Perspective

Therapeutics for COVID-19

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Vaccines and monoclonal antibody treatments to prevent severe coronavirus disease 2019 (COVID-19) illness were available within a year of the pandemic being declared but there remained an urgent need for therapeutics to treat patients who were not vaccinated, were immunocompromised or whose vaccine immunity had waned. Initial results for investigational therapies were mixed. AT-527, a repurposed nucleoside inhibitor for hepatitis C virus, enabled viral load reduction in a hospitalized cohort but did not reduce viral load in outpatients. The nucleoside inhibitor molnupiravir prevented death but failed to prevent hospitalization. Nirmatrelvir, an inhibitor of the main protease (Mpro), co-dosed with the pharmacokinetic booster ritonavir, reduced hospitalization and death. Nirmatrelvir–ritonavir and molnupiravir received an Emergency Use Authorization in the United States at the end of 2021. Immunomodulatory drugs such as baricitinib, tocilizumab and corticosteroid, which target host-driven COVID-19 symptoms, are also in use. We highlight the development of COVID-19 therapies and the challenges that remain for anticoronavirals.

More than three years into the coronavirus disease 2019 (COVID-19) pandemic, >757 million confirmed cases, including >6.8 million deaths, have been reported worldwide as of 21 February 2023 (ref. 1). COVID-19 is the third coronavirus disease in the past 20 years[2]. Although severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) were severe in terms of mortality rates, they failed to spread around the world[3].

COVID-19 disease is highly variable. An exploratory analysis of 72,314 cases in China in February 2020 reported that most (81%) infected individuals develop mild-to-moderate disease, 14% develop severe respiratory disease and 5% progress to critical illness including respiratory failure[4,5]. Mild disease includes fever, respiratory symptoms (cough and sore throat), a loss of taste and/or smell, headache, myalgias and gastrointestinal symptoms (nausea, vomiting and/or diarrhoea). Individuals with moderate disease have lower respiratory tract illness with symptoms that can include shortness of breath with exertion and signs of moderate pneumonia, for example, a respiratory rate of 20–29 breaths per minute, yet able to maintain 94% oxygen saturation on room air at sea level. Severe COVID-19 can manifest with shortness of breath at rest, respiratory distress, including progression of clinical signs to a respiratory rate of ≥30 breaths per minute, an oxygen saturation of

≤ 93% on room air at sea level or a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of <300 mm Hg. Critical disease is defined by evidence of respiratory failure, shock or multi-organ failure. Those with severe and critical disease are at increased risk of death or developing complications including arrhythmias, acute kidney injury, thrombo-embolic events and septic shock[6,7]. Even in those that recover from COVID-19 infection, irrespective of the acuity of disease, some people have persistent symptoms, known as long COVID[8,9].

The US Centers for Disease Control and Prevention (CDC) COVID-19 case surveillance report analysed 1.3 million COVID-19 cases in the United States between January and May 2020, and found that the hospitalization rate was 14%, 2% required intensive care and, overall, 5.4% died[10]. Populations at increased risk of severe disease and hospitalization include those older than 60 yr or with specific co-morbidities including hypertension, diabetes, cardiovascular disease, chronic lung disease and obesity[10–12]. Risk factors for death due to COVID-19 include male sex, Black race, older age and underlying medical conditions, including chronic kidney disease and cardiovascular disease[13]. Institutionalized individuals, including older individuals living in residential facilities or incarcerated persons, also have an increased mortality risk[14,15]. In a CDC report characterizing COVID-19 among assisted-living

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facilities with available data across the United States, COVID-19 infections were fatal in 21.4% of 24,435 residents, compared with a 2.5% overall fatality in the general population (4.7 million) of those states[16].

A global vaccination campaign sought to prevent disease, disrupt transmission of the virus and reduce the need for therapeutics. Several vaccines have been approved by the World Health Organization (WHO) for the prevention of COVID-19 (ref. 17). However, there are many obstacles to global vaccination: time, resources to manufacture vaccines, costs and availability of personnel to immunize people, varying levels of vaccine efficacy and durability, limited response to vaccination in immunocompromised patients, vaccine hesitancy, emergence of more transmissible variants and finally, future pandemic coronaviruses that we have not seen yet. Therefore, drugs to treat SARS coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, are still needed.

Monoclonal antibody therapies for COVID-19 were available 10 months after the pandemic was declared[18–20] but variants have rendered many of these ineffective[21,22]. Oral therapies that can be administered outside of hospitals are a vital tool in fighting the pandemic. So far, two oral therapeutics have been authorized in The US and Europe: nirmatrelvir administered with ritonavir (Pfizer)[23] and molnupiravir (Merck)[24].

Here we review the approaches taken by pharmaceutical companies, government agencies and academia working together to develop COVID-19 therapeutics.

Identifying therapeutic targets

Antiviral design requires an understanding of the virus and the clinical outcomes of infection. For SARS-CoV-2, infection can be divided into four stages that are characterized by distinct clinical signs and symptoms increasing in severity as the disease progresses that require different interventions (Fig. 1a)[5,25–28]. Stage 0, preceding SARS-CoV-2 infection and/or exposure, is the ideal point for prophylactic administration of vaccines, neutralizing antibodies or antivirals with an acceptable safety profile. Antibody and antiviral therapies, administered intravenously or orally during Stage 1, will also have an impact because this is when viral replication occurs. At the beginning of the pandemic there were uncertainties around the length of this stage. SARS-CoV-2 initially causes an acute viral infection akin to influenza. Antiviral drug treatment for influenza needs to be administered within the first 48 h of symptom onset[29]. Through clinical trials, we know that antibodies for COVID-19 treatment can be administered up to 10 d after symptom onset[30,31] and oral antivirals can be administered within 3–5 d following the onset of symptoms to be effective[32–36]. Studies have shown that SARS-CoV-2 viral replication peaks by approximately 3 d into symptom onset and tends to clear in 5.9–7.6 d, depending on vaccination status, after which the clinical manifestations and disease severity are driven by a dysregulated immune response to SARS-CoV-2, as shown in Stages 2 and 3 (refs. 37–39). As diagnostics have become more available, it is clear that for some patients the virus can linger and that later detection of the virus can be associated with symptom relapse[40].

The SARS-CoV-2 lifecycle and potential targets for antiviral therapies are shown in Fig. 1b. In Stage 2 patients develop a viral pneumonia with cough and fever, and prominent lung inflammation causes hypoxia and shortness of breath, which may or may not require oxygen supplementation. Chest imaging reveals characteristic lung abnormalities such as bilateral infiltrates or ground glass opacities[28]. Stage 3, the most severe disease, is a hyperinflammatory state characterized by acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS)/shock, coagulation disorders and cardiac failure, with a very high mortality rate. Patients in Stages 2 and 3 need agents that target the host inflammatory response in addition to antivirals, and immunomodulatory therapy is often required in Stage 3 (Fig. 1a). The cascade of inflammatory reactions seen in patients with advanced COVID-19, which might be affected by immunomodulatory agents, is shown in Fig. 1c. Patients who progress to Stage 3 also often require mechanical ventilation (Fig. 1a)[28]. Some individuals may experience post-COVID conditions (Stage 4) following acute infection, which can include post-acute hyperinflammatory illnesses such as multi-system inflammatory syndrome in children and adults or late sequelae such as long COVID[41,42].

Treatment early in the pandemic

The standard of care for patients was primarily supportive care at first. Azithromycin and/or hydroxychloroquine were administered as possible treatment for COVID-19 and antibiotics were utilized for possible bacterial co-infections in hospitalized patients, despite unproven efficacy. A literature review that included nine studies published by early 2020 concluded that 72% of hospitalized patients with COVID-19 were empirically treated with antimicrobials but only 8% were diagnosed with a bacterial or fungal co-infection[43]. Azithromycin has in vitro antiviral activity possibly limiting viral replication[44], and hydroxychloroquine has been shown to have antiviral activity against SARS-CoV-2 in vitro and block viral entry[45]; when combined in vitro, they were observed to have a synergistic effect on SARS-CoV-2 infection[46]. However, hydroxychloroquine and azithromycin were not effective in clinical trials and are not recommended for the treatment or prevention of COVID-19 by the National Institutes of Health (NIH) Treatment Guidelines Panel[47]. These combinations were routinely used early in the pandemic. With later data showing that these regimens yield no clinical benefit, it provides a caution as to how limited in vitro data can be misinterpreted. Similarly, no specific recommendations for empiric antimicrobials are supported by the NIH COVID-19 Treatment Guidelines Panel due to insufficient data. Vitamins and mineral supplements—including zinc, which at high concentrations is thought to impair replication in some RNA viruses—were also studied early in the pandemic. In a multicenter retrospective cohort study that evaluated the addition of zinc to hydroxychloroquine in hospitalized patients, no benefit was shown[48], and it is not currently recommended for the treatment of patients with COVID-19.

As the clinical manifestations, pathogenesis and complications of COVID-19 infection were better characterized, clinicians focused on triaging and monitoring patients at high risk for progression of respiratory symptoms. The NIH COVID-19 Treatment Guidelines Panel

Fig. 1 | COVID-19 pathogenesis and therapy targets. a, Disease time course, symptoms and interventions. SIRS, systemic inflammatory response syndrome; TBD, to be determined. **b**, The SARS-CoV-2 lifecycle. SARS-CoV-2 enters host cells via binding of the viral spike protein to the ACE2 receptor and the TMPRSS2-mediated viral membrane fusion with the plasma membrane, followed by pre-activation of the spike protein by proprotein convertase furin and further processing by cathepsin in the endosome as well as TMPRSS2 on the plasma membrane[174–176]. These host binding receptors and processing enzymes provide possible therapeutic targets that are under exploration. Once in the cytoplasm, the viral RNA is released, a portion of the genome is translated and the resulting polyproteins undergo protease cleavage, yielding non-structural proteins that form components of the RNA replication complex, including RNA-dependent RNA polymerase[217,218]. Impairment of the viral proteases has demonstrated the value of these antigens as therapeutic targets. The RNA genome replication provides an avenue of therapeutic intervention via nucleoside analogues. ER, endoplasmic reticulum. **c**, COVID-19-associated immunomodulatory effects. Cell death and viral infection will drive a proinflammatory cytokine release in the host, leading to an inflammatory cycle and possible cytokine storm. Further disease progression results in tissue damage and ultimately the development of ARDS[219,220]. Reducing inflammation and targeting proinflammatory mediators is a promising approach to treat later stages of COVID-19 disease. WBCs, white blood cells. Panels adapted from: **b**, ref. 221 under a Creative Commons license CC BY 4.0; **c**, ref. 222 under a Creative Commons license CC BY 4.0.
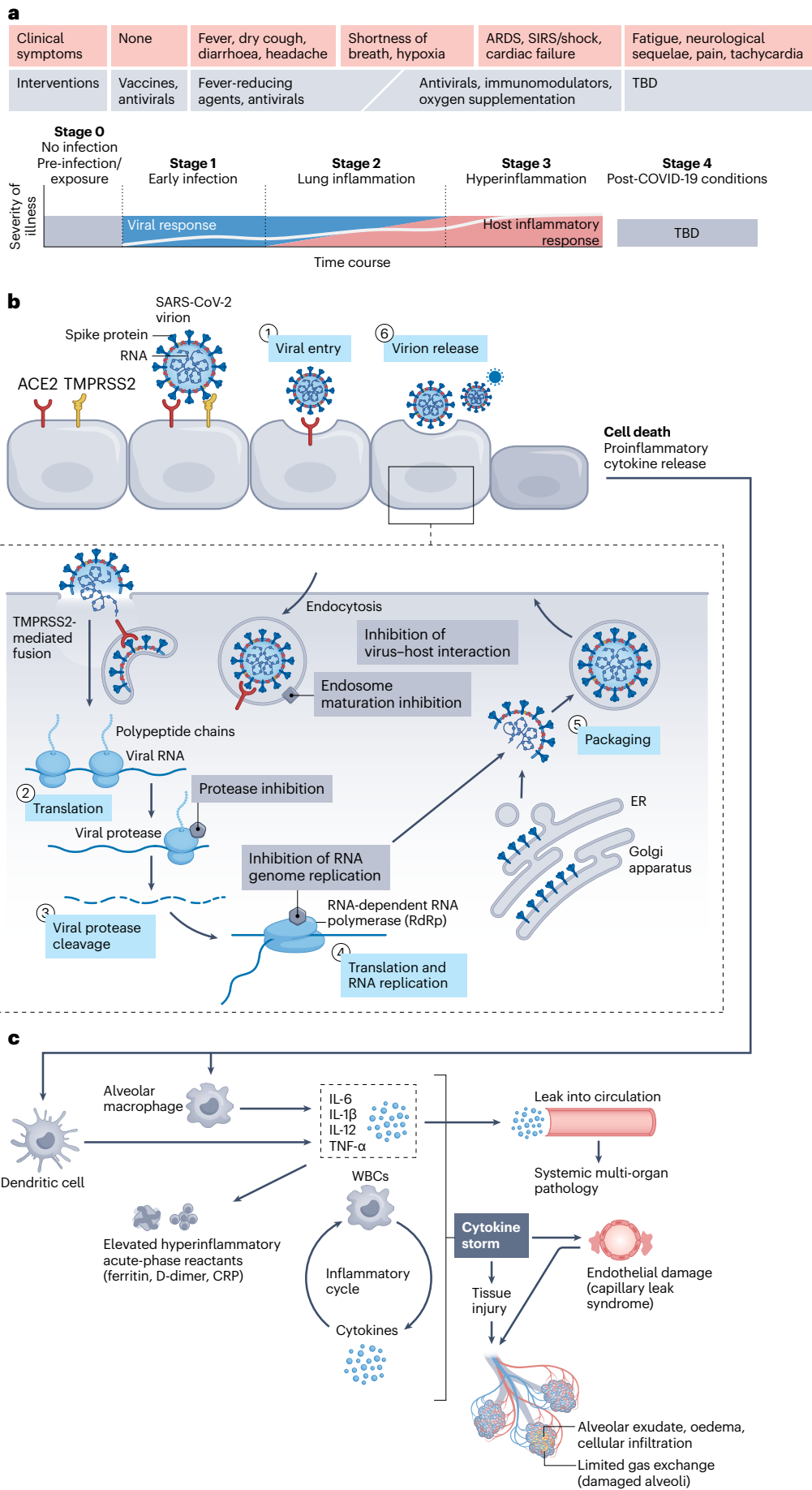
recommends providing timely supplemental oxygenation, as appropriate, and the use of high-flow nasal cannula in patients with acute hypoxemic respiratory failure is preferred over non-invasive positive pressure ventilation due to better outcomes, including a reduced rate of intubation[49]. When the high incidence of venous thrombo-embolic events was recognized, prophylactic anticoagulation was incorporated into the guidelines for patients hospitalized with COVID-19. Clinical recommendations continued to evolve as more data accumulated on what worked, in the absence of effective therapies.

Therapeutics development in a pandemic

Initial therapeutic development activities focused on repurposing licensed drugs (antiviral and immunomodulating) or agents that had existing clinical or non-clinical toxicology data, monoclonal antibodies that targeted the SARS-CoV-2 Wuhan variant spike protein and de novo drug development. Higher priority was given to drug repurposing and monoclonal antibodies due to the time that it takes to identify a new molecule, complete Investigational New Drug-enabling studies and produce the Good Manufacturing Practice clinical material in initial efforts to develop drugs against COVID-19.

Drug repurposing

Protease inhibitors, lopinavir–ritonavir and nelfinavir, and the antimalarial drug chloroquine had in vitro and/or in vivo antiviral activity for SARS or MERS coronaviruses[50–52]. However, in vitro anti-SARS activity of lopinavir and chloroquine/hydroxychloroquine has failed to translate into clinical benefit in COVID-19 clinical trials[53,54]. This might reflect a failure of the initial in vitro testing to distinguish between a true antiviral effect and cellular toxicity or could be due to the limitations of the cell models utilized[55–57]. Notably, these agents also failed to demonstrate a compelling antiviral effect using in vivo animal models, suggesting that in vivo models are a necessary intermediate step in the evaluation of repurposed agents before resource-intensive clinical evaluation[58]. During the early HIV pandemic drug development focused on in vitro activity and demonstrating that the appropriate level of drug could be detected in a patient[59]. Although repurposing screens can be accelerated towards clinical evaluation, screening and evaluation tools must be robust if we are to avoid the unnecessary use of resources in the midst of a pandemic.

Early repurposing efforts also included the assessment of antiviral agents in pre-licensure evaluation for the treatment of other viral infections. Such efforts focused on nucleotide prodrugs. One such prodrug, remdesivir (also known as GS-5734), demonstrated antiviral activity against various RNA viruses—including yellow fever, Dengue type 2, influenza A, parainfluenza 3 and SARS viruses[60,61]—and had been tested for activity against Ebola in a randomized clinal trial, although it did not meet mortality-related efficacy endpoints[62]. Other prodrugs include AT-527, active against hepatitis C virus (HCV)[63]; favipiravir, approved for pandemic influenza in Japan[64]; and molnupiravir (also known as MK-4482, EIDD-2801 and EIDD-1931-isopropyl ester), whose active component, N-hydroxycytidine (also known as EIDD-1931), was initially discovered as a bacterial mutagen[65–67] but subsequently demonstrated activity against influenza virus[68,69], respiratory syncytial virus[70] and various coronaviruses[71].

With pandemic preparedness in mind, several coronavirus academic laboratories had already generated an Investigational New Drug application to investigate the activity of molnupiravir against Venezuelan equine encephalitis virus[72]. Another repurposed drug for COVID-19 is nitazoxanide (Alinia, Romark Laboratories), the US Food and Drug Administration (FDA)-approved broad-spectrum thiazolide agent that has been used to treat various helminthic, protozoal and viral infections (including influenza virus, rotavirus, norovirus, and hepatitis B and C viruses)[73]. In a recent review, nitazoxanide's mechanism of antiviral activity against SARS-CoV-2 was proposed to include inhibition of viral entry and multiplication[74]. Ivermectin is an FDA-approved

antiparasitic drug that was also repurposed after in vitro data indicated that it inhibited SARS-CoV-2 viral replication. It was also postulated to inhibit viral entry by preventing the attachment of the spike protein to the human cell membrane[75,76]. Subsequent clinical studies failed to demonstrate any clinical benefit with ivermectin[77,78].

Remdesivir (Veklury; developed by Gilead Sciences) is administered by intravenous infusion and is the only agent resulting from drug repurposing campaigns in early 2020 to achieve success in the first year of the pandemic, receiving full approval from the FDA in October 2020 for the treatment of COVID-19 in patients requiring hospitalization, just nine months after the first reports of COVID-19 in the United States[79]. Such rapid progression of remdesivir was enabled by pre-clinical characterization of in vitro and in vivo activity of the product against related coronaviruses, pharmacokinetic evaluation in healthy human volunteers and safety data acquired in an unsuccessful clinical trial for Ebola[61], all of which occurred before the onset of the current SARS-CoV-2 pandemic. It should be noted that the WHO SOLIDARITY trial was unable to reproduce the positive findings from the remdesivir ACTT-1 trial[54,80]. In a Phase 3 study (DisCoVeRy, NCT04315948) conducted in hospitalized patients with COVID-19 receiving standard of care with remdesivir compared with standard of care alone, no clinical benefit with remdesivir was observed in patients who were symptomatic for more than 7 d (ref. 81). In addition, a retrospective study on the impact of timing of remdesivir treatment and mortality benefit showed that patients with moderate-to-severe COVID-19 with treatment initiation ≤9 d from the onset of symptoms compared with >9 d from symptom onset had significantly lower odds of death (odds ratio = 0.43; 95% confidence interval, 0.25–0.75; $P = 0.003$)[82]. This may be driven by the pathology of SARS-CoV-2, where the opportunity to mitigate against severe disease with an antiviral may diminish as the disease progresses from one primarily attributable to viral damage to host cells to one attributable to host inflammatory response, similar to what is observed for anti-influenza treatments that need to be administered early in the course of disease to be effective[29]. This is supported by a Phase 3 study (PINETREE, NCT04501952) that was conducted with patients who were either outpatients or residing in skilled nursing facilities. In this study, remdesevir given within 7 d of symptom onset reduced the risk of hospitalization by 87% compared with placebo in patients at high risk of severe disease[83]. Following these findings, remdesivir's approval was expanded to high-risk non-hospitalized patients[84]. Clinical development of inhaled remdesivir[85] in a Phase 1b/2a study (NCT04539262) as well as pre-clinical development of an oral prodrug of remdesivir (GS-621763)[86] are ongoing. In addition, Shanghai Junshi Biosciences has advanced the oral remdesivir derivate VV116, which has completed a non-inferiority observer-blinded randomized Phase 3 trial (NCT05341609) versus Paxlovid (see the section 'Protease inhibitors') in seven hospitals in China for the treatment of mild-to-moderate COVID-19 (ref. 87). VV116 was recently approved for marketing in China[88].

Other repurposed drugs have also been clinically assessed for activity against COVID-19. AT-527 (Atea Pharmaceuticals), an HCV compound, was evaluated in a Phase 2 randomized trial in non-hospitalized adult patients with mild or moderate COVID-19 (NCT04709835). Treatment with AT-527 did not result in a clear reduction in SARS-CoV-2 viral load compared with the placebo (primary endpoint) in the overall population of patients with mild or moderate COVID-19 (ref. 89). Further Phase 2 evaluation of safety and efficacy of AT-527 in hospitalized patients with moderate COVID-19 is ongoing (NCT04396106). Clinical trials were also conducted in several countries to evaluate the safety and efficacy of favipiravir, an orally administered anti-influenza drug[90]. For example, in a randomized, double-blinded, multicenter and placebo-controlled trial conducted in Saudi Arabia in adult patients with mild COVID-19, 1,800 mg favipiravir administered twice on day 1, followed by 800 mg twice daily (n = 112) for a total of 5–7 d did not reduce time to viral clearance within 15 d of starting the treatment, thus

demonstrating lack of efficacy for favipiravir therapy[91]. Nitazoxanide (Alinia, Romark Laboratories) was evaluated in a multicenter randomized clinical trial in patients with mild COVID-19. In comparison to the placebo, the drug did not have an effect on symptom resolution after 5 d of therapy, although it significantly reduced viral load ($P = 0.006$)[92]. At present, the COVID-19 Treatment Guidelines Panel recommends against the use of nitazoxanide for the treatment of COVID-19, except in a clinical trial[93]. In a randomized Phase 3 trial, three repurposed drugs—ivermectin, metformin and fluvoxamine—were evaluated for the early treatment of COVID-19 in adults who were either overweight or obese. None of the three medications had a significant effect on the prevention of a serious outcome defined as hypoxaemia, emergency department visit, hospitalization or death[94].

The pre-pandemic development of molnupiravir (also known as MK-4482; Lagevrio, Merck) as a treatment for coronaviruses was slowed by mutagenic potential[65,67,95]. This oral compound entered clinical studies in healthy individuals in April 2020 (NCT04392219)[96] and progressed to patients in June 2020 (NCT04405570)[97]. Pivotal efficacy studies were initiated in October 2020 in hospitalized (NCT04575584) and non-hospitalized (NCT04575597) adults with COVID-19. Following an interim analysis, it was concluded that molnupiravir was unlikely to provide clinical benefit in hospitalized patients and the inpatient MOVe-IN study was discontinued[98,99]. At the time of hospitalization patients are usually in the later stages of disease (Stages 2 and 3) and further out from disease onset, thus limiting the impact of antivirals on disease course. In contrast, the outpatient MOVe-OUT study demonstrated that earlier treatment (≤5 d) decreased the risk of hospitalization or death in at-risk patients when compared with placebo[97]. Molnupiravir achieved an Emergency Use Authorization (EUA) in the United States on 23 December 2021 for the treatment of mild-to-moderate COVID-19 in adults at high risk for progression to severe COVID-19, including hospitalization or death[24]. However, a recently published study conducted in the UK found that molnupiravir did not reduce the frequency of COVID-19–associated hospitalizations or death of high-risk vaccinated adults (≥50 yr or 18–49 yr with a high-risk condition)[100]. In addition, in all immunocompromised patients treated with molnupiravir who did not clear SARS-CoV-2 infection after treatment, SARS-CoV-2 rapidly accrued new mutations in the spike protein, including nonsynonymous mutations that altered the amino-acid sequence, which were persistent or even fixed in the virus population[101]. The authors suggest that treatment with molnupiravir may 'supercharge' viral evolution in immunocompromised patients.

Beyond these targeted repurposing efforts, several additional initiatives to identify candidate agents that may be repurposed for use in treating COVID-19 have been undertaken. On 10 March 2020 the Bill and Melinda Gates Foundation announced the launch of the Therapeutics Accelerator, supported by US$125 million from the Wellcome Trust, Mastercard and the Bill and Melinda Gates Foundation, with an additional US$250 million subsequently committed by a variety of individuals and institutions[102]. The Accelerator adopted a three-pronged approach to identifying candidate compounds for COVID-19: (1) testing approved drugs, (2) screening libraries of agents with confirmed safety data and (3) evaluating novel agents (including antibodies) for anti-SARS-CoV-2 activity. As part of this effort, various collaborations were established between Calibr, the drug development division of Scripps Research, and a number of outside research teams to screen the ReFRAME drug repurposing collection (comprised of >14,000 compounds that have been approved by the FDA for other diseases or have been extensively tested for human safety) for agents active against SARS-CoV-2 (ref. 103). Initial publications of the ReFRAME library screening report the identification of numerous agents for which the effective concentrations against SARS-CoV-2 can probably be attained in patients, of which apilimod and camostat mesilate seem to have undergone the most extensive follow-on testing. Apilimod, a PIKfyve kinase inhibitor that was originally developed for the treatment

of autoimmune conditions[104], is thought to prevent intracellular trafficking of the virus following entry into host cells and its evaluation has subsequently begun in a clinical trial in non-hospitalized adults with confirmed COVID-19 infection (NCT04446377). Verge Genomics has also repositioned their selective oral PIKfyve inhibitor, originally developed for amyotrophic lateral sclerosis, for COVID-19 clinical studies[105]. Camostat mesilate, an inhibitor of the human serine protease transmembrane protease serine 2 (TMPRSS2) thought to be required for entry of the virus into host cells, is approved in Japan for the treatment of chronic pancreatitis and postoperative reflux esophagitis[106]. Camostat mesylate was investigated in multiple clinical trials in both hospitalized and non-hospitalized adults with confirmed COVID-19 infection[107–111].

In addition to the ReFRAME library screening, numerous other efforts to identify potential candidates for repurposing have been undertaken, including in silico docking, biochemical screens, cell-based screens and in vivo testing[58]. Given the number of potential candidates identified, additional testing in in vitro and/or in vivo models with high confidence in translatability to clinical efficacy will be an important step in prioritizing agents for further clinical evaluation.

Immunotherapeutics

In emergency phases of disease outbreaks, passive transfusion of convalescent blood products has often been used and a number of case reports in early 2020 reported evidence of benefit among patients with COVID-19 who received convalescent plasma[112]. However, challenges exist with this therapy—these include collection, pathogen inactivation, standardization of dosing and the assumption that the donor has had a robust neutralizing antibody response to the virus. Despite these limitations, plasma infusion can be administered to patients who are immunocompromised and patients who are hospitalized before symptom onset.

Rapid identification and characterization of potent neutralizing monoclonal antibodies targeting the SARS-CoV-2 spike protein is possible using high-throughput amplification, cloning, expression and functional screening of heavy- and light-chain pairs of SARS-CoV-2-specific immunoglobulins from sorted memory B cells isolated from peripheral blood mononuclear cells of donors that have strong SARS-CoV-2-neutralization activity in convalescent plasma[113,114]. Mono- or polyclonal antibody cocktails can be accelerated into clinical testing, as observed to date with two monoclonal antibody cocktails and two single monoclonal antibodies that received an EUA by the FDA for the treatment of COVID-19 outpatients who are at high risk for progressing to severe COVID-19 (Regeneron Pharmaceuticals, casirivimab with imdevimab (REGEN-COV)[31,115]; Eli Lilly, bamlanivimab with etesevimab[30,116]; GSK, sotrovimab (Xevudy)[117] and Eli Lilly, bebtelovimab[118]). Another monoclonal antibody cocktail, tixagevimab with cilgavimab (Evusheld, AstraZeneca), received an EUA for pre-exposure prophylaxis for people who are at high risk of severe COVID-19 outcomes[21,119]. As SARS-CoV-2 continued to evolve, changes in the spike protein led to EUAs being withdrawn for all of the monoclonal antibodies—including casirivimab with imdevimab, bamlanivimab with etesevimab, sotrovimab and bebtelovimab—due to loss of efficacy[21,22].

Anti-inflammatory and immunomodulatory therapies

Targeting host responses using anti-inflammatory and immunomodulating drugs may be useful in later stages of COVID-19. For example, treatment with corticosteroids (dexamethasone) reduced mortality within a 28-d period in patients hospitalized with COVID-19 who received oxygen supplementation or required invasive mechanical ventilation compared with those who received standard of care (29.3% versus 41.4%; rate ratio, 0.64; 95% confidence interval, 0.51–0.81)[120]. The treatment, however, could potentially be deleterious for patients with active viraemia[120]. An orally administered immunomodulating inhibitor of Janus kinase (JAK), baricitinib (Olumiant, Eli Lilly), in combination
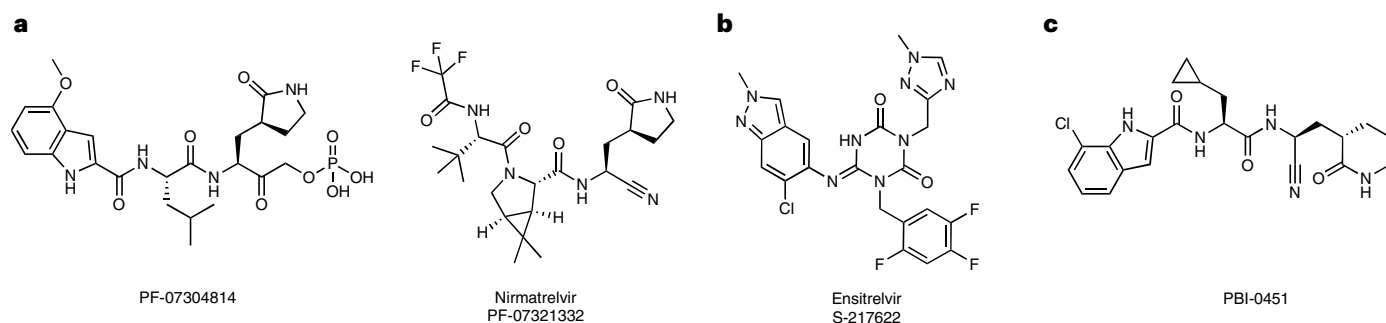
Fig. 2 | Structures of clinical SARS-CoV-2 Mpro inhibitors. a, Optimization starting from intravenous SARS-CoV-2 parent PF-00835231, focused on structure activity relations for potency, permeability and clearance for improved bioavailability. **b**, S-217622. **c**, PBI-0451.

with remdesivir improved outcomes for hospitalized patients with late-stage disease, reducing the time to recovery to within 29 d after initiating treatment compared with placebo with remdesivir, resulting in an EUA[121,122]. In combination, corticosteroids and baricitinib are recommended by the WHO for patients with severe or critical COVID-19 (refs. 123,124). In May 2022 baricitinib was approved by the FDA for the treatment of COVID-19 in hospitalized adults requiring various degrees of oxygen support[125,126]. In December 2022, Eli Lilly withdrew its EU marketing authorization application for the use of baricitinib in the treatment of hospitalized COVID-19 patients who require supplemental oxygen[127].

Interleukin (IL) inhibitors have also been investigated, with an IL-1 inhibitor (IL-1R antagonist, anakinra (Kineret, Swedish Orphan Biovitrum)), showing a significant benefit against mortality (hazard ratio, 0.450; 95% confidence interval, 0.204–0.990; $P = 0.047$) in hospitalized patients with COVID-19, respiratory insufficiency and evidence of inflammation, whereas IL-6 inhibitors (monoclonal antibodies to IL-6 and IL-6 receptor) did not have an effect in this assessment (hazard ratio, 0.900; 95% confidence interval, 0.412–1.966; $P = 0.79$)[128]. However, the study design was an observational cohort study that included only a small number of patients where 62 received an IL-1 inhibitor and 55 received an IL-6 inhibitor. In a large randomized, controlled, open-label, platform ReCOVERY clinical trial in hospitalized patients with COVID-19 that had hypoxia and systemic inflammation, a monoclonal antibody to IL-6, tocilizumab (Actemra, Genentech), significantly improved the 28-d survival ($P = 0.0028$) and other clinical outcomes[129]. Tocilizumab received an EUA in June 2021 for the treatment of hospitalized patients receiving corticosteroids and supplemental oxygen[130].

Initial promising results were also seen for the antiviral cytokine candidate peginterferon lambda. Type III interferon lambdas are a recently discovered class of interferons that stimulate antiviral immune responses that are largely exerted at epithelial surfaces such as the respiratory and gastrointestinal tracts[131]. Due to a less ubiquitous receptor expression, type III interferons as therapeutic agents are more tolerable than type I interferons[131]. Peginterferon lambda is an investigational therapeutic agent that was originally developed for the treatment of HCV[132] and is currently being developed by Eiger BioPharmaceuticals for the treatment of COVID-19. In a randomized placebo-controlled Phase 3 study in non-hospitalized adult patients with COVID-19 at high risk of progressing to severe illness, a single subcutaneous dose of peginterferon lambda reduced the risk of hospitalization or emergency room visits by 50% and the risk of death by 60% (ref. 133).

Another agent is sabizabulin (also known as Veru-111), a bis-indole compound undergoing development by Veru Inc. that inhibits tubulin polymerization, blocking intracellular virus trafficking, and exhibits broad anti-inflammatory and antiviral activity in pre-clinical studies[134]. In a randomized Phase 3 study in hospitalized patients with moderate-to-severe COVID-19 at high risk for ARDS, an interim analysis demonstrated a 55% reduction in the COVID-19-related risk of death

following oral treatment with 9 mg sabizabulin compared with placebo[134]. The FDA granted Fast Track designation to the sabizabulin COVID-19 clinical programme in January 2022 (ref. 135).

Antivirals for SARS-CoV-2

With the exception of monoclonal antibodies and the intravenous treatment remdesivir, no new antiviral agents were available 12 months after the pandemic was declared. Several antivirals, including protease inhibitors and spike protein inhibitors, have subsequently advanced to clinical trials.

Protease inhibitors

One notable therapeutic target is the main protease (Mpro, also known as 3C-like protease, 3CL)[136]. Mpro is responsible for hydrolysis of the viral replicase polyproteins pp1a and pp1ab to produce functional proteins during replication. Mpro is an attractive target as the sequence is highly conserved across MERS-CoV, SARS-CoV-1 and SARS-CoV-2, with a cysteine-histidine dyad active site that has no human homologue[136]. The first protease inhibitors were developed to treat chronic infections associated with HIV and HCV, and have proven to be safe and effective antiviral treatments[137,138]. Pfizer had two protease inhibitors, PF-07304814 and nirmatrelvir (also known as PF-07301332; the active Mpro inhibitor of Paxlovid; Fig. 2a), that were clinically evaluated to potentially treat COVID-19. Both PF-07304814 and nirmatrelvir are peptidomimetic covalent inhibitors that mimic the peptide substrate of the cysteine proteases. Peptidomimetics are designed to mitigate the poor absorption and metabolic stability of peptide drugs, which are usually driven by proteolysis that can limit bioavailability. Intravenous dosing can be used to address the challenges and is a common option used with hospital-based antiviral agents. PF-07304814, which is administered through the intravenous route, is a prodrug of a compound identified in 2003 during a SARS-CoV-1 discovery effort[139]. PF-07304814 was found to be a specific inhibitor of Mpro with broad in vitro activity across different SARS-CoV-2 variants and other coronaviruses tested[140]. Unlike Merck's molnupiravir, a toxicology package had not been completed on this compound before the pandemic. Between January 2020 and August 2020, the prodrug was developed, scaled up and evaluated in toxicology studies to permit an open Investigational New Drug in August to initiate testing in hospitalized patients (NCT04535167). PF-07304814 required being administered as a continuous intravenous infusion for 5 d, which made clinical studies challenging. In addition, protease inhibitors were expected to have the greatest benefit during the acute phase of disease, before hospitalization. The development of PF-07304814 was halted in early 2022 (ref. 141).

Nirmatrelvir was a new Mpro inhibitor that was identified by Pfizer as part of a COVID-19 discovery programme initiated early in 2020, with an approach taken to attempt to maximize the oral bioavailability[142]. This novel oral candidate was discovered in July 2020 and underwent pre-clinical toxicology studies and scale-up during

the latter part of 2020 to enable clinical studies to be initiated in March 2021 (NCT04756531). Although nirmatrelvir had increased oral bioavailability, the majority of its metabolites are from cytochrome P450 (CYP)-mediated oxidations[143]. Co-dosing with the CYP-3 inhibitor ritonavir helped maximize the oral exposures of nirmatrelvir to median levels of 5× the 90% effective concentration from in vitro assays, and a Phase 2/3 pivotal study, Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR; NCT04960202) was initiated in July 2021 (ref. 142). In EPIC-HR, risk reductions of 88–89% at preventing hospitalization and 100% at preventing death were demonstrated in unvaccinated patients at high risk of severe disease[32]. This study led to Paxlovid (nirmatrelvir co-dosed with ritonavir) being granted an EUA on 22 December 2021 for the treatment of high-risk outpatients with mild-to-moderate COVID-19 (ref. 23).

Two other Phase 2/3 efficacy trials of nirmatrelvir–ritonavir were also conducted: Evaluation of Protease Inhibition for COVID-19 in Post-Exposure Prophylaxis (EPIC-PEP; NCT05047601) and Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients (EPIC-SR; NCT05011513). EPIC-PEP, initiated in September 2021, assessed whether individuals exposed to patients with COVID-19 could be protected from acquiring symptomatic COVID-19. Although the study did not meet its primary endpoint, compared with placebo, risk reductions of 32% and 37% were observed in adults who received Paxlovid for 5 and 10 d, respectively, to prevent infection[144]. EPIC-SR, initiated in August 2021, assessed the efficacy and safety of nirmatrelvir–ritonavir in non-hospitalized symptomatic adults with COVID-19 at low risk of progressing to severe illness. Although the novel primary endpoint of self-reported sustained alleviation of all symptoms for four consecutive days was not met, analyses showed a non-significant relative risk reduction in hospitalizations and death compared with the placebo group—51% for all patients enrolled through December 2021 and 57% for vaccinated patients with at least one risk factor for severe COVID-19—providing support for the efficacy data observed in the EPIC-HR study. In addition, a nominally significant 62% decrease in COVID-19-related medical visits per day across all patients, relative to the placebo group, was observed. Due to a very low rate of hospitalization or death observed in the standard-risk patient population, enrollment was ceased and the study was terminated[145].

Similar to PF-07304814, nirmatrelvir has the potential for broad coronavirus activity with good margins in pre-clinical safety studies and a clean genotoxicity profile, and displays potent in vitro inhibitory activity against SARS-CoV-2 variants of concern, including Omicron[146–150]. The potential for resistance has also been evaluated; the non-synonymous mutation rate (substitution per residue per year) was estimated to be lower for Mpro (2.43×10^{-4}) compared with the RNA-dependent RNA polymerase (9.18×10^{-4})[151]. Early in vitro analysis using sequential drug passaging has demonstrated that resistance to nirmatrelvir can occur[152–154], however, at this time no clinical SARS-CoV-2 resistance to nirmatrelvir has been reported[155]. The pharmacokinetic profile of nirmatrelvir is improved by the co-dosing of ritonavir; however, ritonavir is a strong CYP-3 inhibitor and may increase the concentrations of certain concomitant medications due to drug–drug interactions. A thorough review of the medication list of the patient is needed before initiating nirmatrelvir–ritonavir, with possible dose adjustment required of the concomitant medication or selection of an alternative COVID-19 therapeutic should there be concern for a drug–drug interaction that might lead to potentially serious and/or life-threatening adverse events[156,157]. Next-generation peptidomimetic protease inhibitors have the potential to be further optimized to improve pharmacokinetics to remove the need to co-dose ritonavir.

In July 2021 Shionogi & Co. announced the initiation of a Phase 1 clinical trial of the oral drug S-217622 (also known as ensitrelvir; Fig. 2b) in Japan[158]. S-217622 is claimed to be a selective inhibitor of Mpro that was demonstrated to reduce viral load in pre-clinical in vivo studies of SARS-CoV-2-infected animals[159]. Subsequently, Shionogi & Co. initiated a Phase 2/3 trial (jRCT2031210350) to evaluate the efficacy and safety of a 5-d treatment with S-217622 compared with placebo in patients with asymptomatic and mild COVID-19 infections[160]. Results were recently released from a Phase 2b study where S-217622-treated patients had shortened duration of shedding of infectious virus and experienced a significant reduction in viral RNA on days 2, 4, 6 and 9 compared with placebo[161]. However, there was no significant difference in the total score of the 12 symptoms between the two groups. In addition, Todos Medical and NLC Pharma initiated Phase 2 trials with Tollovir (NLC-V-01), a Mpro inhibitor, at the Shaare Zedek Medical Center in Jerusalem, Israel[162]. A double-blind, placebo-controlled and randomised Phase 2 trial evaluating the safety and efficacy of Tollovir in hospitalized patients reported positive results[163]. The study included small numbers of participants (11 Tollovir-treated and 9 placebo-treated) yet reported a shorter time to clinical improvement and decreased incidence of death (0% (0/11) versus 22% (2/9))[164]. Pardes Biosciences is developing PBI-0451 (Fig. 2c), an orally administered coronavirus Mpro inhibitor that has demonstrated in vitro activity against multiple coronaviruses, including SARS-CoV-2 and variants of concern such as Delta and some Omicron lineages, as well as other human coronaviruses of pandemic potential (SARS and MERS) and common cold-related coronavirus strains (OC43 and 229E)[165]. PBI-0451 has shown favourable safety and tolerability in a Phase 1 trial (NCT05011812), and the antiviral activity, safety and efficacy of this investigational compound, compared with placebo, are being evaluated in a Phase 2 double-blind randomized study in non-hospitalized symptomatic adults with COVID-19 (NCT05543707)[166]. In March 2022 Enanta Pharmaceuticals received an FDA fast track designation for EDP-235, a novel oral Mpro inhibitor, which has now completed Phase 1 trial (NCT05246878)[167]. Aligos Therapeutics in collaboration with KU Leuven have also announced the selection of the drug candidate ALG-097558 (a potent oral Mpro inhibitor) for the treatment and prevention of COVID-19, planning to file a Phase 1 trial application in the second half of 2022 (ref. 168).

Spike protein inhibitors

Mono- or multi-specific engineered designed ankyrin repeat proteins (DARPins)[169], similar to monoclonal antibodies in their ability to bind antigen, are also in development as a potential antiviral immunotherapy for COVID-19. The DARPin candidate molecule for COVID-19 ensovibep (also known as MP0420, Novartis) comprises three individual domains, each highly neutralizing to SARS-CoV-2, and effectively blocks the receptor-binding domain of the SARS-CoV-2 spike protein due to cooperative binding[170]. This design ensures strong neutralization, even in the presence of mutations of the spike protein, and limits the development of escape mutants. An ability of ensovibep to protect against SARS-CoV-2 variants of concern, including Omicron, in a pre-clinical model has been reported[171]. In a Phase 2 randomized study in non-hospitalized adult patients with COVID-19 (NCT04828161), a 78% reduction in risk of hospitalization and/or emergency room visits related to COVID-19, or death, compared with placebo was observed following a single intravenous dose of ensovibep. A significant reduction in the viral load over 8 d compared with placebo was also observed[172].

Early phase pre-clinical therapeutic development

For the early viral infection stages, cell entry and endosomal trafficking are attractive points of intervention with the primary focus being on human host targets. Given that angiotensin-converting enzyme 2 (ACE2) is the receptor to SARS-CoV-2, it makes it a compelling target for blocking cell entry during infection. Profiling of inhibitors of ACE2 catalytic enzymatic function has demonstrated that the catalytic activity of ACE2 and binding event of SARS-CoV-2 to ACE2 are independent. The vast number of ACE2 catalytic inhibitors have not been shown to block an in vitro infection[173]. Alternatively, the use of recombinant ACE2 as a decoy strategy to block SARS-CoV-2 cell entry is currently in clinical trials by Apeiron Biologics (NCT04335136). Further

Table 1 | FDA-authorized or -approved COVID-19 therapeutics[a]

Therapeutic	Company	Drug class/target	FDA status and authorization/ approval date for COVID-19	Route of administration and duration	Approved patient group	Reference
Dexamethasone	Multiple	Corticosteroids	Repurposed	Oral, 10 d	Treatment in hospitalized patients with severe COVID-19 who require supplemental oxygen, including mechanical ventilation.	120,201–203
Remdesivir	Gilead Sciences	Nucleotide analogue prodrug	Approval, 22 October 2020	IV, 3–5 d	Treatment in hospitalized adults and paediatric patients (≥28 d)[b], and in non-hospitalized adults and paediatric patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.	79,204
Baricitinib	Eli Lilly	JAK inhibitor	EUA, 19 November 2020; approval, 10 May 2022	Oral, 14 d	Treatment in hospitalized adults (≥18 yr) with COVID-19 receiving dexamethasone and requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. EUA for hospitalized paediatric patients (≥2 yr) requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.	121,125
Nirmatrelvir–ritonavir[c]	Pfizer	Mpro inhibitor with ritonavir booster	EUA, 22 December 2021	Oral, 5 d	Treatment in adults and paediatric (≥12 yr) patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.	205
Molnupiravir[c]	Merck	Ribonucleoside prodrug	EUA, 22 December 2021	Oral, 5 d	Treatment in adult individuals (≥18 yr) with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.	206
Tocilizumab	Genentech	Human monoclonal antibody/IL-6 receptor	EUA, 24 June 2021	IV	Treatment in hospitalized adults and paediatric (≥2 yr) patients receiving dexamethasone and requiring supplemental oxygen, mechanical ventilation or ECMO.	130
Casirivimab–imdevimab[d]	Regeneron Pharmaceuticals	Human monoclonal antibodies/SARS-CoV-2 spike protein	EUA, 21 November 2020; amended, 24 January 2022	IV or SC	Treatment in adults and paediatric (≥12 yr) individuals with mild-to-moderate COVID who are at high risk for progression to severe COVID-19, or post-exposure prophylaxis.	20,115,207
Bamlanivimab–etesevimab[d]	Eli Lilly	Human monoclonal antibodies/SARS-CoV-2 spike protein	EUA, 9 February 2021; amended, 24 January 2022	IV	Treatment in adult and paediatric patients (including neonates) with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, or post-exposure prophylaxis.	116,207,208
Sotrovimab[d]	GSK	Human monoclonal antibody/SARS-CoV-2 spike protein	EUA, 26 May 2021; amended, 23 February 2022	IV	Treatment in adult and paediatric (≥12 yr) individuals with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization and death.	209,210
Bebtelovimab[d]	Eli Lilly	Human monoclonal antibody/SARS-CoV-2 spike protein	EUA, 22 February 2022; amended, 30 November 2022	IV	Treatment in adult and paediatric (≥12 yr) patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by the FDA are not accessible or clinically appropriate.	118,211,212
Tixagevimab–cilgavimab[d]	AstraZeneca	Human monoclonal antibodies/SARS-CoV-2 spike protein	EUA, 8 December 2021; amended, 26 January 2023	IV	COVID-19 pre-exposure prophylaxis for adult and paediatric (≥12 yr) patients who either have moderate-to-severely compromised immune system or are not recommended to be COVID-19 vaccinated due to a history of severe adverse reaction to a COVID-19 vaccine or component.	119,213

[a]EUA/authorization status on 3 February 2023 (ref. 214). [b]NIH guidelines do not recommend treatment with remdesivir in paediatric patients <12 yr at present due to insufficient evidence (Table 3a in ref. 215 and ref. 216). [c]Not authorized for pre- or post-exposure prevention of COVID-19 or for initiation of treatment in patients hospitalized due to COVID-19. [d]No longer authorized for the treatment of COVID-19 or for post-exposure prevention of COVID-19. ECMO, extracorporeal membrane oxygenation; IV, intravenous; SC, subcutaneous.

opportunities to target ACE2 internalization or shedding from the cell membrane, in addition to allosteric small molecules that could disrupt the SARS-COV-2 spike protein-binding site, could be a future avenue for drug discovery.

In conjunction with binding SARS-CoV-2 to ACE2, human host proteases that process the spike protein post binding to ACE2 are required for viral entry. It has been demonstrated that the SARS-CoV-2 spike glycoprotein is cleaved by the host serine protease TMPRSS2 and proprotein convertase furin[174–176]. As discussed earlier, several repurposed approved human protease inhibitors have entered human trials[107,108,177–179]. If successful in the clinical studies, future research and development of more potent selective inhibitors targeting specific

BOX 1

Advantages and disadvantages of COVID-19 antiviral drugs

The COVID-19 therapeutics that have been FDA approved or authorized are summarized in Table 1. The immunomodulators that are currently part of the treatment strategy in patients with severe disease where the cytokine pathway is inappropriately amplified and the immune response is dysregulated include dexamethasone, baricitinib and tocilizumab. Tocilizumab is an IL-6 receptor antagonist and baricitinib inhibits JAK enzymes; thus, both serve to mitigate activation of inflammation and acute phase reactants. In addition, baricitinib may prevent the virus entering cells by binding to AAK1. However, these repurposed drugs are limited to administration in those hospitalized with COVID-19 requiring oxygen supplementation, with baricitinib and tocilizumab reserved for those considered to have rapidly increasing oxygen needs and systemic inflammation. Monoclonal antibodies, including casirivimab with imdevimab and bamlanivimab with etesevimab, are COVID-19 therapeutics that were made available earlier in the pandemic for the treatment of those with mild-to-moderate disease at high risk for progression to severe disease. Monoclonal antibodies target the spike protein of SARS-CoV-2, thereby blocking the attachment of the spike protein to the human ACE2 receptors and inhibiting viral entry. Although this proved to be an efficacious mechanism in preventing disease progression in this population, the utility of specific monoclonal antibodies was limited by the emergence of variants with a mutation of the spike protein that rendered this class of drugs ineffective. Thus, new monoclonal antibodies would be needed once a new variant of concern becomes the predominant strain. Further limitations with monoclonal antibodies include the need to be administered in a healthcare setting via an intravenous or subcutaneous route, and the costs associated with the treatment and its administration[223]. The three antivirals authorized or approved for the treatment of COVID-19 include remdesivir, molnupiravir and nirmatrelvir. Remdesivir, a nucleotide analogue prodrug, is a repurposed drug that was the first FDA-approved drug for the treatment of COVID-19; however, its use has been limited to select populations in the in- and outpatient setting and requires administration in a healthcare setting. Molnupiravir is a ribonucleoside prodrug that targets the RNA-dependent RNA polymerase and interferes with viral replication[224]. Molnupiravir showed lower clinical efficacy in Phase 3 trials than the preferred regimens of either nirmatrelvir or intravenous remdesivir and thus is designated as an alternative treatment option by the NIH Treatment Panel for non-hospitalized adults at risk for progression to severe disease. However, there are no clinical trials that have directly compared these three regimens. The third antiviral, nirmatrelvir, as mentioned previously, is specific for Mpro and has a broad activity across different SARS-CoV-2 variants as well as a marked efficacy in those with mild-to-moderate disease at risk for disease progression. However, nirmatrelvir requires co-administration with ritonavir, which may limit this medication for some patients due to drug–drug interactions. All three antivirals have been shown to remain active with Omicron and some of the variants of concern in vitro[149,150,155,225], thus possibly circumventing the main limitation experienced with monoclonal antibodies at this time.

human proteases for the spike glycoprotein may be warranted; however, off-target activity with human proteins is something that will need to be monitored closely.

Additional targets recently discovered to block the viral entry of SARS-CoV-2 into lung epithelial cells were shown to regulate endocytosis, including AP2-associated protein kinase 1 (AAK1)[180]. AAK1 is a known regulator in AT2 alveolar epithelial cells and has been proposed as a target to block virus entry into cells[180]. Baricitinib, a JAK 1 and 2 inhibitor, was shown to also bind to AAK1 through screening of approved drugs[180]. Baricitinib has already been evaluated in multiple trials, primarily for anti-inflammatory pharmacology, but selective targeting of AAK1 to prevent virus entering cells may be an additional strategy for possible intervention of an early infection[181].

Viral proteases are of a particular interest given that they are required for viral replication and, if targeted, selectivity would spare directly targeting the host. In addition to Mpro agents in clinical trials from Pfizer and Shionogi & Co., additional antiviral Mpro inhibitors are in pre-clinical development. The COVID Moonshot international consortium, initiated early in the pandemic, is focused on the discovery of antiviral Mpro inhibitors using the novel open-science crowdsourced approach[182]. Beyond Mpro inhibition, a second viral protease required for SARS-CoV-2 replication is papain-like protease (PLpro). PLpro is required by SARS-CoV-2 to generate the replicase complex but also acts as a protease and cleaves both human ubiquitin and ISG15, which are regulators of the host innate immune response for viral evasion[183]. This dual pharmacology could address viral replication at the initial stages as well as possibly at the later inflammatory stages. There are no publicly disclosed clinical agents for PLpro at present.

Outlook

Although a coronavirus pandemic was perhaps predictable[184], the world was woefully unprepared[3]. Despite this, vaccine development and initial deployment was achieved in under 12 months, a process that usually takes tens of years[185]. Symptomatic infections can occur in populations that are vaccinated, enabling ongoing community transmission[186,187]. Antiviral discovery and development therefore still have an important role to play in the control and mitigation of COVID-19 infection and transmission. FDA-authorized or FDA-approved COVID-19 therapeutics are summarized in Table 1. Advantages and disadvantages of COVID-19 antiviral drugs are discussed in Box 1. In March 2022 the WHO provided a Strategic Preparedness and Response Plan to end the acute phase of the pandemic, requiring two objectives to be attained: first, reduction in the incidence of SARS-CoV-2 infections and second, prevention, diagnosis and treatment of COVID-19 (ref. 188). Over the course of the pandemic we have moved closer to achieving these goals, the management of hospitalized patients improved, therapeutics administration expanded in the in- and outpatient settings, and vaccines were realized. Drug development progressed rapidly to clinic during the pandemic, owing in part to public–private partnerships (for example, NIH's Accelerating COVID-19 Therapeutic Interventions and Vaccines, ACTIV), substantial investments made in needed research infrastructure (for example, biosafety level 3 facilities), advances made in the use of the ReFRAME library to identify molecules and innovative ways to accelerate clinical trials (flexibility of protocols), to name a few.

From a drug development perspective, we have learned that we can design and pre-clinically evaluate new molecules quickly. The initial focus on screening the FDA-approved drugs, or agents that are close to or currently in clinical trials, with the goal of repurposing towards COVID-19 treatments, has informed possible future avenues for discovery. Potential targets to treat early stage infection or prophylactic treatment following potential exposure for both virus and host show promise. In later stages, primary efforts have focused on host immunity targets to control cytokine storm effects and inflammation, although treatments to lower viral load continue to be of interest as well, particularly for immunocompromised patients.

We still have a lot to learn about COVID-19 pathogenesis and treatment. Although it is caused by an acute-phase virus, where antiviral treatment needs to be initiated early, its deleterious impact can result in severe disease and persistence of chronic symptoms for weeks or even months, despite no conclusive evidence of a viral reservoir. As diagnostic tests became more available, a phenomenon known as COVID rebound was reported, where the patient could test positive for the virus and/or have disease symptoms a few days after clearing the virus[189,190]. The aetiology of viral load rebound is unknown and in the general untreated outpatient population, viral load rebound has been observed in up to 12% of cases[40]. Only a smaller proportion of those with viral load rebound – 1-2% – also reported symptom rebound following initial improvement[40]. Viral load rebound has also been observed in patients treated with Paxlovid and molnupiravir[191]. In a retrospective analysis of the EPIC-HR (NCT04960202) population and a small case series of patients treated with nirmatrelvir–ritonavir, viral load rebound was not associated with the development of resistance[192,193]. Although these rebounds have not been associated with serious outcomes, it highlights how hard it is to control the transmission of COVID-19 for patients with prolonged detectable virus. As with viral rebound, the aetiology, manifestations and possible preventative measures and/or treatment of post-COVID conditions are not fully understood. These include long COVID, also known as post-acute sequelae of SARS-CoV-2 (PASC) and post-COVID-19 syndrome. This is a growing area of unmet medical need, with an estimated global prevalence of 37 and 32% of those with COVID-19 having experienced persistent symptoms due to COVID-19 at 30 and 90 d, respectively[194]. Extensive research efforts are ongoing to both classify the disease—which may actually be several syndromes—and determine the cause. Early hypotheses include residual viraemia, reactivated latent viraemia from other viruses such as Epstein–Barr virus and the activation of autoantibodies[195–197]. These studies have shown that autoantibodies increase over time during COVID-19 infection. Studies of patients with existing autoimmune diseases may also shed more light on the pathophysiology of long COVID. A study in patients with established primary Sjögren's syndrome and recent COVID-19 infection identified that 29% of the study population had symptoms past 12 weeks, with raised levels of lactate dehydrogenase and C-reactive protein, supplemental oxygen and hospital admission being associated with a higher risk (odds ratio >5) of developing long COVID[198]. There is also hope in the autoimmune disorder community that the increased investment into long COVID research may find improved treatments for them. In February 2022 the US government committed over one billion dollars for long COVID research, for which its flagship programme RECOVER (https://recovercovid.org/) aims to understand, prevent and treat long-term health effects related to COVID.

Despite the severity of COVID-19 infections and the uncertainties of the long-term effects of PASC, three years into the COVID-19 pandemic we seem to be in a state of COVID-19 fatigue. Public health measures designed to prevent the spread of disease have all but stopped and fatigue is also making it harder to estimate the actual overall burden, as many people do not test themselves and those who do, do not always report it. As of 15 February 2023, although 79.0% of the US adult population (≥18 yr) had completed the primary vaccine series, only 19.3% had received the updated bivalent booster dose[199]. The vaccination rates were higher in the older adults (age ≥65 yr) for both the primary series (94.2%) and the bivalent booster dose (41.0%)[199]. Furthermore, in the period between 3 October 2021 and 24 December 2022, among unvaccinated people aged ≥12 yrs in the US, there was an approximately 14-fold increased risk of dying from COVID-19 compared with people who received the bivalent booster vaccine[200]. This is compounded by the early monoclonal antibodies losing efficacy as the virus mutates. This emphasizes the need for safe and effective COVID-19 therapies that have different mechanisms of action, can be deployed across the population to provide treatment options and can reduce the potential for resistance development.

Although remdesivir, nirmatrelvir–ritonavir and molnupiravir were developed with unprecedented speed, we need to find ways to further accelerate small molecule development from the approximately 2 yr it took to develop antivirals that could be administered by the patient at home to circumvent serious disease. Although we are unable to predict the culprit of the next pandemic, to enable rapid development of therapeutics, we would need small molecules identified that have already progressed through early pre-clinical and clinical evaluation, similar to the readiness by which remdesivir was positioned at the outset of the pandemic. Ideally, these candidates would mechanistically be able to target the conserved region of the pathogen and not be easily rendered ineffective across strains. It would behove us to continue to use infrastructure developed in the COVID-19 pandemic to advance development of antivirals for other pathogens in preparation for the next pandemic.

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Competing interests

The authors are paid employees of Pfizer Inc. and own Pfizer stock at the time of writing this manuscript.

Additional information