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Primer

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Acute SARS-CoV-2 infection

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a respiratory pathogen that emerged in December 2019 and caused a global pandemic by March 2020, with >7 million deaths due to coronavirus disease 2019 (COVID-19) globally as of September 2025. The clinical syndrome of COVID-19 ranges from asymptomatic infection to severe disease with pneumonia and death. SARS-CoV-2 variant type, inoculum, previous exposure and host factors influence the clinical trajectory. Identification of key structural proteins of SARS-CoV-2 and insights into the pathophysiology of the immune response to infection led to the development of effective preventive (vaccines and monoclonal antibodies) and therapeutic (antivirals and immunomodulatory agents) agents. Antiviral agents, such as remdesivir and nirmatrelvir-ritonavir, inhibit viral replication and immunomodulatory agents, such as tocilizumab and baricitinib, act to reduce a dysregulated immune response to SARS-CoV-2. The pandemic had economic and socio-cultural consequences that affected the quality of life and overall life expectancy of individuals. As the emergency phase of the pandemic concludes, robust monitoring and surveillance systems must be sustained and research to improve vaccines and therapeutics must continue to maintain control of SARS-CoV-2 in the population and be prepared for emerging pathogens with pandemic potential.

Sections

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a respiratory infection that can result in coronavirus disease 2019 (COVID-19). Clinically, the severity of symptoms exists on a spectrum, ranging from asymptomatic to severely symptomatic, and varies according to virus variant type, previous antigenic exposures (through vaccination and/or infections) and host characteristics.

The first cases of SARS-CoV-2 infection were reported in December 2019, describing a cluster of patients in Wuhan, Hubei Province, China, who experienced an atypical pneumonia that did not respond to standard treatments[1–3]. The genetic sequence of SARS-CoV-2 was determined in early January 2020 and disseminated shortly thereafter via online platforms. Over the next few weeks, the virus was identified in several countries with an increasing number of severe pneumonias attributed to SARS-CoV-2. However, it was not until 11 March 2020, when >118,000 infections and >4,200 deaths due to COVID-19 had been described in 114 countries, that the WHO declared the outbreak of COVID-19 a pandemic[4,5].

SARS-CoV-2 is classified as a species of the *Severe acute respiratory syndrome-related coronavirus*, family *Coronaviridae*, subfamily *Coronavirinae*, of the genus Betacoronavirus[6]. Other Betacoronavirus members that infect humans include HCoV-OC43, HCoV-HKU1, SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), with SARS-CoV-1 and SARS-CoV-2 sharing ~79% genetic similarity at the nucleotide level[7]. SARS-CoV-2 is a positive-sense, single-stranded RNA virus with a genome of approximately 30 kb (ref. 8).

In this Primer, we discuss the epidemiology, pathophysiology and virology of SARS-CoV-2 as well as the clinical diagnosis, screening, prevention and management of SARS-CoV-2 infection, with a primary focus on adult populations. We also highlight the social burden and effects on quality of life. Finally, we address the current gaps in our understanding of SARS-CoV-2 and COVID-19 and the necessary short-term and long-term priorities for research and public health.

Epidemiology

Incidence, mortality and risk factors

According to the WHO, as of September 2025, around 779 million cases of COVID-19 and around 7 million deaths have been confirmed globally[9]. The countries with the highest cumulative number of COVID-19 cases include the USA, China and India, and the USA, Brazil and India have the highest cumulative number of deaths due to COVID-19 (ref. 9). Owing to difficulties with disease diagnosis and death certification attribution, it is highly likely that the reported incidence and mortality of COVID-19 are an underestimate, especially in many low-income and middle-income countries[10]. Global excess mortality for COVID-19 in the first 2 years of the pandemic was estimated to be 14.83 million, 2.74 times higher than the 5.42 million deaths reported to be due to COVID-19 for the same period[11].

Since the beginning of the pandemic, age has remained the strongest risk factor associated with severe COVID-19 outcomes, with individuals >65 years of age at the highest risk[12,13]. Of note, most available data relate to risk from the beginning of the pandemic before vaccination was widely implemented and do not encompass the effects of vaccination and different variant strains. Biological sex as a variable has also been explored for COVID-19 outcomes, with evidence of increased COVID-19 severity and mortality in men[14]. Data from countries where SARS-CoV-2 testing was widespread regardless of symptomatology, such as South Korea, show that women acquire infection at similar rates to men but have a lower case fatality rate[15]. A comparative analysis of COVID-19 case fatality rates of 38 countries demonstrated that the average male case fatality rate was 1.7 times greater than the average female case fatality rate[14]. The exact mechanisms for these sex-based differences are unclear and likely multifactorial given that many dimensions of biological sex (such as sex hormones and genomic and epigenetic differences) likely affect immune responses[16–18].

Certain ethnicities are more at risk of severe disease, reflecting social determinants of health[19]. For example, in the USA, a cross-sectional analysis of counties found that a disproportionate number of Latino and Black communities were affected by COVID-19, although other factors, such as average household size, educational level and use of public transportation, were independent predictors of higher COVID-19 cases and deaths[20]. Data from South Africa demonstrate the effect of ethnicity and socio-economic status on in-hospital COVID-19 mortality, showing an increased risk of mortality in Black compared with white patients and in those admitted to public-sector hospitals compared with private health care[21].

Several comorbidities have been associated with more severe COVID-19 clinical outcomes (defined as the requirement for supplemental oxygenation, hospitalization and COVID-19-attributed death[22]). Throughout the early stages of the pandemic, individuals with histories of cardiac disease, chronic kidney disease, obesity, pulmonary disease, malignancy, diabetes mellitus, liver disease and chronic neurological disorders were found to have an increased risk of hospitalization and mortality due to COVID-19 in large prospective studies in the UK, China and the USA[23–27]. Of note, pulmonary diseases, such as chronic obstructive pulmonary disease, asthma and interstitial lung diseases, are associated with more severe disease and COVID-19 outcomes likely due to baseline physiological and immune dysregulation[28]. In South Africa, individuals with HIV and immunosuppression had an increased risk of mortality[29]. Regarding other immunocompromising conditions, data from early in the pandemic suggested high mortality among those who had received solid-organ transplants or had a haematological malignancy, although results between studies differed depending on the type of immunocompromising condition[30–33].

Many of these medical conditions tend to occur together in patients, termed multimorbidity (two or more long-term conditions)[34], and may have important and distinct pathophysiological mechanisms that result in increased COVID-19 severity or complications[35–37]. However, it is difficult to discern causality given that several confounders are likely at play, which may either increase or decrease the effects measured by evaluating severe COVID-19 outcomes. For example, the threshold for hospital admission or intubation might be lower for an individual with underlying comorbidities, thus increasing the perceived risk of severe outcomes for these patients if outcomes in studies are measured by hospitalizations or need for mechanical ventilation. Additionally, pre-existing immunity (from vaccination and/or infection) and the type of circulating variant likely modulate risk in individuals with comorbidities, with most studies that evaluated comorbidities reporting on associations before vaccination or infection was widespread. Furthermore, individuals who perceive that their risk is increased due to an underlying medical condition may be more likely to practice social mitigation practices, such as masking, and reduce exposure risks[38]. Thus, further studies are warranted to clarify which specific populations with comorbidities may be at most risk for severe outcomes in the current era.

SARS-CoV-2 mutations and variants

The distribution of variants continues to rapidly evolve. Organizations such as the Centers for Disease Control and Prevention and

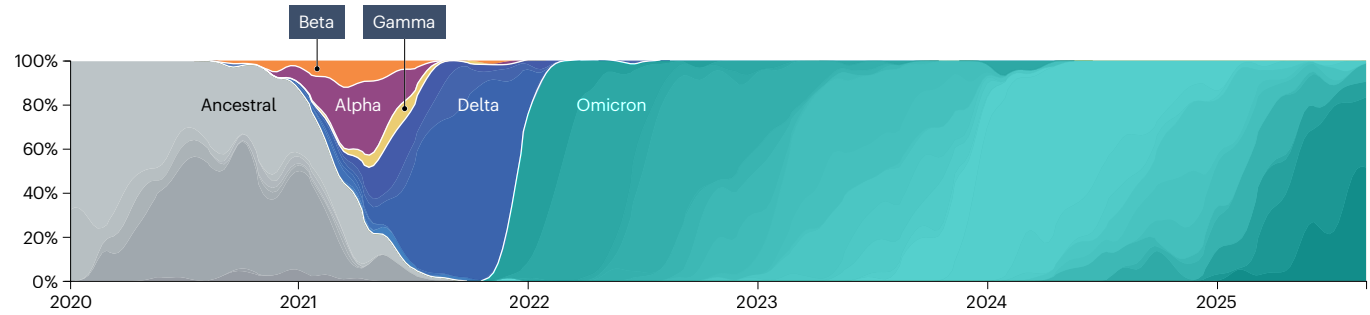


Fig. 1 | Evolution of SARS-CoV-2. The frequencies (prevalence) of different severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lineages fluctuated during the coronavirus disease 2019 (COVID-19) pandemic globally. Initially, the ancestral strain dominated with relative evolutionary stasis over the first year. A second phase started in 2020 with the emergence of the Alpha, Beta and Gamma strains. The Delta lineage then replaced these variants and dominated for the second half of 2021. From late 2021 until now, the Omicron lineage has been the dominant, with emergence of different Omicron sub-lineages (denoted by different colour shades). Adapted from https://nextstrain.org/ncov/gisaid/global/all-time, CC BY 4.0.

WHO use a combination of strategies for surveillance, including variant and genomic surveillance by national and regional variant proportions, traveller-based genomic surveillance, and wastewater surveillance[39]. Several other forms of surveillance arose during the pandemic, including digital surveillance technologies, artificial intelligence-driven modelling, zoonotic monitoring systems and symptom surveys[40]. Of note, genomic surveillance is the most accurate method to confirm SARS-CoV-2 infection but can be costly and low-income and middle-income countries may lack resources and training to sustain it. Surveillance based on clinical reporting may be limited because patients with mild disease may not be counted if treatment is not sought, and testing capacity at various centres may prioritize those with more severe disease[41].

SARS-CoV-2 variants of concern (VOCs) are categorized by the WHO using Greek letters, with parent lineages including Alpha, Beta, Gamma, Delta and Omicron[42]. Most publicly available sequences since February 2022 report circulating Omicron viruses (98%), with various sub-lineages of Omicron emerging due to antigenic drift. Through surveillance, in addition to VOCs, the WHO also reports variants under monitoring and variants of interest as defined by the WHO Technical Advisory Group on Virus Evolution[43].

The mutational rate and profile of SARS-CoV-2 genome sequences have undergone dynamic changes. The mutation rate of a virus is defined as changes in base pairs or larger genomic regions per replication cycle. RNA viruses can have wide variations in mutation rates, ranging between 10^{-6} and 10^{-4} substitutions per nucleotide per cell infection[44]. For example, influenza viruses have a mutation rate of $0.6–2.0 \times 10^{-6}$ (ref. 45). The mutation rate for SARS-CoV-2 is similar and estimated to be between 1×10^{-6} and 2×10^{-6} substitutions per nucleotide per cell infection[46]. Replication errors that occur can result in insertions and deletions in the sequence that generate diversity, thereby leading to the development of new variants that can be associated with increased infectivity[47].

Three distinct evolutionary phases of SARS-CoV-2 evolution have been described: the first 8 months of relative evolutionary stasis (ancestral strain), followed by the emergence of three distinct and divergent lineages (Alpha, Beta and Gamma), followed by a more gradual evolution of the virus within lineages[46] (Fig. 1). Interestingly, the second phase was characterized by the Alpha, Beta and Gamma lineages expanding from different geographic locations: the UK, South Africa and Brazil, respectively[48–50]. These variants soon spread worldwide. The Delta variant was first identified in India late in 2020 and rapidly replaced the other variants due to antibody evasion in individuals who had previously been infected with other variants or vaccinated[51,52]. In the third evolutionary phase, the Omicron variant (first identified in Botswana and South Africa) became the dominant strain since its emergence in late 2021 (ref. 53). This phase has been marked by more gradual and successive Omicron sub-lineages, with shared mutations among these sub-lineages in the SARS-CoV-2 spike gene[54].

Mechanisms/pathophysiology

Virus structure, infection and replication cycle

SARS-CoV-2 is a positive-sense single-stranded RNA virus, ~30 kb in size, classified in the genus Betacoronavirus of the family *Coronaviridae*[55]. The subfamily *Orthocoronavirinae* further divides into four genera: Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gammacoronavirus. SARS-CoV-2 belongs to the Betacoronavirus genus; other coronaviruses in this genus include SARS-CoV-1 and MERS-CoV[56]. The origin of SARS-CoV-2 is not known, although given the high genetic similarity between SARS-CoV-1 and SARS-related bat coronavirus, it is likely that SARS-CoV-2 originated in bats[7,57,58]. Additional evidence suggests that Malayan pangolins are likely an intermediate host, given the genetic similarity between coronaviruses isolated from pangolins and SARS-CoV-2, with nearly identical amino acid identity of the receptor-binding domain of the spike protein[58,59].

The structural proteins of SARS-CoV-2 include the spike protein, envelope protein, membrane protein and nucleocapsid protein[56,60]. The open reading frames (ORFs) that encode these proteins are located in the 3′ part of the genome, with additional ORFs that encode for accessory proteins located between them.

SARS-CoV-2 entry into the host cell involves the use of several key host attachment and entry factors (Fig. 2). SARS-CoV-2 entry depends on both angiotensin-converting enzyme 2 (ACE2) and TMPRSS2: the spike glycoprotein binds to the ACE2 receptor, and the host cell surface serine protease TMPRSS2 primes the spike protein for entry[61–63]. The spike protein itself consists of subunit S1, which mediates attachment to the cell membrane, and subunit S2, which has a role in fusion with the cell membrane[64]. The receptor-binding domain of the spike protein (within the S1 subunit) is important in the host-cell receptor interaction, as the receptor-binding domain binds to ACE2 (ref. 65).

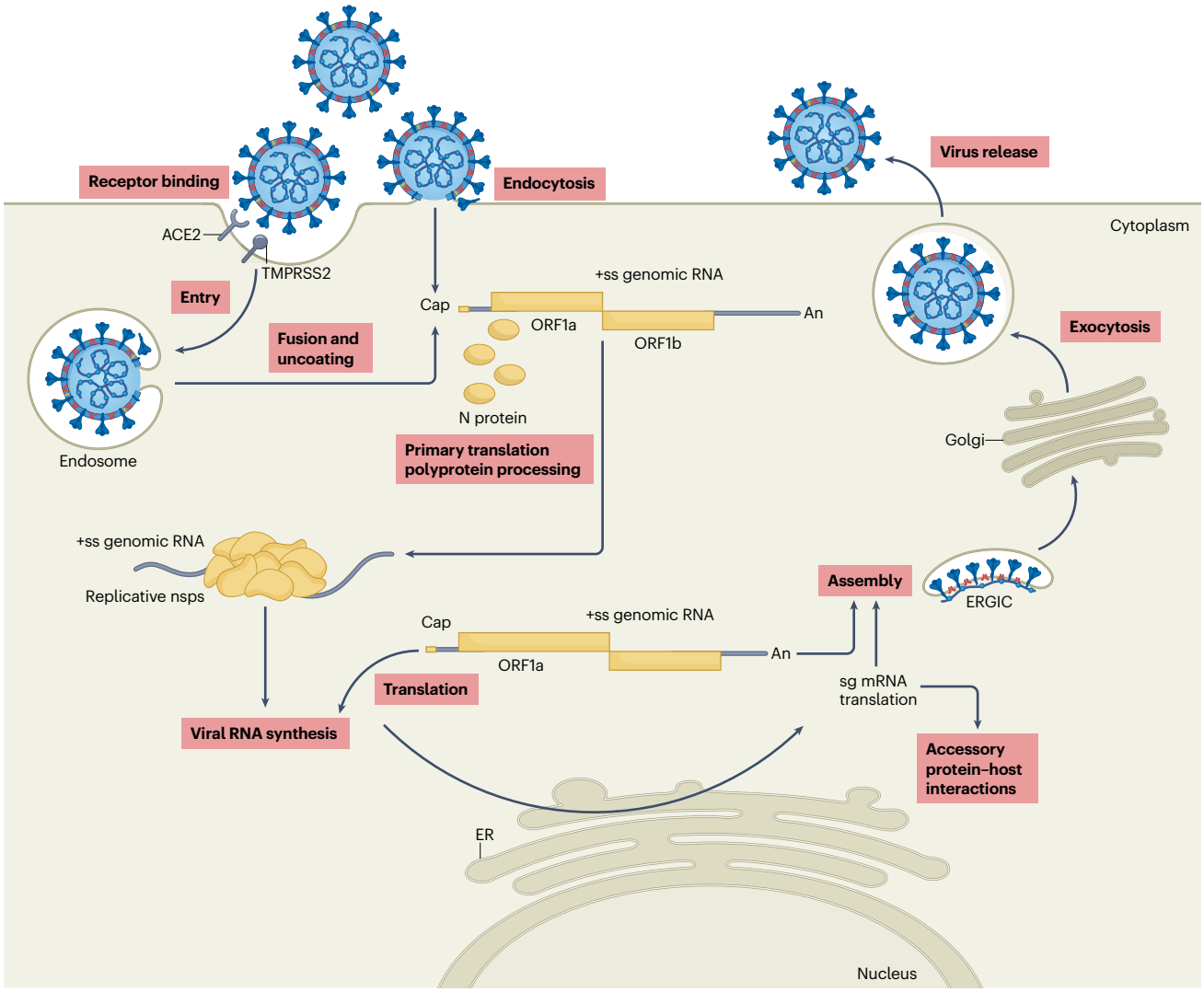


Fig. 2 | Life cycle of SARS-CoV-2. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) particles first bind to the host cell's angiotensin-converting enzyme 2 (ACE2) receptor using the receptor-binding domain of the spike protein, with the host cell surface serine protease TMPRSS2 assisting in priming and entry. If the virus–ACE2 complex does not encounter TMPRSS2, then the virus–ACE2 complex can be internalized via clathrin-mediated endocytosis. After entry, fusion and uncoating of the viral particle occur, and the genomic RNA is released. Primary translation of the RNA occurs via the open reading frames ORF1a and ORF1b. The structural nucleocapsid (N) protein is released into the cytoplasm. From the primary translational process, individual non-structural proteins (nsps) are formed that create the viral replication and transcription complex. New negative-strand guide RNA (not shown), which serves as a template for viral replication and creation of positive-sense single-strand (+ss) RNA, as well as subgenomic (sg) mRNAs are synthesized. The sg mRNAs are then translated into structural proteins. The structural proteins are then assembled in the rough endoplasmic reticulum (ER) and transit through the ER–Golgi intermediate compartment (ERGIC) and new virions are formed. The last step involves exocytosis of the newly formed virions from the host cell via the Golgi apparatus. Adapted from ref. 61, Springer Nature Limited.

Upon cell entry, the spike protein is cleaved via cellular proteases, enabling release of the spike fusion peptide and viral entry with subsequent uncoating of the genomic RNA[66]. Translation of the genomic RNA occurs next to two ORFs (ORF1a and ORF1b). The resulting polyproteins include non-structural proteins and replicase polyproteins that form an RNA-dependent RNA polymerase complex. New negative-strand guide RNA and subgenomic RNAs for viral replication and transcription are formed within the RNA-dependent RNA polymerase complex. The subgenomic RNAs are then translated into structural spike, envelope, membrane and nucleocapsid proteins. The proteins are assembled in the rough endoplasmic reticulum and the endoplasmic reticulum–Golgi intermediate compartment and new virions are formed. Finally, the virions are exocytosed from the cell.

The anatomical distribution of the host receptors has important implications for clinical infection and manifestation. ACE2 is expressed in both the upper respiratory epithelia as well as the lower respiratory tract, enabling SARS-CoV-2 to target these areas and replicate abundantly[61,67]. Physiologically, ACE2 regulates the

renin–angiotensin–aldosterone system and therefore has an important role in haemodynamic regulation. As SARS-CoV-2 competes for ACE2 receptor binding, the renin–angiotensin–aldosterone system pathways are disrupted, which has been linked to COVID-19 progression[68].

Pathophysiology

Stage 1: viral-mediated cell damage. SARS-CoV-2 primarily targets alveolar epithelial cells via ACE2 receptors, where it replicates extensively. Cell damage starts immediately after virus entry (Fig. 2). The amount of cell damage correlates with the severity of illness, which is why COVID-19 was initially classified as a viral pneumonia. The virus can also infect endothelial cells[69], via the ACE2 receptor or other potential receptors, resulting in either productive or non-productive infections. COVID-19 is now recognized as a multisystem disease affecting multiple organs, including the cardiovascular system, coagulation system, brain, liver and kidney[70]. Additionally, viral components directly engage innate pattern recognition receptors. For instance, SARS-CoV-2 infection can induce Z-RNA formation in the cytoplasm of infected cells, which activates the ZBP1–RIPK3–MLKL necroptosis pathway and drives the secretion of inflammatory cytokines[71]. Subsequently, damage-associated molecular patterns and cytokines released from infected cells may further damage bystander cells.

Damage to both the respiratory epithelium and endothelium disrupts the alveolar–capillary barrier, which can enable the virus to enter the bloodstream and spread to extrapulmonary organs. Although overt evidence of viraemia is lacking, the detection of virions in extrapulmonary organs suggests that viraemia may occur very early, for example, during the first week of infection[72]. The presence of viraemia correlates with the degree of viral replication in the lungs[73]. Of note, RNAaemia (detectable levels of viral RNA in the blood) has been reported in 11% (95% CI 0.5–18%) of patients with mild-to-moderate disease, in 36% (95% CI 26–46%) of those with severe disease, and in 65% (95% CI 56–75%) of those with critical disease[74]; however, the techniques and, therefore, threshold of viraemia differed among studies. The presence of viable viruses in the blood, along with the conditions and patterns of viral entry into the bloodstream, requires further investigation.

At this stage, dysfunction of antiviral immunity may be the key factor driving subsequent immune dysregulation, a hyperinflammatory state with excessive production of cytokines, and progression to severe disease. SARS-CoV-2 proteins, particularly non-structural proteins, interact with molecules in the interferon-producing pathway to evade immune surveillance, reducing or delaying the production and activity of type I interferons (with absent IFNβ and diminished IFNα) and type III interferons[75–77]. This sets the stage for immune cell dysfunction in stage 2, marked by the concomitant rather than consecutive occurrence of both pro-inflammatory and anti-inflammatory responses.

Stage 2: immunopathology. This stage of COVID-19 pathogenesis is characterized by severe immune dysregulation with subsequent immunosuppression (Fig. 3). A reduction in plasmacytoid dendritic cells impairs viral control, contributing to pathological inflammation[78]. Reduced levels of lymphocytes with functional exhaustion, particularly a marked decrease in $CD8^+$ T cells and natural killer cells[79,80], further exacerbate the condition. Additionally, emergency myelopoiesis (the production of non-lymphoid leukocytes), along with dysfunctional mature neutrophils and HLA-DR^{lo} monocytes, is associated with the immunosuppressive state[81].

Furthermore, the massive recruitment and activation of immune cells, including neutrophils, monocyte-derived macrophages and T cells, lead to substantial cytokine release. Early clinical reports have observed substantially elevated levels of cytokines, such as IL-6, IL-8 and TNF, in critically ill patients[3], suggesting that cytokine dysregulation is a key driver of tissue damage. This provides a theoretical basis for the development of various immune-modulatory drugs. Of note, although the term 'cytokine storm' is often used to describe this state, it may not be entirely appropriate in this scenario, as cytokine levels are only moderately elevated in severe COVID-19 compared with bacterial sepsis. Notably, in patients with COVID-19 and secondary bacterial infections, IL-6 levels can increase 10-fold to 200-fold, substantially elevating mortality[82–84].

In addition to cytokine dysregulation, systemic complement activation[85] and inflammation of the endothelium[86] lead to microvascular immunothrombosis[87], which is a key feature of severe COVID-19. These processes, in turn, may lead to widespread damage in the lungs and extrapulmonary organs. The virions disseminating through the bloodstream also affect extrapulmonary organs. Although data are limited, it has been hypothesized that trace amounts of virus detectable in peripheral organs may trigger local immune cell infiltration[88]. Coupled with systemic cytokine dysregulation and thrombosis, this dual assault ultimately leads to viral sepsis and, in some cases, death.

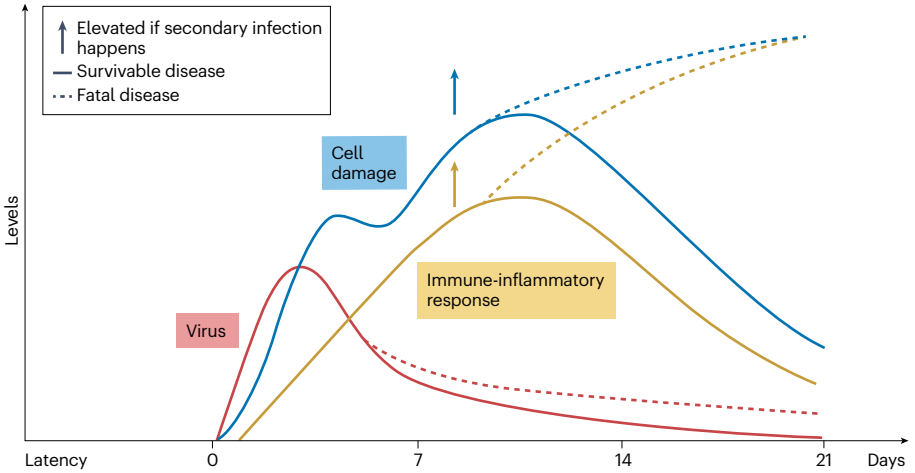
The escape of the virus from immune surveillance, leading to efficient replication and dissemination via viraemia, is the cause of severe progression. Direct viral damage, combined with immunopathology from cytokines and immune cells, results in functional cell injury or death, which directly leads to organ dysfunction and eventually death. Secondary bacterial infection is another crucial event that triggers high-level production of cytokines and substantially increases mortality[89] (Fig. 3). The mechanisms by which the virus enters the bloodstream, the factors driving progression from mild to severe disease in different individuals, and the most effective interventions still require further investigation.

Stage 3: chronic active infections. The acute infection of SARS-CoV-2 typically resolves within 2–3 weeks, often with a faster recovery in those individuals who have been previously infected and/or vaccinated. However, emerging evidence shows that SARS-CoV-2 clearance may be delayed in the respiratory tract and various other tissues[90]. Samples from the lower respiratory tract can remain consistently positive on viral culture for SARS-CoV-2 despite negative pharyngeal swab tests, with positivity reported up to 4 weeks after symptom onset[91]. In immunocompromised patients, SARS-CoV-2 may persist longer and may be associated with prolonged symptoms, radiological changes, and inflammation and may require an extended course of antiviral therapy[92]. These patients can also experience persistent and recurrent fever, cough and hypoxia[93], indicating a chronic infection rather than infection relapse. Chronic active SARS-CoV-2 infection has been proposed to describe this clinical phenomenon[94]. Clinical research and therapeutic interventions tailored to this demographic are still lacking.

Diagnosis, screening and prevention

Clinical diagnosis and symptoms

The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic infection to fatal illness from pneumonia (with fever, cough and dyspnoea) and respiratory failure (from acute respiratory distress syndrome). Other complications related to COVID-19 can also occur. Asymptomatic infections are estimated to occur in ~40% of infected individuals, but this rate varies depending on SARS-CoV-2 variant and pre-existing immunity[95]. Severe disease most commonly affects people



Viral load and viraemia	+/+++	–/++	–/+	
Type I interferons from pDCs and NK cells	+++/+	+/+++	–/++	
Cytokines from NEUs and MoMs	+/++	++/+++	+/++	
Cytotoxity of $CD8^+$ CTLs	–/+	+/++	+/++	
Complement and coagulation	+/++	++/+++	+/++	
Pulmonary cell damage	+/++	++/+++	+/++	
Extrapulmonary cell damage	–/+	+/++	–/++	

Survival in mild cases
Survival in severe cases

Fig. 3 | Immune dysregulation and cell damage during severe SARS-CoV-2 infection. In patients who survive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, SARS-CoV-2 viraemia (red solid line) peaks within the first 7 days of infection, followed by an immune-inflammatory response (brown solid line) that peaks between 7 and 14 days. Cell damage (blue solid line) is biphasic, occurring first in the context of direct viral cytotoxicity followed by further cell damage due to the immune-inflammatory response. In patients with secondary bacterial or fungal infection, both the immune-inflammatory response (brown arrow) and cell damage (blue arrow) are exacerbated, which increases the likelihood of fatal outcomes. In patients who do not survive coronavirus disease 2019 (COVID-19), with or without a secondary infection, the immune-inflammatory response (brown dashed line) and cell damage (blue dashed line) progressively worsen, and viraemia may be prolonged (red dashed line). The table presents the dynamic levels of viral load and viraemia, type I interferons from plasmacytoid dendritic cells (pDCs) and natural killer (NK) cells, cytokines from neutrophils (NEUs) and monocyte-derived macrophages (MoMs), cytotoxicity of $CD8^+$ cytotoxic T lymphocytes (CTLs), complement and coagulation, and pulmonary and extrapulmonary cell damage across different disease stages in mild (purple) and severe (green) survival cases. (–) absent or negligible levels; (+) mild; (++) moderate; (+++) severe.

of advanced age and those with comorbidities. The incubation period varies between 2 and 14 days and is 3–5 days on average[24]. Typically, patients present with cough, myalgia and headache. Upper respiratory symptoms are common with Omicron variants. In addition, diarrhoea as well as alterations in smell and taste have been observed[96]. During the course of the COVID-19 pandemic, the clinical spectrum and severity of the disease in the general population have evolved. Mild disease became more common owing to widespread vaccination, previous infections and the emergence of virus variants, such as Omicron, that tend to cause less severe illness, particularly in vaccinated individuals[97]. However, vulnerable populations, such as those of advanced age and immunocompromised individuals, remain at an increased risk of severe disease and complications.

Diagnostic tests

An accurate diagnosis of SARS-CoV-2 infection is crucial in guiding patient treatment, infection control practices in hospitals, and public health actions. Virological confirmation through laboratory or point-of-care tests remains essential because symptoms and signs alone cannot reliably differentiate COVID-19 from other respiratory tract infections. The nucleic acid amplification test (NAAT) and rapid antigen test (RAT; also known as the lateral flow assay) are the mainstays of diagnosis[98,99]. NAAT, usually by reverse transcription–polymerase chain reaction (RT-PCR), is the preferred laboratory diagnostic test for hospitalized patients as it is highly sensitive and specific with a short turnaround time. Furthermore, NAAT is a suitable test for pooled specimens and was used widely for community screening[100]. SARS-CoV-2 RT-PCR

has been incorporated into most commercially available multiplex PCR respiratory panels. However, there are several caveats associated with NAAT. First, prolonged shedding of SARS-CoV-2 RNA can occur, and sporadic shedding can be detected even among immunocompetent patients for a few weeks after symptom onset[100]. Second, NAAT can only be performed in clinical laboratories equipped for molecular diagnostic testing. However, fully automated NAAT assays are now available, making NAAT possible even at the point of care. Third, mutations at the target sites of the RT-PCR primers or probes can lead to false-negative results. For example, the Alpha variant contained a deletion at the spike protein amino acid residues 69 and 70, leading to the failure of some RT-PCR assays[101].

RAT is a suitable alternative when molecular testing is not available, for example, for home testing. RAT is highly specific, technically simple and cheap, with results usually available within 15–20 min. Although RAT overall has a lower sensitivity than NAAT (60–70% versus 80–90%)[102,103], RAT sensitivity can be >80% within the first 5 days of illness for symptomatic individuals when the viral load is highest[102,104]. Furthermore, the sensitivity of RAT can be enhanced through serial testing[105]. Despite mutations at the target site (usually the nucleocapsid protein), the sensitivity of RAT remains similar for most variants[106]. However, some mutations in the nucleocapsid protein have been associated with RAT failure[107].

Serological assays for SARS-CoV-2 usually identify antibodies against the N or spike protein. However, serological assays should not be used for diagnosing acute infection because antibodies are typically not detectable within 10 days of symptom onset[108], and the majority of the population has now been infected and/or vaccinated. Thus, serological assessment would show high positivity in a population that is not necessarily associated with acute infection. During the early stages of the COVID-19 pandemic, serological tests were useful for retrospective diagnosis, which was especially important for contact tracing and for patients with immune-mediated complications of COVID-19, such as multisystem inflammatory syndrome in children, in whom the initial SARS-CoV-2 infection had not been diagnosed[109]. Furthermore, serological assays were previously used to measure seroprevalence and assess the level of humoral immunity in a population[110]. However, serological assays should be used cautiously. For example, some patients who had a previous SARS-CoV-2 infection may not have detectable levels of antibody due to the waning of antibody levels over time or the absence of an antibody response in some immunocompromised patients[111].

Next-generation sequencing has also been used for diagnostic testing[112]. One potential advantage of this technique is that it can provide information on novel variants in addition to detecting SARS-CoV-2 infection in general[113]. However, next-generation sequencing is not widely used because of the relatively high cost and required technical expertise.

Specimen type

The type of specimen is an often-overlooked aspect of diagnostic testing. Nasopharyngeal swab is the specimen of choice for diagnostic testing of respiratory viruses[114]. Nasal swab is less sensitive than nasopharyngeal swab[115] but is clinically useful, as nasal swabs can be collected by patients themselves, which is particularly useful for home testing with RAT[116]. A high concordance has been reported in the results of self-collected nasal swabs and those collected by healthcare workers[117]. For patients who are intubated, bronchoalveolar lavage (collection of samples from the lower respiratory tract) may also be used as a specimen type for testing[118].

Saliva was not recommended as a specimen type for diagnostic testing of respiratory viruses before the COVID-19 pandemic[114]. However, saliva has been used widely during the COVID-19 pandemic. The advantages of saliva as a specimen are that it can be self-collected without any invasive procedures, which facilitates testing in the community, and its capacity to be used in pooled testing, which can aid in community surveillance[119,120]. The test sensitivity of saliva is comparable to that of nasopharyngeal swab[121].

Indications for testing

Testing for SARS-CoV-2 should be performed when the result can affect decisions on patient management, infection control or public health. The Centers for Disease Control and Prevention recommends SARS-CoV-2 testing for people who have symptoms of COVID-19 and for asymptomatic individuals who have had known exposure to someone with COVID-19 (ref. 122). This is especially important for individuals with increased risk of severe disease, who therefore require early antiviral treatment, such as older adults and those who have comorbidities or are immunocompromised. Screening tests can be considered when early identification can result in actions that mitigate the risk of infection in individuals at high risk. Testing strategies should be tailored to individual settings, taking into account resource limitations and the benefits associated with the testing.

Vaccination

More than 13 billion doses of vaccines against SARS-CoV-2 have been administered to date, making it the largest immunization effort in history and the most ambitious public health endeavour, owing to its urgency, scale and collaborative efforts[123]. It is estimated that >14 million lives have been saved by vaccines against SARS-CoV-2 (ref. 124). Several COVID-19 vaccines have been approved for use by the WHO through Emergency Use Listing since December 2020 from different manufacturers and platforms, including inactivated or weakened virus vaccines, protein-based vaccines, viral vector vaccines and mRNA vaccines[125,126].

The recommendations on who should get vaccinated vary between countries. The WHO Strategic Advisory Group of Expert's on Immunization (SAGE) outlined three priority-use groups for COVID-19 vaccination: high (which includes oldest and older adults with multiple significant comorbidities, younger adults with significant comorbidities, children aged 6 months and older with immunocompromising conditions, health-care workers, and pregnant persons), medium (healthy adults and children and adolescents with comorbidities) and low (healthy children and adolescents, aged 6 months to 17 years)[127]. Recommendations differ for each high, medium and low group for primary series and booster vaccinations. Disease burden in specific age groups, cost effectiveness and opportunity costs must also be evaluated for each country.

Although efficacy trials provided evidence that different vaccines against SARS-CoV-2 protect against COVID-19 (refs. 128–133), the immunity against disease wanes over time and with the emergence of VOCs. However, it is important to note that all vaccines provide strong protection against serious outcomes such as severe illness, hospitalization and death. Pooled analyses from the vaccine efficacy trials demonstrate that levels of binding and neutralizing antibodies against the spike protein and its receptor-binding domain are the primary immune correlates of protection against symptomatic infection[134]. However, data regarding correlates of protection against severe COVID-19 are limited.

To overcome waning immunity and emergence of VOCs, vaccination recommendations include additional doses, which, until the autumn of 2022, included more doses of the vaccine that target the ancestral strain. Since then, updated vaccines have been available to better target the antigenic landscape of SARS-CoV-2 variants, including bivalent (prototype/wild type and Omicron BA.4/5) vaccines and updated monovalent (Omicron XBB.1.5 and KP.2 for mRNA vaccines; JN.1 for protein-based product) vaccines[135–137]. The effectiveness of updated vaccines, although more pronounced for older and immunocompetent adults, still fades over time, highlighting the constant need for revaccination[138]. These vaccine effectiveness findings should be interpreted as the incremental benefit provided by COVID-19 vaccination in a population with a high prevalence of infection-induced immunity, as hybrid immunity further provides protection against serious outcomes[139]. Boosters remain effective in decreasing the severity of COVID-19 (ref. 140).

The number of doses in a primary vaccination series varies depending on the vaccine type as well as on the host (for example, those who are immunocompromised) and their age (for example, those <5 years of age). Booster vaccinations are recommended annually, although moderate to severely immunocompromised individuals may receive booster vaccinations more frequently[141]. Additional doses can be given from the same manufacturer or a different one (mixing-and-matching approach), offering greater effectiveness than homologous boosting according to some studies[142,143]. Contraindications are rare and typically include a severe allergic reaction, such as anaphylaxis, to a previous COVID-19 vaccine dose or to a component of the vaccine or due to a known (diagnosed) allergy to a component of the vaccine. Co-administration, if needed, particularly with other vaccines against other respiratory viruses, is safe and does not negatively affect vaccine immunogenicity[144]. With the availability of vaccines for respiratory syncytial virus, influenza and COVID-19, many manufacturers are developing combination respiratory disease virus vaccines to streamline protection against these infections and improve vaccination uptake, especially in populations at risk.

Vaccine recipients should be advised that adverse effects after COVID-19 vaccination are common and include local (for example, pain at the injection site, redness, swelling and ipsilateral axillary lymph node enlargement) and systemic reactions (for example, fever, fatigue and headache). These expected adverse effects are mild to moderate, limited to 2–3 days after vaccination and could be associated with slightly higher immunogenicity[145]. Serious adverse events are very rare and include myocarditis and pericarditis (mainly seen in male adolescents and young adults), are generally self-limited and occur within 1 week of vaccination[146]. The risk of developing myocarditis or pericarditis also tends to be elevated after the second dose, especially when the time interval between doses is short[147]. Other very rare serious adverse effects include vaccine-associated immune thrombotic thrombocytopenia or thrombosis with thrombocytopenia syndrome following receipt of adenoviral vector vaccines, typically 3–30 days after vaccination and affecting 0.5–0.8 per 100,000 vaccinated individuals[148]. In addition, Guillain–Barré syndrome can occur within 6 weeks following receipt of adenoviral vector vaccines (reporting odds ratio 14.88, 95% CI 14.26–15.53)[149].

Monoclonal antibodies for prevention

Although SARS-CoV-2 vaccines have been effective for most individuals, the vaccines are less effective for individuals who cannot mount an adequate response to vaccines, for example, those who are immunocompromised due to underlying disease or immunotherapies[150–152]. Several monoclonal antibodies against SARS-CoV-2 have been developed, which function by blocking cell entry, and have been evaluated in immunocompromised populations as an alternative or adjunct to vaccination to prevent severe COVID-19 (ref. 153). However, although many of these products were effective against the circulating strains at the time of development, they have become less efficacious due to antibody evasion as SARS-CoV-2 variants have evolved, creating a risk of emergence of resistance during monoclonal antibody therapy[154,155]. Only one monoclonal antibody (pemivibart) is currently available under FDA Emergency Use Authorization for moderately-to-severely immunocompromised individuals to prevent severe SARS-CoV-2 (ref. 156). Pemivibart was approved based on immunobridging data (use of an immunological correlate of protection to estimate the effectiveness of an intervention) from previous efficacy trials for a parent monoclonal antibody, adintrevimab. Hence, there are limited efficacy data to support the use of pemivibart against SARS-CoV-2 variants that were not circulating during the adintrevimab trials. The clinical use and effectiveness of pemivibart must therefore be closely monitored.

Management

Treatment in the community

The focus of treatment of early-stage COVID-19 in at-risk patients in the community is antiviral therapy to prevent progression to moderate or severe disease (Table 1).

Antivirals. Nirmatrelvir is an oral antiviral that inhibits coronavirus 3C-like protease, an enzyme involved in SARS-CoV-2 replication. It is formulated with ritonavir, an antiviral that inhibits CYP3A-mediated metabolism of nirmatrelvir, thereby increasing the plasma concentration of nirmatrelvir[157]. In the Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) trial in symptomatic adults with COVID-19 who were at high risk of progression to severe disease, treatment with nirmatrelvir plus ritonavir within 3 days of symptom onset reduced the number of hospital admissions or deaths compared with placebo (0.72% versus 6.45%; difference −5.81%, 95% CI −7.78% to −3.84%; $P < 0.001$). There were no deaths in the nirmatrelvir plus ritonavir group compared with nine deaths in the placebo group[158]. Of note, the EPIC-HR trial was conducted in previously SARS-CoV-2 naive individuals, before vaccination was available. Importantly, CYP3A inhibition (by ritonavir) also alters the levels of other drugs that are dependent on the same enzyme for their metabolism, with the potential for multiple important, possibly life-threatening drug interactions that must be addressed by the prescriber. The subsequent EPIC trial in those at standard risk for severe COVID-19 or those at high risk but vaccinated (EPIC-SR) did not demonstrate therapeutic benefit[159].

Molnupiravir is another oral antiviral that inhibits replication of SARS-CoV-2. In the MOVe-OUT trial in non-hospitalized symptomatic adults within 5 days of laboratory-confirmed SARS-CoV-2 infection and with a heightened risk of developing severe COVID-19, treatment with molnupiravir reduced hospital admissions compared with placebo (6.8% versus 9.7%; difference −3.0%, 95% CI −5.9% to −0.1%) with only one death in the molnupiravir group compared with nine deaths in the placebo group[160]. By contrast, in the PANORAMIC trial of non-hospitalized symptomatic adults within 7 days of laboratory-confirmed SARS-CoV-2 infection, there was no difference in rates of hospitalization or death between the molnupiravir and control groups (1% in both), although

Table 1 | Antivirals for SARS-CoV-2

Antiviral	Mechanism of action	Target population	Route of administration	Other features
Remdesivir	Nucleoside analogue that inhibits RNA-dependent RNA polymerase of SARS-CoV-2	Adults and children (≥28 days old who weigh ≥3 kg) and are at high risk of severe COVID-19	Intravenous infusion	Start as soon as possible and within 7 days of symptom onset. Benefit is seen in both hospitalized and non-hospitalized patients at risk of severe COVID-19 but intravenous administration is less practical for community use
Nirmatrelvir with ritonavir	SARS-CoV-2 main protease (M^{pro}) inhibitor; ritonavir co-administered to increase plasma concentrations of nirmatrelvir by inhibiting CYP3A	Adults and children (≥12 years old)	Oral	Start as soon as possible and within 5 days of symptom onset. Must monitor drug–drug interactions owing to ritonavir
Molnupiravir	Introduces errors in viral genome and subsequent inhibition of replication, following its metabolism to a cytidine nucleoside analogue that is phosphorylated to active ribonucleoside triphosphate and incorporated into SARS-CoV-2 RNA by viral RNA polymerase	Adults	Oral	Start as soon as possible and within 5 days of symptom onset. Potential toxic effects in children and pregnant women limit use in these populations

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

time to recovery was quicker in the molnupiravir group (estimated benefit ~4 days)[161]. It is important to note that the MOVe-OUT trial included unvaccinated patients, whereas 94% of the PANORAMIC trial population had three or more SARS-CoV-2 vaccine doses. As the effects of molnupiravir in children and in pregnancy are not known, and the effects on hospitalization and death seem smaller, nirmatrelvir plus ritonavir is recommended over molnupiravir[162].

Monoclonal antibodies. Sotrovimab is a human monoclonal antibody that binds to the SARS-CoV-2 spike protein, preventing the virus from entering cells. In the COVID-19 Monoclonal antibody Efficacy Trial–Intent to Care Early (COMET-ICE) in non-hospitalized symptomatic adults within 5 days of laboratory-confirmed SARS-CoV-2 infection and with a risk factor for developing severe COVID-19, treatment with a single intravenous infusion of sotrovimab led to a reduction in the number of hospital admissions or deaths compared with placebo (1% versus 6%; adjusted relative risk 0.21, 95% CI 0.09–0.50; $P < 0.001$)[163]. However, sotrovimab is likely to be less effective against newer variants of SARS-CoV-2 as it does not bind to these[164].

Similarly, the combination of the human monoclonal antibodies tixagevimab and cilgavimab given intramuscularly to non-hospitalized, unvaccinated adults within 3 days of positive SARS-CoV-2 testing and 7 days of symptom onset reduced severe COVID-19 or death compared with placebo (4% versus 9%; absolute risk reduction 4.5%, 95% CI 1.1–8.0%; $P < 0.0001$)[165]. However, tixagevimab and cilgavimab are likely to be less effective against newer variants of SARS-CoV-2 as they do not bind to these owing to escape mutations[166].

Treatment in hospital and intensive care

In moderate or severe disease that requires admission to hospital or intensive care, the focus of clinical management initially focuses on treating the patient's response to the infection (in terms of symptomatology such as fever, hypoxaemia and cough) rather than direct antiviral therapy. Supportive therapy for these patients may consist of antipyretics (for example, acetaminophen), analgesics for pain (for example, NSAIDs) and oxygen supplementation, ranging from nasal canula to mechanical ventilation, depending on the clinical severity. For patients with hypoxaemia due to COVID-19, the target SpO_2 range is 92–96%[167,168].

Remdesivir. Remdesivir is an intravenous nucleoside drug that inhibits viral replication. It was developed for hepatitis C infection and repurposed for SARS-CoV-2 infection. In the ACTT-1 trial in hospitalized patients with COVID-19, those treated with remdesivir had a shorter time to recovery (median 10 days) than those in the placebo group (median 15 days; rate ratio for recovery (incidence recovery rate of placebo group divided by that of remdesivir group) 1.29, 95% CI 1.12–1.49; $P < 0.001$)[169]. This effect was largely confined to those less severely ill patients who required no or simple facemask oxygen compared with those who required high-flow oxygen or higher levels of ventilatory support. There was no statistically significant difference in mortality over 29 days between the remdesivir and placebo groups.

In the subsequent Solidarity trial, which was organized by WHO and enrolled over 14,000 hospitalized adults ≥18 years of age with COVID-19 in 35 countries, there was no statistically significant difference in mortality in the overall population (rate ratio 0.91, 95% CI 0.82–1.02)[170]. In those patients not ventilated at inclusion, 12% of patients in the remdesivir group died compared with 14% in the control group (RR 0.86, 95% CI 0.76–0.98) but no benefit was seen in sicker patients already mechanically ventilated. Remdesivir is, therefore, not recommended for patients who receive mechanical ventilation according to the results of this trial; of note, however, the study was underpowered to fully assess this population. A systematic review and meta-analysis of nine randomized controlled trials that evaluated remdesivir in adult hospitalized populations remained underpowered to assess the effects of remdesivir on outcomes for patients who were ventilated[171]. However, in larger, real-world cohort studies, survival benefits have been demonstrated for patients on mechanical ventilation who received remdesivir[172]. In addition, secondary analyses of the ACTT-1 trial demonstrated that higher baseline plasma SARS-CoV-2 viral loads were associated with more severe clinical outcomes, and decreasing viral SARS-CoV-2 in the blood with remdesivir improved outcomes[173,174].

Remdesivir has also been evaluated in non-hospitalized patients at risk of disease progression, with treatment leading to a reduction in hospitalization or death compared with placebo (0.7% versus 5.3%; HR 0.13, 95% CI 0.03–0.59; $P = 0.008$)[175]. However, the requirement for intravenous administration makes remdesivir a less practical option for community use than oral antivirals.

Glucocorticoids. Low-dose dexamethasone (a glucocorticoid) in the RECOVERY trial of hospitalized patients led to a reduction in mortality compared with that in a control group (22.9% versus 25.7%; adjusted RR 0.83, 95% CI 0.75–0.93; $P < 0.001$), although no effect and possible harm were seen in those patients who did not require oxygen supplementation[176]. A subsequent meta-analysis of glucocorticoids for patients not receiving oxygen confirmed a higher mortality in patients who did not require oxygen and received glucocorticoids compared with placebo[177]. However, the general drug class effect of other glucocorticoids, including hydrocortisone[178] and methylprednisolone, has been shown to reduce mortality in patients who are critically ill and was confirmed in a meta-analysis of seven trials (odds ratio 0.66, 95% CI 0.53–0.82)[179]. Corticosteroids are, therefore, recommended for all hospitalized patients with COVID-19 requiring oxygen therapy.

Immunomodulatory agents. Among immunomodulatory therapies, treatment with tocilizumab, an IL-6 receptor antagonist, in the REMAP-CAP trial led to reduced mortality and duration of organ support in patients who were critically ill (hospital mortality 28% in the tocilizumab group compared with 36% in the control group; >99.6% probability of superiority)[180]. The RECOVERY trial subsequently confirmed the beneficial effect of tocilizumab in a wider hospitalized population with inflammation (C-reactive protein ≥75 mg/l and requiring oxygen therapy), with mortality of 31% versus 35% in the tocilizumab and control groups, respectively ($P = 0.0028$). A meta-analysis of 27 trials including >10,000 patients was consistent with the beneficial effect of anti-IL-6 therapy but benefit was seen only in patients treated concomitantly with corticosteroids and tocilizumab (OR 0.77, 95% CI 0.68–0.87), potentially explaining the lack of benefit seen in trials completed early in the pandemic. Further meta-analysis suggested that tocilizumab and sarilumab, another IL-6 receptor antagonist, both had similar beneficial effects[181]. However, given that benefits were only detected in open-label trials and not in placebo-controlled trials, the use and benefits of tocilizumab remain an open question. Of note, the combination of tocilizumab and remdesivir for hospitalized patients requiring supplemental oxygen did not shorten hospitalization duration compared with those who received remdesivir only in a randomized controlled trial[182].

Baricitinib, a Janus kinase (JAK) inhibitor, was shown in multiple trials to improve some clinical outcomes[183–185]. In the COV-BARRIER trial of patients hospitalized with COVID-19 but not requiring mechanical ventilation, treatment with baricitinib did not alter the primary outcome (prevention of disease progression) but did lead to a reduction in 28-day mortality compared with a control group (8% versus 13%)[183]. In an exploratory trial following the study design of COV-BARRIER, the efficacy of baricitinib plus standard of care was evaluated in critically ill patients requiring mechanical ventilation or extracorporeal membrane oxygenation. Treatment with baricitinib significantly reduced the 28-day all-cause mortality (HR 0.54, 95% CI 0.31–0.96; $P = 0.030$; 46% relative reduction; absolute risk reduction 19%) but the overall sample size was relatively small[184]. The RECOVERY trial subsequently reported a mortality of 12% in the baricitinib group compared with 14% in the control group (adjusted RR 0.87, 95% CI 0.77–0.99; $P = 0.028$)[186]. In this trial, 23% of patients were treated concomitantly with tocilizumab and the beneficial effects of baricitinib were still seen (RR 0.79, 95% CI 0.63–1.00). A meta-analysis of individual participant data from randomized controlled trials demonstrated that JAK inhibitors reduced mortality across all levels of respiratory support needs in hospitalized patients[187].

Monoclonal antibodies. Although combination of the monoclonal antibodies casirivimab and imdevimab was shown to reduce mortality in seronegative patients hospitalized with COVID-19 (ref. 188), these specific monoclonal antibodies are not effective against new strains of SARS-CoV-2 and are therefore no longer recommended for treatment.

Antithrombotic agents. Thromboembolic disease is a key feature of severe COVID-19, and various anti-coagulation therapeutic strategies have been evaluated. A therapeutic dose of heparin when given to non-critically ill hospitalized patients in a large multi-platform trial led to reduced mortality and duration of organ support (adjusted hospital mortality reduction of 4%, 95% CI 0.5–7.2%)[189]. This beneficial effect was seen irrespective of D-dimer level, a test for blood clotting. A similar reduction in mortality was seen in the FREEDOM COVID trial of non-critically ill patients treated with therapeutic dose heparin (HR 0.70, 95% CI 0.52–0.93; $P = 0.01$)[190]. However, when therapeutic dose heparin was given to critically ill patients either initially[189,191] or continued from when they were non-critically ill[192], it was ineffective and may have led to harm (in terms of major bleeding events). Subsequent exploratory analyses demonstrated heterogeneity of treatment effects, in that heparin was more likely to be beneficial in those who were less severely ill or had lower BMI and more likely to be harmful in sicker patients and those with higher BMI[193].

Antiplatelet strategies, whether aspirin[194,195] or P2Y12 inhibitors (such as clopidogrel[195] or ticagrelor[196]), were not effective at improving short-term outcomes. However, during long-term follow-up of patients in the REMAP-CAP trial, treatment with an antiplatelet agent had a high probability (95.0%) of reduced 180-day mortality compared with patients randomized to the control group, and a similarly high probability (97.4%) of improving quality of life at 6 months[197].

Statins. Simvastatin has been shown to have anti-inflammatory and immunomodulatory effects and has been proposed as a possible treatment for hyperinflammatory acute respiratory distress syndrome[198]. A meta-analysis of non-randomized trials suggested a possible benefit of statins for COVID-19 (ref. 199), and in the REMAP-CAP trial simvastatin treatment had a high probability (96%) of reducing mortality and organ support compared with control, but this did not reach the pre-defined threshold of efficacy (99%)[200].

Treatment in specific groups

Immunocompromised patients. Patients who are immunocompromised, whether due to an underlying condition or immunosuppressive treatment, are at a particularly high risk of severe COVID-19 even after the introduction of vaccines and often have extended periods of viral replication and shedding due to inability to clear the virus[201]. Treatment with antiviral therapies as early as possible is important in these patients. In general, treatment should follow the same guidelines as for the general population. Decisions about modifying existing immunosuppressive therapies should be made by appropriate specialists (for example, transplant physicians and oncologists) depending on the patient's individual immunocompromising characteristics and risk factors for development of severe COVID-19.

Many immunocompromised patients may have delayed virus clearance and, therefore, prolonged treatment and/or dual therapy with antivirals should be considered[202,203]. Convalescent plasma has been shown to be ineffective in treating a broad population of hospitalized patients with COVID-19 (refs. 204–206), but there was potential benefit from convalescent plasma in the REMAP-CAP trial

in the subgroup of immunocompromised patients in intensive care (n = 126 patients; posterior probability of superiority 89.8%)[206]. The CONFIDENT trial of high-titre convalescent plasma in mechanically ventilated critically ill patients led to a reduction in mortality from 45.0% in the control group to 35.4% in the treated group (P = 0.03), with a difference in restricted mean survival time (convalescent plasma minus standard care) at day 28 of 0.33 days (95% CI −1.27 to 1.92 days)[207]. A meta-analysis of randomized trials and observational studies suggested that convalescent plasma may be associated with mortality benefit in the subgroup of immunocompromised patients, although the data should be interpreted cautiously given the inclusion of case reports and observational studies in the report[208]. Monoclonal antibodies that block SARS-CoV-2 have also been evaluated as treatment for immunocompromised individuals, although with varying efficacy and overall high morbidity and mortality despite monoclonal antibody therapy[209]. Combination antiviral therapy has been proposed for this population; however, further research is warranted to determine the optimal duration of treatment and appropriate combination of antivirals and/or monoclonal antibodies.

Pregnancy. Pregnant and postpartum women with COVID-19 are more likely to be admitted to the intensive care unit or to need mechanical ventilation than non-pregnant women of the same age[210]. In general, treatment strategies should be similar to those in the general population, although any effect of treatment on the fetus must be considered. Treatment decisions should be made using a shared decision-making process and considering individual risk–benefit balances.

Molnupiravir should not be used in pregnant women due to possible teratogenic effects. There is a lack of data that can guide the decision of whether to use nirmatrelvir-ritonavir or remdesivir, although no safety concerns have been identified[211]. Antibody therapies against SARS-CoV-2 are generally considered safe in pregnancy. It is recommended to use low-dose prednisolone or hydrocortisone rather than dexamethasone, which crosses the placenta. Although information is limited, treatment with tocilizumab and sarilumab should be strongly considered in severe COVID-19 in pregnancy[212–214].

Quality of life

The impact of COVID-19 is often measured in numbers of cases and deaths, but the social burden of the disease and its effects on quality of life have also been immense. Survey tools to evaluate quality of life have been adapted and used during the course of the pandemic to determine the effects of COVID-19 illness (acute infection and sequelae), fear of infection, responsiveness of the government, and the social and psychological effects of quarantine, shut-downs and masking[215–217]. The evaluation of health-related quality of life (HRQoL) includes multiple dimensions, including mental, social, physical and emotional functions, at either the individual or population level[218].

The most widely used generic survey tools used to evaluate COVID-19-related HRQoL include the EQ-5D-5L (EuroQol, 5 Dimensions, 5 Levels), SF-36 (36-item Short-Form Health Survey) and SF-6D (Short-Form 6 Dimensions)[219,220], with translations available in many languages[221]. Disease-specific instruments relating to pulmonary disease include the Clinical COPD Questionnaire and the St. George Respiratory Questionnaire, both of which have been applied to study the effects of COVID-19 (refs. 222–224).

Surveys evaluating various domains of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression in both high-income and low-income countries show that around one-third of people with confirmed or suspected COVID-19 reported perceived worsening of their health during the first year of the pandemic, with anxiety or depression being the domain most affected, especially among younger age groups (18–24 years old) and women[222,225–229]. In addition, worsening health has been associated with an increased number of long-term health conditions. Lower-income countries reported a greater degree of worsening health, although the negative effects on mental health were described in all countries across the economic spectrum[230]. Future studies are warranted to determine the long-term effects of COVID-19 on HRQoL.

The average lifespan of individuals across populations has also been greatly affected by COVID-19, probably owing to both direct mortality outcomes from COVID-19 and indirect effects on health and economics. Many studies have estimated the effect of COVID-19 on life expectancy from reports in 2020 compared with pre-pandemic data and have described decreased life expectancies due to COVID-19 (refs. 231–233). Decreased life expectancy related to the COVID-19 pandemic has disproportionally affected men and certain ethnic groups; notably, decreased life expectancy was found among Latino and Black populations compared with white populations in the USA[234,235]. As overall life expectancy was projected to increase in 2020 if the pandemic had not occurred, the effect of COVID-19 on life expectancy is probably even greater, as previous studies only compared 2020 to pre-pandemic years[236,237]. Accounting for this factor and using the Lee–Carter model to estimate the loss of life expectancy due to COVID-19 across 27 countries, one study estimated that an average of 1.33 years (95% CI 1.29–1.37 years) were lost for individuals at age 15 years, and an average of 0.91 years (95% CI 0.88–0.94 years) for individuals at age 65 years[236]. There was variability between different countries using this model. For context, the excess number of years of life lost due to COVID-19 in 2020 was more than five times greater than the overall years lost owing to the seasonal influenza pandemic in 2015, when evaluated across 37 countries[238].

Outlook

Despite the major and rapid scientific advances that occurred immediately after the discovery of SARS-CoV-2, gaps remain in SARS-CoV-2 basic, translational and clinical research that affect management and public health considerations moving forward. Future research should focus on specific areas to advance our understanding, which may also have implications for other respiratory viruses and emerging pathogens.

Detection

The exact origin of SARS-CoV-2, as well as intermediate hosts and potential for new animal host species, has not been completely elucidated. The origin of SARS-CoV-2 has been a focus of intense scientific effort and debate, with zoonotic emergence[239] versus 'laboratory-escape' as leading hypotheses. There is greater evidence for a zoonotic emergence given the close genetic sequencing to animal reservoirs[57,58]. For example, the genetic sequence of SARS-CoV-2 closely resembles coronaviruses that circulate in horseshoe bats[239]. Although resolving the exact origin is unlikely to occur, we need to enhance biosecurity in both settings. Biosecurity in laboratory research with potential pathogens of outbreak potential must be re-enforced globally. Even more important is the need to detect and limit 'zoonotic spill-over' events that continue to happen for various pathogens such as influenza, SARS-CoV, Ebola, Marburg and mpox[240,241]. Understanding and defining the reservoir and transmission dynamics of potential pandemic pathogens using molecular tools, environmental sampling and animal-based

surveillance methods will be important to identifying potential outbreaks early and then containing them quickly[242]. Animal trafficking, such as for sale, enables spread of potential pathogens beyond their natural reservoirs, and intermediate animal hosts in markets (such as pangolins, minks, civet cats and raccoon dogs) may lead to spill-over events to humans[59,243]. Regardless of the origin of a pathogen, once efficient pathogen adaptation to humans occurs, humans may become the dominant host who amplifies and transmits the pathogen, as is currently the case for SARS-CoV-2 and influenza annually. Nevertheless, a further understanding of potential animal reservoirs and intermediate hosts is essential to enact measures to prevent future zoonotic crossover events and have appropriate surveillance mechanisms in place to identify virus diversity in different animal hosts and potential emerging threats (formulated in the WHO One Health strategy)[244].

Transmission dynamics

An important property of SARS-CoV-1 transmission dynamics is human-to-human contagion occurring days after symptom onset and nearly all infected becoming symptomatic[245,246]. This enables a targeted public health response in which symptoms are an important guide to enable a proportionate health care-based and public health response. However, SARS-CoV-2 can be asymptomatic or have substantial viral shedding before symptom onset. This subtle change in biology dramatically affects transmission dynamics and how to design a rational, sustainable and broadly acceptable response to limit transmission.

Masking, early testing and non-pharmaceutical interventions had a mitigating effect on the spread of SARS-CoV-2, especially early in the pandemic. This is best shown by the pandemic policy response in some countries, such as New Zealand, and by models in which aggressive control policies on a population level resulted in a reduced increase of infected individuals in a given population[247–250]. Although it is clear that respiratory droplets are the primary mode of transmission, aerosolized spread, fomite contamination and faecal–oral transmission events have also been reported[251]. Our understanding of the underlying mechanisms of SARS-CoV-2 transmission remains crude, as do the peak timing of infectiousness, distance from infected source, and environmental factors that affect transmission and specific host immune-mediated factors that lead to an increased likelihood of transmission. Further research is warranted to investigate these questions, especially now that populations have experienced widespread antigen exposure due to vaccination and infection, which may change early studies of transmission dynamics. Insights are important to update current hospital control measures for SARS-CoV-2 and to be prepared for future variants or other respiratory viruses that may warrant broad-based public health measures.

Immunological correlate or surrogate of protection

Neutralizing antibodies have been shown to correlate with protection against severe disease both by vaccination and passive antibody treatment[252]. However, a specific antibody level for neutralization has not been described, and different variants may require varying neutralizing antibody levels depending on the activity of the specific antibody against the infecting strain, antibody concentration at the site of exposure and viral inoculum[252]. A clear correlate or surrogate of protection is imperative as this can lead to more rapid and easier monitoring of vaccine and monoclonal antibody effectiveness and enable 'bridging' to populations, such as immunocompromised individuals, that may not be able to undergo large-scale clinical trials by using a clear cut-off of a correlate of protection[253]. Furthermore, other components of the immune system, such as T cells, Fc effector antibodies and mucosal immunity, likely have a role in creating durable protection[254]. The degree to which these analytes could be used as a correlate of protection (independently or in combination) against different end points of interest warrants further evaluation.

Long COVID

Another area that warrants further research is the prolonged health complications associated with COVID-19 after the initial acute phase, referred to as long COVID[255]. A myriad of symptoms that affect multiple organ systems have been linked to long COVID. However, there is still a large knowledge gap pertaining to the exact definition of long COVID, its pathophysiology and the host characteristics that may predispose an individual to developing the condition. Ultimately, a better understanding of the pathogenesis, which is likely multifactorial and varied, of long COVID is essential to develop appropriate therapeutics and identify individuals at risk.

New preventive strategies and therapeutics

Investment into monoclonal antibody and vaccine development technologies can enable more rapid development and manufacturing scale-up against novel SARS-CoV-2 variants of concern and novel pathogens. Although the currently approved COVID-19 vaccines had remarkable efficacy in the phase III licensure trials[128,130,131], there is a need to develop improved vaccines that have enhanced breadth across emerging variants, are durable, and reduce or block transmission. Several candidate vaccines are in preclinical studies or early phase I trials that seek to better target mucosal, cellular and humoral immune responses to achieve one or more of these goals. Research on next-generation COVID-19 vaccines also explores innovative delivery methods, such as intranasal sprays, aerosolization and microneedle patches, to enhance accessibility and immunogenicity. These advanced methods aim to improve ease of administration, promote mucosal immunity, and offer broad and durable protection against the virus, potentially reducing transmission and improving overall vaccine uptake[256]. However, in parallel, we must intensify our efforts for the implementation of vaccines to increase uptake, especially as new technologies and improved vaccines become available. The production of novel, more durable SARS-CoV-2 vaccines will only be effective if the population is willing to receive them; vaccine hesitancy must be understood and addressed with equal resources and efforts[257,258].

New therapeutics for prophylaxis and treatment for SARS-CoV-2 are needed, especially for populations that cannot mount appropriate protective immune responses to vaccines, for example, immunocompromised individuals and older adults, as well as for patients with severe COVID-19, which was a group for which study populations were largely underpowered in many of the primary randomized controlled trials that evaluated COVID-19 therapeutics. The knowledge from early randomized controlled trials to support current therapeutic strategies may be limited due to changing variants, a population that is no longer immunologically naive to SARS-CoV-2, and dynamic changes in non-pharmaceutical intervention policies such as masking and quarantine. New agents should aim to have limited drug–drug interactions, be well tolerated and be available in oral formulations. In addition, end points of therapeutic clinical trials for SARS-CoV-2 should be reconsidered given that the population has largely been exposed to SARS-CoV-2 through vaccination and infection. Clinical trials early in the pandemic evaluated how treatments affected rates of severe disease (such as hospitalization and intensive care unit admissions) and death.

However, given that COVID-19 tends to be more attenuated in a population that is no longer sero-naive to SARS-CoV-2 (ref. 259), there should be a shift in how treatment efficacy is assessed to focus more on a reduction of symptoms or missed days of school or work. Several small-molecule antivirals that inhibit coronavirus 3C-like protease (simnotrelvir, mindeudesivir, leritrelvir, ensitrelvir and atilotrelvir) have demonstrated efficacy in accelerating symptom resolution or alleviation for patients with mild-to-moderate COVID-19 in randomized controlled trials, and further evaluation to determine the best use of these agents is warranted[260–264].

WHO strategy

Looking to the future, the WHO has outlined a strategic plan to transition the initial critical emergency response to COVID-19 towards a more sustained, long-term effort that focuses on disease prevention, control and management[265]. Continued global surveillance and collaboration are key features to maintaining an active monitoring system for possible surges or new variants. A key measure aligned with this goal is pandemic preparedness, which will require continued resources and support for all countries. As we have learned — but are quick to forget — infectious diseases do not recognize geographic borders and, therefore, a concerted global effort must be maintained to keep SARS-CoV-2 (and other emerging pathogens) under control.

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Introduction (A.C.S.); Epidemiology (A.C.S. and G.E.G.); Mechanisms/pathophysiology (B.C., A.C.S. and L.R.B.); Diagnosis, screening and prevention (K.K.W.T. and N.R.); Management (A.C.G.); Quality of life (A.C.S. and G.E.G.); Outlook (A.C.S., L.R.B. and A.M.H-R.); overview of the Primer (all authors).

Competing interests
A.C.S. is involved in human immunodeficiency virus (HIV), coronavirus (COVID) and other vaccine clinical trials conducted in collaboration with the National Institutes of Health (NIH), HIV Vaccine Trials Network, COVID Vaccine Prevention Network, International AIDS Vaccine Initiative, Crucell/Janssen and Moderna. K.K.W.T. has received free admission to London Calling 2024, a conference organized by Oxford Nanopore Technologies. Emory receives funds for N.R. to conduct research from Sanofi, Lilly, Merck, Quidel, Immorna, Vaccine Company and Pfizer. N.R. served on selected advisory boards for Sanofi, Seqirus, Pfizer and Moderna and is a paid clinical trials safety consultant for ICON, CyanVac, Imunon and EMMES. She also receives payments for co-authoring the COVID-19 vaccines chapter in Up to Date. A.C.G. has consulted for AstraZeneca and for Partner Therapeutics, with fees paid to his institution. L.R.B. reports research support from the NIH (including National Institute of Allergy and Infectious Diseases and the National Center for Advancing Translational Sciences), Wellcome Trust, and the Bill & Melinda Gates Foundation, outside of the submitted work; has served on a Data and Safety Monitoring Board, SMC, and advisory committee for NIH and the Food and Drug Administration; and is involved in HIV, COVID and other vaccine clinical trials conducted in collaboration with the NIH, HIV Vaccine Trials Network, COVID Vaccine Prevention Network, International AIDS Vaccine Initiative, Crucell/Janssen, Moderna, Military HIV Research Program, the Bill & Melinda Gates Foundation, and the Ragon Institute. G.E.G., B.C. and A.M.H.-R. declare no competing interests.

Additional information

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