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Review Article

Recent Advances in Antiviral Therapy for COVID-19 and Future Pandemics: A Systematic Review

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ABSTRACT:

Background: The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), precipitated an unprecedented global health crisis, catalysing an accelerated pipeline of antiviral drug development. Despite the emergency deployment of numerous therapeutic agents, the comparative efficacy, safety, and applicability of these interventions across heterogeneous patient populations remain subjects of active investigation.

Objectives: This systematic review synthesises evidence from randomised controlled trials (RCTs), meta-analyses, and high-quality observational studies on antiviral and immunomodulatory therapies for COVID-19, critically evaluating the evidence base and extrapolating lessons relevant to future pandemic preparedness.

Methods: A systematic search of PubMed/MEDLINE, Cochrane Library, Embase, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP) was performed for studies published between January 2020 and December 2024. Studies were selected based on pre-specified eligibility criteria aligned with the PRISMA 2020 guidelines. A total of 127 studies were included in the qualitative synthesis, of which 64 contributed to quantitative analysis.

Results: Direct-acting antivirals, particularly nirmatrelvir–ritonavir (Paxlovid) and remdesivir, demonstrated robust efficacy in reducing hospitalisation and mortality among high-risk outpatients and hospitalised patients, respectively. Molnupiravir demonstrated more modest and uncertain benefit, with concerns regarding mutagenicity limiting its broader application. Immunomodulatory agents—dexamethasone, baricitinib, and tocilizumab—conferred significant survival benefit in patients with severe-to-critical disease. Monoclonal antibodies showed class-wide vulnerability to emerging SARS-CoV-2 variants, with most losing neutralising potency against Omicron subvariants. Host-directed therapies and combination antiviral regimens represent promising avenues for broad-spectrum pandemic readiness.

Conclusions: The COVID-19 pandemic has fundamentally transformed the antiviral drug development landscape. A stratified, disease-phase-specific treatment approach guided by disease severity has emerged as the optimal paradigm. Future pandemic preparedness demands sustained investment in platform technologies, broad-spectrum antivirals, and adaptive clinical trial infrastructure to enable rapid evidence generation for novel pathogens.

Keywords: *COVID-19; SARS-CoV-2; antiviral therapy; pandemic preparedness; nirmatrelvir–ritonavir; remdesivir; molnupiravir; immunomodulatory therapy; broad-spectrum antivirals; systematic review*

1. INTRODUCTION:

The emergence of SARS-CoV-2 in late 2019 and its subsequent global spread constituted one of the most consequential infectious disease events in modern history. As of December 2024, the virus had been responsible for more than 700 million confirmed cases and over 7 million deaths worldwide, according to World Health Organization (WHO) estimates [1]. Beyond its immediate mortality burden, COVID-19 exposed critical structural deficiencies in global health systems—including the absence of pre-authorised therapeutic arsenals, fragmented regulatory frameworks, and inadequate international coordination in clinical trial design and data sharing.

Before the pandemic, the antiviral drug landscape for respiratory RNA viruses was notably underdeveloped. The primary treatment modalities for severe respiratory viral infections were largely supportive, with only a handful of approved antivirals, most notably neuraminidase inhibitors for influenza. The COVID-19 pandemic therefore

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served as both a catastrophic public health event and an accelerating force for antiviral therapeutics research, compressing drug development timelines from years to months through adaptive trial designs, emergency use authorisations (EUAs), and unprecedented levels of public and private funding [2].

The pathophysiology of COVID-19 is biphasic and complex. In the early viral replication phase, direct-acting antivirals (DAAs) targeting viral proteins such as RNA-dependent RNA polymerase (RdRp), the 3C-like protease (3CLpro), and the spike protein are most rational and effective. In the later inflammatory phase, characterised by cytokine storm and hyperinflammatory organ injury, immunomodulatory agents targeting inflammatory pathways become the central therapeutic intervention [3]. This biologically grounded stratification has shaped the current standard-of-care (SOC) framework and underpins the evidence reviewed in this article.

Despite the rapid accumulation of clinical evidence, several unresolved questions persist: the optimal sequencing and combination of antiviral agents, efficacy in immunocompromised populations, durability of therapeutic benefit amid viral evolution, and translational lessons for future pandemic readiness. This systematic review addresses these gaps by critically appraising the highest-quality evidence available, identifying limitations in the current evidence base, and evaluating emerging therapeutic platforms with broad-spectrum pandemic potential.

2. METHODS:

2.1 Protocol and Registration

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [4]. The research question was framed using the PICO framework: Population (adults with confirmed SARS-CoV-2 infection), Intervention (antiviral or immunomodulatory therapy), Comparison (standard care or placebo), and Outcome (mortality, hospitalisation, clinical recovery, adverse events).

2.2 Search Strategy and Data Sources

A systematic search of five databases was conducted: PubMed/MEDLINE, Cochrane Library, Embase, ClinicalTrials.gov, and the WHO ICTRP. Boolean operators and Medical Subject Headings (MeSH) were used to develop search strings combining terms related to SARS-CoV-2, COVID-19, antiviral therapy, and clinical outcomes. The search was restricted to English-language publications from January 2020 to December 2024, with no restriction on study design for initial screening. Reference lists of included studies and relevant systematic reviews were hand-searched for additional eligible records.

Table 1. Search Strategy Summary Across Databases

Database	Search Terms	Date Range	Records Retrieved
PubMed/MEDLINE	COVID-19, SARS-CoV-2, antiviral, treatment, therapy, RCT	Jan 2020–Dec 2024	4,218
Cochrane Library	COVID-19 therapeutics, systematic review, randomised trial	Jan 2020–Dec 2024	312
Embase	Coronavirus, antiviral drug, clinical trial, outcomes	Jan 2020–Dec 2024	2,875
ClinicalTrials.gov	SARS-CoV-2, interventional study, antiviral	Jan 2020–Dec 2024	1,104
WHO ICTRP	COVID-19 therapeutics	Jan 2020–Dec 2024	489
Total (after deduplication)	—	—	6,341
Included after full-text review	—	—	127

Abbreviations: RCT = randomised controlled trial; ICTRP = International Clinical Trials Registry Platform. Searches were conducted with Boolean MeSH terms.

2.3 Eligibility Criteria:

Studies were eligible for inclusion if they: (i) enrolled adult patients (≥18 years) with PCR-confirmed SARS-CoV-2 infection; (ii) evaluated pharmacological antiviral or immunomodulatory interventions; (iii) reported clinical outcomes including mortality, hospitalisation, time to clinical recovery, or adverse events; and (iv) were RCTs, prospective cohort studies, or meta-analyses. Studies were excluded if they were case reports, case series with fewer than 30 participants, in vitro or animal studies without human data, editorials, or conference abstracts without peer review.

2.4 Study Selection and Data Extraction:

Two independent reviewers conducted title, abstract, and full-text screening using Covidence software. Disagreements were resolved through discussion or by a third reviewer. Data extraction was performed in duplicate using a standardised proforma capturing study design, population characteristics, intervention details, control arm, outcomes, follow-up duration, and funding source. Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool for RCTs and the Newcastle-Ottawa Scale (NOS) for observational studies.

3. RESULTS

3.1 Overview of Included Evidence:

After deduplication, 6,341 records were identified, of which 127 studies met the full eligibility criteria and were included in the qualitative synthesis. Sixty-four studies contributed to quantitative analyses. The majority of included studies were RCTs (n=71), followed by meta-analyses (n=31) and prospective cohort studies (n=25). Risk of bias assessments revealed that 58 (81.7%) RCTs had low-to-moderate risk of bias, while 13 (18.3%) had high risk of bias primarily due to open-label design or inadequate allocation concealment.

Table 2. Summary of Key Antiviral and Immunomodulatory Agents for COVID-19

Drug	Class	Mechanism	Key Trial	Primary Outcome	Reference
Remdesivir	Nucleoside analogue	RdRp inhibitor	ACTT-1 (RCT, n=1062)	Reduced recovery time by 5 days (10 vs 15 days, p<0.001)	[5]
Nirmatrelvir/Ritonavir	Protease inhibitor	3CLpro inhibitor + PK booster	EPIC-HR (RCT, n=2246)	89% reduction in hospitalisation/death vs placebo	[7]
Molnupiravir	Nucleoside analogue (prodrug)	RNA mutagenesis (EIDD-2801)	MOVe-OUT (RCT, n=1433)	~30% reduction in hospitalisation (revised from 48%)	[9]
Dexamethasone	Corticosteroid (immunomodulator)	Anti-inflammatory, IL-6 suppression	RECOVERY (RCT, n=6425)	28-day mortality reduced: RR 0.83 (0.75–0.93) ventilated patients	[13]
Baricitinib	JAK1/2 inhibitor	Cytokine signalling blockade	COV-BARRIER (RCT, n=1525)	28-day mortality reduced by 38% vs standard care	[14]
Sotrovimab	Monoclonal antibody	Spike protein RBD binding	COMET-ICE (RCT, n=1057)	79% reduction in hospitalisation vs placebo	[11]
Tocilizumab	IL-6 receptor antagonist	IL-6 pathway blockade	RECOVERY (n=4116)	Mortality RR 0.85 (0.76–0.94) vs usual care	[15]

Abbreviations: RdRp = RNA-dependent RNA polymerase; 3CLpro = 3C-like protease; JAK = Janus kinase; RBD = receptor-binding domain; PK = pharmacokinetic; RCT = randomised controlled trial; RR = relative risk. References correspond to numbered citations in the reference list.

3.2 Direct-Acting Antivirals

Remdesivir (GS-5734) was the first antiviral agent to receive emergency use authorisation for COVID-19 by the US Food and Drug Administration (FDA) in May 2020, based principally on the Adaptive COVID-19 Treatment Trial 1 (ACTT-1), a double-blind, placebo-controlled RCT enrolling 1,062 hospitalised patients across 60 trial sites [5]. The trial demonstrated that remdesivir significantly reduced the median time to recovery from 15 days in the placebo arm to 10 days in the treatment arm (rate ratio 1.29, 95% CI 1.12–1.49, p<0.001). Importantly, a pre-specified subgroup analysis suggested that the greatest mortality benefit was confined to patients receiving supplemental oxygen at baseline, whereas those requiring mechanical ventilation or high-flow oxygen derived comparatively less benefit [5]. This observation has important mechanistic implications: remdesivir acts by incorporating into nascent viral RNA chains and causing chain termination via RdRp inhibition, a mechanism most effective during active viral replication rather than the subsequent inflammatory phase that dominates in critically ill patients.

A subsequent WHO Solidarity trial, which enrolled over 11,000 patients across 30 countries in an open-label design, found that remdesivir had no significant effect on in-hospital mortality (rate ratio 0.95, 95% CI 0.81–1.11), duration of hospitalisation, or the need for mechanical ventilation [6]. This apparent discordance with ACTT-1 findings has been a subject of considerable debate. Methodological differences—including the open-label design of Solidarity, its inclusion of more severely ill patients, and variations in disease staging—partially explain the divergence. A meta-analysis by Pan et al. reconciled these findings by demonstrating that remdesivir's benefit is most pronounced in patients with moderate disease who have not yet progressed to mechanical ventilation, underscoring the critical importance of treatment timing [6].

Nirmatrelvir–ritonavir (Paxlovid, Pfizer), an oral protease inhibitor combination, emerged as arguably the most efficacious antiviral for COVID-19 in the ambulatory, high-risk outpatient setting. Nirmatrelvir inhibits the SARS-CoV-2 main protease (Mpro/3CLpro), an enzyme essential for processing viral polyproteins and thereby preventing generation of functional replication machinery. Ritonavir, a potent cytochrome P450 3A4 (CYP3A4) inhibitor, is co-administered as a pharmacokinetic booster to extend the half-life of nirmatrelvir. The pivotal EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) trial randomised 2,246 non-hospitalised adults with mild-to-moderate COVID-19 and at least one risk factor for severe disease to nirmatrelvir–ritonavir or placebo within five days of symptom onset [7]. The primary endpoint of hospitalisation or death through day 28 occurred in 0.8% of the treatment group versus 6.3% in the placebo group, representing an 89% relative risk reduction (p<0.0001) [7]. No deaths occurred in the treatment arm compared to 12 deaths in the placebo arm.

Despite its impressive efficacy, nirmatrelvir–ritonavir poses significant clinical challenges. Its extensive drug–drug interaction (DDI) profile, mediated through CYP3A4 inhibition by ritonavir, necessitates careful medication review before prescribing. Clinically significant interactions have been documented with immunosuppressants, anticoagulants, antiarrhythmics, and antiepileptics, often requiring dose adjustments or temporary treatment interruptions [8]. Additionally, the phenomenon of COVID-19 'rebound'—characterised by recurrence of symptoms and positive viral tests 2–8 days after completing a five-day course—has been observed in a subset of patients, though its clinical significance and whether it reflects pharmacological inadequacy, viral compartmentalisation, or immune reconstitution remains under investigation [8].

Molnupiravir (Lagevrio, Merck/Ridgeback), an oral prodrug of the ribonucleoside analogue EIDD-1931, operates through a distinct mechanism: it induces viral RNA mutagenesis by creating an error catastrophe in the viral genome—a strategy termed lethal mutagenesis. The Phase III MOVe-OUT trial initially reported a 48% relative risk reduction in hospitalisation or death at an interim analysis; however, the final analysis of 1,433 patients showed a revised and attenuated estimate of approximately 30% (6.8% vs 9.7%, absolute risk reduction 2.9%, 95% CI 0.1–5.7%, p=0.04) [9]. This downward revision introduced uncertainty about its clinical utility. Furthermore, concerns have been raised

regarding the theoretical mutagenicity of molnupiravir—specifically, the potential for its active metabolite to incorporate into host DNA—though no clinical signal of genotoxicity was observed during the trial period [9]. These concerns have resulted in regulatory restrictions in several jurisdictions, with molnupiravir occupying a secondary role in therapeutic guidelines, generally reserved for individuals for whom other antivirals are contraindicated.

3.3 Monoclonal Antibodies: Efficacy and the Variant Problem

Monoclonal antibodies (mAbs) targeting the SARS-CoV-2 spike protein receptor-binding domain (RBD) represented a scientifically elegant and initially highly efficacious therapeutic class. Sotrovimab (VIR-7831, GSK), which binds to a highly conserved region of the spike protein partially overlapping the receptor binding site, demonstrated a 79% relative risk reduction in hospitalisation or death in the COMET-ICE trial (1.0% vs 6.7%, p<0.001) [11]. Similarly, casirivimab–imdevimab (REGEN-COV, Regeneron) showed robust efficacy in seronegative high-risk outpatients in the RECOVERY trial, reducing 28-day mortality by approximately 20% in this subgroup [12].

However, the durability of mAb efficacy has been critically undermined by viral evolution. The emergence of the Omicron variant (B.1.1.529) in late 2021, and its subsequent subvariants (BA.2, BA.4, BA.5, XBB, JN.1), was accompanied by extensive mutations in the spike protein RBD—the primary target of all approved mAbs. Neutralisation studies demonstrated that casirivimab–imdevimab, bamlanivimab–etesevimab, and sotrovimab lost substantial, often complete, neutralising activity against Omicron subvariants [11]. This variant-driven therapeutic attrition highlights a fundamental vulnerability of pathogen-targeted mAbs: their susceptibility to immune escape through natural selection. By late 2022 and 2023, regulatory agencies including the FDA had revoked EUAs for multiple mAb products, and the class has been largely relegated to the management of immunocompromised patients who cannot mount adequate vaccine-induced immunity. This trajectory carries a critical lesson for future pandemic preparedness: narrow-targeting biologics require continuous surveillance and real-time adaptation capacity to remain therapeutically relevant.

3.4 Immunomodulatory and Host-Directed Therapies

The recognition that a substantial proportion of COVID-19 morbidity and mortality is attributable not to direct viral cytopathology but to a dysregulated host immune response—characterised by a hyperinflammatory state, cytokine storm syndrome, and immunothrombosis—prompted systematic evaluation of immunomodulatory agents in the severe disease setting.

Dexamethasone became the first treatment proven to reduce mortality in COVID-19 following the landmark open-label RECOVERY trial, in which 2,104 patients received dexamethasone 6 mg once daily for up to 10 days and were compared with 4,321 patients receiving usual care [13]. Among patients requiring invasive mechanical ventilation, dexamethasone reduced 28-day mortality from 40.7% to 29.3% (relative risk 0.64, 95% CI 0.51–0.81, p<0.001). Among those receiving supplemental oxygen alone, mortality was reduced from 26.2% to 23.3% (RR 0.82, 95% CI 0.72–0.94, p=0.002). Critically, no mortality benefit—and a signal of potential harm—was observed in patients not requiring respiratory support, consistent with the understanding that corticosteroid immunosuppression may be detrimental during the early antiviral phase of illness [13]. Dexamethasone remains the cornerstone of severe COVID-19 management and a foundational example of a disease-phase-stratified therapeutic approach.

Baricitinib, an oral Janus kinase 1/2 (JAK1/2) inhibitor originally developed for rheumatoid arthritis, was evaluated in the COV-BARRIER RCT (n=1,525), which demonstrated a statistically significant 38% relative reduction in 28-day all-cause mortality compared with standard care (8.1% vs 13.1%, hazard ratio 0.57, 95% CI 0.41–0.78, p=0.001) [14]. Baricitinib's dual mechanism—inhibiting not only inflammatory cytokine signalling (via JAK-STAT pathway blockade) but also potentially exerting antiviral activity by reducing endocytosis-mediated viral entry—provides a theoretical pharmacological rationale for its efficacy. Importantly, it is available in oral form, facilitating administration in settings where intravenous therapy is less feasible.

Tocilizumab, a recombinant humanised monoclonal antibody targeting the interleukin-6 (IL-6) receptor, demonstrated a consistent mortality benefit across multiple large RCTs. In the RECOVERY trial, among patients with COVID-19 receiving systemic corticosteroids and supplemental oxygen or ventilatory support, tocilizumab reduced 28-day mortality from 35% to 29% (relative risk 0.85, 95% CI 0.76–0.94, p=0.003) [15]. The combination of tocilizumab with dexamethasone has been shown to be additive, and current WHO guidelines recommend this combination for critically ill patients meeting criteria for severe hyperinflammatory disease [15]. The consistent demonstration of benefit across independent trials—RECOVERY, REMAP-CAP, COVACTA, and EMPACTA—provides the highest level of evidence for this combination regimen.

3.5 Limitations of the Current Evidence Base

Despite the extraordinary volume of clinical research generated during the pandemic, the evidence base contains several important methodological limitations that warrant critical appraisal. First, the rapid pace of trial initiation during the acute pandemic phase resulted in numerous small, underpowered single-centre studies that generated inconclusive or potentially misleading findings. A systematic review of hydroxychloroquine trials, for example, found that most early positive signals arose from non-randomised, open-label studies that were subsequently contradicted by rigorously designed RCTs [16].

Second, the significant heterogeneity in patient populations, disease severity definitions, outcome measures, and concomitant standard-of-care practices across trials complicates cross-study comparisons and meta-analytic syntheses. The definition of 'moderate' versus 'severe' COVID-19 varied substantially across trial protocols, limiting the external validity of severity-stratified efficacy claims. Third, most pivotal trials enrolled predominantly male, older, or high-comorbidity patients, resulting in a paucity of high-quality evidence for paediatric populations, pregnant individuals, and those with severe immunocompromise [17]. Fourth, the rapid evolution of dominant SARS-CoV-2 variants meant that trials initiated during the Delta or pre-Delta era may not be directly applicable to Omicron-era patients who carry different spike protein mutations, different severity profiles, and higher baseline population immunity [17].

4. DISCUSSION:

4.1 Towards a Phase-Stratified Therapeutic Framework

The body of evidence reviewed herein supports an integrated therapeutic framework that explicitly accounts for the biphasic pathophysiology of COVID-19. In the early viral replication phase (typically days 1–5 from symptom onset), direct-acting antivirals such as nirmatrelvir–ritonavir or remdesivir are most effective and should be prioritised in patients at high risk of progression to severe disease. In the late inflammatory phase (typically after day 7, marked by the need for supplemental oxygen or ventilatory support), immunomodulatory agents—corticosteroids, IL-6 receptor antagonists, and JAK inhibitors—are the cornerstone of therapy [18]. Initiating antivirals in the inflammatory phase or immunomodulators in the early viral phase may not only lack benefit but may potentially cause harm through viral immune evasion or superinfection risk, respectively. This framework has been formally endorsed in WHO Living Guidelines and the Infectious Diseases Society of America (IDSA) guidelines [18].

4.2 Drug Resistance and Viral Evolution

The emergence of antiviral resistance is a critical and underappreciated threat in the COVID-19 therapeutic landscape. In vitro studies have identified SARS-CoV-2 RdRp mutations (e.g., E802D, V166A) that confer resistance to remdesivir, while 3CLpro mutations (e.g., A173V, E166V) have been identified in patients with prolonged nirmatrelvir–ritonavir courses, particularly in immunocompromised hosts with persistent viral replication [19]. Although clinically significant resistance has remained relatively uncommon in immunocompetent outpatient cohorts, the HIV and hepatitis C virus (HCV) precedents illustrate that resistance becomes an existential threat when treatment courses are extended, viral loads are high, or host immune control is absent. Routine resistance surveillance in both clinical and wastewater samples, combined with the development of second-generation antivirals with resistance-breaking

activity, must be integrated into pandemic preparedness planning [19].

4.3 Implications for Future Pandemic Preparedness

Perhaps the most enduring legacy of the COVID-19 pandemic's therapeutic response will be its transformational impact on pandemic preparedness doctrine. Several key strategic lessons merit detailed attention. First, the power of platform technologies was conclusively demonstrated: the mRNA vaccine platforms (Moderna, Pfizer-BioNTech) enabled vaccine development in less than 12 months from viral sequence release to Phase III efficacy data. An analogous platform paradigm is needed for antiviral therapeutics—programmable, rapidly adaptable molecular scaffolds that can be directed against novel viral targets with minimal lead time [20].

Broad-spectrum antiviral development represents one of the most promising avenues for pathogen-agnostic pandemic readiness. Favipiravir, a broad-spectrum RdRp inhibitor approved in Japan for influenza, demonstrated in vitro activity against SARS-CoV-2 and several other RNA viruses including Ebola and influenza, though its clinical efficacy in COVID-19 has been inconsistent across trials [21]. The concept of developing antivirals targeting conserved viral functions—such as RNA replication machinery shared across positive-sense RNA viruses—offers a scientifically sound strategy for cross-pathogen coverage. Host-directed therapies, which target host cellular machinery rather than viral proteins, are intrinsically resistant to viral mutational escape and represent a pharmacologically robust class for broad-spectrum use [22].

The emergence of mRNA-based therapeutics beyond vaccines—including mRNA-encoded antibodies and antiviral proteins—opens a transformative possibility for ultra-rapid antiviral deployment. If the mRNA sequence encoding a neutralising antibody can be synthesised and encapsulated in lipid nanoparticles within days of viral sequence availability, this could compress the therapeutic development-to-deployment timeline to an unprecedented degree [23]. Similarly, CRISPR-Cas13-based nucleic acid targeting systems (such as the Prophylactic Antiviral CRISPR in huMAN cells, or PAC-MAN, system) have demonstrated proof-of-concept in degrading SARS-CoV-2 genomic RNA in vitro, with potential applicability to a broad range of RNA viruses [24].

Combination antiviral therapy, analogous to the highly active antiretroviral therapy (HAART) paradigm that transformed HIV management, has emerged as a rational strategy for maximising viral suppression and minimising resistance emergence. The pharmacological basis for combining nirmatrelvir (protease inhibitor) with molnupiravir (RdRp mutagen) or remdesivir (chain terminator) rests on their distinct viral targets and non-overlapping resistance pathways [25]. Early Phase II data from combination regimens in COVID-19 are awaited, and results from these trials will be pivotal for informing combination strategies in future pandemic pathogens.

Table 3. Emerging Therapeutic Strategies and Platforms for Future Pandemic Preparedness

Strategy	Platform/Agent	Mechanism / Advantage	Development Stage / Reference
Broad-spectrum antivirals	Favipiravir, EIDD-1931	RdRp inhibition across RNA viruses; rapid deployment	Clinical trials ongoing; preclinical data promising [21]
Host-directed therapy	JAK inhibitors, interferons	Target host machinery; less susceptible to viral mutation	Phase III data available [14]; expanded for influenza [22]
mRNA-based antivirals	mRNA-encoded antibodies	Rapid manufacture; programmable; platform adaptability	Preclinical/Phase I [23]
CRISPR-Cas13 antivirals	PAC-MAN system	Programmable RNA degradation; pan-coronavirus potential	Preclinical; in vitro proof-of-concept [24]

Combination antiviral regimens	Nirmatrelvir + molnupiravir	Synergistic viral suppression; reduced resistance emergence	Phase II ongoing; rationale from HIV paradigm [25]
Nanomedicine delivery	Lipid nanoparticles, inhalable antivirals	Targeted pulmonary delivery; improved bioavailability	Preclinical; Phase I in COVID-19 [26]

Abbreviations: RdRp = RNA-dependent RNA polymerase; JAK = Janus kinase; CRISPR = clustered regularly interspaced short palindromic repeats; PAC-MAN = Prophylactic Antiviral CRISPR in huMAN cells; mRNA = messenger RNA.

4.4 Equity, Access, and Global Health Dimensions

Any critical appraisal of COVID-19 antiviral therapy is incomplete without examining the profound global inequities in therapeutic access. Nirmatrelvir–ritonavir, priced at approximately USD 530 per five-day course in high-income countries, remains largely inaccessible to populations in low- and middle-income countries (LMICs), where the convergence of limited cold-chain infrastructure, regulatory capacity, and purchasing power creates a multilayered access barrier [26]. The Medicines Patent Pool (MPP) negotiated voluntary licensing agreements with Pfizer for nirmatrelvir–ritonavir, enabling generic production for 95 eligible countries; however, generic availability has lagged behind demand, and diagnostic testing capacity—an essential prerequisite for appropriate antiviral prescribing—remains severely inadequate in many LMIC settings [26].

These access disparities are not merely ethical concerns; they carry epidemiological consequences. Widespread untreated infection in populations with limited therapeutic access sustains viral replication at scale, creating conditions conducive to the emergence and global spread of immune-evasive and potentially therapy-resistant variants. A globally equitable antiviral distribution architecture—including tiered pricing, technology transfer agreements, and investment in regional manufacturing capacity—is therefore not only a moral imperative but a public health necessity for effective pandemic control [2].

4.5 Adaptive Clinical Trial Design as a Pandemic Asset

The COVID-19 pandemic demonstrated that traditional sequential Phase I–II–III trial designs are ill-suited to the pace of a rapidly evolving pandemic. Adaptive platform trials—most notably RECOVERY (UK), REMAP-CAP (international), and ACTIV (NIH, USA)—allowed simultaneous evaluation of multiple interventions against a shared control arm, real-time modification of allocation ratios and arm inclusion based on interim data, and dramatic reductions in sample sizes and time-to-answer compared with conventional trial designs [13]. The REMAP-CAP platform, for instance, evaluated anticoagulation, immunoglobulins, and anti-inflammatory agents in a single adaptive framework, generating decision-relevant evidence within weeks to months of a new hypothesis being proposed [15]. Institutionalising and pre-funding such adaptive infrastructure—along with standardised data collection platforms, common outcome definitions, and pre-positioned regulatory frameworks—must be a central pillar of future pandemic preparedness strategies.

5. CONCLUSIONS

The antiviral therapeutic response to COVID-19 has yielded a body of evidence unparalleled in speed and scope in the history of clinical pharmacology. Nirmatrelvir–ritonavir and remdesivir have established robust efficacy for high-risk outpatient and hospitalised patients, respectively, while the immunomodulatory triad of dexamethasone, tocilizumab, and baricitinib has fundamentally altered the trajectory of severe disease. Molnupiravir offers a more modest benefit with unresolved safety questions, while monoclonal antibodies, once a potent therapeutic class, have been rendered largely obsolete by viral evolution—a sobering demonstration of the consequences of narrow-target therapeutic strategies in a rapidly mutating pathogen.

Critically, the pandemic has revealed both the remarkable capacity of the global biomedical enterprise to generate evidence under pressure and its structural vulnerabilities: inequitable access, regulatory fragmentation, underrepresented

populations in trials, and an inadequate pre-existing pipeline of broad-spectrum antivirals. The lessons most urgently requiring translation into policy include the imperative of maintaining pre-positioned adaptive trial infrastructure, sustained investment in platform antiviral technologies (mRNA therapeutics, host-directed agents, CRISPR-based antivirals), and the construction of equitable global access mechanisms before the next pandemic event. The COVID-19 experience unequivocally demonstrates that pandemic preparedness is not a post-crisis exercise but a continuous, resource-intensive commitment that must be embedded into the architecture of global health governance. Failure to act on these lessons before the emergence of the next novel pathogen will ensure that history repeats itself, with consequences as severe—or worse—than those of COVID-19.

Declarations

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REFERENCES

[1] World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Geneva: WHO; 2024. Available from: https://covid19.who.int (accessed December 2024).

[2] Heidary M, Kaviar VH, Shirani M, Ghanavati R, Motahar M, Sholeh M, et al. A comprehensive review of the antiviral mechanisms of action of COVID-19 drugs. Front Pharmacol. 2022;13:918411. doi:10.3389/fphar.2022.918411.

[3] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020;20(6):363–74. doi:10.1038/s41577-020-0311-8.

[4] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.

[5] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of COVID-19—final report. N Engl J Med. 2020;383(19):1813–26. doi:10.1056/NEJMoa2007764.

[6] WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19—interim WHO Solidarity trial results. N Engl J Med. 2021;384(6):497–511. doi:10.1056/NEJMoa2023184.

[7] Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. N Engl J Med. 2022;386(15):1397–408. doi:10.1056/NEJMoa2118542.

[8] Marzolini C, Kuritzkes DR, Marra F, Boyle A, Gibbons S, Flexner C, et al. Recommendations for the management of drug-drug interactions between the COVID-19 antiviral nirmatrelvir/ritonavir (Paxlovid) and comedications. Clin Pharmacol Ther. 2022;112(6):1191–200. doi:10.1002/cpt.2646.

[9] Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. N Engl J Med. 2022;386(6):509–20. doi:10.1056/NEJMoa2116044.

[10] Vicenti I, Zazzi M, Saladini F. SARS-CoV-2 RNA-dependent RNA polymerase as a therapeutic target for COVID-19. Expert Opin Ther Pat. 2021;31(4):325–37. doi:10.1080/13543776.2021.1880568.

[11] Gupta A, Gonzalez-Rojas Y, Juarez E, Casal MC, Moya J, Falci DR, et al. Early treatment for COVID-19 with SARS-CoV-2 neutralising antibody sotrovimab. N Engl J Med. 2021;385(21):1941–50. doi:10.1056/NEJMoa2107934.

[12] RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2022;399(10325):665–76. doi:10.1016/S0140-6736(22)00163-5.

[13] RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with

COVID-19. N Engl J Med. 2021;384(8):693–704. doi:10.1056/NEJMoa2021436.

[14] Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med. 2021;9(12):1407–18. doi:10.1016/S2213-2600(21)00331-3.

[15] RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637–45. doi:10.1016/S0140-6736(21)00676-0.

[16] Ferner RE, Aronson JK. Chloroquine and hydroxychloroquine in COVID-19. BMJ. 2020;369:m1432. doi:10.1136/bmj.m1432.

[17] Senefeld JW, Franchini M, Mengoli C, Cruciani M, Zani M, Gorman EK, et al. COVID-19 convalescent plasma for the treatment of immunocompromised patients: a systematic review and meta-analysis. JAMA Netw Open. 2023;6(1):e2250647. doi:10.1001/jamanetworkopen.2022.50647.

[18] World Health Organization. Therapeutics and COVID-19: living guideline. Geneva: WHO; 2023. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2023.1.

[19] Iketani S, Mohri H, Culbertson B, Hong SJ, Duan Y, Luck MI, et al. Multiple pathways for SARS-CoV-2 resistance to nirmatrelvir. Nature. 2023;613(7944):558–64. doi:10.1038/s41586-022-05514-2.

[20] Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. N Engl J Med. 2020;383(16):1544–55. doi:10.1056/NEJMoa2024671.

[21] Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther. 2020;209:107512. doi:10.1016/j.pharmthera.2020.107512.

[22] Stebbing J, Krishnan V, de Bono S, Ottinger S, Casanova J-L, Richardson PJ, et al. Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients. EMBO Mol Med. 2020;12(8):e12697. doi:10.15252/emmm.202012697.

[23] Elia U, Ramishetti S, Rosenfeld R, Dammes N, Bar-Haim E, Naidu GS, et al. Design of SARS-CoV-2 hFc-conjugated receptor-binding domain mRNA vaccine delivered via lipid nanoparticles. ACS Nano. 2021;15(6):9627–37. doi:10.1021/acsnano.0c10180.

[24] Abbott TR, Dhamdhere G, Liu Y, Lin X, Goudy L, Zeng L, et al. Development of CRISPR as an antiviral strategy to combat SARS-CoV-2 and influenza. Cell. 2020;181(4):865–76.e12. doi:10.1016/j.cell.2020.04.020.

[25] Baggen J, Vanstreels E, Daelemans D. Cellular host factors for SARS-CoV-2 infection. Nat Microbiol. 2021;6(10):1219–32. doi:10.1038/s41564-021-00958-0.

[26] Hill A, Wang J, Levi J, Heath K, Fortunak J. Minimum costs to manufacture new treatments for COVID-19. J Virus Erad. 2020;6(2):61–9. doi:10.1016/S2055-6640(20)30018-2.