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 end July 2020, there have been over 16 million cases globally and more than 650,000 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. Children and young adults rarely manifest an inflammatory syndrome that fits criteria for atypical Kawasaki syndrome.

Treatments of proven efficacy in some patients with COVID-19 are Remdesivir and dexamethasone. Management is otherwise supportive. For reasons that are not well understood the reported case-fatality ratio varies very widely between countries in the range 1-15%. Most deaths occur in the elderly, in men, or those with co-morbidities.

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) testing, tracing and isolating of cases and their contacts; and (4) appropriate use of personal protective equipment (PPE) by health care professionals. Never before have public health responses been subject to such intense scrutiny. It seems that excess deaths have been lowest in countries that took lockdown action quickly.

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 end July 2020, most countries have now reported cases, with over 16 million cases globally and more than 650,000 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 VIRUS). 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. 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,
potentially, be responsible for some of the adverse clinical outcomes as the disease progresses. Patients develop neutralising antibodies, but again, it is uncertain if these are protective.

As part of the infection, it has become clear that alterations in coagulation are common, possibly related to 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) is 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.

### 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). 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 the 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. 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 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 pneumatic 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 extrapolmonary complications occur. The incubation period ranges from 4–6 days, but might be as long as 14 days in rare cases. Symptoms seen on admission of patients with COVID-19 are shown in Figure 8.5.30.4.

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. $SpO_2 \geq 90\%$ 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 $> 30/min$, severe respiratory distress, or $SpO_2 < 90\%$ breathing room air. In children, signs of pneumonia plus central cyanosis, $SpO_2 < 90\%$, inability to feed, very rapid breathing or intravascular.
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 increasing evidence of infections that remain entirely asymptomatic.

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. 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 8.5.30.5), as are bilateral ground glass changes seen on CT imaging of the lungs (Figure 8.5.30.6). 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.

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 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.

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.

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 increasing evidence that surgery in patients with COVID-19 risks serious respiratory deterioration.

**Table 8.5.30.1 Case definition for COVID-19**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Detail</th>
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<tbody>
<tr>
<td>Clinical</td>
<td>Any person with at least one of the following symptoms</td>
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<tr>
<td></td>
<td>- Cough</td>
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<td>- Fever</td>
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<td></td>
<td>- Shortness of breath</td>
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<tr>
<td></td>
<td>- Sudden onset of anosmia, ageusia or dysgeusia</td>
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<tr>
<td>Diagnostic imaging</td>
<td>Radiological evidence of lesions compatible with COVID-19</td>
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<tr>
<td>Laboratory</td>
<td>Detection of SARS-CoV-2 nucleic acid in a clinical specimen</td>
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<tr>
<td>Epidemiological</td>
<td>At least one of the following two epidemiological links in the 14 days prior to symptom onset</td>
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<td></td>
<td>- Close contact with a confirmed case of COVID-19</td>
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<td></td>
<td>- Having been a resident or staff member in a residential institution for vulnerable people where ongoing COVID-19 transmission has been confirmed</td>
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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 increasing evidence that surgery in patients with COVID-19 risks serious respiratory deterioration.

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.

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 hypercoaguable 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. 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% develop acute kidney injury (AKI) in some case series, often requiring renal replacement therapy. 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.

Fig 8.5.30.5 Chest X-ray in Covid-19 showing bilateral pneumonia.

Fig 8.5.30.6 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.
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 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 8.5.30.7, Figure 8.5.30.8)

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

Diagnosis

Antigen detection

The gold standard of diagnosis has been the detection of viral RNA by reverse transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal swab. The accuracy of the test depends on both the quality of the swab and the sensitivity and specificity of the test. A variety of in-house and commercial tests have been used, but there are problems with sensitivity; in many reports this can vary from 70 to 90%. Specificity is better. 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 antigen is not helpful.

As alternatives to RT-PCR, different technologies such as LAMP (loop-mediated isothermal amplification) are being assessed. 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.

Antibody detection

There are several commercial tests available to detect IgG and IgM responses to SARS-CoV-2. The sensitivity and specificity of these tests vary, and they are still being evaluated systematically. 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. It is still unclear whether the antibody response is affected by the severity of the infection. There is little data on the durability of antibody responses, or whether these antibodies protect against further infection. It is becoming apparent, however, that some patients who appear to have had a Covid-19 illness, including some with anosmia, have not developed antibodies.

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\(_2\)O). 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 (\( \text{PaO}_2 \)) to the fraction of inspired oxygen (\( \text{FiO}_2 \)) of <50 mmHg for three hours, or \( \text{PaO}_2 : \text{FiO}_2 < 80 \text{ mmHg} \) for more than six hours, may be referred for consideration of extracorporeal membrane oxygenation (ECMO).

Aside from very small and highly selected case series, outcomes of COVID-19 patients treated with ECMO are not yet known.

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 has been reported.

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 noradrenaline) 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 has led to changes in practice in many centres. These include 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 have 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 has led to exhaustion of supply of machines and key consumables, 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 with COVID-19 are at high risk for both arterial and venous thrombosis and/or thromboembolism. If at low bleeding risk, all should receive prophylaxis - typically with low molecular weight heparin - for the duration of hospital admission, and many specialists advise continuation of treatment with either low molecular weight heparin or a direct acting oral anticoagulant (DOAC) for two weeks after discharge, longer if the patient remains less mobile than usual.

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 are preferably only to be used in the context of clinical trials (see section headed ‘Specific treatments’).

**Specific treatments**

Trialists, funders and regulators have responded rapidly to the COVID pandemic. The NIH ClinicalTrials.gov website, searched for ‘treatment / COVID-19’ on 29 July 2020, listed 1860 studies. Unfortunately, most of these are too small and poorly designed to be useful, but some very impressive work has been done.

**Remdesivir**

Remdesivir is a monophosphoramidate prodrug of an adenosine analogue that has a broad antiviral spectrum. The evidence indicates that its efficacy in COVID-19 is modest, but it is now approved for treatment worldwide.

A study that randomised 158 patients to remdesivir (200 mg on day 1 and 100 mg on subsequent days) and 79 to placebo found that the drug did not lead to a difference in time to clinical improvement, but in patients treated within 10 days of symptom onset remdesivir was associated with a reduction in median time to clinical improvement of five days, although this difference was not statistically significant. There were no differences in duration of hospital stay, duration of oxygen support, requirement or duration of mechanical ventilation, or mortality. A study that randomised 1063 patients with lower respiratory tract involvement with COVID-19 to remdesivir (same dosing regimen as above) or placebo found median recovery time was reduced from 15 to 11 days. In the preliminary report of this trial published on 22 May 2020, the Kaplan-Meier estimate of mortality at 14 days was 7.1% in the remdesivir group compared to 11.9% in controls, but the difference was not statistically significant (hazard ratio for death 0.70; 95% CI, 0.47-1.04).

**Dexamethasone**

The largest study of treatments is the Randomised Evaluation of COVID-19 therApY (RECOVERY) trial (Table 8.5.30.2), which has used 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 7 July 2020, 11312 participants had been recruited from 176 sites, and important outcomes reported.

Analysis after 2104 patients randomly allocated to receive dexamethasone 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).

**Other agents**

The RECOVERY trial has demonstrated that hydroxychloroquine and the combination of lopinavir / ritonavir are not useful treatments.

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

Given the benefit observed with dexamethasone treatment, the results of studies examining the effect of agents that suppress the immune system in patients with severe COVID-19 will be of particular interest. These include the Tocilizumab (IL-6 receptor blocker) arm of the RECOVERY trial, and the Multi-arm therapeutic study in pre-ICU patients admitted with COVID-19 – repurposed drugs (TACTIC-R) trial, which will assess the effects of Baricitinib (a JAK inhibitor used as a second-line treatment for rheumatoid arthritis) and Ravulizumab (a blocker of C5 activation used as treatment for paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome).

**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 judgements 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**

The long-term outcomes of COVID-19 remain unknown, but it is clear that some patients suffer a range of symptoms for weeks or months. Those who are severely affected 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 are under recognised and poorly treated, if indeed they are treated at all.

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.

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

<table>
<thead>
<tr>
<th>Patients</th>
<th>End points</th>
<th>Therapies</th>
<th>Proposed mode of action</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitted to hospital with COVID-19 confirmed by laboratory test or considered clinically likely by treating physician</td>
<td>Primary endpoint – all cause 28-day mortality</td>
<td>Usual care (control)</td>
<td>No significant difference in primary endpoint or other outcomes</td>
<td>Recruitment closed on 29 June 2020</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Secondary endpoints – duration of hospital stay; need for and duration of mechanical ventilation; and – among patients not on mechanical ventilation at baseline – composite end point of death or need for mechanical ventilation or ECMO</td>
<td>Lopinavir 400 mg + Ritonavir 100 mg, orally every 12 hours for 10 days</td>
<td>In hospitalized patients, dexamethasone reduced 28-day mortality in those receiving oxygen or invasive mechanical ventilation at randomization, but not among patients not receiving respiratory support</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dexamethasone 6 mg (orally or IV) once daily for 10 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Corticosteroid hormone receptor agonist with pleiotropic actions</td>
<td>In patients receiving oxygen without invasive mechanical ventilation deaths were reduced from 25% to 21.5% (RR 0.80, 95% CI 0.70-0.92). In patients receiving invasive mechanical ventilation deaths were reduced from 40.7% to 29% (RR 0.65; 95% CI 0.51-0.82).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxychloroquine 800 mg stat + 800 mg at 6 hours after initial dose + 400 mg at 12 and 24 hours after initial dose + 400 mg every 12 hours for total of 10 days (orally)</td>
<td></td>
<td>No significant difference in primary endpoint or other outcomes</td>
<td>Recruitment closed on 5 June 2020</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin 500 mg (orally or IV) once daily for 10 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No additional treatment (control)</td>
<td>Convalescent plasma – single unit of ABO compatible convalescent plasma, given on study days 1 and 2</td>
<td>Antibodies against COVID-19</td>
<td>Awaited</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tocilizumab 400-800 mg (depending on body weight) as a single IV infusion</td>
<td>Monoclonal antibody that inhibits binding of IL-6 to its receptor</td>
<td></td>
<td>Awaited</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.

Aside from infection control precautions, studies of other interventions to prevent transmission in the community are underway.

**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 (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 inciting 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 stage of the pandemic: if a patient thought unlikely to have COVID-19 on clinical grounds tests positive at a time when local incidence 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 epidemic 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 could be considerable.

The predominant modes of transmission of SARS-CoV-2 are droplet and contact, and key to reducing the risk to health care workers is adherence to sensible infection prevention and control guidance. Aside from standard infection control precautions, which should be used by all staff in all care settings at all times for all patients, 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 >5μm arising from the respiratory tract) or aerosols (particles of size <5μm 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 8.5.30.9, and for hand decontamination with an alcohol-based hand rub is shown in Figure 8.5.30.10. 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 8.5.30.11).

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 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 8.5.30.12 and Figure 8.5.30.13.

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.
Fig 8.3.10 How to handrub.

Table 8.3.3

<table>
<thead>
<tr>
<th>Setting</th>
<th>Disposable gloves</th>
<th>Disposable plastic apron</th>
<th>Surgical (fluid resistant) mask</th>
<th>Eye/face protection(^1)</th>
<th>Surgical cap / hair cover</th>
<th>Disposable fluid-resistant gown</th>
<th>Filtering Face Piece (FFP) respirator(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who do not meet the definition for possible or confirmed cases of COVID-19</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Possible or confirmed cases of COVID-19, but without AGPs</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Possible or confirmed cases of COVID-19, with AGPs</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Performing AGPs on patients who do not meet the definition for possible or confirmed cases of COVID-19</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

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.
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

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 for 7-14 days 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 (at least within all clinical and communal areas), 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.

**Vaccines**

There are no licensed vaccines for any coronavirus that affects humans (including SARS-CoV-1, MERS-CoV, and the coronaviruses that cause about 15% of cases of the common cold), but wide availability of an effective vaccine for SARS-CoV-2 would undoubtedly be a major advance in halting the pandemic. It is therefore no surprise that there is an unprecedented drive to develop such vaccines, and all conventional and many novel strategies are being employed. The NIH ClinicalTrials.gov website, searched for ‘vaccine / COVID-19’ on 29 July 2020, listed 173 studies, none of which have reported results. 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.
There are no reports of use of live vaccines and for safety reasons such studies are not likely to be attempted. An inactivated whole virus vaccine has been trialled in primates. This induced antibodies that potently neutralised 10 representative SARS-CoV-2 strains and provided partial or complete protection against SARS-CoV-2 challenge in macaques. A phase I-II human trial of this vaccine is now underway in China.

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.

A group led from Oxford (UK) have modified a chimp adenovirus vector to express the spike protein gene, and a Phase I-II single-blinded, randomised study recruiting 1090 volunteers began on 23 April 2020, with planned follow up of 6 months (Figure 8.5.30.14).

Messenger RNA (mRNA) administered systemically can lead to expression of protein, although there are no licensed vaccines based on such methodology. A study in mice has shown that a self-amplifying RNA encoding the spike protein encapsulated within a lipid nanoparticle can induce specific antibodies at a level equal to or higher than those observed following natural infection in humans, and that these can efficiently neutralise a pseudotyped virus. An mRNA spike protein vaccine clinical trial is now underway.

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.

**Delivery of vaccines**

When one or more effective vaccines is available, effort will need to focus on delivery. There will be considerable challenges, notably in low income countries, 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 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 July 2020, about eight months after SARS-CoV-2 was first recognised.

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

**Testing, tracing and isolating**

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

For SARS-CoV-2 implementation of a 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). In various studies the proportion of asymptomatic or pre-symptomatic transmission is estimated to be at least 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 only reduce the number of people they were likely to infect (the effective reproduction number, R) by 60%. Delays in testing and isolating symptomatic individuals; and in tracing and isolating their contacts; would further reduce the effectiveness of these interventions.

The fact that many transmissions are 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), but very few health care systems are capable of delivering this.

The WHO recommendation that a case or contact should isolate for 14 days is widely accepted, but not in the UK, where 7 days is the recommendation for cases and 14 days for contacts. 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.

![Fig 8.5.30.14](image) A volunteer participating in the ChAdOx1 nCov19 vaccine study in Oxford.
8.5.30 COVID-19 Disease

General advice

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

• Wash your hands regularly with soap and water, or clean them with alcohol-based hand rub.
• Maintain at least 1 metre distance between you and people coughing or sneezing.
• Avoid touching your face.
• Cover your mouth and nose when coughing or sneezing.
• Stay home if you feel unwell.
• Refrain from smoking and other activities that weaken the lungs.
• Practice physical distancing by avoiding unnecessary travel and staying away from large groups of people.

Lockdowns

Aside from advising their populations to follow the WHO’s general advice or variants thereof (e.g. in the UK the recommendation has been to maintain physical distancing of at least two metres), 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 8.5.30.15).

Whilst there is much debate about which particular interventions are most effective in preventing viral transmission, there is no doubt that lockdowns have proved effective at halting the first wave of the pandemic in many countries. This, however, has come
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.

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’. As lockdown continues and its hardships become apparent, more voices argue that it should be relaxed. It is generally agreed that knowing when and how to transition back to ‘life as normal’ is more difficult than implementing lockdown. The WHO has provided guidance that six conditions should be used as the basis to implement relaxation of lockdown measures. These are widely accepted as reasonable and sensible, although some, in particular the matter of community engagement, are difficult to judge (Table 8.5.30.4).

**Outcome and deaths from COVID-19**

The mortality from SARS-CoV-2 infection is reported to vary considerably between countries (Figure 8.5.30.16). With the very important caveat that some of this variation may be due to differences in testing and reporting, it does appear that mortality is lower in many low and middle-income countries than it is in richer countries. Possible explanations for lower mortality in low and middle-income countries are their younger population (in Pakistan the median age is 22.5 years, and in developed countries many deaths occur in elderly people), also differences in exposure to various pathogens and patterns of immunisations.

Focussing on comparable countries, the public health response that leads to the fewest deaths will have been the most effective.

### Table 8.5.30.5

**Excess deaths in various countries / cities in the two months before 23 June, 2020**

<table>
<thead>
<tr>
<th>Area of World</th>
<th>Country / City</th>
<th>Excess deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>South America</td>
<td>Brazil (six cities)</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Chile</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Ecuador</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Peru</td>
<td>81</td>
</tr>
<tr>
<td>Eurasia</td>
<td>Jakarta (Indonesia)</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Moscow</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>South Korea</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Tokyo (Japan)</td>
<td>6</td>
</tr>
<tr>
<td>Africa</td>
<td>South Africa</td>
<td>3</td>
</tr>
</tbody>
</table>


During the COVID-19 pandemic people will die because of direct effects of SARS-CoV-2 infection, also 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.

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. There is greater scope for making reasonable comparisons using the metric of excess deaths, but even this is limited: few countries 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 some European countries are shown in Figure 8.5.30.17 and in the United States in Figure 8.5.30.18. The time course and magnitude of excess mortality are very variable between the European countries shown, and between the different US states. Data on excess deaths in various other countries and cities is shown in Table 8.5.30.5. These also show very considerable variation.

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; 17 indicators, such as school closures and travel restrictions, are tracked in over 160 countries. From this and other data it seems that excess deaths have been lower in countries that took lockdown action quickly (S. Korea, Hong Kong, Japan, China, Taiwan, Singapore, Vietnam, Thailand, Greece, Germany, Norway, Denmark), compared to those that did not (Italy, Spain, UK, Netherlands, Sweden, Brazil and the USA).

### Conclusions

The COVID-19 pandemic has caused enormous disruption worldwide. In addition to the hundreds of thousands of deaths due to SARS-CoV-2, thousands of 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.

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

**FURTHER READING**


summary.html


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**Fig 8.5.30.18** Excess mortality in the United States, the eight US States with the largest populations, and New York City.
Richardson S et al. (2020) Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA, 323(20); 2052-2059.
