clinical risk. Pregnant women should be offered the Pfizer/BioNTech or Moderna vaccines unless they have already had one dose of the AstraZeneca vaccine, in which case they should complete the course with the AstraZeneca vaccine.[451]
  - The US Centers for Disease Control and Prevention recommends that all pregnant women or women who are thinking about or trying to become pregnant should be vaccinated.[376] Pregnant women who choose to receive a vaccine are encouraged to enroll in the v-safe programme. [CDC: v-safe COVID-19 vaccine pregnancy registry]
  - The American College of Obstetricians and Gynecologists recommends that pregnant women have access to vaccines. Women should have access to available information about the safety and efficacy of the vaccine, including information about data that are not available. A conversation between the patient and the clinical team may assist with the decision. Pregnant women who decline vaccination should be supported in their decision.[452]
- **Breastfeeding**
  - Use caution in breastfeeding women as there are limited safety and efficacy data available. Studies have found robust secretion of SARS-CoV-2 specific immunoglobulin A (IgA) and IgG antibodies in breast milk after vaccination.[453] [454] Vaccine-associated mRNA was not detected in 13 milk samples collected 4 to 48 hours after vaccination from 7 breastfeeding individuals.[455] However, further research is required.
  - The WHO recommends that vaccines may be used in lactating women as in other adults. The WHO does not recommend discontinuing breastfeeding because of vaccination.[342] [343] [344] [345] [346] [347]
  - The Royal College of Obstetricians and Gynaecologists in the UK recommends that breastfeeding women can receive a vaccine and there is no need to stop breastfeeding to have the vaccine.[451]
  - The US Centers for Disease Control and Prevention recommends that all lactating women should be vaccinated, although it acknowledges that there are limited safety data available in lactating women and the infant.[376]
  - The American College of Obstetricians and Gynecologists recommends that vaccines should be offered to lactating individuals similar to non-lactating individuals.[452]
- **Children and adolescents**
  - The Pfizer/BioNTech vaccine has been authorised for use in young people aged 12 to 15 years in many countries, including the UK, Europe, and the US.[456] [457] [458] [459] Authorisation was based on an ongoing randomised, placebo-controlled clinical trial in the US of over 2000 participants that reports 100% efficacy from 7 days after the second dose.[460] Due to the limited number of children included in the study, the trial could not have detected rare adverse effects. Safety monitoring of VAERS noted over 9000 reports of adverse events post-vaccination

in adolescents aged 12 to 17 years (as of 16 July 2021), 9.3% of which were for serious adverse events including myocarditis (4.3%).<sup>[461]</sup>

- The WHO recommends considering the use of the Pfizer/BioNTech vaccine in children aged 12 to 15 years only when high vaccine coverage with 2 doses has been achieved in high-priority groups. Children aged 12 to 15 years with comorbidities that put them at significantly higher risk of serious disease, alongside other high-risk groups, may be offered vaccination.<sup>[342]</sup>
  - The UK's JCVI recommends that children who are at increased risk of serious disease are offered the Pfizer/BioNTech vaccine, including children aged 12 to 15 years with severe neurodisabilities, Down's syndrome, immunosuppression, and multiple or severe learning disabilities. The JCVI also recommends that children aged 12 to 17 years who live with an immunosuppressed person should be offered the vaccine. The JCVI advises that all 16- to 17-year-olds should now be offered a first dose of the Pfizer/BioNTech vaccine. This is in addition to the existing offer of 2 doses of vaccine to 16- to 17-year-olds who are in at-risk groups. Pending further evidence on effectiveness and safety in this age group, a second vaccine dose is anticipated to be offered later to increase the level of protection and contribute towards longer-term protection.<sup>[462]</sup> The JCVI does not recommend vaccination in young people aged 12 to 15 years who do not have underlying health conditions as the health benefits of vaccination were only marginally greater than the potential known harms.<sup>[463]</sup> Despite this, the UK government recommends offering a vaccine to all 12- to 15-year-olds.<sup>[378]</sup>
  - The European Medicines Agency has also approved the Moderna vaccine in young people aged 12 to 17 years.<sup>[464]</sup> An ongoing phase 2/3 randomised controlled trial found that the Moderna vaccine has an acceptable safety profile in adolescents aged 12 to 17 years, and the immune response was similar to that in young adults.<sup>[465]</sup>
  - There are currently no efficacy or safety data for children <12 years of age; however, clinical trials are in progress, and a decision about the 5- to 11-year-old age group is expected soon.
  - Recommendations on vaccinating children and adolescents vary; check your local guidance.
- **Older people and people with comorbidities**
    - The WHO recommends that older people (without an upper age limit) and people with comorbidities that have been identified as increasing the risk for severe disease may be vaccinated.<sup>[342] [343] [344] [345] [346] [347]</sup>
  - **Current or previous SARS-CoV-2 infection**
    - Delayed vaccination is recommended in people with current acute COVID-19 (or any other acute febrile illness) until they have recovered from the acute illness and the criteria for discontinuation of isolation have been met.<sup>[342] [343] [344] [345] [346] [347]</sup>
    - Delayed vaccination is recommended in people who previously received passive antibody therapy for COVID-19 (for at least 90 days).<sup>[342] [343] [344] [345] [346] [347]</sup>
    - 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 immunisation after infection may be advisable.<sup>[342] [343] [344] [345] [346] [347]</sup>
    - Emerging evidence suggests that one dose of the vaccine may be sufficient for people who have already been infected with SARS-CoV-2.<sup>[466] [467]</sup> Emerging preprint (not peer reviewed) data suggests that people who have had previous SARS-CoV-2 infection are unlikely to become reinfected whether or not they receive the vaccine.<sup>[468]</sup> A higher rate of adverse effects has been reported after the first dose of the vaccine in people with a history of SARS-CoV-2 infection compared with participants who had not previously been infected, but not after the second dose.<sup>[469]</sup>
  - **Immunocompromised**
    - The WHO recommends that immunocompromised people and people living with HIV who have no contraindications to vaccination may be vaccinated if they are part of a group recommended for vaccination.<sup>[342] [343] [344] [345] [346] [347]</sup>

- Emerging preprint (not peer reviewed) data from the UK indicate that the Pfizer/BioNTech and AstraZeneca vaccines are effective at preventing symptomatic disease in the majority of people with underlying health conditions who are clinically vulnerable. Efficacy was reduced in immunocompromised patients after one dose; however, after a second dose there was only a small and non-significant reduction in vaccine efficacy.[470] Another preprint (not peer reviewed) study (the OCTAVE trial) found that 11% of immune vulnerable patient groups failed to generate SARS-CoV-2 spike protein antibodies 4 weeks after two doses.[471] A third (booster) dose is now being tested in these patients.[472] Further research is needed to understand vaccine efficacy among immunosuppressed groups.
  - A small study found that the AstraZeneca vaccine was safe and immunogenic in people with HIV infection with well-suppressed viraemia and good CD4 cell counts. Further data are required to test the durability of this response and in those who are viraemic or have low CD4 cell counts.[473]
  - A third/booster dose of an mRNA vaccine may be recommended in certain immunocompromised patients (see above).
- Autoimmune disease**
    - The WHO recommends that people with autoimmune conditions who have no contraindications to vaccination may be vaccinated if they are part of a group recommended for vaccination.[342] [343] [344] [345] [346] [347]
    - It is uncertain whether vaccines may cause an exacerbation of pre-existing autoimmune diseases; however, there are case reports of new or flares of existing autoimmune conditions in Israel.[474] Available evidence suggests that vaccination does not trigger disease exacerbation or relapse or vaccine failure in patients with multiple sclerosis; however, evidence is limited and vaccine timing may need to be individually tailored depending on the disease-modifying agent the patient is taking.[475] A small study in patients with systemic lupus erythematosus found that the risk of disease flare was approximately 3%; however, the study had limitations (no control group, self-reporting).[476] A case of reactivation of IgA vasculitis has been reported.[477]
    - Seroconversion rates after vaccination are lower in patients with immune-mediated inflammatory disease, and some therapies (e.g., anti-CD20 therapies such as rituximab and anticytotoxic T-lymphocyte associated antigen therapies such as abatacept) may result in poorer responses.[478] In patients with psoriasis, seroconversion rates after vaccination were lower in patients receiving immunosuppressants, with the lowest rate in those receiving methotrexate. Neutralising activity was preserved in those receiving targeted biological agents.[479] Patients with a history of taking CD20 B-cell-depleting treatments may have blunted humoral and cell-mediated immune responses elicited by mRNA vaccines.[480]
    - A third/booster dose of an mRNA vaccine may be recommended in certain immunocompromised patients (see above).
  - Malignancy and solid organ or stem cell transplant recipients**
    - Emerging data suggest that vaccine efficacy may be lower in cancer patients and solid organ transplant recipients.[481] [482] [483] [484] [485] [486] [487] [488] [489] [490]
    - Frequent and high levels of humoral responses have been identified in allogeneic haematopoietic stem cell transplant recipients after two vaccine doses.[491] [492]
    - Patients with lymphoma can develop a robust serological response as early as 6 months after treatment.[493]
    - Patients with haematological malignancies mount blunted and heterogeneous antibody responses. People treated with Bruton tyrosine kinase inhibitors, ruxolitinib, venetoclax, and anti-CD20 antibody therapies appear to be most affected.[494] [495]
    - A third/booster dose of an mRNA vaccine may be recommended in certain immunocompromised patients (see above).

### Vaccines: real world efficacy data

- Initial authorisation of vaccines was based on interim analyses of ongoing phase 3 clinical trials with a median follow-up of 2 months. Overall vaccine efficacy for preventing symptomatic infection

- was reported as 95% (Pfizer/BioNTech), 94.1% (Moderna), 74% (AstraZeneca), and 66.9% (Janssen).[496] [497] [498] [499]
- Observational evidence from the initial global vaccine rollout suggested real-world efficacy in reducing the rate of symptomatic or asymptomatic infection, disease severity, hospitalisation, death, and possibly even reinfection.[500] [501] [502] [503] [504] [505] [506] [507] [508] [509] [510] [511] [512] [513] [514] [515] [516] [517] [518] [519]
  - Evidence suggests that current vaccines may be effective against the Delta variant after two doses, but with reduced efficacy after one dose. Efficacy is comparable to vaccine efficacy against hospitalisation from the Alpha variant, but may be less effective against infection compared with the Alpha variant.[520] [521] [522] [523]
  - Evidence suggests that vaccine efficacy decreases over time following initial vaccination and immunity wanes, especially against the Delta variant. Humoral response appears to be substantially decreased among men, people aged ≥65 years, and immunosuppressed people.[524] [525] [526] [527] [528] [529]
    - Recent data from the UK estimated vaccine efficacy to be 49% to 58% in late July 2021.[530]
    - Recent data from Israel estimated vaccine efficacy to be 39% in late July 2021.[531]
    - Recent data from the US estimates that vaccine efficacy against infection declined from 88% during the first month after full vaccination to 47% after 5 months, based on data up to August 2021. However, vaccine efficacy against hospitalisation was high (93%) overall up to 6 months.[532] Data from Qatar show a similar trend.[533]
    - Emerging evidence (including preprint data that has not been peer reviewed) suggests that natural immunity may confer longer-lasting and stronger protection against infection, symptomatic disease, and hospitalisation caused by the Delta variant, or other variants of concern, compared with vaccine-induced immunity.[350] [534]
  - **Previous trials of coronavirus vaccines identified cellular immunopathology and antibody-dependent enhancement as potential safety issues.** [535] [536]
    - 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.[496] [497] The possibility of antibody-dependent enhancement in people receiving vaccines based on the original virus strain spike sequence who are then exposed to the Delta variant has not been studied.[537]

### Infection prevention and control for healthcare professionals

- Consult local infection prevention and control protocols; only basic principles from the World Health Organization guidelines are detailed here.[538] [539]
- Screen all people, including patients, visitors, and others entering the facility, for COVID-19 at the first point of contact with the health facility to allow for early recognition.
- Immediately isolate all suspected or confirmed cases in a well-ventilated 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 adequately ventilated room and ensure there is at least 1 metre (3 feet) between patients.
- Implement standard precautions at all times:
  - 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 suspected or confirmed cases are admitted:

- Wear a medical mask, gloves, an appropriate gown, and eye/face protection (e.g., goggles or a face shield)
- Respirators may be used instead of medical masks in all settings based on health workers' values and preferences (including settings where aerosol-generating procedures are not performed)
- Appropriate mask fitting should always be ensured
- Use single-use or disposable equipment.
- Implement airborne precautions when performing aerosol-generating procedures, including placing patients in a negative pressure room and wearing a particulate respirator.
  - Some countries and organisations 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.
- Appropriate personal protective equipment gives healthcare workers a high level of protection.
  - 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 serological testing when they returned home, despite all participants having direct contact with COVID-19 patients and performing at least one aerosol-generating procedure.[540]
  - 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.[541]
- Avoid in-person assessment of patients with suspected COVID-19 in primary care when possible to avoid infection. Most patients can be managed remotely by telephone or video consultations.[542]
  - [\[BMJ: covid-19 in primary care \(UK\)\]](#)
  - [\[BMJ: covid-19 – a remote assessment in primary care\]](#)
- Detailed infection prevention and control guidance is available:
  - [\[WHO: infection prevention and control during health care when coronavirus disease \(COVID-19\) is suspected or confirmed\]](#)
  - [\[CDC: interim infection prevention and control recommendations for healthcare personnel during the coronavirus disease 2019 \(COVID-19\) pandemic\]](#)
  - [\[BMJ: covid-19 – PPE guidance\]](#)

### Infection prevention and control for the general public

- Public health recommendations vary between countries and you should consult your local guidance. It is generally recommended that people stay at least 1 to 2 metres (3-6 feet) away from others (recommendations vary between countries), wash their hands often with soap and water (or hand sanitiser that contains at least 60% alcohol), cover coughs and sneezes, wear a mask, avoid crowds and poorly ventilated spaces, clean and disinfect high touch surfaces, monitor their health and self-isolate or seek medical attention if necessary, and get vaccinated.[543] [544]
  - [\[WHO: coronavirus disease \(COVID-19\) advice for the public\]](#)
- **Alcohol-based hand sanitiser** : may be recommended in situations where it is not possible to use soap and water; however, adverse events have been reported including:[545] [546] [547] [548]
  - Headache, nausea, and dizziness due to inhalation of vapours, especially in enclosed or poorly ventilated spaces

- Methanol poisoning (including cases of permanent blindness and death) due to ingestion or frequent repeated topical use
  - Accidental ingestion and unintentional ocular exposures, especially by children
  - Antimicrobial resistance.
- **Face masks** : the WHO advises that in areas of known or suspected community or cluster transmission, people should wear a non-medical 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; in situations when physical distancing cannot be maintained and the person has a higher risk of severe complications (e.g., older age, underlying condition); carers and those living with suspected or confirmed cases when in the same room, regardless of whether the case has symptoms. Children aged up to 5 years should not wear masks for source control, while a risk-based approach is recommended for children aged 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.[77]
    - There is no high-quality or direct scientific evidence to support the widespread use of masks by healthy people in the community setting. Data on effectiveness is based on limited and inconsistent observational and epidemiological studies.[77]
    - The only randomised controlled trial to investigate the efficacy of masks in the community found that the recommendation to wear surgical masks when outside the home did not reduce infection compared with a no mask recommendation. However, the study did not assess whether masks could decrease disease transmission from mask wearers to others (source control).[549] Evidence from randomised controlled trials for other respiratory viral illnesses shows no significant benefit of masks in limiting transmission but is of poor-quality and not SARS-CoV-2-specific.[550]
    - A Cochrane review found that wearing a mask may make little to no difference in how many people caught influenza-like illnesses. However, this was based on low-certainty evidence, and does not include results of studies from the current pandemic.[551]
    - A living rapid review found that the evidence for mask effectiveness for respiratory tract infection prevention is stronger in healthcare settings compared with community settings; however, direct evidence on comparative effectiveness in SARS-CoV-2 infection is insufficient. The strength of evidence for any mask use versus non-use in community settings is low.[552] [553]
    - Cloth masks have limited efficacy in preventing viral transmission compared with medical-grade masks and the efficacy is dependent on numerous factors (e.g., material type, number of layers, fitting, moisture level), and may result in increased risk of infection.[554] [555]
    - There are harms and disadvantages of wearing masks (e.g., headache, breathing difficulties, facial skin lesions, psychological issues, difficulty communicating, increased viral load).[77] There are insufficient data to quantify all of the adverse effects that might reduce the acceptability, adherence, and effectiveness of face masks.[556] [557]
    - [BMJ: mask related acne ('maskne') and other facial dermatoses]
  - **Non-pharmaceutical interventions** : many countries have implemented non-pharmaceutical interventions in order to reduce and delay viral transmission (e.g., social distancing, city lockdowns, stay-at-home orders, curfews, non-essential business closures, bans on gatherings, school and university closures, remote working, quarantine of exposed people).
    - Implementing any non-pharmaceutical interventions was associated with a significant reduction in case growth when comparing countries with more restrictive non-pharmaceutical interventions to countries with less restrictive non-pharmaceutical interventions. However, there was no clear, significant beneficial effect of more restrictive non-pharmaceutical interventions compared with less restrictive nonpharmaceutical interventions in any of the countries studied.[558]
    - 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.[559]
  - **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 (e.g., cancer, severe respiratory condition, chronic kidney disease,

immunosuppression). Shielding involves minimising all interactions between those who are extremely vulnerable and other people to protect them from coming into contact with the virus.

- The UK shielding programme ended in September 2021. The guidance for clinically extremely vulnerable people is to follow the same advice as the rest of the population, with any additional precautions determined by the individual and their healthcare professional.[\[560\]](#)
- Shielding advice may be available in other countries; consult local public health guidance.
- **Travel-related control measures** : many countries have implemented measures including complete or partial closure of borders, entry or exit screening, and/or quarantine of travellers.
  - Low- to very low-certainty 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).[\[561\]](#)
  - 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.[\[562\]](#) Entry screening at three major US airports found a low yield of laboratory-diagnosed cases (one case per 85,000 travellers) between January and September 2020.[\[563\]](#)
  - 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 modelling studies that make assumptions on important model parameters.[\[564\]](#)
  - The psychosocial effects of enforced quarantine may have long-lasting repercussions.[\[565\]](#)  
[\[566\]](#)
  - [\[Public Health England: travel abroad - step by step\]](#)

### Lifestyle modifications

- Lifestyle modifications (e.g., smoking cessation, weight loss) may help to reduce the risk of infection, and may be a useful adjunct to other interventions.[\[567\]](#)
- The WHO recommends that tobacco users stop using tobacco given the well-established harms associated with tobacco use and second-hand smoke exposure.[\[238\]](#) Public Health England also recommends stopping smoking.
  - [\[Public Health England: COVID-19 – advice for smokers and vapers\]](#)

### Pre-exposure or post-exposure prophylaxis

- There are no treatments recommended for pre-exposure prophylaxis, except in the context of a clinical trial.[\[568\]](#)
- Casirivimab/imdevimab has been granted an emergency-use authorisation/conditional marketing authorisation for post-exposure prophylaxis in select people in some countries. See the [\[Emerging\]](#) section for more information.

## Patient discussions

### General discussions

- Communicate with patients and their families and carers, and support their mental wellbeing to help alleviate any anxiety and fear they may have. Signpost to charities and support groups.[\[600\]](#)



- 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, diarrhoea, or vomiting in children may indicate paediatric inflammatory multisystem syndrome (PIMS). Reassure the patient that they are likely to feel much better in a week if their symptoms are mild.[600]
- Discuss who to contact if their symptoms get worse, or if PIMS is suspected. Offer telephone or video consultations as appropriate.[600]
- 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.[600]

### Pulse oximetry

- Patients may be required to use a pulse oximeter in the home setting. Patient education and appropriate follow-up are required.
  - [\[Health Education England: adult pulse oximetry monitoring video\]](#)

### 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:
  - [\[WHO: coronavirus disease \(COVID-19\) travel advice\]](#)
  - [\[CDC: COVID-19 – travel\]](#)
  - [\[NaTHNaC: travel health pro\]](#)
  - [\[Public Health England: travel abroad from England during coronavirus \(COVID-19\)\]](#)
  - [\[UK Department for Transport\]](#)
  - [\[Smartraveller Australia: COVID-19\]](#)
  - [\[Government of Canada: coronavirus disease \(COVID-19\) – travel, testing, quarantine and borders\]](#)
  - [\[Ministry of Manpower Singapore: advisories on COVID-19\]](#)

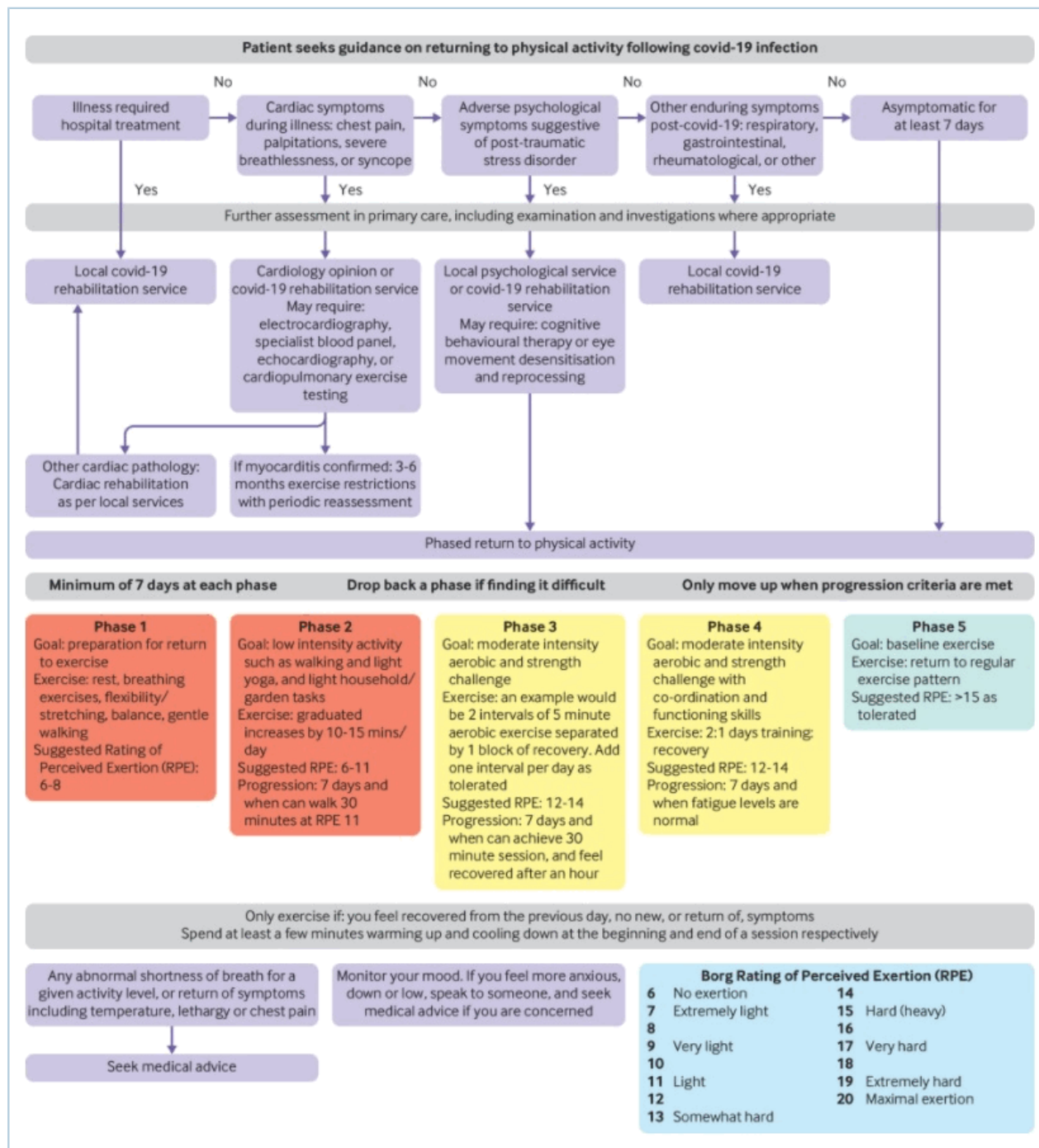
### Pets and animals

- 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.[1407]

- 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 may be more susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, while dogs and other livestock have no or low susceptibility. Non-human primates (gorillas) and large cats in captivity (lions, tigers, pumas, cougars, snow leopards) and domestic pet cats have tested positive after contact with symptomatic humans. 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.[1408] [1409] [1410] [1411] [1412]
- 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.[1413]
- [CDC: animals and COVID-19]

### 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.[1414]
- Guidance on return to sports after COVID-19 in children is available from the American Academy of Pediatrics:
  - [AAP: COVID-19 interim guidance – return to sports and physical activity]
- Clinical or subclinical myocarditis has been reported in competitive athletes with recent infection that restricts them from training and competitive play.[1415]



*Suggested return to physical activity after COVID-19: risk stratification to exclude features suggestive of myocarditis or post-acute COVID-19 and phased resumption of physical activity after 7 days without symptoms*

BMJ. 2021;372:m4721

**Resources**

- [WHO: coronavirus disease (COVID-19) pandemic]
- [CDC: COVID-19]
- [NHS England: coronavirus (COVID-19)]
- [NHS England: COVID-19 patient rehabilitation booklet]
- [NHS England: your COVID recovery]

# Monitoring

## Monitoring

**Regularly monitor the following in hospitalised patients** to facilitate early recognition of deterioration and monitor for complications:[120] [611]

- Vital signs (temperature, respiratory rate, heart rate, blood pressure, oxygen saturation)
- Haematological 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

- Utilise medical early warning scores that facilitate early recognition and escalation of treatment of deteriorating patients (e.g., National Early Warning Score 2 [NEWS2], Paediatric Early Warning Signs [PEWS]) where possible.[120]
- There are a lack of data on the value of using these scores in patients with COVID-19 in the primary care setting.
  - A systematic review and meta-analysis found that the NEWS2 score had moderate sensitivity and specificity in predicting the deterioration of patients with COVID-19. The score showed good discrimination in predicting the combined outcome of the need for intensive respiratory support, admission to the intensive care unit, or in-hospital mortality.[604]
- 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.[1391]

### 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.[888] Perform fetal growth ultrasound 14 days after resolution of symptoms.[890]

### 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.[120]
- 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.[1392]
- More than half of patients discharged from hospital had lung function and chest imaging abnormalities 12 weeks after symptom onset.[1393] Pulmonary function tests may reveal altered diffusion capacity, a restrictive pattern, or an obstructive pattern.[1394]

### Prognostic scores

- Various prognostic and clinical risk scores are being researched or developed for COVID-19 (e.g., A-DROP, APACHE II, CALL, COPE, COVID-GRAM, COVID-19MRS, COVID-19 SEIMC, QCOVID, SCARP, SOARS, 3F, 4C).[1395] [1396] [1397] [1398] [1399] [1400] [1401] [1402] [1403] [1404] [1405] [1406] However, further external validation across various populations is needed before their use can be recommended.

- The World Health Organization recommends using clinical judgement, 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.<sup>[120]</sup>

# Complications

| Complications  | Timeframe       | Likelihood  |
|--|-----------------|-------------|
| <b>post-intensive care syndrome</b>  | <b>variable</b> | <b>high</b> |
| <p>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 minimised with medication management, physical rehabilitation, family support, and follow-up clinics.[568]</p>   |                 |             |
| <b>venous thromboembolism</b>  | <b>variable</b> | <b>high</b> |
| <p>The pooled incidence of venous thromboembolism, deep vein thrombosis, and pulmonary embolism among hospitalised 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.[1199] While venous thromboembolism appears to be frequent in hospitalised COVID-19 patients, one systematic review and meta-analysis found that the overall risk of venous thromboembolism did not significantly differ between COVID-19 and non-COVID-19 cohorts with similar disease severity, except for patients admitted to the intensive care unit. This suggests that severe disease that requires intensive care unit admission may be a risk factor for developing venous thromboembolism.[1200] Pulmonary embolism is rare in patients presenting to the accident and emergency department, but the incidence is approximately 9-fold higher than in the general non-COVID-19 population.[1201] COVID-19 patients with thromboembolic events have 1.93 times the odds of dying compared with patients without venous thromboembolism.[1202] Thromboembolic events are rare in children.[1203]</p> <p>Coagulopathy in COVID-19 has a prothrombotic character, which may explain reports of thromboembolic complications.[1204] 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).[1205] Thrombotic events may be due to cytokine storm, hypoxic injury, endothelial dysfunction, hypercoagulability, and/or increased platelet activity.[1206]</p> <p>The risk factors with the most evidence for being predictive of venous thromboembolism are older age and elevated D-dimer levels.[1207] Male sex, obesity, mechanical ventilation, intensive care unit admission, severe parenchymal abnormalities, and elevated white blood cells have also been identified as risk factors for pulmonary embolism.[1208] Patients with very high D-dimer levels have the greatest risk of thrombosis and may benefit from active monitoring.[755] [756]</p> <p>If venous thromboembolism is suspected, perform a computed tomographic angiography or ultrasound of the venous system of the lower extremities.[1209]</p> <p>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.[568]</p> <p>Initial parenteral anticoagulation with a low molecular weight heparin or unfractionated heparin is preferred in acutely ill hospitalised 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</p> |                 |             |

| Complications   | Timeframe       | Likelihood  |
|---|-----------------|-------------|
| <p>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.[832]</p> <p>The American Society of Hematology has published draft guideline recommendations on the use of anticoagulation in patients with COVID-19.[1210]</p> <p>A high incidence (14.7%) of asymptomatic deep vein thrombosis was reported in a cohort of patients with COVID-19 pneumonia.[1211] An autopsy study of 12 patients revealed deep vein thrombosis in 58% of patients in whom venous thromboembolism was not suspected before death.[1212] These studies highlight the importance of having a high suspicion for venous thromboembolism in patients who have signs of coagulopathy, including elevated D-dimer level.</p> <p>While these patients are at higher risk of thrombotic events, they may also be at an elevated risk for bleeding. In a small retrospective study, 11% of patients at high risk of venous thromboembolism also had a high risk of bleeding.[1213]</p> <p>Antiphospholipid antibodies (mainly lupus anticoagulant) were detected in nearly half of patients in one meta-analysis and systematic review, with an increased prevalence in patients with severe and critical disease. However, there does not currently appear to be any association between this finding and disease outcomes (e.g., thrombosis, mortality).[1214]</p> <p>It has been suggested that a new term (e.g., COVID-19-associated pulmonary thrombosis, diffuse pulmonary intravascular coagulopathy, or microvascular COVID-19 lung vessels obstructive thrombo-inflammatory syndrome [MicroCLOTS]) be used rather than the term pulmonary embolism as it has been hypothesised that the pathophysiology is different; local thrombi are formed in the lung vessels due to a local inflammatory process rather than the classical emboli coming from elsewhere in the body.[1215] [1216] [1217] However, this has not become accepted practice.</p> <p>Cases of arterial thrombosis, cerebral venous thrombosis, splanchnic vein thrombosis, and acute limb ischaemia secondary to thrombosis have been reported.[1218] [1219] [1220] [1221] [1222] [1223] The prevalence of arterial thromboembolism appears to be substantial at 3.9%; however, evidence is limited.[1199]</p> |                 |             |
| <b>cardiovascular complications</b>   | <b>variable</b> | <b>high</b> |
| <p>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.[1224] [1225] These complications can occur on presentation or develop as the severity of illness worsens.[1226] 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.[1227]</p> <p>Cardiovascular complications have been reported in 14.1% of patients during hospitalisation, with an overall case fatality rate of 9.6%. Patients with pre-existing cardiovascular comorbidities or risk factors are at higher risk for cardiovascular complications and mortality. Complications include arrhythmias or palpitations (18.4%), myocardial injury (10.3%), angina (10.2%), acute myocardial infarction (3.5%), and acute heart failure (2%).[1228] Cases of fulminant myocarditis, cardiac tamponade, cor pulmonale, takotsubo syndrome, and pericarditis have also been reported.[1229] [1230] [1231] [1232] [1233] A Cochrane review found that the most common cardiovascular complications were cardiac arrhythmias, heart failure, and arterial and venous occlusive events.[193] The most common arrhythmias reported during hospitalisation were supraventricular and ventricular arrhythmias. QT interval changes and ST-segment deviation have been reported.[1234] QT interval prolongation has been reported independent of whether the patient is taking drugs that prolong the QT interval.[1235]</p>   |                 |             |

| Complications   | Timeframe       | Likelihood  |
|---|-----------------|-------------|
| <p>Laboratory biomarkers may help identify those at greater risk of developing cardiovascular complications and of death.<a href="#">[193]</a> Elevated cardiac biomarkers and emerging arrhythmia are associated with the development of severe disease and the need for intensive care admission.<a href="#">[1236]</a></p> <p>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 non-invasive or invasive ventilation, and have a higher risk of thromboembolic events and septic shock compared with patients without a history of cardiac disease.<a href="#">[1226]</a> <a href="#">[1237]</a> <a href="#">[1238]</a> <a href="#">[1239]</a> <a href="#">[1240]</a></p> <p>Perform 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 ischaemia; 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.<a href="#">[600]</a></p> <p>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.<a href="#">[600]</a></p> <p>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.<a href="#">[1227]</a> 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.<a href="#">[1241]</a></p> <p>Infection may have longer-term implications for overall cardiovascular health; however, further research is required.<a href="#">[1242]</a> 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 pre-existing conditions, severity and overall course of the acute illness, and time from the original diagnosis.<a href="#">[1243]</a></p> |                 |             |
| <b>acute kidney injury</b>  | <b>variable</b> | <b>high</b> |
| <p>The pooled incidence of acute kidney injury is 10.6%, which is higher than the incidence in hospitalised patients without COVID-19.<a href="#">[1244]</a> Incidence varies widely across studies, with estimates of approximately 20% reported in some meta-analyses.<a href="#">[1245]</a> <a href="#">[1246]</a> 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.<a href="#">[1244]</a> Presence of diabetes, hypertension, chronic kidney disease, and tumour history was associated with increased incidence of acute kidney injury at population level across different settings. Patients with a history of kidney transplant had a higher incidence of acute kidney injury; however, their risk of death was lower.<a href="#">[1245]</a> Use of renin-angiotensin-aldosterone system blockade drugs is also significantly associated with an increased risk of acute kidney injury in hospitalised patients.<a href="#">[1247]</a></p> <p>In a small UK cohort, 29% of hospitalised 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 paediatric inflammatory multisystem syndrome.<a href="#">[1248]</a></p> <p>Can develop at any time before, during, or after hospital admission. Causes include haemodynamic changes, hypovolaemia, viral infection leading directly to kidney tubular injury, thrombotic vascular processes, glomerular pathology, or rhabdomyolysis. May be associated with haematuria, proteinuria, and abnormal serum electrolyte levels (e.g., potassium, sodium).<a href="#">[600]</a> Direct kidney infection has been confirmed in an autopsy study of a single patient.<a href="#">[1249]</a></p>  |                 |             |



| Complications   | Timeframe       | Likelihood    |
|---|-----------------|---------------|
| <p>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 haemodialysis if CRRT is not available or possible.<a href="#">[568]</a></p> <p>Monitor patients with chronic kidney disease for at least 2 years after acute kidney injury.<a href="#">[600]</a></p> <p>Cases of nephritis and collapsing glomerulopathy have been reported.<a href="#">[1250]</a> <a href="#">[1251]</a></p>  |                 |               |
| <b>acute liver injury</b>   | <b>variable</b> | <b>medium</b> |
| <p>Liver injury may be associated with pre-existing liver disease, viral infection, drug toxicity, systemic inflammation, hypoxia, or haemodynamic 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 was 19% and 22%, respectively. The prevalence of hypertransaminasaemia was higher in patients with severe disease compared with patients with non-severe disease.<a href="#">[1252]</a> 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.<a href="#">[1253]</a></p> <p>Risk factors associated with severe liver injury include older age, pre-existing liver disease, and severe COVID-19.<a href="#">[1254]</a></p> <p>Medications used in the treatment of COVID-19 (e.g., lopinavir/ritonavir, remdesivir, tocilizumab) may have a detrimental effect on liver injury.<a href="#">[1255]</a></p> <p>Guidelines on the management of liver derangement in patients with COVID-19 have been published.<a href="#">[1256]</a></p>  |                 |               |
| <b>neurological complications</b>   | <b>variable</b> | <b>medium</b> |
| <p>Patients commonly have central or peripheral neurological complications, possibly due to viral invasion of the central nervous system, inflammatory response, or immune dysregulation.<a href="#">[1257]</a> Neurological complications occur across the lifespan in the context of infection, with and without known comorbidities, and with all disease severities (including asymptomatic patients).<a href="#">[1258]</a></p> <p>Neurological manifestations have been reported in 22% to 35% of patients across studies. Central nervous system manifestations were more common than peripheral nervous system manifestations.<a href="#">[1259]</a> A retrospective electronic health records study of nearly 240,000 patients found that approximately one third of patients received a neurological 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.<a href="#">[1260]</a></p> <p>Neurological complications include, but are not limited to, acute cerebrovascular disease, impairment of consciousness, ataxia, seizures, corticospinal tract signs, meningoencephalitis, encephalopathy, encephalomyelitis (including acute disseminated encephalomyelitis), peripheral demyelinating lesions, peripheral neuropathies, cerebral venous sinus thrombosis, myopathy, acute transverse myelitis, 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.<a href="#">[1259]</a> <a href="#">[1261]</a> <a href="#">[1262]</a> <a href="#">[1263]</a> <a href="#">[1264]</a></p> <p>Patients may present with these manifestations, or they may develop them during the course of the disease. Neurological complications tend to develop 1 to 2 weeks after the onset of respiratory disease.<a href="#">[1265]</a></p> <p>Acute cerebrovascular disease (including ischaemic stroke, haemorrhagic stroke, cerebral venous thrombosis, and transient ischaemic attack) has been reported in 0.5% to 5.9% of patients. The most</p> |                 |               |

| Complications | Timeframe | Likelihood |
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common type was ischaemic stroke (0.4% to 4.9%).<sup>[1257]</sup> Patients with severe disease are at an increased risk of ischaemic stroke compared with patients with non-severe disease.<sup>[1266]</sup> Stroke is relatively frequent among hospitalised 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.<sup>[1267]</sup> <sup>[1268]</sup> Stroke presents later in severe disease, and earlier in mild to moderate disease.<sup>[1269]</sup> Patients may present with ischaemic stroke during the convalescent phase of infection, including younger people <50 years of age with asymptomatic or pauci-symptomatic COVID-19.<sup>[1270]</sup> Ischaemic 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.<sup>[1271]</sup> Guidelines for the management of acute ischaemic stroke in patients with COVID-19 infection have been published.<sup>[1272]</sup>

Guillain-Barre syndrome has been reported. Both post-infectious and pre-infectious patterns have been reported.<sup>[1257]</sup> The pooled prevalence among hospitalised and non-hospitalised patients was 0.15%.<sup>[1273]</sup> 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 patients. A higher prevalence of the classic sensorimotor form and acute inflammatory demyelinating polyneuropathy have been reported, although rare variants have also been noted.<sup>[1274]</sup> 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).<sup>[1273]</sup>

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.<sup>[1275]</sup>

Patients with pre-existing neurological disorders may develop an exacerbation of their neurological symptoms and severe COVID-19.<sup>[1276]</sup>

Patients may show cerebral changes on magnetic resonance imaging months after recovery, suggesting that long-term consequences may be possible.<sup>[1277]</sup>

Neurological involvement is common in children and adolescents. In a case series of 1695 patients <21 years of age, 22% of patients had documented neurological involvement. Those with neurological involvement were more likely to have an underlying neurological 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 oedema.<sup>[1278]</sup>

|  |                 |               |
|--|-----------------|---------------|
| <b>post-COVID-19 syndrome (long COVID)</b> | <b>variable</b> | <b>medium</b> |
|--|-----------------|---------------|

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.

**Definition** : case definitions vary. The World Health Organization defines it as a condition that occurs in people with a history of probable or confirmed SARS-CoV-2 infection, usually occurring 3 months from the onset of symptoms and lasting for at least 2 months, that cannot be explained by an alternative diagnosis.<sup>[1279]</sup> The UK National Institute for Health and Care Excellence defines it as 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.<sup>[1280]</sup> The US 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.<sup>[1281]</sup> The syndrome is not thought to be linked to disease severity or specific signs and symptoms during the acute phase of illness.<sup>[1280]</sup> Protracted symptoms are common after many viral and bacterial infections, including influenza. However,

| Complications | Timeframe | Likelihood |
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while the clinical features were also observed after influenza infection, the incidence appears to be higher after COVID-19.[1282] The neurological symptoms are similar to symptoms of other neurological conditions such as chronic fatigue syndrome and functional neurological disorder.[1283]

**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, obesity, severe clinical status, higher number of comorbidities, higher symptom load, hospital admission, and oxygen supplementation in the acute phase, although data is lacking.[1284] [1285] [1286] A study in the UK found that 38% of patients reported at least one persistent symptom, and 15% reported three or more persistent symptoms, lasting 12 weeks or more (a weighted population prevalence of persistent symptoms of 5.8% for one and 2.2% for three or more symptoms).[1287] Approximately 63% of patients report at least one symptom at 30 days after symptom onset/hospitalisation, with 71% reporting at least one symptom after 60 days, and 46% at 90 days or more in a systematic review and meta-analysis. The most commonly reported persistent symptoms were dyspnoea and fatigue.[1288] Persistent symptoms have been reported up to 12 months after discharge, but most people had a good and functional recovery during 1-year follow-up.[1289] [1290] 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.[1291] [1292] 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 non-hospitalised patients.[1293] Persistent symptoms have been reported in pregnant women and children, but appear to be less common in children compared with adults.[568] [1294] [1295] The frequency and characteristics of this syndrome are still under investigation in children and adolescents.[13]

**Diagnosis** : use a holistic, person-centred 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 hypoxaemia, signs of severe lung disease, cardiac chest pain, multisystem inflammatory syndrome in children) urgently to the relevant acute services.[1280]

**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, weakness, malaise, impairment of concentration, 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).[568] [1296] [1280] [1297] Gastrointestinal sequelae including loss of appetite, nausea, acid reflux, and diarrhoea are common in patients 3 months after discharge.[1298] The most common symptoms at 1-year follow-up were fatigue, sweating, chest tightness, anxiety, and myalgia.[1299] Some of the symptoms may overlap with post-intensive care syndrome (see above). The inability to return to normal activities, emotional and mental health outcomes, and financial loss are common.[1300]

**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., full 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.[568] [1296] [1280] Approximately 50% of patients had residual abnormalities on chest CT and pulmonary function tests at 3 months.[1301] 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.[1302]

**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

**Complications****Timeframe****Likelihood**

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 personalised, 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 neurological symptoms that are new, persistent, or progressive.[1296] [1280]

**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.[1280]

[NICE COVID-19 rapid guideline: managing the long-term effects of COVID-19]

[BMJ webinar: long COVID – how to define it and how to manage it]

[BMJ: long covid - mechanisms, risk factors, and management]

**Complications** **Timeframe** **Likelihood**

thebmj Visual summary

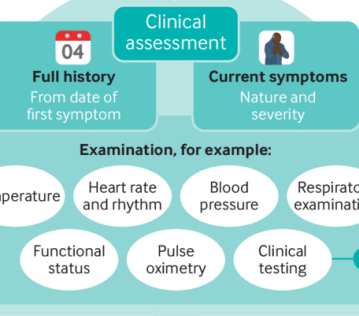
**"Long covid" in primary care**  
Assessment and initial management of patients with continuing symptoms

Post-acute covid-19 appears to be a multi-system disease, sometimes occurring after a relatively mild acute illness. Clinical management requires a whole-patient perspective. This graphic summarises the assessment and initial management of patients with delayed recovery from an episode of covid-19 that was managed in the community or in a standard hospital ward.

**An uncertain picture**  
The long term course of covid-19 is unknown. This graphic presents an approach based on evidence available at the time of publication. However, caution is advised, as patients may present atypically, and new treatments are likely to emerge

**Managing comorbidities**  
Many patients have comorbidities including diabetes, hypertension, kidney disease or ischaemic heart disease. These need to be managed in conjunction with covid-19 treatment. Refer to condition specific guidance, available in the associated article by Greenhalgh and colleagues

**Safety netting and referral**  
The patient should seek medical advice if concerned, for example:  
Worsening breathlessness  
PaO<sub>2</sub> < 96% Unexplained chest pain  
New confusion Focal weakness  
Specialist referral may be indicated, based on clinical findings, for example:  
➔ **Respiratory** if suspected pulmonary embolism, severe pneumonia  
➔ **Cardiology** if suspected myocardial infarction, pericarditis, myocarditis or new heart failure  
➔ **Neurology** if suspected neurovascular or acute neurological event  
Pulmonary rehabilitation may be indicated if patient has persistent breathlessness following review



**Investigations**

Clinical testing is not always needed, but can help to pinpoint causes of continuing symptoms, and to exclude conditions like pulmonary embolism or myocarditis. Examples are provided below:

**Blood tests**

- Full blood count
- Electrolytes
- Liver and renal function
- Troponin
- C reactive protein
- Creatine kinase
- D-dimer
- Brain natriuretic peptides
- Ferritin – to assess inflammatory and prothrombotic states

**Other investigations**

- Chest x ray
- Urine tests
- 12 lead electrocardiogram

**Social, financial, and cultural support**

Prolonged covid-19 may limit the ability to engage in work and family activities. Patients may have experienced family bereavements as well as job losses and consequent financial stress and food poverty. See the associated article by Greenhalgh and colleagues for a list of external resources to help with these problems

**Medical management**

- Symptomatic, such as treating fever with paracetamol
- Optimise control of long term conditions
- Listening and empathy
- Consider antibiotics for secondary infection
- Treat specific complications as indicated

**Self management**

- Diet
- Sleep
- Quitting smoking
- Limiting alcohol
- Limiting caffeine
- Daily pulse oximetry
- Attention to general health
- Rest and relaxation
- Self pacing and gradual increase in exercise **if tolerated**
- Set achievable targets

**Mental health**

**In the consultation:**

- Continuity of care
- Avoid inappropriate medicalisation
- Longer appointments for patients with complex needs (face to face if needed)

**In the community:**

- Community linkworker
- Patient peer support groups
- Attached mental health support service
- Cross-sector partnerships with social care, community services, faith groups

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See more visual summaries <http://www.bmj.com/infographics>

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*"Long covid" in primary care*  
BMJ. 2020;370:m3026

|                       |                 |               |
|-----------------------|-----------------|---------------|
| <b>cardiac arrest</b> | <b>variable</b> | <b>medium</b> |
|-----------------------|-----------------|---------------|

**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.[1303]

thebmj Visual Abstract

### Cardiac arrest with covid-19

In-hospital incidence in critically ill patients

**Summary** In-hospital cardiac arrest is common in critically ill patients with covid-19 and is associated with poor survival, even with cardiopulmonary resuscitation, particularly among older patients

**Study design** Cohort study | Prospective | Multicenter (68 across US)

**Population** 5019 adults admitted to intensive care units with severe covid-19  
 701 had in-hospital cardiac arrest  
*Of those with cardiac arrest, Mean age: 63 years, Sex: 65% men, Race: 21% non-hispanic white, 32% non-hispanic black*

**Exposure** Incidence of in-hospital cardiac arrest and cardiopulmonary resuscitation

**Outcomes**

Overall survival rate after cardiopulmonary resuscitation was similar to non-covid-19 related critical illness \*

5019 Total cohort population

14.0% Had in-hospital cardiac arrest (701)

57.1% Received cardiopulmonary resuscitation (400)

12.0% Survived to discharge (48)

58.3% Discharged with normal or mild neurological impairment (28)

<http://bit.ly/BMJc19ca>
\* [pubmed.ncbi.nlm.nih.gov/32438836](http://pubmed.ncbi.nlm.nih.gov/32438836)
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*Cardiac arrest with COVID-19*  
*BMJ. 2020;371:m3513*

|                            |                 |            |
|----------------------------|-----------------|------------|
| <b>sepsis/septic shock</b> | <b>variable</b> | <b>low</b> |
|----------------------------|-----------------|------------|

| Complications   | Timeframe       | Likelihood |
|---|-----------------|------------|
| <p>Sepsis (diagnosed according to Sepsis-3 or according to the presence of infection-related organ dysfunction necessitating organ support/replacement) has been reported in 78% of intensive care unit patients and 33% of hospitalised patients.[1304]</p> <p>Guidelines for the management of shock in critically ill patients with COVID-19 recommend a conservative fluid strategy (crystalloids preferred over colloids, buffered/balanced crystalloids preferred over unbalanced crystalloids) and a vasoactive agent. Noradrenaline (norepinephrine) is the preferred first-line agent. Vasopressin or adrenaline (epinephrine) can be added to noradrenaline if target mean arterial pressure cannot be achieved with noradrenaline alone.[568] [824] Low-dose corticosteroid therapy is recommended for refractory shock.[568]</p>  |                 |            |
| <b>disseminated intravascular coagulation</b>   | <b>variable</b> | <b>low</b> |
| <p>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/haemorrhage or venous thromboembolism.[1305] 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 non-survivors compared with survivors.[1306]</p> <p>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.[1307]</p> <p>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 <math>\geq 4</math> or a markedly elevated D-dimer level.[1308] In patients with heparin-induced thrombocytopenia (or a history of it), argatroban or bivalirudin are recommended.[1305]</p> <p>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.[1307] [611]</p> |                 |            |
| <b>acute respiratory failure</b>  | <b>variable</b> | <b>low</b> |
| <p>Reported in 8% of patients in case series.[35]</p> <p>Leading cause of mortality in patients with COVID-19.[1120]</p> <p>Children can quickly progress to respiratory failure.[1309]</p> <p>Patients with COVID-19 may have a higher risk of developing ventilator-associated pneumonia compared with patients without COVID-19. Overall, ventilator-associated pneumonia was reported in 48.2% of mechanically ventilated patients and the mortality rate was 51.4%.[1310]</p>  |                 |            |
| <b>cytokine release syndrome</b>  | <b>variable</b> | <b>low</b> |
| <p>Cytokine release syndrome may cause ARDS or multiple-organ dysfunction, which may lead to death.[1311] Elevated serum proinflammatory cytokines (e.g., tumour 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 haemophagocytic lymphohistiocytosis, which may be fatal.[34] [762] [1312] [1313] [1314] Interleukin-6, in particular, has been associated with severe COVID-19 and increased mortality.[1315]</p>  |                 |            |

| Complications | Timeframe | Likelihood |
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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 tumour necrosis factor alpha, and fewer CD4+ and CD8+ T cells.[1316]

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.[1317]

Cytokine release syndrome has been reported in children, although cases appear to be rare.[1318] See the section below on paediatric inflammatory multisystem syndrome.

|   |                 |            |
|---|-----------------|------------|
| <b>paediatric inflammatory multisystem syndrome</b> | <b>variable</b> | <b>low</b> |
|---|-----------------|------------|

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 post-infectious inflammatory process. The syndrome has a strong temporal association with SARS-CoV-2 infection.[1319] [1320] [1321] 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.[1322] Also known as PIMS, multisystem inflammatory syndrome in children (MIS-C), paediatric 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.[573] [1321] [1323] [1324] 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, diarrhoea), and significantly elevated inflammatory markers.[1319] [1320] Additional clinical and laboratory characteristics including thrombocytopenia, fatigue, headache, myalgia, sore throat, and lymphadenopathy have been suggested to refine the case definition.[19] Mucocutaneous findings may be present, many of which overlap with Kawasaki disease.[1325]

Three types of clinical manifestations have been recognised: persistent fever and gastrointestinal symptoms (the most common type); shock with heart dysfunction; and symptoms coincident with the diagnostic criteria for Kawasaki disease.[1326]

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 neurological 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%.[1327] The majority of patients had good outcomes with no significant medium- or long-term sequelae at 1-year follow-up in a small cohort of patients.[1328]

In the UK, 78 cases were reported across 21 paediatric intensive care units in a multicentre 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 diarrhoea 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.[1329]

In the US, 5217 cases have been reported, with 46 deaths (as of 4 October 2021).[1330] In a US case series of 1116 patients diagnosed with MIS-C, those with MIS-C were more likely to have the following characteristics compared with patients with severe COVID-19: age 6 to 12 years; non-Hispanic Black ethnicity; cardiorespiratory involvement; cardiovascular without respiratory involvement; mucocutaneous



| Complications  | Timeframe       | Likelihood |
|--|-----------------|------------|
| <p>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.[1331] Factors associated with more severe outcomes (e.g., intensive care unit admission, decreased cardiac function, shock, myocarditis) include: age &gt;5 years; non-Hispanic Black ethnicity; symptoms of dyspnoea or abdominal pain; elevated C-reactive protein, troponin, ferritin, D-dimer, brain natriuretic peptide, or interleukin-6; and reduced lymphocyte or platelet counts.[1332]</p> <p>The most common cardiovascular complications include shock, cardiac arrhythmias, pericardial effusion, and coronary artery dilatation.[1333] 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%.[1334]</p> <p>Management is mainly supportive and involves a multidisciplinary team (paediatric infectious disease, cardiology, rheumatology, critical care). Patients are commonly managed with intravenous immunoglobulin, vasopressor support, corticosteroids, immune modulators, anticoagulation, antiplatelet therapy, and respiratory support.[1319] [1320] A national consensus management pathway from the UK is available.[1335] The optimal choice and combination of immunomodulating therapies have not been definitively established, but intravenous immunoglobulin and/or corticosteroids are generally considered first-line treatment, with interleukin-1 antagonists reserved for refractory cases.[568] Initial treatment with intravenous immunoglobulin plus a corticosteroid was associated with a lower risk of new or persistent cardiovascular dysfunction compared with intravenous immunoglobulin alone in one cohort study.[1336] However, another cohort study found no evidence of substantial differences in two primary outcomes (inotropic support or mechanical ventilation by day 2 or later or death; and reduction in disease severity on an ordinal scale by day 2) among children who received the three most common treatments for this disorder (i.e., intravenous immunoglobulin alone, intravenous immunoglobulin plus a corticosteroid, and corticosteroids alone).[1337] The American College of Rheumatology has published guidelines on the diagnosis and management of MIS-C.[1338]</p> <p>Follow-up of patients at 6 months found that while cardiac, gastrointestinal, renal, haematological, and otolaryngology outcomes largely resolved at 6 months, muscular fatigue and emotional lability were common.[1339]</p> <p>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.[1340] 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.[1341]</p> <p>Cases of MIS-C have been reported in neonates and temporally associated with antenatal exposure.[1342] [1343]</p> <p>Multisystem inflammatory syndrome has been reported in adults.[1344]</p> |                 |            |
| <b>vaccine-induced immune thrombocytopenia and thrombosis (VITT)</b>   | <b>variable</b> | <b>low</b> |
| <p>Also known as thrombosis with thrombocytopenia syndrome (TTS) and vaccine-induced prothrombotic immune thrombocytopenia (VIPIT).</p> <p><b>Definition</b> : thromboembolic events with thrombocytopenia after vaccination with adenovirus vector-based COVID-19 vaccines (e.g., AstraZeneca, Janssen).[381] The vaccines may trigger the development of an immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4, which clinically mimics autoimmune heparin-induced thrombocytopenia.[1345] [1346] [1347] The link between</p>   |                 |            |

| Complications | Timeframe | Likelihood |
|---------------|-----------|------------|
|---------------|-----------|------------|

vaccination and the formation of anti-PF4 antibodies is yet to be determined. Anti-PF4 antibodies are transient in most patients, but pathogenic platelet-activating anti-PF4 antibodies may persist for more than 12 weeks in some patients.<sup>[1348]</sup> The blood clots occur in unusual sites and 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. These events can rapidly progress and may be life-threatening or fatal.<sup>[382] [383] [387]</sup> A causal relationship is plausible based on current information. Evidence to date does not suggest that these vaccines cause venous thromboembolism without thrombocytopenia.<sup>[382] [383] [384] [385] [386] [387]</sup> There has been no safety signal following receipt of mRNA vaccines, although a small number of cases have been reported.

**Epidemiology** : very rare. 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.<sup>[1349]</sup> Data suggest that there is a slightly higher incidence reported in younger adult age groups.<sup>[383]</sup> Most of the cases reported occurred in women under 60 years of age within 2 to 3 weeks of receiving their first dose.<sup>[382] [387]</sup> Cases have also been reported after this period, up to 48 days after vaccination.<sup>[1350]</sup> See the [\[Prevention\]](#) section for more information.

**Diagnosis** : advise vaccine recipients who experience any severe symptoms from around 4 to 30 days after vaccination to seek urgent medical attention.<sup>[384] [1351]</sup> Approximately half of patients present with cerebral venous sinus thrombosis.<sup>[1352]</sup> Headache is the most common presenting symptom, and may precede VITT by several days.<sup>[1353] [1354]</sup> Signs and symptoms listed by Public Health England include: new-onset headache that is getting worse and does not respond to simple analgesics; an unusual headache that seems worse when lying down or bending over, or may be accompanied by blurred vision, nausea and vomiting, speech difficulty, weakness, drowsiness, or seizures; new unexplained pinprick bruising or bleeding; and shortness of breath, chest pain, leg swelling, or persistent abdominal pain. Ask about vaccination history in people with suspected VITT. Refer people who are acutely unwell to the emergency department immediately.<sup>[1351]</sup> Report all cases to local health authorities and through local vaccine adverse event reporting systems.

**Investigations** : order a full 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 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 or normal fibrinogen. Antibodies to platelet factor 4 have also been identified. Order same-day imaging studies based on location of symptoms to confirm the site of thrombosis. Repeat imaging may be required in patients whose blood tests suggest probable VITT, but no thrombosis is seen on initial imaging or there is clinical or laboratory suspicion of progression.<sup>[1351] [1355] [1356] [1357] [1358] [1359]</sup>

**Differential** : other possible causes of thrombocytopenia with thrombosis include cancer, antiphospholipid syndrome, heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, and paroxysmal nocturnal haemoglobinuria. Consider alternative diagnoses in people whose blood tests indicate it is unlikely they have VITT. A small number of people with VITT do not have thrombocytopenia at presentation. Therefore, repeat a full blood count after 2 to 3 days or if symptoms worsen, if a high clinical suspicion of VITT remains. Discuss the need for further investigations with a haematologist.<sup>[1351]</sup>

**Management** : promptly treat patients. Consult a haematologist when making decisions about starting or adding treatments. There is limited information about the optimal treatment of this condition; however, management is similar to heparin-induced thrombocytopenia. First-line treatment is urgent administration of intravenous immunoglobulin. A second dose may be considered if there is an inadequate response after 2 to 3 days. Some experts also recommend the use of corticosteroids, especially if intravenous immunoglobulin treatment is insufficient. Anticoagulate with a non-heparin-based therapy such as a direct oral anticoagulant, fondaparinux, danaparoid, or argatroban, depending on the clinical picture, as soon as the benefit outweighs the risk of bleeding. Review response to anticoagulation if the patient's clinical condition changes, and adjust treatment if needed. Avoid platelet transfusions, heparin (including heparin flushing solution), low molecular weight heparin, and vitamin K antagonists (e.g., warfarin). Consider

| Complications   | Timeframe       | Likelihood |
|---|-----------------|------------|
| <p>plasma exchange, fibrinogen replacement, or rituximab in select patients. Some patients may require surgery to treat thrombosis.[1351] [1355] [1356] [1357] [1358] [1359]</p> <p><b>Monitoring</b> : after discharge, the patient should be under the care of a haematologist. Assess symptoms and measure D-dimer, fibrinogen, and platelet counts every 2 to 3 days for the first 2 weeks. Repeat enzyme-linked immunosorbent assay (ELISA) for platelet factor 4 antibodies weekly for the first 4 weeks. Repeat tests monthly for the first 6 months and, if no relapses occur, reduce the frequency of testing to every 3 months. When platelet 4 antibodies are no longer detected, review the need for ongoing treatment and monitoring.[1351]</p> <p><b>Prognosis</b> : mortality due to complications has been reported to be 39%.[1353] Fibrinogen levels, age, platelet count, and the presence of intracerebral haemorrhage or cerebral venous thrombosis are significantly associated with an increased risk of mortality.[1360]</p> <p>Management is evolving and there are differences between the guidelines available. Consult the most current local guidelines for more detailed information on the diagnosis and management of this condition. Consult local guidelines for advice on further vaccination after an episode of VITT.</p> <p><a href="#">[National Institute for Health and Care Excellence: vaccine-induced immune thrombocytopenia and thrombosis (VITT)]</a></p> <p><a href="#">[Examples of learned societies with treatment recommendations]</a></p>  |                 |            |
| <b>pregnancy-related complications</b>  | <b>variable</b> | <b>low</b> |
| <p>Pregnancy outcome is usually good, although there are little data on exposure during early pregnancy.[24]</p> <p>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 non-pregnant reproductive-aged women. Pregnant women may also be at an increased risk of maternal death. Risk factors for serious complications include pre-existing comorbidities (e.g., chronic hypertension, diabetes), high maternal age, non-White ethnicity, presence of pregnancy-specific conditions (e.g., gestational diabetes, pre-eclampsia), and high body mass index.[22] [23] Infection during pregnancy is associated with an increased risk of pre-eclampsia.[1361]</p> <p>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]</p> <p>The overall rates of stillbirths and neonatal deaths do not seem to be higher than the background rates.[22] [23] [1362] 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.[1363]</p> <p>Limited low-quality evidence suggests that the risk of infection in neonates is extremely low. Most infections are acquired in the postnatal 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.[22] [23] [1364]</p> |                 |            |
| <b>aspergillosis</b>  | <b>variable</b> | <b>low</b> |
| <p>Invasive pulmonary aspergillosis has been reported in critically ill patients with moderate to severe ARDS.[1365] [1366] [1367] Aspergillosis has been reported in 10.2% of patients admitted to the intensive care unit. The mortality rate was high at 54.9%.[1368]</p>  |                 |            |

| Complications   | Timeframe       | Likelihood |
|---|-----------------|------------|
| <p>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 radiological or clinical features.<a href="#">[863]</a> <a href="#">[1369]</a></p> <p>Prescribe appropriate antifungal therapy according to local guidelines.<a href="#">[1370]</a> Voriconazole levels may need monitoring more frequently in COVID-19 patients due to increased toxicity in these patients.<a href="#">[1371]</a> Guidance on the diagnosis and management of COVID-19-associated pulmonary aspergillosis has been published.<a href="#">[1372]</a></p>   |                 |            |
| <b>mucormycosis</b>   | <b>variable</b> | <b>low</b> |
| <p>Mucormycosis (also known as ‘black fungus’) has been reported rarely.<a href="#">[588]</a> <a href="#">[1373]</a> <a href="#">[1374]</a> Approximately 275 cases have been reported globally as of 21 June 2021, with 233 of those cases reported from India.<a href="#">[1375]</a> The number of cases in India increased significantly during its second wave.<a href="#">[1376]</a></p> <p>The main risk factors are male sex, uncontrolled diabetes, and immunosuppression (e.g., due to corticosteroid therapy).<a href="#">[588]</a> <a href="#">[1377]</a> <a href="#">[1378]</a></p> <p>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; haemoptysis; necrotic eschar on skin, palate, or nasal turbinates). Do not hesitate to order appropriate investigations.<a href="#">[1379]</a> The median time to interval between diagnosis of COVID-19 and evidence of mucormycosis was 15 days. Rhino-orbital mucormycosis was most common (42%), followed by rhino-orbito-cerebral mucormycosis (24%), and pulmonary mucormycosis (10%).<a href="#">[1377]</a></p> <p>Management strategies in the context of COVID-19 include, but are not limited to: controlling hyperglycaemia, 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.<a href="#">[1379]</a></p> <p>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.<a href="#">[1379]</a></p> <p>Prevention involves controlling hyperglycaemia; monitoring blood glucose level in COVID-19 patients after discharge (whether or not they are diabetic); and judicious use of corticosteroids, antibiotics, and antifungals.<a href="#">[1379]</a></p> <p>Overall mortality in India (36.5%) was less than that for globally reported cases (61.9%), likely due to the predominance of rhino-orbital mucormycosis in India.<a href="#">[1375]</a></p> |                 |            |
| <b>pancreatic injury</b>  | <b>variable</b> | <b>low</b> |
| <p>Mild pancreatic injury (defined as elevated serum amylase or lipase levels) has been reported in 17% of patients in one case series.<a href="#">[1380]</a> It is unknown whether this is a direct viral effect or due to the harmful immune response that occurs in some patients. Patients had an increased risk of severe pancreatitis and necrotising pancreatitis, and a longer length of hospital stay.<a href="#">[1381]</a> Prior history of pancreatitis does not appear to be a risk factor for pancreatic inflammation in patients with COVID-19.<a href="#">[1382]</a></p>  |                 |            |
| <b>autoimmune haemolytic anaemia</b>  | <b>variable</b> | <b>low</b> |
| <p>Warm or cold autoimmune haemolytic anaemia (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</p>   |                 |            |

| Complications  | Timeframe       | Likelihood |
|--|-----------------|------------|
| patients had indolent B lymphoid malignancy. It is unknown whether the haemolytic anaemia is related to COVID-19 infection. <a href="#">[1383]</a>   |                 |            |
| <b>immune thrombocytopenia</b>   | <b>variable</b> | <b>low</b> |
| Immune thrombocytopenia has been reported rarely. The majority of cases were in patients >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 immunoglobulin, and thrombopoietin-receptor agonists. <a href="#">[1384]</a>   |                 |            |
| <b>subacute thyroiditis</b>  | <b>variable</b> | <b>low</b> |
| 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. <a href="#">[1385]</a>  |                 |            |
| <b>gastrointestinal complications</b>  | <b>variable</b> | <b>low</b> |
| <p>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 ischaemia.<a href="#">[1386]</a></p> <p>Macrovascular arterial/venous thrombosis has been identified in almost 50% of patients with bowel ischaemia. Overall mortality in COVID-19 patients with gastrointestinal ischaemia and radiologically evident mesenteric thrombotic occlusion was 38.7% and 40%, retrospectively.<a href="#">[1387]</a> Patients with intestinal ischaemia generally present with abdominal pain and vomiting. Management includes gastric decompression, fluids, haemodynamic support, and surgery.<a href="#">[1388]</a></p> <p>Patients may have an increased risk of gastrointestinal bleeding compared with the general population; however, evidence is limited. The overall gastrointestinal bleeding rate has been reported to be 2%.<a href="#">[1389]</a> Risk factors for gastrointestinal haemorrhage in COVID-19 patients include history of gastrointestinal bleeding and anticoagulant use.<a href="#">[1390]</a></p> |                 |            |

## Prognosis

### Mortality

**The leading cause of death is respiratory failure from acute respiratory distress syndrome (ARDS).** [\[1120\]](#)

- 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%).[\[1121\]](#)
- There is no evidence to suggest worse outcomes (i.e., mechanical ventilator-free days, length of stay in intensive care unit or hospital, or mortality) for patients with COVID-19-related ARDS compared with the general ARDS population.[\[1122\]](#)

- 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.[1123]
- Other common causes of death include sepsis or septic shock, sepsis-related multiorgan failure, bacterial or viral co-infections, venous thromboembolism, and cardiac failure.[1124]

### **Mortality rate depends on age and the presence of underlying medical conditions.**

- People <65 years of age have a very small risk of death even in pandemic epicentres, and deaths in people <65 years of age without any underlying conditions is rare.[1125]
- Deaths in children and young people are rare. According to preprint (not peer reviewed) data from the first pandemic year in England, 25 children and young people died, equivalent to an infection fatality rate of 5 per 100,000 and a mortality rate of 2 per million. This indicates that >99.995% of children recover from infection. The children who died were mainly >10 years of age and of Asian and Black ethnicity.[1126]
- Approximately 99% of patients who died of COVID-19 had at least one underlying health condition in a US cohort study. The strongest risk factors for death were obesity, anxiety and fear-related disorders, and diabetes, as well as the total number of underlying conditions.[180]

### **Mortality rates are high in critically ill patients.**

- Global all-cause mortality was 35% in the intensive care unit and 32% in hospital for critically ill patients for the year 2020. However, mortality rates vary between regions. For example, the mortality was as high as 48% in Southeast Asia and as low as 15% in America.[1127]

### **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.[1128]
- Mortality rates decreased sharply in the US over the first 6 months of the pandemic.[1129] [1130] 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.[1131] 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.[1132]
- 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.[1133]
- The US Centers for Disease Control and Prevention's current best estimate of the IFR, according to age (as of 19 March 2021):[127]
  - 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%.
- 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.[1134]
- These estimates have limitations and are likely to change as more data emerge over the course of the pandemic.

### 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% (as of 10 October 2021).[1135] The pooled CFR in the general population in a systematic review and meta-analysis was 1%.[1136] 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%.[34]
- 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).[9] [1137]
- CFR increases with age.
  - In the US, the majority of deaths were in patients aged ≥65 years. The CFR was highest among patients aged ≥85 years (10% to 27%), followed by those aged 65 to 84 years (3% to 11%), then those aged 55 to 64 years (1% to 3%), and finally those aged 20 to 54 years (<1%).[11]
  - In China, the majority of deaths were in patients aged ≥60 years.[9] The CFR was highest among patients aged ≥80 years (13.4%), followed by those aged 60 to 79 years (6.4%), and then those aged <60 years (0.32%).[1137]
  - In Italy, the CFR was highest among patients aged ≥80 years (52.5%), followed by those aged 70 to 79 years (35.5%), and then those aged 60 to 69 years (8.5%).[1138]
  - Deaths are rare in children.[11] [18] In one study, 70% of deaths occurred in those aged 10 to 20 years, 20% in those aged 1 to 9 years, and 10% in children under 1 year of age.[1139]
- CFR increases with the presence of comorbidities.
  - In China, the majority of deaths were in patients who had pre-existing 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).[9]
- CFR increases with disease severity.
  - The pooled CFR in hospitalised patients was 13%.[1136] The CFR is highest in patients with critical disease, ranging from 26% to 67% in studies.[9] [1140] [1141]

### 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.[1142]
- 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 recognised; however, a positive PCR test does not necessarily equal a diagnosis of COVID-19, or mean that a person is infected or infectious.[1143] [1144]
- 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.[1145]

- 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.[1142] [1146]

## Prognostic factors

Prognostic factors that have been associated with increased risk of severe disease, hospitalisation or intensive care unit admission, poor outcomes, and mortality include:[1147] [1148] [1149] [1150] [1151] [1152] [1153]

- **Patient factors**

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

- **Presence of comorbidities**

- Hypertension
- Cardiovascular disease
- Cerebrovascular disease
- Peripheral artery disease
- Dementia
- Diabetes
- Chronic respiratory disease (e.g., COPD, obstructive sleep apnoea)
- Active malignancy
- Immunosuppression
- Chronic kidney or liver disease
- Rheumatological disease
- Bacterial or fungal co-infection

- **Symptoms/signs**

- Myalgia
- Pharyngalgia
- Sputum production
- Chills
- Nausea
- Dyspnoea
- Chest tightness
- Dizziness
- Headache
- Haemoptysis
- Tachypnoea
- Hypoxaemia
- Respiratory failure
- Hypotension
- Tachycardia



- **Complications**

- Shock
- Acute infection or sepsis
- Acute kidney, liver, or cardiac injury
- Acute respiratory distress syndrome
- Venous thromboembolism
- Arrhythmias
- Heart failure

- **Investigations**

- Lymphopenia
- Leukocytosis
- Neutrophilia
- Thrombocytopenia
- Hypoalbuminaemia
- Liver or kidney impairment
- Elevated inflammatory markers (C-reactive protein, procalcitonin, ferritin, erythrocyte sedimentation rate)
- Elevated lactate dehydrogenase
- Elevated creatine kinase
- Elevated cardiac markers
- Elevated D-dimer
- Elevated interleukin-6
- PaO<sub>2</sub>/FiO<sub>2</sub> ≤200 mmHg
- 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.<sup>[1154]</sup>

## 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 hospitalised 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 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.<sup>[1155]</sup>

Approximately 9% of over 106,000 patients were readmitted to the same hospital within 2 months of discharge from the initial hospitalisation. 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:<sup>[1156]</sup>

- Age ≥65 years
- Presence of chronic conditions (COPD, heart failure, diabetes, chronic kidney disease, obesity)
- Hospitalisation within the 3 months preceding the first COVID-19 hospitalisation
- 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, dyspnoea, 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.[1157]

## 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.[1158]

### 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%.[1159] 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.[1160] 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.[1161]
- 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).[1162] 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.[1163]

### Cases of reinfection are rare.

- Cases of possible reinfections have been estimated to be approximately 0.4% in the UK (as of 30 May 2021). However, only 53 cases were confirmed out of the 15,893 possible reinfections. Current evidence suggests that most reinfections will not cause symptoms. There is currently no evidence that variants of concern are more likely to cause reinfection than others.[1164]
- 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.[1165]
- Cases of reinfection with SARS-CoV-2 variants have been reported in Brazil, the UK, and South Africa.[1166] [1167] [1168] [1169]

### Consider reinfection in the following circumstances: [1158]

- 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 epidemiological information to inform whether reinfection is likely. Confirmation of reinfection should be obtained through whole genome sequencing of paired specimens, if available.[1158]

## 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.[\[1158\]](#)

## 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.[\[1170\]](#)

### 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.[\[1171\]](#)
- Approximately 85% to 99% of infected people develop detectable neutralising antibodies within 4 weeks following natural infection. However, this varies depending on disease severity, study setting, time since infection, and method used to measure antibodies.[\[1172\]](#) [\[1173\]](#)
- 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 neutralising antibodies, which may persist for several months. Some adults do not develop antibodies after infection; the reasons for this are unclear.[\[1174\]](#)
- Maternal IgG antibodies to SARS-CoV-2 have been found to transfer across the placenta after infection in pregnant women.[\[1175\]](#)
- Extreme-aged (some over 100 years), frail residents of a long-term care facility have been found to elicit a robust immune response that was capable of neutralising the SARS-CoV-2 virus.[\[1176\]](#)
- There were some early studies that suggested asymptomatic people may have a weaker antibody response to infection; however, this has not been confirmed.[\[1177\]](#)
- Current evidence suggests that the immune responses remain robust and protective against reinfection in most people for at least 10 months after infection (the longest follow-up data is currently only 10 months).[\[1178\]](#) [\[1179\]](#)
- Some SARS-CoV-2 variants with key changes in the spike protein have a reduced susceptibility to neutralisation 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.[\[1172\]](#)

### 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.[\[1180\]](#)
- 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.[\[1181\]](#) [\[1182\]](#)
- Emerging data suggest that T-cell responses are largely unaffected by SARS-CoV-2 variants.[\[1183\]](#) [\[1184\]](#)

### Evidence suggests that infection with SARS-CoV-2 is likely to confer protective immunity against reinfection. [\[1185\]](#) [\[1186\]](#) [\[1187\]](#) [\[1188\]](#)

- A meta-analysis found a high (87%) level of protection after infection that persisted for at least 1 year.[\[1189\]](#)

- 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.[1190]
- 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.[1191]
- 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.[1192]
- 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.[1193]
- 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.[1194]
- 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.[1195]
- A study in over 2000 staff and residents across 100 long-term care facilities in England found that antibodies provided high levels of protection against reinfection for up to 10 months in both staff and residents. Previous infection reduced the risk of reinfection by approximately 85% in residents and 60% in staff members.[1196]

### Pre-existing 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 recognise 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.[1197] Approximately 5% of uninfected adults and 62% of uninfected children aged 6 to 16 years had antibodies that recognise SARS-CoV-2 in one study.[1198]
- 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 pre-existing immunity to SARS-CoV-2 in the human population is required.

## Diagnostic guidelines

### United Kingdom

#### COVID-19: guidance for health professionals

**Published by:** Public Health England

**Last published:** 2021

#### COVID-19: investigation and management of suspected SARS-CoV-2 reinfections

**Published by:** Public Health England

**Last published:** 2021

#### Assessment of COVID-19 in primary care

**Published by:** Scottish Intercollegiate Guidelines Network

**Last published:** 2021

#### COVID-19 position statement: presentations and management of COVID-19 in older people in acute care

**Published by:** Scottish Intercollegiate Guidelines Network

**Last published:** 2021

### Europe

#### COVID-19 pandemic

**Published by:** European Centre for Disease Prevention and Control

**Last published:** 2021

## International

### Country & technical guidance - coronavirus disease (COVID-19)

**Published by:** World Health Organization

**Last published:** 2021

### Recommendations for national SARS-CoV-2 testing strategies and diagnostic capacities

**Published by:** World Health Organization

**Last published:** 2021

### Infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed: interim guidance

**Published by:** World Health Organization

**Last published:** 2021

### Diagnostic testing for SARS-CoV-2: interim guidance

**Published by:** World Health Organization

**Last published:** 2020

### Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays: interim guidance

**Published by:** World Health Organization

**Last published:** 2020

### Public health surveillance for COVID-19: interim guidance

**Published by:** World Health Organization

**Last published:** 2020

### Prevention, identification and management of health worker infection in the context of COVID-19

**Published by:** World Health Organization

**Last published:** 2020

### Use of chest imaging in COVID-19: a rapid advice guide

**Published by:** World Health Organization

**Last published:** 2020

## North America

### Interim guidelines for collecting and handling of clinical specimens for COVID-19 testing

**Published by:** Centers for Disease Control and Prevention

**Last published:** 2021

### Interim infection prevention and control recommendations for healthcare personnel during the coronavirus disease 2019 (COVID-19) pandemic

**Published by:** Centers for Disease Control and Prevention

**Last published:** 2021

### Overview of testing for SARS-CoV-2 (COVID-19)

**Published by:** Centers for Disease Control and Prevention

**Last published:** 2021

### Interim guidelines for COVID-19 antibody testing

**Published by:** Centers for Disease Control and Prevention

**Last published:** 2021

### COVID-19 real-time learning network

**Published by:** Infectious Diseases Society of America

**Last published:** 2021

### Infectious Diseases Society of America guidelines on the diagnosis of COVID-19: antigen testing

**Published by:** Infectious Diseases Society of America

**Last published:** 2021

### COVID-19 interim guidance

**Published by:** American Academy of Pediatrics

**Last published:** 2021

### COVID-19 testing guidance

**Published by:** American Academy of Pediatrics

**Last published:** 2021

### Infectious Diseases Society of America guidelines on the diagnosis of COVID-19: molecular diagnostic testing

**Published by:** Infectious Diseases Society of America

**Last published:** 2020

### Infectious Diseases Society of America guidelines on the diagnosis of COVID-19: serologic testing

**Published by:** Infectious Diseases Society of America

**Last published:** 2020

### Infectious Diseases Society of America guidelines on infection prevention in patients with suspected or known COVID-19

**Published by:** Infectious Diseases Society of America

**Last published:** 2020

## Asia

### A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia

**Published by:** 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

### Diagnosis and clinical management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

**Published by:** Peking Union Medical College Hospital

**Last published:** 2020



# Treatment guidelines

## United Kingdom

### BMJ's coronavirus (covid-19) hub

**Published by:** BMJ

**Last published:** 2021

### COVID-19 rapid guideline: managing COVID-19

**Published by:** National Institute for Health and Care Excellence

**Last published:** 2021

### COVID-19

**Published by:** National Institute for Health and Care Excellence

**Last published:** 2021

### COVID-19: guidance for health professionals

**Published by:** Public Health England

**Last published:** 2021

### Coronavirus specialty guides

**Published by:** NHS England

**Last published:** 2021

### COVID-19: the green book, chapter 14a

**Published by:** Public Health England

**Last published:** 2021

### COVID-19: investigation and management of suspected SARS-CoV-2 reinfections

**Published by:** Public Health England

**Last published:** 2021

### Community palliative, end of life and bereavement care in the COVID-19 pandemic

**Published by:** Royal College of General Practitioners; Association for Palliative Medicine

**Last published:** 2021

### Coronavirus (COVID-19) infection in pregnancy

**Published by:** Royal College of Obstetricians and Gynaecologists

**Last published:** 2021

### COVID-19: information for the respiratory community

**Published by:** British Thoracic Society

**Last published:** 2021

### COVID-19 position statement: presentations and management of COVID-19 in older people in acute care

**Published by:** Scottish Intercollegiate Guidelines Network

**Last published:** 2021

### COVID-19 rapid guideline: managing the long-term effects of COVID-19

**Published by:** National Institute for Health and Care Excellence

**Last published:** 2020

## Europe

### Management of hospitalised adults with coronavirus disease-19 (COVID-19)

**Published by:** European Respiratory Society

**Last published:** 2021

### COVID-19

**Published by:** European Centre for Disease Prevention and Control

**Last published:** 2021

### Recommendations for COVID-19 clinical management

**Published by:** National Institute for the Infectious Diseases (Italy)

**Last published:** 2020

## International

### Country & technical guidance - coronavirus disease (COVID-19)

**Published by:** World Health Organization

**Last published:** 2021

### COVID-19 clinical management: living guidance

**Published by:** World Health Organization

**Last published:** 2021

### Therapeutics and COVID-19: living guideline

**Published by:** World Health Organization

**Last published:** 2021

### Drugs to prevent COVID-19: WHO living guideline

**Published by:** World Health Organization

**Last published:** 2021

### COVID-19 guidance and the latest research in the Americas

**Published by:** Pan American Health Organization

**Last published:** 2021

### Surviving Sepsis Campaign guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19) in the ICU

**Published by:** Surviving Sepsis Campaign

**Last published:** 2021

### Home care for patients with suspected or confirmed COVID-19 and management of their contacts: interim guidance

**Published by:** World Health Organization

**Last published:** 2020

### Criteria for releasing COVID-19 patients from isolation: scientific brief

**Published by:** World Health Organization

**Last published:** 2020

### Mask use in the context of COVID-19: interim guidance

**Published by:** World Health Organization

**Last published:** 2020

### Rapid advice guidelines for management of children with COVID-19

**Published by:** International multidisciplinary working group

**Last published:** 2020

### ISTH interim guidance on recognition and management of coagulopathy in COVID#19

**Published by:** International Society of Thrombosis and Haemostasis

**Last published:** 2020

### Global interim guidance on coronavirus disease 2019 (COVID-19) during pregnancy and puerperium from FIGO and allied partners: information for healthcare professionals

**Published by:** International Federation of Gynecology and Obstetrics

**Last published:** 2020

## International

### ISUOG interim guidance on coronavirus disease 2019 (COVID-19) during pregnancy and puerperium: information for healthcare professionals – an update

**Published by:** International Society of Ultrasound in Obstetrics and Gynecology

**Last published:** 2020

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## North America

### Coronavirus disease 2019 (COVID-19) treatment guidelines

**Published by:** National Institutes of Health

**Last published:** 2021

### COVID-19 real-time learning network

**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

**Published by:** Infectious Diseases Society of America

**Last published:** 2021

### Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19)

**Published by:** Centers for Disease Control and Prevention

**Last published:** 2021

### Healthcare workers: information on COVID-19

**Published by:** Centers for Disease Control and Prevention

**Last published:** 2021

### Interim clinical considerations for use of COVID-19 vaccines currently approved or authorized in the United States

**Published by:** Centers for Disease Control and Prevention

**Last published:** 2021

### Interim guidance for managing healthcare personnel with SARS-CoV-2 infection or exposure to SARS-CoV-2

**Published by:** Centers for Disease Control and Prevention

**Last published:** 2021

### COVID-19 interim guidance

**Published by:** American Academy of Pediatrics

**Last published:** 2021

### Novel coronavirus 2019 (COVID-19)

**Published by:** American College of Obstetricians and Gynecologists

**Last published:** 2021

### Caring for children and youth with special health care needs during the COVID-19 pandemic

**Published by:** American Academy of Pediatrics

**Last published:** 2021

### Coronavirus disease (COVID-19): outbreak update

**Published by:** Government of Canada

**Last published:** 2021

### Management of infants born to mothers with suspected or confirmed COVID-19

**Published by:** American Academy of Pediatrics

**Last published:** 2021

## North America

### Interim guidance for implementing home care of people not requiring hospitalization for coronavirus disease 2019 (COVID-19)

**Published by:** Centers for Disease Control and Prevention

**Last published:** 2020

### Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the Anticoagulation Forum

**Published by:** Anticoagulation Forum

**Last published:** 2020

### Evaluation and management considerations for neonates at risk for COVID-19

**Published by:** Centers for Disease Control and Prevention

**Last published:** 2020

## Asia

### Clinical guidance for management of adult COVID-19 patients

**Published by:** All India Institute Of Medical Sciences; Indian Council of Medical Research **Last published:** 2021

### Clinical guidance for management of adult COVID-19 patients

**Published by:** Indian Council of Medical Research **Last published:** 2021

### Updates on Singapore's COVID-19 situation

**Published by:** Ministry of Health Singapore **Last published:** 2021

### Coronavirus disease

**Published by:** Chinese Center for Disease Control and Prevention **Last published:** 2021

### COVID-19 infection

**Published by:** Japanese Association for Infectious Diseases **Last published:** 2021

### Management of critically ill patients with COVID-19 in ICU: statement from front-line intensive care experts in Wuhan, China

**Published by:** Chinese expert working panel **Last published:** 2020

### Handbook of COVID-19 prevention and treatment

**Published by:** First Affiliated Hospital, Zhejiang University School of Medicine **Last published:** 2020

### Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7)

**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

### Diagnosis and clinical management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

**Published by:** Peking Union Medical College Hospital **Last published:** 2020

## Oceania

### Coronavirus disease 2019 (COVID-19)

**Published by:** Department of Health Australia **Last published:** 2021

## Online resources

1. [WHO: tracking SARS-CoV-2 variants \(external link\)](#)
2. [PHE: investigation of SARS-CoV-2 variants of concern – technical briefings \(external link\)](#)
3. [CDC: SARS-CoV-2 variant classifications and definitions \(external link\)](#)
4. [Diagnosis \(external link\)](#)
5. [WHO: coronavirus disease \(COVID-19\) dashboard \(external link\)](#)
6. [UK Office for National Statistics: coronavirus \(COVID-19\) infection survey, UK statistical bulletins \(external link\)](#)
7. [GenBank \(external link\)](#)
8. [Complications \(external link\)](#)
9. [WHO: COVID-19 vaccines technical documents \(external link\)](#)
10. [Pfizer/BioNTech COVID-19 vaccine \(external link\)](#)
11. [Moderna COVID-19 vaccine \(external link\)](#)
12. [AstraZeneca COVID-19 vaccine \(external link\)](#)
13. [Janssen COVID-19 vaccine \(external link\)](#)
14. [Public Health England: COVID-19 vaccination information for healthcare practitioners \(external link\)](#)
15. [CDC: interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States \(external link\)](#)
16. [Yellow Card: coronavirus \(COVID-19\) \(external link\)](#)
17. [Vaccine Adverse Event Reporting System \(VAERS\) \(external link\)](#)
18. [EudraVigilance \(external link\)](#)
19. [WHO: Adverse Event Following Immunization \(AEFI\) form \(external link\)](#)
20. [CDC: v-safe COVID-19 vaccine pregnancy registry \(external link\)](#)
21. [BMJ: covid-19 in primary care \(UK\) \(external link\)](#)
22. [BMJ: covid-19 – a remote assessment in primary care \(external link\)](#)



23. [WHO: infection prevention and control during health care when coronavirus disease \(COVID-19\) is suspected or confirmed \(external link\)](#)
24. [CDC: interim infection prevention and control recommendations for healthcare personnel during the coronavirus disease 2019 \(COVID-19\) pandemic \(external link\)](#)
25. [BMJ: covid-19 – PPE guidance \(external link\)](#)
26. [WHO: coronavirus disease \(COVID-19\) advice for the public \(external link\)](#)
27. [BMJ: mask related acne \('maskne'\) and other facial dermatoses \(external link\)](#)
28. [Public Health England: travel abroad - step by step \(external link\)](#)
29. [Public Health England: COVID-19 – advice for smokers and vapers \(external link\)](#)
30. [Emerging \(external link\)](#)
31. [BMJ Practice Pointer: remote management of covid-19 using home pulse oximetry and virtual ward support \(external link\)](#)
32. [Criteria \(external link\)](#)
33. [Centre for Evidence-Based Medicine: are you infectious if you have a positive PCR test result for COVID-19? \(external link\)](#)
34. [BMJ Practice Pointer: interpreting a covid-19 test result \(external link\)](#)
35. [BMJ practice pointer: testing for SARS-CoV-2 antibodies \(external link\)](#)
36. [BSTI: radiology decision tool for suspected COVID-19 \(external link\)](#)
37. [BSTI: lung ultrasound \(LUS\) for COVID-19 patients in critical care areas \(external link\)](#)
38. [BMJ Best Practice: management of co-existing conditions in the context of COVID-19 \(external link\)](#)
39. [British Association of Dermatologists: Covid-19 skin patterns \(external link\)](#)
40. [NHS England: pulse oximetry to detect early deterioration of patients with COVID-19 in primary and community care settings \(external link\)](#)
41. [BMJ: interpreting a lateral flow SARS-CoV-2 antigen test \(external link\)](#)
42. [WHO: public health surveillance for COVID-19 – interim guidance \(external link\)](#)
43. [CDC: coronavirus disease 2019 \(COVID-19\) 2020 interim case definition \(external link\)](#)
44. [PHE: COVID-19 – investigation and initial clinical management of possible cases \(external link\)](#)

45. [ECDC: case definition for coronavirus disease 2019 \(COVID-19\) \(external link\)](#)
46. [WHO: home care for patients with suspected or confirmed COVID-19 and management of their contacts \(external link\)](#)
47. [CDC: interim guidance for implementing home care of people not requiring hospitalization for coronavirus disease 2019 \(COVID-19\) \(external link\)](#)
48. [Clinical Frailty Scale \(external link\)](#)
49. [ACOG: outpatient assessment and management for pregnant women with suspected or confirmed novel coronavirus \(COVID-19\) \(external link\)](#)
50. [BMJ rapid recommendations: a living WHO guideline on drugs for COVID-19 \(external link\)](#)
51. [Global coronavirus COVID-19 clinical trial tracker \(external link\)](#)
52. [RECOVERY trial \(external link\)](#)
53. [WHO: COVID-19 “Solidarity” therapeutics trial \(external link\)](#)
54. [NICE COVID-19 rapid guideline: managing the long-term effects of COVID-19 \(external link\)](#)
55. [BMJ webinar: long COVID – how to define it and how to manage it \(external link\)](#)
56. [BMJ: long covid - mechanisms, risk factors, and management \(external link\)](#)
57. [Prevention \(external link\)](#)
58. [National Institute for Health and Care Excellence: vaccine-induced immune thrombocytopenia and thrombosis \(VITT\) \(external link\)](#)
59. [Examples of learned societies with treatment recommendations \(external link\)](#)
60. [Health Education England: adult pulse oximetry monitoring video \(external link\)](#)
61. [WHO: coronavirus disease \(COVID-19\) travel advice \(external link\)](#)
62. [CDC: COVID-19 – travel \(external link\)](#)
63. [NaTHNaC: travel health pro \(external link\)](#)
64. [Public Health England: travel abroad from England during coronavirus \(COVID-19\) \(external link\)](#)
65. [UK Department for Transport \(external link\)](#)
66. [Smartraveller Australia: COVID-19 \(external link\)](#)

67. [Government of Canada: coronavirus disease \(COVID-19\) – travel, testing, quarantine and borders](#) (*external link*)
68. [Ministry of Manpower Singapore: advisories on COVID-19](#) (*external link*)
69. [CDC: animals and COVID-19](#) (*external link*)
70. [AAP: COVID-19 interim guidance – return to sports and physical activity](#) (*external link*)
71. [WHO: coronavirus disease \(COVID-19\) pandemic](#) (*external link*)
72. [CDC: COVID-19](#) (*external link*)
73. [NHS England: coronavirus \(COVID-19\)](#) (*external link*)
74. [NHS England: COVID-19 patient rehabilitation booklet](#) (*external link*)
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# Images

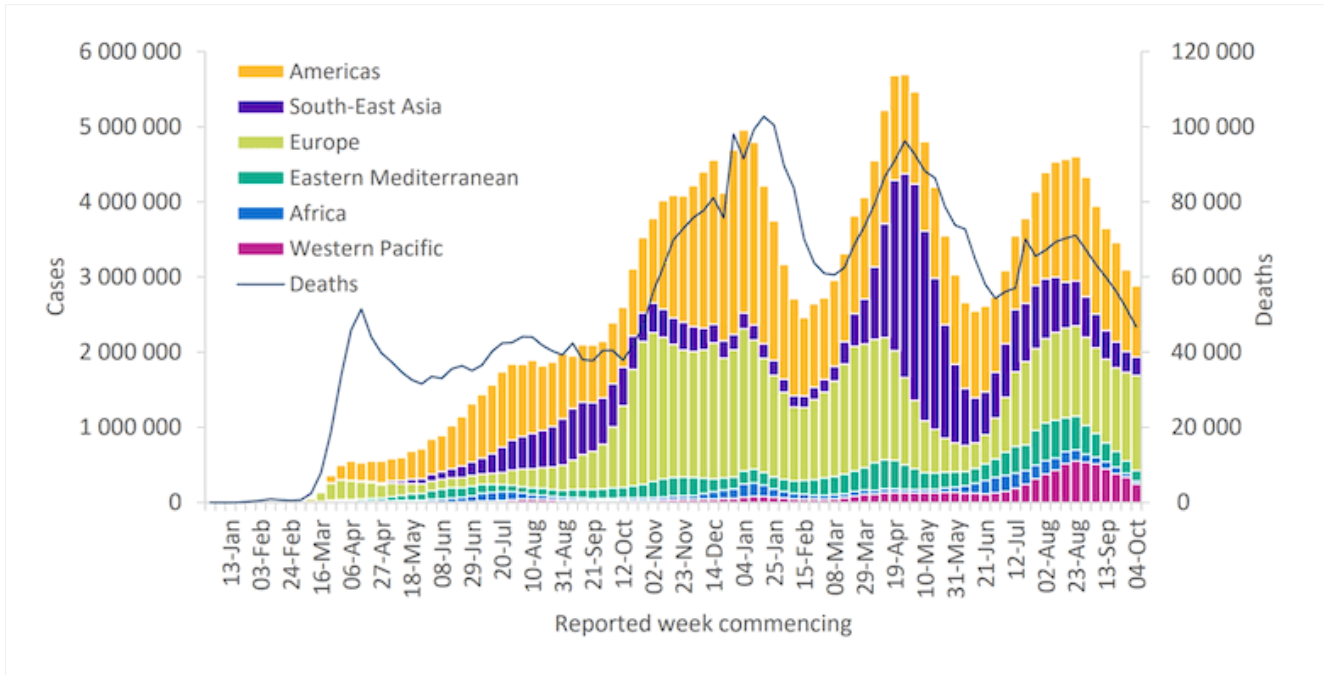
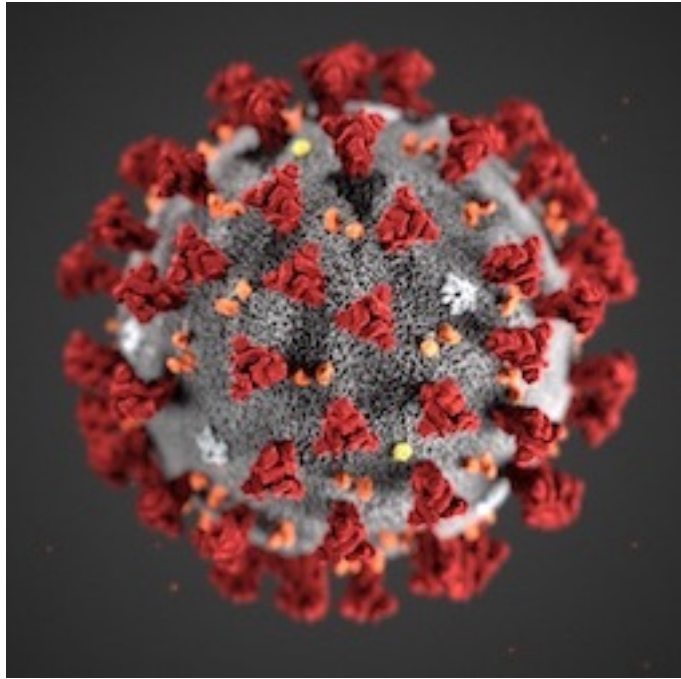


Figure 1: Number of COVID-19 cases reported weekly by WHO Region, and global deaths, as of 10 October 2021

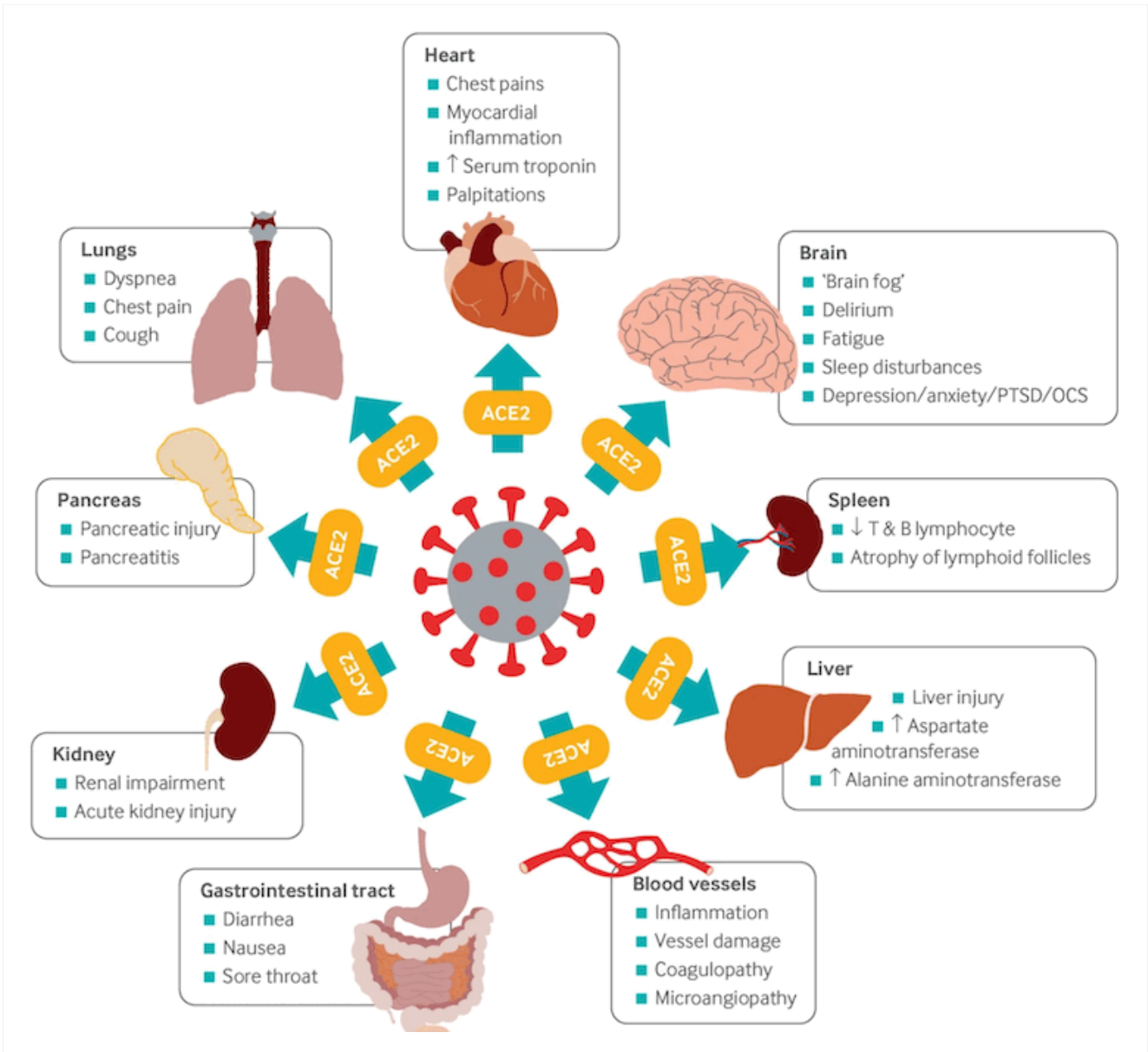
World Health Organization





*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*



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Figure 3: Multi-organ complications of COVID-19 and long COVID. The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor

BMJ. 2021;374:n1648

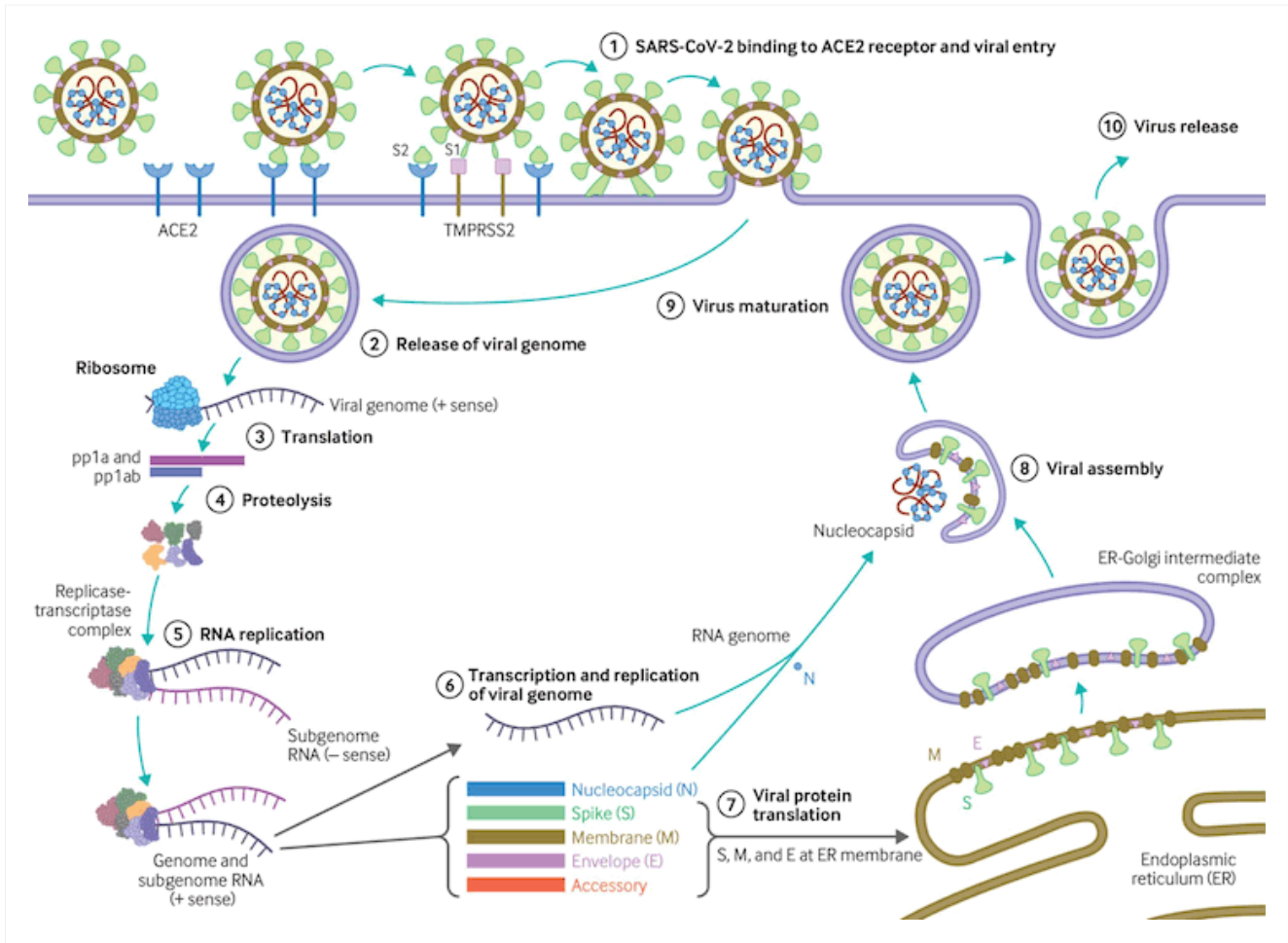


Figure 4: Virus replication cycle

BMJ. 2020;371:m3862

|                        | 0-4 years | 5-17 years | 18-29 years     | 30-39 years | 40-49 years | 50-64 years | 65-74 years | 75-84 years | 85+ years |
|------------------------|-----------|------------|-----------------|-------------|-------------|-------------|-------------|-------------|-----------|
| <b>Hospitalisation</b> | <1 x      | <1 x       | Reference group | 2x          | 2x          | 4x          | 6x          | 9x          | 15x       |
| <b>Death</b>           | <1 x      | <1 x       |                 | 4x          | 10x         | 35x         | 95x         | 230x        | 610x      |

Figure 5: Risk for hospitalisation and death by age group (rate ratios compared with 18- to 29-year-olds)

Table based on data from the CDC

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### Asymptomatic covid-19 detection

Performance of the Innova antigen rapid lateral flow test

 Summary



Innova lateral flow test (LFT) can be useful for identifying infections among people who declare no symptoms of covid-19, particularly those with high viral load and so more likely to infect others

 Study design



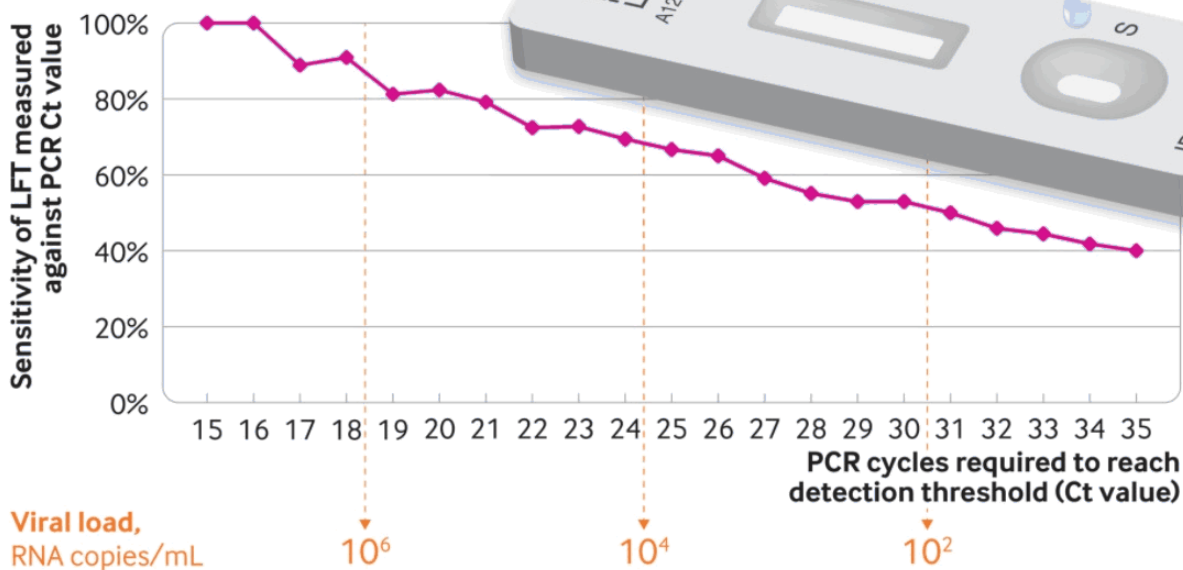
Cross sectional | Compared LFT with RT-qPCR\* | Two self-administrated swab samples per participant taken within minutes

 Population



5869 individuals attending asymptomatic testing sites in Liverpool, UK, between 6 and 29 November 2020 | 46% men | 49.8 years old (mean) | 82% white ethnicity

 Outcomes



<http://bit.ly/BMJlftsens>

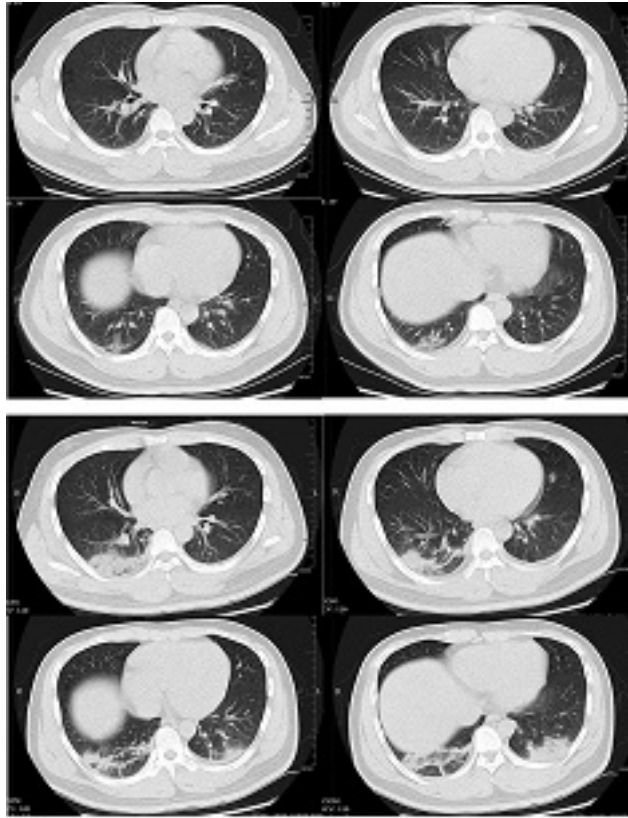
\* Quantitative reverse-transcriptase polymerase chain reaction

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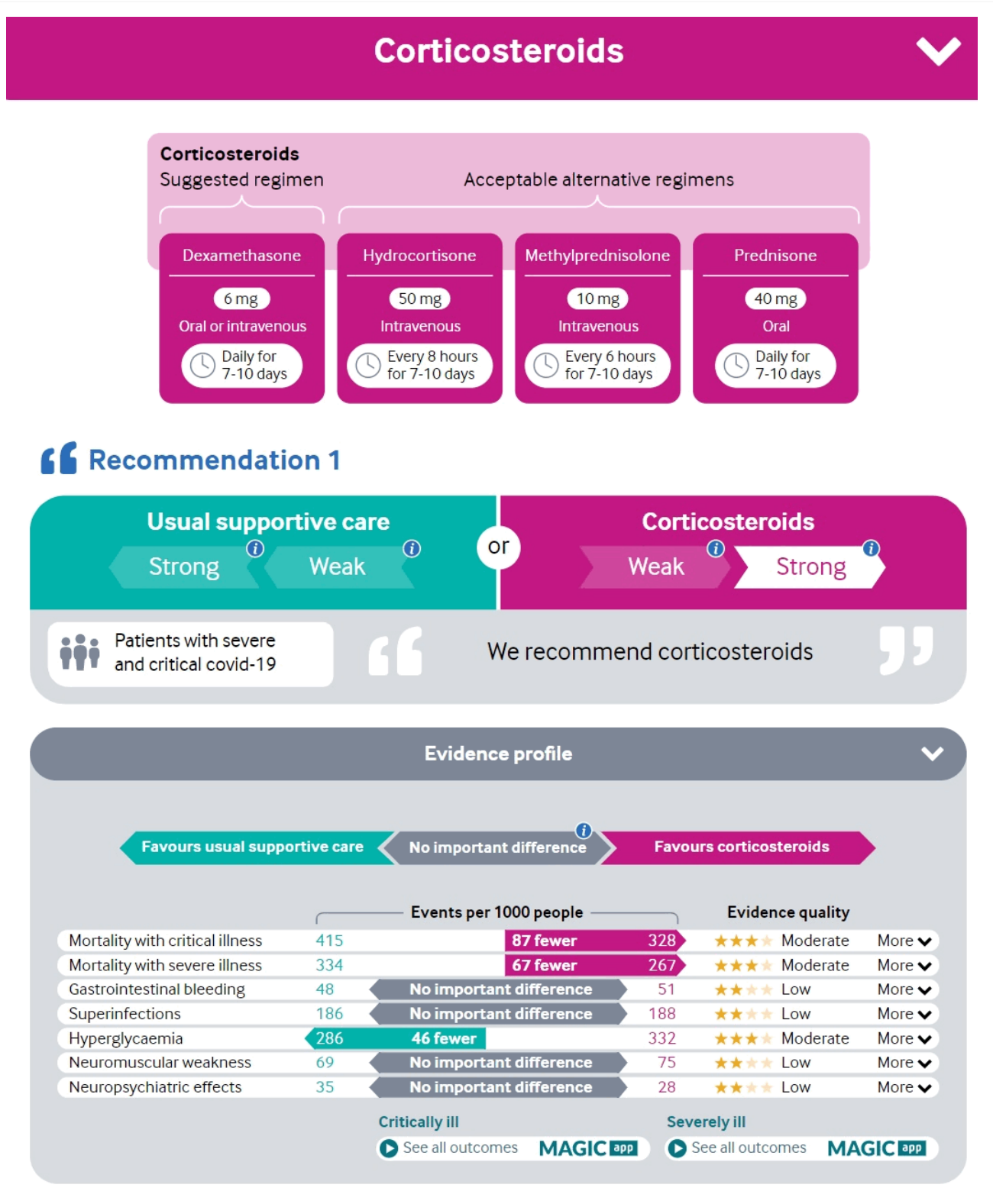
Figure 6: Performance of the Innova SARS-CoV-2 antigen rapid lateral flow test

BMJ. 2021;374:n1637



*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*



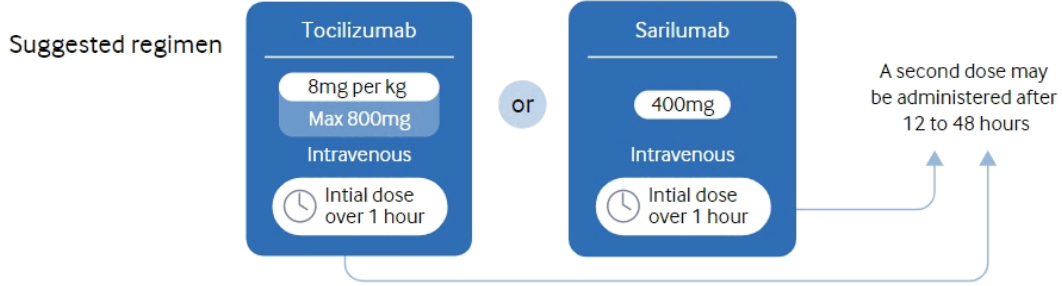


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Figure 8: Recommendations and evidence for the use of corticosteroids in hospitalised patients with COVID-19

BMJ. 2020;370:m3379

# IL-6 receptor blockers



## Recommendation 1

Strong
Weak

or

Weak
Strong

Patients with severe and critical covid-19

“ We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) ”

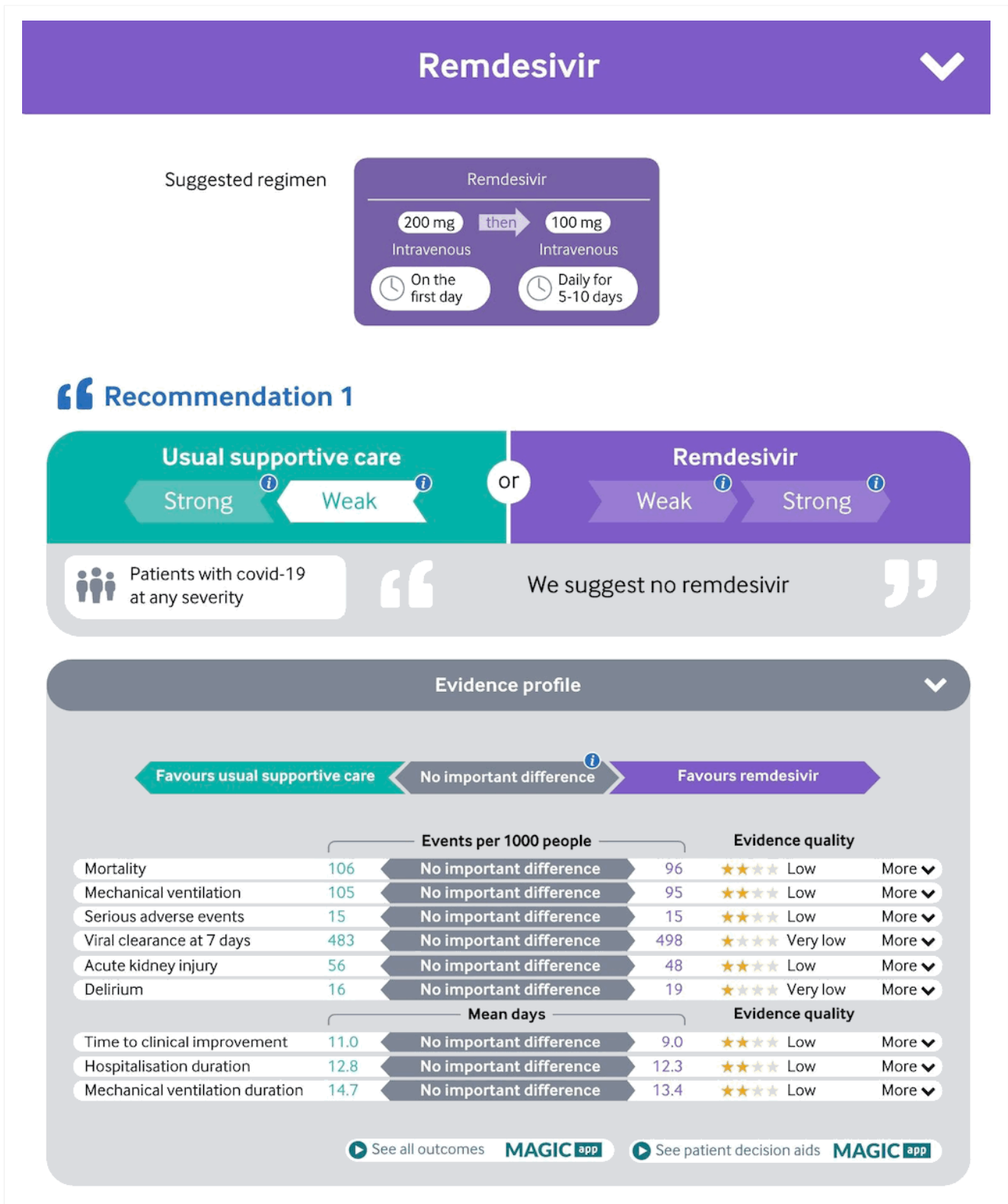
### Evidence profile

Favours usual supportive care
No important difference
Favours IL-6 receptor blockers

|                             | Events per 1000 people |                            | Evidence quality   |
|-----------------------------|------------------------|----------------------------|--------------------|
| Mortality                   | 130                    | 15 fewer 115               | ★★★★ High More     |
| Mechanical ventilation      | 86                     | 23 fewer 63                | ★★★★ High More     |
| Serious adverse events      | 9                      | No important difference 5  | ★★★★ Very low More |
| Bacterial infections        | 101                    | No important difference 96 | ★★★★ Low More      |
|                             | Mean days              |                            | Evidence quality   |
| Duration of ventilation     | 14.7                   | 1.2 fewer 13.5             | ★★★★ Low More      |
| Duration of hospitalisation | 12.8                   | 4.5 fewer 8.3              | ★★★★ Low More      |

[See all outcomes](#)
MAGIC app

Figure 9: Recommendations and evidence for the use of IL-6 inhibitors in hospitalised patients with COVID-19  
 BMJ. 2020;370:m3379



IMAGES

Figure 10: Recommendations and evidence for the use of remdesivir in hospitalised patients with COVID-19  
 BMJ. 2020;370:m3379

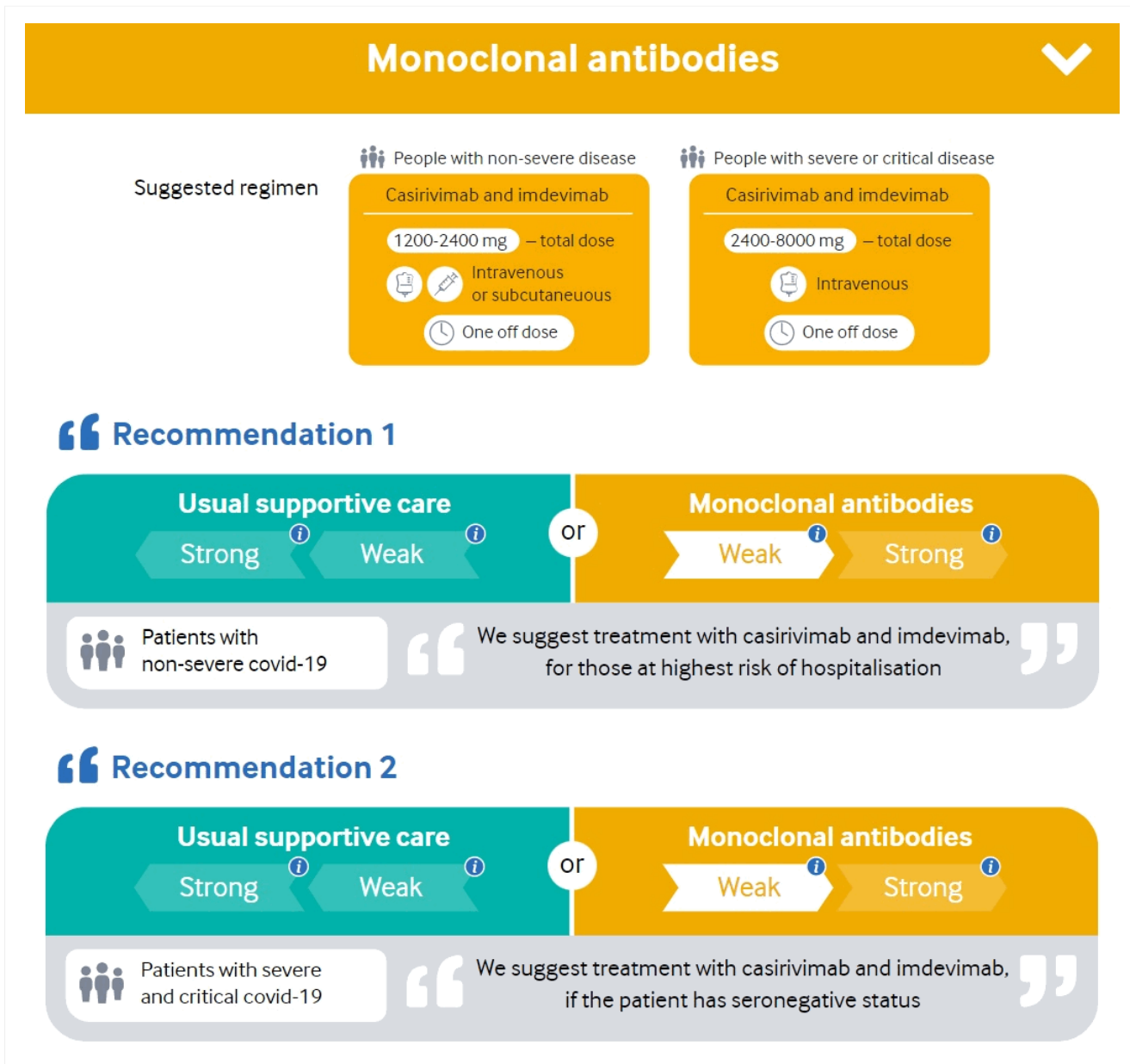
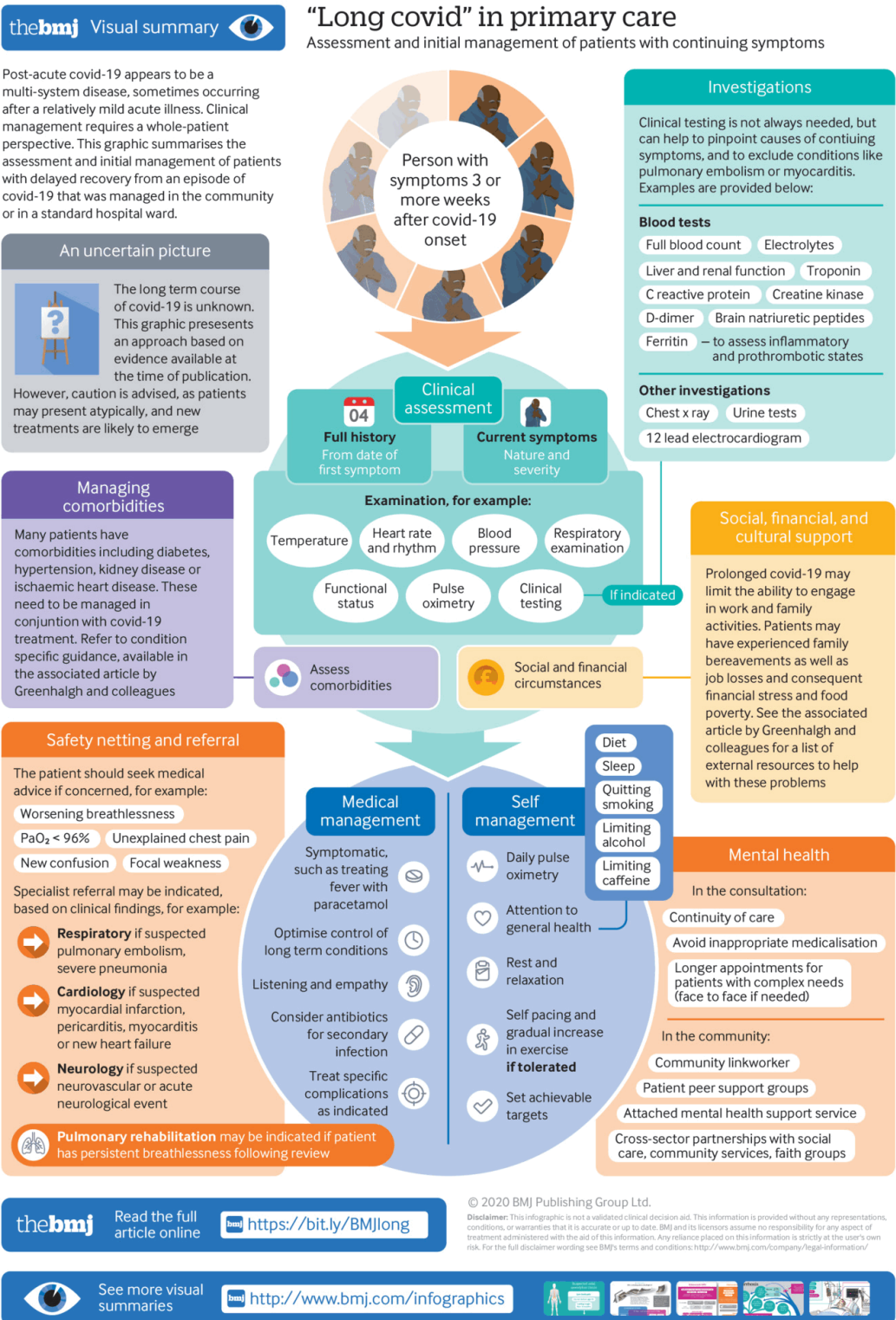


Figure 11: Recommendations for the use of casirivimab/imdevimab in patients with COVID-19

BMJ. 2020;370:m3379



IMAGES

Figure 12: Long covid" in primary care

BMJ. 2020;370:m3026

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### Cardiac arrest with covid-19

In-hospital incidence in critically ill patients

**Summary**



In-hospital cardiac arrest is common in critically ill patients with covid-19 and is associated with poor survival, even with cardiopulmonary resuscitation, particularly among older patients

**Study design**



Cohort study



Prospective



Multicenter (68 across US)

**Population**



5019 adults admitted to intensive care units with severe covid-19  
701 had in-hospital cardiac arrest



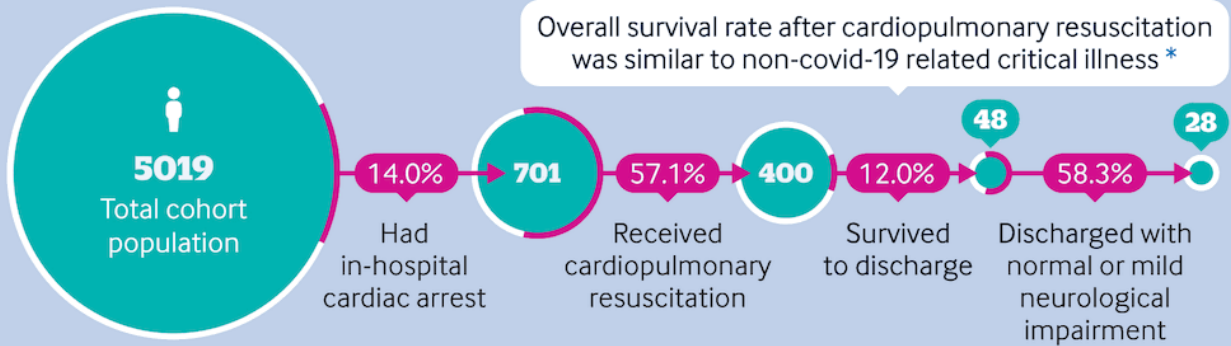
Of those with cardiac arrest, Mean age: 63 years, Sex: 65% men, Race: 21% non-hispanic white, 32% non-hispanic black

**Exposure**

Incidence of in-hospital cardiac arrest and cardiopulmonary resuscitation



**Outcomes**



<http://bit.ly/BMJc19ca>

\* [pubmed.ncbi.nlm.nih.gov/32438836](https://pubmed.ncbi.nlm.nih.gov/32438836)

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Figure 13: Cardiac arrest with COVID-19

BMJ. 2020;371:m3513

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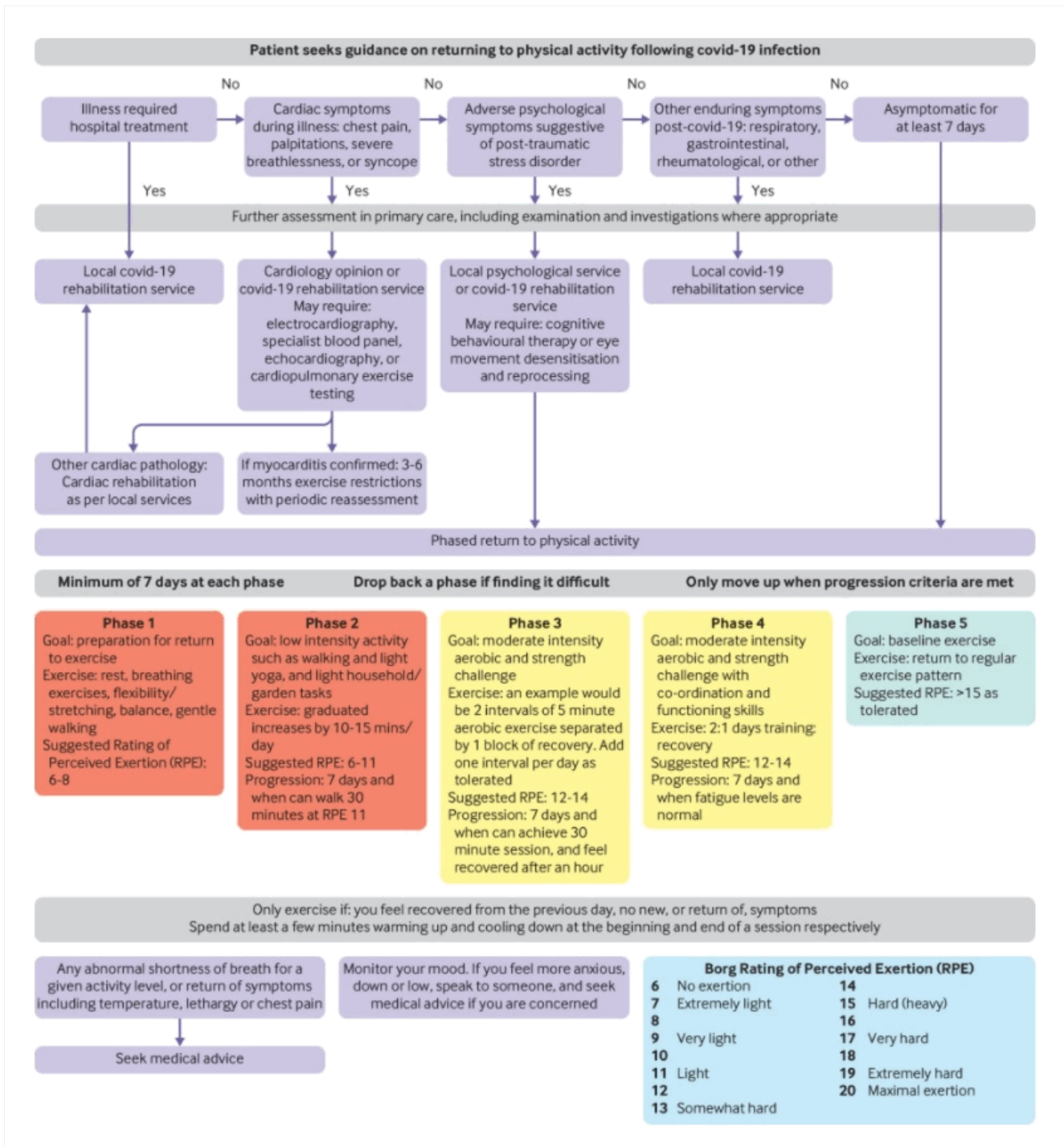


Figure 14: Suggested return to physical activity after COVID-19: risk stratification to exclude features suggestive of myocarditis or post-acute COVID-19 and phased resumption of physical activity after 7 days without symptoms

BMJ. 2021;372:m4721

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