

COVID-19 Disease

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ESSENTIALS

A novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), first appeared in the city of Wuhan in Central China in December 2019. Initial cases appeared to be centred on a so-called wet market, but the outbreak spread rapidly. The World Health Organisation (WHO) declared a Pandemic Health Emergency of International Concern on 30 January, 2020. By mid February 2021, there have been over 110 million cases globally and more than 2.4 million deaths.

The most typical symptoms are respiratory: cough, fever and shortness of breath. Sudden onset of anosmia, ageusia or dysgeusia are characteristic. Bilateral ground glass changes are often seen on CT imaging of the lungs. Detection of SARS-CoV-2 nucleic acid in a clinical specimen is diagnostic. Pneumonia and/or Acute Respiratory Distress Syndrome are the most common life-threatening complications, but thrombo-embolic disease, acute kidney injury, cardiac and neurological manifestations can also be serious. Most patients who survive the acute illness recover completely, but some suffer from a very wide variety of persistent symptoms, termed 'long Covid'. Children and young adults rarely manifest an inflammatory syndrome that fits criteria for atypical Kawasaki syndrome.

Dexamethasone is of proven efficacy in patients with COVID-19 who are requiring treatment with supplemental oxygen, and Tocilizumab (an anti-interleukin-6 receptor monoclonal antibody) is of proven efficacy in hypoxic patients with evidence of systemic inflammation. Remdesivir (an antiviral agent) may be of value in some cases. Management is otherwise supportive. For reasons that are not well understood the reported case-fatality ratio varies very widely between countries in the range 1–8.5%. Most deaths occur in the elderly or those with co-morbidities, and people from Asian, Black, mixed or other ethnic groups are at greater relative risk than whites.

Measures to prevent the spread of SARS-CoV-2 infection include (1) general advice for all—e.g. frequent handwashing, social distancing; (2) lockdowns—measures imposed by governments to reduce the frequency and proximity of contacts between individuals; (3) finding, testing, tracing and isolating of cases and their contacts; (4) vaccination—several vaccines have been proven to be effective, with mass immunization campaigns beginning from December 2020; and (5) appropriate use of personal protective equipment (PPE) by health care professionals. Never before have public health responses been subject to such intense scrutiny.

Introduction

In December 2019 cases of pneumonia of unknown etiology were seen in the city of Wuhan in Central China. This was first reported internationally on 31 December, 2019, as a severe acute respiratory syndrome. The number of cases increased rapidly in Wuhan and in Hubei Province before spreading further in China, with evidence of person to person spread. The outbreak was thought to be centred on a so-called wet market, the Huanan Seafood Wholesale Market. Most of the early cases in China were associated with contacts with residents of Wuhan.

In early January 2020 the Chinese Centres for Disease Control determined that this outbreak was caused by a novel coronavirus, now called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Spread beyond China was confirmed by the first case reported in Thailand on 13 January, 2020; followed by the first European case reported in France on 25 January, and the first UK case on 31 January. The first major European outbreak occurred in northern Italy.

The World Health Organisation (WHO) declared a Pandemic Health Emergency of International Concern (PHEIC) on 30 January 2020. By mid-February 2021, most countries had reported cases, with over 110 million cases globally and more than 2.4 million deaths.

Aetiology and pathogenesis

In early January 2020 a new virus was isolated and characterised from broncho-alveolar lavage fluid from a patient in China with the new syndrome. The virus was grown on human airway epithelial cells, Vero E6 cells, and HuL-7 cells. It was characterised by next generation sequencing and shown to be a betacoronavirus—a single strand, positive sense RNA virus. Subsequently, similar methods were used to identify the virus in nine more patients, eight of whom were from the Wuhan wet market outbreak. There was 99.98% sequence identity in the virus from all of these patients.

This new virus is distinct from SARS-CoV (79% similar) and from MERS-CoV (50% similar), and it has 85% homology with a bat coronavirus, bat-SL-CoVZC45. On electron microscopy the virus shows some pleomorphism, with a diameter varying between 60–140 nm, and with spikes of 9–12 nm length (**Figure 8.5.30.1**).

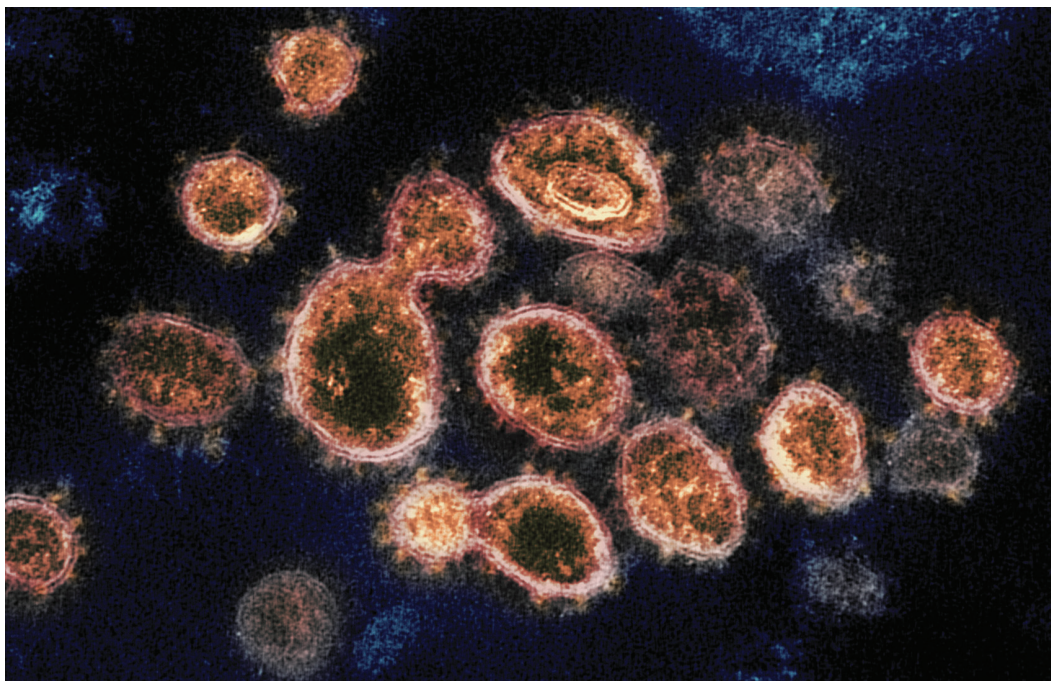


Fig. 8.5.30.1 Transmission electron microscope image of SARS-CoV-2. The spikes on the outer edge of the virus particles give coronaviruses their name, crown-like.

Image captured and colourised at NIAID's Rocky Mountain Laboratories in Hamilton, Montana. (<https://www.flickr.com/photos/niaid/49557785662/in/album-72157712914621487/>) Credit: NIAID (<https://creativecommons.org/licenses/by/2.0/>)

There are four structural proteins: spike, membrane, envelope and nucleocapsid. The spike protein is the main inducer of neutralising antibodies.

The new virus was originally termed 2019-nCoV but is now called SARS-CoV-2. Like SARS-CoV-1, which caused a significant outbreak in 2002, this new virus uses Angiotensin Converting Enzyme 2 (ACE2, whose normal action is to convert the vasoconstrictor angiotensin II into the vasodilator angiotensin) as a receptor to which the spike protein binds. The mechanism of viral entry into cells is shown in **Figure 8.5.30.2**. ACE2 is widely distributed in the upper respiratory tract but is also found in the endothelium in the lungs, kidneys, heart, gastrointestinal tract and most blood vessels.

The presence of ACE2 in many tissues no doubt explains some of the clinical features of the disease caused by SARS-CoV-2.

The immune responses to SARS-CoV-2 are not yet fully understood but, in addition to innate immune responses, there is activation of CD4+ and CD8+ lymphocytes. It is not certain if the virus infects peripheral blood mononuclear cells, although this is likely. Detailed analysis of the initial immune responses of infected patients is revealing differences between those who subsequently progress to having mild or severe disease. In convalescing patients, broad T cell responses to the spike and membrane protein can be seen. Although the role of T cells in the disease is still unclear, they might help to clear the virus but could also be responsible for some of the adverse

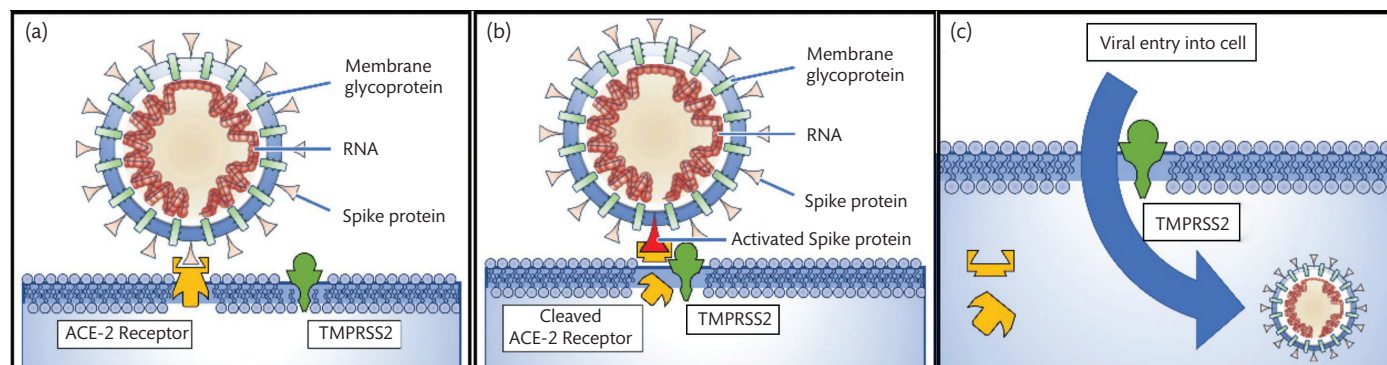


Fig. 8.5.30.2 The mechanism by which SARS-CoV-2 enters cells. (a), the coronavirus spike protein binds to angiotensin converting enzyme 2 (ACE-2) receptors on the surface of the target cell. (b), the type II transmembrane serine protease (TMPRSS2) binds to and cleaves the ACE-2 receptor, which activates the spike protein. (c), cleaved ACE-2 and the activated spike protein facilitate viral entry.

Reproduced from Rabi FA, Al Zoubi MS, Kasasbeh GA, Salameh DM, Al-Nasser AD. SARS-CoV-2 and Coronavirus Disease 2019: What We Know So Far. *Pathogens*, 2020;**9**(3):231. Published 2020 Mar 20. doi:10.3390/pathogens9030231 (<https://creativecommons.org/licenses/by/4.0/>)

clinical outcomes as the disease progresses, which is the rationale for trials of use of agents that inhibit the immune system in patients whose clinical condition is worsening over time. Patients develop neutralising antibodies, which provide some degree of protection, but the level of these antibodies vary and might be lower in those with mild disease.

As part of the infection, it has become clear that alterations in coagulation are common, possibly related to increased levels of interleukin-6 (IL-6). Plasma levels of fibrinogen and d-dimer are often markedly raised. This has led to the recognition of increased risks of thromboembolic disease in those infected.

Epidemiology

The onset of the current pandemic was reported first from Wuhan, a city of about 11 million inhabitants in Hubei province in central China. Physicians there started to see cases of 'pneumonia of unknown etiology'; the patients had a fever, chest X-ray changes suggesting pneumonia, low or normal white cells counts, and no response to 3–5 days of antibiotic therapy. Of the 45 cases first investigated, most had had some contact with the wet market in Wuhan. The median age of these patients was 59 years, and 56% were male. There were no children younger than 15 years. Most patients only sought medical attention after 5–6 days of illness, and there was a mean of about 12.5 days between symptom onset and admission to hospital. As the local outbreak increased it appeared that the mean incubation period for the disease was 5.2 days (4–7 days). The numbers of new cases initially doubled every 7.4 days. Household clusters accounted for up to 80% of cases in China.

In the absence of measures to control viral spread, the basic reproduction number (R_0) of SARS-CoV-2 (the expected number of cases directly generated by a single case in a population where all individuals are susceptible to infection) in the first wave of the pandemic was estimated to be between 2.2 and 3. For comparison the R_0 values for other well-known infectious diseases are: seasonal influenza, 0.9–2.1; pandemic influenza, 1.4–2.8; common cold, 2–3; chicken pox, 10–12; measles, 12–18.

The actual (as opposed to basic) reproduction number (R) is affected by the implementation of public health control measures, and if R is suppressed to a value <1 for a sustained period the number of cases in the population will fall. However, if mutations were to arise that increased R_0 , it would be expected that—other things being equal— R would rise and with it the number of cases. In December 2020 the Covid-19 Genomics UK (COG-UK) consortium detected such a variant (the first 'variant under investigation' in that month, hence initially named VUI-202012/01 but now generally termed B.1.1.7). This was defined by a set of 17 mutations, the most significant probably being an N501Y mutation in the spike protein responsible for viral binding to the ACE2 receptor. The first known case was in September 2020. It appears to have a selective advantage over other variants, with a rate of transmission estimated by the UK's New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) to be 71% higher, and in January 2021 it was responsible for most cases in the UK. It has subsequently been reported in many other countries, but whether it has arisen independently or through contact with cases from the UK remains unclear in most instances. The same N501Y mutation certainly seems to have

arisen independently in South Africa. There is no strong evidence that B.1.1.7 produces disease of a different severity to that caused by other strains of SARS-CoV-2, or that vaccination will offer any lesser protection against it. More recently a further variant (E484K) has arisen causing alterations in the spike protein such that it is less susceptible to neutralizing antibodies induced by natural infection.

Evolution of the pandemic

As Wuhan is a major travel hub, cases of disease appeared rapidly in other parts of China outside of Hubei province. Cases were then reported in other countries in Asia, usually with an epidemiological link to Wuhan. Further cases were soon reported from the United States and Europe, with a large outbreak in northern Italy. By this stage the disease was called coronavirus disease—now known as COVID-19.

It was quickly recognised that SARS-CoV-2 was spread person to person and seemed more infectious than either SARS-CoV-1 (R_0 0.19–1.08) or MERS-CoV (R_0 0.3–0.8). In China, Wuhan city and Hubei province were effectively 'locked down' to limit population movement and to try to find and isolate those with infection. Other countries adopted a variety of methods to attempt to limit spread of the virus, including travel restrictions, social distancing, isolation of cases, contact tracing, lockdowns and quarantines. These are discussed in the section of this chapter headed 'public health response'.

Risk factors

Increasing age and male gender are both associated with risk of infection and risk of severe disease. There is also a clear increased risk in people with Black, Asian or minority ethnic backgrounds (BAME). Clinical factors found to be important, both in terms of risk of infection and severity of infection, include chronic cardiopulmonary disease, diabetes, hypertension, obesity, and chronic kidney disease, all of which have all been associated with poorer outcomes in a variety of studies (Figure 8.5.30.3). Other factors are urban environments and social deprivation. Curiously, current cigarette smoking appears to be protective.

It became clear early in the Chinese outbreak and has been seen in every other country with COVID-19 that healthcare workers are at increased risk of infection, and every country affected has seen deaths of some healthcare workers from this infection. Preventing transmission from patients to health care workers, and from health care workers to patients and colleagues, is a substantial concern, further discussed in the section of this chapter headed 'Preventing transmission of infection'.

Transmission

SARS-CoV-2 is primarily spread by airborne transmission through droplets and aerosols. There is some evidence of transmission by fomites as well, with the virus able to remain viable on some surfaces for hours to days, but this is thought to be a minor aspect of transmission. There are high levels of virus in the nasopharynx early in the infection, including for a day or two before symptoms begin. Adults appear to have more virus than children, possibly because of increased expression of ACE2. The highest viral loads are in the first week of illness, indicating that this is the most infectious period. Although viral RNA can be detected in the nasopharynx for some weeks after infection and recovery, it has been difficult to isolate viable virus after about 8 days. Viral RNA can also be found in the

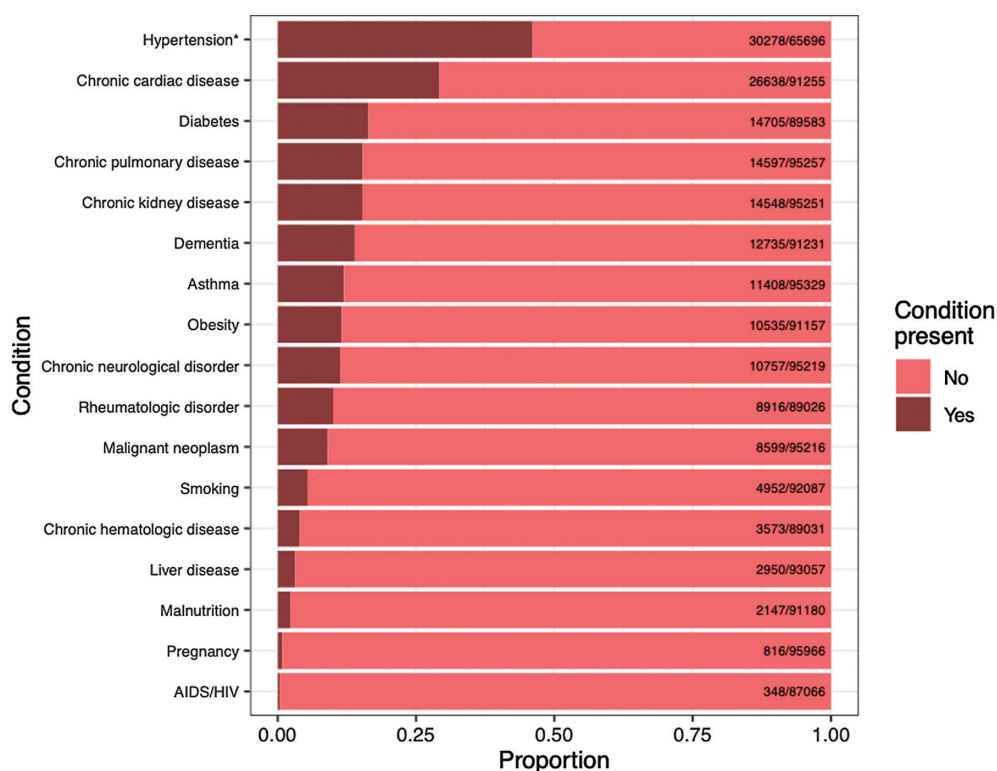


Fig. 8.5.30.3 Frequency of comorbidities or other conditions on admission of patients with COVID-19.

Reproduced from Hall M, et al. (2020). ISARIC clinical data report 20 November 2020. Posted 23 September 2020. <https://www.medrxiv.org/content/10.1101/2020.07.17.20155218v5.full.pdf> (<https://creativecommons.org/licenses/by-nd/4.0/>). The report contained data entered for 122361 individuals from 578 sites in 42 countries.

stool, although there is little evidence of faecal-oral spread. In severe cases virus can also be found transiently in the blood.

Clinical features

COVID-19 disease was initially thought to be primarily a pneumonic illness. Although it was recognised that many cases were mild, severe cases leading to death were not uncommon and it was soon appreciated that non-pulmonary presentations and extrapulmonary complications occur. The incubation period ranges from 4–6 days, but might be as long as 14 days in rare cases. Patients admitted to hospital can display a wide range of symptoms, which can be clustered into distinct sub-groups (Figure 8.5.30.4). The core symptoms are fever, cough and dyspnoea. These can be associated with three other symptoms or groups of symptoms—fatigue and confusion; diarrhoea and vomiting; and productive cough. Patients presenting with fever alone (pauci-symptomatic), cough and dyspnoea (but afebrile), and confusion are other recognized patterns. The prognosis for patients with different symptom clusters is different: those presenting with core symptoms in combination with fatigue and confusion, or with confusion alone, do particularly badly (Fig 8.5.30.5).

The WHO and other organisations have published case definitions for possible, probable and confirmed cases of COVID-19 (Table 8.5.30.1).

The WHO has defined mild, moderate and severe disease categories of COVID-19, as well as a critical disease category.

Mild disease: symptoms meeting the case definition of COVID-19, such as fever and cough, possibly with myalgia, fatigue or altered sense of taste and smell, but who have no evidence of pneumonia or hypoxia.

Moderate disease: an adult or adolescent with clinical features of pneumonia (fever, cough, shortness of breath and tachypnoea) without hypoxia; i.e. $\text{SpO}_2 \geq 90\%$ breathing room air. In children, clinical signs of non-severe pneumonia with no signs of severe disease.

Severe disease: Adults or adolescents with clinical pneumonia plus a respiratory rate $> 30/\text{min}$, severe respiratory distress, or $\text{SpO}_2 < 90\%$ breathing room air. In children, signs of pneumonia plus central cyanosis, $\text{SpO}_2 < 90\%$, inability to feed, very rapid breathing or indrawing.

Critical disease: acute respiratory distress syndrome (ARDS) or sepsis or septic shock.

In series so far, about 40% of cases are mild, 40% moderate and 15% severe, with about 5% being critical. Depending on the setting, between 20–30% of cases are admitted to hospital. It is very likely that a significant number of mild cases go unrecognised, and there is clear evidence of infections that remain entirely asymptomatic.

Acute COVID-19 - Pneumonia and Acute Respiratory Distress Syndrome (ARDS)

The onset of the pandemic began with the recognition of a new type of pneumonia characterised by fever, cough and shortness of breath (Figure 8.5.30.6). Hypoxia in association with these symptoms was common, and in most cases there were radiographic changes. In early reports from China around 70% had a cough upon admission to hospital, but only 44% had a fever, although 89% developed a high temperature at some stage. Bilateral infiltrates on chest X-ray are typical (Figure 8.5.30.7), as are bilateral ground glass changes seen on CT imaging of the lungs (Figure 8.5.30.8). Some (17.9%) with relatively mild disease had normal chest X-rays on admission, but this was uncommon (2.9%) in those with severe disease. Overall, 56.4% had ground glass changes on CT scan.

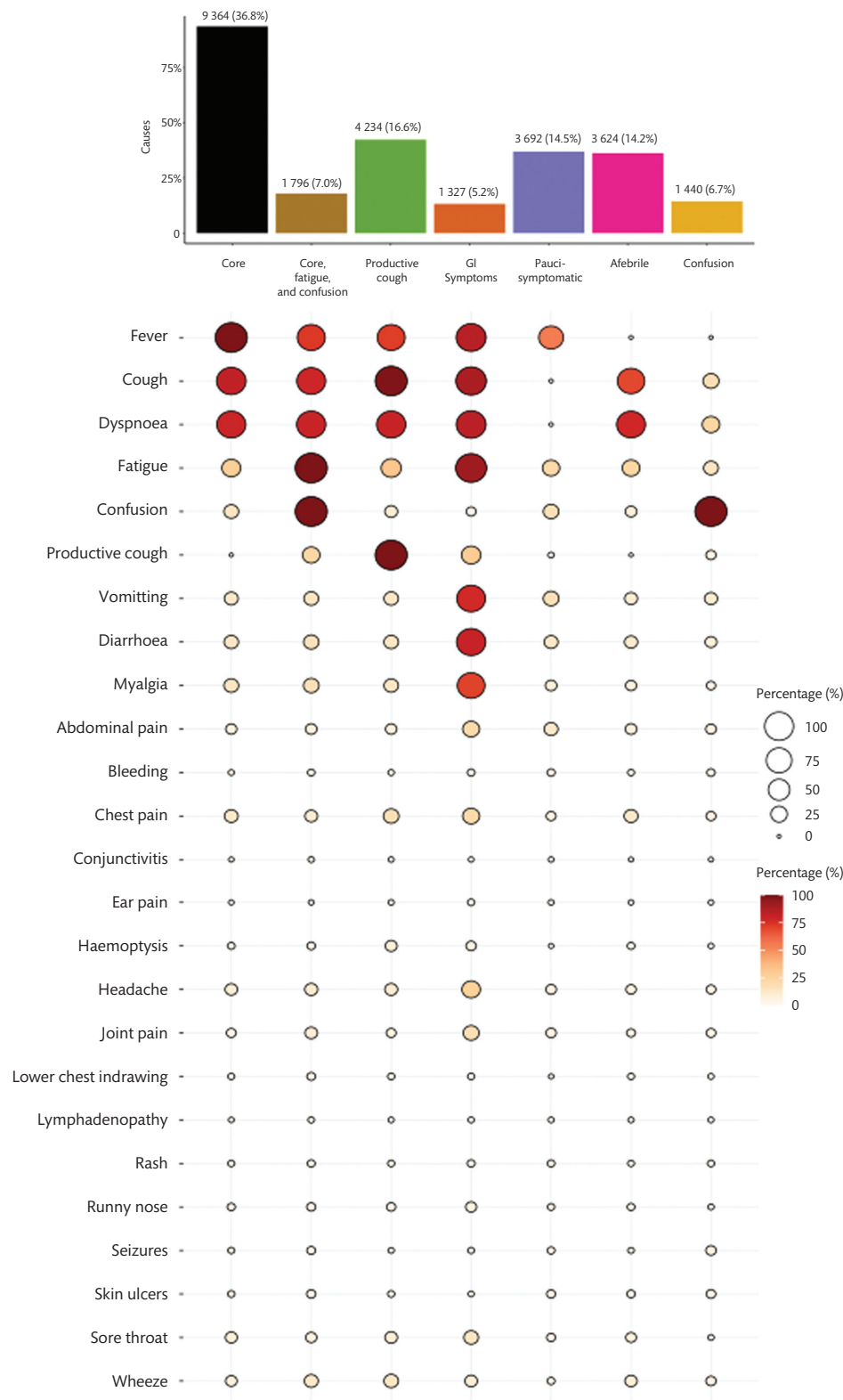


Fig. 8.5.30.4 Symptom clusters in patients with COVID-19.

Reproduced from Millar JE, et al. (2020). Robust, reproducible clinical patterns in hospitalised patients with COVID-19. Posted 10 September 2020. <https://www.medrxiv.org/content/10.1101/2020.08.14.20168088v2.full.pdf> (<https://creativecommons.org/licenses/by-nd/4.0/>). Based on structured clinical data from 59011 patients, showing cluster identities, proportions and patterns.

Pneumonia typically starts after about day 5 of the illness. The patient might have normal oxygen saturation initially, with low oxygen requirements, but this can change—sometimes within hours. Some patients seem to tolerate very low oxygen saturations without

showing any major signs of breathing difficulty. The consensus is to try to maintain oxygen saturations between 90–94%.

Most patients can be managed on a general medical ward with careful attention to treating the hypoxia with supplementary oxygen

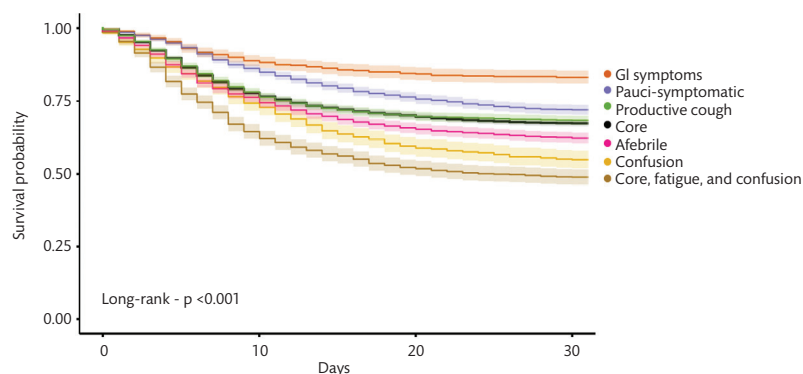


Fig. 8.5.30.5 Survival of patients with COVID-19 depending on symptoms at presentation. Unadjusted 30-day in hospital mortality is shown by cluster. Kaplan-Meier curves, those discharged before 30 days were assumed to have survived for 30 days.

Reproduced from Millar JE, et al. (2020). Robust, reproducible clinical patterns in hospitalised patients with COVID-19. Posted 10 September 2020. <https://www.medrxiv.org/content/10.1101/2020.08.14.20168088v2.full.pdf> (<https://creativecommons.org/licenses/by-nd/4.0/>). Based on structured clinical data from 59011 patients, showing cluster identities, proportions and patterns.

delivered via a face mask. Some patients require more intensive oxygen therapy with either high flow nasal oxygen, CPAP or NIV in order to maintain reasonable oxygen saturations.

About 20% of those admitted need critical care, many of whom need ventilating. A few deteriorate rapidly and require intubation and mechanical ventilation soon after admission, but the gradual development of increasing hypoxia after 5–10 days of admission is also well recognised.

ARDS can develop and lead the patient to require intubation, or it might develop in a patient already intubated. Patients with COVID-19 often behave differently from those with ARDS due to other causes. Often the lungs remain quite compliant and ventilation can be maintained with low pressures.

Table 8.5.30.1 Case definition for COVID-19

Criteria	Detail
Clinical	<ul style="list-style-type: none"> Any person with at least one of the following symptoms Cough Fever Shortness of breath Sudden onset of anosmia, ageusia or dysgeusia
Diagnostic imaging	Radiological evidence of lesions compatible with COVID-19
Laboratory	Detection of SARS-CoV-2 nucleic acid in a clinical specimen
Epidemiological	At least one of the following two epidemiological links in the 14 days prior to symptom onset <ul style="list-style-type: none"> Close contact with a confirmed case of COVID-19 Having been a resident or staff member in a residential institution for vulnerable people where ongoing COVID-19 transmission has been confirmed
Case classification	
Possible case	Any person meeting the clinical criteria
Probable case	Any person meeting the clinical criteria with an epidemiological link OR any person meeting the diagnostic imaging criteria
Confirmed case	Any person meeting the laboratory criteria

Source data from European Centre for Disease Prevention and Control, Case definition for coronavirus disease 2019 (COVID-19), as of 3 December 2020. <https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition>

An important management issue is deciding with the patient and/or their family what the ceiling of care should be, and whether intensive care is appropriate. This is of particular importance because many of those who become very unwell with COVID-19 are frail or have multiple co-existing co-morbidities.

There is little to suggest super-added bacterial infection in most patients; this probably complicates less than 10% of cases. Similarly, the infection does not seem to exacerbate airways disease in either asthma or COPD. There is evidence that surgery in patients with COVID-19 risks serious respiratory deterioration.

Acute COVID-19 - Non-pulmonary complications

Septic shock and multi-organ failure

Around 5% of cases of severe COVID-19 develop a syndrome of septic shock requiring inotropic support. Secondary infection with bacteria or fungi is rare, so this appears to be a direct or (more likely) indirect viral effect. This syndrome typically appears in the second week of illness and has been attributed to immune dysfunction leading to a cytokine storm. Levels of IL-6 and d-dimer are extraordinarily high, suggesting vascular and endothelial effects. Ferritin, C-reactive protein, and procalcitonin levels are also raised in most patients. The septic shock is usually associated with multi-organ failure and a high mortality.



Fig. 8.5.30.6 Clinicians in Beijing assess a new patient with COVID-19.

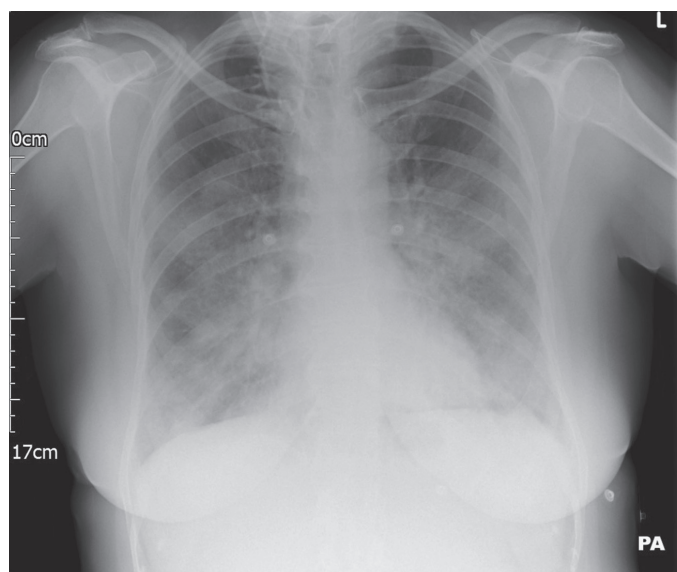


Fig. 8.5.30.7 Chest X-ray in Covid-19 showing bilateral pneumonia.

Thrombo-embolic disease

The very high levels of d-dimer and fibrinogen seen in patients with COVID-19 likely explain the fact that pulmonary emboli are common, and the thrombosis seen in very small lung vessels might contribute to the profound hypoxia seen in this condition. The hypercoagulable state might also contribute directly to kidney injury and lead to an increased risk of damage to other organs, such as the heart and brain. Prophylactic anticoagulant therapy has become a routine part of treating COVID-19 as a consequence of these poorly understood risks.

Acute kidney injury

Many patients with severe COVID-19 have proteinuria and up to 37% developed acute kidney injury (AKI), often requiring renal replacement therapy, in some case series in the first wave of the pandemic. Examination of autopsy material typically reveals acute tubular injury, and the presence of intracellular viral particles has been reported. Collapsing glomerulopathy has been described in Black patients presenting with nephrotic range proteinuria and AKI.

Cardiac disease

Elevated troponin levels have been found in many patients with severe disease, as have increased levels of BNP (brain-type natriuretic peptide). Cases of myocarditis have been reported and cardiac involvement, evidenced by these biomarkers, is associated with worse outcomes. The mechanisms involved are unclear but might involve direct viral infection: there have been reports of viral RNA being found in heart muscle, and autopsy studies show inflammatory myocardial infiltrates with macrophages and T cells. Hypoxia and respiratory disease can adversely affect the heart, and the heart can also be affected by the severe inflammatory responses seen, leading to cardiac muscle inflammation or to thrombotic events, including myocardial infarction. Echocardiographic studies have been limited by the difficulties of doing these tests in sick patients requiring infection control measures and use of personal protective equipment (PPE).

Neurological disease

Headache and dizziness are commonly reported and anosmia and altered taste are recognised symptoms, with anosmia a criterion in the case definition of COVID-19. With large numbers of frail and elderly patients admitted to hospitals with COVID-19 it became apparent that delirium was a very common feature. Some patients

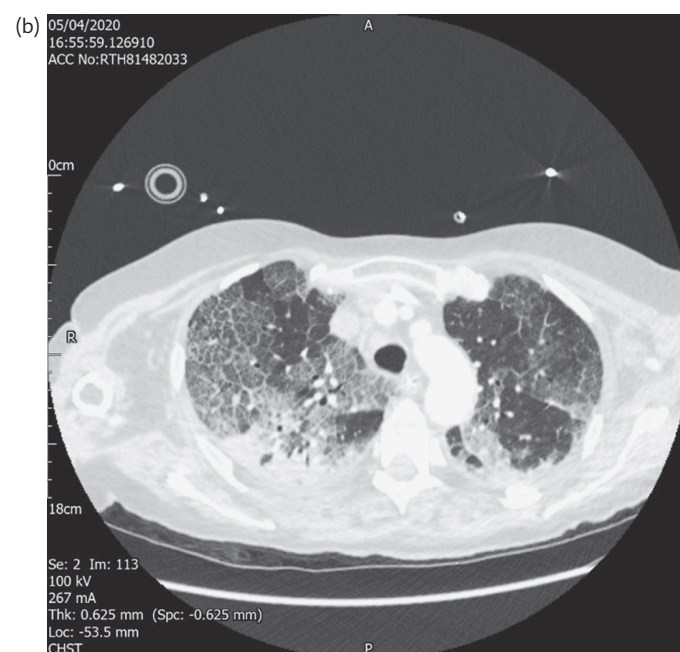
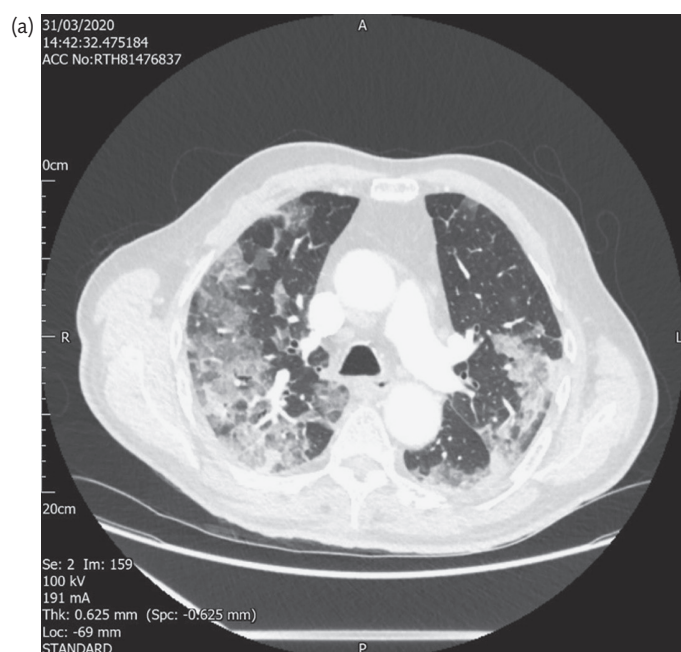


Fig. 8.5.30.8 Transverse thin-section CT scans in two patients with COVID-19 pneumonia. Panel (a) shows typical peripheral ground glass changes. Panel (b) shows the mosaic, or crazy paving, pattern as the disease progresses.

become encephalopathic and, undoubtedly, there will be cases of hypoxic brain injury. A recent autopsy study did not find evidence of virus in the brains of those studied.

Other neurological manifestations have been reported, including strokes in relatively young patients with no obvious risk factors, which seem likely to be a consequence of the abnormal clotting seen in this disease. There are also case reports of Guillain-Barre syndrome; whether this is a direct viral effect or an immunological consequence of infection is unclear. Prolonged ICU stays with severe COVID-19 can result in critical illness polyneuropathy. Other neurological manifestations that have been reported include ataxia, seizures, neuralgia, skeletal muscle injury, corticospinal tract signs, meningitis and encephalitis. Recent reports suggest an increased risk of acute demyelinating encephalomyelopathy (ADEM).

Skin disease

A variety of cutaneous manifestations have been reported in patients with COVID-19 (Figure 8.5.30.9 and 8.5.30.10).

Autoimmune and inflammatory diseases following COVID-19

Severe infection in children is rare, but many centres have reported a severe inflammatory disease in children with COVID-19 that fits the criteria for atypical Kawasaki syndrome (see Chapter 19.11.12) and has been named Paediatric Inflammatory Multisystem Syndrome (PIMS) temporally associated with COVID-19. An Italian study showed that COVID-19 increased the risk of Kawasaki 30-fold and that those infected tended to be older and have more cardiac involvement compared to children with this syndrome in the period



Fig. 8.5.30.9 Skin manifestations in COVID-19. (a, b), areas of oedema and erythema with vesicles or pustules on the fingers and toes; (c), monomorphic vesicles; (d), urticarial lesions.

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



Fig. 8.5.30.10 Skin manifestations in COVID-19. (a), maculopapular eruption with some perifollicular lesions; (b), infiltrated papules on the back of the hand and wrist; (c), erythema multiforme like lesions on the back of the fingers, hand and wrist; (d), livedoid areas on the buttocks.

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

before COVID-19. Similar presentations are rarely seen in adolescents and young adults.

Long COVID

Most patients with COVID-19 infection are asymptomatic or recover fully within a few weeks, but some do not. There is no internationally accepted definition, but the UK NICE COVID-19 rapid guideline published in December 2020 defined acute COVID-19 as symptoms and signs of COVID-19 for up to four weeks; ongoing symptomatic COVID-19 as symptoms and signs of COVID-19 from 4–12 weeks; and post COVID-19 syndrome as symptoms and signs 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. The term ‘long COVID’ is commonly used to include both ongoing symptomatic COVID-19 and post COVID-19 syndrome.

Patients report a very wide variety of persistent symptoms following COVID-19 infection (Table 8.5.30.2). A study from Wuhan, where the pandemic started, reported that 6 months after acute infection requiring hospital admission, survivors were mainly troubled with fatigue or muscle weakness (63%), sleep difficulties (26%), and anxiety or depression (23%). Such symptoms are not uncommon following any severe acute illness, and their frequency following SARS-CoV-2 infection is similar to that reported in follow up studies of SARS-CoV-1 survivors. Those who had a more severe acute illness were more likely to have abnormal chest imaging and more severe pulmonary diffusion impairment on follow up. The long term prognosis of long COVID remains unknown.

Diagnosis

Detection of viral RNA

The gold standard of diagnosis is the detection of viral RNA by reverse transcriptase polymerase chain reaction (RT-PCR) from a clinical sample, usually a nasopharyngeal swab. The accuracy of the test depends on the quality of the swab, but analytical sensitivity and specificity should both be above 95%. Studies are underway using different specimens, such as single nasal or single pharyngeal swabs, or using saliva. Viraemia appears to be transient, so testing of blood samples for viral RNA is not helpful.

As alternatives to RT-PCR, different technologies for detecting the presence of viral RNA (e.g. LAMP, loop-mediated isothermal amplification) can also provide high analytical sensitivity and specificity. This technology is relatively simple: the equipment is less elaborate and can be used by staff after brief training. Such assays lend themselves to point of care testing.

Detection of antigen

This is the aim of the many COVID-19 rapid antigen test kits, often termed ‘lateral flow tests’. A nose or throat swab, although some tests use saliva, is placed in a buffer solution that lyses any cellular or viral material present. A drop of the solution is placed in the well of the test device, where it is drawn down onto an adsorbent strip. As it moves along the strip the solution reaches a set of labelled antibodies that recognize viral epitopes. The solution, now containing both labelled antibodies bound to viral epitopes and free labelled

Table 8.5.30.2 Common symptoms of long COVID.

Symptom type	Symptoms
Respiratory	Breathlessness Cough
Cardiovascular	Chest tightness Chest pain Palpitations
Generalised	Fatigue Fever Pain
Neurological	Cognitive impairment ('brain fog', loss of concentration, poor memory) Headache Sleep disturbance Of peripheral neuropathy Dizziness Delirium
Gastrointestinal	Abdominal pain Nausea Diarrhoea Anorexia
Musculoskeletal	Joint pain Muscle pain
Psychological / psychiatric	Depression Anxiety
Ear, nose and throat	Tinnitus Earache Sore throat Dizziness Loss of taste and/or smell
Dermatological	Rashes

Modified from NICE guideline [NG188]. COVID-19 rapid guideline: managing the long-term effects of COVID-19.

antibodies, migrates further down the strip. A line of fixed antibodies that recognize and bind to viral epitopes forms the test zone, and a second line of fixed antibodies that recognize the labelled antibodies forms the control zone. The presence of a coloured band in the control zone indicates that the test has worked; if virus has been detected a coloured band also appears in the test zone. Results are available in 10–30 minutes.

The advantages of lateral flow tests include simplicity (people can administer the test themselves) and speed. The main disadvantage is lack of sensitivity (Fig. 8.5.30.11), although the best-performing tests have very high specificity (>99%). In other words, they are good 'rule in' tests but not good 'rule out' tests.

Antibody detection

There are several commercial tests available to detect IgG and IgM responses to SARS-CoV-2. Some kits detect antibodies to the spike protein, some to nucleocapsid, and some to both proteins. Antibodies generally appear about 7 to 10 days after infection, IgM before IgG as expected, and levels are usually highest a few weeks after infection. A Cochrane review found that antibody tests one week after symptoms started only detected 30% of patients with COVID-19, hence they cannot play a primary role in diagnosis of acute presentations. Patients with severe infection do appear to generate a more pronounced antibody response than those with mild disease, and the presence of anti-spike or anti-nucleocapsid antibodies is associated with a substantially reduced risk of SARS-CoV-2 reinfection in the ensuing six months

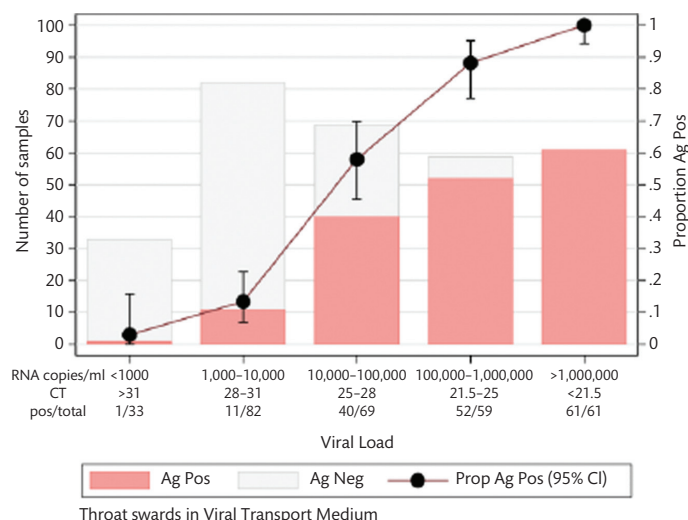


Fig. 8.5.30.11 Sensitivity of lateral flow tests. Clinical samples were placed in viral transport medium allowing direct comparison of viral load determined by PCR and antigen tests. Samples with a PCR Cycle Threshold (CT) of <25.5 (calculated as viral load >10⁵ RNA copies/ml) had a 90% or greater chance of being detected as antigen positive, but samples with CT 28–31 – which would clinically be reported as positive – were detected in only about 12% of cases.

From - Preliminary report from the Joint PHE Porton Down & University of Oxford SARS-CoV-2 test development and validation cell: rapid evaluation of lateral flow viral antigen detection devices (LFDs) for mass community testing. 8 Nov 2020. https://www.ox.ac.uk/sites/files/oxford/media_wysiwyg/UK%20evaluation_PHE%20Porton%20Down%20University%20of%20Oxford_final.pdf (Open Government Licence v3.0)

(adjusted incidence rate ratio 0.11 with 95% confidence interval 0.03–0.44 in a study of health care workers). Some patients who appear to have had COVID, including some with anosmia, have not developed antibodies.

Long COVID

There is no diagnostic test for long COVID and it is likely that a number of different conditions may contribute to persistent symptoms after acute SARS-CoV-2 infection, e.g. post intensive care syndrome, post viral fatigue syndrome, ongoing symptomatic COVID-19, post COVID-19 syndrome. Some patients may suffer with more than one of these syndromes at the same time. It is likely to be unhelpful to pursue debate about whether a particular patient does or does not have long COVID, because the approach to management should not be altered by the presence or absence of this label. If a patient has persistent symptoms after SARS-CoV-2 infection and feels benefit from being given a diagnosis of long COVID, there seems little to be gained for that patient by disputation.

Management

Minor symptoms

Many cases of SARS-CoV-2 infection are asymptomatic or minimally symptomatic. Fever and myalgia can be treated with paracetamol or ibuprofen (initial concern that the latter may be associated with adverse outcome has not been substantiated). Cough may be helped by encouraging patients to avoid lying on their back, also by taking a teaspoonful of honey. Codeine linctus and (second

choice) morphine sulphate should only be prescribed if the cough is distressing. Antibiotics should not be recommended.

Patients with minor symptoms should be counselled about signs of worsening disease that should prompt them to seek urgent care. These include light-headedness, breathing difficulty and chest pain.

In many countries COVID-19 is a notifiable disease, requiring the relevant authorities to be informed of all cases.

Management of complications

The general approach to the seriously ill or deteriorating patient is described in Chapter 17.1, management of acute respiratory failure in Chapter 17.5, and the circulation and circulatory support of the critically ill in Chapter 17.6. The following discussion relates to particular aspects in the management of patients with COVID-19.

Respiratory support

Adults with respiratory distress should receive emergency airway management (if needed) and oxygen therapy, initially to target $\text{SpO}_2 > 94\%$. A target $\text{SpO}_2 > 90\%$ can be introduced when the patient is stable. Techniques such as positioning with high supported sitting may ease breathlessness, reduce energy expenditure and improve oxygenation. Increased production or retention of airway secretions, or weak coughing, may be helped by gravity-assisted drainage and encouragement of active cycles of breathing technique.

Any patient with respiratory manifestations of COVID-19 needs to be monitored closely for signs of deterioration, most particularly development of acute respiratory distress syndrome (ARDS). In selected patients a trial of high-flow nasal oxygen or non-invasive ventilation by continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) may be appropriate, all of which are currently regarded as potential aerosol generating procedures requiring enhanced protection for staff (see section headed 'Preventing transmission of infection'). Intubation should not be delayed if the patient deteriorates or does not improve after a short trial of these non-invasive methods of respiratory support.

Mechanical ventilation should be implemented in line with standard practice of protective lung ventilation, employing an initial target tidal volume of 6 ml/kg predicted body weight and a low inspiratory pressure (plateau pressure < 30 cm H_2O). Deep sedation may be required to achieve this. Permissive hypercapnia is tolerated. Prone ventilation for 12–16 hours per day is recommended, where possible. The optimum level of positive end-expiratory pressure (PEEP) to employ is uncertain, and in routine practice this is adjusted depending on individual response. Use of high PEEP and prolonged high-pressure recruitment manoeuvres (temporary sustained increase in airway pressure with the intention of opening collapsed alveoli) was found to cause harm in a randomised trial, and recruitment manoeuvres should not be used unless the particular patient responds favourably to an initial application of them.

Patients with refractory hypoxaemia despite protective lung ventilation, e.g. ratio of partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) of < 50 mmHg for three hours, or $\text{PaO}_2/\text{FiO}_2 < 80$ mmHg for more than six hours, may be referred for consideration of extracorporeal membrane oxygenation (ECMO). A study of data from 1035 patients suggests the mortality 90 days after the initiation of ECMO in patients with SARS-CoV-2 infection is in the range 35–40%, but no randomized controlled trials have been reported and hence definitive conclusions cannot be drawn as to whether ECMO provides benefit.

Fluid management, septic shock and acute kidney injury

Concern that aggressive fluid resuscitation may worsen oxygenation and precipitate or prolong the need for mechanical ventilation in circumstances where availability of such support is limited has led to recommendations that intravenous fluids should be used cautiously. Such an approach may be in part responsible for the high incidence of acute kidney injury that was found in early reports.

Patients with clinical evidence of tissue hypoperfusion (particularly cool peripheries and/or oliguria and/or elevated serum lactate) should be given rapid boluses of 250–500 ml of crystalloid fluid, repeated depending on response. Intravenous fluids should be reduced or stopped if there is no response to fluid loading or signs of volume overload appear. As is routine, vasopressors (usually nor-epinephrine in the first instance) are used when shock persists despite fluid resuscitation, with an initial blood pressure target typically being a mean arterial pressure > 65 mmHg.

It is clearly appropriate to stop angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) if patients are hypotensive or hyperkalaemic, but otherwise there is no evidence that stopping these drugs reduces the severity of COVID-19 disease.

There are no particular theoretical reasons for changing the indications for or means of delivery of renal replacement therapy in the context of COVID-19, but resource constraint led to changes in practice in many centres in the first wave of the pandemic. These included raising the threshold for initiation of renal replacement therapy and use of different techniques to provide it. In high income countries virtually all renal replacement therapy provided in ICUs has been by continuous haemofiltration or haemodiafiltration, but many centres faced a challenge of needing to treat unprecedented numbers of patients, compounded by the hypercoagulable state induced by COVID-19 causing problems with clotting of the extracorporeal circuit. This led to exhaustion of supply of machines and key consumables in some centres, with clinicians forced to look to other techniques. These have included the use of peritoneal dialysis and sustained low-efficiency dialysis (SLED), which has the advantage of not requiring specialised pre-manufactured fluid solutions.

Thromboembolism

Patients admitted to hospital with COVID-19 are at high risk for both arterial and venous thrombosis and/or thromboembolism. Thromboprophylaxis should be given to all excepting those at very high risk of bleeding. The optimal regimen is unclear: prophylactic dose low molecular weight heparin (LMWH) is generally given to patients managed on a ward, but—following interim data showing benefit of therapeutic anticoagulation in moderately ill but not severely ill patients on critical care units—intermediate dose LMWH considered for patients in critical care. Continuation of treatment with either low molecular weight heparin or a direct acting oral anticoagulant (DOAC) for up to four weeks after discharge is recommended in patients deemed to be at high risk of VTE and low risk of bleeding.

Autoimmune and inflammatory diseases following COVID-19

Management is supportive. The finding of very high levels of IL-6 has led to use of agents that block the IL-6 receptor (tocilizumab, sarilumab), with some case reports suggesting benefit, although it is typically impossible to be certain of cause and effect in the context of multiple interventions in a very sick patient. Treatments

aimed at suppressing immune responses in this group of patients are preferably only to be used in the context of clinical trials (see section headed 'Specific treatments').

Specific treatments

Triallists, funders and regulators have responded rapidly to the COVID pandemic. The NIH ClinicalTrials.gov website, searched for 'treatment / COVID-19' on 16 January 2021, listed 2868 studies. Unfortunately, most of these are too small and poorly designed to be useful, but some very impressive work has been done. The largest study of treatments, the Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial, is using an adaptive design allowing an independent data monitoring committee to perform interim assessments of whether the randomised comparisons have provided evidence on mortality that is strong enough to affect treatment strategies. As of February 2021, over 37000 participants had been recruited from 178 sites, and important outcomes reported.

Dexamethasone

Analysis of the RECOVERY trial after 2104 patients randomly allocated to receive dexamethasone (6 mg once daily for 10 days) were compared with 4321 patients concurrently allocated to usual care showed that dexamethasone reduced deaths by one-fifth in patients receiving oxygen without invasive mechanical ventilation and by one-third in patients receiving invasive mechanical ventilation. Dexamethasone is now standard of care in these circumstances. Mortality was not reduced in patients not receiving respiratory support at randomisation (17.0% vs 13.2%; RR 1.22, 95% CI 0.93–1.61), and steroids should not be used in patients with non-severe COVID-19 (Fig. 8.5.30.12).

A study of intravenous hydrocortisone (50 or 100 mg four times daily) was stopped when the effects of dexamethasone in the RECOVERY trial were released into the public domain, but its findings were consistent with the RECOVERY results.

Remdesivir

Remdesivir is a monophosphoramidate prodrug of an adenosine analogue that has a broad antiviral spectrum. An early randomized study showed that giving remdesivir (200 mg on day 1 and 100 mg on subsequent days) to patients with lower respiratory tract involvement with COVID-19 found median recovery time was reduced from 15 to 11 days, and largely on the basis of this it was

approved for treatment worldwide. In November 2020 the WHO issued a conditional recommendation against its use in hospitalized patients, regardless of disease severity, because of lack of evidence that it improved survival or other outcomes.

Interleukin-6 receptor antagonists

The finding of high levels of interleukin-6 in severe cases of SARS-CoV-2 infection led naturally to the hypothesis that blocking its action might be therapeutic. Tocilizumab and sarilumab are anti-interleukin-6 receptor monoclonal antibodies approved for the treatment of several inflammatory diseases. The Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP) reported (as of 16 January 2021 as a pre-print) that both tocilizumab and sarilumab reduced the need for organ support and improved survival in critically ill patients. The RECOVERY trial, reported on 11 February 2021 (as a pre-print), randomised patients with hypoxia and evidence of systemic inflammation (CRP >75 mg/L) to tocilizumab or usual care: 29% of 2022 given tocilizumab died, compared with 33% of 2094 who received usual care. This benefit was seen regardless of the level of respiratory support and was additional to the benefits of systemic corticosteroids, which were being given to 82% of patients at randomisation.

A single dose of Tocilizumab (400–800 mg depending on estimated body weight), repeated 12–24 hours later if the patient has not improved, is now standard of care for patients with the characteristics of those entered into the RECOVERY trial.

Plasma therapy

On the basis that antibodies are a crucial part of the host response to infection, several randomized trials have been undertaken to see if convalescent plasma is efficacious. One study that recruited 228 patients with severe Covid-19 pneumonia showed no benefit. Another small study was stopped early, after recruitment of only 160 patients, but reported that early administration of high titre plasma reduced progression to 'severe respiratory disease' in infected older adults (75 yr or older, or 65–74 yr with a comorbidity increasing risk of a poor outcome) who were mildly ill. Life-threatening respiratory disease, critical systemic illness, or death, alone or in combination were not significantly different (relative risk 0.58 with plasma, 95% CI 0.24–1.41). On 15 January 2021 the RECOVERY trial closed recruitment to convalescent plasma treatment because its independent data monitoring committee, based on 1873 reported deaths in 10406

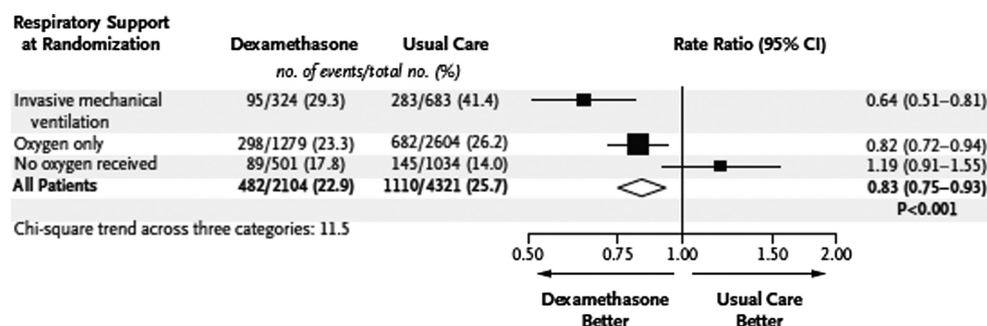


Fig. 8.5.30.12 Effect of dexamethasone on 28-day mortality, according to respiratory support at randomization.

From RECOVERY Collaborative Group. (2020) Dexamethasone in hospitalized patients with Covid-19 – preliminary report. *N Engl J Med*, doi: 10.1056/NEJMoa2021436 with permission from Massachusetts Medical Society.

randomised patients, found no difference in the primary end point of 28-day mortality (18% with both plasma and usual care). Based on these studies it does not seem appropriate to use plasma therapy in patients who are ill with COVID-19, and the evidence for use in those with mild disease is weak.

Other agents

Trials done so far have clearly shown that some of the early treatments suggested, such as hydroxychloroquine and azithromycin, have no benefit. New data on other therapies are becoming available almost every day. Information from a living systematic review of drug treatments for COVID-19 is shown in **Figure 8.5.30.13**. Aside from corticosteroids, two agents listed are particularly worthy of comment.

Recombinant human granulocyte colony stimulating factor (rhG-CSF)—the data come from a single trial of 200 lymphopenic patients, half of whom were given rhG-CSF in addition to usual care. The primary end point was the time from randomization to improvement of at least one point on a seven-category disease severity score. rhG-CSF did not accelerate clinical improvement, but the number of patients developing critical illness or dying might have

been reduced, although these findings were graded as having low or very low certainty. Further studies are needed before rhG-CSF could be recommended as a standard treatment.

Colchicine—effect was reported on duration of hospital stay and not on any more significant clinical outcome. Further information on colchicine's role in treatment should be available when the relevant arm of the RECOVERY trial reports, but it cannot yet be regarded as a standard of care.

Given the consideration that immune dysfunction may drive some of the pathology of severe COVID-19, trials of immune suppressants in such cases will be of particular interest. Aside from IL-6 receptor blockers, discussed above, the effect of Baricitinib (a JAK inhibitor used as a second-line treatment for rheumatoid arthritis) is being assessed in the RECOVERY and TACTIC-R (MulTi-Arm therapeutic sTudy in pre-ICU patients admitted with COVID-19—Repurposed drugs) trials, and the latter is also testing Ravulizumab (a blocker of C5 activation used as treatment for paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome).

Patients with suspected or confirmed COVID-19 should not be prescribed antibiotics unless there is suspected bacterial

	Mortality	Mechanical ventilation	Adverse events	Admission to hospital	Viral clearance at 7 days	Duration of hospital stay	ICU length of stay	Duration of mechanical ventilation	Time to symptom resolution	Time to viral clearance	Ventilator free days
Standard care*	130 per 1000	116 per 1000	15 per 1000	43 per 1000	484 per 1000	13 days	13 days	15 days	11 days	10 days	11 days
Azithromycin	6 (-40 to 62)	1 (-60 to 90)				0.4 (-2.9 to 3.9)					-1.7 (-5.1 to 1.8)
Colchicine	-106 (-129 to 42)					-1.6 (-2.8 to -0.3)**					
Corticosteroids	-17 (-34 to 1)	-29 (-54 to 1)			5 (-426 to 458)	-0.9 (-3.4 to 1.7)	-3.8 (-5.9 to -1.8)	-1.4 (-3.4 to 0.62)			2.6 (0.2 to 5.0)
Favipiravir	63 (-113 to 773)				81 (-301 to 399)						
Hydroxychloroquine	11 (-11 to 38)	20 (-18 to 76)	16 (-11 to 192)**	-26 (-38 to 12)**	18 (-293 to 334)	0.1 (-1.9 to 2.0)			-2.0 (-4.0 to 0.1)	-0.7 (-4.3 to 4.8)**	
Hydroxychloroquine + azithromycin	-48 (-103 to 66)	58 (-32 to 216)				0.6 (-1.2 to 2.4)**					
Interferon beta	2 (-35 to 35)	-13 (-60 to 45)									
Interferon gamma					436 (-215 to 516)						
Interferon kappa+ trefoil factor 2					290 (-334 to 503)						
Lopinavir-ritonavir	-12 (-31 to 10)	10 (-31 to 60)			-235 (-449 to 164)	-0.4 (-1.7 to 0.6)**			-1.0 (-4.1 to 3.2)		
Nitazoxanide											
rhG-CSF	-102 (-124 to -41)	-96 (-108 to -68)				-0.7 (-2.3 to 1.0)**			-0.8 (-4.5 to 4.6)		
Remdesivir	-12 (-35 to 14)	-33 (-65 to 1)	0 (-9 to 40)		14 (-429 to 460)	-0.2 (-1.9 to 1.2)**		-1.3 (-4.1 to 1.5)	-2.0 (-4.2 to 0.9)		
Tocilizumab	5 (-46 to 81)	-35 (-80 to 54)	-8 (-15 to 300)**			-2.5 (-6.9 to 1.8)	-4.5 (-13.8 to 4.9)		-1.8 (-5.0 to 3.4)		4.7 (-4.2 to 13.9)
Umifenovir	-130 (-130 to 870)										

Most beneficial Intermediate benefit Not different from SC Harmful

High/moderate certainty Low/very low certainty

*The expected risk of each outcome with standard care is reported in the grey row. Numbers in the coloured cells are the estimated risk differences (95% CI) per 1000 patients or mean difference (95% CI) in days when compared to standard care

** The best estimate of effect was obtained from direct evidence

Empty cells: there was no evidence for the specific intervention

rhG-CSF: Recombinant human granulocyte colony-stimulating factor

Fig. 8.5.30.13 Treatment Systematic Review. Summary of effects of different treatments compared with standard of care.

Reproduced from Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ*. 2020 Jul 30; 370:m2980. doi: 10.1136/bmj.m2980. Update in: *BMJ*. 2020 Sep 11;370:m3536. Update in: *BMJ*. 2020 Dec 17;371:m4852. PMID: 32732190; with permission from BMJ. Accessed 17 January 2021. Note that this review was conducted before the outcomes using Tocilizumab in the REMAP-CAP and RECOVERY trials were reported.

superinfection as evidenced by purulent sputum, neutrophilia or a raised serum procalcitonin, or if bacterial pneumonia is a plausible differential diagnosis. Excepting in the influenza season, empiric oseltamivir is not indicated.

Other issues

Ethical challenges

The burden of COVID-19 has led to many ethical questions, notably including prioritisation of treatment. In simple terms, if there aren't enough ventilators, who should get one? It is no surprise that there are no clear-cut answers, but the pandemic has stimulated a proliferation of discussion of ethical issues in much the same way as it has done SARS-CoV-2 biomedical research. Principles that seem to be broadly but not universally accepted include maximising benefits (saving the most lives, or the most life-years), treating people equally (random selection among patients with similar prognosis), promoting and rewarding benefit to others (which accords priority to health care workers who become ill), and giving priority to the worst off (sickest first or youngest first). The judgments that need to be made here are excruciatingly difficult, and decision making of this sort should not fall on the shoulders of the treating physician. There is an unmet need for clear prioritisation guidelines that are accepted by populations (and which may differ between populations who prioritise different things), also the development within hospitals of agreed and practical means of applying such guidelines that relieve individual front-line clinicians of the burden.

End of life care

The pandemic has led many people, particularly those who are old and frail, to think of the prospect that they might die sooner rather than later. Advanced care planning should focus on encouraging them to talk about their concerns and their priorities with their loved ones, providing information to support such conversations in a kind but realistic way. Managed well, these conversations can strengthen relationships, as well as leading to a documented plan of treatment preferences (including place of care, level of treatment, resuscitation status) that is pragmatically useful if the worst happens.

Rehabilitation

Patients who are severely affected with COVID-19 and need mechanical ventilation do so for longer than most patients who require such support on intensive care units for other reasons. They are, therefore, likely to suffer a greater degree of deconditioning, and those who survive require physical, cognitive and/or psychological rehabilitation. These issues were under-recognised in the early stages of the pandemic, but the needs of patients with long COVID are now better understood, although provision for these needs remains very patchy.

Mental health

The most obvious and dramatic consequences of SARS-CoV-2 infection relate to physical health, but 'lockdown' has increased social isolation and loneliness, which are strongly associated with anxiety, depression, self-harm, and suicide attempts. It is not clear how best to provide mental health care in the context of the pandemic, but emphasis needs to be put on finding ways of promoting good mental

health while people are isolating or shielding in their homes, and of treating those with mental health conditions remotely.

Mental health of health care workers

Many health care workers are used to and appear to thrive on long hours with high stress, and these challenges were present in abundance in the first wave of the pandemic. However, as health care systems try to deal with the second wave, more consideration has been given to its impact on health care workers themselves. Aside from the obvious risks of acquisition SARS-CoV-2 infection (see Preventing transmission of infection) and exacerbation of individual tendencies to some mental health disorders, these impacts are now being described in terms of 'moral distress'. This describes the building up of profound unease in health care professionals who are unable to fulfill what they consider to be their professional obligations to provide care of good quality because of the circumstances that they find themselves in, which they feel powerless to do anything about. It is not clear how colleagues suffering from moral distress can best be helped, but acknowledging the issue must be a pre-requisite.

Management of long COVID

Patients with persistent symptoms after acute SARS-CoV-2 infection require a sympathetic approach, assessment for treatable medical complications or conditions, and support for rehabilitation.

Preventing transmission of infection

COVID-19 cases in the community

All patients and those living with them should follow current local guidance and/or laws that are intended to reduce the chances of transmission of the virus to other people. The details vary from country to country, sometimes from area to area within a country; in all countries they change with time, sometimes from week to week. It is essential that health care workers keep themselves well informed on these matters, which are discussed in the section of this chapter headed 'Public health response'.

The WHO recommends that anyone with suspected COVID-19 who is isolating at home should wear a surgical, fluid resistant face mask, as should anyone who is caring for them. It is important to recognise, however, that wearing a mask is not a substitute for control measures such as hand hygiene and physical distancing.

COVID-19 cases in hospital or other care facilities

Patient to patient transmission

To prevent transmission of SARS-CoV-2 from patient to patient it is clearly necessary to separate those who are infected and capable of infecting others from those who are not. In an ideal facility for the purposes of managing the COVID-19 pandemic, all patients arriving in hospital would be assessed and managed in single rooms until it was clearly established that they did or did not have SARS-CoV-2 infection. There are very few such facilities, and none that we are aware of in large hospitals. Indeed, few Emergency Departments are designed in a way that allows straightforward cohorting of large numbers of potentially infected patients to separate them from many others who are unlikely to be

infected: most will have one or two rooms in which single patients can be isolated.

All Emergency Departments should try, so far as they can, to triage patients on arrival into those who are likely to have COVID-19 (typically managed in a 'red' area / ward) and those unlikely to be infected ('green'). All should be tested for infection (preferably by swabs for RNA-based analysis) as soon as possible, with results obtained as rapidly as possible, to enable appropriate onward placement onto red or green wards of those requiring admission (and notification of infection status for any being returned to their normal place of residence, which is particularly important for those living in care homes). Whilst waiting for swab results to support red/green assignment, or for placement of patients that have been exposed and may be incubating infection, many hospitals have developed 'amber' areas or wards, where patients are managed in single rooms or on wards with reduced capacity, reduction in the number of open beds allowing greater than normal physical distancing between patients.

There are many nuances and difficulties with such arrangements, including but not limited to the following. Some patients may be thought very likely to have COVID-19 on clinical grounds and yet their RNA-based test is negative: where should they be placed? The pre-test possibility of a patient having COVID-19 will vary substantially depending on the prevailing local incidence rate: if a patient thought unlikely to have COVID-19 on clinical grounds tests positive at a time when this is low, the test is likely to be a false positive—so where should they be placed? Given that most hospitals have a limited number of side rooms, should these be used to isolate patients who have COVID, or to protect those who do not? The least worst answer will likely depend on the stage of the pandemic: in simple terms, if most patients in the hospital do not have COVID the priority will be to isolate those that do, but if most patients in the hospital have COVID the priority may switch to isolating those that do not. There are no right answers to these questions. Any plan that says, 'this is what we're going to do', will undoubtedly fail: no battle plan ever survives contact with the enemy (paraphrase of Helmuth von Moltke the Elder). Difficult judgements, requiring intelligent clinical leadership, need to be made hour by hour and day by day as circumstances change.

Patient to health care worker or health care worker to patient transmission

Very few doctors working in high- and middle-income countries, and few working in low income countries, have ever experienced a situation in which there was significant concern that a patient might give them a life-threatening disease. Outbreaks of Ebola and various other viral haemorrhagic fevers are geographically very restricted, and the rare cases of these conditions that are managed in high- and middle-income countries (typically health care workers who have been repatriated when they became ill) are cared for by specialist teams in centres with biocontainment facilities. All is now changed, changed utterly. Many doctors and other health care workers have cared for and are caring for patients with COVID-19, and many have been infected, sometimes from patients or other health care professionals at work, and occasionally with fatal outcome.

Preventing spread of COVID-19 from patients to health care workers, and from health care worker to patients, is of vital

importance. Aside from the fundamental point that stopping the pandemic requires reducing viral transmission, those employing health care staff have a duty of care towards them, and the impact on the provision of all elements of health care—not just for those suffering from COVID-19—of very large numbers of health care staff becoming ill or having to isolate for other reasons is considerable.

The predominant modes of transmission of SARS-CoV-2 are droplet and contact, and key to reducing the risk of transmission is adherence to sensible infection prevention and control guidance, e.g. social / physical distancing (whenever possible), optimal hand hygiene, frequent surface decontamination and provision of adequate ventilation. Aside from these, there is a need for additional precautions to reduce the risks of transmission via contact (direct or from the immediate care environment), droplets (particles of size $>5\mu\text{m}$ arising from the respiratory tract) or aerosols (particles of size $<5\mu\text{m}$ arising from the respiratory tract).

Many different organisations, ranging from the WHO to national health bodies to clinical specialty societies to individual hospitals, have produced guidance on which precautions are required in which circumstances, and what personal protective equipment (PPE) is needed. There is reasonably good concordance between most of these many guidance documents, but there has been much debate in a situation where facts are scarce, risks are high, many are frightened, and some lack trust in those leading health services. Acknowledging this context, the guidance produced by Public Health England is regarded by most as being reasonable.

A key standard precaution is hand hygiene. The proper technique for hand washing is shown in [Figure 8.5.30.14](#), and for hand decontamination with an alcohol-based hand rub is shown in [Figure 8.5.30.15](#). One or other of these should be performed before every episode of direct patient care and after any activity that potentially results in contamination of the hands. Audits of compliance with hand hygiene often reveal that this is poor, and it is regrettable and should be a cause of shame that doctors frequently feature amongst the non-compliant.

The level of PPE recommended depends on the risk of SARS-CoV-2 transmission ([Table 8.5.30.3](#)). Standard PPE of plastic apron, surgical (fluid resistant) face mask, eye protection (if worn), and disposable gloves should be used when direct patient care is given to an individual who does not meet the definition for a possible or confirmed case of COVID-19 ([Figure 8.5.30.16](#)).

When working in areas with possible or confirmed cases, many hospitals require staff to wear surgical scrubs (which are not traditionally regarded as items of PPE) and standard PPE (including eye protection) throughout the duration of their shift, with the apron and gloves changed after every direct patient contact. Some hospitals also require staff to wear surgical caps in this scenario.

Further enhancement of PPE is required in cohorted areas where aerosol generating procedures (AGPs) are frequently carried out with suspected or confirmed cases of COVID-19, most obviously including critical care areas. Aside from surgical scrubs, core PPE to be worn throughout the duration of a shift consists of a water-repellent gown, a filtering face piece (FFP) mask (preferably an FFP3 mask, which filters at least 99% of airborne particles; FFP2 and N95 respirators filter at least 94% and 95% of airborne particles respectively), eye protection, theatre cap (not recommended in all guidance), and disposable gloves. An apron is worn for direct patient

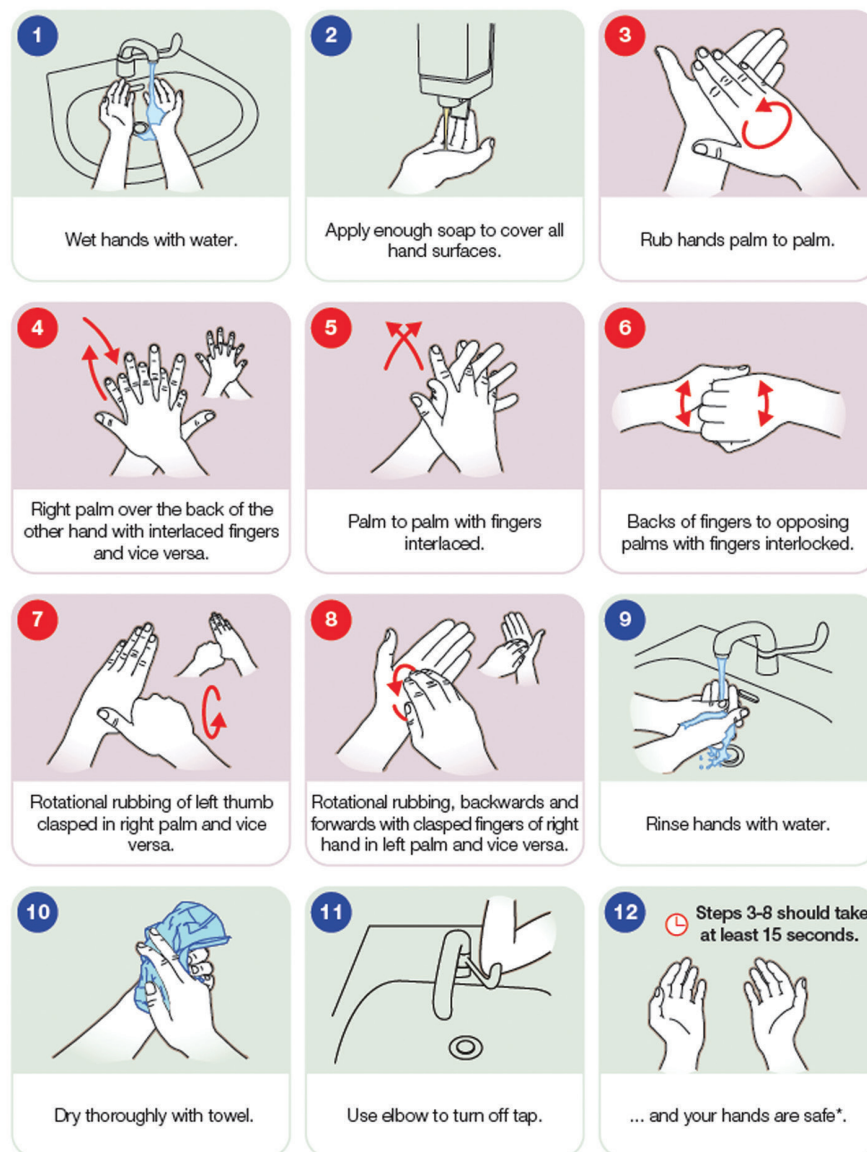


Fig. 8.5.30.14 How to handwash. Footnote: Steps 3-8 should take at least 15 seconds.
With permission from Public Health England, Crown Copyright 2020 (Open Government Licence v3.0).

contact, and gloves and apron are changed after every direct patient contact. The correct methods for putting on and taking off PPE for aerosol generating procedures are shown in [Figure 8.5.30.17](#) and [Figure 8.5.30.18](#).

It should be self-evident, but is nevertheless worth emphasising, that FFP masks are only effective if worn correctly. Whether or not an individual has been fit tested with a particular mask, much more important is that they perform a fit check each and every time they put a mask on, and that they do not enter the clinical area until they have established that there are no leaks ([Figure 8.5.30.19](#)).

Procedures currently considered to be potentially infectious AGPs for COVID-19 are:

- Intubation, extubation and related procedures, for example, manual ventilation and open suctioning of the respiratory tract (including the upper respiratory tract)
- Tracheotomy or tracheostomy procedures (insertion or open suctioning or removal)
- Bronchoscopy and upper ENT airway procedures that involve suctioning
- Upper gastro-intestinal endoscopy where there is open suctioning of the upper respiratory tract
- Surgery and post-mortem procedures involving high-speed devices
- Some dental procedures (for example, high-speed drilling)
- Non-invasive ventilation (NIV); Bi-level Positive Airway Pressure Ventilation (BiPAP) and Continuous Positive Airway Pressure Ventilation (CPAP)
- High frequency oscillatory ventilation
- Induction of sputum
- High flow nasal oxygen

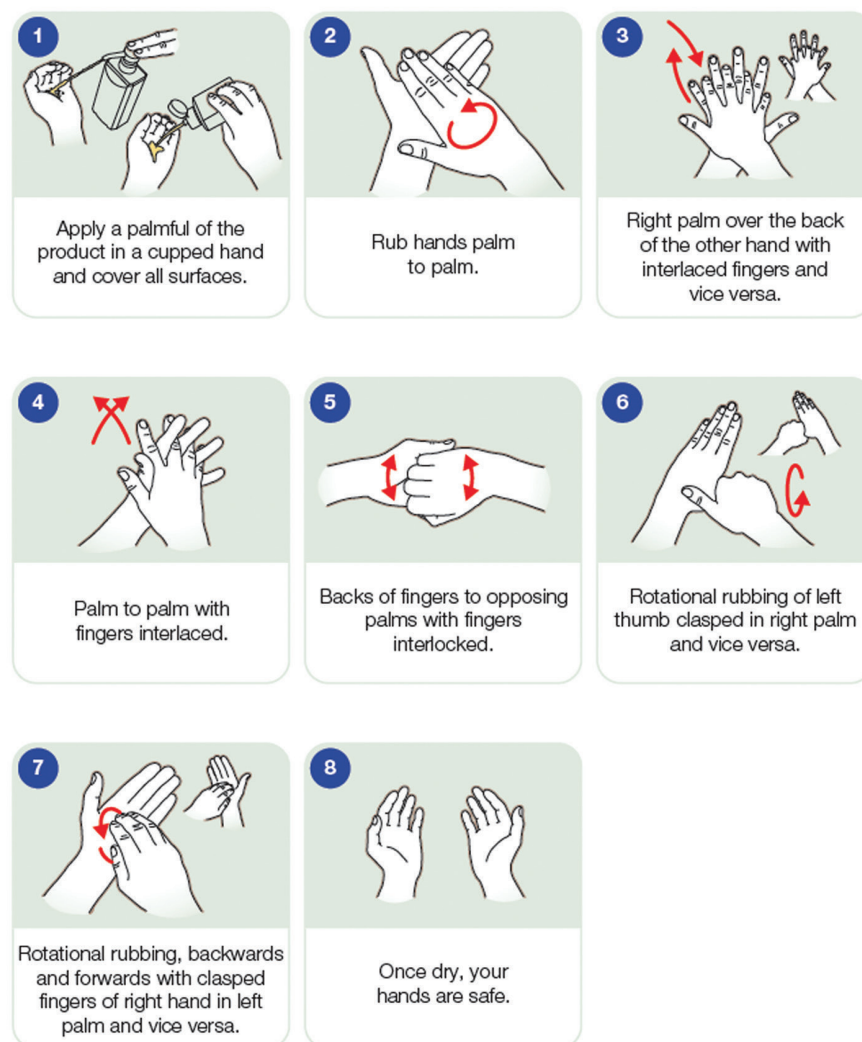


Fig. 8.5.30.15 How to handrub.

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Table 8.5.30.3 Recommended PPE for healthcare workers in secondary care inpatient settings

Setting	Disposable gloves	Disposable plastic apron	Surgical (fluid resistant) mask	Eye/face protection ¹	Surgical cap / hair cover	Disposable fluid-resistant gown	Filtering Face Piece (FFP) respirator ²
Patients who do not meet the definition for possible or confirmed cases of COVID-19	✓	✓	✓ ³	? ⁴	×	×	×
Possible or confirmed cases of COVID-19, but without AGPs	✓	✓	✓	✓	? ⁵	×	×
Possible or confirmed cases of COVID-19, with AGPs	✓	✓	×	✓	✓ ⁶	✓	✓
Performing AGPs on patients who do not meet the definition for possible or confirmed cases of COVID-19	✓	✓	×	✓	✓ ⁶	✓	✓

Notes: AGP, aerosol generating procedure.

⁽¹⁾ May be single or re-usable face or eye protection (visor or goggles).

⁽²⁾ Preferably FFP3.

⁽³⁾ Public Health England (PHE) recommends (20 May 2020) usage based on risk assessment as determined by individual staff, but used consistently by patient-facing staff in most UK hospitals.

⁽⁴⁾ Based on risk assessment as determined by individual staff.

⁽⁵⁾ Not included in PHE recommendations but often worn by staff in most UK hospitals.

⁽⁶⁾ Not included in PHE recommendations but consistently worn by staff in most UK hospitals. This table based on guidance from PHE, with modification.

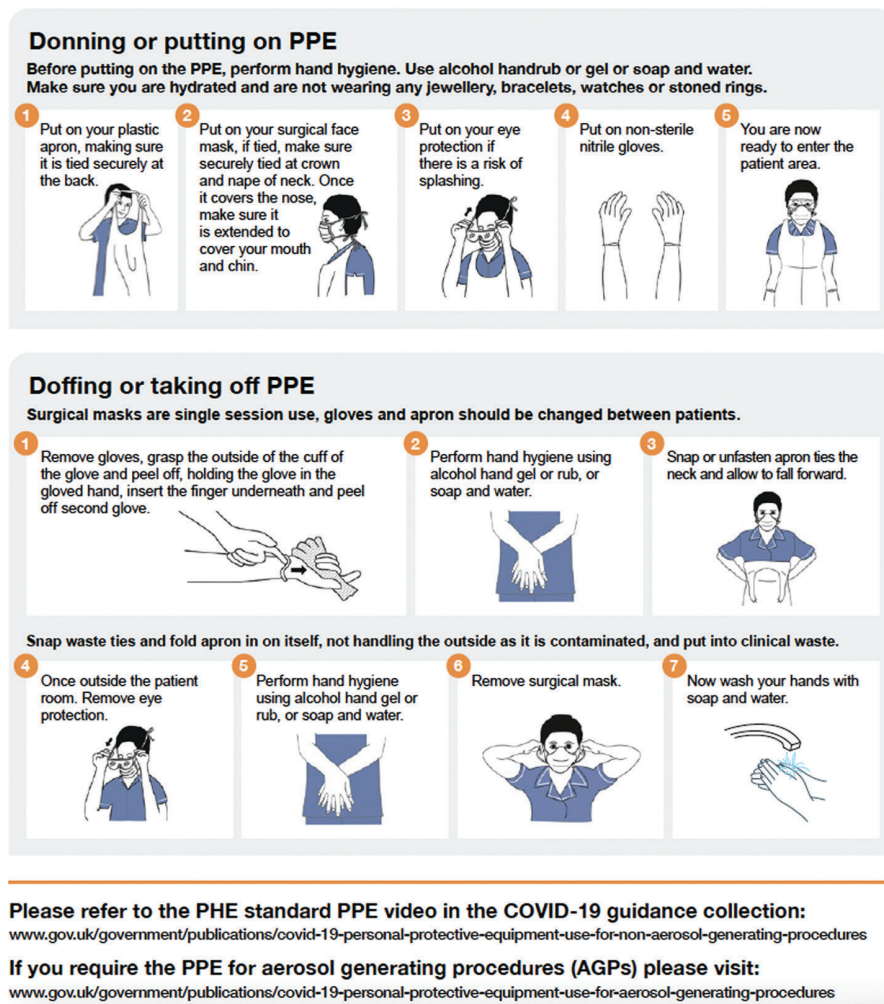


Fig. 8.5.30.16 How to put standard PPE on, and how to take it off.

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At present, standard recommendation is that all AGPs are performed by staff wearing enhanced PPE, even when the patient has an extremely low chance of having SARS-CoV-2 infection, for instance because they have been isolating before an elective procedure and have a negative PCR-based swab test within last 48 hr or so. It is not clear whether such caution is necessary. The time it takes to perform procedures is greatly prolonged by that needed for donning and doffing of enhanced PPE, and visual impairment caused by some types of eye protection, particularly those prone to mist up, can be problematic. It may be that the requirements for usage of enhanced PPE will be relaxed when more information on risk in different scenarios becomes available, but for the moment a strategy of being safe rather than sorry has very reasonably been adopted.

Aside from infection control precautions, studies of other interventions are underway. Giving hydroxychloroquine to asymptomatic people with moderate or high-risk exposure to SARS-CoV-2 does not prevent them from becoming infected or ill.

Health care worker to health care worker transmission

Screening of asymptomatic hospital health care workers has demonstrated clusters of infection in particular clinical areas or

wards. Analysis of such instances has shown that they can arise despite good compliance with infection control practices and PPE policies in the delivery of patient care, with the most probable explanation being transmission of SARS-CoV-2 infection between staff, likely occurring in staff rest areas. It is therefore important that staff are provided with areas where they can respect social distancing whilst taking a break, drinking or eating. In the same vein, employers can also usefully facilitate staff travel to and from work, such that employees' use of crowded public transport is reduced.

Other important things that can be done to reduce viral spreading include the development of a culture where all staff self-isolate if they develop concerning symptoms (rather than fail to 'admit weakness' and 'soldier on'), regular hand washing becomes the norm, all wear surgical fluid resistant masks within hospital premises (excepting when they are in a room on their own), and it is acceptable to remind or challenge colleagues if they do not do these things. Along with these a rapid and efficient process for staff testing is necessary to avoid prolonged exclusion from work of those who do not have SARS-CoV-2 infection, and to allow focus on outbreaks if and when they occur.

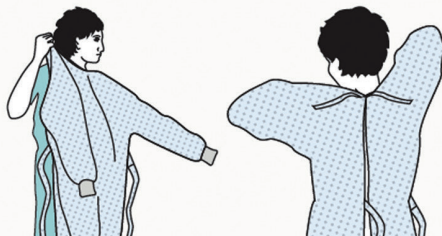
Pre-donning instructions

- ensure healthcare worker hydrated
- tie hair back
- remove jewellery
- check PPE in the correct size is available

Perform hand hygiene before putting on PPE

1

Put on the long-sleeved fluid repellent disposable gown

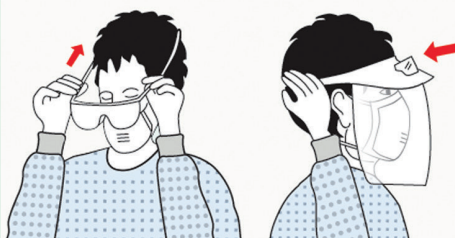
**2**

Respirator

Perform a fit check.

**3**

Eye protection

**4**

Gloves

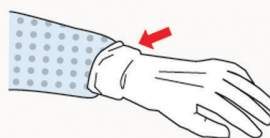


Fig. 8.5.30.17 Putting on (donning) personal protective equipment for aerosol generating procedures.

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Vaccines

The SARS-CoV-2 pandemic has stimulated an unprecedented drive to develop vaccines, and all conventional and many novel strategies are being employed. The NIH ClinicalTrials.gov website, searched for 'vaccine / COVID-19' on 18 January 2021, listed 363 studies. In the understandable effort to make rapid progress, it is to be hoped that appropriate care is taken over safety considerations and that participants are not exposed to unacceptable levels of risk, but it is truly remarkable that in under 12 months several vaccines have been developed, tested and are now being administered to many people.

Live, attenuated and inactivated viral vaccines

There are no reports of use of live vaccines and for safety reasons such studies are not likely to be attempted. A phase I-II human trial of an inactivated whole virus vaccine, conducted in China, demonstrated the development of neutralizing antibodies in >95% of recipients, with no concerning safety signals. Phase III trials are being conducted in Brazil, Indonesia and Turkey. As of mid-January 2021 results had not been peer-reviewed, but an overall efficacy of around

50% has been reported, with much higher efficacy at preventing severe and moderate COVID-19 disease.

Vaccines directed against the spike protein of SARS-CoV-2

The SARS-CoV-2 spike protein is critical for entry of the virus into cells, and antibodies that target the spike protein can prevent viral entry and thereby hopefully impede viral replication.

Messenger RNA vaccines

Messenger RNA (mRNA) administered systemically can lead to expression of protein, although before the SARS-CoV-2 pandemic there were no licensed vaccines based on such methodology.

The Pfizer and BioNTech COVID-19 vaccine, BNT162b2, is a lipid nanoparticle-formulated, nucleoside-modified RNA encoding the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation. In a study of 43548 participants, two doses administered 21 days apart were 95% effective in preventing SARS-CoV-2 infection, with no concerning safety signals. The vaccine is now available for clinical use, although the requirement for very low temperature (-70°C) for shipping and

PPE should be removed in an order that minimises the potential for cross contamination.

The order of removal of PPE is as follows:



Fig. 8.5.30.18 Taking off (doffing) personal protective equipment for aerosol generating procedures.

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storage is a significant practical challenge that will limit roll out in many parts of the world, as will its cost.

The Moderna vaccine, mRNA-1273, is a lipid nanoparticle encapsulated mRNA vaccine expressing the prefusion-stabilised spike glycoprotein. In a study of 30420 volunteers, two doses administered

28 days apart were 94% effective in preventing SARS-CoV-2 infection, with no concerning safety signals. The vaccine is now available for clinical use. The fact that it can be kept in a conventional freezer (-20°C) makes delivery easier than for the Pfizer and BioNTech vaccine, but not without difficulty in many parts of the world. Cost will be a limiting factor in many countries.



Fig. 8.5.30.19 PPE in use.

Viral vector vaccines

A group led from Oxford (UK) used a replication-deficient chimp adenovirus vector to express the spike protein gene. Interim analysis of the effects of vaccination of 11636 participants (**Figure 8.5.30.20**) has been reported: two doses of vaccine were administered to most, with an interval between doses of 4–12 weeks. In those who received two standard doses, vaccine efficacy was 62% (versus 1.6% control). Very curiously, efficacy was higher (90% versus 2.2%) in those who inadvertently received a low dose followed by a standard dose, which has led to much speculation and ongoing work. There were no concerning safety signals. The vaccine is now available for clinical use and has two significant advantages over mRNA-based vaccines. First, it requires a refrigerated (rather than -20°C or -70°C) cold



Fig. 8.5.30.20 A volunteer participating in the ChAdOx1 nCov19 vaccine study in Oxford.

chain. Secondly, Oxford-AstraZeneca's US\$2-3 per dose agreement. Both support availability in low and middle income countries, and this global pandemic will not be controlled if only the rich can afford to be vaccinated. Early data suggest that this vaccine can also lower the risk of those vaccinated becoming infected and transmitting the virus to others. It is likely that the other vaccines based on the spike protein will be similar.

Other spike protein vaccines

A third type of vaccine (Novavax) is based on a recombinant spike protein given with an adjuvant. This has been shown to produce good immune responses and preliminary data from a Phase III study suggest good efficacy, including against the new variants of the virus currently circulating.

Numerous other trials are under consideration or underway, including administration of DNA encoding the spike protein, or of recombinantly made spike protein itself, or spike protein tip (the part that binds to ACE2 receptors on human cells).

Other vaccines

Vaccines made for a particular purpose can have pleiotropic effects. For instance, BCG vaccine was developed to protect against tuberculosis, but provides some protection against other diseases. Some epidemiological studies have proposed that high uptake of BCG and/or other vaccinations within a country are associated with reduced incidence of COVID. Other studies have contested such claims, but nevertheless studies are underway to find out whether BCG or other existing vaccines can protect against COVID. The chances that they will provide significant protection are remote.

Outstanding vaccination issues

The fact that in January 2021 there were at least three effective vaccines against SARS-CoV-2 is a source of great encouragement that

the pandemic may be halted, but there are many outstanding issues. Matters of particular importance include the following:

- How long will protection last for?—the studies reported have median follow-up times of 2-3.4 months after the second dose.
- How important is the timing of the second dose of vaccine?—recent data from the Oxford/AstraZeneca vaccine studies suggest good protection up to 12 weeks after the initial dose.
- How effective is a single dose of vaccine?—in all studies there was evidence of efficacy before the administration of the second dose. The degree of protection is not certain, but after discounting infection occurring shortly after the first dose, efficacy against symptomatic COVID-19 in the range 73–89% has been reported from days 15–21 until two weeks after the second dose. This has led some to argue that the public health priority should be to vaccinate as many people as possible with a single dose, rather than half as many with two doses. However, recent preliminary data suggests that whilst almost all people under the age of 80 years generate a good antibody response to a single dose of the Pfizer vaccine, many over the age of 80 do not, although the implications of this (and whether it is the same for other vaccines) is not clear.
- Will the virus mutate to become resistant to the immune response induced by current vaccines?—the fact that antibodies are generated against many epitopes on the spike protein, which is fundamental to the virus, suggests that the doomsday scenario of a completely resistant virus is unlikely to occur, but it is probable that there will be differences in susceptibility of individual variants, and those that are less susceptible to vaccine-induced immune responses (such as those with the E484K mutation) will be at a selective advantage in spreading through the population. It is possible that, as with vaccination against influenza, annual vaccination against the prevalent strains of SARS-CoV-2 will become the new normal.
- Vaccination in low and middle income countries—there will be considerable challenges in delivery, and these will be a real test of international political leadership. But if ever there was a

demonstration that we all share one world and ignore problems in other countries at our peril, the COVID-19 pandemic is it.

Public health response

Never before has a public health matter been subject to as much scrutiny as the response to the COVID-19 pandemic. The blizzard of information and misinformation on all media platforms is unprecedented and has created an environment in which it is often very difficult to distinguish fact from fiction. Intense pressure on politicians in democracies, very few of whom feel able to publicly admit to uncertainty, or that their country might not have been well prepared, or to resist the temptation to promise that a new approach will work wonders, has led to erratic public health responses worldwide. The most effective public health response to the pandemic will be known only in retrospect, and only preliminary observations can be made now, in February 2021, about a year after the WHO declared the pandemic.

The challenge of trying to halt the spread of SARS-CoV-2

Finding, testing, tracing and isolating

The key public health intervention to control the spread of an infectious disease is to find individuals who have the disease, isolate them whilst they are infectious, and to trace their contacts and isolate them for the duration of the condition's incubation period. The words find, test, trace and isolate have become commonplace in governmental media briefings worldwide.

For SARS-CoV-2 implementation of a find, test, trace and isolate strategy is more difficult than for most other infective conditions because its serial interval (the time between symptom onsets in successive cases in a transmission chain) is less than its incubation period (the time between infection and onset of symptoms in an individual). About 20–30% of people infected with SARS-CoV-2 remain asymptomatic, and these can pass the infection on to others, albeit with lower likelihood than those who are symptomatic (relative risk 0.35). In various studies the proportion of asymptomatic or pre-symptomatic transmission is estimated to be around 40%. This means that, even if a testing process was so efficient that it could determine instantly that a symptomatic person was infected with SARS-CoV-2, putting them immediately into quarantine would not reduce the effective reproduction number of the virus (R) by more than 60%. Delays in testing and isolating symptomatic individuals; and in tracing and isolating their contacts; would further reduce the effectiveness of intervention.

The fact that many transmissions are asymptomatic or pre-symptomatic is reasonable ground for arguing for regular testing of all members of a population, or for those members of a population at higher risk of acquiring infection (e.g. health care workers, hospital inpatients or care home residents).

The WHO recommendation that a case or contact should isolate for 14 days is widely accepted, but different rules apply in different countries, e.g. 10 days in the UK (as of mid-February 2021). The practicalities of 'isolation' are also variable. In many countries, patients who are not ill enough to require hospital admission are

moved to isolation in community facilities or requisitioned hotel accommodation if they are unable to isolate at home. In other countries, including the UK, there is no systematic intervention of this type, and considerable uncertainty about what the injunction to 'self-isolate' means for an individual living in a multi-occupancy home.

General advice

The WHO has provided the following general advice to prevent infection and slow transmission of COVID-19:

- Social distancing
 - Maintain at least a 1-metre distance between yourself and others
- Wear a mask
 - Make wearing a mask a normal part of being around other people
- Make your environment safer
 - Avoid the 3C's: spaces that are Closed, Crowded or involve Close contact
 - Meet people outside
 - Avoid crowded or indoor settings
 - Open a window
- Practice good hygiene
 - Wash your hands regularly with soap and water, or clean them with alcohol-based hand rub
 - Avoid touching your eyes, nose and mouth
 - Cover your mouth and nose with your bent elbow or tissue when coughing or sneezing
 - Clean and disinfect surfaces frequently, especially those which are regularly touched
- Do the right thing if you feel unwell
 - Know the full range of symptoms of COVID-19
 - Stay home and self-isolate even if you have minor symptoms such as cough, headache and mild fever
 - Seek medical attention immediately if you have fever, cough and breathing difficulty
 - Keep up to date on the latest information from trusted sources

Lockdowns

Aside from advising their populations to follow the WHO's general advice or variants thereof, governments have imposed a range of measures on their populations to reduce the frequency and proximity of contacts between individuals. These include a range of types of lockdowns (requirement for people to stay where they are) and curfews (typically referring to a time when individuals must return to and stay in their houses or homes), and it was estimated that by the first week of April 2020 more than half of the world's population were subject to such restrictions ([Figure 8.5.30.21](#)).

Whilst there is much debate about which particular interventions are most effective in preventing viral transmission, there is no doubt that lockdowns were effective at halting the first wave of the pandemic in many countries. This, however, came at considerable price, including increased morbidity and mortality from other illnesses, adverse effects on mental health, and economic depression, the consequences of which are always felt most severely by the poor and disadvantaged.



Fig. 8.5.30.21 Public health warnings have become familiar to the public.

Recognising that it is much, much easier to criticise than to make difficult decisions, in many countries there are articulate groups arguing that ‘the government locked down too late’ or ‘in the wrong way’. Others draw attention to the harms caused by lockdowns and emphasise that governments do not just have to weigh health considerations when making judgements about public policy. Knowing when and how to transition back to ‘life as normal’ is very difficult. The WHO has provided guidance that six conditions should be used as the basis to implement relaxation of lockdown measures, some of which, in particular the matter of community engagement, are difficult to judge (Table 8.5.30.4).

Outcome and deaths from COVID-19

It is extremely difficult to make fair comparisons of COVID-19 related death rates between countries given massive variations in testing for SARS-CoV-2 infection, and in how causes of death are recorded. The population death rates attributed to COVID-19 in

various countries are shown in Fig. 8.5.30.22. The case fatality rate is also reported to vary considerably (Figure 8.5.30.23). Some of this variation may be due to differences in testing and reporting, but it does appear that mortality is low in some low and middle-income countries. Possible explanations for this are their younger population (in developed countries many deaths occur in elderly people), also differences in exposure to various pathogens and patterns of immunisations.

During the COVID-19 pandemic people will die because of direct effects of SARS-CoV-2 infection, but also from indirect effects caused by the inability of health systems to provide care for non-COVID illnesses and/or the reluctance of individuals to seek care because of worry that doing so may expose them to high risk of infection. There is greater scope for making reasonable comparisons between countries, or different areas within countries, using the metric of excess deaths, which does not depend on attribution of cause. However, even this information is limited: few countries

Table 8.5.30.4 The WHO’s six conditions for relaxation of lockdowns

Condition	Comment
COVID-19 transmission is controlled	There may be sporadic cases and clusters of cases from known contacts or importations, but the health system should be able to cope with these whilst maintaining considerable capacity in reserve
Sufficient health system and public health capacities are in place	There must be capacity to test all suspected cases within 24 h of identification and sampling, and isolate all confirmed cases effectively and immediately until they are no longer infectious. All close contacts could be traced, quarantined and monitored for 14 days
Outbreak risks in high-vulnerability settings are minimized	There must be appropriate measures in place to minimize the risks of new outbreaks and of nosocomial transmission, e.g. appropriate infection prevention / control measures and provision of PPE in health care facilities and residential care settings
Workplace preventive measures are established	These include assurance of physical distancing, handwashing facilities, respiratory etiquette and (possibly) temperature monitoring
Risk of imported cases managed	Measures must be in place to rapidly detect and manage suspected cases in travelers, including the capacity to quarantine individuals
Communities are fully engaged	Behavioural prevention measures must be maintained. All must understand the need to detect and isolate all cases.

Source data from WHO. Modified from - Transitioning to and maintaining a steady state of low-level or no transmission. <https://www.who.int/thailand/news/detail/18-04-2020-transitioning-to-and-maintaining-a-steady-state-of-low-level-or-no-transmission> (accessed 21 January, 2021).

have systems in place to report the number of people that died in a given week or month, and such data is not available for recent years in most low and middle-income countries.

Where data are available, a consistent feature is that mortality rates are highest in urban areas worldwide, and overall excess deaths are higher—sometimes very much higher—than those reported as due to COVID-19. Excess deaths in England since the start of the pandemic are shown in Fig 8.5.30.24. As can be seen in Fig 8.5.30.25 and Fig 8.5.30.26, mortality has been 17–27% above baseline for all age groups over 45 years, with the absolute numbers of excess deaths greatest in those aged over 75 years. Excess deaths were greater in

males and females of Asian, Black, mixed and other ethnic groups than they were in whites (Fig 8.5.30.27 and Fig 8.5.30.28).

The numbers and time courses of excess deaths in selected countries are shown in Fig 8.5.30.29. Aside from the UK, Italy and Spain have had the highest population death rates of European countries; Sweden was notable in not introducing lockdown measures of the type implemented in most other countries during the first wave of the pandemic; New Zealand’s governmental response, which was to implement strict control measures early on, has been widely applauded by medical commentators. The situation, however, is complex, and there are many differences between Italy, Spain, Sweden,

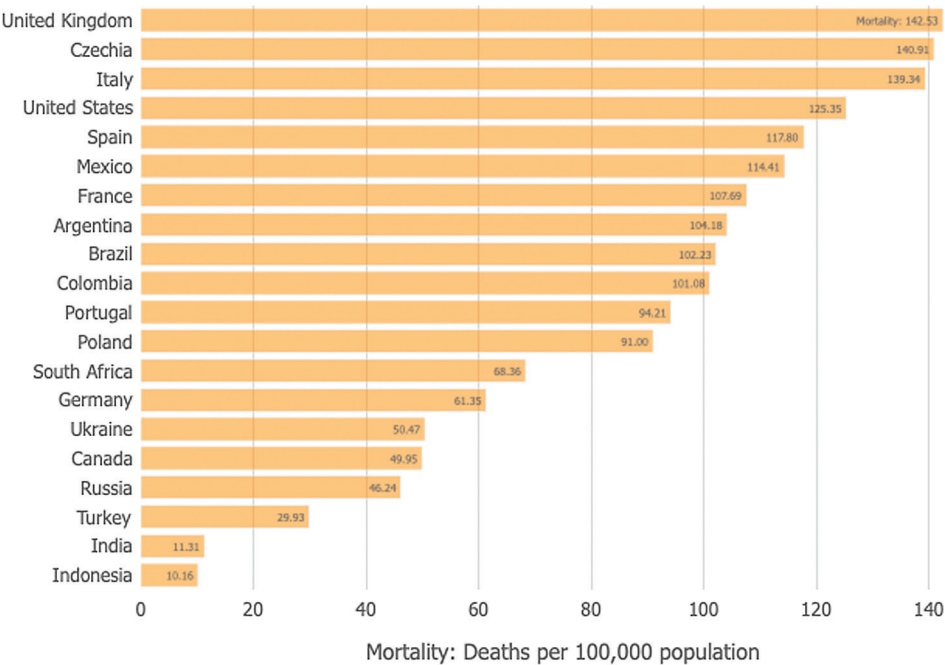


Fig. 8.5.30.22 COVID-19 mortality in various countries.
Source data from <https://coronavirus.jhu.edu/data/mortality> (accessed 22 January, 2021).

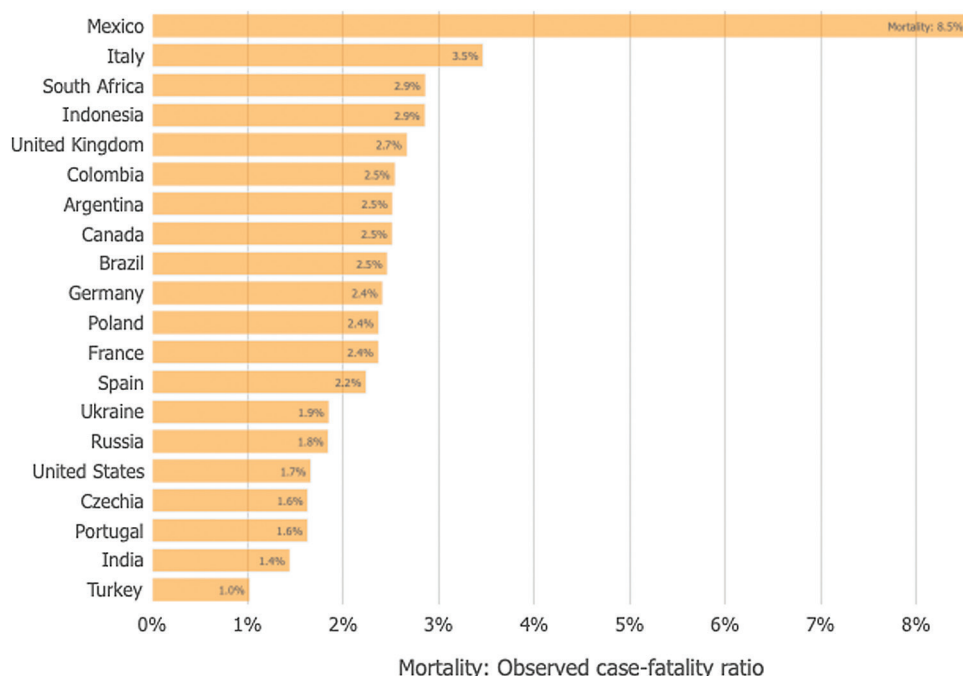


Fig. 8.5.30.23 Observed case-fatality ratio for COVID-19 in various countries.

Source data from <https://coronavirus.jhu.edu/data/mortality> (accessed 22 January, 2021).

New Zealand and the United States other than governmental actions in response to the pandemic.

The Oxford COVID-19 Government Response Tracker (<https://www.bsg.ox.ac.uk/research/research-projects/coronavirus-government-response-tracker>) is a tool that systematically collects information on governmental policy responses to the pandemic: 18 indicators, such as school closures and travel restrictions, are tracked in over 180 countries. Summation of scores of these indicators is used to calculate a government response stringency index, and it might be supposed that a more stringent response (most restrictive) would be associated with a lower growth rate of cases. Fig. 8.5.30.30 shows that there is no strong correlation between the stringency of governmental response in different countries and their growth in cases. This does not, of course, mean that governmental public health interventions are of no value, but it does suggest that ‘more must be better’ is probably incorrect. Careful analysis of the data to find out if particular

interventions are associated with beneficial outcomes may be of great value.

Conclusions

The COVID-19 pandemic has caused enormous disruption worldwide. In addition to the millions of deaths due to SARS-CoV-2, others have died as a consequence of the impact on the delivery of healthcare by systems under tremendous stress. It is feared that many deaths have resulted from treatable diseases in people who were afraid to attend hospitals or otherwise unable to access care. Many healthcare workers have died, and others will have significant psychological sequelae from dealing with this disease. In addition, the social and economic effects of lockdowns in many countries are only just beginning to be assessed.

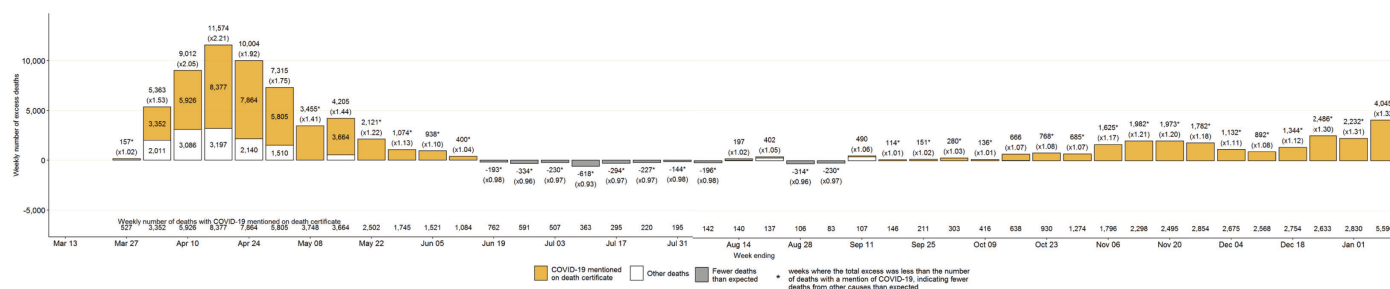


Fig. 8.5.30.24 Weekly excess deaths in England by date of registration from end March 2020 to January 2021. It can be seen that the first wave of the pandemic caused a period of excess deaths from March–June 2020, which was followed by a period of fewer than expected deaths until the second wave began in September / October 2020.

Reproduced from <https://fingertips.phe.org.uk/static-reports/mortality-surveillance/excess-mortality-in-england-latest.html> (accessed 22 January, 2021) with permission from Public Health England, Crown Copyright 2020 (Open Government Licence v3.0)

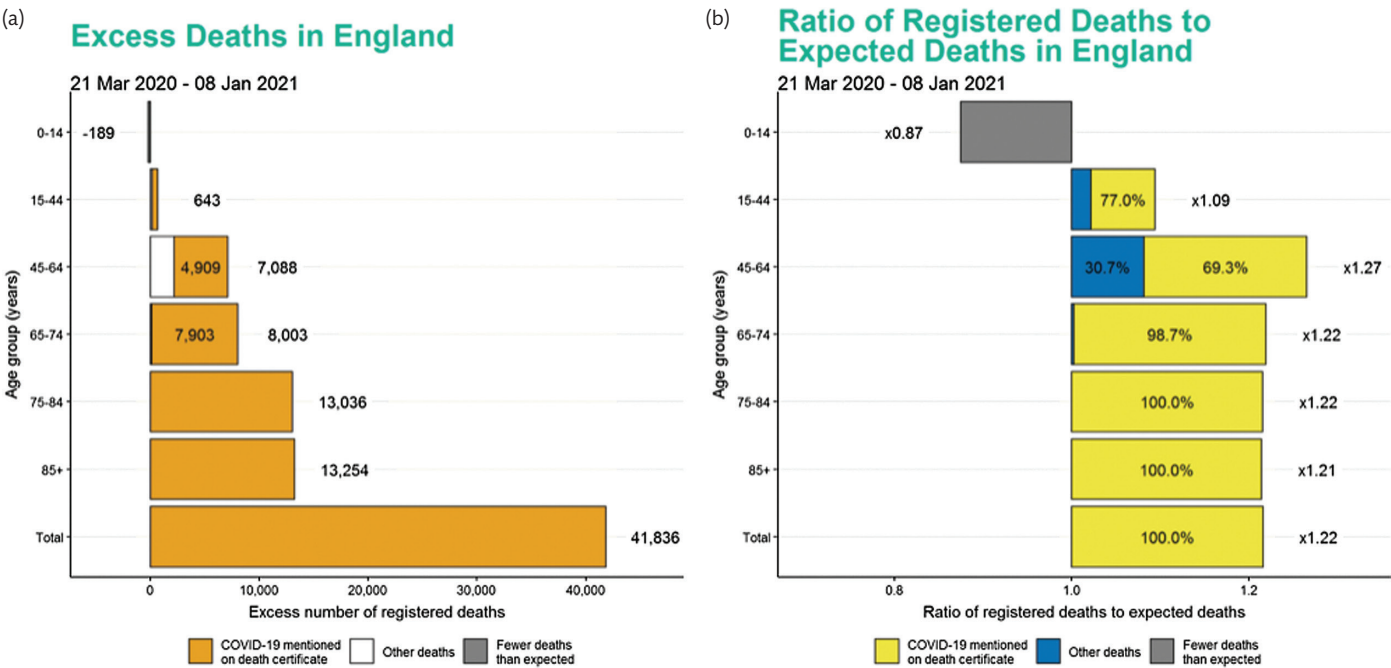


Fig. 8.5.30.25 Excess deaths by age (panel A), and ratio of registered to expected deaths by age (panel B), for males in the England from March 2020 to January 2021.

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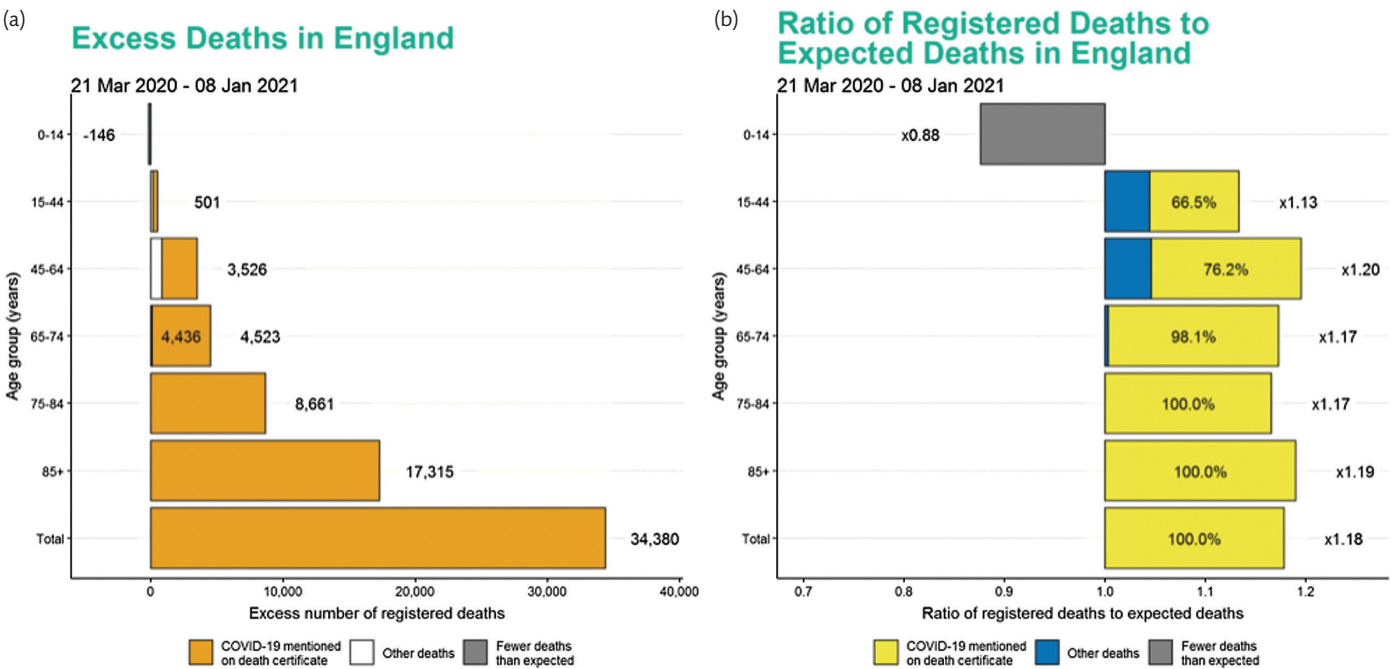


Fig. 8.5.30.26 Excess deaths by age (panel A), and ratio of registered to expected deaths by age (panel B), for females in the England from March 2020 to January 2021.

Reproduced from <https://fingertips.phe.org.uk/static-reports/mortality-surveillance/excess-mortality-in-england-latest.html> (accessed 22 January, 2021) with permission from Public Health England, Crown Copyright 2020 (Open Government Licence v3.0)

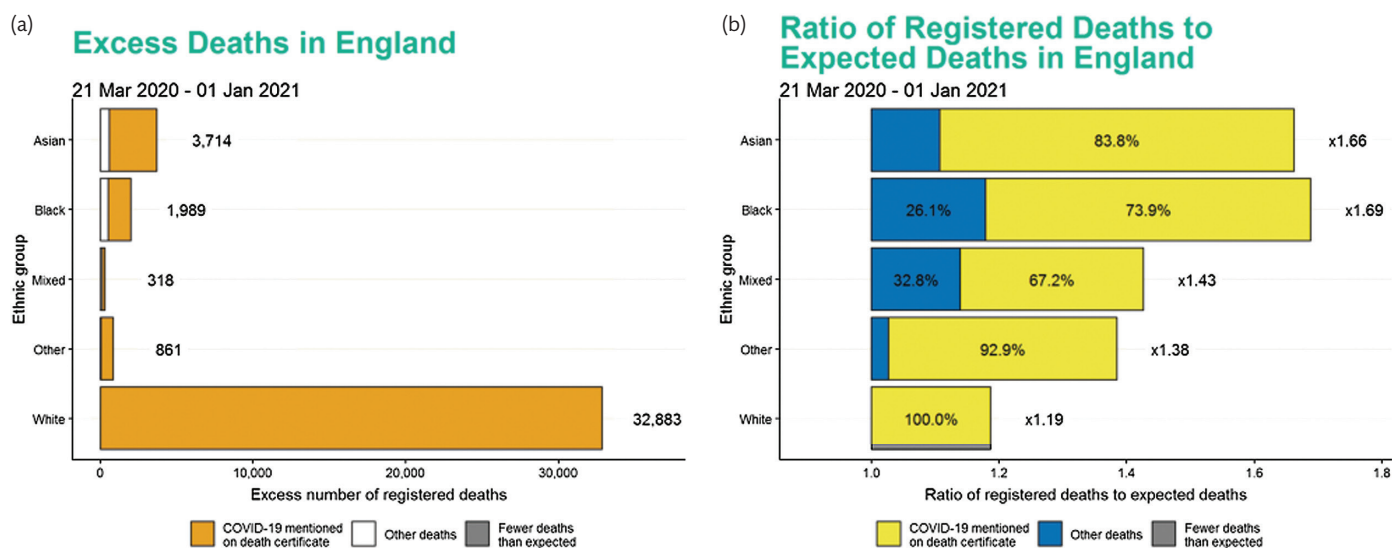


Fig. 8.5.30.27 Excess deaths by ethnic group (panel A), and ratio of registered to expected deaths by ethnic group (panel B), for males in the England from March 2020 to January 2021.

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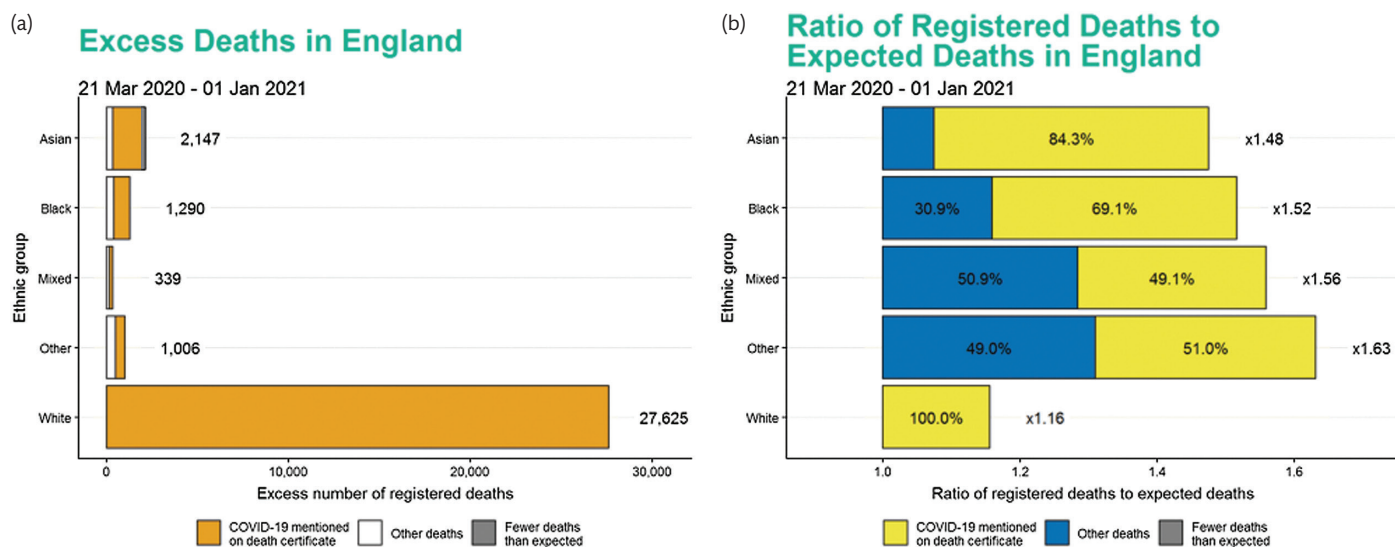


Fig. 8.5.30.28 Excess deaths by ethnic group (panel A), and ratio of registered to expected deaths by ethnic group (panel B), for females in the England from March 2020 to January 2021.

Reproduced from <https://fingertips.phe.org.uk/static-reports/mortality-surveillance/excess-mortality-in-england-latest.html> (accessed 22 January, 2021) with permission from Public Health England, Crown Copyright 2020 (Open Government Licence v3.0)

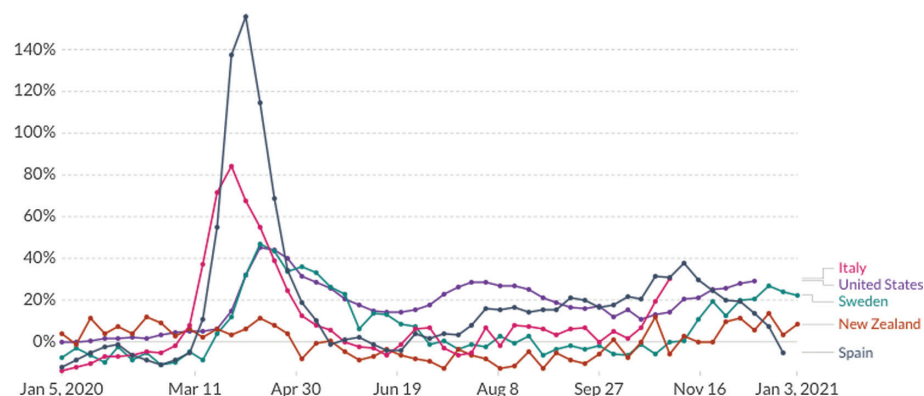


Fig. 8.5.30.29 Excess mortality during the COVID-19 pandemic in selected countries. Shown is how the weekly number of deaths from all causes for all ages in 2020-21 differs as a percentage from the average number of deaths in the same week over the years 2015-19.

Reproduced from <https://ourworldindata.org/excess-mortality-covid> (source data from The Human Mortality Database) (accessed 22 January, 2021) (<https://creativecommons.org/licenses/by/4.0>)

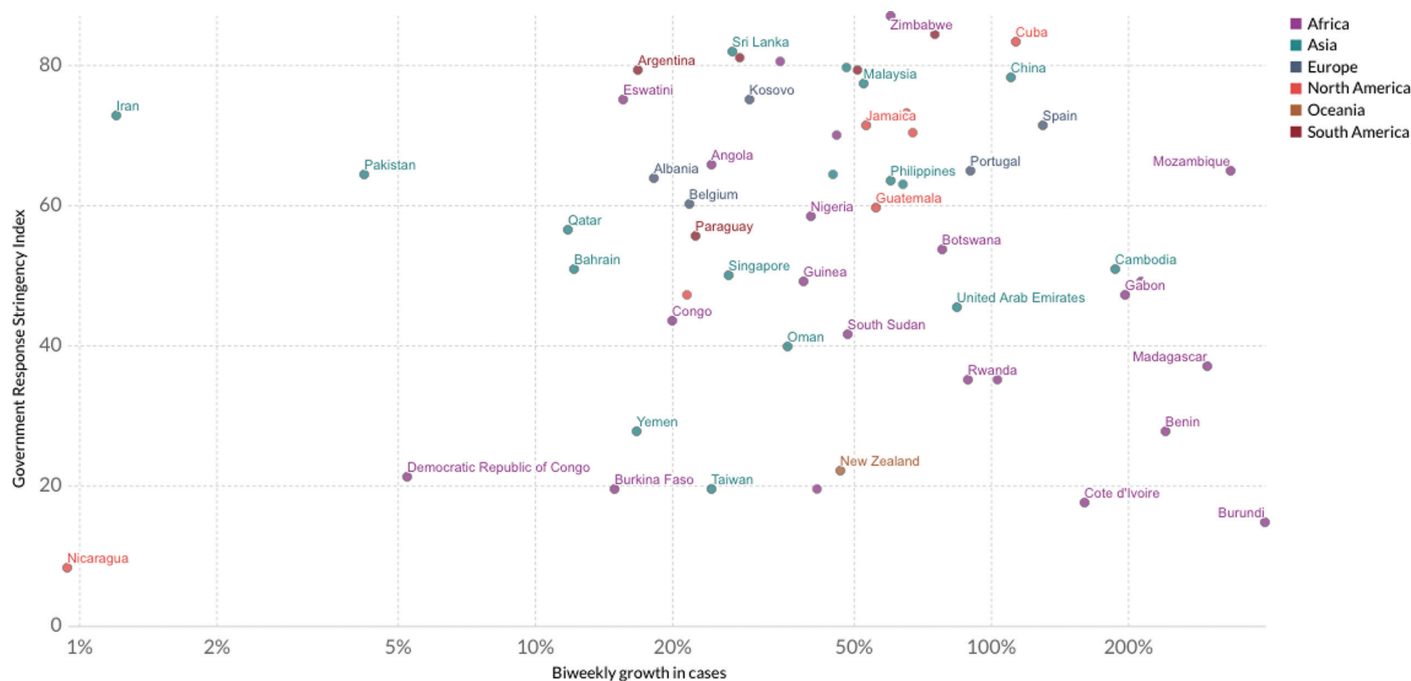


Fig. 8.5.30.30 Government response stringency and growth in cases. The government response stringency index, rescaled to a value from 0 to 100 (100 = strictest response), is plotted against the biweekly growth rate in cases, which measures the percentage change in number of confirmed new cases over the last 14 days relative to the previous 14 days.

Reproduced from <https://ourworldindata.org/grapher/government-response-stringency-index-vs-biweekly-change-in-confirmed-covid-19-cases?minPopulationFilter=1000000&time=latest> (source data from Thomas Hale, Sam Webster, Anna Petherick, Toby Phillips, and Beatriz Kira (2020). Oxford COVID-19 Government Response Tracker, Blavatnik School of Government and COVID-19 Data Repository by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University) (accessed 23 January, 2021) (<https://creativecommons.org/licenses/by/4.0>)

It is hoped that important lessons can be learned from this pandemic so that nations and societies are better prepared for future waves of COVID-19, also the almost inevitable appearance at some stage of another pandemic.

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